Contrast enhanced endoscopic ultrasound in the diagnosis of pancreatic metastases

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Abstract

Aim: Less than 5% of pancreatic masses represent metastases and differentiation from primitive tumors using endoscopic ultrasound (EUS) is difficult. The aim of our work was to assess the diagnostic value of contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) for pancreatic metastases. Material and methods: We retrospectively analyzed patients with pancreatic metastasis identified during a 8 year period in a tertiary medical center. Results: We included in the study 20 patients evaluated with EUS and CH-EUS. The primary tumor was localized in the kidney (6 cases), lung (5 cases), colon (3 cases), skin (2 patients) and stomach, breast, ovary and liver (1 patient each). Only 11 patients (55%) (kidney, lung, liver, ovary or skin metastases), presented hypervascularity at EUS and arterial hyperenhancement on CH-EUS, with similar diagnostic value. All renal metastases were hyperenhanced (the negative predictive value 100%) and the stomach, colon and ovary metastases were hypoenhanced. The fast wash-out of contrast substance was encountered in all cases or renal, pulmonary and digestive metastases, but with 53.3-64.3% specificity for the different origin of pancreatic metastases. Conclusions: The vascularity assessments on conventional EUS or CH-EUS are similar for pancreatic metastases of different origin. EUS tissue acquisition remains mandatory for the diagnosis.

Keywords: CH-EUS (contrast-enhanced harmonic endoscopic ultrasound); endoscopic ultrasound; pancreatic metastasis; secondary pancreatic tumor

Introduction

The pancreatic malignant tumors are represented by adenocarcinoma (85%) and neuroendocrine tumors (5%), while about 2% are metastases [1–12], which are recognized in the context of the patient history. The pathology exam is compulsory for avoiding the misdiagnosis with a pancreatic adenocarcinoma, with different natural history and management. The endoscopic ultrasound fine needle aspiration (EUS-FNA) is a superior procedure and the least invasive method for diagnosing pancreatic adenocarcinoma with a sensitivity of 86.8-93% and specificity of 90.4-95.8% [13-18]. The accuracy of endoscopic ultrasound fine needle aspiration (EUS-FNA) for diagnosing pancreatic metastases was reported as 89-93.3% [3,4,7,10,19,20]. These metastatic lesions are mostly hypervascular [10] and this is highlighted by contrast-enhanced harmonic endoscopic ultrasound (CH-EUS) [19,20,21]. While pancreatic adenocarcinoma is mostly hypovascular and hypoenhanced during CH-EUS, neuroendocrine tumors are iso/hyperenhanced [22]. Autoimmune pancreatitis are iso/hyperenhanced, with slower wash-out compared to adenocarcinoma [23]. Metastases
can have a hyperenhanced aspect (renal cell carcinoma or melanoma) or a hypovascular aspect (colon cancer, breast carcinoma) [24] and a consensus considering their aspect during CH-EUS does not exist. Moreover, a separate analysis of the arterial and wash-out phases during contrast enhancement has not been done and could be important to predict malignancy.

The aim of our study was to assess the potential role of CH-EUS in the diagnostic algorithm for pancreatic metastases.

**Material and methods**

A retrospective study was performed in a tertiary medical center. After approval by the Institutional Review board, data were collected from the database entries between January 2012 and October 2020.

We included patients diagnosed with pancreatic metastasis on EUS-FNA and evaluated by CH-EUS. Computed tomography (CT) was performed in all cases. The final diagnosis of pancreatic metastases had been based on the pathology results of the EUS-FNA specimen. We excluded patients without histologic confirmation of their lesion.

For each patient, the oncologic history, the presence of other metastatic sites, the EUS appearance (including location, vascularity and size of the tumor), the CH-EUS characteristics (arterial enhancement and wash-out) and the pathological result were assessed. All patients had given their informed consent for EUS and CH-EUS examination.

**EUS procedure**

A linear echoendoscope (GF-UCT 180 AL5; Olympus, Japan) with AlokaProsound F75 ultrasound machine (Olympus) and 22G standard needles (EZShot2; Olympus, Europe; or Expect; BostonScientific, Europe) were used for all the procedures. The EUS-FNA procedures were conducted by endoscopists with over four years of experience in this procedure (A.S, O.M, C.P.). The transduodenal approach identified lesions located in the pancreatic head or in the uncinate process and the transgastric approach identified lesions located in the pancreatic body or tail. The location, size and the vascularisation, using power Doppler, were assessed and the diameters of the Wirsung and the common bile duct were measured.

**CH-EUS procedure**

The contrast agent SonoVue (2.4 mL, Bracco) was injected, with dual display of contrast harmonics (mechanical index 0.2) and B-mode EUS. The uptake of contrast in the microvessels of the lesion compared to the surrounding normal parenchyma was assessed during the arterial phase (the first 25–30 s) and the wash-out of contrast during the venous phase (30–45 seconds after injection) [25]. Uptake was categorized as hyper-, iso-, or hypoenhancement, and wash-out as slow (>45 s) or fast (≤45 s).

**EUS-FNA procedure**

Once the 22G EUS-FNA needle tip reached the lesion, sampling was done using the fanning and slow-pull techniques. Onsite cytopathology was unavailable and two or three passes were performed, based on the visual assessment of acquisition of core of over 4 mm in length, as previously described [26,27]. The patients were followed up for at least 8 h after the procedure.

**Preparation of samples**

The core was expelled into 10% buffered formalin by reintroduction of the stylet. The samples were embedded in paraffin and then stained with hematoxylin–eosin, with or without immunohistochemistry assessment (at the discretion of pathologist who also had access to the clinical and imaging information).

**Statistical analysis**

Qualitative data are reported as numbers of the total evaluated sample and percentages. Age and the largest diameter of the masses are reported as medians and interquartile range (IQR).

The utility of the evaluated methods for differentiating metastases from primary tumors originating from a specific organ as compared to all other origins was assessed using the sensitivity, specificity, positive and negative predictive values, likelihood ratios (LR), and the clinical utility index (CUI). The CUI value is considered fair when 0.49≤CUI<0.81 and excellent for values ≥0.81 (CUI). A test with a positive LR between 5 and 10 and a negative LR between 0.2 and 0.1 is considered to provide strong diagnostic evidence. A diagnostic test able to confirm the disease (“rule-in”) has a fair or excellent positive CUI while a diagnostic test able to “rule-out” (disease is unlikely) has a fair or excellent negative CUI [28].

**Results**

From 2,560 EUS examinations for pancreatic lesions during the study inclusion period, 28 patients (1%) had pancreatic metastases and 20 patients (0.7%) were analyzed with CH-EUS, so they were included in the analysis. The evaluated sample had a median age of 62 (IQR 56–66) years and included male:female ratio = 1:1. The origin of the pancreatic metastases, concomitant metastases, and their histology are reported in Table I, with adenocarcinoma being the most frequent primary tumor type.

Immunohistochemistry was used in 17/20 cases (85%); standard staining provided an adequate diagnosis
in the remaining three patients (melanoma 1, colonic cancer 1 and lung cancer 1).

The diagnosis of pancreatic metastasis was incidental during their follow-up for cancer in 14 patients (no symptoms) or at the same time with the primary tumor in 6 patients.

**EUS morphology**

The masses were hypoechoic and hypovascularized in 11 patients (55%). Multiple (2–4) lesions were observed in 6 patients with kidney (n=5) or lung (n=1) carcinoma.

The location of the pancreatic metastases (or the largest mass in the case of multiple lesions) was the pancreatic head (n=8, 40%), pancreatic neck (n=4, 20%), body (n=2, 10%) or tail (n=6, 30%). The median size of tumors was 30 mm (IQR 22–36).

**CH-EUS enhancement**

The arterial hyperenhancement was present in 11 cases (55%) (fig 1, fig 2), the rest of the cases showing hypoenhancement (n=9) (Table II). All lesions with hypervascularization showed hyperenhancement at CH-EUS. The diagnostic values for vascularity findings (hyperenhancement and wash-out) is detailed in Table III.

The two cases of pancreatic metastasis originating from melanoma, showed different behavior at CH-EUS: one showing arterial hyperenhancement had no histological signs of necrosis and the other demonstrating arterial hypoenhancement and signs of necrosis at histology (fig 3).

**Table I. The origin of pancreatic metastases and their histology in 20 patients**

<table>
<thead>
<tr>
<th>Origin</th>
<th>Pancreatic metastases, n</th>
<th>Adenocarcinoma</th>
<th>Clear cell carcinoma</th>
<th>Small cell carcinoma</th>
<th>Squamous Carcinoma</th>
<th>Melanoma</th>
<th>Concomitant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>-</td>
<td>Liver, brain</td>
</tr>
<tr>
<td>Kidney</td>
<td>6</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Adrenal glands</td>
</tr>
<tr>
<td>Colon</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>Skin</td>
</tr>
<tr>
<td>Gastric</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Liver</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Liver, peritoneum</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Liver, lung, psoas</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

n, number of patients; EUS, endoscopic ultrasound; CH-EUS-contrast enhanced endoscopic ultrasound

**Table II. Characteristics of vascularity of pancreatic metastases assessed by power Doppler EUS and CH-EUS in 20 patients.**

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Histology</th>
<th>Type</th>
<th>Hypervascular pattern EUS, n</th>
<th>Arterial hyperenhancement</th>
<th>Venous wash-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Small cell carcinoma</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Fast</td>
</tr>
<tr>
<td></td>
<td>Squamous carcinoma</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>Fast</td>
</tr>
<tr>
<td>Kidney</td>
<td>Clear cell carcinoma</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>Fast</td>
</tr>
<tr>
<td>Colon</td>
<td>Adenocarcinoma</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>Fast</td>
</tr>
<tr>
<td>Skin</td>
<td>Melanoma</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>Slow/Fast</td>
</tr>
<tr>
<td>Stomach</td>
<td>Adenocarcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Fast</td>
</tr>
<tr>
<td>Liver</td>
<td>Adenocarcinoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Fast</td>
</tr>
<tr>
<td>Breast</td>
<td>Adenocarcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Fast</td>
</tr>
<tr>
<td>Ovary</td>
<td>Adenocarcinoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Fast</td>
</tr>
</tbody>
</table>

n, number of patients; EUS, endoscopic ultrasound; CH-EUS-contrast enhanced endoscopic ultrasound

**Fig 1.** Pancreatic metastasis from small cell pulmonary carcinoma: a) B-mode endoscopic ultrasound showing a hypoechoic lesion; b) contrast-enhanced ultrasound, arterial phase (28 seconds), showing hyperenhancement.
In this retrospective study we found that CH-EUS has the same diagnostic value as power-Doppler EUS in the pancreatic metastases characterisation and added no supplementary information.

Pancreatic metastases are not frequently found. In surgical series they have been reported in up to 3.9% [12]. In the EUS retrospective series conducted over 2 to 14 years, their frequency varies between 0.73% to 10% (Supplementary Table), including the 1% that we reported for 8 years.

We found the kidney to be the most frequent location for the primary tumor of pancreas metastases; this increased frequency has been previously noted by other authors [3,5,8,9,11,29-34]. The lung, breast, colon, ovaries, skin, connective tissue thyroid, liver and brain were also described as the origin sites of metastases [6-12,35].

A systematic review considering the motivations of the correct diagnosis for the origin of pancreatic metastases assessed the possibility for surgery as part of the cancer management. The authors found that clear cell carcinoma was the histological type that would most frequently benefit from pancreatic surgery, followed by sarcoma and colonic carcinoma [5].

During B-mode EUS all our metastases had a hypoechoic aspect, but only 55% had hypervascularization. The hypoechoic aspect is considered to be present in the majority of pancreatic metastases (80-100%) together with inhomogeneous content and with a well-defined border [3,19,29], but, especially in metastases of colon and breast adenocarcinoma, the very well delineation was not found in all our cases. The hyperechoic metastases were described in primary renal tumor (4 cases) or hepatocellular carcinoma (1 case) [3,10]. Palazzo et al [36] found a marginal hypoechoic zone in 66% of pancreatic metastases of renal origin during EUS assessment, but this was not seen in our cases.

The CH-EUS characterization of various types of solid pancreatic lesions [19-21,35-37]; used Sonovue [19-21] or Sonazoid [37] or Definity [38] as contrast agents. The arterial phase hypoenhancement diagnosed pancreatic adenocarcinoma with 93% sensitivity and 80% spec-

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**Table III. Diagnostic value of vascularity findings in pancreatic metastases during EUS or CH-EUS**

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>+LR</th>
<th>-LR</th>
<th>+CUI</th>
<th>-CUI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypervascularity during EUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary cancer</td>
<td>40</td>
<td>53.3</td>
<td>22</td>
<td>72.7</td>
<td>0.86</td>
<td>1.13</td>
<td>0.08</td>
<td>0.388</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>100</td>
<td>64.3</td>
<td>54.5</td>
<td>100</td>
<td>2.8</td>
<td>0</td>
<td>0.54</td>
<td>0.64</td>
</tr>
<tr>
<td>Digestive cancer</td>
<td>20</td>
<td>46.7</td>
<td>11.1</td>
<td>63.6</td>
<td>0.38</td>
<td>1.71</td>
<td>0.02</td>
<td>0.29</td>
</tr>
<tr>
<td>Arterial hyperenhancement on CH-EUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary cancer</td>
<td>60</td>
<td>46.7</td>
<td>27.3</td>
<td>77.8</td>
<td>1.13</td>
<td>0.86</td>
<td>0.16</td>
<td>0.36</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>100</td>
<td>64.3</td>
<td>54.5</td>
<td>100</td>
<td>2.8</td>
<td>0</td>
<td>0.54</td>
<td>0.64</td>
</tr>
<tr>
<td>Digestive cancer</td>
<td>80</td>
<td>33.3</td>
<td>28.6</td>
<td>83.3</td>
<td>1.2</td>
<td>0.6</td>
<td>0.22</td>
<td>0.27</td>
</tr>
<tr>
<td>Fast wash-out on CH-EUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary cancer</td>
<td>100</td>
<td>53.3</td>
<td>41.7</td>
<td>100</td>
<td>0.14</td>
<td>0</td>
<td>0.41</td>
<td>0.53</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>100</td>
<td>64.3</td>
<td>54.5</td>
<td>100</td>
<td>2.8</td>
<td>0</td>
<td>0.54</td>
<td>0.64</td>
</tr>
<tr>
<td>Digestive cancer</td>
<td>100</td>
<td>53.3</td>
<td>41.7</td>
<td>100</td>
<td>0.14</td>
<td>0</td>
<td>0.41</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio; CUI, clinical utility index; EUS, endoscopic ultrasonography, CH-EUS, contrast enhanced endoscopic ultrasonography.
hyperenhancement during the arterial phase [39-41]. The hyperenhanced lesions as predictors of neuroendocrine tumors proved a 79-96% sensitivity and 82-99% specificity [36,42], proving that other pancreatic lesions such as autoimmune pancreatitis, mass-forming chronic pancreatitis, lymphoma or metastases could have this aspect after contrast injection. A heterogenous enhancement or a hypoenhancement of a neuroendocrine tumour is associated with malignancy [36,39].

We found that 55% of patients had hyperenhanced lesions, similar to the hypervascularity during power Doppler assessment. In the literature, the proportion of hyperenhanced metastases varies from 36% to 100% [19-21,43]. All our renal metastases showed hyperenhancement, with a sensitivity of 100%, but low specificity (64.3%), similar to other published studies [19-21,43]. In our group, the diagnostic CUI value for hyperenhancement was similar to hypervascularity value during power Doppler EUS assessment, but was still within a poor range. The metastasis from colon, stomach and ovary adenocarcinoma were hypoenhanced, an observation that has been reported before [41]. However, the behaviour at CH-EUS cannot be always predicted; one of our two melanoma metastases showed hypoenhancement whereas the other was hyperenhanced and other authors found isoenhancement [19,41].

The fast wash-out was encountered in all but one skin metastases, resulting in a sensitivity of 100%, but a moderate specificity of 53.3-64.3%. Also, the fast wash-out represented a good indicator for malignancy, but the CUI values evidenced limited clinical utility.

A comparison of 17 renal cell carcinoma metastases with 79 neuroendocrine tumor reported that metastases occurred in older patients, were more often multiple and had slow wash-out (7/8 (88%) vs. 4/59 (7%), p<0.001) compared to neuroendocrine tumors [37]. In contrast, we found fast wash-out in all our six cases of renal carcinoma metastases. Perhaps this difference is related to the pharmacodynamics of Sonazoid, which remains longer than Sonovue in the small vessels due to their presence in the Kupffer cells for 10 minutes and this allows a prolonged post-vascular phase, which is better for analysis. Based on these findings, could differentiate neuroendocrine tumors from pancreatic metastases originating from renal cancer with 93% accuracy, 88% sensitivity and modest 64% positive predictive value [37].

The most important limitation of our study is its retrospective character from a single center with a large volume of EUS procedures, which can add bias to our results. Secondly, because of the low incidence of this pathology, the number of patients included is relatively small, but this is also the case for other reports. Also, given that we found both hyper- and hypoenhancement, the lack of quantitative analysis of contrast imaging for our patient group could raise a question about the objectivity of our analysis. However, there is only one study with quantitative analysis in pancreatic metastases using Sonazoid [37]. The reported accuracy metrics must be interpreted with caution because the sample is small, so generalization is not recommended. A multicenter study with appropriate sample size is needed to support our findings. Another limitation is the lack of comparison with other pancreatic tumors, such as pancreatic adenocarcinoma or neuroendocrine tumors, but this is related to the retrospective and descriptive character of the study.

In conclusion, pancreatic metastases are a rare finding, the kidney being the most common primary site of the malignancy. EUS diagnosis based exclusively on EUS morphology or CH-EUS appearance, in these heterogeneous lesions according to the origin, is not enough and EUS tissue acquisition remains mandatory. The CH-EUS vascularity assessment was similar to power Doppler EUS appearance for pancreatic metastases.

**Conflict of interest:** none

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