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REVIEW

Utility of endoscopic ultrasound and endoscopy in diagnosis and management of hepatocellular carcinoma and its complications: What does endoscopic ultrasonography offer above and beyond conventional cross-sectional imaging?

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Abstract

Hepatocellular carcinoma constitutes over 90% of the primary liver tumors, the rest being cholangiocarcinoma. It has an insidious presentation, which is responsible for the delayed presentation. Hence, the management strategy relies on screening to diagnose it an early stage for curative resection and/or treatment with local ablative techniques or chemotherapy. However, even with different screening programs, more than 60% of

tumors are still detected at an advanced stage, leading to an unchanged mortality rate, thereby implying a room for improvement in the screening and diagnostic process. In the last few years, there has been evolution of utility of endoscopy, specifically endoscopic ultrasonography along with Fine needle aspiration, for this purpose, which we comprehensively review in this article.

Key words: Hepatocellular carcinoma; Liver; Cancer; Fine needle aspiration; Endoscopy; Endoscopic ultrasound; Endoscopic ultrasonography; Staging; Management; Treatment

Core tip: Hepatocellular carcinoma (HCC) constitutes the commonest primary liver cancer, and if diagnosed at an early stage, has better prognosis. Of late, there has been evolution of utility of endoscopic techniques, specifically endoscopic ultrasonography (EUS) with fine needle aspiration, for this purpose. EUS is superior over computed tomography in detecting hepatic lesions smaller than 1cm, and also allows FNA for accurate histopathological diagnosis. This strategy is particularly useful for indeterminate nodules, with non-specific imaging characteristics. Role of EUS in diagnosis and management of HCC are the focus of this article. In addition, other endoscopic techniques, including esophagogastroduodenoscopy and endoscopic retrograde cholangio-pancreatography, are of immense use in management of complications of HCC, which are also briefly discussed in this review.

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INTRODUCTION

Hepatocellular carcinoma (HCC) constitutes the most common primary liver cancer. It is the fifth most frequent cancer and the second commonest cause of cancer related death worldwide[1], the occurrence of which is more in men and increases with age. Over 75% of HCC in the United States is due to hepatitis C and B viral infections. Successful management strategy relies on screening with the help of imaging techniques to diagnose it at an early stage for curative resection and/or treatment with local ablative techniques or chemotherapy. Tumors diagnosed at an early stage have a better prognosis with a five-year survival rate up to 80%[2]. However, more than 60% of tumors are still detected at an advanced stage, thereby implying that there is a room for improvement in the screening and diagnostic process[3]. In the last few years, there have been few studies evaluating the utility of endoscopy, and specifically endoscopic ultrasonography (EUS) along with fine needle aspiration (FNA), for this purpose, which we attempt to review in this article.

Utility of EUS and endoscopy in diagnosis and staging of HCC

Diagnosis of HCC is often difficult and usually occurs late in the course of chronic liver disease because of absence of any pathognomonic signs or symptoms[4]. Even with the current screening strategies, vast majority of cases of HCC are diagnosed at an advanced stage and hence palliative treatments are the only available options[5,6]. Current guidelines for diagnosis of HCC involve frequent monitoring of liver nodules < 1 cm with abdominal ultrasound and advanced imaging for nodules > 1 cm. Imaging options include liver ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) scans[7,8]. Barcelona convention of HCC experts agreed on non-invasive establishment of a radiological diagnosis requiring a > 2 cm focal hepatic lesion in cirrhotic patient confirmed by 2 different imaging techniques. However, for lesions < 2 cm, histological confirmation was deemed necessary[9,10] (Figure 1). The American Association for Study of liver Disease guidelines recommend biopsy of lesions under 2 cm only if there is no pathognomonic imaging (wash out) and an alfa-feto protein (AFP) below 200 ng/mL. This is where EUS may be potentially used safely and effectively to obtain cytology or histology from the lesion, even in patients with cirrhosis.

Traditional esophagogastroduodenoscopy is useful prior to EUS in evaluating the grade of esophageal or gastric varices if any, as lot of these patients have HCC complicating cirrhosis. EUS combines two different investigations-endoscopy and ultrasound-into one, to acquire images from the digestive tract and surrounding organs. Considering its proximity to the surrounding organs, it is more accurate than traditional US. EUS further combined with fine needle aspiration (FNA) or fine needle biopsy (FNB) offers further evaluation of a suspected lesion often with rapid on-site evaluation (ROSE). Currently, it is mostly used for diagnosis and staging of pancreatic cancer and for staging of esophageal cancer[11,12]. However, over the last decade, there have been efforts to define role of EUS in evaluation of liver lesions-particularly metastatic lesions and HCC[13-14], which forms the focus of our discussion.

EUS and EUS-FNA vs other imaging techniques (US, CT and MRI)

The superiority of EUS over CT in detecting hepatic lesions smaller than 1cm was demonstrated as early as 1999[14]. Imaging with CT scans and MRI may have a high miss rate in the diagnosis of HCC. Several studies have reported a sensitivity of 60%-68% with CT scans,

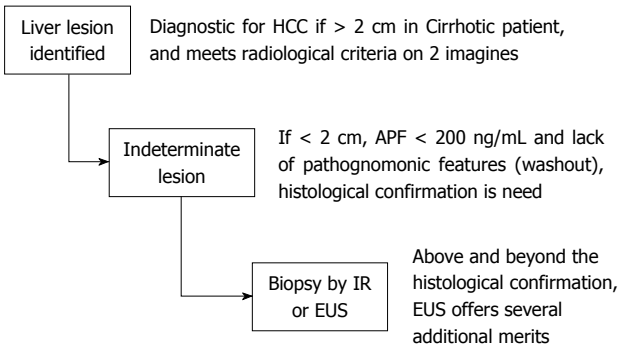

Figure 1 Diagnostic algorithm discussing role of endoscopic ultrasonography (EUS), and potential merits. Potential advantages of EUS in the management algorithm (1) Stratification of indeterminate nodules, especially in high-risk patients, with negative imaging characteristics, which may eventually change the management[14]; (2) In detection and characterization of smaller lesions < 2 cm[14,19,113]; (3) If a lesion is found by EUS, cytology / histology can be obtained in the same session rather than performing another procedure at later time[19]; (4) Assessment of portal vein invasion, spread to other vasculature and lymph nodes[26,118]; (5) The ability to sample enlarged regional lymph nodes for preoperative staging[118]; (6) Therapeutic roles: tumor ablation by intratumoral injection of absolute alcohol, radiofrequency probes, fiducial placement for stereotactic radiotherapy, brachytherapy using radioactive seeds and EUS guided biliary drainage[121]. EUS: Endoscopic ultrasonography.

based on the type of study and the technique of CT scan, for diagnosis of HCC[15,16]. Awad *et al*[17] studied the role of EUS in pre-operative evaluation of HCC, compared it with CT and found EUS to be a feasible investigation for the purpose examined. EUS diagnosed hepatic lesions between 0.3-14 cm, detected new/additional lesions in 28% of patients (all lesions < 0.5 cm), could more reliably detect smaller lesions and successfully differentiated hemangiomas among lesions which appeared suspicious for HCC on CT. In this study, EUS led to change of management in around 67% of patients. In the study by DeWitt *et al*[18], EUS diagnosed malignancy in over 40% with previously negative traditional imaging, having an impact on management in 84% either by making new diagnoses or by upstaging thus avoiding un-necessary surgery. Singh *et al*[19] conducted a prospective study to compare the accuracy of EUS and EUS-FNA with CT for detection of HCC. They found that for diagnosis of HCC, EUS had a sensitivity of 100% as compared to 71% for CT although the specificity and positive predictive values were much lower (25% *vs* 67% and 60% *vs* 71%, respectively)[19]. However, when combined with FNA, EUS had accuracy of 94% in comparison to 69% with CT scan[19]. EUS was able to detect significantly more lesions in the left lobe of the liver, sample hilar nodes (non-feasible by traditional imaging methods)[20] and characterize lesions that were too small and indeterminate for HCC on a CT scan. They proposed a diagnostic algorithm for evaluating high-risk patients with negative imaging. Choudhary *et al*[21] in their prospective study of over 50 patients showed that EUS-FNA of lymph nodes detected in patients with HCC confirmed metastasis and hence precluded transplantation in over a third of the patient cohort.

MRI with angiography has been shown to be better than CT for diagnosis of HCC, the benefit being mostly for detection of nodules between 10-20 mm[22,23]. At present, it is considered the gold standard for staging of HCC prior to surgery[22,24]. The accuracy of EUS alone for accurate diagnosis of liver lesions may only be 65%, but it increases to ~ 94% when combined with FNA which is similar to that of MRI[19]. However, in the same study EUS was found to detect a significantly higher number of nodular lesions than MRI (P = 0.04)[19]. In addition, few other reports have also supported the use of FNA to identify lesions missed by CT scan[25-27], which may be of clinical significance only if their size is over 1 cm, in which case, biopsy could be accomplished at the time of EUS.

Lai *et al*[25], Storch *et al*[26] and Michael *et al*[27], independently demonstrated the safety of EUS-FNA to diagnose HCC as the cause of portal vein thrombosis. In all three reports, CT scan showed portal vein thrombosis without any definite hepatic mass, but FNA of the thrombus was used to diagnose malignant HCC, thus proving it to be a tumor thrombus rather than a bland one, thereby changing the management. In addition to the role of EUS to provide tissue diagnosis, it also provides better visualization of the portal vein and the FNA needle also has to travel a short distance only[28,29]. Doppler ability of EUS helps choose an avascular trajectory for the needle.

Data on utility of EUS in primary diagnosis of hepatic lesions and HCC is limited (Figure 2). One of the earliest studies looking at role of EUS in liver lesions was conducted by Nguyen *et al*[14] who prospectively evaluated the livers of 574 patients with history or suspicion of malignancy with EUS. Hepatic lesions were found in 14 patients, only 3 of who had a lesion previously detected by CT scan. Moreover, amongst these 14 patients, while 7 carried a diagnosis of malignancy, the other 50% received the initial diagnosis with help of EUS-FNA. Since this study did not include any patients with primary HCC, its results cannot be fully extrapolated to HCC patients. Similar studies were conducted by DeWitt *et al*[18] in 2003, Prasad *et al*[30] in 2004 and Crowe *et al*[31] in 2006, underscoring the benefits of EUS and EUS-FNA in diagnosis of liver metastasis (Figure 3). More recently, Fujii-Lau *et al*[32] proposed EUS-derived criteria for distinguishing benign from malignant metastatic solid hepatic masses, but are not specific for HCC. The authors suggested using 7 EUS features, which had fair-moderate inter-observer agreement among expert endosonographers, and yielded an area under the receiver-operating curve (AUC) of 0.92, and overall positive predictive value of 88%.

Previous studies have upheld that diagnosis of HCC is highly dependent on size of the lesion. For lesions < 2 cm, accurate diagnosis requires presence of histologic confirmation, which is currently achieved using CT-guided percutaneous route[33]. EUS with FNA/FNB is an alternate strategy. In their prospective study of 17

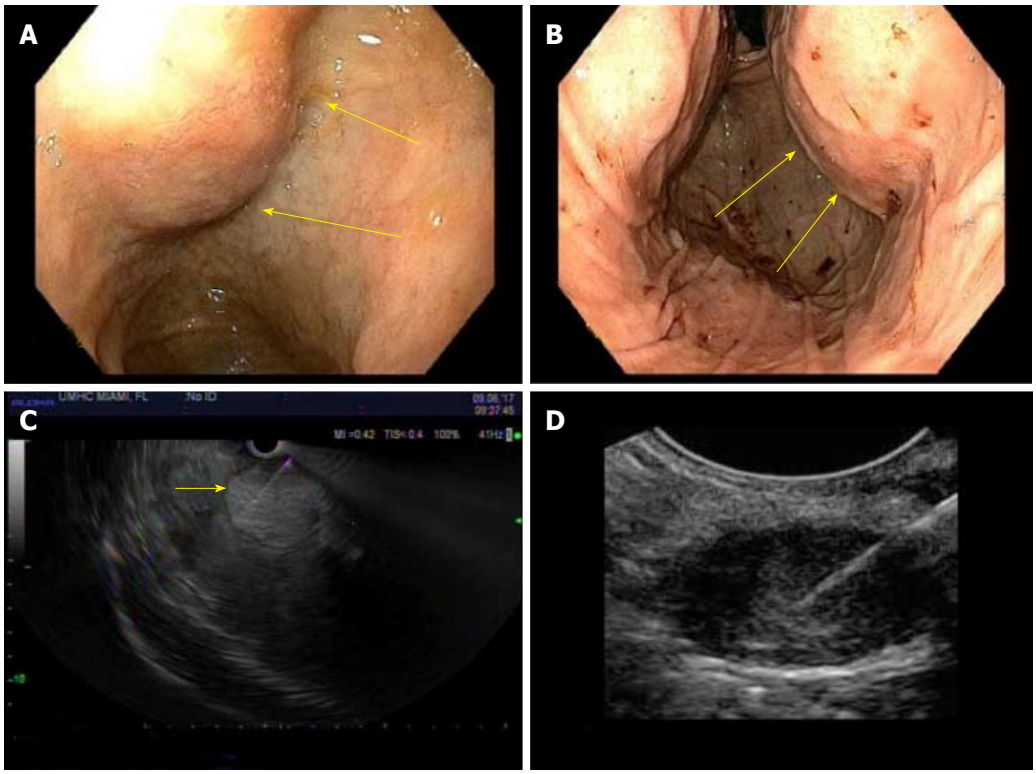

Figure 2 Endoscopic ultrasonography (EUS) diagnosis of primary liver tumors. A and B: Indentations seen in the duodenal bulb and stomach, from large lesions in the right and left lobes of the liver; C: On EUS, the entire liver tissue was seen replaced by numerous hyperechoic lesions of medium size, causing hepatomegaly and hence indentations. Fine needle aspiration (FNA) of a prominent and accessible hyperechoic lesion obtained, which was diagnostic of neuroendocrine tumor; D: In another patient, EUS-FNA of solitary hypoechoic liver lesion obtained, which diagnosed hepatocellular carcinoma.

patients (10 with malignancy), Singh *et al*[19] found 5 lesions < 2 cm, of which three were diagnosed to be malignant using EUS-FNA and the rest two were benign with the smallest lesion to undergo FNA being 4 mm in size. In cirrhosis, hyperintense non-dysplastic nodules are commonly seen on MRI, which may be indistinguishable from dysplastic lesions[34]. This happens more frequently in cases of smaller lesions, which makes it even more difficult to evaluate[35]. Smaller lesions are difficult to characterize by either CT or traditional US as HCC can present with hypoechoic, hyperechoic or isoechoic lesions. Targeted EUS-FNA can be performed on these lesions to obtain histologic confirmation. A multi-centric study reported EUS-FNA to diagnose malignancy in 89% patients, after traditional US guided FNA was non-diagnostic[36]. It is also well known that presence of dysplastic nodules in liver is a major risk factor for development of HCC, especially in presence of HBsAg and anti-hepatitis C virus antibodies[37-39].

Use of endoscopy for staging of HCC

There exist various staging systems for HCC, including American joint committee on Cancer (AJCC) TNM (which does not incorporate hepatic function and reserve, which are major determinants of outcome), Cancer of the Liver Italian Program (CLIP) score, Japanese Staging System and Japan Integrated Staging (JIS) score (which includes TNM + Child-Pugh score), GRoupe d'Etude et de Traitement du Carcinoma Hépatocellulaire (GRETCH) system (which includes serum AFP + liver function parameters and portal vein thrombosis) and Chinese University Prognostic Index (CUPI) (combines conventional TNM + serum AFP + liver function parameters). The Barcelona Clinic Liver Cancer (BCLC) staging system is a comprehensive scheme using variables related to tumor size, number of nodules, liver functional status, physical status, and cancer-related symptoms, and links the five stages described with a treatment algorithm. The purpose of BCLC was to stratify patients into treatment groups according to the extent of the disease and the predicted prognosis[40]. The consensus statement of the American Hepato-Pancreato-Biliary Association, updated in 2010, recommends the use of the TNM system to predict outcomes following resection or liver transplantation and the BCLC scheme for patients with advanced HCC who are not candidates for surgery[41]. Since we know that EUS/EUS-FNA may detect smaller liver tumors more effectively than available imaging, sample the lymph nodes and metastatic lesions, we hypothesize that EUS/EUS-FNA may play a strong role in the diagnosis of indeterminate lesions.

Utility of EUS and endoscopy in general management of a patient with HCC

In addition to EUS improving staging and diagnostic yield of HCC, other endoscopic modalities might play a

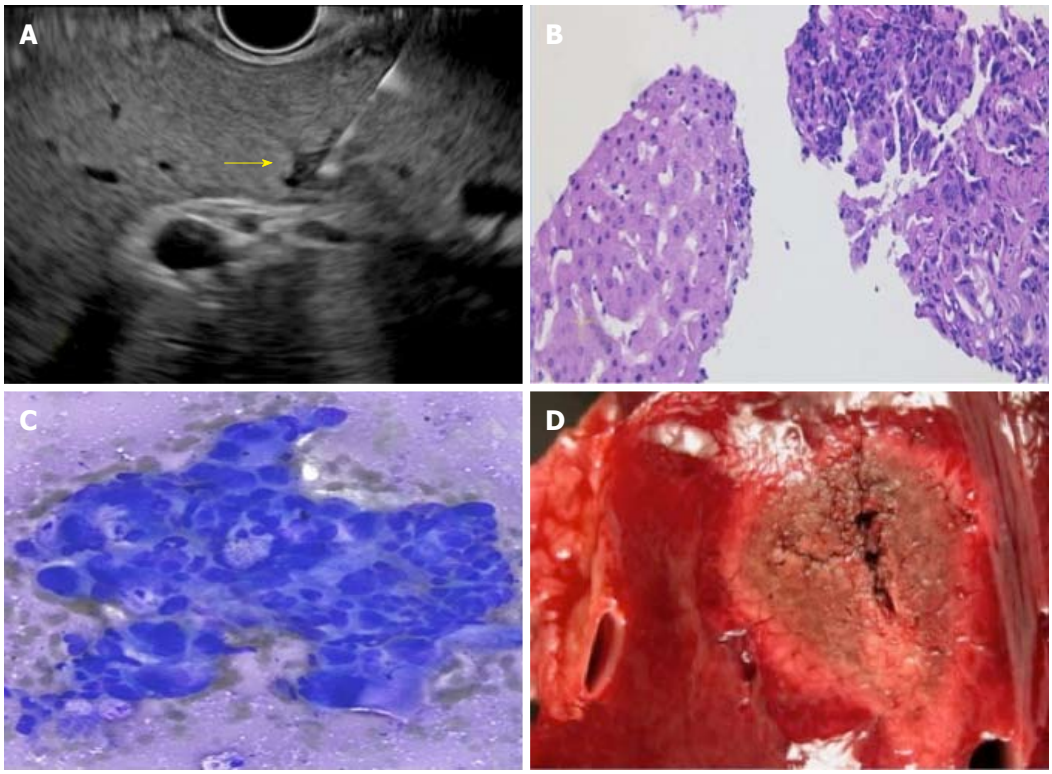

Figure 3 Endoscopic ultrasonography diagnosis of secondary liver lesions. A: Fine needle aspiration performed on small hypoechoic lesion in the liver; B and C: Pathology suggested pancreatic metastatic lesion; D: Partial hepatectomy performed for a solitary metastatic lesion.

role in comprehensive management of these patients. HCC develops on a background of cirrhotic liver in most circumstances; hence all the clinical manifestations of a cirrhotic liver may be seen, ranging from splenomegaly, ascites, and jaundice to formation of varices and variceal bleeding due to portal hypertension (PHT). Esophageal varices are treated with band ligation and rarely with sclerotherapy. However gastric varices may be managed either with endoscopic injection of cyanoacrylate glue or EUS guided coil embolization and glue injection[42]. EUS could also be used to confirm obliteration of the varices, perforators and peri/paraesophageal varices presence of which might predict recurrence[43]. Along with this, occult gastrointestinal bleeding (OGIB) can also be observed in patients with HCC either due to small bowel varices, portal hypertensive enteropathy, metastasis or mucosal erosions which are observed with a higher frequency in patients with HCC[44]. These can be diagnosed with capsule endoscopy (CE) and managed with deep enteroscopy (spiral, single or double balloon). Kunizaki *et al*[45] described a case where a patient with metastatic HCC developed OGIB secondary to a small bowel metastatic lesion diagnosed with double balloon enteroscopy (DBE).

Endoscopic palliation of obstructive jaundice in HCC

Jaundice occurs infrequently in HCC, and only 1%-12% of patients manifest with obstructive jaundice as the initial complaint[46]. Cholestasis occurs due to bile duct occlusion, which may be from benign causes (blood clots, pus, or sludge), malignant causes (primary intra-biliary malignant tumors, HCC with invasion to bile ducts, or metastatic cancer with bile duct invasion) or combination or progressive terminal liver failure (advanced underlying cirrhosis). Furthermore, trans-catheter arterial chemoembolization (TACE) can also increase probability of tumor thrombi obstructing the biliary tree[47]. The ominous features indicative of malignant obstruction are high level of serum AFP, history of cholangitis with dilation of intrahepatic bile duct, aggravating jaundice and rapidly deteriorating liver function[46].

Various endoscopic techniques find utility in such scenarios. Choledochoscopy and bile duct brush cytology are useful endoscopic techniques in differentiating obstruction due to intraluminal mass, infiltrating ductal lesions or extrinsic compression[48-49]. Besides technical difficulties in accessing the bile duct with tumor fragments or protrusion and possible strictures, endoscopic biliary drainage (EBD) is frequently debated because of the short survival of these patients. EBD, achieved *via* bilio-nasal and bilio-duodenal drainage, could be considered for palliation in these patients with obstructive jaundice caused by tumor fragments and/or protruding into the CBD lumen. Endoscopic retrograde cholangiography (ERC) may be diagnostic as well as therapeutic in such cases as it can relieve jaundice *via* biliary stenting[50]. In terms of choice of stent, metal stent is preferred for palliation of malignant biliary obstruction due to larger lumen ensuring patency over longer period of time[51-54]. Plastic stents would be more cost effective if the life expectancy is under 3 mo. Cho

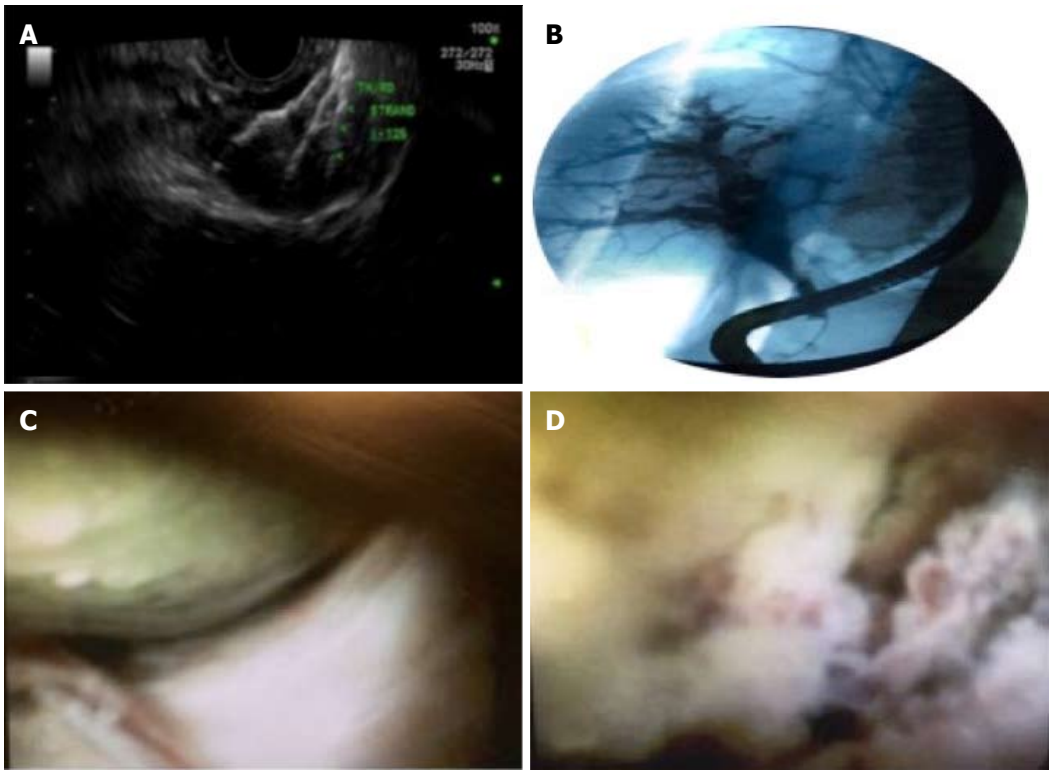

Figure 4 Other novel uses of endoscopic ultrasonography and cholangioscopy in hepatocellular carcinoma diagnosis and management. A: HCC EUS guided Brachytherapy: Radioactive seeds loaded and deployed with endoscopic ultrasound, similar to fiducial placement, as an alternative to transarterial chemoembolization therapy; B, C and D: Patient with choledochal cyst, found to have ectopic HCC, diagnosed with digital cholangioscopy and biopsies[122].

et al[55] evaluated the effects of biliary drainage on clinical outcomes in patients with obstructive jaundice secondary to HCC. They observed that patients with bilirubin >13 mg/dL and Child-Turcotte-Pugh class C did not have effective biliary drainage, which correlated with decreased mean survival time in such patients[55]. Choi *et al*[56] also showed that presence of portal vein thrombosis is also correlated with ineffective drainage of the biliary tree along with the above-mentioned factors. A recent study also advocated that while there was no statistical difference in rate of successful drainage with ERC compared to percutaneous cholangiography (PTC), ERC had longer duration of drainage patency, thus the first choice for palliative biliary drainage[57]. More recently, EUS guided biliary drainage is increasingly being used when endoscopic retrograde cholangiopancreatography fails[58]. Thus, the combination of palliative endoscopic methods may relieve jaundice, ensure a good quality of life and possibly prolong survival of this type of HCC patients.

Utility of EUS and endoscopy in treatment of HCC

HCC tends to stay within the liver, with late occurrence of distant metastases. Hence, early diagnosis and an effective local therapy can have a great impact on the course of the disease and outcome. Curative liver resection and orthotopic liver transplant (OLT) are the best modalities of treatment, however, only 10%-50% of patients get to them due to impaired liver function and the delay in diagnosis[59]. For these reasons, local therapy to treat such subset of patients has garnered a lot of interest, with the modalities including radiofrequency ablation (RFA), microwave ablation (MWA), percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), radioembolization (TARE), cryoablation, brachytherapy, stereotactic radiotherapy (Figure 4), systemic and molecularly targeted therapies (Sorafenib).

Local ablation (using RFA or PEI) is the standard of care for BCLC stage 0-A not suitable for surgery. This can be administered by various routes including laparoscopy, percutaneous route or endoscopy. The latter is still mostly at experimental stage, though there has been progress made over the years. Before the advent of RFA, PEI was the most widely accepted, minimally invasive method for treating such patients. However, RFA has been proven to be a very safe procedure with a reported mortality rate of less than 1% and a complication rate of 3%-7%[60-61]. It is utilized in patients who do not meet the criteria for surgical resection of the tumor or OLT, and has been studied in patients with HCC $\leqslant$ 4 cm[62]. Recent meta-analysis suggests that overall and disease-free survival rates continue to improve with RFA, despite an increase in the size and numbers of tumors treated[63]. RFA has been shown to be more efficacious with higher tissue necrosis rate, decreased local recurrence and higher cancer free survival rates, than other local ablative techniques like PEI[61,64-66]. These facts have been demonstrated

in studies evaluating RFA over a long period of time, which make RFA one of the established treatments for local and small HCC at present[67-71]. However, it is associated with more complications than PEI, especially when RFA is performed on a lesion in proximity to a large vessel or another visceral organ, and may lead to bleeding, hemothorax or gastric perforation[54,72]. RFA can be delivered by either a percutaneous, endoscopic or surgical approach, latter being most invasive[73]. Percutaneous approach is less invasive but is more often associated with tumor seeding[74-75]. On the other hand, open surgical approach is highly invasive with an increased rate of complications. RFA using thoracoscopy or laparoscopy is associated with less blood loss, post-operative complications and duration of surgery while delivering similar success rates for treatment of HCC as open RFA[76-78]. It can also be combined with other local therapies for HCC like TACE which is better than RFA alone[79,80]. With these merits, it's the first line treatment for small sized HCCs that are not suitable for surgical resection and can act as a bridging therapy before liver transplantation. EUS-guided Nd: YAG laser ablation of caudate lobe HCC and EUS-guided ethanol ablation of deep HCC closer to IVC have also been reported[81-82]. Nakaji *et al*[83] showed that twelve patients with early stage HCC of the caudate lobe, who underwent EUS guided ethanol injection, had overall survival rates of 91.7%, 75% and 53% at 1, 2 and 3 years respectively. Recurrence was seen in 2 cases after 3 and 9 mo respectively[83]. Laser ablation *via* percutaneous route has been shown to be useful[84,85]. Di Matteo *et al*[81] successfully delivered Nd:YAG laser ablation *via* EUS in a patient with HCC to obtain encouraging results. Hybrid approach may be an alternative to consider, using percutaneous ablation for deep seated, while endoscopic ablation for superficial HCC[86]. Another example of successful hybrid technique was laparoscopic RFA while cooling bile ducts *via* endoscopic nasobiliary drainage tube, to prevent bile duct injury, to manage HCC located adjacent to the Glisson's capsule in the hilar region in two patients[87]. Conceptually, EUS may also have similar use, especially for easily accessible lesions.

Among patients with large multifocal HCC or noncurative (inoperable/non-ablatable) tumor characteristics, TACE is used as first-line, especially for BCLC stage B multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread. This technique involves the injection into the arteries feeding the tumor, a mixture of a chemotherapeutic agent (doxorubicin, cisplatin, mitomycin, and epirubicin) and embolic material, to potentially obtain higher intra-tumoral drug concentrations compared with intravenous therapy, with occlusion of the blood vessel causing infarction and necrosis, thus causing shrinkage. In future, EUS guided intra-tumoral administration of chemotherapy may be considered. Artifon *et al*[88] utilized EUS to deliver intra-arterial chemotherapy for liver metastases in colon cancer patients. The authors reported a statistically significant decrease in the median hospital stay after such a procedure, while maintaining the safety profile and response rates. This technology is still in a nascent phase.

Microwave ablation (MWA) is a newer loco-regional therapy for HCC, especially in patients who are not candidates for surgical resection. Currently, RFA is the most popular loco-regional therapeutic modality throughout the world, but has significant limitations including higher complication rates, especially in HCC lesions located close to the gallbladder, liver capsule, and diaphragm, or near large vessels, which may be associated with incomplete ablation due to the "heat-sink" effect[89-91]. These situations may render at least 10%-25% of patients with HCC ineligible for RFA[89]. In such difficult to treat tumors, MWA can be offered as an alternative ablation strategy, since it provides a homogeneous and more predictable ablation zone[92-94]. MWA also offers improved efficacy for perivascular tumors, since the faster heating and higher temperatures provided by microwave energy allow heat-sink effect reduction[93,95]. Shibata *et al*[96] demonstrated statistically comparable local control rates of 89% for MWA as compared to 96% for RFA in a randomized study. The survival benefit remains similar in both the techniques with fewer complications associated with MWA as compared to RFA. Shi *et al*[97] reported MWA to be as effective as surgical resection for solitary HCC ≤ 3 cm. The overall 1-, 3-, and 5-year survival rates were 94%, 70%, 52% for the MWA group and 94%, 72%, 60% for the resection group[97].

Transarterial radioembolization (TARE) delivers microspheres impregnated with the radioisotope yttrium-90 (Y90, 90Y) through the hepatic vasculature directly to the target tumor, thus allowing for safe administration of high radiation doses to the tumor burden. This strategy is usually utilized in patients with unresectable HCC, deemed not to be good candidates for TACE, or those with failed prior TACE procedures[98]. TARE is delivered in a lobar fashion, rather than segmental fashion as is TACE, and can target more lesions at the same time. Thus, most of the patients undergoing TARE have much more advanced disease, as compared to those undergoing TACE. Currently, two Y90 products are commercially available: TheraSphere_ glass microspheres (BTG, Canada) and SIR-Spheres_resin microspheres (Sirtex Medical, Woburn, MA, United States). Salem *et al*[99] showed a trend towards a higher response rate for patients who underwent TARE as compared to TACE (49% *vs* 36%, respectively, P = 0.104). Also, time-to-progression was longer following TARE than TACE (13.3 mo *vs* 8.4 mo, respectively, P = 0.046), although median survival times were not statistically different[99]. TARE is associated with fewer side effects, and is considered as an outpatient procedure, as opposed to TACE, which typically requires post-procedure hospitalization. TARE may also be used in patients with portal vein thrombosis and has been shown to downstage patients outside of transplant criteria from UNOS stage T3 to T2, helping them under-

go transplant[100,101].

Contrast-enhanced ultrasound (CE-US) has been demonstrated to have superiority over CE-CT for detection of residual tumors after TACE[102]. With improved imaging technique with EUS, availability of contrast-enhanced option in EUS and its inherent ability to detect smaller lesions, contrast-enhanced EUS (CE-EUS) is emerging as a newer technique to assess the treatment effects of TACE on HCC in the caudate lobe of the liver[103], previously difficult to assess with CE-US.

Treatment of complications

Treatment of HCC by local therapies can result in several serious complications, which may be managed endoscopically. TACE can lead to formation of biliary stricture, variceal bleeding, bile leak and hepatoduodenal fistulae; all of which have been reported to be managed endoscopically[104-107]. A hepatoduodenal fistula is a rare complication, which ideally should be resected surgically. Recently, endoscopic closure of the fistula using histoacryl injection has been described in a case report[104]. Similarly, use of RFA has been associated with the formation of biliocutaneous fistula that can be managed endoscopically[105] and infected biloma drained *via* trans-gastric route[108]. RFA can also lead biliary stricture, which can further lead to sepsis and liver failure. This can be prevented by "cooling" the bile ducts using endoscopic nasobiliary drainage (ENBD) tube, during RFA[106]. Bile leak following TACE for HCC has been successfully managed with choledochoscope-assisted fibrin glue[107].

EUS guided portal vein interventions in HCC: EUS based portal vein interventions are emerging as newer diagnostic and therapeutic techniques in HCC. EUS-FNA can be used to differentiate between a bland *vs* tumor thrombus in the portal vein, which can help us in the correct staging of HCC. The approach for this technique is trans-duodenal (25 gauge needle) which has been shown to cause less sampling errors, thus leading to fewer false positive or negative results, as compared to trans-hepatic approach with US/CT. This technique has also shown to cause less biliary and vascular injury as well. EUS-FNA has also been shown in several case reports in diagnosing tumor thrombus in the portal vein from HCC without visualization of any hepatic mass on the imaging[25-27].

There are few experimental animal studies being performed to assess the efficacy of EUS-guided portal vein chemotherapy injections in anaesthetized pig models. The advantage of this technique will be a higher hepatic and lower systemic chemotherapy drug levels. Thus, it is hypothesized that it may lead to lower systemic toxicities in patients with diffuse liver metastasis[109]. In another animal model, selective PV embolization has been demonstrated for causing the contralateral hypertrophy of the liver lobe. This helps in resection in hepatic malignancies without compromising the liver function[110]. Further human studies are needed to validate the therapeutic benefits of EUS guided portal vein interventions suggested by these animal studies.

Limitations and adverse events related to EUS

In spite of the zeal generated by these studies, like every technique, EUS also comes with its share of controversies and limitations[111,112]. The major criticism is that large-scale studies and randomized controlled trials evaluating the role of EUS in the management of HCC are still lacking. In addition, it may also be associated with multiple technical problems like difficulty to visualize and sample right lobe lesions that need a transduodenal approach[14]. Although sensitivity is high in reported cases, EUS may also miss smaller lesions, especially if farther from the probe, which may also pose challenges when attempting to perform FNA. While lesions in peri-hepatic region, hilum, caudate lobe, left lobe and part of right lobe in proximity to the falciform ligament (Liver segments 1, 2, 3 and 4) may be easy to evaluate with EUS, the remainder of the right lobe (segments 5-8) may pose a technical challenge. There are no studies yet to evaluate which hepatic segments are consistently seen by EUS. Furthermore, not only does EUS add to the overall cost of the work-up, it also involves a long and complex learning curve for the operator, which is yet another Understand factor in this conundrum. This limits its availability and accessibility.

An additional debate in the utility of EUS-FNA for evaluation of liver cancers is the potential for tumor seeding along the needle track and peritoneal spillage, which are known to occur with the more traditional radiologic approach. This has already been reported in pancreatic cancer; but in liver biopsy the increased vascularity of the tumor and the distance between the gut wall and the liver capsule theoretically increases the risk[113]. EUS-guided tissue acquisition is not feasible if an avascular trajectory cannot be obtained when viewed under Doppler. Moreover, pneumobilia, calcification, metal stents, fatty infiltration and fibrosis could interfere with the image quality. Furthermore, HCC being a much more vascular tumor than pancreatic cancer, further augments the potential risk of tumor spillage. However, needle tracking has been observed in less than 2% of cases of percutaneous biopsy and is more common in lesions > 2 cm[114,115], although, analogous data for EUS-FNA is lacking. Complications are more in those individuals with moderate ascites and decompensated liver disease. Though intravenous contrast is not used unlike traditional cross sectional imaging, newer technology like power doppler, tissue harmonic imaging, real time elastography and contrast enhanced imaging offer promise in differentiating various lesions.

Due to the mechanical properties of large echoendoscope, with longer fixed segment at the tip, coupled with learning curve of therapeutic endoscopists, the adverse events with EUS are greater than standard upper or lower endoscopic procedures, perforation being the most feared. Esophageal perforation was noted in 8 of almost 85000 diagnostic EUS in Germany[116], and 16

of almost 44000 EUS in United States[117], half of which were by endosonographers during early learning phase. Duodenal perforation is more common, accounting for 6 of 10 GI perforations reported in a prospective United States registry of almost 14000 EUS[118]. Overall mortality with EUS is reported around 0.02%[118], and another study attributed 73% of all EUS-related mortalities (13/18) to duodenal tears with retroperitoneal perforations[119]. Cognizance of these occurrences is essential for therapeutic endoscopist attempting any of the above-discussed EUS maneuvers. For liver lesions in particular, the overall rate of complications was noted to be approximately 1% in a multi-centric international survey, including biliary sepsis (0.6%), local bleeding (0.6%), fever (1.2%) and pain (1.2%)[36].

CONCLUSION

In summary, we have reviewed the current literature on the utility of endoscopic techniques, with a special focus on EUS, in management of HCC, especially as an adjunct to traditional imaging. The current HCC staging systems and diagnostic guidelines do not yet utilize EUS, as most of the literature on its use is either from retrospective studies or small prospective analysis, without any dedicated randomized controlled trials. However, we have presented the data on the increasing role of EUS in the diagnosis of indeterminate and small lesions, and highlighted the settings where lesions can be better visualized with EUS for diagnosis and treatment. If incorporated on a more regular basis, EUS/EUS-FNA can potentially further help in the accurate staging of HCC, thereby impacting management strategies in selected patients, especially with indeterminate nodules. Other endoscopic modalities find their potential role in the treatment of HCC itself and management of complications as result of current approved treatments. This is an evolving field, and we anticipate greater use of endoscopy in these scenarios with further progression of research in this field, leading to improved clinical care.

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