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REVIEW

Management of mucinous cystic neoplasms of the pancreas

Mario Testini, Angela Gurrado, Germana Lissidini, Pietro Venezia, Luigi Greco, Giuseppe Piccinni

Mario Testini, Angela Gurrado, Germana Lissidini, Pietro Venezia, Giuseppe Piccinni, Unit of Endocrine, Digestive and Emergency Surgery, Department of Biomedical Sciences and Human Oncology, Section of General and Oncologic Surgery, University Medical School of Bari, 70124 Bari, Italy
Luigi Greco, Department of Emergency and Organ Transplantation, University Medical School of Bari, 70124 Bari, Italy
Author contributions: Testini M and Gurrado A wrote the review; Lissidini G, Venezia P, Greco L and Piccinni G contributed to the literature search.
Correspondence to: Mario Testini, MD, Professor, Unit of Endocrine, Digestive and Emergency Surgery, Department of Biomedical Sciences and Human Oncology, Section of General and Oncologic Surgery, University Medical School of Bari, Policlinico, Piazza Giulio Cesare, 11, 70124 Bari, Italy. mario.testini@chirgen2.uniba.it
Telephone: +39-80-5592882 Fax: +39-80-5592882
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Abstract

The purpose of this study was to investigate the actual management of mucinous cystic neoplasm (MCN) of the pancreas. A systematic review was performed in December 2009 by consulting PubMed MEDLINE for publications and matching the key words "pancreatic mucinous cystic neoplasm", "pancreatic mucinous cystic tumour", "pancreatic mucinous cystic mass", "pancreatic cyst", and "pancreatic cystic neoplasm" to identify English language articles describing the diagnosis and treatment of the mucinous cystic neoplasm of the pancreas. In total, 16322 references ranging from January 1969 to December 2009 were analysed and 77 articles were identified. No articles published before 1996 were selected because MCNs were not previously considered to be a completely autonomous disease. Definition, epidemiology, anatomopathological findings, clinical presentation, preoperative evaluation, treatment and prognosis were reviewed. MCNs are pancreatic mucin-producing cysts with a distinctive ovarian-type stroma localized in the body-tail of the gland and occurring in middle-aged females. The majority of MCNs are slow growing and asymptomatic. The prevalence of invasive carcinoma varies between 6% and 55%. Preoperative diagnosis depends on a combination of clinical features, tumor markers, computed tomography (CT), magnetic resonance imaging, endoscopic ultrasound with cyst fluid analysis, and positron emission tomography-CT. Surgery is indicated for all MCNs.

Key words: Pancreatic cystic lesion; Pancreatic mucinous cystic neoplasm; Pancreatic mucin-producing cysts; Pancreatic cystic neoplasm; Pancreatic ovarian-type stroma

Peer reviewer: Christopher Christophi, Professor and Head of the University of Melbourne Department of Surgery, Austin Hospital, Melbourne, 145 Studley Road, Victoria 3084, Australia

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INTRODUCTION

Becourt first described cystic lesions of the pancreas in 1824[1]. In 1978, Compagno *et al*[2] first classified cystic tumors into serous cystic neoplasms (SCNs) and mucinous cystic neoplasms (MCNs) of the pancreas and identified MCN as a distinct disease occurring almost exclusively in the pancreas body and tail of middle-aged women[2,3]. Until 1996, when the World Health Organization distinguished between intraductal papillary mucinous neoplasms (IPMNs) and MCNs, emphasizing the presence of ovarian stroma in the latter, and until 1997 when the Armed Forces Institute of Pathology confirmed this distinction, MCN and IPMNs were frequently confused[3-7]. Nowadays, they represent two distinct neoplasms with different biologic behaviour, pathologic features, and prognosis[8-11].

Although until 1987, Warshaw *et al*[12] considered that pseudocysts account for the majority of pancreatic cys-

tic lesions, nowadays mucinous and serous cystic tumors represent 50%-60% of all cystic lesions[13]. Nevertheless pancreatic cystic neoplasms occur with less frequency than solid ones[4,14,15], but are now found with increasing frequency compared to the past due to the improvement and refining of modern imaging techniques like multidetector, three-dimensional computed tomography (CT) or magnetic resonance imaging (MRI), or endoscopic ultrasound (EUS)[16].

The aim of this study was to review the literature to clarify the management of cystic mucinous neoplasm of the pancreas.

LITERATURE SEARCH

A comprehensive literature review was performed in December 2009 by consulting PubMed MEDLINE for publications, matching the key words of "pancreatic mucinous cystic neoplasm", "pancreatic mucinous cystic tumor", "pancreatic mucinous cystic mass", "pancreatic cyst" and "pancreatic cystic neoplasm" to identify English language articles on MCNs.

Only studies including series with more than four patients affected by MCNs were included. Articles reporting reviews, case reports, abstracts and studies on only IPMNs, SCNs or pancreatic pseudocysts were excluded. Definition, epidemiology, anatomopathological findings, clinical presentation, preoperative evaluation, treatment and prognosis were analyzed.

A total of 16 322 references ranging from January 1969 to December 2009 were analyzed ("pancreatic mucinous cystic neoplasm", n = 930; "pancreatic mucinous cystic tumor", n = 924; "pancreatic mucinous cystic mass", n = 143; "pancreatic cyst", n = 6215; "pancreatic cystic neoplasm", n = 8110) and 77 articles were selected[10,14,17-89]. No articles before 1996 were usable because MCNs were not previously considered as a completely autonomous disease[9-11,17,77,86,89,90].

DEFINITION AND EPIDEMIOLOGY

MCNs are defined as mucin-producing and septated cyst-forming epithelial neoplasia of the pancreas with a distinctive ovarian-type stroma. Usually solitary, their size ranges between 5 and 35 cm with a thick fibrotic wall and without communication with the ductal system[11]. MCNs are rare and, in most series, less common than IPMNs and SCNs[73]. MCNs show a female to male ratio of 20 to 1 and a mean age at diagnosis of between 40 and 50 years (range 14-95 years)[6,7,10,11,91-93]. The site of the neoplasm is in the body and tail of the pancreas in 95%-98% of cases[3,7,9,34,35,89,94,95]. When localized in the pancreatic head, mucinous cystoadenocarcinoma is more prevalent[7,10].

Invasive carcinoma incidence in MCN varies between 6% and 36%[8-11,14,34,35,86]. The Ulm series reported on 39 patients with MCNs and a malignant histology in 51%, including carcinoma *in situ* and advanced cancer[11]. The explanation of this wide range may be the difficulty in interpreting the data on the prevalence of carcinoma because the majority of series have only indicated the advanced form.

ANATOMOPATHOLOGICAL FINDINGS

Macroscopically, MCNs usually appear as solitary, multilocular or unilocular lesions with a mean size of 7-8 cm (range 0.5-35 cm) with a thick fibrotic wall and containing mucin, even when hemorrhagic, watery or necrotic content is observed[8].

In 2004, the consensus conference of the International Association of Pancreatology in Sendai (Japan)[8,9] established that the histological presence of unique ovarian-type stroma was mandatory to diagnose MCN and that this was not found in other pancreatic neoplasms[10,73,93]. MCNs display no communication with the pancreatic ductal system, although some studies suggested that a small proportion of MCNs may show microscopic communication with the pancreatic ducts[68,96,97].

Under light microscopy, the cysts are lined by a columnar mucin-producing epithelium with different grade of dysplasia: mild (MCN adenoma), moderate (MCN borderline), and severe (MCN carcinoma *in situ*)[98]. The epithelial lining is positive for CKs (CK7, CK8, CK18, CK19), EMA and, less frequently, CK20, CEA, DUPAN-2 and CA 19-9[8,10,67]. An invasive adenocarcinoma of the tubular or ductal type is associated in about one-third of cases[6]. The immunophenotype of ovarian-type stroma is similar to the normal ovarian one with positivity for vimentin, calretinin, tyrosine hydroxylase, SMA, α-inhibin, Melan-A, CD99 and Bcl-2 and frequently for PR and ER. The origin of ovarian stroma of the pancreas is still being debated[99]. A stimulation of endodermal immature stroma by female hormones or primary yolk cell implantation in the pancreas has been suggested in literature[10] because buds of the genital tract and dorsal pancreas are adjacent to each other during embryogenesis. Moreover, dorsal pancreatic enlargement mainly gives rise to the pancreatic body and tail, and this could explain the predilection of MCNs for the distal pancreas[17].

Although the pathologic diagnosis of malignancy is based on invasion of the pancreatic parenchyma or metastases[5], MCNs that do not have conclusive evidence of carcinoma are considered premalignant[7].

A thickened wall with peripheral calcification and papillary proliferations, vascular involvement and hypervascular pattern should be considered as suggestive of MCN with malignant changes[68,95]. Although the invasive MCN (mucinouscystoadenocarcinoma or mucinous cystic neoplasm with associated invasive carcinoma) is generally a tubular/ductal carcinoma[8], rare histological variants are represented by undifferentiated carcinoma with osteoclast-like giant cells[100], adenosquamous or colloid cells[101], or sarcomatoid carcinoma[99], carcinosarcoma and choriocarcinoma[8,102].

The increasing degree of dysplasia and tendency for invasion have been correlated with activating point mutations in the *k-ras* gene and mutations in the *TP5* gene[8,103,104]; moreover, the discovery that the inactiva-

tion of SMAD4/DPC4 in the epithelium of the invasive MCNs, but not in the ovarian-like stroma, could suggest that the ovarian-type stroma is not neoplastic[105].

CLINICAL PRESENTATION

The majority of MCNs are slow growing and asymptomatic[95]. In a series of 212 consecutive patients with cystic pancreatic lesions, 36.7% were asymptomatic and among them 28% had MCNs; in the symptomatic group, 16% had MCN[106]. In spite of these lesions being occasionally discovered in patients scanned for other indications[16,35,107], the typical clinical appearance is characterized by epigastric heaviness and fullness (60%-90%) or by an abdominal mass (30%-60%)[7,10,12,35,89,106,108]. Nausea, vomiting (20%-30%) and back pain (7%-40%) can also be present.

No specific symptom was significantly associated with a likelihood of malignancy[35] although increasing anorexia and weight loss (10%-40%) may be associated with malignant changes[7,12,35,89,95,106,108,109].

PREOPERATIVE EVALUATION

MCNs main differential diagnosis includes other neoplastic cystic lesions (serous cystic neoplasm and the intraductal papillary mucinous neoplasms) and non-neoplastic cystic lesions (pancreatic pseudocysts). There is no single discriminating test, but preoperative diagnosis depends on a combination of modes, including clinical features, tumor markers, CT and MRI, EUS with cyst fluid analysis, and positron emission tomography (PET).

High values of CEA and CA 19-9 show a high positive predictive value for pancreatic malignancy or premalignancy in the preoperative assessment of pancreatic cystic mass (70%-100%)[9,95,110]. A CEA level of more than 400 ng/mL is a good predictor of malignancy in MCNs (sensitivity 45%-50%, specificity 95%-100%, accuracy 75%-80%)[107,111,112].

Trans-abdominal ultrasound examination has a low accuracy (50%) for cystic neoplasms of the pancreas[89].

EUS improves that accuracy and allows better evaluation of the wall as it may show separation or nodules within the cyst. Furthermore, EUS can be used to obtain aspiration of the cyst contents and to perform a biopsy of the wall. Cyst fluid amylase concentration of < 250 U/L has been considered capable of excluding pseudocysts of the pancreas (sensitivity 40%-45%, specificity 95%-100%, accuracy 60%-65%), while CEA < 5 ng/mL could suggest a benign etiology (sensitivity 45%-50%, specificity 95%-100%, accuracy 65%-70%)[31,111]. EUS-FNA cytology and cyst fluid CEA greater than 192 ng/mL show the highest accuracy (79%) for differentiating mucinous cystic from non-mucinous cystic neoplasms[113]. On the contrary EUS morphology alone cannot distinguish between the two groups[47,50,113].

In any case, the main differential diagnosis of MCNs is with SCNs which have a low CEA in the fluid and an equal distribution throughout the pancreas, with pancreatic pseudocysts (PC) that usually show necrotic debris within the cyst cavity, and with branch duct IPMNs communicating with the ductal pancreatic system and consequently showing elevated cystic fluid amylase[3].

Although pancreatitis may be present in the history of patients with pancreatic cystic neoplasms, when a cyst arises in a patient with chronic pancreatitis, the most frequent diagnosis is PC[109]. On the other hand, when pancreatitis is unexpected and occurs for the first time, the cyst could be a tumor, determining the development of pancreatitis due to compression of the pancreatic duct[13]. This is a crucial problem, because the risk of managing cystic mucinous neoplasms in patients with a prior history of pancreatitis, like pseudocysts by a pseudocyst-jejunal anastomosis or pseudocyst-gastrostomy, is higher than usual, with disastrous long-term prognosis[12,83]. Proper sampling of pseudocysts is essential and should consist of sampling of the cyst wall during surgery or analysis of cyst content during minimal access drainage procedures. Although the clinical context, radiological imaging and biochemical findings may help differentiate PC from cystic neoplasms, small lesions may be problematic.

The image based classification system proposed by Sahani *et al*[107], in which cystic pancreatic lesions are classified in four subtypes, is reported in Table 1.

The demonstration of a solid component, invasion outside the confines of the pancreas, or pancreatic duct obstruction through EUS is highly indicative of malignancy with sensitivity, specificity and accuracy of 70%, 100% and 60%, respectively[107]. However, in the absence of these findings the ability of EUS to diagnose malignancy is limited with an overall sensitivity, specificity and accuracy of 56%, 45% and 51%, respectively[113]. The added advantage of EUS in performing aspiration of cyst content and sampling of the cyst wall and septa or mural nodules is that it allows small lesions as well as suspicious areas to be analysed. Laparoscopic and intraoperative ultrasounds are highly operator dependent with an accuracy

Table 1 Imaging-based classification system of cystic pancreatic lesions

Type of lesions	Morphologic features	Pancreatic cystic lesions
Unilocular cyst	Without internal septation and solid component or wall calcification	Serous cystic neoplasm, intraductal papillary mucinous neoplasm[1], pancreatic pseudocyst
Microcystic lesion	Six or more cysts with diameter 0.2 mm-2 cm, external lobulation, fibrous central scar with or without stellate calcifications	Serous cystic neoplasm
Macrocystic lesions	Diameter > 2 cm, with internal septation and solid component or wall calcification	Intraductal papillary mucinous neoplasm[1], mucinous cystic neoplasm[2]
Cyst with a solid component	Unilocular or multilocular	Intraductal papillary mucinous neoplasm[1], mucinous cystic neoplasm[2]

[1]With or [2]without communication with main duct, respectively.

ranging from 40% to 90%[3,114-120].

Multidetector computed tomography and magnetic resonance cholangiopancreaticography (MRCP) play a critical role in assessment, defining size, septation, calcifications, nodules of the wall, and communication with the ductal system of the pancreatic cyst.

At cross-sectional imaging, the MCN appears as a unilocular or multilocular single macrocyst with a solid component, with no communication with the main duct[95,107,121]. The internal architecture of the cyst, including septa and internal wall, is best appreciated with MR imaging[122,123].

Recently, Kim *et al*[60] defined some significant CT features for differentiating MCNs from SCNs and IPMNs: the shape is smooth in MCNs, multicystic and lobulated in SCNs, and pleomorphic and clubbed finger-like in IPMNs; the main pancreatic duct is not dilated or proximally only in SCNs, and if dilated, whole in IPMN.

In spite of the improvement in pancreatic tumor visualization resulting from CT and MRI, the ability to perform diagnosis of these techniques individually - as well as EUS - remains poor (25%-30%)[6,124,125]. In a multivariate analysis by Visser *et al*[14] in 2008, the combination of CT and MRI data showed an accuracy ranging from 44% to 83%.

Cross-sectional imaging generally shows peripheral calcification, a thickened wall, papillary proliferations, vascular involvement and hypervascular pattern in the cases of malignant MCNs[36,95,126]. Although peripheral eggshell calcification is not easily detected by CT, this is a specific feature of the MCNs and is highly predictive of malignancy[126].

The clinical value of MRCP is similar to endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography[127] but an MR multi-imaging protocol, which includes MR cross-sectional imaging, MRCP and dynamic contrast-enhanced MR angiography, integrates the advantages of multiple imaging techniques without morbidity[128-131].

The role of PET in managing pancreatic cystic lesions is currently limited but recent studies report detection of malignant pancreatic cysts with sensitivity and positive predictive values above 90%[132,133].

In spite of a complete diagnostic assessment, the surgeon's preoperative diagnosis is correct in one-third of cases, incorrect in another third, and non-specific in the remainder[6,14].

TREATMENT

Surgical excision is indicated for all MCNs considered premalignant. Factors influencing treatment include tumor histological features, the patient's age and surgical risk, and tumor size and location.

Left pancreatectomy

Because mucinous cystic adenoma of the pancreas are usually localized at the level of the body and tail of the pancreas, the most common operation performed to cure these neoplasms is distal pancreatectomy (Figure 1), which is a safe procedure in high volume centres (overall postoperative morbidity ranging from 5% to 50% and a mortality rate of 0%)[3,7,20,35,134,135]. The main complication, pancreatic fistula, occurs in 15%-20% of cases[136].

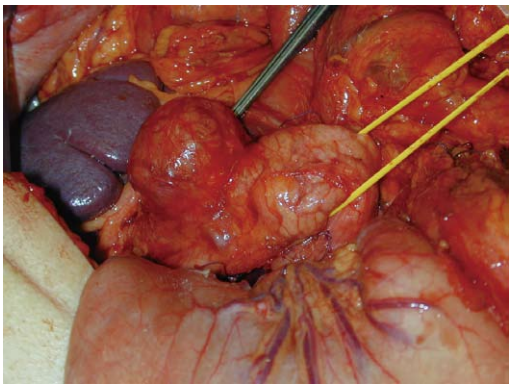

Figure 1 Distal pancreatectomy. Dissection of the pancreas in a patient with mucinous cystic neoplasm.

The distal pancreatectomy technique was first described in 1913 by Mayo[137] and the spleen-preserving distal pancreatectomy was outlined in 1943 by Mallet-Guy *et al*[138]. Preservation of the spleen can be performed with or without preservation of the splenic artery and vein. In 1988, Warshaw described a technique without the preservation of the splenic artery and vein, ligating the splenic vessels at the hilum[139]. Although this method appears technically less difficult and can be performed in a shorter operating time, it has been associated with a higher incidence of spleen vascular insufficiency[140]. However, this procedure should be considered in the event of an inflamed or fibrosed splenic artery and vein[139]. Spleen-preserving techniques must be avoided when in the presence of the largest tumors or risk factors for invasive malignancy, such as the size of the lesion, eggshell calcifications and mural nodules, in order to perform the complete oncological lymph node dissection[9,27,31]. However, these techniques are preferred in all other cases to avoid long term infectious and haematological complications[3,20,27,139].

Studies comparing patients undergoing distal pancreatectomy with or without splenectomy show no significant differences compared to perioperative complications, mean operating time, pancreatic fistula rate, length of hospital stay and mortality[20,108,135,141,142].

MCNs affecting the pancreatic neck or the proximal body could be managed either by an extended right or, more frequently, by an extended left pancreatectomy. These extended resections of normal pancreatic tissue may induce endocrine and exocrine insufficiency respectively in 30%-35% and 15%-20%, which in a benign or premalignant disease could be discussable[143-147].

Middle pancreatectomy

Middle pancreatectomy can be considered in the surgical management of MCNs located at the level of the pancreatic proximal body or neck, preserving endocrine and

exocrine function with respect to extended left pancreatectomy or pancreaticoduodenectomy, and also preserving the spleen.

The main pitfalls of this technique are the technical difficulty, the higher incidence of postoperative complications and the risk of recurrence from potentially residual neoplasm[9,146-153].

Different techniques have been proposed for gastrointestinal reconstruction, including jejunal anastomosis of the stump or the distal stump, with pancreaticoduodenal or pancreaticogastric anastomosis[143,148-156].

In the literature, mortality after middle pancreatectomy was none and the overall morbidity was 25%-35%[147-149,155-157]. The incidence of overall pancreatic fistula was 22%-45% and the type of reconstruction through Roux-en-Y pancreatojejunostomy or pancreaticogastrostomy did not affect the rate of any complication[147-149,155-157]. Moreover, the incidence of endocrine and exocrine insufficiency after middle pancreatectomy was 4%-7% and 5%-8%, respectively[147-149,155-157].

Enucleation

Because the probability of malignancy in patients with MCNs smaller than 2 cm without nodules is very low, enucleation could be performed to avoid post-operative pancreatic insufficiency[35]. This procedure is proposed for patients with MCNs smaller than 2 cm with benign features and superficially located[146,155,156]. Enucleation can be performed without risk of recurrence but has been associated with a higher incidence of pancreatic fistula (30%-50%)[158-160].

Whipple procedure

A major oncologic resection, applying a Kausch-Whipple or pylorus-preserving technique, is recommended for MCNs that are localized monocentrically in the head.

The operative mortality ranges from 0% to 5% and is generally related to pancreatic anastomosis complications[136,161]. The most common complications following the Whipple procedure are delayed gastric emptying and the pancreatic fistula occurring in 5%-10% and 6%-20% of operations, respectively[136,161-163].

When an enucleation is impossible or contraindicated, MCNs localized monocentrically in the pancreatic head that do not have an association with an invasive pancreatic cancer could be treated by duodenum-preserving total pancreatic head resection[34,94,164-167].

This procedure shows significant advantages when compared to Traverso-Longmire or Whipple pancreaticoduodenectomy, as regards the postoperative rate of morbidity and mortality, glucose metabolism, hospitalization and costs[11,168].

Lymphadenectomy

Pancreatectomy with lymph node dissection is necessary when an invasive carcinoma is suspected. Although the preoperative and intraoperative assessment of the grade of invasiveness is often difficult, whenever any doubt exists typical resection with lymph node dissection must be pursued[9]. There is no evidence in literature of invasive mucinous cystic adenocarcinoma with distant lymph node metastases, so only a loco-regional lymphadenectomy is justified[3,35]. Because the probability of malignancy is very low in the cases of small MCNs without nodules, lymphadenectomy can be avoided[3,146].

Laparoscopy

In the cases of benign-appearing and small malignant lesions (< 5 cm), a minimally invasive approach may be considered[35]. Recent experiences from high-volume centers demonstrate that the laparoscopic approach for distal pancreatectomy for MCNs of the body and tail of the pancreas is feasible and safe[169]. The complication rate of laparoscopic distal splenopancreatectomy (Lap SDP) ranges between 15% and 20%[30,46,170-173] with a mortality rate of 0%. In spleen-preserving laparoscopic pancreatic (Lap SPDP) resection, the overall morbidity ranges from 25% to 40% with a mortality rate of 0%[30,46,169-173]. The overall reported pancreatic fistula was 5%-8% and 10%-15% after Lap SPDP and Lap SDP, respectively[30,46,170-173]. This laparoscopic approach decreases the hospital stay and minimizes the cosmetic impact of the surgical wound[30,169,174,175].

Chemotherapy

Gemcitabine (GEM) is the standard therapy for advanced pancreatic cancer[176]. Its effectiveness against advanced MCNs has been reported[177,178].

Recently, some combinations have been reported to be superior to GEM alone[177,179-181]. GEM-oxaliplatin treatment has been proposed to be more effective in terms of clinical progression-free survival[177].

Discordant results on survival were reported by phase Ⅱ and Ⅲ trials combining GEM and inhibitors of epidermal growth factor receptor (cetuximab) and vascular endothelial growth factor (bevacizumab)[182-184].

Other modest but interesting advances have been provided by combinations such as GEM-capecitabine and GEM plus a platinum salt[185]. In spite of this, survival results remain disappointing.

Conservative treatment

A conservative management with regular follow-up has been proposed in the presence of asymptomatic cystic lesions of the pancreas smaller than 3 cm without mural nodules, because the reported risk of malignancy in these cysts was found to be 3%[11,35,63,186]. The suggested follow-up consisting of cross-sectional imaging and FNA cytology should be performed every 6 mo for a period of 2 years and yearly after that. This should be continued for at least 4 years and then the interval of follow-up can be lengthened after 6 years of no change[31,52,186]. When the cyst enlarges or when symptoms occur (in up to 20% of patients after follow-up), surgery is mandatory. The reported incidence of the subsequent resection due to change of the clinical, radiological and biochemical features of the lesions after initial conservative treatment was 4%-10% and malignancy rate in these cases was 3%[23,63].

PROGNOSIS

After resection, in the absence of invasive carcinoma, prognosis of MCNs is excellent, with an overall survival rate of 100%[5-7,10,35] and patients do not need follow-up, since several studies have shown that the risk of recurrence following resection is 0%[11,18]. Patients with invasive mucinous cystadenocarcinoma, show a 5-year survival rate of 20%-60%, which is much better than that for non-MCN-associated ductal adenocarcinoma[5-8,11,17,35,73,86]. When an anaplastic carcinoma of the pancreas associated with MCN is reported, the prognosis is obviously extremely poor, with a 3-year survival rate lower than 3%[5-8,11,17,35,73,86].

CONCLUSION

Although the histological distinction between MCNs and IPMNs, through the identification of ovarian stroma initially, is very important in clinical practice, the management of MCNs has not yet been standardized and continues to evolve.

The approach to patients with suspected MCN is based on EUS and cross-sectional imaging in association with FNA cytology, detecting an incidence of correct differentiation between mucinous cystic and non-mucinous cystic neoplasms of 75%.

Because at present we are unable to identify the benign MCNs that will progress into invasive carcinoma, all MCNs should be resected, regardless of size, in patients who are fit candidates for surgery, because surgery is routinely curative in the cases of non-invasive tumor. Moreover, the non-operative management based on periodic CT or MRI requires years of careful follow-up with a high cost of imaging and the enucleation technique carries the risk of non-oncological radicality. In patients with non-invasive MCN after complete anatomic resection, postoperative surveillance is unnecessary.

In order to obtain more benefit by applying adjuvant chemotherapy for the treatment of the advanced MCNs, further research focused on sequential cellular transformation from benign to malign tumor and on new combinations, incorporating the new targeted therapies and identifying potential predictive factors of response, is required to be able to offer effective tailored treatment to these patients.

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