

The Role of Endoscopic Ultrasound in M-Staging of Gastrointestinal and Pancreaticobiliary Cancer



C Jenssen and C Siebert, Krankenhaus Märkisch Oderland GmbH, Wriezen, Germany
U Gottschalk, Caritas Klinikum-Pankow, Berlin, Germany

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Abstract

Endoscopic ultrasound (EUS) is an inevitable tool for locoregional staging of upper gastrointestinal, rectal, and pancreaticobiliary cancer. Transabdominal ultrasound (TUS) and computed tomography (CT) are the most important methods used for the detection of liver metastases and other distant metastases. However, despite its limited operation range, EUS and EUS-guided fine-needle biopsy (EUS-FNB) may add value to TUS and CT by detecting and proving 'occult' liver metastases and malignant ascites as well as nonregional lymph node metastases, adrenal metastases, and pleural carcinosis in approximately 5–20% of cases of pancreaticobiliary and upper gastrointestinal tract cancer. This article is part of an expert video encyclopedia.

Keywords

Endomicroscopy; Endoscopic ultrasound (EUS); Endoscopic ultrasound-guided fine-needle biopsy; Gastrointestinal cancer; Pancreaticobiliary cancer; Staging; Video.

Video Related to this Article

Video available to view or download at [doi:10.1016/S2212-0971\(13\)70047-5](https://doi.org/10.1016/S2212-0971(13)70047-5)

Materials

- Radial echoendoscope: EG-3670 URK; Pentax Europe GmbH, Hamburg, Germany or longitudinal echoendoscope: EG-3870 UTK; Pentax Europe GmbH, Hamburg, Germany.
- High-end ultrasound platform: HI vision Preirus; Hitachi Medical Systems, Wiesbaden, Germany.
- 22-gauge endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) needles; Olympus Medical Hamburg, Germany; Mediglobe, Achenmühle, Germany.
- SonoVue[®]; Bracco Imaging Deutschland, Konstanz, Germany.

Background and Endoscopic Procedure

The ideal pretherapeutic cancer staging strategy provides reliable information on both locoregional and distant tumor spread. Guidelines recommend computed tomography (CT) and transabdominal ultrasound (TUS) as the most important methods for the detection of liver metastases and other distant metastases in pancreaticobiliary and upper gastrointestinal tract cancer (M-staging).^{1–4} The role of EUS in most guidelines is confined to locoregional staging.^{1,2,4} Despite the high sensitivity of CT in detecting liver metastases and malignant

ascites, due to limited spatial resolution of CT, liver and adrenal metastases < 10 mm, small nonregional lymph nodes metastases (e.g., in the mediastinum) and very small amounts of ascites may escape detection in cancer patients. EUS has been shown to be very sensitive in detecting peritoneal fluid of only several milliliters and also liver metastases down to < 5 mm, which are not detectable by CT.^{5–7} However, EUS is not capable of visualizing the whole liver and all mediastinal, retroperitoneal, and visceral lymph node stations. Several studies have shown a high clinical impact of EUS and EUS-FNA in patients with esophageal, gastric, and pancreatic cancer, far beyond the classification of T-stage and N-stage.⁸ In a recent study in patients with gastric cancer, EUS demonstrated suspected distant metastases in 35% of patients, and EUS-FNA proved distant spread ultimately in 16.2% of patients.⁹ The most frequent locations of distant metastases in this study were mediastinal lymph nodes (65.6%), followed by nonregional abdominal lymph nodes (11.5%), liver metastases (9.8%), malignant ascites (6.6%), and adrenal or omental metastases (each 1.2%). As judged by the board of surgeons, EUS-FNA resulted in a change in the planned management in 14.5% of gastric cancer patients undergoing EUS, avoiding unnecessary surgery and indicating palliative treatment.⁹ Very similar results have been reported for patients with gastric, esophageal, pancreatic, and pancreaticobiliary cancers: in approximately 5–20% of cases distal metastatic spread was proved by EUS and EUS-FNA, changing management plans in most cases.^{10–13} Patients with EUS-FNA-proven distant metastases of upper gastrointestinal and pancreaticobiliary cancer have a very poor prognosis.^{6,14} Therefore, in those patients, surgical exploration and further imaging should be avoided and palliative treatment should be initiated without delay.

Beyond pretherapeutic M-staging, EUS and EUS-FNA may play a pivotal role in detecting and diagnosing recurrence or late distant spread of gastrointestinal cancer.^{15–19} Owing to

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recent progress in palliative treatment, especially of colorectal and gastric cancer, this strength of EUS-FNA should be widely used.

Pitfalls

- False-positive findings of EUS-FNA are reported to occur in approximately 1.1–2.2% of pancreatic cancers and in up to 7.6% of gastric and esophageal cancers.^{20,21} They are due to:
 - Tumor cell contamination of gastrointestinal fluid.^{22,23}
 - Inadvertent needle passage through the primary tumor of the gastrointestinal wall (e.g., gastric cancer).²⁴
 - Inappropriate biopsy sequence.⁸
- Nondiagnostic biopsies or false-negative findings are due to technical failure, sampling error, or interpretation error. Dependent in particular from target tissue, false-negatives may occur in up to 20% of cases.⁸

Key Learning Points/Tips and Tricks

- In 5–20% of pancreaticobiliary and upper gastrointestinal cancers, hitherto unrecognized systemic malignant disease is detected by systematic EUS examination and may be proved by EUS-FNA.
- Endosonographic staging examinations of pancreaticobiliary, esophageal, and gastric cancer should not be restricted to locoregional (TN) staging; moreover, in every patient careful inspection of potential sites of metastatic spread, in particular mediastinal and other nonregional lymph node stations, (left) liver lobe, (left) adrenal gland, and pancreas, should be performed in addition. Ascites, pleural effusions, and peritoneal or pleural nodules should be watched out for.
- EUS-guided fine-needle biopsy (EUS-FNB) should be used to prove distant metastasis, peritoneal carcinosis, or pleural carcinosis in all cases in which other imaging methods have failed, or biopsy guidance by TUS or CT is regarded inappropriate or potentially unsafe.
- Penetration of the needle through obvious neoplastic tissue in the gastrointestinal wall must be avoided.
- According to the rules of TNM-classification,^{25,26} a positive finding of EUS-FNB for distant metastases is classified pM1. Conversely, a negative cytopathological finding is classified cM0 unless, due to clinical and imaging findings, a high suspicion of metastasis is maintained (in this case the correct classification is cM1).
- In cases with suspected distant malignant spread, EUS-FNB should follow an inverse TNM-schedule. Particularly in a patient with a pancreatic mass which is suspicious for pancreatic cancer, a potential distant metastasis should be sampled first. If necessary, the same needle may be used subsequently for biopsy of a locoregional lymph node or of the pancreatic mass itself.
- EUS and EUS-FNB have a high yield for the detection and/or proof of postoperative recurrence of pancreaticobiliary and gastrointestinal cancers, including colorectal cancer. Immunohistochemistry is helpful for differentiation

between recurrence of the previous cancer on the one hand and a second malignant tumor on the other.

Complications and Risk Factors

The complication rate of EUS-FNB is approximately 1–2%.¹⁶ A systematic review demonstrated that EUS-FNB is exceptionally safe for mediastinal lymph nodes (complication rate: 0.38%), abdominal masses (complication rate: 0.26%), and adrenal gland biopsies (complication rate: 0%; only a few case reports of complications). EUS-FNB had an associated overall morbidity of 2.33% for liver lesions and 3.53% for ascites.²⁷ EUS-FNB of ascites carries a low but relevant risk of peritonitis.²⁸ Therefore, the authors propose peri-interventional antibiotic treatment.²⁷

Annotations

In all videos cephalad direction is displayed on the right side of the screen (yellow marker). The following abbreviations are used in images:

- c – Clinical (staging)
- CK – Cytokeratin
- CT – Computed tomography
- EGD – Esophagogastroduodenoscopy
- ERCP – Endoscopic retrograde cholangio-pancreaticography
- EUS – Endoscopic ultrasound
- M – Distant metastasis
- N – Nodal metastasis
- p – Pathological (staging)
- T – (primary) Tumor

Scripted Voiceover

Part 1

Time (min:sec)	Voiceover text
00:00–00:21	Part 1 of the video demonstration describes the role of endoscopic ultrasound (EUS) and EUS-guided fine-needle biopsy (FNB) for the diagnosis of distant metastasis in primary staging of pancreaticobiliary and upper gastrointestinal cancer.
00:22–00:52	Cytopathological proof of distant metastases dramatically changes therapeutic management and prognosis of patients with pancreaticobiliary and gastrointestinal cancer. To avoid false-positive diagnoses, EUS-FNB should follow an inverse TNM-schedule. Following this sequence, the same needle may be used subsequently for biopsy of a locoregional lymph node or of a potential pancreatic primary itself.
00:53–01:20	The first case describes a 78-year-old man presenting with weight loss and abdominal pain. Transabdominal ultrasound shows a large hypoechoic mass lesion of the pancreatic tail and body, but no solid liver lesions.

	(01:05) Computed tomography confirms the large pancreatic mass encasing the celiac trunk and hepatic artery, but also detects several small hypodense liver lesions, highly suspicious for metastases.		This finding is indicative for mediastinal lymph node metastasis, and pretherapeutic tumor classification is cT3 cN0 pM1.
01:21–02:11	From a position in the upper gastric body longitudinal EUS the huge hypoechoic mass lesion and adjacent hypoechoic lymph nodes are shown. (01:37) Turning the scope counterclockwise the left liver lobe is visualized. Liver parenchyma is heterogeneous, and a 1 cm solid lesion is delineated very well. EUS-guided fine-needle biopsy is performed using a 22-Gauge aspiration needle. Three needle passes are performed, and the lesion is fanned by the needle several times.	06:41–07:05	Due to iron deficiency anemia and weight loss, gastroscopy is performed on a 63-year-old female patient. A tumor of the gastric cardia is found, and endoscopic biopsy proves adenocarcinoma. Besides wall thickening of the gastroesophageal junction CT shows small cysts and two suspicious lesions of the left liver lobe.
02:12–02:48	Semi-liquid material is smeared onto glass slides, and small tissue cores are fixed in formaline solution. Both, cytological and histological examinations give evidence for metastasis of a poorly differentiated adenocarcinoma. (02:36) In particular, periodic acid Schiff-staining finely depicts the malignant infiltration of liver tissue. Pretherapeutic tumor stage therefore is cT4 cN1 pM1.	07:06–07:36	Longitudinal EUS is performed and shows infiltration far beyond the gastroesophageal wall with penetration of the gastric serosa and esophageal adventitia, small amounts of ascites, and an adjacent lymph node metastasis. Local tumor stage therefore is cT4a cN1.
02:49–03:12	The second case illustrates the potential of EUS to detect and prove occult liver metastases. A 75-year-old patient presented with obstructive jaundice caused by a small mass lesion of the ampullary region. (03:08) Endoscopic retrograde cholangiopancreatography (ERCP) was performed, and the distal bile duct stricture was drained using a plastic endoprosthesis.	07:37–08:21	Moreover, EUS gives proof of solid liver lesions in the vicinity of small liver cysts, which are harder compared to liver parenchyma. Using a 22-Gauge aspiration needle, a biopsy of the suspicious liver lesion is performed.
03:13–04:15	Longitudinal endoscopic ultrasound shows the hypoechoic mass lesion of the papilla, slight dilatation of the pancreatic duct, and effective drainage of the bile duct. (03:31) Withdrawal of the scope to the stomach allows visualization of the left liver lobe, showing a small, subcentrimetric hypoechoic mass lesion, which was not shown by ultrasound and CT previously. (03:43) Using a 22-Gauge aspiration needle, EUS-guided fine-needle biopsy is performed. Several studies have shown that EUS-guided biopsy of liver lesions is effective and safe with a complication rate of approximately 2.3%.	08:22–08:54	Cytologic and histologic findings confirm liver metastasis. Pretherapeutic tumor stage therefore is cT4a cN1 pM1. Palliative chemotherapy is initiated.
04:16–04:28	Histology of the small liver lesion proves metastatic infiltration with an undifferentiated cancer.	08:55–09:08	A 78-year-old male patient presents with weight loss and vomiting. In gastroscopy a stenosing gastric cancer is found. CT detects no liver metastases.
04:29–06:13	A 58-year-old patient complains about vomiting, bloating, and weight loss. Gastroscopy results in a diagnosis of poorly differentiated cancer of the gastric antrum and body. (04:45) CT shows marked thickening of the gastric wall, but no liver metastases. (04:55) However, enlarged mediastinal lymph nodes and a small nodule of the right lung are found, suspicious for distal malignant spread. (05:09) Longitudinal EUS shows malignant infiltration involving all layers exceeding the muscularis propria without penetrating the serosa, corresponding to a tumor stage cT3. Large infracarinal lymph nodes with focal hypoechoic infiltration are depicted and sampled using a 22-Gauge aspiration needle. Care is taken to target the small hypoechoic areas within the lymph node, which are suspected to harbor small metastatic infiltrations.	09:09–10:00	Longitudinal EUS shows thickening and infiltration of all wall layers. There is high suspicion of subserosal infiltration, but gastric serosa seems not to be penetrated. This finding corresponds with local stage T3, and – according to guidelines – perioperative chemotherapy would be appropriate. However, there is a small amount of ascites, and the perigastric fluid is not completely anechoic. (09:40) This finding is highly suspicious for peritoneal metastasis. Proof of peritoneal carcinosis would change the management of the patient significantly, indicating palliative surgery. However, in this case EUS-guided fine-needle aspiration is not suited for proof of malignant ascites, because the needle would penetrate the primary tumor, potentially being contaminated by tumor cells. Therefore, in this case staging laparoscopy is performed to prove the palliative situation.
06:14–06:40	Histology shows anthracotic lymph node tissue and a so-called anthracosis-granuloma, but no malignant infiltration (06:24). However, smear cytology demonstrates a group of atypical glandular epithelia.	00:12–00:24	Five years after surgery for ampullary cancer, a 72-year-old woman presents with weight loss. Transabdominal ultrasound demonstrates very small amounts of ascites.

Part 2

<i>Time (min:sec)</i>	<i>Voiceover text</i>
00:00–00:12	Beyond pretherapeutic M-staging, EUS and EUS-FNA may play a pivotal role in detecting and diagnosing recurrence or late distant spread of gastrointestinal cancer. This role is highlighted by the following case studies.
00:12–00:24	Five years after surgery for ampullary cancer, a 72-year-old woman presents with weight loss. Transabdominal ultrasound demonstrates very small amounts of ascites.

00:25–00:55	EUS detects several hypoechoic lymph nodes in the subdiaphragmal region in the neighborhood of the left adrenal gland and the celiac ganglia.	04:33–04:50	EUS-guided biopsy is performed using a 22-Gauge standard aspiration needle. Of course, heparin treatment has been interrupted before.
00:56–01:08	Traditional B-mode criteria are typical for malignancy, and real-time elastography supports the suspicion of malignant lymph node infiltration by showing a hard pattern.	04:51–05:32	In good accordance to CT, radial EUS of the rectum shows the mass lesion of the vaginal stump. However, it is not clear, whether this lesion represents the primary tumor of the mediastinal lymph node metastases or rather a pelvic metastasis of the previous cecal cancer. (05:21) Again, in elastography this lesion codes blue, indicating a higher stiffness compared with the surrounding tissue.
01:09–01:24	EUS-guided biopsy is performed using a 22-Gauge aspiration needle. Material is obtained for smear cytology as well as for histology.		
01:25–01:45	The aspirate shows normal lymphocytes and malignant infiltration of the lymph node by a well-differentiated adenocarcinoma.	05:33–05:58	After having changed the echoendoscope, we perform a transrectal EUS-guided biopsy. There is a lot of resistance to the 22-Gauge needle; however, sufficient material is obtained for cytopathological examination. Prophylactic antibiotics have been shown to be dispensable in the case of transrectal EUS-guided biopsy.
01:46–02:36	Turning the scope counterclockwise reveals ascites and peritoneal nodules, which are relatively hard. (02:00) Again, EUS-guided biopsy is performed, targeting the peritoneal nodule. In order to minimize fluid aspiration, no suction is applied. EUS-guided aspiration of ascites carries a relevant risk of peritonitis and therefore has an associated overall morbidity of approximately 3.5%. To prevent infection of ascites, in this case intravenous antibiotics are administered at the time of intervention.	05:59–06:56	Cytological smears and tissue cores from the mediastinal lymph nodes as well as from the pelvic mass show malignant infiltration by an adenocarcinoma. (06:22) Tumor cells stain negative for cytokeratine 7 and TTF1, (06:35) but positive for cytokeratine 20. This is a typical immunophenotype of intestinal adenocarcinoma, and diagnosis of late pelvic and mediastinal metastases of cecal adenocarcinoma is established.
02:37–03:22	Cytologic smears of ascites show papillary groups of epithelial cancer cells. (02:49) Moreover, small tissue cores obtained from the peritoneal nodule prove peritoneal carcinosis. (03:00) Immunostaining is positive for cytokeratine 7. Therefore, diagnosis in this case is late nodal and peritoneal metastasis of ampullary cancer. Palliative treatment is initiated.	06:57–07:40	The last case describes a 61-year-old male patient who was treated 2 years previously with perioperative chemotherapy and surgery for locally advanced gastric cancer. Regular follow-up detects a splenic mass lesion. In abdominal and chest CT there is no other suspicious lesion. (07:15) Because of lung emphysema percutaneous biopsy is considered to be risky, and therefore longitudinal EUS is performed. From a position within the jejunal pouch there is direct endosonographic access to the spleen. The splenic lesion is hypoechoic and heterogeneous. Moreover, it is harder than the surrounding splenic tissue. A malignant splenic tumor is highly probable, and metastasis of gastric cancer is suspected.
03:23–03:46	A 76-year-old woman with a history of colon cancer 7 years previously is admitted to the hospital with hoarseness, acute dyspnea and right femoral thrombosis. (03:36) Chest CT not only detects thromboembolic material with the pulmonary arteries, but also enlarged mediastinal lymph nodes.		
03:47–03:58	Moreover, abdominal CT shows mass lesions of the right iliac fossa and at the vaginal stump 15 years after hysterectomy for large uterine leiomyoma.	07:41–08:13	For EUS-guided biopsy we use the 22-Gauge aspiration needle. Several case series have shown EUS-guided biopsy of splenic lesions to be a safe and effective technique. No serious complications have been described. With only one needle pass we are able to harvest material, which is sufficient for cytological and histological examination.
03:59–04:32	At the moment, there are various possible diagnostic explanations for these diagnostic findings, for example malignant gynecological tumor with mediastinal lymph node metastases or late mediastinal and pelvic metastases of cecal cancer. Longitudinal EUS reproduces the CT findings of suspicious infracarinal pathological lymph nodes (04:22). As expected, these nodes are harder in comparison with the surrounding mediastinal tissue.	08:14–08:59	Both smear cytology and histology show a mixed population of lymphoid cells and infiltration of poorly differentiated adenocarcinoma within fragments. Immunostaining for cytokeratins 7, 5 and 6,

for p63 and for TTF1 is negative. (08:36) However, the tumor cells stain positive for a pancyokeratin marker and for the intestinal marker cyokeratin 20. This constellation confirms the diagnosis of splenic metastasis of gastric cancer. Consequently, splenectomy and adjuvant chemotherapy are planned.

09:00–09:30 if needed longer (10:00)

In conclusion, despite its limited operation range, EUS and EUS-guided fine-needle biopsy may add value to percutaneous ultrasound and CT by detecting and proving 'occult' distant metastases and malignant ascites in approximately 5–20% of cases of pancreaticobiliary and upper gastrointestinal tract cancer. To avoid false-positive diagnoses, penetration of the aspiration needle through neoplastic infiltrations of the gastrointestinal wall must be avoided, and EUS-guided fine-needle biopsy should follow an inverse TNM-schedule. Moreover, EUS and EUS-guided fine-needle biopsy play an important role for the detection and cytopathological proof of postoperative recurrence of pancreaticobiliary and gastrointestinal cancers.

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