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Metastatic tumors in the pancreas: the role of endoscopic ultrasound-guided fine-needle aspiration

Maite Betés[1], Santiago González-Vásquez[2], Alejandro Bojórquez[1], María Dolores Lozano [3], Jose Ignacio Echeveste[3], Laura García-Albarrán[4], Miguel Muñoz-Navas[1] and José Carlos Súbtil[1]

[1]Digestive Diseases Service. Clínica Universidad de Navarra. Pamplona, Spain. [2] Digestive Diseases Service. Clínica Universidad de Navarra. Madrid, Spain. [3]Anatomic Pathology Service. Clínica Universidad de Navarra. Pamplona, Spain. [4]Digestive Diseases Service. Hospital Virgen de la Concha de Zamora. Zamora, Spain

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Correspondence: Maite Betés. Servicio de Aparato Digestivo. Clínica Universidad de Navarra. Av. Pio XII, 36. 31008 Pamplona, Navarra. Spain

e-mail: mbetesi@unav.es

ABSTRACT

Background and objectives: there are few published data on the use of EUS guided fine-needle aspiration in secondary pancreatic lesions. We describe the largest series published so far in a European country.

Patients and methods: a retrospective review of the cases identified in our institution from 2004 to 2016 has been recorded. The clinical data are described, comparing the latency period from the primary tumor diagnosis to the detection of the pancreatic metastasis and the survival of patients according to the cytological diagnosis.

Results: forty-four patients were diagnosed with pancreatic metastasis using EUS guided fine needle aspiration. Ancillary cytological studies were performed in 28 (63.6%). The most common primary tumor sites were kidney and lung. Thirty-four patients (77.3%) had a previous history of malignancy, with a latency period ranging

from 6 months to 18.8 years. Patients diagnosed with primary renal carcinoma had a significantly longer latency period and longer survival compared to those with primary lung cancer. In 13 patients, EUS was either the only technique that detected the PM or showed a greater number of intrapancreatic lesions. These metastases were significantly smaller than those diagnosed by other imaging studies (11.9 ± 4.1 mm vs 30.7 ± 19.8 mm, $p < 0.001$).

Conclusions: EUS guided fine-needle aspiration plays a crucial role in the diagnosis of pancreatic metastases and may have a major clinical impact. Patients with renal cell carcinoma could benefit from long-term follow-up with EUS.

Key words: Echoendoscopy. Fine needle aspiration. Pancreatic metastases.

INTRODUCTION

Most malignant lesions of the pancreas are primary tumors, mainly adenocarcinomas. Up to 2-5% of malignant lesions are a metastasis from other tumors (1,2). Thus, it may be difficult to distinguish a primary from a secondary lesion via imaging studies.

The diagnostic yield of the endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in primary pancreatic tumors has been well studied and has a sensitivity and specificity of 90-100% (3-7). However, there are few data published in the scientific literature with regard to the use of EUS-FNA in secondary pancreatic lesions. Most are case reports and small case series. Only four case series of more than 40 patients were found after a review of the literature (8-11). A recent study suggests that the diagnostic accuracy of the EUS-FNA is lower in metastatic lesions than in primary pancreatic lesions (12).

We present the experience in our center in the diagnosis of patients with pancreatic metastases (PM) with EUS-FNA and the relevance of the results for treatment planning. To our knowledge, this is one of the largest series published to date and the first from a European country.

PATIENTS AND METHODS

The data of all EUS-FNA performed of pancreatic lesions in our center during a 12-year period, from September 2004 to November 2016, were reviewed. Patients diagnosed with PM via EUS-FNA were included. In all cases, the pancreas was first explored by a radial echoendoscope (GF-UMQ 140, GF-UM160 or GF-UE160AL5) and then a linear echoendoscope (GF-UC30P, GF-UCT140AL5 or GF-UCT180), which was used for FNA using a 22G or a 25G needle. There was an on-site cytopathologist who indicated the number of passes required to obtain sufficient sample for a diagnosis. In patients with multiple PMs, FNA was performed for all lesions or at least for those located in different regions of the pancreas.

The past medical history and imaging studies of patients were reviewed and the following data were collected: age, sex, primary tumor histology, age at tumor diagnosis, age at PM diagnosis, latency period between diagnosis of primary tumor and metastasis, symptoms caused by PM, first imaging study used to diagnose PM, size and number of PM (the largest lesion was taken for the descriptive study if there were multiple lesions), PM location, presence of metastases in other organs, number of needle passes in PM and other lesions, treatment received after diagnosis, follow-up time and clinical outcome (survival status at the end of data collection). The Ethics Committee authorized access to the electronic medical history of the patients that had undergone EUS-FNA.

The statistical program SPSS version 24.0 was used for the statistical analysis. Quantitative variables are shown as the mean and standard deviation (parametric) or as the median and interquartile range (non-parametric) and the qualitative variables as a number and percentage. The Student's t-test was used for the comparison of means for two independent means and the log-rank test was used for the survival analysis. A p-value of < 0.05 was considered as statistically significant.

RESULTS

Of the 1,128 patients that underwent EUS-FNA of a solid pancreatic lesion from 2004 to 2016, 44 (3.9%) were diagnosed with PM, 28 (63.3%) were male and 16 (36.6%) were female. The median age at diagnosis was 58.6 ± 11.7 years. The histologic nature of the lesions was as follows: 12 (27.7%), renal clear cell carcinoma; ten (22.7%), lung

cancer; six (13.6%), melanoma; five (11.3%), colon adenocarcinoma; three (6.8%), endometrial adenocarcinoma; and two (4.5%), soft tissue tumors. The remaining PM were primary tumors including the following: adrenal gland, ovary, esophagus, breast, stomach, cholangiocarcinoma and myeloma.

Ten patients (22.7%) were diagnosed with PM at the same time that they were diagnosed with the primary tumor. The other 34 patients (77.3%) had a previous history of malignancy with a median latency period of 4.8 ± 4.5 years (0.5-18.8 years). Patients with PM from a renal cell carcinoma (RCC) had a significantly longer latency period than those with a primary lung cancer (5.5 ± 3.5 years *vs* 1.1 ± 0.4 years, $p < 0.01$). Fourteen patients had a latency time longer than five years between diagnosis of the primary tumor and the development of metastasis, and six of these were a renal cell carcinoma (Table 1). The patient with the longest latency period had been diagnosed with a breast adenocarcinoma 18.8 years previously.

Twenty-one patients (47.7%) were asymptomatic at the time of diagnosis, and the rest had abdominal pain, jaundice, weight loss and/or other symptoms. Twenty-two patients (50%) were diagnosed during periodic consultations for the primary disease. The remaining 50% were diagnosed by clinical suspicion or altered blood analyses. The metastasis was located in the pancreatic head in 14 patients (31.8%), eight (18.8%) in the isthmus, eight (18.8%) in the pancreatic body, seven (15.9%) in the tail and the remaining in more than one area of the pancreas. Thirty-four patients (77.3%) had only one PM and the other ten cases (22.7%) had two or more metastatic lesions. Of the patients with multiple PM, six (60%) had metastases to other organs as well. The size of the lesions was recorded in 40 patients. The mean size of the metastases was 28.63 ± 19.4 mm. The mean size of the smaller metastases was 9 ± 3.06 mm in patients with multiple PM.

In 39 patients (88.6%), the diagnosis was suspected by other imaging techniques (ultrasound, CT scan, PET or MRI) before EUS-FNA. In five patients (11.4%), the imaging studies performed before the EUS did not find any evidence of intrapancreatic lesions. In these patients, the indications for EUS were as follows. One case with lung adenocarcinoma was evaluated for acute pancreatitis; endoscopy showed that the main pancreatic duct was obstructed by a PM. One melanoma case was evaluated for

acute cholecystitis and bile duct dilatation with uncertain choledocholithiasis. Finally, the PM was an incidental finding of the EUS performed for puncture of an adenopathy in another location different to the pancreas in the three remaining cases. Of the ten patients with multiple PM, the EUS-FNA diagnosed more metastases than previously performed imaging studies in eight (80%) cases (Table 2). PM detected only by EUS (including patients with single or multiple lesions) were significantly smaller than the lesions diagnosed by other imaging studies (11.9 ± 4.1 mm *vs* 30.7 ± 19.8 mm, $p < 0.001$).

A 25G needle was used in 34 patients (77.2%) and a 22G needle was used in the remaining patients. The mean number of passes required for the diagnosis was 2.5 ± 1.3 (1-7 passes). There were no clinically relevant complications related to the endoscopic procedure. Of the 31 patients with metastases in other organs, other metastases were also punctured in 20 cases (64.5%) and a single pass of the PM was required in eleven cases. There were 24 patients in which only the pancreatic lesion was accessible to the EUS-FNA and four or more passes were needed to obtain sufficient material for cytodiagnosis in nine cases (37.5%)**.** Immunohistochemistry was performed in 28 patients (63.6%) in order to confirm the anatomopathologic origin of the pancreatic lesion. The diagnosis implied a change in therapeutic approach in 39 (92.85%) of 44 patients. Surgery was the treatment of choice in five of these cases, and four of them had metastases of renal origin.

Thirty-eight patients (86.4%) were followed up to the end of the study. Twenty-seven died with a median survival of seven months, ranging from 0 to 115 months. The primary tumor was a clear cell renal carcinoma in seven of the eleven patients that were alive at the end of the study (63.5%) and also in three of four cases with survival greater than five years after the diagnosis of PM (Table 3). It was also the primary tumor type with longest survival after the diagnosis of PM. This patient underwent a RCC resection in 2001 and presented with three pancreatic lesions in 2006. A duodenopancreatectomy was performed and the patient was alive at the end of the follow-up. Of the ten patients with PM from lung cancer, nine died during the study and one was lost during follow-up. The median survival after diagnosis was six months (3.2-8.7 months), which was significantly lower than that observed in patients with PM

from renal primary tumors (87 months, ranging from 26 to 148 months) (Fig. 1).

DISCUSSION

Most of the malignant masses of the pancreas were primary tumors, either ductal adenocarcinoma or neuroendocrine tumors. Secondary tumors of the pancreas are rare and represent around 2-5% of pancreatic masses in the clinical practice (2); a similar percentage was also observed in our series. Autopsy series have reported that up to 12% of patients with diffuse metastatic disease have pancreatic involvement (13,14). There are no reported large series that describe the diagnosis of PM with EUS-FNA and provide a prolonged follow-up of these patients. Only a few American studies describe series of more than 40 cases (8-11). This is the first European series of a similar size, which additionally provides a prolonged follow-up for the majority of patients.

The primary tumors that most frequently metastasize to the pancreas are renal and lung cancer (11,14), which accounted for almost 50% of the cases in our series. Melanoma was the third most frequent malignancy in our series, probably due to the fact that we are a reference center for the treatment of this tumor. Other studies have reported that colorectal cancer is more frequent than melanoma (13,14). The latency period between the diagnosis of the primary tumor and the diagnosis of PM is variable, which is similar to that published by other authors (15,16). However, and in agreement with the available literature, the latency period differs according to the origin of the primary tumor (17-19), especially for those tumors that frequently produce PM. In our series, 90% of PM from lung cancer had a latency period of less than one year, whereas 50% of renal clear-cell carcinoma primary tumor cases developed PM more than five years after the first diagnosis. Compared to other malignant tumors, late recurrences (more than ten years) are more frequently observed in renal cell carcinoma and a case was reported of a PM diagnosed 21 years after nephrectomy (20). The cancer with the highest latency in our study (18.8 years) was breast adenocarcinoma, which does not frequently present with PM. Therefore, when a solid pancreatic lesion is identified, even though it is a single lesion (which occurs in 77.3% of our cases), the possibility that it is a secondary lesion should be considered. A previous history of a malignant

tumor must be considered, even though the current diagnosis was determined many years before the pancreatic lesion was detected. Therefore, knowing the personal history of cancer is a priority. In addition, the recognition of unusual cytological features in pancreatic punctures should motivate a careful search for an extrapancreatic primary tumor. The collaboration of an experienced cytopathologist is critical and improves diagnostic accuracy as the quantity of material required is indicated. This is especially true for patients that require complementary studies; immunocytochemical study was performed in 63.6% of the cases in our series. The use of EUS fine-needle biopsy for puncture (which was not used in our cases) may facilitate the diagnosis, especially in centers that do not have a pathologist available during the procedure (21-24).

This study did not compare the endosonographic characteristics of the PM with those observed in the primary lesions. The aspects were not uniformly collected in all cases as this was a retrospective series. We believe, according to available literature, that there are no morphological data that allow the diagnosis of secondary lesions to be determined only by ultrasound imaging. The suspicion depends on the clinical data and mainly on the cytological data. We believe that the first step in the management of the lesion is identification via FNA diagnosis.

Ultrasonography, CT scan, MRI and PET are all imaging techniques that can diagnose PM. The superiority of EUS for the detection and characterization of pancreatic tumors is well known (7,25-28). It is especially useful in patients who are allergic to contrast medium in which a CT/MRI scan cannot properly assess the tumor (20). EUS was either the only technique that detected the PM (in five cases) or the technique that distinguished a greater number of intrapancreatic lesions (in 80% of patients with multiple PM) in almost 30% of our patients (13/44). This is a retrospective analysis and the different imaging studies prior to the EUS were not systematically reviewed by an experienced radiologist. Although this may be considered as a formal limitation, we believe it reflects the daily clinical practice as EUS is a crucial technique for the assessment of patients with pancreatic lesions. This is especially true for lesions of a small size; the mean size of PM detected only by EUS was 11.9 mm in this series. It is important to remark that all procedures were initially performed with a radial

echoendoscope and subsequently, with a sectorial one, which was used for the puncture. The results obtained with this combined evaluation may not be reproduced if only the linear echoendoscope is used.

After EUS-FNA, the vast majority of patients underwent a change in therapeutic planning, including indications for surgery. As it is a rare entity, there are no consensus guidelines with regard to the treatment of PM. Many patients are in advanced stages and have poor general health or systemic metastases that negate surgical treatment. However, the therapeutic options depend mostly on the cytological diagnosis. Current trends in surgical oncology include the resection of single lung or hepatic metastases from primary tumors such as colorectal cancer. This results in an increased survival rate and better quality of life if the resection is performed with a low morbidity and mortality (1). The benefit of this type of surgery has not been demonstrated in patients with PM to date but authors are now recommending a surgical treatment in selected cases (1,29,30). This is especially true in patients with single PM from a renal cell carcinoma and with no metastases in other organs, where good results with regard to disease-free survival have been obtained with surgery (31-33). Treatment of multiple PMs without involvement of other organs is controversial. As the available evidence is currently quite poor, some experts consider that a prospective multicenter trial is needed to compare resection with conservative management in these patients (32). In view of our results, a study of these characteristics should include the systematic exploration of the pancreas with echoendoscopy.

The prognosis of patients with PM appears to be better than those with primary tumors of the pancreas. The histological type of pancreatic lesions is the most important factor for survival (19,34,35). Treatment options are largely dependent on a correct pathological diagnosis of PM. In our study, and as described in the literature, patients with a longer survival had primary renal tumors and cases with lung tumors had a lower survival. Renal and lung tumors are the primary malignancies that most frequently metastasize to the pancreas. Thus, the importance of a cytological diagnosis is evident, as the current trend in metastatic lesions of clear cell carcinomas is metastasectomy, as recommended by the most recent guidelines (36). A recent systematic review has shown a five-year survival rate after pancreatectomy for

metastatic renal cancer of 70.4% (32). In our series, the patient with the longest survival after diagnosis had three PM from a renal cancer and underwent a pancreatectomy. Considering the long latency period from the diagnosis of the primary renal tumor to the detection of metastases and the absence of predictive factors of PM in these patients, our study provides new evidence that supports the long-term follow-up of these patients with EUS (1,16,20,27).

CONCLUSIONS

Our results confirm that PM are lesions that are accessible by echoendoscopy. This procedure identifies lesions that have been overlooked by other imaging studies. Thus, suggesting that their diagnosis will increase in the coming years with the generalized use of EUS and the EUS histology needle. Furthermore, EUS should be a first line diagnostic test to optimize treatment in these patients, which may include surgery.

Finally, it is also clear that some of the primary tumors that more frequently metastasize to the pancreas, such as clear cell renal cancer, may have long latency periods and prolonged survival rates with surgical treatment. This data means that EUS should be included in the long-term follow-up of these patients.

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Table 1. Latency period between diagnosis of the primary tumor and diagnosis of pancreatic metastases

Latency period	*n*	*Primary tumor*
PM diagnosed at the same time as primary tumor	10	Lung (6), colon (1), kidney (1), others* (2)
< 1 year	6	Lung (3), kidney (3)
1-5 years	14	Melanoma (4), endometrium (3), colon (2), kidney (2), lung (1), others† (2)
≥ 5 years	14	Kidney (6), melanoma (2), colon (1), others‡ (5)

*Gastric (1), esophagus (1). †Cholangiocarcinoma (1), myeloma (1). ‡Fibrosarcoma (1), adrenal tumor (1), liposarcoma (1), breast (1), ovary (1).

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Table 2. EUS *versus* other diagnostic tests

First diagnostic test	*EUS diagnosed*			*Total*
	Less PM	Same PM	More PM	
CT	1	21	6	28
Abdominal US	0	2	0	2
MRI	0	3	1	4
PET	0	4	1	5
EUS-FNA	0	0	5	5
Total	1	30	13	44

Table 3. Survival at the end of the study

Follow-up time	Alive	Deceased	Total
> 5 years	1 (kidney)	3 (2 kidney, 1 suprarenal)	4
2-5 years	1 (kidney)	2 (kidney, fibrosarcoma)	3
1-2 years	2 (kidney)	6 (2 lung, 2 colon, 2 others*)	8
< 1 year	7 (3 kidney, 4 others[†])	16 (7 lung, 4 melanoma, 5 others[‡])	23
Lost to follow-up			6[§]
Total	11	27	44

*Ovary and melanoma. [†]Endometrium (2), myeloma, liposarcoma. [‡]Kidney, colon, gastric, esophagus, endometrium. [§]Lung, liver, melanoma, colon, kidney and breast.

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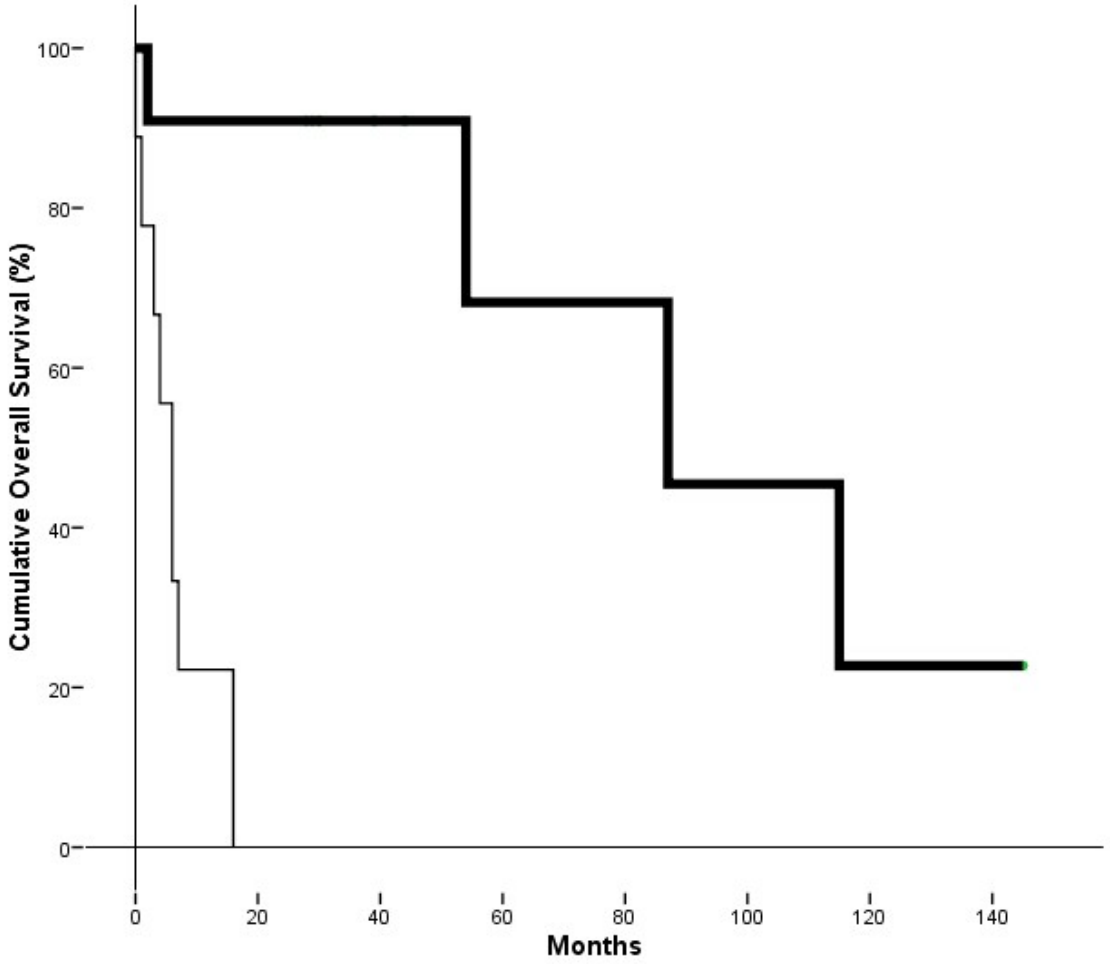

Fig. 1. Survival after PM diagnosis. Comparison between the two tumors that more frequently produce secondary pancreatic lesions (lung and renal cell carcinoma). Log-rank test; median survival: six (lung, thin line) *versus* 87 (kidney, thick line) months; $p < 0.001$.