

Impact of endoscopic ultrasonography on diagnosis of pancreatic cancer

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Abstract Accumulated evidence has revealed that endoscopic ultrasonography (EUS) has had a great impact on the clinical evaluation of pancreatic cancers. EUS can provide high-resolution images of the pancreas with a quality regarded as far surpassing that achieved on transabdominal ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI). EUS is particularly useful for the detection of small pancreatic lesions, while EUS and its related techniques such as contrast-enhanced EUS (CE-EUS), EUS elastography, and EUS-guided fine needle aspiration (EUS-FNA) are also useful in the differential diagnosis of solid or cystic pancreatic lesions and the staging (T-staging, N-staging, and M-staging) of pancreatic cancers. In the diagnosis of pancreatic lesions, CE-EUS and EUS elastography play a complementary role to conventional EUS. When sampling is performed using EUS-FNA, CE-EUS and EUS elastography provide information on the target lesions. Thus, conventional EUS, CE-EUS, EUS elastography, and EUS-FNA are essential in the clinical investigation of pancreatic cancer.

Keywords Endoscopic ultrasonography · Contrast-enhanced endoscopic ultrasonography · Pancreatic cancer

Introduction

Pancreatic cancer is one of the leading causes of cancer-related death. It has a poor 5-year survival rate of around 8–9% [1, 2]. This is primarily because the majority of patients with pancreatic adenocarcinoma progress to either metastatic or locally advanced disease while in the asymptomatic phase. However, if pancreatic cancer is detected in the early stage (i.e., less than 2.0 cm), it has a relatively better prognosis. Therefore, accurate detection of small cancers is important for reducing the mortality rate from pancreatic cancer.

The only chance of a cure for pancreatic cancer is surgical resection. Surgery that is able to achieve clear margins and negative lymph nodes leads to a better survival rate. When evaluating the resectability of pancreatic cancer, it is important that vascular invasion, lymph node metastases, and liver metastases are appropriately evaluated.

Endoscopic ultrasonography (EUS) is an ultrasound (US) technique in which the tip of the endoscope is equipped with a high-frequency transducer. High-resolution images of the pancreas can be obtained through the esophagus, stomach, and duodenum, without the disrupting effects of intervening gas, fat, and bone. A large number of studies have demonstrated that EUS and its related techniques, including contrast-enhanced EUS (CE-EUS), EUS elastography, and EUS-guided fine needle aspiration (EUS-FNA), now play an important role in the clinical evaluation of pancreatic cancer, including the detection of small cancers, the differential diagnosis of pancreatic solid or cystic lesions, and the staging of pancreatic cancers.

In this article, the roles of EUS in the clinical investigation of pancreatic cancer, including the characterization

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of solid and cystic pancreatic masses and the staging of pancreatic cancers, are reviewed.

Diagnostic techniques

Conventional EUS

Endoscopic ultrasonography can be classed into two categories: radial and linear. Radial-type EUS provides circumferential views at right angles to the shaft of the scope, similar to those provided by CT scan. Linear format of EUS provides views in the same line or plane as the scope shaft, similar to those obtained with transabdominal US. Pancreas can be observed from 3 stations including body of the stomach, and bulb and the second portion of the duodenum. A typical endoscopic feature of the normal pancreas is a homogeneous ‘salt and pepper’ appearance. EUS has better spatial and time resolution than other imaging methods. In particular, EUS plays an important role for detection of small solid lesions and characterization of cystic lesions.

CE-EUS

Contrast-enhanced-EUS was first reported in 1995 with an intra-arterial CO₂ infusion [3]. After contrast agents for contrast-enhanced Doppler EUS had been improved, contrast-enhanced harmonic EUS was developed in 2008 [4]. Contrast agents consist of gas-filled microbubbles of approximately 2–5 μm in diameter, encapsulated by a phospholipid or lipid shell [5]. After the agents are administered through a peripheral vein, the microbubbles in the contrast agent receive transmitted US waves and are disrupted or stimulated to resonate, thereby producing the signal detected in the US image, which has remarkably low artifact. CE-EUS is often critical for the characterization of solid and cystic pancreatic lesions and the staging of pancreatic cancer with evaluation of lesion vascularity.

EUS elastography

Endoscopic ultrasonography elastography for the evaluation of pancreatic tissue was first reported in 2006 [6]. The equipment can be coupled with conventional EUS without the need for additional devices. There are two types of EUS elastography, strain and shear wave. Strain elastography estimates the stiffness of the target tissue by measuring the degree of strain produced in response to compression. Shear wave elastography involves the emission of focused US from the probe to the target tissue, the so-called ‘acoustic radiation force impulse’ (ARFI), and the stiffness of the target tissue is then estimated by measuring the

propagation speed of the shear wave. Only strain elastography is so far available for EUS. EUS elastography is used to characterize pancreas masses and lymph node metastases of pancreatic cancer as well as to judge the severity of chronic pancreatitis with evaluation of lesion elasticity.

EUS-FNA

EUS-guided fine needle aspiration (EUS-FNA) has been generally used for the sampling of pancreatic tissues since it was first reported in 1992 [7]. In general, 19G–25G caliber needles are inserted under EUS guidance for the pathological diagnosis of pancreatic cancer and lymph nodes and/or hepatic metastasis of pancreatic cancer. EUS-FNA is superior to other methods such as ERCP in terms of tissue acquisition and safety. The overall complication rate of EUS-FNA is 0.82%, including complications such as pain (0.38%), bleeding (0.10%), and pancreatitis (0.4%; $n = 8246$) [8].

Identification and characterization of solid pancreatic masses

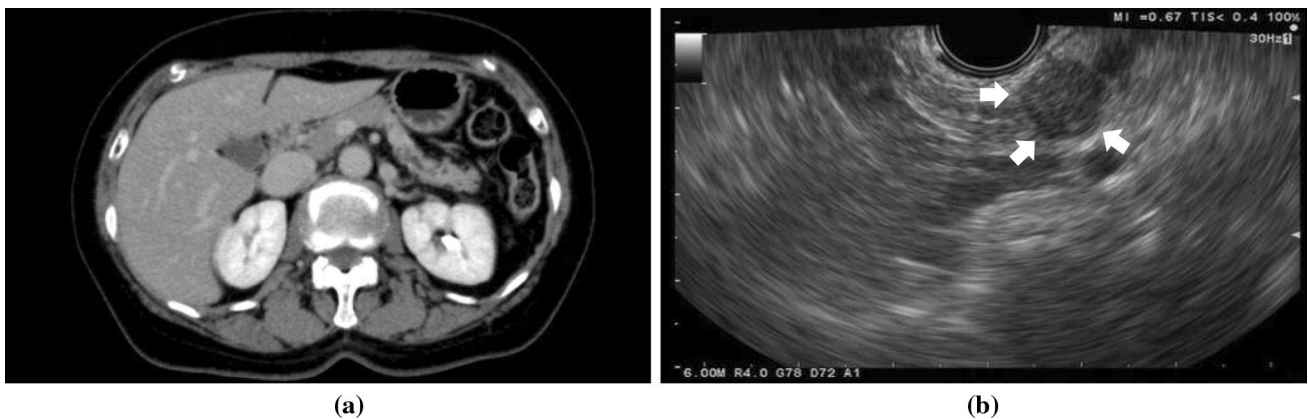
Conventional EUS

EUS is now regarded as the most sensitive imaging modality for the detection of pancreatic lesions. Most solid pancreatic lesions are depicted as a heterogeneous hypoechoic mass, irrespective of the pathological type. Across 22 studies covering 1170 patients, the median sensitivity of EUS for the detection of pancreatic tumors was 94% [9–30] (Table 1). The sensitivity of EUS was shown to be superior to that of computed tomography (CT; 98% vs 74%) in 19 comparative studies ($n = 895$) [9–21, 23–25, 28–30]. The sensitivity of EUS was also shown to be superior to that of transabdominal US (94% vs 67%) in four comparative studies ($n = 259$) [9, 10, 15, 30]. However, studies comparing EUS with magnetic resonance imaging (MRI) are rare.

As it has a high resolution, EUS is particularly useful for the detection of small pancreatic lesions. In a report comparing the performance of different modalities for detecting pancreatic tumors < 30 mm in diameter ($n = 49$), the sensitivities of EUS, CT, and MRI were 93%, 53%, and 67%, respectively [11]. For the detection of pancreatic tumors ≤ 20 mm, EUS had higher sensitivity than contrast-enhanced CT (94.4 vs. 50.0%, $n = 36$) [29]. Several reports show that EUS could detect pancreatic tumors that were not identified on other modalities (Fig. 1) [24, 31–33] and a meta-analysis summarizing these four studies ($n = 206$) reported that the sensitivity of EUS for detecting pancreatic malignancy when multidetector CT findings were

Table 1 Sensitivities of conventional EUS and other imaging modalities for the detection of pancreatic masses

Number	Author	Year	References	Number of patients	EUS	CT	US	MRI
1	Rösch et al.	1991	[9]	102	99	77	67	–
2	Palazzo et al.	1993	[10]	49	91	66	64	–
3	Müller et al.	1994	[11]	33	94	69	–	83
4	Marty et al.	1995	[12]	37	92	63	–	–
5	Melzer et al.	1996	[13]	12	100	83	–	–
6	Howard et al.	1997	[14]	21	100	67	–	–
7	Sugiyama et al.	1997	[15]	73	96	86	81	–
8	Legmann et al.	1998	[16]	30	100	92	–	–
9	Gress et al.	1999	[17]	81	100	74	–	–
10	Midwinter et al.	1999	[18]	34	97	76	–	–
11	Harrison et al.	1999	[19]	19	89	68	–	–
12	Mertz et al.	2000	[20]	31	93	53	–	–
13	Rivadeneira et al.	2003	[21]	44	100	68	–	–
14	Ainsworth et al.	2003	[22]	22	87	–	–	96
15	Kitano et al.	2004	[23]	65	95	68	–	–
16	Agarwal et al.	2004	[24]	71	100	86	–	–
17	Dewitt et al.	2004	[25]	80	98	86	–	–
18	Borbath et al.	2005	[26]	59	98	–	–	88
19	Hocke et al.	2008	[27]	194	79	–	–	–
20	Jemaa et al.	2008	[28]	42	100	88	–	–
21	Sakamoto et al.	2008	[29]	36	94	50	–	–
22	Kamata et al.	2014	[30]	35	100	56	39	50
	Total number of patients			1170	1170	895	259	149
	Overall sensitivity				94	74	67	79

**Fig. 1** A case of small ductal carcinoma (8 mm, pancreatic body). Pancreatic mass was not detected by enhanced contrast MDCT (a), whereas detected clearly by endoscopic ultrasound (b, arrowheads)

indeterminate was 85%, with a specificity of 58% [34]. Thus, the high sensitivity of EUS has been repeatedly confirmed. Based on the results of these studies, the clinical guideline of the Japanese Pancreas Society recommended EUS as one of the diagnostic options for patients who possibly have pancreatic cancer, alongside CT and MRI [35].

EUS is useful for the detection of small cancers. Pancreatic cancers of ≤ 1 cm in size, accounting for 0.8% of all pancreatic cancers, has been regarded as so-called early stage cancer whose 5-year survival is reportedly 80.4% [36]. EUS can detect the small masses with a sensitivity of over 80%, which is higher than those with the other imaging methods: US (17–70%), CT (33–75%) and PET

(50%) [35]. EUS reportedly can detect pancreatic tumors that were not identified on CT [23, 37].

As EUS provides high-resolution images, there has been interest in using the technique to screen asymptomatic high-risk cohorts for early cancer detection. Canto and colleagues screened 225 asymptomatic individuals considered at high risk because of hereditary and familial pancreatic cancer [38]. They blindly compared imaging studies including CT, MRI, and EUS and found that EUS was more sensitive for detecting pancreatic abnormalities (42%) than CT (11%) and MRI (33%).

CE-EUS

In contrast to the high sensitivity of EUS for the detection of solid pancreatic masses, it is difficult to distinguish pancreatic cancer from other diseases on EUS imaging alone. Indeed, the specificity of EUS for the diagnosis of malignant pancreatic diseases is reported as 53%, with sensitivity of 95% ($n = 115$) [39].

CE-EUS depicts most pancreatic cancers as a solid lesion with hypoenhancement (Fig. 2). CE-EUS including Doppler and harmonic modes can increase this specificity, with 20 studies ($n = 1909$) showing CE-EUS to have an estimated specificity and sensitivity of 88% and 90%, respectively [27, 29, 37, 40–56] (Table 2). In two meta-analysis, the pooled sensitivity and specificity of CE-EUS were 93–94% and 88–89%, respectively [57, 58].

EUS elastography

The overall sensitivity and specificity of EUS elastography were 93% and 63% in 15 studies ($n = 1568$) [59–73] (Table 3). On EUS elastography, the strain indicating the stiffness of target lesions may help differentiate harder pancreatic cancers from surrounding tissues. In 7 meta-analyses, the pooled sensitivity and specificity were 95–99% and 67–76%, respectively [74–80].

EUS-FNA

The sensitivities and specificities of EUS-FNA for the diagnosis of pancreatic cancer were 85–92% and 96–98%, respectively, in four meta-analyses [81–84] (Table 4). The sensitivity of EUS-FNA for pancreatic cancer exceeded 90% in patients with negative or non-diagnostic sampling from previous endoscopic retrograde cholangiopancreatography (ERCP) [85]. However, EUS-FNA cannot be applied for pancreatic cancers without forming a mass including carcinoma in situ. In those cases, ERCP-based cytology may be helpful for the diagnosis [86].

CE-EUS and EUS elastography may provide complementary information on the diagnosis of pancreatic

cancers, in addition to the yield from EUS-FNA. CE-EUS can help to identify the EUS-FNA target, leading to a reduced requirement for repeated FNA [44, 52, 87]. The specificity of EUS-FNA may be improved when it is used with EUS elastography [70]. When CE-EUS reveals a hypovascular mass or EUS elastography reveals a hard mass in the pancreas with negative EUS-FNA findings, re-examination with EUS-FNA is recommended.

Characterization of cystic pancreatic lesions

Conventional EUS

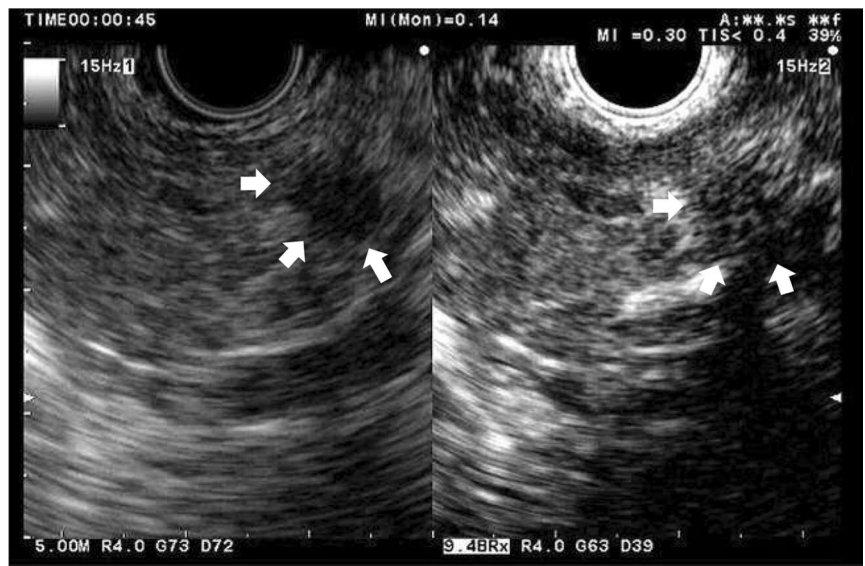
Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are cystic pancreatic lesions with a relatively high potential for malignancy, and it is difficult to exactly evaluate the malignancy of pancreatic cysts. Mural nodules within a cyst and main duct involvement suggest malignant IPMN, as indicated in several guideline [88–90]. There are limited data available on the performance of conventional EUS for the detection of mural nodules of pancreatic cystic lesions [91–96] (Table 5). Recently, Kamata et al. [93] reported that conventional EUS had a sensitivity of 97% and specificity of 40%. Harima et al. [92] reported that the sensitivity and specificity of EUS were 100% and 61%, respectively, while those of CT were 71% and 100%. The sensitivity of CT in comparison with EUS has also been reported to be as low as 24–37% [91, 94].

CE-EUS

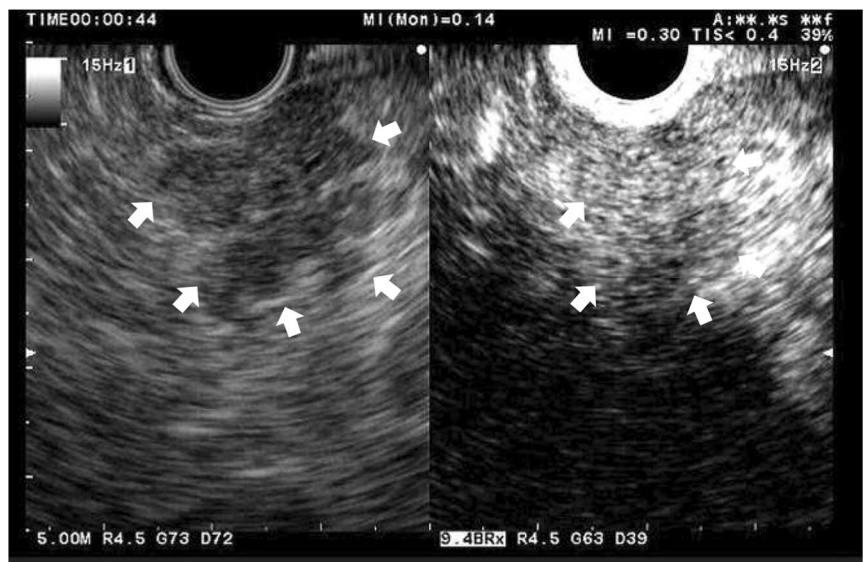
Mural nodules need to be distinguished from mucous clots in IPMN; however, this may sometimes be difficult on conventional EUS alone. In this respect, CE-EUS is useful for the differential diagnosis. CE-EUS depicts vascularity in mural nodules while it depicts no vascularity in mural clots (Fig. 3). Yamashita et al. [96] showed that CE-EUS can distinguish mural nodules from mucous clots with a sensitivity of 100% and a specificity of 80%, while contrast-enhanced multidetector CT achieves values of 58% and 100%, respectively. Harima et al. [92] reported sensitivity and specificity of 100% and 97% for CE-EUS, and 71% and 100% for CT.

CE-EUS is also helpful for estimating the malignant potential of IPMNs [93, 97, 98] (Table 6). Kamata et al. [93] reported that CE-EUS identified mural nodules more accurately than conventional EUS, providing sensitivity and specificity values of 97% and 75% for CE-EUS and 97% and 40% for conventional EUS. Yamamoto et al. [98] reported that the nodule/pancreatic parenchymal contrast ratio has diagnostic power for high-grade dysplasia/

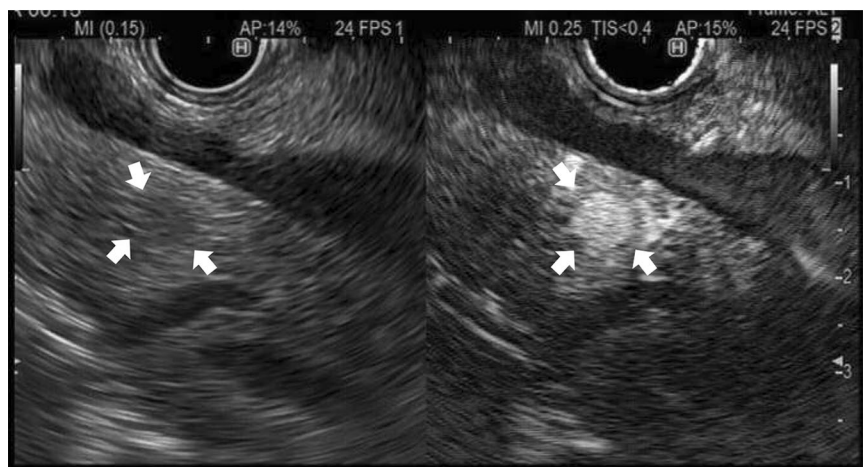
Fig. 2 **a** A typical example of a solid lesion with hypoenhancement (a ductal carcinoma of 10 mm). Conventional EUS shows a hypochoic area (arrowheads) at the pancreas body (left). Contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) indicates that the area is hypovascular (arrowheads) compared with the surrounding tissue (right). **b** A typical example of a solid lesion with isoenhancement (Autoimmune pancreatitis). Conventional EUS shows a hypochoic area (arrowheads) at the pancreas head (left). CH-EUS indicates enhancement in this area similar to the surrounding tissue (arrowheads) (right). **c** A typical example of a solid lesion with hyperenhancement (a neuroendocrine tumor of 8 mm). Conventional EUS shows a hypochoic mass (arrowheads) at the pancreas head (left). CH-EUS indicates that enhancement in the mass is higher than in the surrounding tissue (arrowheads) (right)



(a)

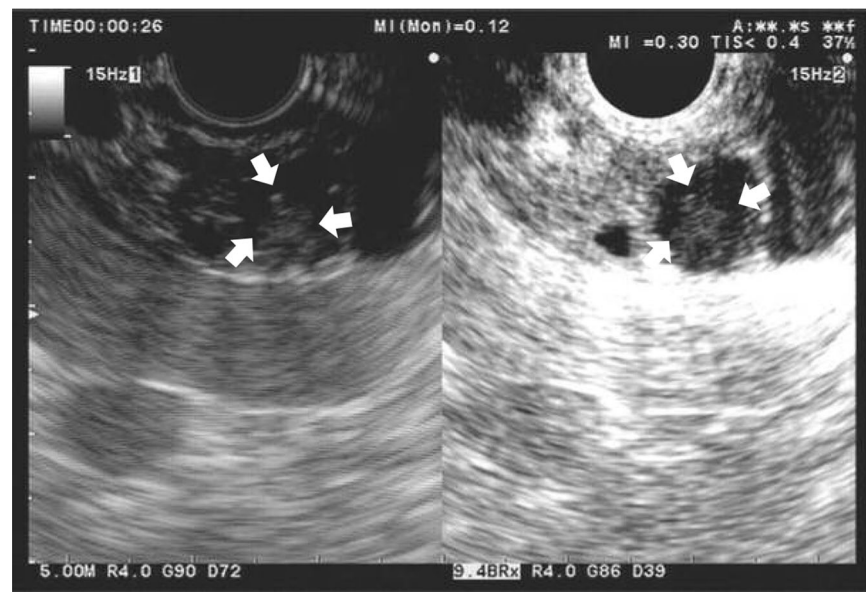


(b)

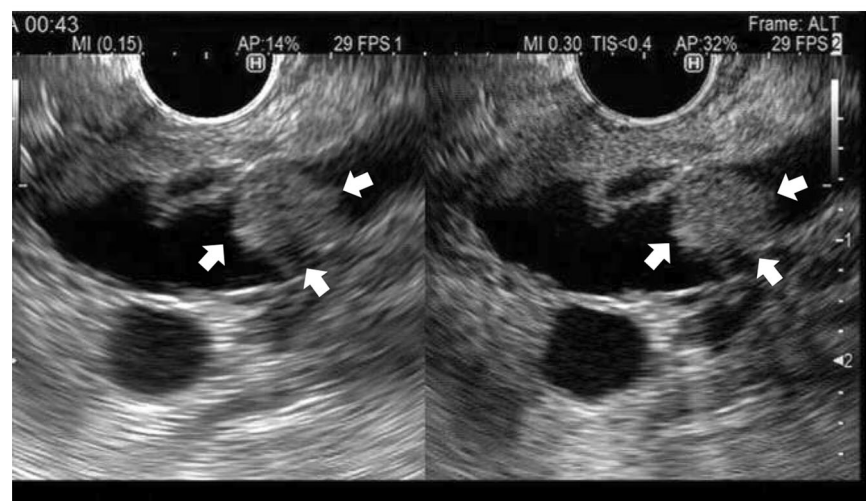


(c)

Fig. 3 a A case of intraductal papillary mucinous neoplasm (IPMN) with mucous clot. Conventional EUS shows echogenic mural lesions (arrowheads) in a cyst cavity (left). Contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) shows no vascularity in the mural lesion (arrowheads) (right). **b** A case of IPMN with mural nodule. Conventional EUS shows echogenic mural lesions (arrowheads) in a cyst cavity (left). CH-EUS shows vascularity in the mural lesion (arrowheads) (right)



(a)



(b)

invasive carcinoma, with a sensitivity of 94% and specificity of 93%. Ohno et al. [97] used CE-EUS to analyze the vascularity patterns of mural nodules in IPMN and reported a sensitivity of 60% and specificity of 93%.

EUS elastography

There are no reports of EUS elastography used for the diagnosis of cystic pancreatic lesions.

EUS-FNA

In two meta-analysis, EUS-FNA-based cytology showed a sensitivity of 51% and specificity of 94% for the diagnosis of malignant pancreatic cystic lesions [99, 100]. The low

sensitivity was due to factors such as sampling error. Although the carcinoembryonic antigen (CEA) level of pancreatic cyst fluid is useful for differentiating mucinous from non-mucinous pancreatic cysts, it does not correlate with the risk of malignancy [101, 102].

The DNA in pancreatic cyst fluid can also be analyzed. However, K-ras or other genetic features associated with cancer, used either alone or in combination with CEA levels, do not allow accurate differentiation of benign from malignant pancreatic cysts [103–108]. MicroRNA (miRNA) has recently been investigated and provided promising results in the differentiation of malignant from premalignant cysts; this requires further studies [109].

Table 2 Diagnostic performance of contrast-enhanced EUS for solid pancreatic masses

Number	Author	Year	References	Number of patients	Sensitivity	Specificity
1	Becker et al.	2001	[41]	23	94	100
2	Hocke et al.	2008	[27]	194	92	96
3	Sakamoto et al.	2008	[29]	36	83	–
4	Dietrich et al.	2008	[42]	93	92	100
5	Fusaroli et al.	2010	[43]	90	96	98
6	Săftoiu et al.	2010	[44]	54	76	95
7	Napoleon et al.	2010	[45]	35	89	88
8	Seicean et al.	2010	[46]	30	80	92
9	Matsubara et al.	2011	[47]	91	96	93
10	Romagnuolo et al.	2011	[48]	21	100	73
11	Kitano et al.	2012	[38]	277	95	89
12	Imazu et al.	2012	[49]	30	100	100
13	Gheonea	2013	[50]	51	94	89
14	Lee et al.	2013	[51]	37	93	100
15	Gincul et al.	2014	[52]	100	96	94
16	Park et al.	2014	[53]	90	92	68
17	Săftoiu et al.	2015	[54]	167	88	100
18	Yamashita et al.	2015	[55]	147	94	71
19	Chantarojanasiri et al.	2017	[56]	136	66	63
20	Leem et al.	2018	[57]	207	82	88
	Total number of patients			1909		
	Overall				90	89
<i>Meta analyses</i>						
1	Gong et al.	2012	[58]	1139	94	89
2	He et al.	2017	[59]	1668	93	88

T-staging of pancreatic cancer

Conventional EUS

In the current AJCC 2010 staging criteria, T3 tumors that are potentially resectable are distinguished from T4 unresectable tumors involving celiac or superior mesenteric arteries [110]. The sensitivity and specificity of EUS for the detection of tumor vascular invasion range from 42% to 91% and 89% to 100%, respectively [17, 18, 20, 21, 111–127] (Table 7). In meta-analyses, the pooled sensitivity and specificity were 66–86% and 89–94%, respectively [128–130]. The sensitivity of EUS varies according to the target vessel. For example, the sensitivity of EUS for tumor invasion of the portal vein (PV) is over 80% [15, 131, 132], and is consistently superior to that of CT [15, 18, 115, 133] and angiography [15, 115, 131, 133]. By contrast, the sensitivity of EUS was low in comparison with that of CT in the superior mesenteric vein, superior mesenteric artery, and celiac artery [18, 20, 113, 133]. This is because it is technically difficult to provide entire images of these vessels, with this sometimes being due to obscuration by a large tumor in the

uncinate or inferior portion of the pancreatic head. In general, angiography is consistently inferior to EUS and CT for assessment of vascular invasion, and has no current role in the staging of pancreatic tumors [112, 128].

CE-EUS

There are few reports of CE-EUS for evaluation of the vascular invasion of pancreatic cancers; however, Imazu et al. [126] reported that the sensitivity and specificity for detecting PV involvement were 100% and 72.6–100%, respectively.

EUS elastography

There are no reports of EUS elastography for T-staging of pancreatic cancer.

EUS-FNA

There are no reports of EUS-FNA for T-staging of pancreatic cancer.

Table 3 Diagnostic performance of EUS elastography for solid pancreatic masses

Number	Author	Year	References	Number of patients	Sensitivity	Specificity
1	Janssen et al.	2007	[60]	73	100	22
2	Giovannini et al.	2009	[61]	121	92	80
3	Iglesias-Garcia et al.	2009	[62]	130	99	86
4	Itokawa et al.	2011	[63]	109	99	71
5	Săftoiu et al.	2012	[64]	258	88	83
6	Hocke et al.	2012	[65]	58	95	33
7	Figueiredo et al.	2012	[66]	47	90	75
8	Dawwas et al.	2012	[67]	111	100	17
9	Lee et al.	2013	[68]	35	93	86
10	Havre et al.	2014	[69]	48	67	71
11	Rustemovic et al.	2014	[70]	149	100	45
12	Kongkam et al.	2015	[71]	38	86	67
13	Opačić et al.	2015	[72]	149	98	50
14	Mayerle et al.	2016	[73]	85	77	65
15	Kim et al.	2017	[74]	157	96	96
Total number of patients				1568		
Overall					93	63
<i>Meta-analyses</i>						
1	Pei et al.	2012	[75]	1042	95	69
2	Mei et al.	2013	[76]	1044	95	67
3	Ying et al.	2013	[77]	893	98	69
4	Li et al.	2013	[78]	781	99	76
5	Hu et al.	2013	[79]	752	97	76
6	Xu et al.	2013	[80]	752	99	74
7	Lu et al.	2017	[81]	1537	97	67

Table 4 Diagnostic performance of EUS-FNA

Number	Author	Year	References	Number of patients	Sensitivity	Specificity
<i>Meta-analyses for solid pancreatic lesions</i>						
1	Hewitt et al.	2012	[82]	4984	85	98
2	Chen et al.	2012	[83]	1860	92	96
3	Puli et al.	2013	[84]	4766	87	96
4	Banafea et al.	2016	[85]	2761	91	97
<i>Meta-analyses for cystic pancreatic lesions</i>						
1	Suzuki et al.	2014	[100]	96	65	91
2	Wang et al.	2015	[101]	1024	51	94

N-staging of pancreatic cancer

Conventional EUS

EUS is useful for the nodal staging of pancreatic cancer. In a meta-analysis (16 studies: $n = 512$), the pooled sensitivity and specificity of EUS were 69% and 81%, respectively [128]. EUS showed higher sensitivity for nodal staging than CT (58% vs 24%, eight studies, $n = 281$) [128]. Although various criteria are suggested, those mostly used are a round shape, hypoechogenicity, a smooth border, and a short axis size greater than 5 mm [10, 18].

The sensitivity of EUS is not so high because metastatic lymph nodes have variable morphologic features and partially because inflammatory changes around cancers and/or a large tumor size lead to poor images of the target lymph nodes.

CE-EUS

Metastatic lymph nodes have been evaluated in a few patients with pancreatic cancer. Miyata et al. [134] analyzed 143 lymph nodes in 109 patients (67 patients with pancreatic cancer) with CE-EUS and found that the

Table 5 Diagnostic performance of EUS and CT for mural nodules of IPMN

Number	Author	Year	References	Number of patients	EUS (conventional EUS or CE-EUS)		CT	
					Sensitivity	Specificity	Sensitivity	Specificity
<i>Conventional EUS</i>								
1	Zhong et al.	2012	[92]	57	75	83	24	100
2	Harima et al.	2015	[93]	50	100	61	71	100
3	Kamata et al.	2016	[94]	70	97	40	–	–
4	Fujita et al.	2016	[95]	21	100	–	37	–
Total number of patients				198				
Overall					85	60	39	100
<i>Contrast-enhanced EUS</i>								
5	Kurihara et al.	2012	[96]	22	88	–	71	–
6	Yamashita et al.	2013	[97]	17	100	80	58	100
7	Harima et al.	2015	[93]	50	100	97	71	100
Total number of patients				89				
Overall					95	84	44	100

Table 6 Diagnostic performance of CE-EUS for malignant IPMN

Number	Author	Year	References	Number of patients	Contrast-enhanced EUS	
					Sensitivity	Specificity
1	Ohno et al.	2009	[98]	87	60	93
2	Kamata et al.	2016	[94]	70	97	75
3	Yamamoto et al.	2016	[99]	30	94	93
Total number of patients				187		
Overall					88	85

sensitivities and specificities of CE-EUS for the diagnosis of metastatic lymph nodes were 83% and 91%, respectively.

EUS elastography

There have been no reports of using EUS elastography for N-staging of pancreatic cancer.

EUS-FNA

The diagnosis of celiac lymph nodes is important from the viewpoint of evaluating surgical indications for pancreatic cancer. For the para-aortic lymph node, the sensitivity and specificity of EUS-FNA for the diagnosis of metastatic lymph nodes were 96.7% and 100%, while the sensitivity of PET-CT was only 53.3% [135].

Although conventional EUS and EUS-FNA may fail to detect small lymph node metastasis, EUS elastography is able to identify the smallest metastatic changes in tissue hardness. CE-EUS is potentially useful for target selection prior to EUS-FNA, and as suggested in the European

guidelines, CE-EUS and EUS elastography provide helpful information on target lymph nodes, especially when target lymph nodes cannot be accessed with EUS-FNA or when samples for pathological evaluation are not fully obtained with EUS-FNA.

M-staging of pancreatic cancer

Conventional EUS

For the detection of non-nodal metastatic cancer including liver metastasis, CT and MRI are superior to EUS, because a certain portion of the right hepatic lobe located away from the upper gastrointestinal tract cannot be visualized with EUS. However, EUS can detect small hepatic lesions that would otherwise be undetected on other imaging modalities. EUS may also identify and sample ascites that may or may not have been previously detected by other imaging studies [136, 137].

Table 7 Diagnostic performances of EUS for the diagnosis of the vascular invasion of pancreatic cancer

Number	Author	Year	References	Number of patients	EUS	
					Sensitivity	Specificity
1	Yasuda et al.	1993	[112]	29	88	78
2	Snady et al.	1994	[113]	38	100	100
3	Gress et al.	1999	[17]	75	91	95
4	Buscail et al.	1999	[114]	32	67	100
5	Midwinter et al.	1999	[18]	30	81	80
6	Ahmad et al.	2000	[115]	89	86	71
7	Rösch et al.	2000	[116]	75	43	91
8	Shoup et al.	2000	[117]	37	20	100
9	Mertz et al.	2000	[20]	16	100	100
10	Yusoff et al.	2003	[118]	45	69	100
11	Rivadeneira et al.	2003	[21]	44	100	100
12	Soriano et al.	2004	[119]	62	42	97
13	Ramsay et al.	2004	[120]	19	56	89
14	Aslanian et al.	2005	[121]	30	50	58
15	Kulig et al.	2005	[122]	45	96	85
16	Fritsher-Ravens et al.	2005	[123]	22	86	73
17	Buchs et al.	2007	[124]	90	55	90
18	Seicean et al.	2008	[125]	30	100	54
19	Bao et al.	2008	[126]	27	80	67
20	Imazu et al.	2010	[127]	11	69	92
21	Tellez-Avila et al.	2012	[128]	50	61	90
	Total number of patients			896		
	Overall				76	86
<i>Meta-analyses</i>						
1	Nawaz et al.	2013	[129]	886	85	91
2	Li et al.	2013	[130]	368	66	94
3	Yang et al.	2014	[131]	729	72	89

CE-EUS

Recently, Minaga et al. [138] reported that the sensitivity and specificity of EUS in the detection of left liver metastatic lesions of pancreatic cancer were 98.9% and 98.4%, respectively, while for CE-CT they were 69.7% and 73.0%, and for conventional EUS they were 97.9% and 97.6% [Minaga DDW abstract].

EUS elastography

There are no reports of EUS elastography for M-staging of pancreatic cancer.

EUS-FNA

Malignant ascites or liver metastases preclude surgical resections and indicate poor survival [139]. EUS-FNA has a sensitivity of 82–94% for the diagnosis of malignant ascites or liver metastasis [140–143]. Therefore, for the

M-staging of pancreatic cancers, even a small quantity of ascites requires careful surveillance with EUS.

Conclusions

Conventional EUS plays an important role in identifying pancreatic masses, particularly those of a small size. CE-EUS and EUS elastography improve the characterization of pancreatic lesions detected on EUS. EUS-FNA has high sensitivity and specificity for the detection of pancreatic cancers. CE-EUS and EUS elastography have a complementary role and assist in identifying target lesions for EUS-FNA.

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