

Mucinous cystadenocarcinoma of the pancreas – outcome following different modes of treatment

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Abstract

Background Mucinous cystadenocarcinomas (MCAC) of the pancreas are rare tumors. When localized to the pancreas alone, surgical resection is mostly associated with a favorable prognosis. The potential value of palliative treatment with chemotherapy for irresectable disease is scarcely described though. The aim of this study was to describe a single-center series of patients with MCAC of the pancreas focusing on the outcome following different treatment strategies.

Methods 15 patients, 10 females and 5 males, with histologically or cytologically verified MCAC, were divided into three groups: surgical resection (n=7), chemotherapy (n=5) and no treatment (n=3).

Results There was no obvious difference in gender distribution between the subgroups. A tendency towards higher age was seen in the group without treatment, as was a larger tumor size as compared to the chemotherapy group. Patients were administered chemotherapy and the group without treatment seemed to present with the same prevalence of metastatic disease (3/5 and 2/3, respectively). All patients in the group without treatment died after in median 1 month following pathological diagnosis. One patient in the chemotherapy group was alive at 9-month follow up, and the others survived a median of 11 months. In the surgically treated group, 4/7 were alive at follow-up of a median of 154 months. Of the three deceased patients who had survived 44, 53 and 151 months, respectively, two had microscopically non-radical resection.

Conclusions MCAC of the pancreas is, when locally confined and without metastases, associated with fairly good prognosis after surgical resection. In inoperable patients and for metastatic disease, outcome is poor.

Keywords mucinous cystadenocarcinoma, pancreas, surgery, chemotherapy, outcome

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Introduction

Cystic neoplasms of the pancreas represent benign, premalignant and true malignant lesions. The most frequently occurring forms of cystic pancreatic neoplasms are serous cystadenomas, intraductal papillary mucinous neoplasms

(IPMN), mucinous cystadenomas (MCA), as well as mucinous cystadenocarcinomas of the pancreas (MCAC). The two latter constitute about half of pancreatic cystic neoplastic lesions, with a reported occurrence rate of 29% and 15%, respectively, while the prevalence of IPMN is about 11% [1,2]. Correct and early characterization of a premalignant or malignant mucinous cystic neoplasm and subsequent adequate surgical resection, if possible, offers a comparably favorable prognosis. However, once invasive or metastasized, the outcome of a cystic pancreatic carcinoma is merely as poor as for ductal adenocarcinomas of the pancreas [3].

About 2.4-14% of pancreatic cancers are cystic [4], and consequently treatment options for MCAC are less evaluated as compared to pancreatic ductal adenocarcinoma. Only a limited number of studies have regarded the value of radiochemotherapy in MCACs [2, 5-9], and most of them only investigated the effect of adjuvant or neoadjuvant radiochemotherapy. There is thus currently a lack of guidelines for treatment of patients with MCACs.

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At the Department of Surgery, Lund University Hospital, patients with suspected MCA and MCAC of the pancreas have been offered surgical resection if surgery has not been contraindicated. In case of local unresectability or distant metastasis in patients with MCAC, palliative chemotherapy in a regimen similar to that given in ductal adenocarcinoma of the pancreas has been considered.

The aim of this study was to describe a single-center series of patients with MCAC of the pancreas, focusing on the outcome following different treatment strategies.

Methods

Patients both operated upon during the period 1988–2009 and registered at the Department of Pathology, Lund University Hospital, were searched for the diagnosis mucinous cystic adenocarcinoma (MCAC). Some surgical specimens were re-examined by a pathologist for verification of the diagnosis. In non-resected patients, the diagnosis was made by fine needle aspiration cytology (FNAC), which in combination with radiological findings rendered the diagnosis MCAC.

Fifteen patients matching the above criteria were reviewed for gender and age, presence of symptoms and clinical parameters at diagnosis, imaging and histological features. Jaundice was determined based on information of the clinical examination or upon serum bilirubin levels increased at least twice above the upper level of normal ($>40 \mu\text{mol/L}$). Weight loss was assessed as any loss of weight, and if quantified, 5 kg weight loss was set as a cut-off. The occurrence of diabetes was determined based on the patients' medical history. Size was determined as the largest measurable tumor diameter, measured on histological specimens in resected patients, and on imaging studies in non-resected patients and if more than one cyst was present, the size of the largest one was addressed. Cystic lesions located in the uncinate process or the head of the pancreas were classified as localized in the head. Dilatation of the pancreatic duct was considered when the diameter exceeded 3 mm. Vascular involvement was defined as involvement of the mesenteric artery, vein, the portal vein or celiac trunk on either computed tomographic imaging, the surgeons' intraoperative assessment, or on histological examination of the resected specimen. Surgical radicality and the potential involvement of the surgical margins was the combined evaluation of the surgeon's opinion and the pathological examination. Abdominal pain was classified as any abdominal complaints, independent of severity.

The date of diagnosis was defined as the time of pathologically verified MCAC.

The patient material was divided into three groups: (1) the group without any treatment consisted of patients without surgical intervention or chemotherapy; (2) patients with surgical resection of the cystic lesion, irrespective of postoperative treatment, and (3) patients receiving palliative chemotherapy.

The chemotherapy treatment was assessed concerning regimen and the response has been described for each case.

Survival was measured from the date of diagnosis. The three groups were compared with respect to the above-mentioned clinical and radiological parameters in order to identify any potential difference in outcome.

Results

In the group without any treatment, all 3 were women, compared to 4 out of 7 in the chemotherapy group, and 3 out of 5 in the surgery group. The mean age at diagnosis was 80 (range 68–84), 65 (range 56–74) and 60 years (32–79), in the respective groups. Weight loss was reported for 3 patients in the surgery group and for 2 patients in the chemotherapy group. The median size of the lesion was 6.5 cm (range 5–8), 4.5 cm (range 1.5–7) and 5 cm (range 4–12) in the group without any treatment, chemotherapy and surgical group, respectively. In the group without treatment, one tumor was localized in the head and two in the body of the pancreas; in the chemotherapy group, three tumors were localized in the head, and two in the body or tail. In the surgical group, two tumors were localized in the head, three in the body/tail and two had multiple locations. Three patients in the chemotherapy group and two patients in the group without any treatment presented with metastases. Two patients in the chemotherapy group had further vascular involvement.

Out of seven surgical patients, two had total pancreatectomy and splenectomy, and the other five partial resection of the pancreas. Radical excision (free resection of margins) was achieved in five patients, while the other two patients had additional radiotherapy. Extended resection was performed in two patients. Six patients had benign lymph node status.

The five patients in the chemotherapy group had gemcitabine-based treatment due to surgically unresectable disease with a mean survival of 11 months, varying from 4 to 37 months. Treatment varied between 2 and 36 months.

Among surgically treated patients, the overall survival was in median 128 (range 33–277) months. At the end of the follow-up period, four patients were still alive. The three patients that died during follow-up survived 44, 53 and 151 months, respectively.

Table 1 displays outcome and follow-up time.

Discussion

In this study, we reviewed records from patients with MCAC subjected to three different modes of treatment. To our knowledge, this is the only study available addressing outcome for patients with MCAC treated with palliative chemotherapy, in a setting larger than individual case reports. Obtaining a correct diagnosis is, of course, of great importance when evaluating outcome after different modes of treatment. Cystic

Table 1 Mucinous cystadenocarcinomas of the pancreas - outcome and follow-up

	Surgery	Palliative radiochemotherapy	No treatment
Died			
Yes	3	4	3
No	4	1	0
Survival (from pathological diagnosis; months)*			
Median	53	11	1
Range	44-151	4-37	1-18
Follow-up time (from pathological diagnosis; months)**			
Median	154	9	
Range	33-277		

* Concerning patients that died during follow-up.

** Only concerning patients still alive.

tumors of the pancreas represent a well known diagnostic dilemma. MCACs can for example be difficult to distinguish from IPMNs, and it has been proposed that the existence of ovarian-type stroma supports the diagnosis [10].

Unless a surgical specimen was available, diagnosis was made by imaging studies, showing a cystic lesion without visible communication with the pancreatic duct, in combination with cytological analysis of tumor tissue or cyst fluid suggestive of MCAC, as neither imaging studies nor cytology alone can fully distinguish between the two entities [11].

The entity intraductal pancreatic neoplasm (IPMN) was more strictly defined first in 1996 by the WHO (World Health Organization), when the IPMN classification was published [12]. All patients included in the present survey, except three patients in the surgical group (diagnosed 1986, 1993, and 1995), were diagnosed in 1996 or later.

Age and gender of the patients, as well as location of the cystic lesion, are clinical features that differ between MCACs and IPMNs. IPMNs are considered to occur preferentially in the head of the pancreas and are equally distributed among men and women, whereas MCACs are reported to occur more frequently in the distal part of the pancreas and almost exclusively in women [13]. In this study, in 6 patients the lesion was found in the head and in 7 patients it was found in the body/tail of the pancreas. However, no lesion was excluded based on location of the tumor, since location is not an obligatory criterion for the diagnosis, and it was considered to potentially cause incorrect exclusions of MCAC in this small retrospective material.

In the group without any treatment, the patient surviving for 18 months was a woman aged 80 with chronic pancreatitis, presenting with abdominal pain and a palpable mass. CT displayed two cysts in the head, maximally 6.5 cm in size, and also a cystic dilatation of the pancreatic duct as seen on MRCP. No other patient without treatment or given chemotherapy had multiple cysts, pancreatitis or any reported deviating morphology of the pancreatic duct.

If any of the lesions in our survey was an IPMN, the survival should be compared with that of irresectable or malignant IPMNs. In one study, non-resected IPMN patients had a median survival of 13 (6–36.5) months [14]. Non-resected MCAC as compared to IPMN had a shorter survival reported in one study [15], and a 2-year survival of 12% in another study [2]. However, in a large study containing only malignant IPMNs, patients with non resectable tumors had a median survival of 3 months [16], which is close to the survival seen in our group of MCAC without any treatment given.

In a large series of patients with resectable MCACs, a 5-year survival of 63% was reported [2]. In another report on resected MCACs, 62% of the patients were disease-free after a mean follow-up of 61 months [17].

Patients with irresectable MCAC have been reported to have a 2-year survival of 12% [2]. In the study by Delcore et al [15], the 3 patients with irresectable disease survived for 4, 7 and 9 months, respectively. The result of poor outcome for patients with irresectable MCACs in our survey thus confirms what has been reported previously.

Only a limited number of studies exist describing the value of radiochemotherapy in MCACs, most of which are case reports addressing adjuvant or neoadjuvant treatment [2]. Downsizing of the tumor, enabling subsequent resection, has been reported after radiotherapy combined with systemic chemotherapy with 5-fluorouracil (5-FU) [5,9]. This combination has also been used in one case after non-radical surgery before a second and successful resection [6]. Systemic chemotherapy with oxaliplatin and gemcitabine has been used to treat a patient with MCAC with liver metastases, where the primary tumor was resected after radiological disappearance of the liver metastases [7].

The only previous case of MCAC with palliative chemotherapy treatment (with Gemcitabine® after distal pancreatectomy) resulted in disappearance of the metastases as seen on computed tomography imaging, and almost normalized serum levels of the tumor marker CA 19-9 [8].

In our study, palliative chemotherapy with Gemcitabine® was given to five patients, with partial radiological remission and stable disease noted in one patient, stable disease in one patient and progression in three patients.

A Cochrane review from 2006 concluded that chemotherapy appeared to prolong life and improve quality of life in patients with advanced pancreatic cancer [18]. Patients with MCAC in this survey, treated with chemotherapy, obtained a median survival in the chemotherapy group of 10.5 months.

For IPMNs there are only two studies available addressing outcome following chemotherapy treatment. An increased survival after surgery and adjuvant 5-FU-based radiochemotherapy for IPMN with lymph node metastases or positive surgical margins was reported. The median survival in that study of IPMNs was 25.8 months and the 2-year survival rate was 56% [19]. However, a recent study addressing outcome for 37 patients with invasive IPMNs given postoperative adjuvant chemoradiation (either 5-FU and/or gemcitabine) failed to show any survival benefit both in the node-positive and the node-negative subgroups [20].

There are reports on the development of MCAC during hormone replacement therapy [21] and pregnancy, and it has been suggested that sex hormones may mediate growth of these tumors [22]. MCACs of the pancreas have been proposed to possess some similar features, such as gender and morphology, with ovarian mucinous cystadenocarcinoma. Further immunohistochemical analyses of MCAC have shown that the expression of proteins (tyrosine hydroxylase, alpha-inhibin, calretinin, progesterone- and estrogen-receptors), normally present in ovarian tissue suggest a possible common pathway for tumor development [23]. Standard treatment for ovarian carcinoma is surgery and postoperative chemotherapy. In case of relapse, second line chemotherapy is generally given, and a platinum-based regimen is recommended [24]. Gemcitabine®,

alone or in combination with other chemotherapeutic agents, has also been proposed as a potential treatment in recurrent ovarian cancer [25,26]. Thus, the similarities of MCAC and ovarian carcinoma may be considered when it comes to palliative chemotherapeutic treatment.

Limitations of the present study are, of course, its retrospective character, the small number of patients, and the wide time frame during which data has been collected. Large, prospective studies may be difficult to obtain due to the comparative rarity of the disease, though further studies are warranted.

In conclusion, survival following surgical resection was better as compared to non-resected patients with MCACs. The value of chemotherapy in MCAC is not known from the literature, and no large series, exceeding the present one, have been reported.

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Summary Box

What is already known:

- Mucinous cystadenocarcinoma of the pancreas is a rare type of tumor with a probably fair outcome when disseminated. Handling of spread disease is scarcely described.

What the new findings are:

- Novel findings provided by this study are that in a comparatively large number of patients (n=15) with verified mucinous cystadenocarcinoma, we describe different types of intervention with good prognosis following surgical resection and poor outcome in inoperable patients and when metastatic disease is present.

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