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POINT OF VIEW

Ultrasonographic contrast agents *versus* sonoelastography in digestive diseases

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ABSTRACT

A review is made of the indications of ultrasonographic contrast enhancement as applied to conventional ultrasonography and endocopic ultrasonography (EUS) as opposed to the use of EUS-sonoelastography today.

Key words: Ultrasonographic contrast media. Contrast-enhanced echoendoscopy. Elastography. Endoscopic sonoelastography. Echoendoscopy with sonoelastography. Neuroendocrine tumors. Pancreatic cancer. Chronic pancreatitis.

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INTRODUCTION

Gastrointestinal real-time, gray-scale ultrasonography (US) has reached high resolution, performance, and sensitivity in the study of biliary, hepatosplenic, pancreatic, and even gastrointestinal (GI) tract conditions. It was then supplemented by color Doppler (CD) and power Doppler or color angiosonography, and more recently by contrast-enhancement (CE) (Gómez, 2007) and three dimensions (3-D) (Muñoz, 2007) in our country (1).

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The same thing happened to echoendoscopy or endoscopic ultrasonography (EUS). Color, sonoelastography, and contrast media have provided US with a new diagnostic and most particularly therapeutic dimension (2).

Color has made it possible to better study blood vessels (portal hypertension and growths).

Sonoelastography and contrast agents have attempted to improve diagnosis and avoid histological studies using fine needle aspiration puncture (FNA) (virtual biopsy) (Figs. 1 and 2).

However, what is the future of CE as applied to ultrasonography (CE-US) or endoscopic ultrasonography (CE-EUS), including intraoperative ultrasonography (CE-IUS)?

The use of CE in these three diagnostic scenarios —US, EUS, IUS— is discussed below.

FACT AND FUTURE OF CE-US

The following indications are now a fact:

- Characterization, delimitation, and detection in the liver of hepatic masses in over 90% of patients (3-5); detection of masses in the spleen and pancreas (6).
- Diagnosis of portal hypertension and portal thrombosis (100%), even if malignant (94%).
- Differentiation between benign and malignant lesions in a percentage above 95% (7).
- Study of GI tract microcirculation: thrombosis, ischemia (8), and inflammatory bowel disease (IBD) (9).
- Ablative therapy control.

The future likely lies in these last two fields:

- Gene therapy
- Functional studies.

FACT AND FUTURE OF CE-EUS

There are no conclusive studies regarding the use of CE-EUS for adenopathies and the GI tract.

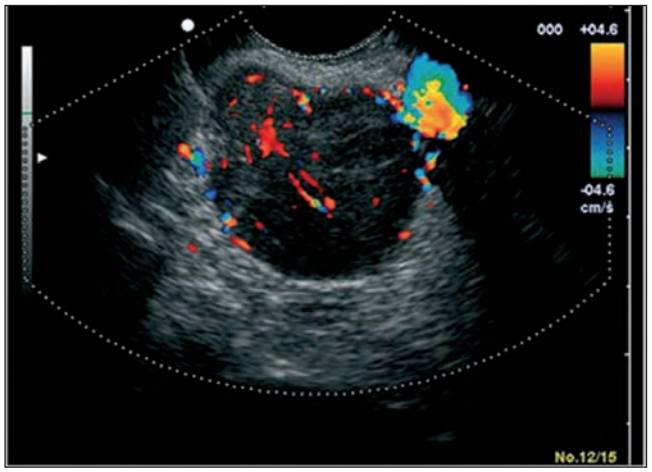

Fig. 1. Hypervascular neuroendocrine tumor (by courtesy of Dr. Dietrich) (2).

In the study of pancreatic conditions using CE-EUS pancreatic cancer (PC) detection —including smaller tumors (11)— is now a fact (10), but the differential diagnosis between adenocarcinoma and chronic nodular pancreatitis remains problematic.

Endoscopic retrograde cholangiography (ERC) and magnetic resonance cholangiography (MRC) have a sensitivity nearing 85%, CT and EUS are above 90%, and EUS-FNA reaches up to 95% (with a mean 86% that boils down to 54% in the presence of chronic pancreatitis) with a specificity of almost 100%, whereas CE-EUS has a sensitivity of 93% and a specificity of nearly 100% (94%).

What about EUS sonoelastograhy?

Most published papers on pancreatic masses show high sensitivity (87%) and moderate specificity in differentiating benign from malignant lesions except for a recent report of low sensitivity and specificity in the diagnosis of even adenocarcinoma (50%) that recommends FNA.

Recent papers (12,13) in our country obtained a sensitivity of 100% and a specificity of 78 and 85%. Therefore, this test may well obtain false positive but no false negative results, interestingly in contrast to EUS-FNA.

Neuroendocrine tumor (NET) detection with CE (Fig. 1) approaches 100% (14) (Giovanninni 7/8: 88%), and the same occurs with NET metastases (15,16). Therefore, it might be indicated for the detection of tumors in patients with multiple endocrine neoplasia (MEN) (small, multiple tumors).

FACT AND FUTURE OF IUS AND CE-LAPUS

It has been shown in 60 patients that CE is more sensitive that intraoperative US (IUS) for the detection of liver metastases, and modifies the management and resection with curative intent in 30% of patients (17).

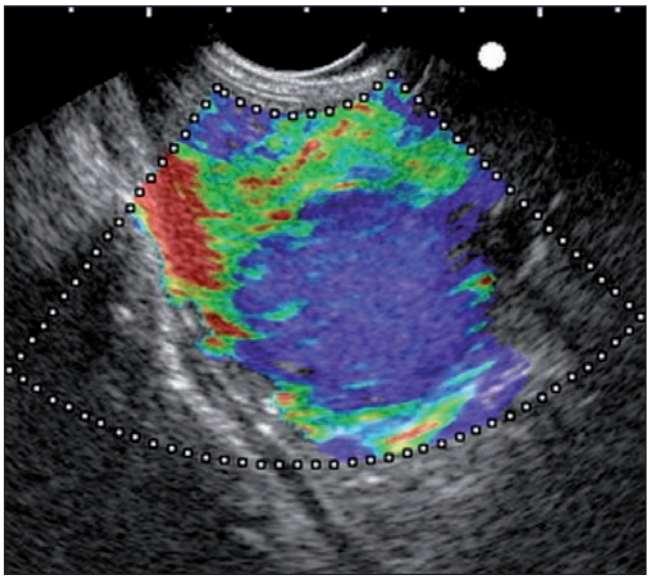

Fig. 2. Pancreatic cancer sonoelastogram (by courtesy of Dr. Giovannini).

Better results have also been obtained with CE-IUS versus IUS in the detection of 20 cases of hepatocarcinoma (HC) on liver cirrhosis (18).

The use of CE will be crucial prior to liver resection and probably pancreas resection in the future.

FUTURE-RELATED CONCLUSIONS

1. Detection of smaller HCs.
2. Ablative therapy control.
3. Detection of overlooked liver micrometastases, particularly from colon cancer.
4. Study of intestinal microcirculation (inflammation, ischemia, thrombosis).
5. Smaller NETs. MEN?
6. Differential diagnosis of PC *versus* CP. Masses.
7. Contribution to liver and possibly pancreatic resection?
8. Gene therapy.
9. Gene therapy control.
10. Other, including functional studies, etc.

ADDENDUM

While CE is not licensed in some countries, its impact has been demonstrated (diagnosis in 90% with modification of patient management in 17.5 and 15.6%, and up to 30% with CE-IUS) (17,19,20), as well as its implementation cost-effectiveness.

Lacking ionizing radiation and with no renal toxicity in over 23,000 patients (scarce morbidity, no mortality) (21), the diagnostic information achieved is comparable to that of CT and MRI (22); for some authors (23) it

Table I. References overview

EUS-Sonoelastography						
Giovannini (35) 2006:	24	pancreas g. (1 NET)	S: 100%	Sp: 67%		
Giovannini (2) 2008:	121	P: 89.2%	S: 80.6%	Sp: 92.3%	PPV: 93.3	NPV: 78%
Giovannini (36) 2009:	121		S: 92.3%	Sp: 80%		
Janssen, 2007:	73 20 PC and 2 NET	P: 73.5	S: 93.8	Sp: 65.4%	PPV: 51.7	NPV: 96.5
Deprez, 2007:	18 7 PC, 3 NET, 6 CP		S: 100%	Sp: 50%	PPV: 77	NPV: 100
Saftoiu, 2007:	7 PC	P: 84.4%	S: 80%	Sp: 91.7%	PPV: 94.1	NPV: 73.7
Hirche (37) 2008:	70 c. 10 C.	P: 45%	S: 41%	Sp: 53%		
Quites previous papers	46 PC and 12 NET (100%)					
Saftoiu (38) 2008:	32 PC, 11 CP, 3	P: 89.7%	S: 91.4%	Sp: 87.9%	PPV: 88.9	NPV: 90.6
Iglesias (12) 2008:	80 c, 10 C	P: 93.7%	S: 100%	Sp: 78.3%		
Iglesias (13) 2009:	130 c, 20 C	P: 94%	S: 100%	Sp: 85.5%		
Iglesias (43) 2010:	86 c (49 CP)		S: 100%	Sp: 92.9% (6 NET)		
Mean		P: 81%	S: 89%	Sp: 76%	PPV: 82%	NPV: 89%

even has enthralling future indications in the diagnosis and even treatment of digestive system conditions (24-29).

Sonoelastography (16,30-34) must improve in the future (2nd or 3rd generation) its sensitivity and specificity for pancreatic tumors, adenopathies, and submucosal tumors in order to compete with contrast media and FNA (Tables I and II).

A novel option would combine sonoelastography and contrast agents in the differential diagnosis between chronic pancreatitis and pancreatic cancer (40) with a gain in specificity and PPV (96%) (Table III).

Table II. References overview

CE-EUS:					
Hirooka 1998	37 c. (Albunex)	S: 100% NET and 75% IPMT			
Becker (39) 2001:	23 (Optison)	S: 94%	Sp: 100%	PPV:100	NPV: 88%
Hocke (10) 2006:	86 CP (Sonovue)	S: 91.1%	Sp: 93.3%		
Sakamoto (11) 2008:	156 PT (Levovist)	S: 94.4%			
Kitano	36 < 2 cm	S: 83.3% *vs.* 50% CT			
Carrara (14)	10 NET (Sonovue)	S: 100%			
Giovanninni 2009 (32) (Sonovue)	7/8 NET (87.5%)	S: 90.9%	Sp: 88.8%	PPV: 88.2	NPV: 91.4
Dietrich (24) 2008: (Levovist)	62 PP, 20 NET (100%)		S: 92%	Sp: 100%	
Napoleón (30) 2010: (Sonovue)	35 c. 18 PC, 9 NET	S: 89% P: 88.5%	Sp: 88%	PPV: 89%	NPV: 88%
Xia (31) 2010:	43 growths	S: 96.3% P: 97.6%	Sp: 100%	PPV:100%	NPV: 94%
Fusaroli (44) 2010: (Sonovue)	90 c. 13 NET (85%)	S: 96%	Sp: 98%		
Mean for all papers:		S: 93%	Sp: 94%	PPV: 94%	NPV: 90%
IPMT:		S: 75%			
PC:		S: 91%	Sp: 93%		
NET:		S: 95%			
CE-US *versus* CE-EUS					
Dietrich (2) 2007:	112 growths: 70 PC	S: 90%	Sp: 100%	PPV: 100	NPV: 85.7
CE-US	42 pancreatic nodules	S: 100%	Sp: 90%	P: 93.8%	
Dietrich (24) 2008: CE-EUS	62 PC, 20 NET (Levovist)	S: 92%	Sp: 100%		

Table III. Algorithm

Diagnostic orientation:			
Pancreatic tumor suspicious of PC by US/ EUS/ CT/ MRI (1st-line imaging techniques): CT + EUS recommended, as well as CA 19.9 measurement			
Possibilities:			
Focal CP and related Pseudotumor Autoimmune disease Tuberculoma Lymphoma Etc.	NET	PC	
Diagnosis by 2nd-line imaging tests:	↓	↓	
EUS-Sonoelastography	<100%?	S: 89%	Sp: 76%
Contrasts (CE)	95%	S: 92%	Sp: 94%
EUS-FNA	90%	S: 86%	Sp: 97%
	Contrasts *vs.* EUS-S?	CE *versus* FNA CE plus EUS-S	
Staging and resectability: EUS more than CT (2)			
Non-resectability: EUS-FNA if preoperative neoadjuvancy (41)			

Modified and extended from references 2, 42, and 45. CP: chronic pancreatitis. PC: pancreatic cancer. NET: neuroendocrine tumor. C: control.

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