The Role of the Oncologist in the Diagnosis and Management of Malignant Cystic Neoplasms

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6.1 Introduction

Cystic tumors are uncommon pancreatic lesions but, at least according to our experience, they account for 30% of radical pancreatic resections. This high frequency can be explained by several reasons but especially by the increasingly widespread use of modern imaging techniques, such that in the clinical workup of unrelated conditions, suspicious cystic pancreatic lesions are often incidentally revealed. The resulting likelihood of early detection has improved the management of these patients.

Thus far, the efficacy of chemo- or radiotherapy in treating malignant cystic tumors has not been demonstrated, leaving surgery as the only therapeutic option. The responsibility of the surgeon in such cases is two-fold, as he or she will be involved in the diagnosis and then in the treatment (resection) of the lesion.

However, for patients in whom surgery is not or not yet an option, close follow-up is mandated. This applies to patients with a benign or indeterminate lesion and to those with coexisting critical conditions. In these patients, the updated WHO classification is useful to understand the relationship between the biological behavior of the tumor and the prognosis. More recently, oncologists have increasingly contributed to the diagnosis and management of patients with malignant cystic neoplasms, as discussed in the following section.

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6.2 The Role of the Oncologist in the Diagnosis and Management of Malignant Cystic Neoplasms

Cystic neoplasms of the pancreas are relatively rare lesions. Most of them are either benign or low-grade indolent neoplasias, with a prognosis significantly better than the dismal outcome of patients with ductal adenocarcinoma [1].

As extensively described elsewhere in this book, cystic neoplasms have been classified by the WHO into four types: serous cystic neoplasms (SCNs), intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and solid pseudopapillary neoplasms (SPNs). This distinction is very important since the four types differ in their malignant potential, which in turn determines their correct management. The mucinous types, i.e., IPMNs and MCNs, are of particular relevance for medical oncologists because of the well-established malignant potential of these tumors.

6.2.1 Serous Cystic Neoplasms

The malignant degeneration of SCNs of the pancreas is very rare. Moreover, the benign and malignant variants have very similar histological appearances, with the only distinguishing characteristic of malignant lesions being their tendency to invade surrounding structure. Metastases to regional lymph nodes, liver, lung, and bone marrow also have been reported. Nonetheless, the prognosis of these patients is very good, and an aggressive surgical approach, when feasible, is the preferred therapeutic approach [2-5] . As noted above, to date, there have been no studies or reports in which chemotherapeutic strategies have been used in this setting.

6.2.2 Mucinous Cystic Neoplasms

In contrast to SCNs, mucinous cystic and intraductal papillary neoplasms share a high tendency to become malignant. At histological evaluation of these tumors, it is common to find all the different steps of tumor progression. Thus, the pathologist must carefully search for foci of carcinoma in situ or invasive carcinoma, neither of which may be visible grossly. Surgery remains the mainstay of cure for patients with MCNs and IPMNs. The timing of surgery and the most appropriate technique are defined based on a multidisciplinary evaluation, considering the preoperative, radiological, and pathological diagnosis, symptoms, size and growth rate of the lesion, and the age and performance status of the patient. When indicated, resection is usually curative. An appropriate follow-up program is then defined based on the risk of recurrence. In selected cases, surgery can be considered also in metastatic disease, as some studies have reported the long-term survival of these patients. As for SCNs, medical oncologists have a marginal role in the management of MCNs and

IPMNs given that, due to the low incidence of malignant and metastatic cystic neoplasms, there are no or only a few clinical studies addressing the efficacy of radio- or chemotherapeutic strategies or the use of common cytotoxic drugs in their treatment.

Several risk factors for malignancy have been defined for patients with MCNs, including tumor size > 4 cm, associated mural nodules, septa, and eggshell calcifications. Surgery, intended as a "standard" pancreatic resection, is the most important and curative approach. If the histological evaluation finds evidence of an invasive carcinoma, a strict follow-up must be programmed, since the risk of recurrence and metastases is high even if the prognosis of these patients is better than that of patients with classical adenocarcinoma, with 5-year survival rates ranging from 15 to 33% [6, 7]. There are a few cases in which mucinous cystadenocarcinoma was detected during pregnancy or in the post-partum period. As MCNs are diagnosed almost exclusively in women, a role for sex hormones in tumorigenesis can be hypothesized. This relationship is also supported by the ovarian-tumor-like stroma that characterizes MCNs. The clinical management in these cases is more complicated, both from the surgical and the oncological point of view [8-10]. Of note, a case of mucinous cystadenocarcinoma during hormone replacement therapy has been reported [11]. It is therefore crucial that women with cystic masses of the pancreas who need hormonal treatment or who wish to become pregnant are carefully monitored, since either of these conditions can be associated with the evolution and transformation of MCN.

Patients with metastatic MCN have a poor prognosis, and they are usually treated according to the same regimen used in patients with adenocarcinoma. Metastatic MCNs can spread to the peritoneum. In one report, a patient with advanced mucinous cystadenocarcinoma with peritoneal dissemination was treated with gemcitabine, with a marked shrinkage of the tumor [12]. In another, intraperitoneal chemotherapy with cisplatin was administered in the treatment of pseudomyxoma peritonei associated with a pancreatic mucinous cystadenocarcinoma, with very good long-term results [13]. A single case of Sister Mary Joseph's nodule, as an umbilical metastasis of mucinous cystadenocarcinoma, was described [14]. In two cases of unresectable cystadenocarcinoma, a combination regimen in which 5-fluorouracil was administered with radiation therapy showed good activity, with marked reduction in tumor size and carcinoembryonic antigen (CEA) levels, allowing subsequent resection of the lesions [15]. Rare tumors, such as anaplastic carcinoma, osteoclast-like giant cell tumor, carcinosarcoma, and undifferentiated carcinoma, can be associated with MCNs; these entities need to be recognized because of their highly aggressive behaviors [16, 17].

A molecular genetic distinction among the various types of cystic neoplasms was recently described, by determining the exon sequences of DNA from the neoplastic epithelium of these tumors. The analysis of only five genes (*VHL, RNF43, CTNNB1, GNAS,* and *KRAS*) was sufficient to distinguish among the different cystic neoplasms [18]. Of note, all five genes encode

either components of the E3 ubiquitin ligase complex or proteins that hence become resistant to degradation by this complex. In a separate study, *GNAS* mutations at codon 201 were detected in 66% of the DNA samples isolated from IPMN cyst fluids. Over 96% of these IPMNs had either a *GNAS* or a *KRAS* mutation and more than half had both mutations. Interestingly, most of the invasive adenocarcinomas that developed in association with IPMNs contained *GNAS* mutations. These mutations were not found either in other types of pancreatic cystic neoplasms or in invasive adenocarcinomas not associated with IPMNs, indicating that GNAS mutation provides a novel molecular pathway leading to IPMN-related pancreatic carcinoma [19]. Thus, when combined with clinical and radiological data, molecular genetic profiles could lead to a more accurate diagnosis and to a more patient-tailored treatment plan.

6.2.3 Intraductal Papillary Mucinous Neoplasms

These tumors can be precursors of invasive carcinomas. Their malignant potential differs depending on the origin of the lesion, as those from the main duct (MD-IPMN) have a higher risk of malignancy than those from branch ducts (BD-IPMN). Surgery is crucial in the management of MD-IPMNs but should also be considered in BD-IPMNs > 3 cm in diameter and in IPMNs with nodules or duct dilatation (mixed IPMN), since in this case the malignant potential is higher. There are no data regarding the efficacy of adjuvant therapy in any of the IPMN types [20]. Interestingly, some authors reported a higher incidence of extrapancreatic malignancies and preneoplastic lesions, especially but not exclusively in the gastrointestinal tract, in patients with IPMNs than in the general population. Thus, the oncologist must bear this information in mind with respect to the long-term follow-up of these patients [21].

6.3 Conclusions

There are very few data supporting the use of chemotherapy in the management of patients with pancreatic cystic neoplasms. Adjuvant treatment is not routinely suggested, considering the low incidence of malignancy of these lesions. In the metastatic setting, there are no specific treatments with demonstrated efficacy; therefore, the common chemotherapeutic regimens used for advanced pancreatic adenocarcinoma should be considered in appropriate cases. Nonetheless, surgery is the only therapeutic strategy that can offer high curative rate to patients with malignant pancreatic cystic neoplasms. Accordingly, every patient should be evaluated carefully to determine eligibility for pancreatic resection, based on a multidisciplinary assessment.

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