# Mucinous Cystic Neoplasms

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## 3.1 Definition and Epidemiology

Mucinous cystic neoplasms (MCNs) are pancreatic cystic epithelial neoplasms occurring almost exclusively in women. They are formed by epithelial cells producing mucin and supported by an ovarian-type stroma, without communication with the pancreatic ductal system. According to the grade of epithelial dysplasia, these tumors are classified as MCN with low-grade dysplasia, moderate dysplasia, or high-grade dysplasia (carcinoma in situ). If there is an invasive carcinoma component, the lesions are designated MCN with associated invasive carcinoma [1].

MCNs are preferentially located in the body and tail of the pancreas. The patient age at presentation range is broad, with an average that seems to depend on the degree of malignancy of the neoplasm. Thus, patients with malignant MCN are typically older, suggesting a time-related degeneration of the tumor from an initially benign lesion. The incidence of malignancy for MCN is 17.5%, as reported in the MGH-Verona series [2]. An early diagnosis of MCN is essential since the prognosis for patients with the malignant form is the same as for those with ductal adenocarcinoma, while for patients with "in situ" MCNs surgery could be curative.

At best, MCN is a pre-malignant lesion and it is therefore important to distinguish it from other cystic lesions of the pancreas. On pathological examination, the same tumor may simultaneously exhibit all the various degrees of malignant transformation. This is of great pathogenic relevance as it suggests an adenoma-carcinoma sequence [3].

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## 3.2 Clinical Findings

The symptoms in MCNs are non-specific and are not particularly helpful in the differential diagnosis of pancreatic cystic lesions. The most frequent symptoms are abdominal discomfort or pain. Uncommonly, the patient complains of abdominal pain located in the upper quadrants that irradiates to the flanks, which could guide a pancreatic localization. However, there may also be non-specific symptoms suggestive of malignancy, such as weight loss, anorexia, and obstructive jaundice.

## 3.3 Diagnostic Imaging

Two patterns of MCN are seen on diagnostic imaging procedures: *macrocystic multilocular* and *macrocystic unilocular* [4]. While not pathognomonic, the former is frequently located in the body-tail of the gland. On ultrasound (US) images, macrocystic multilocular forms appear as a sharply defined mass surrounded by a variably thickened wall (Fig. 3.1). Thin septae delimit the cystic spaces, and calcifications are a common finding. On computed tomography (CT) scan, the pre-contrast phase can easily reveal calcifications. The density of the content of these tumors depends on the amount of mucin or the fluid-fluid level from underlying bleeding. This pattern is clearly demonstrated by contrast medium, as the walls and septae are of lower enhancement than the surrounding pancreatic parenchyma because of the fibrous tissue composition

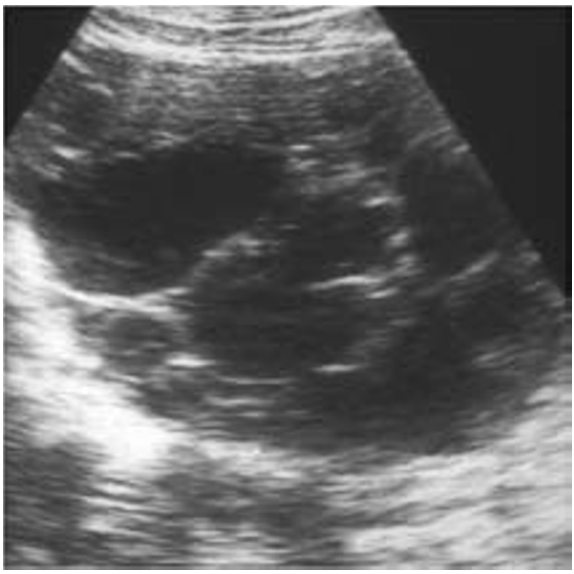


**Fig. 3.1** Mucinous cystedenoma ultrasound. The sonographic scan shows a hypoechoic lesion in the head of the pancreas. The lesions has a macrocystic pattern, as indicated by the large anechoic central areas

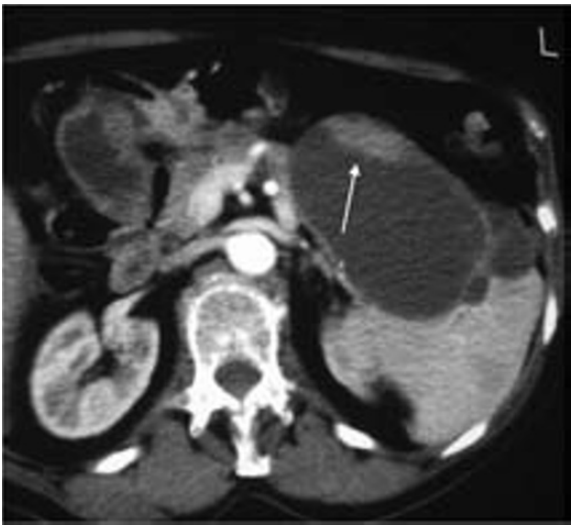


**Fig. 3.2** Mucinous cystedenoma. Axial contrast-enhanced computed tomography scan shows a oligocystic-macrocystic lesion in the body-tail of the pancreas. The cystic lesion contains a mural nodule on the non-dependent wall of the lesion (*arrow*)

and minimal vascularization. The outer wall and septae are of similar thickness. The macrocystic unilocular pattern is less specific and may simulate any other pancreatic cystic mass, at US and at CT. Consequently, in cases with unique cysts with a thin wall, no calcifications, and no parietal nodules the diagnosis is not easily made.

From the radiological point of view, a thickened wall, the presence of papillary projections arising from the wall or septae, evidence of peripheral calcifications, and invasion of the surrounding vascular structures are considered the best signs of malignancy (Fig. 3.2). The diagnosis will be clearer if extracapsular extension of the lesion is detected on CT contrast-enhanced images. When thick walls, thick septae, and calcifications are simultaneously present, the probability of malignancy is 95%. When fewer than three signs are present, the probability of malignancy decreases, and it is zero when there are no calcifications and the septae and the wall are thin. Since calcifications cannot be detected by magnetic resonance imaging (MRI), the primary imaging modality for these patients is CT.

The predominant fluid content of MCNs renders them brighter on T2-weighted MRI, which well depicts the presence, features, and distribution of the internal septae. Magnetic resonance cholangiopancreatography (MRCP) is optimal for the non-invasive assessment of the pancreatic duct system (Wirsung and Santorini ducts) (Fig. 3.3). When the mass is clearly isolated from the ductal system, thereby excluding the possibility of an intraductal tumor, further examination with MRCP is not required (Fig. 3.3).

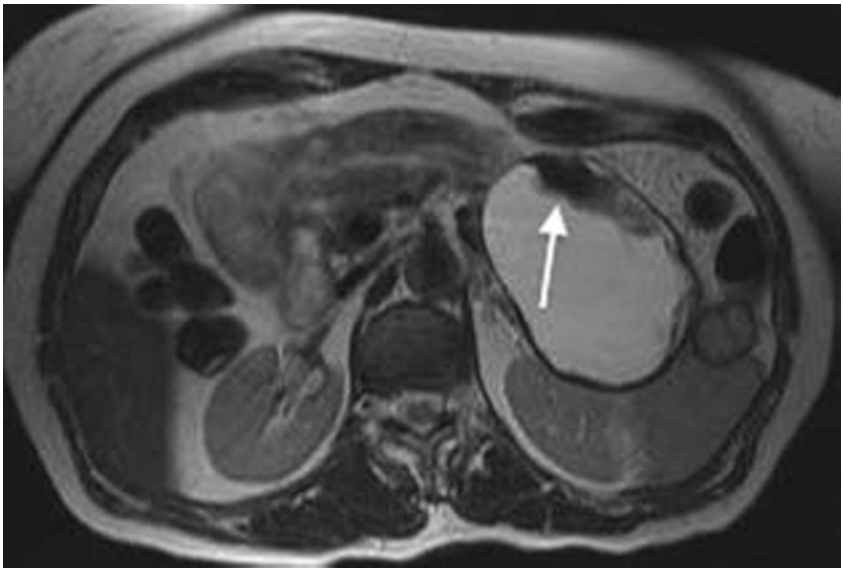


**Fig. 3.3** Mucinous cystedenoma. Axial T2-weighted magnetic resonance image shows a cystic macrocystic lesion in the body-tail of the pancreas, with hypointense mural nodules on the non-dependent wall of the lesion (*arrow*)

## 3.4 Pathology

The overwhelming majority of MCNs occur in the body-tail of the pancreas, where the tumor presents as a round mass with a smooth surface and a fibrous pseudocapsule of variable thickness and frequently containing calcifications. The size of these neoplasms in their greatest dimension ranges from 2 to 35 cm, with an average of 6–10 cm. The cut section shows either a unilocular or a multilocular tumor with cystic spaces ranging in diameter from a few millimeters to several centimeters and containing either thick mucin or a mixture of mucin and hemorrhagic-necrotic material. The internal surface of unilocular tumors is usually smooth and glistening, whereas multilocular tumors often show papillary projections and mural nodules. There is no significant size difference among the different MCN categories, whereas the malignancy of the tumor correlates significantly with the presence of papillary projections and/or mural nodules and multilocularity. As noted above, the tumor does not communicate with the duct of Wirsung or the secondary ducts.

Microscopically, MCNs show two distinct components: an inner epithelial layer and an outer densely cellular "ovarian-like" stromal layer (Fig. 3.4). The mucin-producing epithelium exhibits a spectrum of differentiation, ranging from histologically benign appearing columnar epithelium to severely atypical epithelium.

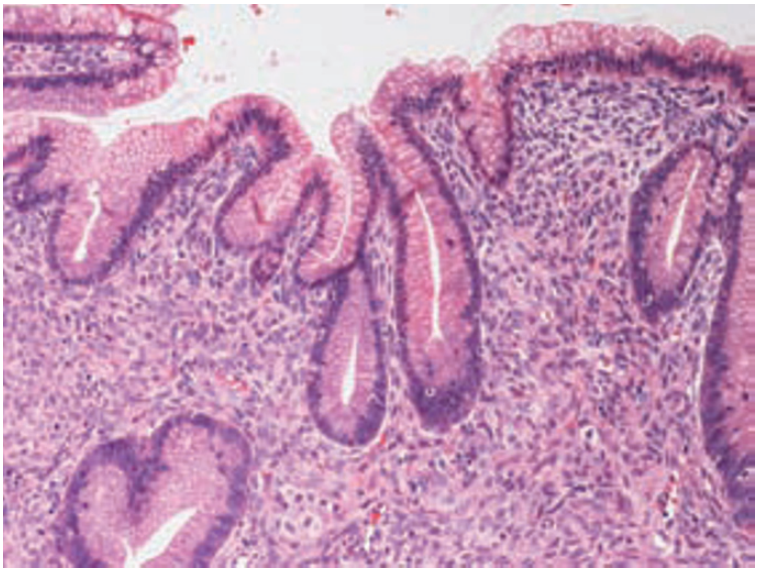


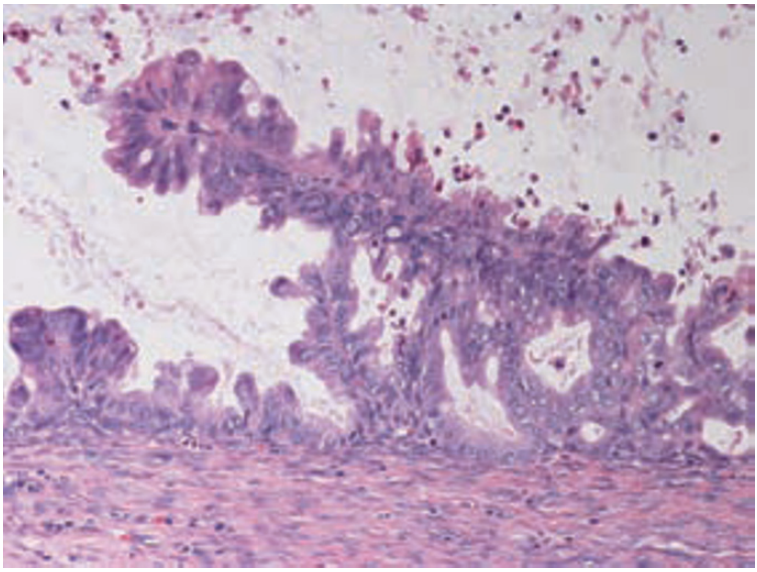
**Fig. 3.4** Mucinous cystic neoplasm with low-grade dysplasia. The cyst wall is lined with a mildly dysplastic columnar epithelium supported by an "ovarian-like" stroma

The recent World Health Organization (WHO 2010) classification of MCNs [5] comprises the three above-mentioned types*:* MCN with low-grade dysplasia, with moderate-grade epithelial dysplasia; and with high-grade dysplasia, characterized by severe dysplasia-carcinoma in situ changes (Fig. 3.5). The presence of carcinomatous stromal invasion defines MCNs with associated invasive carcinoma. The invasive component usually resembles the common ductal adenocarcinoma.

Immunophenotypically, the mucinous epithelial cells show immunoreactivity with epithelial markers, including EMA, CEA, cytokeratins 7, 8, 18, and 19, and MUC5AC, a gastric-type marker of mucin. Focally, there is positivity for intestinal type mucins (MUC2) in goblet cells scattered within the epithelium. The invasive component is frequently positive for MUC1 and p53. The ovarian-like stroma is positive for vimentin, smooth-muscle actin, and progesterone receptors (Fig. 3.6a), while the luteinized epithelioid cells stain for α-inhibin (Fig. 3.6b).

## 3.5 Differential Diagnosis

The macrocystic multilocular pattern is considered typical but it is not pathognomonic. Oligocystic serous cystic neoplasms (SCNs), solid pseudopapillary tumors (cystic variant), and cystic endocrine tumors are identical in appear-



**Fig, 3.5** Mucinous cystic neoplasm with high-grade dysplasia. Papillary projections lined by severe dysplastic epithelium

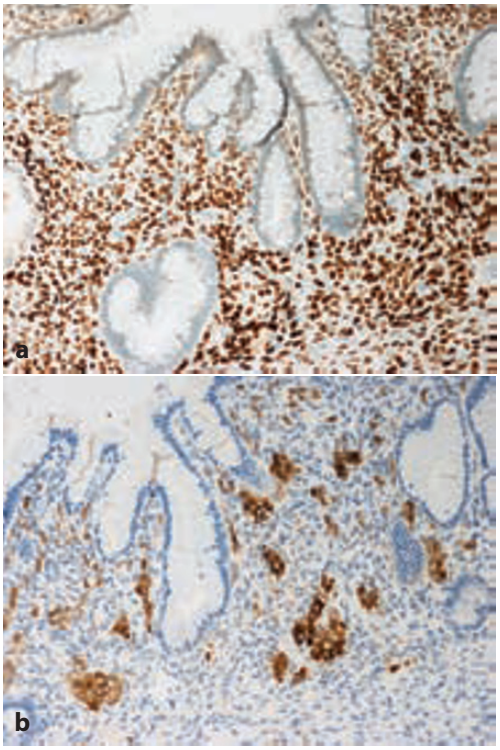



**Fig. 3.6** Mucinous cystic neoplasm. The ovarian-like stroma shows nuclear positivity for progesterone receptors (**a**) and α-inhibin cytoplasmic positivity in the luteinized cells (**b**)

ance to MCNs. In these cases, clinical history and laboratory data are essential for the correct diagnosis. Oligocystic SCN can almost never be pre-operatively differentiated from benign MCN.

In neuroendocrine and pseudopapillary tumors, the cystic component is due to previous necrosis and intratumoral bleeding. In the former, the clinical syndrome might suggest the diagnosis; in the latter, MRI will enhance the differences in the appearance of the fluid content.

Pseudocysts make the diagnosis challenging, as they can resemble the macrocystic unilocular pattern of MCN. If the clinical history is silent, MCN should be suspected.

## 3.6 Treatment

When possible, all MCNs should be resected, both cystadenomas and cystadenocarcinomas. Current thinking is that all MCNs have the potential to progress to malignancy. Given the life-expectancy of most of these patients, almost always middle-aged women, there is a high risk of development of mucinous cystadenocarcinoma, which, unfortunately, has a very low rate of resectability and a very poor prognosis. Predictors of malignancy are: large size (≥ 4 cm) and the presence of nodules, septae, and "eggshell" calcifications. In these cases, surgical "standard" pancreatic resection should be performed, avoiding middle pancreatectomies and spleen-preserving distal pancreatectomies [6, 7].

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