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Editorial Board Member of *World Journal of Gastrointestinal Endoscopy*, Luiz Gustavo de Quadros, MD, MSc, PhD, Professor, Department of Endoscopy, Beneficência Portuguesa Hospital, ABC Medical School, São Bernardo 15015 110, Brazil. gustavo_quadros@hotmail.com

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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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MINIREVIEWS

Endoscopic ultrasound guided interventions in the management of pancreatic cancer

Tossapol Kerdsirichairat, Eun Ji Shin

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Tossapol Kerdsirichairat, Digestive Disease Center, Bumrungrad International Hospital, Bangkok 10120, Thailand

Eun Ji Shin, Division of Gastroenterology and Hepatology, Johns Hopkins Medical Institutions, Baltimore, MD 21287, United States

Corresponding author: Eun Ji Shin, MD, PhD, Associate Professor, Division of Gastroenterology and Hepatology, Johns Hopkins Medical Institutions, 1800 Orleans Street, Sheikh Zayed Tower/Suite 7125H, Baltimore, MD 21287, United States. eshin3@jhmi.edu

Abstract

There has been a growing interest in developing endoscopic ultrasound (EUS)-guided interventions for pancreatic cancer, some of which have become standard of care. There are two main factors that drive these advancements to facilitate treatment of patients with pancreatic cancer, ranging from direct locoregional therapy to palliation of symptoms related to inoperable pancreatic cancer. Firstly, an upper EUS has the capability to access the entire pancreas–lesions in the pancreatic head and uncinate process can be accessed from the duodenum, and lesions in the pancreatic body and tail can be accessed from the stomach. Secondly, there has been a robust development of devices that allow through-the-needle interventions, such as placement of fiducial markers, brachytherapy, intratumoral injection, gastroenterostomy creation, and ablation. While these techniques are rapidly emerging, data from a multicenter randomized controlled trial for some procedures are awaited prior to their adoption in clinical settings.

Key Words: Endoscopic ultrasound-guided intervention; Pancreatic cancer; Fiducials; Ablation; Intratumoral therapy

Core Tip: Interventional endoscopic ultrasound in pancreatic cancer has been developed *via* a through-the-needle fashion, using 2 techniques: Injection and/or placement. Examples of through-the-needle injection techniques include intratumoral therapy, injection of alcohol and bupivacaine for celiac plexus neurolysis, and hydrogel for bleb formation to create space in the pancreaticoduodenal groove for dose-escalation stereotactic body radiation therapy. Examples of through-the-needle placement techniques include placement of fiducial markers, placement of ablative probes for non-thermal and thermal therapies, placement of radioactive seeds for brachytherapy, and placement of a lumen-apposing metal stent to create a gastrojejunostomy in patients with gastric outlet obstruction. The vast majority of these techniques have shown comparable or superior outcomes when compared to conventional interventions and therapies.

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INTRODUCTION

Pancreatic ductal adenocarcinoma has increased in incidence by 0.3% annually since 2006 and is expected to become the second cause of cancer-related death in the year 2030. It has the lowest 5-year relative survival of 11% compared to other solid organ malignancies, with an estimated death toll of 49830 which closely reflects its incidence of 62210 in 2021[1]. Approximately more than half of the patients presented at the metastatic stage, the highest proportion compared to other solid malignancies, while 13% and 29% presented at localized and regional stages, respectively. For those who present without overt evidence of metastasis, surgical resection is the ultimate goal to hopefully provide curative treatment. With the advancement of endoscopic ultrasound (EUS) in both diagnostic and therapeutic aspects of pancreatic cancer management, it has provided treatment options not only by tissue acquisition to get the definitive diagnosis of pancreatic cancer but also by more accurate local disease control in regional or locally advanced stages while awaiting definitive curative surgical resection and through palliative treatments in those with metastasis or advanced disease[2,3]. This review does not include EUS-guided intervention for malignant biliary obstruction.

EUS GUIDED TISSUE ACQUISITION

An initial randomized trial comparing the 22-gauge aspiration and 22-gauge biopsy needles for EUS-guided sampling of solid pancreatic mass lesions showed comparable diagnostic efficacy, technical performance, and safety profile without a significant difference in yield or quality of the histologic core between the two needle types[4]. Subsequent randomized trials with larger sample sizes were able to demonstrate that fewer passes were required to establish a diagnosis of pancreatic malignancy with improved histopathological quality using a fine needle biopsy (FNB) needle[5-7]. The use of the 25 gauge FNB needle was technically feasible, safe, efficient and was comparable to the standard 22 gauge fine needle aspiration (FNA) needle in patients with solid pancreatic masses in the absence of an on-site cytopathologist. The cytological sample quality in the liquid-based preparation and the histological diagnostic yield for specific tumor discrimination of EUS-guided sampling using a 25 gauge FNB needle were significantly higher than those using a 22 gauge FNA needle[8]. In terms of designs of FNB needle, an opposing bevel design provided significantly superior tissue yield and diagnostic performance when compared to a reverse bevel needle[9]. For second generation FNB needles, the diagnostic yield when used primarily without rapid on-site evaluation, was higher when a fork-tip needle, in comparison to a Franseen needle or FNA needle, was used[10,11]. However, a subsequent larger trial revealed that samples with the highest degree of cellularity in a single biopsy, resulting in a diagnostic accuracy of 90% or higher, were collected by FNB needles using the Franseen or fork-tip needle[12]. Another study showed that a 22-gauge Franseen needle provided more tissue for histologic evaluation and better diagnostic accuracy than a 20-gauge lateral bevel needle. These studies led to the technical guideline from the European Society of Gastrointestinal Endoscopy in 2017 suggesting performance of 3-4 needle passes with an FNA needle or 2-3 passes with an FNB needle when on-site cytologic evaluation is unavailable[13]. There may be some theoretical concern that the high yield of FNB needles might come with the cost of possibly higher risk of tract seeding, especially in patients with a resectable solid pancreatic mass, unless the tract itself is planned to be resected[14]. In terms of technique, the stylet slow pullback technique might enable better acquisition of tissue and increased cellularity for the diagnosis of pancreatic tumors suspected to be malignant, compared to the conventional negative suction after stylet removal technique or the non-suction after stylet removal technique, in the absence

of an on-site cytopathologist.

In the era of personalized medicine, next-generation sequencing (NGS) can serve as a complementary diagnostic test and unveil potentially predictive genomic biomarkers for treatment response[15,16]. An initial experience revealed that NGS can be performed on EUS-FNA-derived samples to provide information on *KRAS* mutation status and 160 other cancer genes such as *TP53*, *SMAD4*, *KMT2D*, *NOTCH2*, *MSH2*, *RB1*, *SMARCA4*, *PPP2R1A*, *PIK3R1*, *SCL7A8*, *ATM* and *FANCD2*, to supplement cytological evaluation[17-21]. Similar to the efficacy of FNB over FNA for cellularity, FNB should be considered when tumor genotyping is requested, as it was associated with a higher yield of sufficient sampling for genomic testing, especially in tumors of 3 cm or smaller, and tumors located in the head/neck of the pancreas[22]. Moreover, recent data indicated that studying the expression of a selected gene set could inform the selection of the most appropriate treatment for patients, moving towards an individualized medicine approach. To accomplish this, adequate EUS tissue acquisition will allow providers to build organoids platform that can allow determination of the transcription level of informative genes[23]. Early studies were able to demonstrate the successful isolation of organoids using samples obtained from a 22-gauge FNB needle at the time of the initial diagnosis, which may be helpful in patients with pancreatic cancer that are not surgically resectable[24,25].

EUS GUIDED PLACEMENT OF FIDUCIAL MARKERS

For patients with borderline resectable or locally advanced pancreatic cancer, neoadjuvant chemoradiation plays a vital role. While chemotherapy can potentially control systemic disease, local disease control by radiation therapy has shown additional benefit to hopefully reduce local recurrence after surgical resection[26,27]. Stereotactic body radiation therapy (SBRT) and image guided radiation therapy (IGRT) have increasingly been used in clinical practice since they can provide a higher dose of radiation with a shorter duration of treatment and acceptable rates of toxicity[28]. To be able to focally deliver radiation to the pancreas, which is an organ that moves following respiratory cycles, fiducial marker placement is recommended[29]. The markers are traditionally metallic, made of gold or platinum, or more recently, in hydrogel form, to serve as reference points for planning as well as follow-up daily image guidance over a short course of SBRT/IGRT. EUS-guided fiducial placement has evolved to become the technique of choice to place these fiducial markers, compared to conventional techniques where the markers are either placed surgically or percutaneously under cross-sectional imaging guidance such as computed tomography (CT) or transabdominal ultrasound[30]. The ideal characteristics of fiducial markers should have good visibility, minimal artifacts, and minimal migration over the course of SBRT/IGRT. Fiducials with larger diameters usually provide better visibility, at the cost of greater artifact. Furthermore, fiducial delivery systems that require a 19-gauge needle can pose challenges for EUS-guided fiducial placement when lesions are located at the pancreatic uncinate process. Therefore, the fine balance and preferred types of fiducials should be discussed in a multidisciplinary tumor board setting, especially between the endosonographers and the radiation oncologists. Generally, balanced visibility and artifacts can be achieved with a 0.35- to 0.43-mm diameter, 5- to 10- mm length, coiled or cylindrical gold fiducials[31]. A comparison study of these types of gold fiducials and the newer generations of fiducials, such as platinum or hydrogel, is still in process. A theoretical benefit of hydrogel compared to other metallic fiducials is that it can be injected *via* EUS in a liquid bleb formation to create additional space in the pancreaticoduodenal groove to separate the pancreatic head/neck cancer from the adjacent duodenal C loop (Figure 1) to allow for dose escalation during SBRT/IGRT while avoiding mucosal toxicity to the duodenum[32,33].

EUS-GUIDED INTRATUMORAL THERAPY

Given the close proximity of the probe of the therapeutic echoendoscope and several technologies that can be delivered through FNA needles, multiple modalities for local therapies of pancreatic cancer have been developed. These include placement of radiosensitive devices for brachytherapy, injections of antitumoral agents, access for passing through-the-needle probe for ablative devices, and photodynamic therapy.

EUS-GUIDED BRACHYTHERAPY

Intraoperative interstitial brachytherapy when used at laparotomy can improve local disease control in locally advanced pancreatic cancer. An initial animal study from China implementing EUS as a route for the implantation of radioactive seeds was proven safe and feasible. Shortly after, the group conducted a feasibility study in 15 patients who suffered from unresectable pancreatic cancer, showing 30% of patients had clinical benefit, with complications including pancreatitis and pancreatic fluid collection in

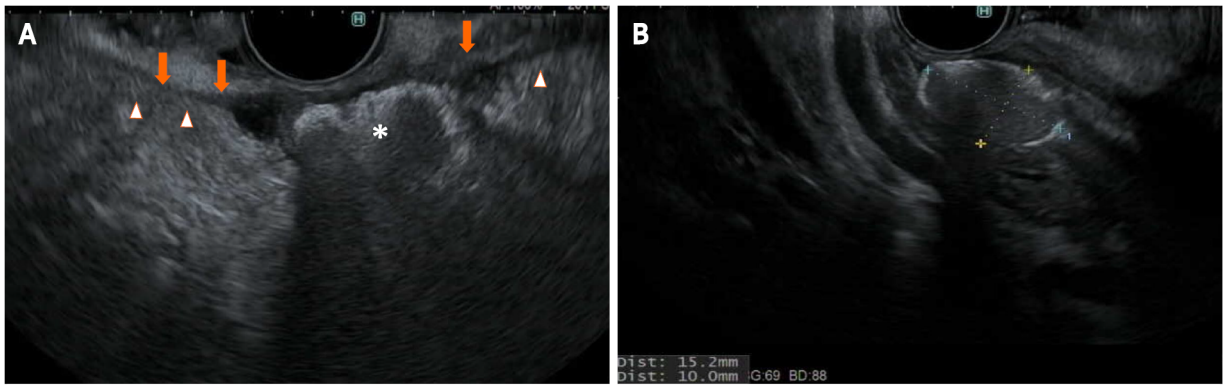

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Figure 1 Pancreaticoduodenal. A: A hydrogel bleb (asterisk) in the pancreaticoduodenal groove. The arrows demonstrate the line of the duodenum. The arrowheads demonstrate the line of the pancreas; B: The size of the hydrogel bleb, measured at 15.2 mm by 10 mm.

20% of patients. This was followed by a prospective cohort of 22 patients with unresectable pancreatic cancer who were treated with radioactive iodine 125 seeds, which resulted in 14% partial remission at 4 wk, 45% with stable disease, and 91% later succumbed to the disease at 2-year follow-up. Another group in China conducted a pilot study in 8 patients with T4 pancreatic cancer, using both intratumoral radioactive seeds and 5-fluorouracil, resulting in a 12% partial response at 3 mo, with overall 50% clinical benefits including a reduction in pain, without complications or hematologic toxicity[34]. Another prospective study showed that EUS-guided implantation of iodine-125 around the celiac ganglia can reduce pain visual analog scale score and analgesic drug consumption in patients with unresectable pancreatic cancer. A special EUS treatment planning system software may play a role in EUS-guided brachytherapy in patients with unresectable cancer, as it demonstrated a rate of partial remission of up to 80% in patients whose minimal peripheral dose was larger than 90 Gy, with a median survival time of 9 mo[35]. In addition to survival benefits, iodine-125 seed implantation placed percutaneously or *via* EUS after relief of obstructive jaundice *via* ERCP can improve biliary stent patency, time to development of gastric outlet obstruction, and improve quality of life by pain relief [36]. More recently, EUS guided placement of phosphorus-32 microparticles alone or with gemcitabine with or without nab-paclitaxel in unresectable locally advanced pancreatic cancer has been reported as alternative brachytherapy options[37,38]. The latter is an ongoing trial.

EUS-GUIDED INJECTION OF ANTITUMORAL AGENTS

Immunotherapy

The hypothesis of intratumoral therapy was based on that of other malignancies where both local disease control effect and systemic response effect (*i.e.*, metastasis) can be achieved through the immune response against the tumors, including breast cancer, renal cell carcinoma, and melanoma[39-43]. In addition, immunological responses induced by zoledronate-pulsed dendritic cell-based vaccines have been associated with therapeutic effects in clinical trials[44,45]. The first pilot study in patients with unresectable pancreatic cancer treated with EUS-guided injection of allogeneic mixed lymphocyte culture proved its feasibility and safety profile[46]. Subsequent pilot studies included an injection of immature dendritic cells in pancreatic cancer refractory to gemcitabine[47], a combination of systemic gemcitabine and intratumoral OK-432-pulsed dendritic cell therapy, followed by an intravenous infusion of lymphokine-activated killer cells stimulated with an anti-CD3 monoclonal antibody[48], and dendritic cell-based vaccination and concomitant chemotherapy in patients with advanced or recurrent pancreatic cancer[49]. The first phase 1 comparative trial of intratumoral injection of immature dendritic cells and OK-432 for resectable pancreatic cancer patients had one in nine patients with transient fever. Two out of nine patients treated with immunotherapy, one of whom had stage IV with distant lymph node metastasis, survived five years without further adjuvant therapy[50]. In a phase I/II trial of comprehensive immunotherapy combined with intratumoral injection of zoledronate-pulsed dendritic cells, intravenous adoptive activated T lymphocytes, and gemcitabine in unresectable locally advanced pancreatic cancer, a synergistic therapeutic response was shown with overall survival and progression-free survival of 12 and 5.5 mo, respectively[51]. To date, there has not been a study of EUS-guided intratumoral injection of other types of immunotherapy such as ipilimumab or nivolumab (Figure 2).

Chemotherapy

Pancreatic cancer is unfortunately insensitive to many chemotherapeutic drugs. It is thought that

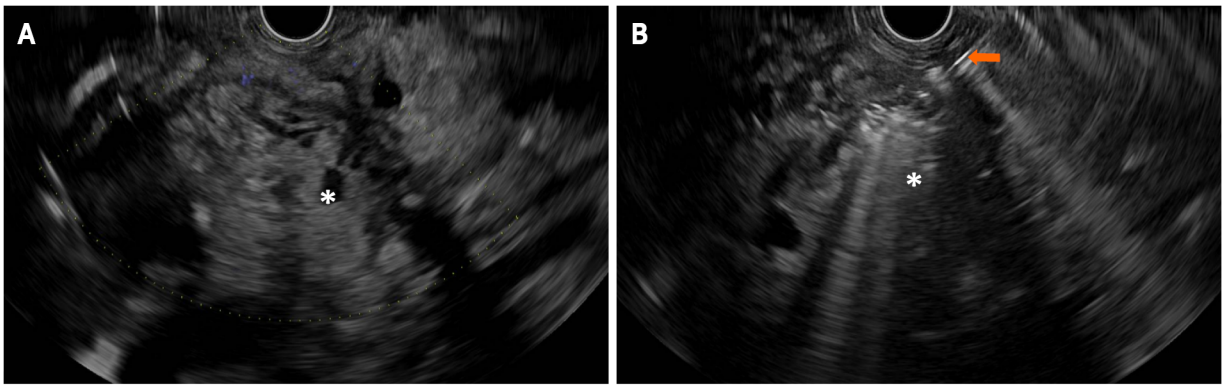

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Figure 2 Immunotherapy. A: An ill-defined heterogeneous mass of known pancreatic ductal adenocarcinoma (asterisk); B: Fine needle injection for intratumoral therapy. The arrows demonstrate a 19-gauge needle. The asterisk indicates the hyperechoic blush of the injectate.

inefficient delivery of chemotherapy into the tumor plays an important role in chemoresistance in pancreatic cancer. A combination therapy that can increase intratumoral vascular density and intramural concentration of gemcitabine was shown to lead to a transient stabilization of disease[52]. The initial experience using OncoGel (Regel/paclitaxel) for local tumor management *via* EUS guided 22-gauge needle in a pig model provided high and sustained localized concentrations of paclitaxel. A feasibility study using EUS-guided injection of gemcitabine in 38 patients with locally advanced and metastatic pancreatic cancer confirmed the safety and efficacy of the technique. More recently, a feasibility study of EUS guided injection of a novel polymer-based microparticles for a drug delivery system in a pig model appeared promising[53]. A phase I study evaluating the role of EUS guided injection of epidermal growth factor receptor antibody cetuximab as a radiosensitizer with chemoradiation for locally advanced pancreatic cancer in 16 patients proved its feasibility and safety profile when administered with abdominal radiation and concurrent gemcitabine. The incidence of grade 1-2 adverse events was 96% and the incidence of grade 3-4 adverse events was 9%[54].

Gene therapy

An initial feasibility study in 21 patients with locally advanced or metastatic pancreatic cancer treated with EUS guided injection of ONYX-015 (dl1520), an E1B-55kD gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells, was promising and generally well-tolerated either alone or in combination with gemcitabine[55]. In a multi-center feasibility study of 50 patients, intratumor delivery of TNFerade biologic (AdGVEFR.TNF.11D), a replication-deficient adenoviral vector that expresses tumor necrosis factor-alpha under the control of the Egr-1 promotor, by EUS-guided injection or percutaneously, combined with chemoradiation in the treatment of locally advanced pancreatic cancer, appeared promising, especially at the maximal tolerated doses. Adverse events such as cholangitis and pancreatitis were observed in 6%. The rate of patients who were able to proceed with surgery and achieve negative margin resection was 12%. In a randomized trial of 304 patients, treatment with TNFerade plus standard of care was safe but not effective for prolonging survival in patients with locally advanced pancreatic cancer[56].

For patients with unresectable pancreatic cancer, an open-label, dose-escalation trial using BC-819, which is a DNA plasmid developed to target the expression of diphtheria-toxin gene under the control of H19 regulatory sequences, in combination with systemic chemotherapy, may provide an additional therapeutic benefit, with minimal adverse events such as asymptomatic elevation of lipase[57]. EUS-guided injection of HF10, a spontaneously mutated oncolytic virus derived from herpes simplex virus 1 that has the potential to show a strong antitumor effect against malignancies without damaging normal tissue, in combination with erlotinib and gemcitabine, was a safe treatment for unresectable locally advanced pancreatic cancer[58]. The EUS-guided injection of STNM01, the double-stranded RNA oligonucleotide that specifically represses carbohydrate sulfotransferase-15, was safe and feasible without any adverse events. The authors also proposed that injections of STNM01 during the start of treatment could lower carbohydrate sulfotransferase-15 level, while its overexpression was associated with worse prognosis[59,60].

An open-label phase 1/2a study in the first-line setting of patients with inoperable locally advanced pancreatic cancer using an EUS guided injection of siG12D-LODER to release a siRNA drug against KRAS (G12D), along with systemic chemotherapy, was promising in terms of potential efficacy that 70% had a reduction in tumor marker CA 19-9, and 80% of patients had either stable disease or partial response with a median overall survival of 15 mo. However, one third of patients experienced serious adverse events.

EUS-GUIDED ABLATIVE THERAPIES

Radiofrequency ablation

Radiofrequency ablation is a local ablative method that can destroy the tumor by thermal coagulation and protein denaturation[61]. A phase II pilot study using radiofrequency ablation *via* a laparotomy in patients with locally advanced pancreatic cancer showed its feasibility and safety profiles with a 24% complication rate, with 9% requiring a reoperation. After a feasibility study in a porcine model, a feasibility study of using EUS-guided radiofrequency ablation of unresectable pancreatic cancer showed promising safety data, with one-third of the patients only developing mild abdominal pain without pancreatitis. The safety profile of the technique was later confirmed by subsequent feasibility studies showing no evidence of early or late major adverse events[62,63]. However, it required an 18-gauge electrode, which could be challenging for the treatment of lesions located in the pancreatic head or uncinate process. A new monopolar radiofrequency probe may be technically more versatile because it can be used through a 22-gauge needle[64]. In patients with locally advanced pancreatic cancer treated with EUS-guided radiofrequency ablation, those with wild-type SMAD4 may have improved survival benefits after treatment[65]. For other solid pancreatic lesions such as pancreatic neuroendocrine tumors and pancreatic insulinoma, EUS-guided radiofrequency ablation has shown clinical benefits such as fewer episodes of hypoglycemia[66,67], regression of neuroendocrine syndromes, improved pancreatic cystic sizes, and complete radiological ablation[64] A prospective study of 29 patients using EUS-guided radiofrequency ablation for pancreatic neuroendocrine tumors (PNET) and pancreatic cystic neoplasms revealed an overall tumor resolution of 86% in PNET and a significant response rate of 71% of patients with cystic neoplasms, with an overall complication rate of 10%.

Another application of radiofrequency ablation is to use it along with a simultaneous cryogenic cooling of carbon dioxide. An animal feasibility study was promising, given that only 14% of pigs developed histochemical pancreatitis after the procedure. The group has expanded this technique to 16 explanted pancreatic tumors from 16 patients, showing that the flexible bipolar ablation device, combining radiofrequency and cryotechnology, can create an ablation zone, defined by histological signs of coagulative necrosis, and that the extent of the ablation zone was related to the duration of application. However, data on this technique in in-vivo studies are still forthcoming.

Laser ablation

An initial animal study using a neodymium-doped:yttrium aluminum garnet (Nd:YAG) was based on the finding that the ablation resulted in a high rate of tissue necrosis and can be considered as a palliative option in patients with hepatocellular carcinoma, liver metastases in colorectal cancer, and malignant thyroid nodules[68-72]. There was no major post-procedural complication and all 8 pigs survived at 24 h after EUS-guided laser ablation of normal pancreatic tissue. The same group conducted another animal study to evaluate tissue temperature distribution, which plays a crucial role in the outcome laser-induced thermal therapy, proving that the tissue downward from the tip is mostly heated at 60 Celsius degree. The authors further conducted a human feasibility study in nine patients with unresectable pancreatic cancer who were unresponsive to previous chemoradiotherapy. Laser ablation was performed by using a 300-micrometer flexible fiber preloaded onto a 22-gauge fine needle. A 1064-nanometer wavelength Nd:YAG was used at different settings (2-4 Watts and 800-1200 Joules), resulting in an ablation area ranging from 0.4 cm^3 with the setting of 2 Watts and 800 Joules, to 6.4 cm^3 with the setting of 4 Watts and 1000 Joules, without adverse events. A comparative study using laser ablation compared to other EUS-guided techniques for patients with unresectable pancreatic cancer is awaiting.

Photodynamic therapy

EUS-guided photodynamic therapy has two steps: An injection of a photosensitizing agent, followed by the insertion of a 19-gauge needle into the targeted area to pass a small quartz optical fiber to illuminate and ablate tissue with the laser light. Initial pilot studies in porcine models using EUS-guided photodynamic therapy appeared promising. In a rabbit model, the efficacy of verteporfin delivery in tumors can be estimated by perfusion CT, to serve as a non-invasive method of mapping photosensitizer dose to enhance the outcomes of ablation with photodynamic therapy[73]. A human feasibility study in four patients with locally advanced pancreaticobiliary malignancies using a second-generation photosensitizer, a chlorin e6 derivative, and a flexible laser probe was promising, with a median volume of necrosis of up to 4 cm^3, no progression of disease over a median follow-up of five months, and no post-procedural complications. A prospective dose-escalation phase 1 study in 12 patients with treatment-naive locally advanced pancreatic cancer using intravenous porfimer sodium and illumination with a 630-nanometer light, followed by a CT scan to document change in pancreatic necrosis, and nab-paclitaxel and gemcitabine, showed an increased volume and percentage of tumor necrosis in 50% of patients after EUS-guided photodynamic therapy, without procedurally related adverse events. Another human feasibility study, which excluded patients with significant metastatic disease burden, disease involving > 50% duodenal or major artery circumference, and recent treatment with curative intent, investigated EUS-guided photodynamic therapy using a different photosensitizer, verteporfin, resulting in tissue necrosis in 62.5% of patients, with a mean diameter of 15.7 mm, and no

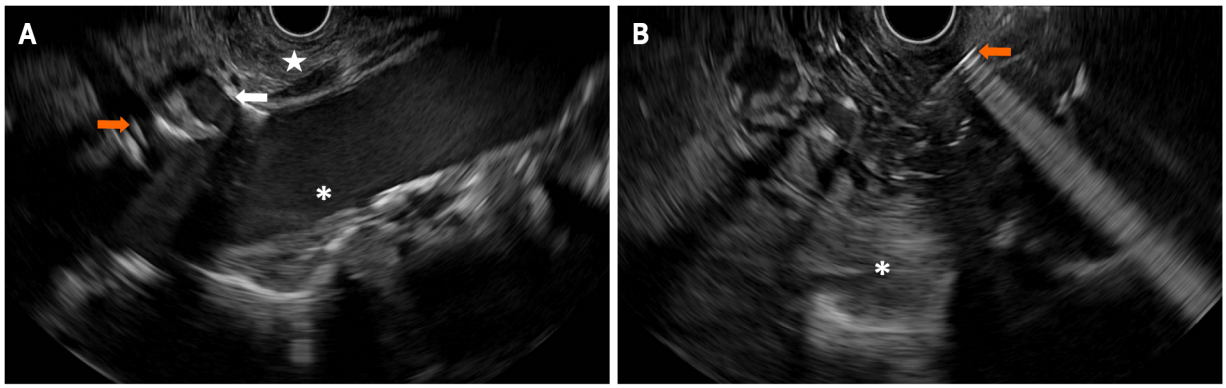

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Figure 3 Endoscopic ultrasound guided celiac plexus neurolysis. A: The structures while the echoendoscope is located at the posterior proximal gastric body/gastric cardia. A star demonstrates the pre-celiac region. The white arrow demonstrates the celiac trunk. A orange arrow demonstrates the superior mesenteric artery. An asterisk indicates the descending abdominal aorta; B: An area of hyperchoic blush of injected dehydrated alcohol (asterisk) delivered from a 19-gauge needle (arrow) for celiac plexus neurolysis.

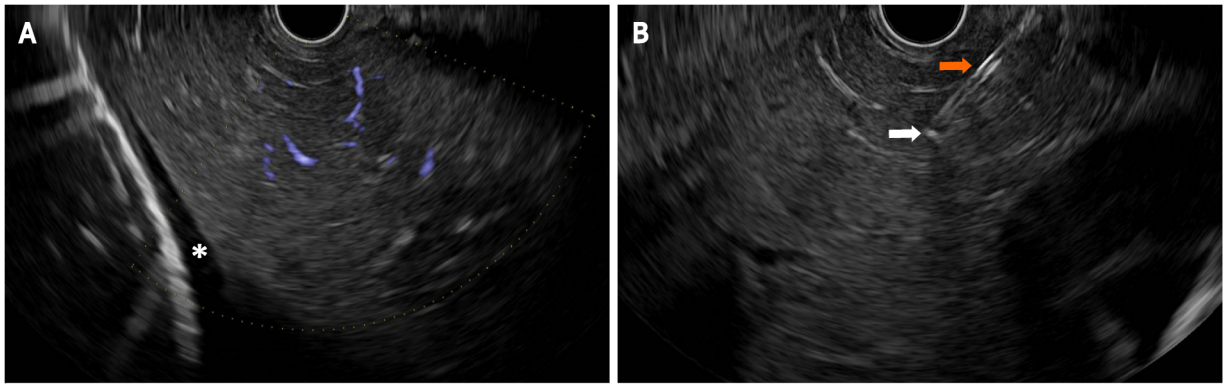

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Figure 4 Endoscopic ultrasound guided liver biopsy. A: Liver parenchyma without major intervening intrahepatic blood vessels, which is an optimal location for endoscopic ultrasound-guided liver biopsy. An asterisk indicates a small amount of perihepatic ascites; B: An endoscopic ultrasound-guided liver biopsy using a heparin-primed wet-suction technique *via* a 19-gauge Franseen needle tip design. The hyperechoic tip of the needle (white arrow) and the shaft of the needle (orange arrow) must be visualized at all times during the fine needle biopsy of the liver.

post-procedural related complications.

Alcohol

The vast majority of studies using EUS-guided ethanol ablation for solid pancreatic tumors are focused on non-functioning pancreatic neuroendocrine tumors and insulinoma[74-76]. Data of EUS-guided ethanol ablation in pancreatic ductal adenocarcinoma, especially in combination with EUS-guided celiac plexus neurolysis, are still needed.

EUS GUIDED CELIAC PLEXUS NEUROLYSIS

EUS-guided celiac plexus intervention has gained popularity in the management of pain from pancreatic cancer due to its safety profile when compared to narcotics[77]. An initial meta-analysis and systematic review showed that the pooled proportion of patients with pancreatic cancer treated with EUS-guided celiac plexus neurolysis had pain relief up to 53%-80% of the time[78-80]. The first randomized controlled trial in 96 patients assigned to either EUS-guided celiac plexus neurolysis or conventional pain management, showed that early EUS intervention reduced pain and may have moderated morphine consumption in patients with painful, inoperable pancreatic cancer, especially at 3 mo after treatment[81]. While the number of injections might not improve the degree of pain relief[82], the targeted celiac ganglia neurolysis was superior to celiac plexus neurolysis. EUS-guided radiofrequency ablation, using a 1 French monopolar probe passed through a 19-gauge targeting the area of celiac plexus or visualized ganglia, showed superiority in pain relief and improved quality of life when

compared to traditional EUS-guided celiac plexus neurolysis. However, a recent study raised the concern that combined celiac ganglion and plexus neurolysis may reduce median survival time without improving pain, quality of life, or adverse events when compared to traditional celiac plexus neurolysis. Furthermore, newer generations of opioids such as oxycodone and fentanyl may be comparable to EUS-guided celiac plexus neurolysis in terms of pain relief, quality of life, and opioid consumption (Figure 3).

EUS GUIDED GASTROENTEROSTOMY

Approximately 50% of patients with pancreatic cancer develop nausea and vomiting from malignant gastric outlet obstruction[83]. In patients with an inoperable stage, this was traditionally managed by endoscopic enteral stent placement or surgical gastrojejunostomy creation, depending on life expectancy. EUS-guided gastroenterostomy creation using a lumen apposing metal stent has emerged and gained in popularity due to a higher rate of initial clinical success and/or a lower rate of stent failure requiring repeat intervention when compared to enteral stent placement[84-86]. Compared to surgical approaches for gastrojejunostomy, EUS-guided gastroenterostomy was associated with fewer adverse events[87,88], shorter time to resume oral intake and chemotherapy, shorter lengths of stay, and reduced hospital costs. The technique of EUS-guided gastroenterostomy has been developed over time. The direct technique, defined by using an electrocautery-enhanced lumen-apposing metal stent, rather than a balloon-assisted approach, resulted in shorter procedure time and comparable clinical success (> 90%). In addition, the clinical success of direct-EUS-guided gastroenterostomy is durable with a low rate of re-intervention based on a long-term cohort[89]. Randomized trials comparing these endoscopic and surgical interventions for palliation of malignant gastric outlet obstruction caused by pancreatic cancer are awaiting. It should be noted that the learning curve of the technique can be challenging as it requires up to 40 procedures to achieve competency, otherwise fatal adverse events can occur at a very high rate (> 10%).

EUS GUIDED LIVER BIOPSY

Immune checkpoint inhibition targeted against cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death protein 1 has shown survival benefit to treat multiple types of advanced cancer, including pancreatic cancer. Hepatotoxicity from checkpoint Inhibitors is a less common type of immune related adverse events, and it is often mild[90,91]. Concurrent treatment with nivolumab and ipilimumab, which is commonly used in pancreatic cancer, increases the risk of hepatotoxicity up to 37% and the risk of high-grade toxicity by up to 15%[92,93]. In complicated or severe forms, or unclear etiologies, liver biopsy can be used to confirm the etiology of injury[93,94], and/or to clarify the diagnosis in those with elevated liver enzymes refractory to steroid or immunosuppressant treatment [95].

EUS-guided liver biopsies have increased in popularity due to their decreased invasiveness compared to surgical routes and comparable tissue acquisition compared to transjugular or percutaneous route [96]. Bilobar liver biopsies, with one needle pass with three to-and-fro needle movements to each lobe of the liver, enhanced the assessment of disease severity due to an increased number of complete portal tracts, and longer aggregate specimen length, without severe adverse events[97]. A 19-guage Franseen-tip or reverse bevel core needle outperformed FNA needles or other types of core needles, resulting in longer aggregate length, more complete portal tracts, and more adequate specimens despite fewer passes. A heparinized wet suction technique can improve tissue adequacy compared with dry needle techniques. A randomized trial using these specific techniques for EUS-guided liver biopsies, compared to other conventional approaches, is needed (Figure 4)[98].

CONCLUSION

EUS-guided interventions provide a broad spectrum of treatment modalities for patients with borderline resectable, locally advanced, and inoperable pancreatic cancer. These include direct treatment for locoregional stages such as ablative therapies, brachytherapy, placement of fiducial markers for SBRT/IGRT, as well as palliative treatments such as EUS-guided gastroenterostomy creation for malignant gastric outlet obstruction and EUS-guided celiac plexus neurolysis to manage pain. While many of these procedures are considered investigational with limited data, particularly those from randomized controlled trials, the vast majority of these techniques have been widely used in clinical practice. For patient safety, it is important to note that most of these procedures should be performed at a facility with a multi-disciplinary tumor board and experienced interventional endosonographers.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Tossapol Kerdsirichairat 0000-0002-6265-2026; Eun Ji Shin 0000-0003-0624-8149.

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MINIREVIEWS

Role of endoscopic ultrasound in esophageal cancer

Mark Radlinski, Vanessa M Shami

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Mark Radlinski, Internal Medicine, University of Virginia, Charlottesville, VA 22901, United States

Vanessa M Shami, Digestive Health Center, University of Virginia Health System, Charlottesville, VA 22901, United States

Corresponding author: Vanessa M Shami, MD, Professor, Digestive Health Center, University of Virginia Health System, POB 800708, Charlottesville, VA 22901, United States. vms4e@hscmail.mcc.virginia.edu

Abstract

Esophageal cancer (ECA) affects 1 in 125 men and 1 in 417 for women and accounts for 2.6% of all cancer related deaths in the United States. The associated survival rate depends on the stage of the cancer at the time of diagnosis, making adequate work up and staging imperative. The 5-year survival rate for localized disease is 46.4%, regional disease is 25.6%, and distant/metastatic disease is 5.2%. Additionally, treatment is stage-dependent, making staging all that much important. For nonmetastatic transmural tumors (T3) and/or those that have locoregional lymph node involvement (N), neoadjuvant therapy is recommended. Conversely, for those who have earlier tumors, upfront surgical resection is reasonable. While positron emission tomography/computed tomography and other cross sectional imaging modalities are exceptional for detecting distant disease, they are inaccurate in staging locoregional disease. Endoscopic ultrasound (EUS) has played a key role in the locoregional (T and N) staging of newly diagnosed ECA and has an evolving role in restaging after neoadjuvant therapy. There is even data to support that the use of EUS facilitates proper triaging of patients and may ultimately save money by avoiding unnecessary or futile treatment. This manuscript will review the current role of EUS on staging and restaging of ECA.

Key Words: Esophageal Cancer; Esophageal adenocarcinoma; Esophageal squamous cell carcinoma; Staging; Endoscopic ultrasound

Core Tip: Esophageal cancer (ECA) affects 1 in 125 men and 1 in 417 for women and accounts for 2.6% of all cancer related deaths. The associated survival rate depends on the stage of the cancer when it is first diagnosed; therefore, adequate work up and staging is imperative. Additionally, treatment is stage-dependent, making staging all that much important. Endoscopic ultrasound has played a key role in the locoregional staging of newly diagnosed ECA and has an evolving role in restaging after neoadjuvant therapy. This manuscript will review the current role of endoscopic ultrasound on staging and restaging of ECA.

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INTRODUCTION

The role of endoscopic ultrasound in esophageal cancer

There will be an estimated 19260 new cases of esophageal cancer (ECA) in the United States in 2021, which accounts for 1.0% of all new cancer cases. The lifetime risk for development of ECA in the United States is 1 in 125 for men and 1 in 417 for women[1]. Mortality from the disease is significant, with an estimated 15530 deaths in 2021, accounting for 2.6% of all cancer related deaths. When evaluating the data from 2011-2017, the 5-year survival rate was found to be 19.9%[2]. The associated survival rate depends on the stage of the cancer when it is first diagnosed. At the time of diagnosis, a significant subset of patients has either locally advanced or metastatic disease, with 34% of patients having regional spread and 39% of patients having distant or metastatic spread. Unfortunately, only 10% of patients present with localized disease. Five-year survival rates, as expected, vary based on disease extent found on index evaluation. The 5-year survival rate for localized disease is 46.4%, regional disease is 25.6%, and distant/metastatic disease is 5.2%.

The workup for esophageal and esophagogastric junction cancers requires accurate staging as treatment protocols are stage dependent. Upper gastrointestinal endoscopy is essential for the initial evaluation of an esophageal mass. Endoscopy with biopsies is often sufficient to establish the diagnosis of ECA, but in the rare instances that biopsies are nondiagnostic, endoscopic ultrasound (EUS), with fine needle aspiration (FNA) of the esophageal wall, can be utilized for tissue diagnosis[3]. Currently, ECA staging as defined by the American Joint Committee on Cancer staging system utilizes tumor-node-metastasis subclassifications, otherwise known as TNM. The TNM classifications refer to the primary tumor (T stage), regional lymph node status (N stage), and presence or absence of metastatic disease (M classification)[4]. After the initial diagnosis of cancer is made, the National Comprehensive Cancer Network recommends obtaining a computed tomography (CT) of the chest/abdomen/pelvis to assess for metastatic disease (this can also help to define local extent of disease and nodal involvement albeit not as well as EUS in most cases). If there is no overt evidence of M1 disease on cross sectional imaging, then both EUS and positron emission tomography (PET) are indicated at this time for further evaluation [5]. The primary strength of EUS as part of this algorithm is in the ability to establish the extent of locoregional involvement in patients without overt metastatic disease.

Since treatment options for ECA are stage dependent, EUS plays an important role by providing accurate T and N staging. Specifically, EUS helps differentiate patients that should undergo neoadjuvant chemotherapy from patients that would benefit from primary surgical resection.

Importance of esophagogastroduodenoscopy examination

In general, the endoscopic report during the workup for ECA should include several components, including the anatomic landmarks, location of the lesion in question, circumferential extent of the cancer, and the general mucosal appearance. The importance of accurately describing the location of the tumor cannot be overemphasized, as many of the cancers labeled as esophageal are in fact either junctional or primary cardiac/gastric. This distinction is primarily determined by where the bulk of the tumor is. The endoscopist needs carefully to examine and document if the cancer involves the cardia or crosses the junction and how long (in cm) it extends proximal to the esophagogastric junction. Additionally, it is important to look for "skip" lesions (submucosal proximal extension of the cancer) so that the surgeons are aware of the extent of the cancer proximally (Figure 1). Similarly, it is important to document if there is Barrett's esophagus that extends proximal to the cancer, since ideally this will also be resected if the patient is appropriate for surgery. Additionally, the most stenotic part of the tumor should be documented so that the endoscopist is aware and proceeds with appropriate caution when passing a larger diameter, often oblique viewing, echoendoscope.

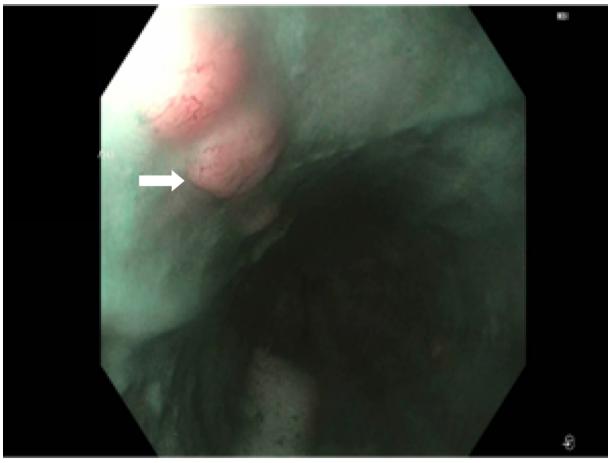

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Figure 1 Endoscopy revealing skip lesions, which represent submucosal spread of the cancer in the proximal esophagus.

EUS AND STAGING

T-Staging

Standard echoendoscopes operate at a frequency of 7.5-12 mHz. EUS can be performed using a radial or linear platform. Radial EUS images at a plane that is perpendicular to the long access of the scope, so the echo ultrasonographer can get a circumferential or 360 view of the ECA. These images are similar to interpreting axial CT slices (Figure 2A). Linear EUS, on the other hand, images parallel to the long access of the scope, and while T-staging is sometimes more challenging, use of this scope allows for performance of FNA or fine needle biopsy (FNB) if needed (Figure 2B). While choice of platform is typically operator dependent, it is common practice that endoscopists start with radial EUS because of the circumferential view. This can be switched to a linear EUS if something is found that needs FNA, such as a lymph node or liver lesion.

After identifying the distal and proximal extent of the cancer, the T-stage is determined. T staging refers to the depth of tumor invasion with respect to the extent of esophageal wall layer involvement. The esophageal wall is comprised of the mucosa, submucosa, muscularis propria, and adventitia. The mucosal wall layer is further subdivided into the epithelium, lamina propria, and muscularis mucosae. A basement membrane separates the muscularis mucosae from the submucosa. EUS helps to define the esophagus as a five layered structure with the first layer (hyperechoic) representing the superficial mucosa, the second (hypoechoic) representing the deep mucosa, the third (hyperechoic) representing the submucosa, the fourth (hypoechoic) the muscularis propria, and the fifth (hyperechoic) the adventitia (Figure 3). When reporting the T stage, the endosonographic report should also include the maximal wall thickness of the cancer.

EUS is particularly helpful with respect to T staging as we can accurately visualize and delineate the esophageal wall layers. Treatment decisions are partially dependent on T staging since depth of cancer penetration is important in predicting the risk of lymph node metastasis. Treatment for locally advanced disease, defined as stage IIB through IIIC, typically is neoadjuvant chemotherapy, with the goal to proceed with surgical resection following restaging, if appropriate. Neoadjuvant chemotherapy is associated with superior pathologic response and improved outcomes in these patients. For patients with surgically unresectable tumors or patients who are poor surgical candidates, definitive chemotherapy is offered.

T(is) refers to high grade dysplasia that is limited to the epithelium and does not penetrate the lamina propria. T1a tumors invade the lamina propria and/or muscularis mucosae, whereas T1b lesions invade into (but not through) the submucosa. By EUS, a T1a layer would invade through the first endosonographic, hyperechoic layer and possibly invade into, but not through the second hypoechoic later. T1b lesions would invade into, but not through the third, hyperechoic layer (Figure 4). T2 lesions invade past the submucosa into the muscularis propria (but do not breach the outer border). By EUS, these would invade into, but not through, the fourth (hypoechoic) layer. T3 lesions invade past the muscularis propria into the adventitia (Figure 5). By EUS, this would denote invasion past the fourth endosonographic layer into the fifth (hyperechoic) layer. T4a and T4b both invade structures adjacent to the esophagus, but T4a are considered resectable (invasion of pleura, pericardium, diaphragm), while T4b are considered unresectable (invasion of the aorta, vertebral body, trachea) (Figure 6). The true positive rate for EUS T-staging ranges between 0.89 (0.86-0.92), as gathered by one meta-analysis of 27 primary articles[6].

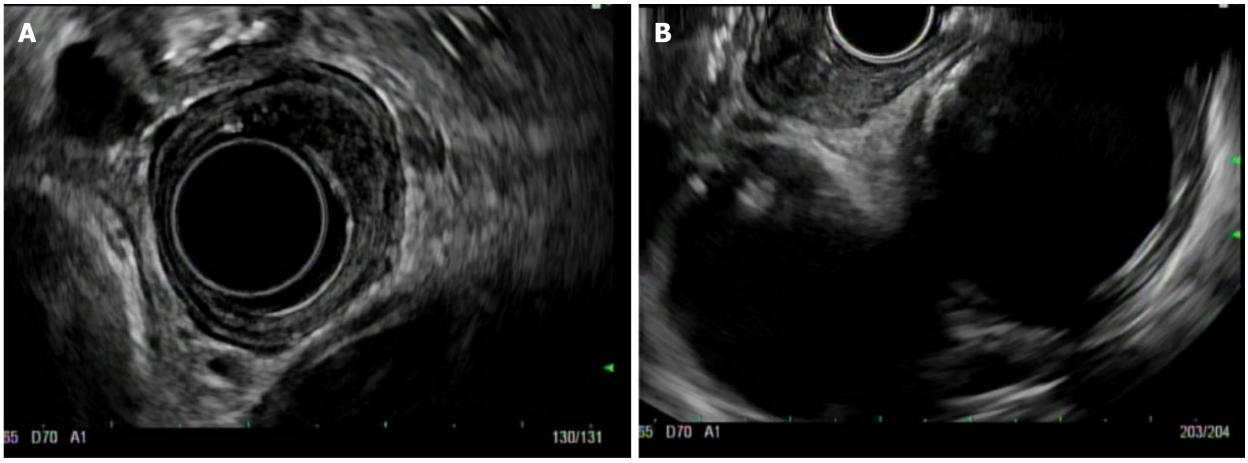

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Figure 2 Radial endoscopic ultrasound view of an early esophageal cancer (A) and linear endoscopic ultrasound view of the same lesion (B).

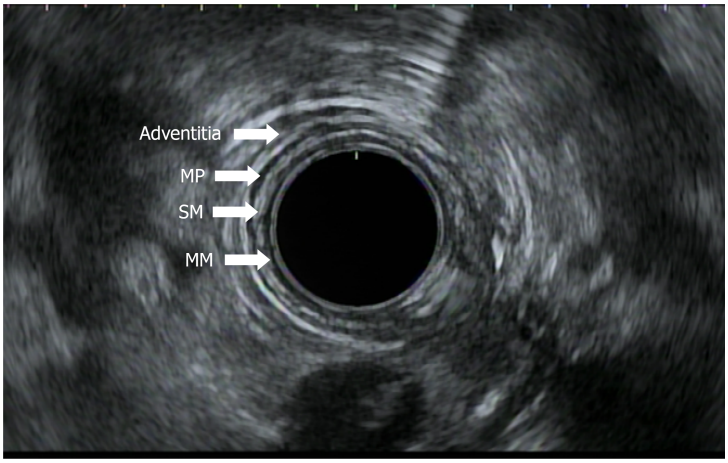

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Figure 3 Endoscopic ultrasound of normal esophageal wall layers. MM: Mucosa; SM: Submucosa; MP: Muscularis propria.

The accuracy of EUS lessens in staging cancers not on either ends of the spectrum (T1 or T/4). In a study by Tekola *et al*[7], 38 patients with ECA who were staged as T2N0 underwent surgery. EUS under staged 32% of these tumors. Other data have shown that up to 55% of tumors staged as T2N0 were shown to have nodal disease on resection. For this reason, many patients staged with T2N0 cancers are now undergoing preoperative chemoradiation. This practice is supported by Capovilla *et al*[11], whose study demonstrated that patients with T2N0 esophageal and squamous cell cancers who underwent neoadjuvant therapy had a statistically higher survival rate than patients who underwent up front surgery. If future studies support this practice, then the importance/ role of EUS in triaging patients to neoadjuvant *vs* surgery may in fact diminish[7-11].

"Importance of history/ presence of dysphagia in T staging": In patients with ECA who have dysphagia, the majority have advanced disease. One study showed that dysphagia was noted in 89% of patients having T3-4 ECA, while only 53% without dysphagia had T3-4 disease ($P < 0.001$). Another study showed similar findings where the presence of dysphagia in the setting of a cancer had a sensitivity 0.89 and sensitivity of 0.88 for at least locally advanced disease. For this reason, in patients with ECA and dysphagia, EUS may be less likely to affect treatment decisions[12,13].

N-staging

Next, the N-stage is determined. The N stage refers to the presence or absence, along with the total number of regional lymph nodes affected. N0 indicates the absence of lymph node involvement, N1 denotes two involved lymph nodes, N2, three to six involved lymph nodes, and N3, seven or more lymph nodes.

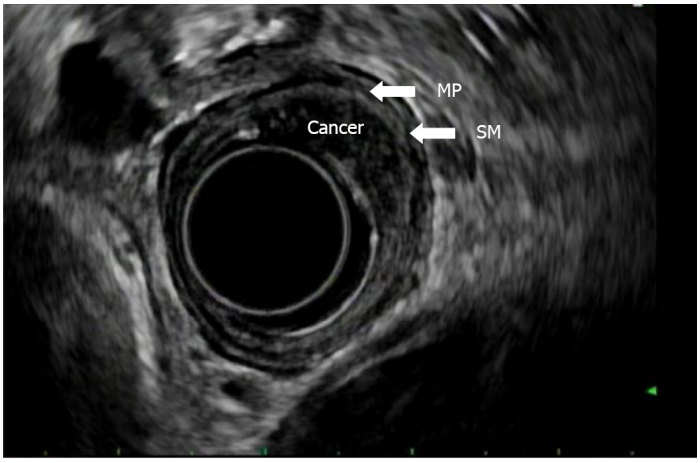

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Figure 4 Endoscopic ultrasound view of a T1b esophageal cancer. The cancer invades the submucosa but not the muscularis propria. SM: Submucosa; MP: Muscularis propria.

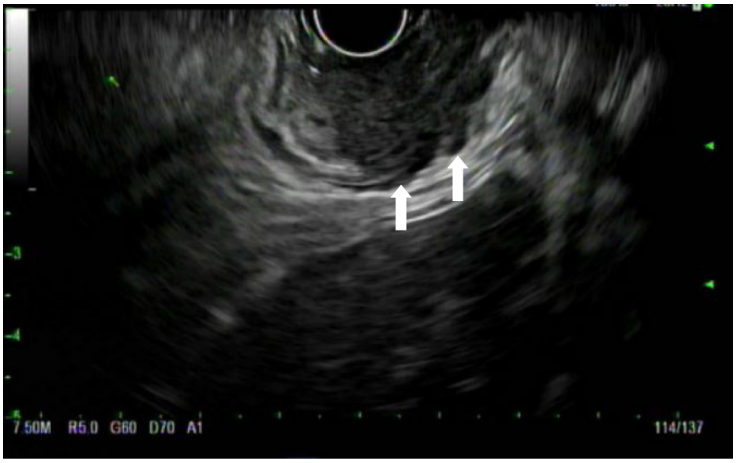

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Figure 5 Endoscopic ultrasound view of a T3 esophageal cancer. The cancer invades through the entire esophageal wall and invades the adventitia.

Endosonographic characteristics of lymph nodes that suggest malignant potential include size greater than 1 cm, round shape, sharp and demarcated borders, and hypoechoic echotexture (Figure 7). When a lymph node is found to possess all four of these aforementioned features, the accuracy of predicting a malignant lymph node is 80%-100%[14,15]. The location of the lymph node may also be informative in differentiation of benign and malignant. For example, the presence of celiac lymph nodes usually indicates pathology since they are not usually present. In one study, 89% of endosonographically detectable celiac lymph nodes were confirmed to be malignant on FNA[16]. Another predictor of malignant lymph node status includes association with T3-T4 staged lesions[17].

EUS has a pooled sensitivity of 59.5% to 97.2% sensitivity for N staging (40%-100% specificity). This is compared to a pooled sensitivity of 24% for distinguishing N0 from N1 by CT (with 100% specificity) [6]. Nodal staging is important prognostically since patients with nodal involvement have been found to have worse prognosis as compared to those who do not (N0 disease). Patients with 0, 1-2, and > 2 malignant appearing, peri-esophageal lymph nodes on index EUS were found to have 66 mo, 14.5 mo, and 6.5 mo, respectively, of median survival time[18].

M-staging

Lastly, distant lymph nodes, the liver, peritoneum, and the left adrenal gland are inspected for lesions. M staging differentiates presence of metastases (M1) *vs* absence of metastases (M0). As previously discussed, there is a limited role for EUS if M1 disease is established on CT. However, EUS at the position of the antrum or bulb of the duodenum can provide an important means for evaluation of peripancreatic or porta hepatis lymph nodes. In the body of the stomach, EUS can evaluate the liver (Figure 8), and in the fundus and cardia, EUS can evaluate perigastric and peripancreatic lymph nodes as well as evaluate the celiac plexus (though the latter is not considered M1). Additionally, EUS can

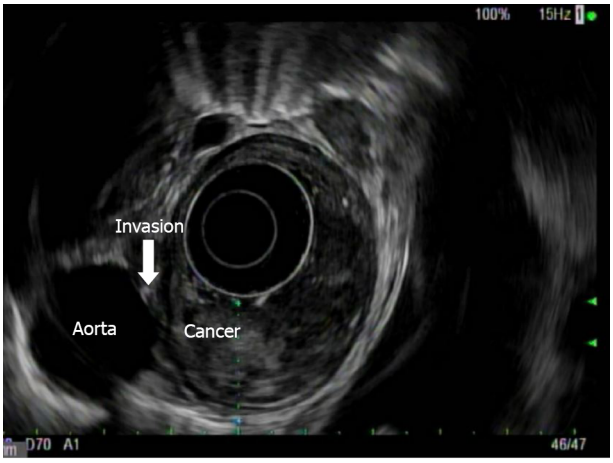

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Figure 6 Endoscopic ultrasound view of a T4 esophageal cancer. The cancer invades the aorta.

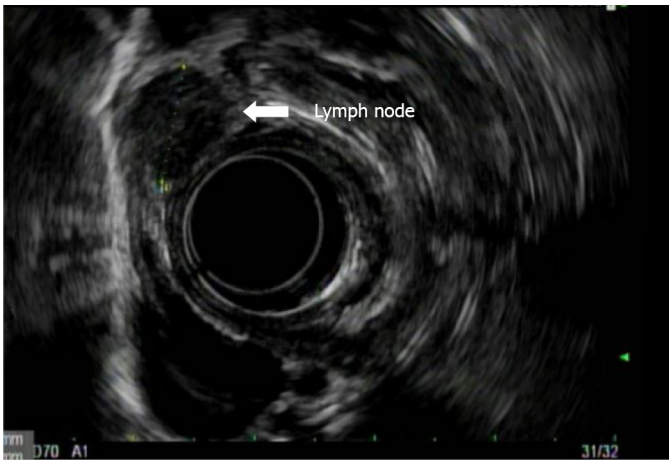

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Figure 7 Endoscopic ultrasound view of a malignant peritumor lymph node. It is hypoechoic, round, and greater than 1 cm in size and has distinct borders.

provide a detailed evaluation of the left adrenal gland and the peritoneum. An important difference between the older classification (American Joint Committee on Cancer) system and the current, affecting the utility of EUS in differentiating M0 from M1 disease, is that the involvement of a celiac lymph node is now considered regional (N) disease and no longer metastatic (M1a).

UTILITY OF EUS IN OBSTRUCTING TUMORS

EUS may not be technically feasible in patients with obstructing cancers. An obstructing tumor can be seen on presentation in up to 30% of cases. There are some risks of dilating a malignant stricture to pass an echo endoscope, including perforation[19]. Additionally, it may be difficult to stage accurately a lesion following esophageal dilation given disruption of normal tissue planes. There is questionable additional benefit of endosonography following the endoscopic finding of a malignant stricture as the presence of a malignant obstruction typically denotes advanced disease (T3-T4)[20]. Patients with malignant obstructions that cannot be traversed have poorer outcomes as compared to patients without evidence of stenosis, with median survivals of 10 mo *vs* 20 mo, respectively.

EUS-FNA

One of the benefits of EUS, specifically linear EUS, is the ability to perform FNA and/or FNB of lymph nodes and lesions in adjacent structures. EUS with FNA has 80% sensitivity in distinguishing T4 from T1-T3 disease and 78% accuracy in nodal staging[21]. In patients with T1-T2 disease, FNA can determine lymph node involvement, which in turn determines if these patients would theoretically need

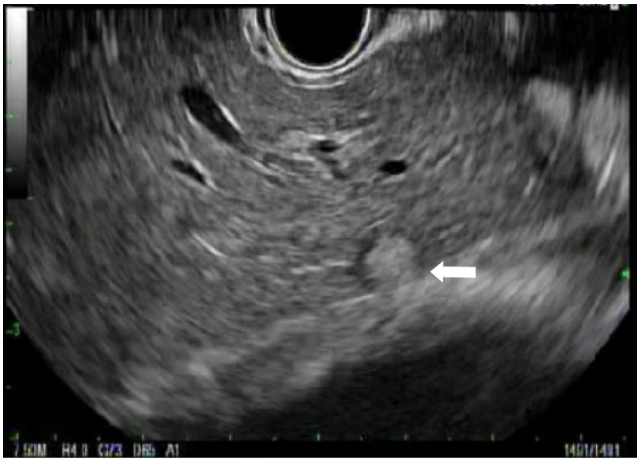

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Figure 8 Endoscopic ultrasound image of a round liver metastasis.

neoadjuvant chemotherapy or proceed directly to surgery. When performing FNA, it is important to avoid passing through the main tumor or major blood vessels to avoid both false positives as well as tumor seeding.

EUS vs other staging modalities

In one study, EUS results altered management by guiding the need for neoadjuvant chemotherapy in 34.8% of patients evaluated[22]. In another retrospective study of 56 patients, EUS was superior in the ability to identify locally advanced disease, with 58.9% sensitivity as compared to 26.8% and 37.5% sensitivity for CT and PET, respectively. EUS, however, is less accurate for early-stage lesions (T1 or T2) as compared with more advanced tumors. Additionally, PET is superior for detection of distant metastasis as compared to EUS, with a sensitivity of 81% *vs* 73% and specificity of 91% *vs* 86%, respectively[23]. EUS also plays an important role in detecting disease recurrence along with restaging after chemotherapy +/- radiation.

With improvements in imaging such as PET/magnetic resonance imaging (MRI), the overall utility of EUS is controversial. In one study of 74 patients undergoing preoperative staging, MRI outperformed EUS with higher specificity and accuracy in T staging[24]. In patients with dysphagia or an obstructing lesion, EUS has less utility given most of these patients have locally advanced disease and thus would not be definitive surgical resection candidates. In one study evaluating 147 patients with esophageal adenocarcinoma and dysphagia, 133 of these patients had a partially or completely obstructing mass on initial endoscopic evaluation. Overall, 128 of these 133 (96%) patients had locally advanced disease[12].

The utility of EUS is also diminished when evaluating early-stage ECA as there is loss of sensitivity for superficial disease. High frequency probes can help to provide better evaluation of the mucosa and the submucosa. In 75%-82% of cases, high frequency probes (12-20 MHz) can help distinguish T1a from T1b disease in patients without evidence of metastatic disease[25]. This can help determine candidacy for endoscopic resection techniques as a curative option during the same session. In another study, the accuracy of T staging when using a high frequency probe was 64% as compared to a conventional radial EUS, which was 49%[26]. When encountering a more superficial lesion that can be endoscopically resected, performing EUS first is helpful in confirming that the muscularis propria is uninvolved and in ruling out malignant lymphadenopathy. Once the lesion is endoscopically resected, then the true pathologic T stage is confirmed.

We have also found that EUS is challenging when evaluating early to intermediate gastroesophageal junction (GEJ) tumors. In one study evaluating EUS in GEJ tumors prior to surgical resection (in patients that had not undergone prior chemotherapy or radiation), EUS T staging was only accurate in 48% of cases (23% percent were under-staged and 29% were over-staged as correlated with pathologic T staging). This inaccuracy was even more pronounced in short segment tumors at the GEJ[27].

Role of EUS in restaging

The role of EUS in staging disease following neoadjuvant therapy is evolving. Patients are typically restaged after completion of neoadjuvant therapy to determine if the next most appropriate step is surgical resection *vs* definitive or palliative chemotherapy. Traditionally, it was thought that EUS is less reliable following neoadjuvant chemotherapy given inflammation and fibrosis sustained during treatment, which affects the ability to interpret reliably an EUS exam. The mucosal changes following neoadjuvant chemotherapy can cause hypoechoic appearance of the esophageal wall and over-staging of tumor invasion, possibly precluding some patients from an appropriate surgical resection. Following

neoadjuvant chemotherapy, a recent meta-analysis and systematic review found the sensitivity and specificity of T1 23% and 95%, T2 29% and 84%, T3 81% and 42%, and T4 43% and 96%, respectively. In the same study, the pooled sensitivity and specificity of N staging was found to be 69% and 52%, respectively[28].

Another retrospective study of 103 patients with locoregionally advanced ECA who had undergone neoadjuvant chemotherapy showed that reduced mass size, as determined by EUS (0.7 *vs* 1.7 cm, P = 0.01), correlated with a pathologic response[29]. However, in this same cohort, fluorodeoxyglucose-PET outperformed EUS in prediction of long-term survival following neoadjuvant chemotherapy (in patients following neoadjuvant chemotherapy but prior to surgical resection).

Even after surgery, EUS can be utilized in determining tumor recurrence, despite post-surgical EUS surveillance not being considered standard of practice at this time. In one small study of 40 patients who had undergone prior surgical resection, 3 recurrences were identified with EUS despite absence of symptoms (no reported dysphagia) and a negative CT[30]. In fact, another study of 43 patients undergoing q6 mo EUS surveillance had a 92% positive predictive value for early recurrence in a population where two-thirds of those with recurrence were asymptomatic[31].

In one meta-analysis, the pooled sensitivity for detecting complete pathologic response following neoadjuvant therapy was 0.35, 0.62, 0.01, and 0.08 for CT, PET-CT, EUS, and MRI, respectively. While the sensitivity of EUS was poor, specificity was 0.99 as compared to 0.83, 0.73, and 0.83 for CT, PET-CT, and MRI, respectively[32].

One multicenter study evaluating 138 patients before and after neoadjuvant therapy showed that EUS was able to detect adequately residual disease in 90% of patients 12 wk following therapy. Specifically, EUS was able to detect residual thickness and residual area of the tumor[33]. Another meta-analysis evaluating EUS for restaging following neoadjuvant chemotherapy found that EUS had a pooled sensitivity and specificity of 81% and 42% in T3 tumors (with markedly lower sensitivities of 23%, 29%, and 43% in T1, T2, and T4 tumors, respectively)[28].

EUS special considerations

Other considerations when discussing the role of EUS in the staging of ECA include the cost effectiveness. EUS performed prior to treatment decisions has been found to save $3443 per patient in its ability to identify stage 1 or stage 4 disease and avoid inappropriate neoadjuvant chemotherapy or surgery[34]. In patients without metastatic disease, EUS is the least expensive staging modality for ECA ($13811) as compared to CT-guided FNA ($14350) or surgery ($13992). While CT is the most appropriate initial staging test in most cases, EUS can theoretically suffice as a reasonable initial study as demonstrated in one single center study. EUS found advanced disease more frequently than CT (44 % *vs* 13%) and is cheaper ($804 *vs* $844) than CT (in cases where the probability of finding advanced disease is less than 20%)[35].

It is also important to note that performing high quality EUS is provider dependent and can vary with skill level and experience. In general, it is believed that at least 100 examinations are needed for a provider to provide T-staging reliably and accurately in ECA. High quality EUS examination also has been shown to improve survival in one randomized control trial of 223 patients with non-metastatic gastroesophageal cancer (hazard ratio of 0.706 with 95% confidence interval from 0.501 to 0.966)[36].

CONCLUSION

EUS has an important role in the staging of ECA. It is superior to cross sectional imaging in the locoregional staging of ECA. Unlike cross sectional imaging, it also has the added advantage to perform FNA and/or FNB of surrounding lymph nodes and organs and, consequently, alter management. Instances when EUS may not be as beneficial are in patients with dysphagia since they most likely have at least advanced locoregional disease and would undergo neoadjuvant or definitive therapy depending on their M status. While less accurate, EUS has an evolving role in neoadjuvant therapy. Since the performance of EUS is operator dependent, it should ideally be performed by physicians specifically trained in EUS.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Mark Radlinski 0000-0002-5078-577X; Vanessa M Shami 0000-00001-7528-5141.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic retrograde cholangiopancreatography for bile duct stones in patients with a performance status score of 3 or 4

Hirokazu Saito, Yoshihiro Kadono, Takashi Shono, Kentaro Kamikawa, Atsushi Urata, Jiro Nasu, Haruo Imamura, Ikuo Matsushita, Tatsuyuki Kakuma, Shuji Tada

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Hirokazu Saito, Shuji Tada, Department of Gastroenterology, Kumamoto City Hospital, Kumamoto City 862-8505, Japan

Yoshihiro Kadono, Department of Gastroenterology, Tsuruta Hospital, Kumamoto City 862-0925, Japan

Takashi Shono, Ikuo Matsushita, Department of Gastroenterology, Kumamoto Chuo Hospital, Kumamoto City 862-0965, Japan

Kentaro Kamikawa, Atsushi Urata, Haruo Imamura, Department of Gastroenterology, Saiseikai Kumamoto Hospital, Kumamoto City 861-4193, Japan

Jiro Nasu, Department of Gastroenterological Surgery, Kumamoto Chuo Hospital, Kumamoto City 862-0965, Japan

Tatsuyuki Kakuma, Department of Biostatics, Kurume University, Kurume City 8300011, Japan

Corresponding author: Hirokazu Saito, MD, Doctor, Department of Gastroenterology, Kumamoto City Hospital, 4-1-60, Higashimachi, Higashi-ku, Kumamoto City 862-8505, Japan. arnestwest@yahoo.co.jp

Abstract

BACKGROUND

As the aging population grows worldwide, the rates of endoscopic retrograde cholangiopancreatography (ERCP) for common bile duct stones (CBDS) in older patients with a poor performance status (PS) have been increasing. However, the data on the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4 are lacking, with only a few studies having investigated this issue among patients with poor PS.

AIM

To examine the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4.

METHODS

This study utilized a retrospective multi-centered design of three institutions in Japan for 8 years to identify a total of 1343 patients with CBDS having native

papillae who underwent therapeutic ERCP. As a result, 1113 patients with a PS 0-2 and 230 patients with a PS 3-4 were included. One-to-one propensity-score matching was performed to compare the safety and efficacy of ERCP for CBDS between patients with a PS 0-2 and those with a PS 3-4.

RESULTS

The overall ERCP-related complication rates in all patients and propensity score-matched patients with a PS 0-2 and 3-4 were 9.0% (100/1113) and 7.0% (16/230; P = 0.37), and 4.6% (9/196) and 6.6% (13/196; P = 0.51), respectively. In the propensity score-matched patients, complications were significantly more severe in the group with a PS 3-4 than in the group with a PS 0-2 group (P = 0.042). Risk factors for complications were indications of ERCP and absence of antibiotics in the multivariate analysis. Therapeutic success rates, including complete CBDS removal and permanent biliary stent placement, in propensity score-matched patients with a PS 0-2 and 3-4 were 97.4% (191/196) and 97.4% (191/196), respectively (P = 1.0).

CONCLUSION

ERCP for CBDS can be effectively performed in patients with a PS 3 or 4. Nevertheless, the indication for ERCP in such patients should be carefully considered with prophylactic antibiotics.

Key Words: Endoscopic retrograde Cholangiopancreatography; Complication; Performance status; Risk factor

Core Tip: In 196 propensity-matched patients, the overall complications and technical success in patients with a performance status (PS) 3 or 4 were comparable to those of patients with a PS 0-2. However, complications were more severe in patients with a PS 3 or 4. In the multivariate analysis, indications of endoscopic retrograde cholangiopancreatography (ERCP) and the absence of antibiotics were significant risk factors for complications. Although ERCP for common bile duct stones can be effectively performed in patients with a PS 3 or 4, the indication for ERCP should be carefully considered, and prophylactic antibiotics should be administered to patients with a PS 3 or 4.

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INTRODUCTION

As the aging population grows worldwide, the rates of endoscopic retrograde cholangiopancreatography (ERCP) among the elderly are increasing. In particular, common bile duct stones (CBDS) are the most common indication for ERCP, and endoscopists often perform ERCP for CBDS in the elderly with poor Eastern Cooperative Oncology Group performance status (ECOG-PS) score[1], which is an objective index of activity in daily life, in clinical practice. Although several studies have reported that the safety and efficacy of ERCP for elderly patients aged ≥ 80-90 years were comparable to those in younger patients, the performance status (PS) score varied in the previous studies[2-10].

PS is an important tool utilized for the clinical determination of the indications and strategies of ERCP for CBDS in elderly patients. Evidence available from studies evaluating the safety and efficacy of ERCP for biliopancreatic diseases in patients with a poor PS score is limited[11,12]. Furthermore, few studies have investigated the safety and efficacy of ERCP for CBDS in patients with a poor PS score. In the present study, we assessed the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4 in comparison with those having a PS score of 0-2.

MATERIALS AND METHODS

Patients and study design

The data of patients with native major duodenal papilla who had undergone therapeutic ERCP for CBDS between April 2012 and February 2020 at Kumamoto Chuo Hospital, Saiseikai Kumamoto Hospital, and Kumamoto City Hospital in Japan were retrospectively reviewed. The exclusion criteria were (1) failure to detect CBDS during ERCP; (2) history of therapeutic ERCP; and (3) and a gastrointestinal tract that has already been surgically altered such as by employing Billroth II or Roux-en-Y reconstruction. The institutional review boards of the participating institutions approved this study and opt-out consent was applied. One-to-one propensity score matching analysis was performed to adjust for confounding factors between patients with a PS score of 0–2 and patients with a PS score of 3 or 4, and the safety and efficacy of ERCP for CBDS were compared between these two groups.

Outcomes and definitions

The primary outcome was the rates of post-ERCP complications and the rate of technical success such as complete stone removal and permanent biliary stent placement.

Post-ERCP complications included post-ERCP pancreatitis (PEP), bleeding, cholangitis, perforation, and aspiration pneumonia. These complications and their severity were diagnosed based on a lexicon for endoscopic complications[13]. When several complications were noted in the same patient, the most severe complication was selected for analysis.

Successful cases of complete stone removal or permanent biliary stent placement were considered a therapeutic success in this study.

Procedure

ERCP was performed in the prone or semi-prone position using side-viewing duodenoscopes (Olympus JF-260, TJF-260V; Olympus Medical Systems, Tokyo, Japan). Midazolam with pethidine hydrochloride was used for the purpose of sedation by the endoscopist. We determined the doses of midazolam and pethidine hydrochloride based on our sedation protocol using the data pertaining to the age and weight of patients. In patients aged 75-89 years and weighing < 70 kg, the dose of pethidine hydrochloride and midazolam was 17.5 mg-35 mg and 1 mg, respectively. In patients aged 75-89 years and weighing ≥ 70 kg, the dose of pethidine hydrochloride and midazolam was 17.5 mg-35 mg and 2 mg, respectively. In patients aged ≥ 90 years, the dose of pethidine hydrochloride and midazolam was 17.5 mg and/or 1 mg, respectively, regardless of the weight of the patients.

When a trainee with experience of < 200 ERCP procedures performed ERCP, an experienced endoscopist supervised them. After biliary cannulation using a standard ERCP catheter and a 0.025-inch guidewire, biliary stent placement or stone removal after endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), or endoscopic papillary large balloon dilation (EPLBD) was performed. The treatment strategy for complete stone removal or permanent biliary stent placement was decided upon by the endoscopist.

Statistical analysis

Chi-squared test or Fisher's exact test was used for categorical variables, and Welch's *t*-test was used for continuous variables. A multivariate logistic regression model employed variables with *P* values < 0.20 in the univariate analyses to identify the predictive factors for post-ERCP complications.

One-to-one propensity score matching with a caliper of 0.2 was performed to adjust for confounding factors associated with post-ERCP complications between patients with a PS score of 0-2 and patients with a PS score of 3 or 4. Factors presented in Table 1 were used to construct propensity scores using the logistics regression model.

All statistical analyses were performed using EZR version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria, version 4.1.0)[14]. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

A total of 1343 patients met the inclusion criteria for this study. Altogether, 1113 and 230 patients were included in the groups with a PS score of 0-2 and 3-4, respectively. Details of patients' characteristics are presented in Table 1. Significant differences were noted in age, sex, indications of ERCP for CBDS, a history of cerebrovascular diseases, a history of multiple underlying diseases, antithrombotic treatment, non-dilated common bile duct (CBD), antibiotics, trainee involvement, difficult cannulation, EST, EPBD, EPLBD, use of balloon catheter, large stones, protease inhibitor, and rectal non-steroidal anti-inflammatory drugs. No significant differences were noted in patients' characteristics between the two groups

Table 1 Baseline characteristics of the patients

	All patients			Propensity score-matched patients		
	Patients with a PS 0-2 (*n* = 1113)	Patients with a PS 3 or 4 (*n* = 230)	*P* value	Patients with a PS 0-2 (*n* = 196)	Patients with a PS 3 or 4 (*n* = 196)	*P* value
Age [mean (SD)]	72.9 (14.0)	84.4 (9.1)	< 0.001	83.6 (8.2)	83.4 (9.2)	0.79
Female (%)	498 (44.7)	146 (63.5)	< 0.001	113 (57.7)	117 (59.7)	0.76
Indications of ERCP for CBDS						
Acute cholangitis (%)	607 (54.5)	194 (84.3)	< 0.001	160 (81.6)	160 (81.6)	1.0
Biliary pancreatitis (%)	59 (5.3)	5 (2.2)	0.041	5 (2.6)	5 (2.6)	1.0
Obstructive jaundice without cholangitis (%)	263 (23.6)	20 (8.7)	< 0.001	21 (10.7)	20 (10.2)	1.0
Asymptomatic CBDS (%)	184 (16.5)	11 (4.8)	< 0.001	10 (5.1)	11 (5.6)	1.0
Underlying diseases						
Diabetes Mellitus (%)	78 (7.0)	12 (5.2)	0.39	14 (7.1)	12 (6.1)	0.84
Cardiovascular diseases (%)	152 (13.7)	42 (18.3)	0.080	40 (20.4)	39 (19.9)	1.0
Cerebrovascular diseases (%)	55 (4.9)	53 (23.0)	< 0.001	31 (15.8)	31 (15.8)	1.0
Dialysis (%)	35 (3.1)	8 (3.5)	0.84	7 (3.6)	8 (4.1)	1.0
Liver cirrhosis (%)	15 (1.3)	0 (0.0)	0.089	0 (0)	0 (0)	1.0
Multiple underlying diseases (%)	99 (8.9)	37 (16.1)	0.002	33 (16.8)	30 (15.3)	0.78
Antithrombotic treatment	280 (25.2)	94 (40.9)	< 0.001	80 (40.8)	73 (37.2)	0.54
Billroth-1 reconstruction (%)	28 (2.5)	6 (2.6)	1.0	8 (4.1)	6 (3.1)	0.79
Post-cholecystectomy (%)	124 (11.1)	19 (8.3)	0.24	19 (9.7)	18 (9.2)	1.0
Presence of gallstones (%)	715 (64.2)	147 (63.9)	0.94	123 (62.8)	121 (61.7)	0.92
Normal serum bilirubin (%)	540 (48.5)	104 (45.2)	0.39	94 (48.0)	87 (44.4)	0.54
Platelet counts [mean (SD)] ($\times 10^6$/L)	19.1 (7.1)	19.5 (9.9)	0.44	18.7 (7.7)	18.6 (7.9)	0.93
PT-INR [mean (SD)]	1.2 (0.91)	1.2 (0.42)	0.29	1.3 (1.8)	1.2 (0.42)	0.47
Non-dilated CBD (< 10 mm) (%)	454 (40.8)	70 (30.4)	0.004	53 (27.0)	60 (30.6)	0.50
Periampullary diverticulum (%)	341 (30.6)	60 (26.1)	0.18	62 (31.6)	56 (28.6)	0.58
Antibiotics (%)	881 (79.2)	216 (93.9)	< 0.001	178 (90.8)	182 (92.9)	0.58
Trainees (%)	199 (17.9)	27 (11.7)	0.026	25 (12.8)	24 (12.2)	1.0
Successful biliary cannulation (%)	1099 (98.7)	225 (97.8)	0.35	192 (98.0)	192 (98.0)	1.0
Difficult biliary cannulation (%)	309 (27.8)	48 (20.9)	0.033	46 (23.5)	42 (21.4)	0.72
Contrast-assisted cannulation (%)	772 (69.4)	168 (73.0)	0.30	135 (68.9)	143 (73.0)	0.44
Wire-guided cannulation (%)	120 (10.8)	23 (10.0)	0.82	21 (10.7)	20 (10.2)	1.0
PGW-assisted cannulation (%)	156 (14.0)	30 (13.0)	0.75	28 (14.3)	26 (13.3)	0.88
Precut sphincterotomy (%)	63 (5.7)	9 (3.9)	0.34	12 (6.1)	7 (3.6)	0.35
Pancreatic injection (%)	513 (46.1)	93 (40.4)	0.13	87 (44.4)	81 (41.3)	0.61
EST (%)	973 (87.4)	186 (80.9)	0.011	154 (78.6)	160 (81.6)	0.53
EPBD (%)	125 (11.2)	38 (16.5)	0.034	38 (19.4)	31 (15.8)	0.43
EPLBD (%)	158 (14.2)	60 (26.1)	< 0.001	53 (27.0)	50 (25.5)	0.82

Use of balloon catheter (%)	896 (80.5)	167 (72.6)	0.010	139 (70.9)	144 (73.5)	0.65
Use of basket catheter (%)	504 (45.3)	105 (45.7)	0.94	102 (52.0)	94 (48.0)	0.48
Mechanical lithotripsy (%)	189 (17.0)	33 (14.3)	0.38	35 (17.9)	32 (16.3)	0.79
Biliary stent placement (%)	945 (84.9)	192 (83.5)	0.62	157 (80.1)	164 (83.7)	0.43
Number of CBD stones [mean (SD)]	2.2 (2.7)	2.5 (2.8)	0.052	2.6 (3.4)	2.6 (3.0)	0.87
Large stones (> 10 mm) (%)	195 (17.5)	61 (26.5)	0.002	57 (29.1)	52 (26.5)	0.65
Prophylactic pancreatic stent placement (%)	169 (15.2)	32 (13.9)	0.69	34 (17.3)	30 (15.3)	0.68
Protease inhibitor (%)	453 (40.7)	65 (28.3)	< 0.001	57 (29.1)	60 (30.6)	0.83
Rectal NSAIDs (%)	117 (10.5)	10 (4.3)	0.003	11 (5.6)	9 (4.6)	0.82

CBD: Common bile duct; CBDS: Common bile duct stones; ERCP: Endoscopic retrograde cholangiopancreatography; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; PS: Performance status; PGW: Pancreatic guidewire.

after propensity score matching.

Endoscopic retrograde cholangiopancreatography-related complications

ERCP-related complications in all patients and propensity score-matched patients are presented in Table 2. The overall ERCP-related complication rates in all patients and propensity score-matched patients in the groups with a PS score of 0-2 and 3-4 were 9.0% (100/1113) and 7.0% (16/230; $P = 0.37$) and 4.6% (9/196) and 6.6% (13/196; $P = 0.51$), respectively. In all patients, complications were more severe in the group with a PS score of 3-4 than in the group with a PS score of 0-2 ($P = 0.063$), although this finding was not statistically significant. In the propensity score-matched patients, complications were significantly more severe in the group with a PS score of 3 or 4 than in the group with a PS score of 0-2 ($P = 0.042$). The incidence rate of each complication, including PEP, bleeding, cholangitis, perforation, and aspiration pneumonia, was not significantly different between the two groups in all patients and propensity score-matched patients. Among all patients, the severity of PEP was significantly higher in patients with a PS score of 3 or 4 than in those with a PS score of 0-2 ($P = 0.034$), and the severity of other complications was not significantly different between the two groups. Among the propensity score-matched patients, the severity of each complication was not significantly different between the two groups.

Therapeutic success rates of ERCP and mean procedure time

Therapeutic success rates of ERCP and mean procedure time are presented in Table 3. Therapeutic success rates, including successful complete stone removal and permanent biliary stent placement, in all patients and propensity score-matched patients were 98.5% (1096/1113) and 97.4% (224/230; $P = 0.26$) and 97.4% (191/196) and 97.4% (191/196; $P = 1.0$), respectively. The rates of successful complete stone removal in all patients and propensity score-matched patients between patients with a PS score of 0-2 and 3 or 4 were 1064/1113 (95.6%) and 200/230 (87.0%; $P < 0.001$) and 92.3% (181/196) and 87.8% (172/196; $P = 0.18$), respectively. The rates of successful permanent biliary stent placement in all patients and propensity score-matched patients between the group with a PS score of 0-2 and 3 or 4 were 2.9% (32/1113) and 10.4% (24/230; $P < 0.001$) and 5.1% (10/196) and 9.7% (19/196; $P = 0.12$), respectively. Mean procedure times were not significantly different in all patients and propensity score-matched patients between the two groups ($P = 0.42$ and $P = 0.77$, respectively).

Predictive factors for ERCP-related complications after ERCP for CBDS

The results of univariate and multivariate analyses for risk factors of ERCP-related complications for CBDS are presented in Table 4. In univariate analysis, there was a significant difference in indications of ERCP for CBDS, absence of antibiotics, prolonged procedure, difficult biliary cannulation, pancreatic injection, contrast-assisted cannulation, prophylactic pancreatic stent placement, normal serum bilirubin level, and pancreatic guidewire-assisted cannulation. In multivariate analysis, indications of ERCP for CBDS and absence of antibiotics were significant risk factors for ERCP-related complications.

DISCUSSION

Several studies reported that ERCP can be performed for biliopancreatic diseases even in elderly patients aged over 80 years[2-10]. However, PS is an important factor in deciding the therapeutic

Table 2 Comparison of endoscopic retrograde cholangiopancreatography-related complications between patients with a performance status score of 0-2 and 3-4

	All patients			Propensity score-matched patients		
	Patients with a PS 0-2 (*n* = 1113)	Patients with a PS 3 or 4 (*n* = 230)	*P* value	Patients with a PS 0-2 (*n* = 196)	Patients with a PS 3 or 4 (*n* = 196)	*P* value
Overall complications, *n* (%)	100 (9.0)	16 (7.0)	0.37	9 (4.6)	13 (6.6)	0.51
Severity of overall complications			0.063			0.042
Mild (%)	65 (65.0)	6 (37.5)		7 (77.8)	3 (23.1)	
Moderate (%)	29 (29.0)	8 (50.0)		2 (22.2)	8 (61.5)	
Severe (%)	6 (6.0)	2 (12.5)		0 (0.0)	2 (15.4)	
PEP (%)	50 (4.5)	5 (2.2)	0.14	3 (1.5)	2 (1.0)	1.0
Severity of PEP (%)			0.034			0.10
Mild (%)	34 (68.0)	3 (60.0)		3 (100.0)	0 (0.0)	
Moderate (%)	14 (28.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Severe (%)	2 (4.0)	2 (40.0)		0 (0.0)	2 (100.0)	
Bleeding (%)	18 (1.6)	4 (1.7)	0.78	1 (0.5)	4 (2.0)	0.37
Severity of bleeding (%)			0.12			0.40
Mild (%)	12 (66.7)	1 (25.0)		1 (100.0)	1 (25.0)	
Moderate (%)	3 (16.7)	3 (75.0)		0 (0.0)	3 (75.0)	
Severe (%)	3 (16.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Cholangitis (%)	18 (1.6)	4 (1.7)	0.78	3 (1.5)	4 (2.0)	1.0
Severity of cholangitis (%)			0.077			0.49
Mild (%)	14 (77.8)	1 (25.0)		2 (66.7)	1 (25.0)	
Moderate (%)	4 (22.2)	3 (75.0)		1 (33.3)	3 (75.0)	
Perforation (%)	10 (0.9)	0 (0.0)	0.23	1 (0.5)	0 (0.0)	1.0
Severity of perforation (%)			1.0			NA
Mild (%)	4 (40.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate (%)	5 (50.0)	0 (0.0)		1 (100.0)	0 (0.0)	
Severe (%)	1 (10.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Pneumonia (%)	4 (0.4)	3 (1.3)	0.10	1 (0.5)	3 (1.5)	0.62
Severity of aspiration pneumonia (%)			1.0			1.0
Mild (%)	1 (25.0)	1 (33.3)		1 (100.0)	1 (33.3)	
Moderate (%)	3 (75.0)	2 (66.7)		0 (0.0)	2 (66.7)	

PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; PS: Performance status; NA: Not available.

strategy in elderly patients with CBDS. Although conservative therapy or therapeutic ERCP can be selected for CBDS in patients with a PS score of 3 or 4, therapeutic ERCP is better because ERCP can resolve CBD obstruction caused by CBDS if ERCP can be performed safely and effectively even in elderly patients with a PS score of 3 or 4.

Only a few studies are available on the association between poor PS and ERCP-related complications. Previous studies reported that the rate of overall ERCP-related complications was not different between patients with a PS score of 0-2 and 3 or 4 having biliopancreatic diseases[12,15] but the rates of aspiration pneumonia and heart failure were higher in patients with a PS score of 3 or 4 than in patients with a PS score of 0-2[12]. Another retrospective study reported that the risk of pulmonary and severe complications was high, although ERCP could be performed effectively in patients with a PS score of 4

Table 3 Comparison of outcomes of endoscopic retrograde cholangiopancreatography between patients with a performance status score of 0-2 and performance status 3-4

	All patients			Propensity score-matched patients		
	Patients with a PS 0-2 (*n* = 1113)	Patients with a PS 3 or 4 (*n* = 230)	*P* value	Patients with a PS 0-2 (*n* = 196)	Patients with a PS 3 or 4 (*n* = 196)	*P* value
Therapeutic success, *n* (%)	1096 (98.5)	224 (97.4)	0.26	191 (97.4)	191 (97.4)	1.0
Successful complete stone removal (%)	1064 (95.6)	200 (87.0)	< 0.001	181 (92.3)	172 (87.8)	0.18
Permanent biliary stent placement (%)	32 (2.9)	24 (10.4)	< 0.001	10 (5.1)	19 (9.7)	0.12
Mean procedure time, min (SD)	27.5 (15.7)	26.5 (15.9)	0.42	26.9 (15.7)	27.3 (16.6)	0.77

PS: Performance status.

[11]. These studies included not only patients with CBDS but also patients with various biliopancreatic diseases.

In this study, we examined the outcomes of ERCP in patients with CBDS, which is the most common indication for ERCP. The rates of therapeutic success, including complete stone removal and permanent biliary stent placement, were comparable between patients with a PS score of 0-2 and those with a PS score of 3 or 4. Although the rates of overall and each ERCP-related complication were not different between the two groups, complications were generally observed to be more severe in patients with a PS score of 3 or 4. Therefore, ERCP for CBDS can be performed effectively in patients with a PS score of 3 or 4. However, endoscopists should try their best to reduce the occurrence of ERCP-related complications because these complications can be more severe in patients with a PS score of 3 or 4.

In this study, indications of ERCP for CBDS and absence of antibiotics were significant risk factors for ERCP-related complications in the multivariate analysis. While the patients with acute cholangitis and biliary pancreatitis had a low risk for ERCP-related complications, those with obstructive jaundice without cholangitis and asymptomatic CBDS had a high risk for ERCP-related complications. Therefore, we emphasize that the indication of ERCP for CBDS should be carefully considered in patients with a PS score of 3 or 4. Although patients with acute cholangitis and biliary pancreatitis should be endoscopically treated, conservative treatment or follow-up strategy might be considered as an appropriate alternative in patients without acute cholangitis, especially those with asymptomatic CBDS. Regarding the use of antibiotics, the European Society of Gastrointestinal Endoscopy guidelines suggested the use of antibiotic prophylaxis in selected patients such as immunocompromised patients[16]. Antibiotic prophylaxis before ERCP to prevent ERCP-related cholangitis and aspiration pneumonia may be administered in patients with a PS score of 3 or 4 because such patients can be immunocompromised.

A previous study revealed that long procedure time was a significant risk factor for ERCP-related complications in patients with a PS score of 4[11]. Although not statistically significant, a prolonged ERCP procedure tended to increase ERCP-related complications in this study. Permanent biliary stent placement without CBDS removal is a therapeutic option to shorten the procedure time. However, a randomized control trial demonstrated that long-term biliary complications at a median follow-up duration of 20 mo were significantly higher in the permanent biliary stent placement group (complication rate: 36%) than in the complete CBDS removal group (complication rate: 14%)[17]. Another retrospective study at a median follow-up duration of 623 d showed similar results[18]. Therefore, complete CBDS removal should be considered at first, and permanent biliary stent placement can be an option in patients with a PS score of 3 or 4 for whom a short prognosis is predicted, who have an underlying disease that is severe, and who are expected to receive prolonged ERCP procedures such as for large and multiple CBDS.

Unlike the results of previous reports[11,12], the rates of aspiration pneumonia were not different between the two groups, and there were no cardiovascular complications in this study. Our sedation protocol using the data pertaining to the age and weight of patients may be attributed to a low incidence of aspiration pneumonia in patients with a PS score of 3 or 4 in this study. Furthermore, careful vital sign monitoring was performed during ERCP, particularly in patients with poor PS.

There are several limitations of this study. First, this was a retrospective study that included specialized centers in Japan. Second, although we balanced patients' characteristics using one-to-one propensity score matching, some unmeasured confounding factors may exist. Therefore, some selection bias may not be excluded. Third, long-term outcomes of ERCP were not examined in this study. Future multicenter studies including large patient cohorts from institutions with different ERCP experiences are warranted to confirm the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4.

Table 4 Predictive factors for endoscopic retrograde cholangiopancreatography (ERCP)-related complications after ERCP for common bile duct stones

	Univariate analysis			Multivariate analysis		
	With complications (*n* = 116)	Without complications (*n* = 1227)	*P* value	Odds ratio	95%CI	*P* value
Indications of ERCP for CBDS			< 0.001	1.1	1.05-1.2	< 0.001
Acute cholangitis (%)	44 (37.9)	757 (61.7)				
Biliary pancreatitis (%)	1 (0.9)	63 (5.1)				
Obstructive jaundice without cholangitis (%)	35 (30.2)	248 (20.2)				
Asymptomatic CBDS (%)	36 (31.0)	159 (13.0)				
Absence of antibiotics (%)	41 (35.3)	205 (16.7)	< 0.001	1.7	1.04-2.7	0.034
Mean procedure time, min [mean (SD)]	33.4 (17.3)	26.7 (15.5)	< 0.001	1.01	1.00-1.02	0.098
Difficult biliary cannulation (%)	50 (43.1)	307 (25.0)	< 0.001	1.3	0.74-2.3	0.36
Pancreatic injection (%)	69 (59.5)	537 (43.8)	0.001	1.4	0.85-2.1	0.20
Contrast-assisted cannulation (%)	68 (58.6)	872 (71.1)	0.008	0.90	0.47-1.7	0.74
Prophylactic pancreatic stent placement (%)	27 (23.3)	174 (14.2)	0.014	0.77	0.45-1.3	0.33
Normal serum bilirubin (%)	68 (58.6)	576 (46.9)	0.019	0.86	0.53-1.4	0.52
PGW-assisted cannulation (%)	24 (20.7)	162 (13.2)	0.034	1.0	0.77-1.3	0.98
Precut sphincterotomy (%)	11 (9.5)	61 (5.0)	0.050	0.96	0.76-1.2	0.76
Age [mean (SD)]	72.5 (14.8)	75.1 (13.9)	0.051	1.0	0.98-1.01	0.66
Non-dilated CBD (< 10 mm) (%)	55 (47.4)	469 (38.2)	0.058	1.3	0.82-1.9	0.30
Protease inhibitor (%)	51 (44.0)	467 (38.1)	0.23			
EPBD (%)	18 (15.5)	145 (11.8)	0.24			
Trainees (%)	24 (20.7)	202 (16.5)	0.24			
Use of basket catheter (%)	47 (40.5)	562 (45.8)	0.29			
EPLBD (%)	15 (12.9)	203 (16.5)	0.36			
Platelet counts [mean (SD)] ($\times 10^6$/L)	19.8 (9.8)	19.1 (7.4)	0.39			
EST (%)	97 (83.6)	1062 (86.6)	0.40			
Rectal NSAIDs (%)	8 (6.9)	119 (9.7)	0.41			
Biliary stent placement (%)	95 (81.9)	1042 (84.9)	0.42			
Number of CBD stones [mean (SD)]	2.1 (3.0)	2.2 (2.7)	0.52			
Post-cholecystectomy (%)	10 (8.6)	133 (10.8)	0.53			
Complete stone removal (%)	108 (93.1)	1156 (94.2)	0.54			
Mechanical lithotripsy (%)	21 (18.1)	201 (16.4)	0.60			
Use of balloon catheter (%)	94 (81.0)	969 (79.0)	0.72			
Wire-guided cannulation (%)	13 (11.2)	130 (10.6)	0.88			
Female (%)	55 (47.4)	589 (48.0)	0.92			
PT-INR [mean (SD)]	1.2 (0.90)	1.2 (0.85)	0.93			
Antithrombotic treatment	32 (27.6)	342 (27.9)	1.0			

Billroth-1 reconstruction (%)	3 (2.6)	31 (2.5)	1.0
Presence of gallstones (%)	75 (64.7)	787 (64.1)	1.0
Successful biliary cannulation (%)	115 (99.1)	1209 (98.5)	1.0
Large stones (> 10 mm) (%)	22 (19.0)	234 (19.1)	1.0

CBDS: Common bile duct stones; CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography; PT- EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; PGW: Pancreatic guidewire; NSAIDs: Nonsteroidal anti-inflammatory drugs; INR: Prothrombin time-international normalized ratio.

In conclusion, ERCP for CBDS in patients with a PS score of 3 or 4 can be performed effectively. Thus, endoscopists should not be reluctant to perform ERCP for CBDS in patients with a PS score 3 or 4. Nevertheless, the indication of ERCP for CBDS, particularly in patients with asymptomatic CBDS, requires careful consideration, and antibiotics should be used before ERCP in patients with a PS score of 3 or 4.

CONCLUSION

ERCP for CBDS in patients with a PS score of 3 or 4 can be performed effectively. Thus, endoscopists should not be reluctant to perform ERCP for CBDS in patients with a PS score 3 or 4. Nevertheless, the indication of ERCP for CBDS, particularly in patients with asymptomatic CBDS, requires careful consideration, and antibiotics should be used before ERCP in patients with a PS score of 3 or 4.

ARTICLE HIGHLIGHTS

Research background

In parallel with the growing aging population worldwide, endoscopic retrograde cholangiopancreatography (ERCP) is being increasingly used in the treatment of common bile duct stones (CBDS) in patients with a poor performance status (PS). Therefore, determining the safety and efficacy of ERCP for CBDS in patients with a PS score of 3 or 4 is essential.

Research motivation

PS is an important tool to elucidate the indications and strategies of ERCP for CBDS in elderly patients. However, few studies examined the safety and efficacy of ERCP for CBDS in patients with a poor PS.

Research objectives

To examine the safety and efficacy of ERCP for CBDS in patients with poor PS, which is defined as a PS score of 3 or 4.

Research methods

We reviewed the medical records of three institutions in Japan from April 2012 to February 2020. The exclusion criteria were (1) failure to detect CBDS during ERCP; (2) history of therapeutic ERCP; and (3) and an already surgically altered gastrointestinal tract including Billroth II or Roux-en-Y reconstruction. Finally, we identified 1343 patients with choledocholithiasis who met the inclusion criteria for the study, and 1113 and 230 patients had PS scores of 0-2 and 3 or 4, respectively. One-to-one propensity score matching was performed to compare the safety and efficacy of ERCP for CBDS between patients with PS scores of 0-2 and 3 or 4.

Research results

The overall ERCP-related complication rates in all patients with PS scores of 0-2 and 3 or 4 were 9.0% (100/1113) and 7.0% (16/230; $P = 0.37$), respectively. In the propensity score-matched group, the overall ERCP-related complication rates were 4.6% (9/196) and 6.6% (13/196; $P = 0.51$) among patients with PS scores of 0-2 and PS 3-4, respectively, and complications were significantly more severe in the group with a PS score of 3-4 than in the groups with a PS score of 0-2 ($P = 0.042$). In multivariate analysis, risk factors for ERCP-related complications were indication of ERCP and absence of antibiotics ($P < 0.001$ and $P = 0.034$, respectively). Particularly, absence of acute cholangitis including asymptomatic CBDS, was associated with increased risk of ERCP-related complications. Therapeutic success rates, including complete CBDS removal and permanent biliary stent placement, in propensity score-matched patients

with PS scores of 0-2 and 3 or 4 were 97.4% (191/196) and 97.4% (191/196), respectively (P = 1.0).

Research conclusions

ERCP for CBDS can be performed effectively in patients with a PS score of 3 or 4. The rates of ERCP-related complications were similar between the patients with PS scores of 0-2 and 3 or 4; however, their severity was higher in the group with a PS score of 3 or 4 than in the group with a PS score of 0-2. The indication of ERCP for CBDS, particularly in patients with asymptomatic CBDS, requires careful consideration, and antibiotics should be administrated before ERCP in patients with a PS score of 3 or 4.

Research perspectives

The retrospective study design that included specialized centers in Japan was an important limitation of this study. Future multicenter studies including large patient cohorts from institutions with different ERCP experiences are warranted to confirm our findings.

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FOOTNOTES

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Country/Territory of origin: Japan

ORCID number: Hirokazu Saito 0000-0001-8729-9604; Yoshihiro Kadono 0000-0003-2358-120X; Takashi Shono 0000-0002-7577-2991; Kentaro Kamikawa 0000-0002-7783-7584; Atsushi Urata 0000-0001-8232-0988; Jiro Nasu 0000-0001-8555-7454; Haruo Imamura 0000-0001-6825-3758; Ikuo Matsushita 0000-0001-5160-8823; Tatsuyuki Kakuma 0000-0002-3713-3099; Shuji Tada 0000-0001-9087-5457.

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ORIGINAL ARTICLE

Retrospective Study

Improving sessile serrated adenoma detection rates with high definition colonoscopy: A retrospective study

Abhinav Sehgal, Soorya Aggarwal, Rohan Mandaliya, Thomas Loughney, Mark C Mattar

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Abhinav Sehgal, Department of Gastroenterology, Georgetown University School of Medicine, Washington, DC 20007, United States

Soorya Aggarwal, Rohan Mandaliya, Thomas Loughney, Mark C Mattar, Division of Gastroenterology, MedStar Georgetown University Hospital, Washington, DC 20007, United States

Corresponding author: Abhinav Sehgal, BSc, Academic Research, Department of Gastroenterology, Georgetown University School of Medicine, 3800 Reservoir Road NW, Washington, DC 20007, United States. as4426@georgetown.edu

Abstract

BACKGROUND

Sessile serrated adenomas (SSAs) are important premalignant lesions that are difficult to detect during colonoscopy due to poor definition, concealment by mucous caps, and flat appearance. High definition (HD) colonoscopy may uniquely aid in the detection of these inconspicuous lesions compared to standard definition (SD) colonoscopes. In the absence of existing clinical guidelines to obligate the use of HD colonoscopy for colorectal cancer screening in average-risk patients, demonstrating the benefit of HD colonoscopy on SSA detection rate (SSADR) may help strengthen the evidence to recommend its use in all settings.

AIM

To evaluate the benefit of HD colonoscopy compared to SD colonoscopy on SSADR in average-risk patients undergoing screening colonoscopy.

METHODS

Data from screening colonoscopies for patients aged 50-76 years two years before and two years after the transition from SD colonoscopy to HD colonoscopy at our large, academic teaching center were collected. Patients with symptoms of colorectal disease, positive occult blood test, history of colon polyps, cancer, polyposis syndrome, inflammatory bowel disease or family history of colon cancer or polyps were excluded. Patients whose endoscopists did not perform colonoscopies both before and after scope definition change were also excluded. Differences in individual endoscopist SSADR, average SSADR, and overall SSADR with SD colonoscopy *vs* HD colonoscopy were also evaluated for significance.

RESULTS
A total of 3657 colonoscopies met eligibility criteria with 2012 colonoscopies from the SD colonoscopy period and 1645 colonoscopies from the HD colonoscopy period from a pool of 11 endoscopists. Statistically significant improvements of 2.30% in mean SSADR and 2.53% in overall SSADR were noted with HD colonoscopy (P = 0.00028 and P = 0.00849, respectively). On the individual level, three endoscopists experienced statistically significant benefit with HD colonoscopy (+5.74%, P = 0.0056; +4.50%, P = 0.0278; +4.84%, P = 0.03486).

CONCLUSION
Our study suggests that HD colonoscopy statistically significantly improves sessile serrated adenoma detection rate in the screening of average risk patients during screening colonoscopy. By improving the detection and removal of these lesions, adoption of HD colonoscopy may reduce the significant premalignant burden of sessile serrated adenomas.

Key Words: Colonoscopy; High definition; Standard definition; Sessile serrated adenoma; Colorectal cancer screening

Core Tip: Sessile serrated adenomas (SSA) have become increasingly recognized as important premalignant lesions that are difficult to detect during colonoscopy due to similarity in appearance to surrounding colonic mucosa. We performed a retrospective study to evaluate the impact of high definition (HD) colonoscopy compared to standard definition colonoscopy on SSA detection rate (SSADR) during screening colonoscopy. Our study found a statistically significant benefit to SSADR with HD colonoscopy that also met benchmark detection rates. To our knowledge, this study is the first to show the utility of HD colonoscopy for SSADR in average-risk patients, thereby demonstrating it as an important tool for routine colorectal cancer screening. In the absence of a strong clinical guideline to obligate the use of HD colonoscopy, the benefit demonstrated to SSADR by HD colonoscopy in our study may help strengthen the evidence to recommend its use in all settings.

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INTRODUCTION

Serrated adenomatous lesions have been increasingly recognized for their potential for transformation into malignancy more rapidly than conventional adenomas, contributing to approximately 15%-30% of all colorectal cancers (CRC). Serrated adenomas are typically classified into three types: sessile serrated polyps/adenomas (SSA), hyperplastic polyps (HP), and traditional serrated adenomas (TSA). Among these subtypes, SSAs are important due to their malignant potential and difficulty in detection during colonoscopy given poor circumscription, concealment by mucous caps, and flat appearance[1,2]. An analysis of two databases of screening colonoscopies in 2012 approximated that the prevalence of proximal serrated polyps (SSA, HP, and TSA) may be as high as 18%-20%[3]. Given the prevalence of SSAs, their difficulty in detection and their significant malignant potential, there is a critical need to improve the detection of this subtype of serrated lesions during screening colonoscopy[1].

Few endoscopic interventions have been found to meaningfully improve SSA detection rate (SSADR). Slower withdrawal time has shown efficacy according to a Dutch study that reported an OR of 1.12 (95%CI: 1.10-1.16) for proximal serrated polyp (SSA, HP, and TSA) detection with longer withdrawal times[4]. This is supported by data from the New Hampshire colonoscopy registry that demonstrated an increasing rate of serrated lesion detection (SSA and HP) per minute between 6-9 min of withdrawal time[4,5]. Similarly, chromoendoscopy with indigocarmine dye as surface contrast agent has also been suggested to enhance the detection of sessile lesions (SSA and HP) compared to conventional colonoscopy (1.19 *vs* 0.49 per patient, P < 0.001)[6]. Finally, use of the mucolytic agent acetic acid compared to normal saline during colonoscopy has been shown to significantly improve SSA detection in the right colon (13.5% *vs* 0.5%, P < 0.001)[7]. Interventions that have shown negligible improvement in SSADR include: narrowed spectrum endoscopy, antispasmodics, and wide angle and enhanced

mucosal views. High definition (HD) colonoscopy, on the other hand, has been cited as possibly beneficial in the detection of serrated polyps by the British Society of Gastroenterology, although data is lacking on its efficacy[1].

Though HD colonoscopy has been touted for its perceived benefits in the detection of adenomas due to heightened image resolution and magnification, there is still a lack of sufficient high quality data to obligate its use. The most recent position by the European Society of Gastrointestinal Endoscopy (ESGE) on the adoption of HD colonoscopy for overall adenoma detection in average risk patients is weak, citing inconsistent trial results, which may deter centers that currently use SD colonoscopy from adopting HD colonoscopy[8,9]. Given the lack of data on the adoption rate of HD colonoscopy outside of tertiary care centers, proving the benefit of HD colonoscopy on the detection of premalignant SSAs, specifically, may help strengthen the evidence behind its use in all settings.

Given the limited high-quality data supporting the use of HD colonoscopy in screening average-risk populations, it is understandable that there is also minimal data specifically on the impact of HD colonoscopy and SSADR. A recent study by Roelandt *et al*[10] that compared effects of endoscopy system, colonoscope definition, and virtual chromoendoscopy performed a subgroup SSADR analysis found significant benefit with 582 HD colonoscopies compared to 505 SD colonoscopies (8.2% *vs* 3.8%, respectively). However, a significant limitation of this study, was its inclusion of diagnostic (32.1%) as well as surveillance colonoscopies (29.3%), likely performed to increase sample size but potentially misrepresenting the improvement in SSADR that can be attributed to HD colonoscopy[10,11]. Another study by East *et al*[12] of 72 standard colonoscopies and 58 HD colonoscopies that investigated improvements in hyperplastic polyp detection (defined to include SSA and HP) with optimized withdrawal technique found a nonsignificant improvement with HD colonoscopy. It should be noted, however, that given the small study size, the benefit to SSADR may not be detectable especially given that SSAs make up a relatively lower proportion of all polyps detected on colonoscopy[12].

Based on the limited high powered, high quality studies available on detection of SSAs in HD colonoscopy, there is room in the literature for additional study on this subject. As such, we performed a retrospective study to evaluate the impact of HD colonoscopy compared to SD colonoscopy on SSADR exclusively during screening colonoscopy. Our secondary analysis compared overall adenoma detection rates with HD colonoscopy *vs* SD colonoscopy at our center.

MATERIALS AND METHODS

Materials

All colonoscopies performed at our tertiary medical center in the two years before and after the transition from SD colonoscopy to HD colonoscopy on June 2nd, 2018 were identified. All other procedural elements were uniform during the 4-year study period. All pathology specimens were reviewed solely by the pathology department at our institution. For the primary SSADR analysis, each colonoscopy report and associated pathology report during the defined study period were collected, from which patient demographics, colonoscopy date, colonoscopy indication, colonoscopy findings (polyp/lesion presence and type), and endoscopist data were compiled. For the secondary analysis involving adenoma detection rate (ADR), preexisting ADR data from our center with the same inclusion criteria during the same time period was used.

Inclusion criteria

All patients aged 50-76 years who underwent a screening colonoscopy between June 1, 2016 – June 2, 2020 were included. Patients with any symptoms of colorectal disease, positive occult blood test, history of colon polyps, cancer, polyposis syndrome, inflammatory bowel disease or family history of colon cancer or polyps were excluded. Patients whose endoscopists did not perform colonoscopies both before and after scope definition change were also excluded.

Statistical analysis

All statistical analyses were performed with Microsoft Excel and JMP PRO 15 software. Two-sided *P*-values < 0.05 were considered significant. Biostatistical analysis was performed by the authors.

The average age and the sex distribution of the SD colonoscopy group (June 1, 2016 – June 1, 2018) and the HD colonoscopy group (June 2, 2018 – June 2, 2020) were compared for demographic data. These comparisons were only performed with data from the SSADR analysis.

The primary outcome measure was SSA detection rate (SSADR), defined as the proportion of eligible colonoscopies in which at least one SSA was identified, for both the SD and HD colonoscopy periods. Individual differences in endoscopist SSADRs with SD colonoscopy and HD colonoscopy were evaluated by Z-test. Mean SSADR and overall SSADR were also reported. Mean SSADRs were calculated as the average of the individual endoscopist SSADRs. The difference in mean SSADRs with SD and HD colonoscopy was evaluated with the paired *t*-test. Overall SSADRs were calculated as the sum of all SSA-positive colonoscopies over the total number of eligible colonoscopies. The difference in overall SSADR with SD and HD colonoscopy was evaluated with the Z-test.

Table 1 Demographic characteristics of the standard definition colonoscopy and high definition colonoscopy groups

Variable	Standard definition, *n* = 2012	High definition, *n* = 1645	*P* value
Age (yr), mean (range)	59.3 (50-76)	59.2 (50-76)	0.985
Gender, male (%)	896 (44.5%)	757 (46.0%)	0.36812

Table 2 Endoscopist, overall, and average sessile serrated adenomas detection rates with corresponding colonoscopy volumes during standard definition colonoscopy and high definition colonoscopy

Endoscopist	Standard definition		High definition		Δ	*P* value (α < 0.05)
	Eligible colonoscopies	SSADR	Eligible colonoscopies	SSADR		
1	166	4.22%	229	2.18%	-2.03%	0.24604
2	303	2.97%	279	4.66%	1.69%	0.28462
3	82	0.00%	124	2.42%	2.42%	0.1556
4	171	5.26%	37	5.41%	0.14%	0.9681
5	63	0.00%	51	3.92%	3.92%	0.11184
6	135	1.48%	98	4.08%	2.60%	0.21498
7	125	1.60%	76	2.63%	1.03%	0.61006
8	410	6.34%	356	12.08%	5.74%	0.0056
9	238	1.68%	97	6.19%	4.50%	0.0278
10	191	2.62%	161	7.45%	4.84%	0.03486
11	128	3.91%	137	4.38%	0.47%	0.8493
Overall	2012	3.43%	1645	5.96%	2.53%	0.00028
Average	182.91	2.73%	149.54	5.04%	2.30%	0.00849

SSADR: Sessile serrated adenomas detection rate.

A secondary outcome measure was ADR, defined as the proportion of eligible colonoscopies in which at least one adenoma of any type was identified. Individual differences in endoscopist ADRs with SD and HD colonoscopy were evaluated with the Z-test. Mean ADR and overall ADR were also reported. Mean ADRs were calculated as the average of the individual endoscopist ADRs. The difference in mean ADRs with SD and HD colonoscopy was evaluated with the paired *t*-test. Overall ADRs were calculated as the sum of all SSA-positive colonoscopies over the total number of eligible colonoscopies. The difference in overall ADR with SD and HD colonoscopy was evaluated with the Z-test.

RESULTS

Following review of the data, 3657 cases met eligibility criteria with 2012 colonoscopies in the SD group and 1645 colonoscopies in the HD group for the SSADR analysis. Eleven endoscopists performed colonoscopies both before and after implementation of HD colonoscopy on June 2, 2018.

Demographic analysis of the SD and HD groups (Table 1) show the average age in both groups was 59 years and that males comprised approximately 45% of both groups. There was no significant difference in average age or sex distribution between the SD and HD groups.

The mean SSADRs with SD colonoscopy and HD colonoscopy were 2.73% and 5.04%, respectively, yielding a statistically significant improvement of 2.30% (P = 0.00028). Comparison of the overall SSADRs also showed a statistically significant improvement from 3.43% with SD colonoscopy to 5.96% with HD colonoscopy (Δ 2.53%, P = 0.00849). Most of the endoscopists also demonstrated individual increases in SSADR with HD colonoscopy. On the individual level, three endoscopists experienced statistically significant benefit with HD colonoscopy (+5.74%, P = 0.0056, +4.50%, P = 0.0278, +4.84%, P = 0.03486). One endoscopist had a reduction in SSADR, but this difference was statistically nonsignificant (-2.03%, P = 0.24604) (Table 2 and Figure 1A).

Table 3 Endoscopist, overall, and average adenoma detection rates with corresponding colonoscopy volumes during standard definition colonoscopy and high definition colonoscopy

Endoscopist	Standard definition		High definition		Δ	*P* value (α < 0.05)
	Eligible colonoscopies	ADR	Eligible colonoscopies	ADR		
1	262	30.15%	250	28.80%	-1.35%	0.72786
2	492	25.20%	311	44.37%	19.17%	< 0.00001
3	49	6.12%	104	38.46%	32.34%	< 0.00001
6	145	31.72%	104	39.42%	7.70%	0.20766
7	245	21.22%	127	31.50%	10.27%	0.02926
8	493	31.64%	360	43.61%	11.97%	0.00034
9	283	29.68%	78	32.05%	2.37%	0.68916
10	289	24.91%	162	38.27%	13.36%	0.00288
11	91	42.86%	138	43.48%	0.62%	0.92828
Overall	2349	27.88%	1634	38.86%	10.98%	< 0.00001
Average	261	27.06%	181.6	37.77%	10.72%	0.01522

ADR: Adenoma detection rate.

Preexisting ADR data was only available for nine of the eleven endoscopists. The mean ADRs with SD colonoscopy and HD colonoscopy were 27.06% and 37.77%, respectively, yielding a significant improvement of 10.72% (P = 0.01522). Comparison of the overall ADRs also showed a significant improvement with HD colonoscopy (Δ 10.98%, P < 0.00001). Most of the endoscopists demonstrated individual increases in ADR with HD colonoscopy. Five of these endoscopists saw significant benefit. One endoscopist had a minimal reduction in ADR, but this difference was nonsignificant (Table 3 and Figure 1B).

DISCUSSION

Identifying techniques that improve the detection of SSAs will help reduce interval colon cancer in screening colonoscopy[1,3]. In the absence of high-quality evidence to obligate the use of HD colonoscopy for the average-risk population, we performed a retrospective study to evaluate the benefit of HD colonoscopy compared to SD colonoscopy on SSADR during screening colonoscopy[8]. In addition to the significant improvements to both average and overall SSADRs, benefit from HD colonoscopy was further underscored by the average SSADR surpassing the serrated lesion benchmark detection rate of 7% (inclusive of HPs)[1,11]. To our knowledge, this study is the first to illustrate the utility of HD colonoscopy for SSADR in average risk patients, solidifying its role as a tool in high quality CRC screening.

Notably, our study demonstrated significant benefit to all adenoma/polyp detection rates, not simply SSADR. It should be acknowledged, however, that it is possible that our ADR outcomes were improved slightly by the independent improvement of endoscopists during the four-year study period or by HD colonoscopy itself. Interestingly, our data is also consistent with an existing study by Waldmann *et al*[13] that reported significant increases in ADR with HD colonoscopy in endoscopists with historically lower ADR , as each of the four endoscopists in our study with an ADR < 30% experienced statistically significant increases in ADR with HD colonoscopy. In contrast, four of the five endoscopists with an ADR ≥ 30% with SD colonoscopy did not experience such improvement with HD colonoscopy in our study, further supporting the selective benefit of HD colonoscopy for endoscopists with lower ADRs.

A major strength to our study is the exclusion of surveillance and diagnostic procedures to focus solely on screening colonoscopies. This is in contrast to the existing study by Roelandt *et al*[10] on HD colonoscopy and SSADR that included both diagnostic and surveillance colonoscopies in its analysis. Our criteria allow for our results to be more generalizable to average risk patients and more applicable to benchmark detection rates set for the screening population[11]. Another advantage was that our study was sufficiently powered compared to any other available literature similarly studying SSADR with HD colonoscopy to date[10,12].

In acknowledging the strengths to our data, it is also important to consider why this improvement to SSADR has not clearly been reflected in the overall ADRs in existing study on HD colonoscopy, as

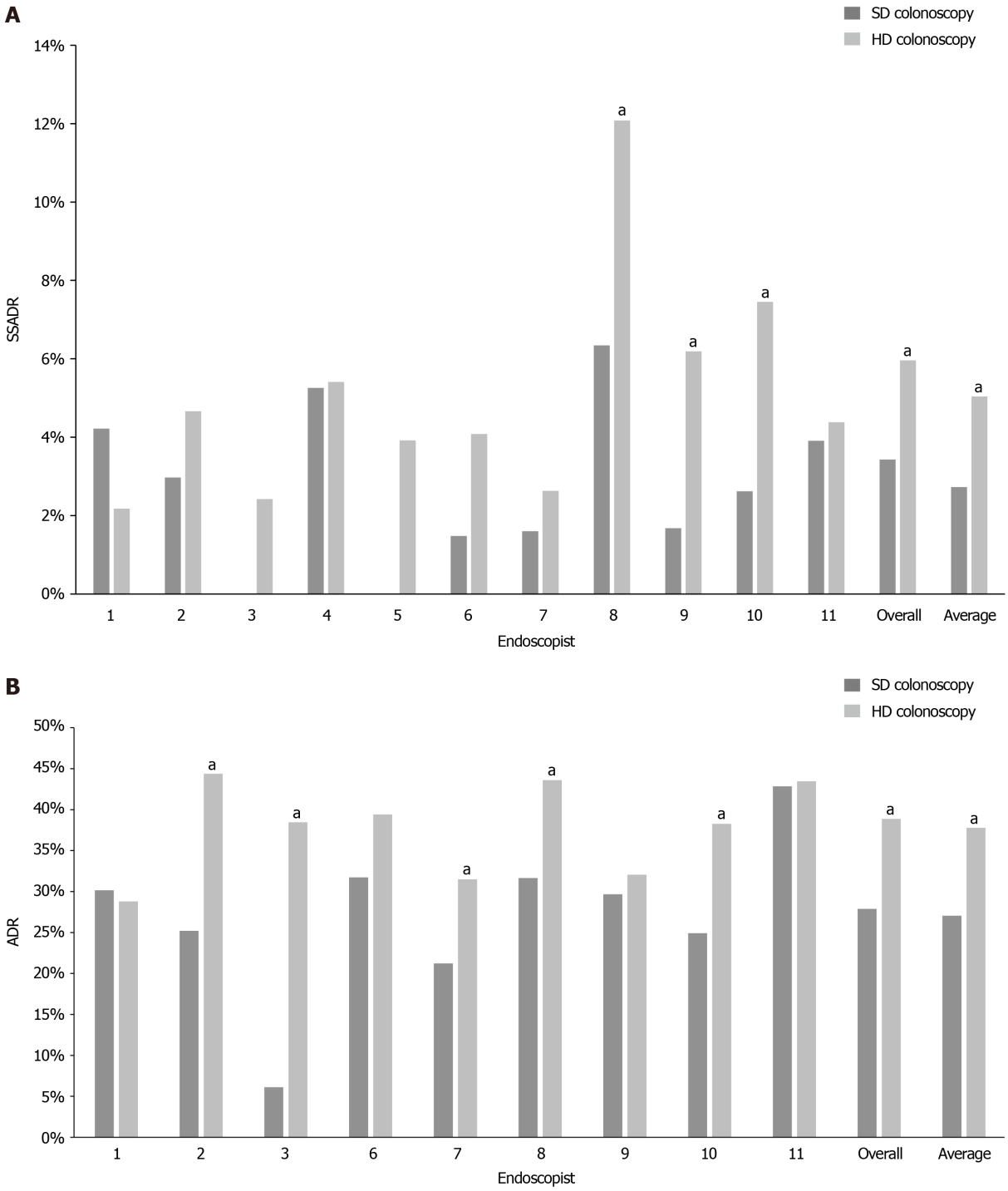

Figure 1 Endoscopist, overall, and average sessile serrated adenomas detection rates (A) and adenoma detection rates (B) during standard definition colonoscopy and high definition colonoscopy. [a]*P* < 0.05. SSADR: Sessile serrated adenomas detection rate; ADR: Adenoma detection rate; SD: Standard definition; HD: High definition.

demonstrated by the weak recommendation by the ESGE on the utility of HD colonoscopy[8]. It is possible that higher quality endoscopes have more utility in the detection of subtle SSA lesions than in the detection of adenomatous polyps that have been historically easier to identify, perhaps limiting the overall benefit of HD colonoscopy on detection of the conventional adenomas. Thus, as SSAs make up a relatively small component of overall ADR compared to conventional adenomas, the significant improvement to SSADR may be undetectable when assessing the improvement to all adenoma detection with HD colonoscopy. In this way, our results help to highlight a significant benefit of HD colonoscopy that may have been overlooked in prior studies of HD colonoscopy focused on overall ADR. This allows for stronger recommendations for the use of HD colonoscopy given that improved SSA detection is an unmet need in screening colonoscopy.

We acknowledge some limitations to our study. A main limitation is the retrospective design of the study. In addition, while the longitudinal nature of the study permitted a relatively large number of colonoscopies to be included in our analysis, the four-year period allowed for changing skill level of endoscopists over time. Another limitation is that our study did not control for withdrawal time. In studies past, this has been one factor that has been demonstrated to significantly improve SSADR with maximum benefit at 9 min of withdrawal time[4,5]. Nevertheless, the withdrawal times of our endoscopists may have been optimized on average as the mean withdrawal time of academic gastroenterologists has been reported to be 9.1 min[5,14]. Another consideration arises from a lack of control for bowel preparation quality in our study. Although two prior studies that have evaluated the impact of bowel preparation on SSA detection found a nonsignificant impact of bowel preparation on SSADR, a 2016 prospective study reported significant decrease in SSADR with bowel preparation quality that is below high quality in a population of veterans with high adenoma prevalence, suggesting that our study's lack of exclusion of colonoscopies with suboptimal bowel preparation may have falsely lowered our SSADR results[4,15,16]. We also acknowledge discrepancies of eligible colonoscopy totals for the SSADR data collected directly for this study and ADR data collected from a preexisting study at our center, likely due to differences in the manual review of eligible colonoscopies during respective data compilations. COVID-19 also significantly impacted elective procedures in 2020, reducing the number of colonoscopies in the HD colonoscopy group.

CONCLUSION

In conclusion, our study suggests that high definition colonoscopy significantly improves sessile serrated adenoma detection in the screening of average risk patients. By improving the detection and removal of these lesions, adoption of high definition colonoscopy may reduce the significant premalignant burden of sessile serrated adenomas.

ARTICLE HIGHLIGHTS

Research background

Sessile serrated adenomas (SSA) have become increasingly recognized as important premalignant lesions that are difficult to detect during colonoscopy due to similarity in appearance to surrounding colonic mucosa. Hypothesizing that higher resolution colonoscopy may improve SSA detection rates (SSADR), we performed a retrospective study to evaluate the impact of high definition (HD) colonoscopy compared to standard definition (SD) colonoscopy on SSADR during screening colonoscopy. To our knowledge, this study is the first to study the utility of HD colonoscopy for SSADR in average-risk patients. In the absence of a strong clinical guideline to obligate the use of HD colonoscopy, the benefit demonstrated to SSADR by HD colonoscopy in our study may help strengthen the evidence to recommend its use in all settings.

Research motivation

To our knowledge, there has been no study on the efficacy of HD colonoscopy *vs* SD colonoscopy on SSADR in average risk patients undergoing screening colonoscopy only. Furtheremore, the most recent position by the European Society of Gastrointestinal Endoscopy on the adoption of HD colonoscopy for overall adenoma detection in average risk patients is weak, citing inconsistent trial results, which may deter centers that currently use SD colonoscopy from adopting HD colonoscopy. Given the lack of data on the adoption rate of HD colonoscopy outside of tertiary care centers, proving the benefit of HD colonoscopy on the detection of premalignant SSAs, specifically, may help strengthen the evidence behind its use in all settings.

Research objectives

We performed a retrospective study to evaluate the impact of HD colonoscopy compared to SD colonoscopy on SSADR exclusively during screening colonoscopy. Our secondary analysis compared overall adenoma detection rates (ADR) with HD colonoscopy *vs* SD colonoscopy at our center. By demonstrating that high definition colonoscopy significantly improves sessile serrated adenoma detection in the screening of average risk patients, the adoption of high definition colonoscopy may be universally recommended to reduce the significant premalignant burden of sessile serrated adenomas.

Research methods

All colonoscopies performed at our tertiary medical center in the two years before and after the transition from SD colonoscopy to HD colonoscopy on June 2nd, 2018 were identified. For the primary SSADR analysis, each colonoscopy report and associated pathology report during the defined study

period were collected, from which patient demographics, colonoscopy date, colonoscopy indication, colonoscopy findings (polyp/Lesion presence and type), and endoscopist data were compiled. For the secondary analysis involving ADR, preexisting ADR data from our center with the same inclusion criteria during the same time period was used. The average age and the sex distribution of the SD colonoscopy group (June 1, 2016 – June 1, 2018) and the HD colonoscopy group (June 2, 2018 – June 2, 2020) were compared for demographic data, using only data from the SSADR analysis. The primary outcome measure were differences in individual endoscopist, overall, and mean SSA detection rate (SSADR) (defined as the proportion of eligible colonoscopies in which at least one SSA was identified) for the SD and HD colonoscopy periods. The secondary outcome measure was differences in individual endoscopist, overall, and mean overall adenoma detection rate (defined as the proportion of eligible colonoscopies in which at least one adenoma of any type was identified) for the SD and HD colonoscopy periods.

Research results

There was no significant difference in average age or sex distribution between the SD and HD groups. The mean SSADRs with SD colonoscopy and HD colonoscopy were 2.73% and 5.04%, respectively, yielding a statistically significant improvement of 2.30% (P = 0.00028). Comparison of the overall SSADRs also showed a statistically significant improvement from 3.43% with SD colonoscopy to 5.96% with HD colonoscopy (Δ 2.53%, P = 0.00849). On the individual level, three endoscopists experienced statistically significant benefit with HD colonoscopy (+5.74%, P = 0.0056, +4.50%, P = 0.0278, +4.84%, P = 0.03486). Preexisting ADR data was only available for nine of the eleven endoscopists. The mean ADRs with SD colonoscopy and HD colonoscopy were 27.06% and 37.77%, respectively, yielding a significant improvement of 10.72% (P = 0.01522). Comparison of the overall ADRs also showed a significant improvement with HD colonoscopy (Δ 10.98%, P < 0.00001). Most of the endoscopists demonstrated individual increases in ADR with HD colonoscopy. Five of these endoscopists saw significant benefit.

Research conclusions

To our knowledge, this study is the first to show the utility of HD colonoscopy for SSADR in average-risk patients, thereby demonstrating it as an important tool to improve the detection and removal of these premalignant lesions during routine colorectal cancer screening. Furthermore, in the absence of a strong clinical guideline to obligate the use of HD colonoscopy, the benefit demonstrated to SSADR by HD colonoscopy in our study may help strengthen the evidence to recommend its use in all settings.

Research perspectives

Future research endeavors should include randomized control trials to assess the efficacy of HD *vs* SD colonoscopy in average-risk patients undergoing screening colonoscopy only.

FOOTNOTES

Author contributions: Sehgal A, Aggarwal S, Mandaliya R, Loughney TM, and Mattar MC designed the research study; Sehgal A and Aggarwal S performed the research; Sehgal A collected and analyzed the data; Sehgal A and Aggarwal S wrote the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: As our retrospective study qualified as a quality improvement project, our institution did not require IRB approval for our study.

Informed consent statement: As our study was a quality-improvement study with retrospective chart review, informed consent was not necessary at our institution. Any and all details that might disclose the identity of the subjects included in our study were omitted.

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Country/Territory of origin: United States

ORCID number: Abhinav Sehgal 0000-0001-7410-8768; Soorya Aggarwal 0000-0003-0990-632X; Rohan Mandaliya 0000-0002-0749-9022; Thomas Loughney 0000-0002-8691-2072; Mark C Mattar 0000-0002-9339-1607.

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ORIGINAL ARTICLE

Observational Study

Endoscopic resection of superficial bowel neoplasia: The unmet needs in the Egyptian practice

Mohamed H Emara, Mariam Zaghloul, Haidi Karam-Allah Ramadan, Salem Youssef Mohamed, Mohammed Tag-Adeen, Ahmed Alzamzamy, Mohamed Alboraie, Ahmad Madkour, Ahmed Youssef Altonbary, Tarik I Zaher, Ahmed Abo Elhassan, Nermeen Abdeen, Mohammed Hussien Ahmed

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Mohamed H Emara, Mariam Zaghloul, Mohammed Hussien Ahmed, Department of Hepatology, Gastroenterology and Infectious Diseases, Kafrelsheikh University, Kafr Elshiekh 33516, Egypt

Haidi Karam-Allah Ramadan, Department of Tropical Medicine and Gastroenterology, Assiut University, Assiut 71515, Egypt

Salem Youssef Mohamed, Department of Internal Medicine, Faculty of Medicine, Gastroenterology and Hepatology Unit, Zagazig University, Zagazig 44519, Egypt

Mohammed Tag-Adeen, Division of Gastroenterology and Hepatology, Department of Internal Medicine, South Valley University, Qena Faculty of Medicine, Qena 83523, Egypt

Ahmed Alzamzamy, Department of Gastroenterology and Hepatology, Maadi Armed Forces Medical Complex, Military Medical Academy, Cairo 11841, Egypt

Mohamed Alboraie, Department of Internal Medicine, Al-Azhar University, Cairo11884, Egypt

Ahmad Madkour, Department of Endemic Medicine, Helwan University, Cairo 11795, Egypt

Ahmed Youssef Altonbary, Department of Gastroenterology and Hepatology, Mansoura University, Mansoura 35516, Egypt

Tarik I Zaher, Department of Tropical Medicine, Zagazig University, Zagazig 44519, Egypt

Ahmed Abo Elhassan, Department of Tropical Medicine, Suez Canal University, Ismailia 41522, Egypt

Nermeen Abdeen, Department of Tropical Medicine, Alexandria University, Alexandria 21526, Egypt

Corresponding author: Mohamed H Emara, MD, Professor, Department of Hepatology, Gastroenterology and Infectious Diseases, Kafrelsheikh University, Algeish, Kafr Elshiekh 33516, Egypt. emara_20007@yahoo.com

Abstract

BACKGROUND

Management of superficial bowel neoplasia (SBN) in early stages is associated with better outcomes. The last few decades experienced a paradigm shift in the management of SBN with the introduction of advanced endoscopic resection techniques (ERTs). However, there are no clear data about the aspects of ERTs in Egypt despite the growing gastroenterology practice.

AIM

To investigate the knowledge, attitude, and practice of ERTs toward management of SBN among Egyptian practitioners and the suitability of the endoscopy units' infrastructures toward these techniques.

METHODS

An online 2-pages questionnaire was used. The first page comprised demographic data, and questions for all physicians, about the knowledge (11 questions) of and attitude (5 questions) toward ERTs as a therapeutic option for SBN. The second page investigated the practice of ERTs by endoscopists (6 questions) and the infrastructures of their endoscopy units (14 questions). The survey was disseminated through July 2021 and the data were collected in an excel sheet and later analyzed anonymously.

RESULTS

The complete responses were 833/2300 (36.2%). The majority of the participants were males (n = 560, 67.2%), middle-aged (n = 366, 43.9%), consultants (n = 464, 55.7%), gastroenterologists (n = 678, 81.4%), spending ≥ 15 years in practice (n = 368, 44.2%), and were working in university hospitals (n = 569, 68.3%). The majority correctly identified the definition of SBN (88.4%) and the terms polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) (92.1%, 90.2%, and 89.1% respectively). However, 26.9%, 43.2% and 49.5% did not recognize the clear indication of polypectomy, EMR, and ESD respectively. Although 68.1% of physicians are convinced about the ERTs for management of SBN; only 8.9% referred all candidate cases for ERTs. About 76.5% of endoscopists had formal training in the basic polypectomy techniques while formal training for EMR and ESD was encountered only in 31.9% and 7.2% respectively. About 71.6% and 88.4% of endoscopists did not perform EMR or ESD in the last one year. Consequently, the complication rate reported by endoscopists was limited to 18.1% (n = 103) of endoscopists. Only 25.8% of endoscopists feel confident in the management of ERTs-related complications and a half (49.9%) were not sure about their competency. Regarding the end-oscopy units' infrastructures, only 4.2% of the centers had their endoscopes 100% armed with optical enhancements and 54.4% considered their institutions ready for managing ERTs-related complications. Only 18.3% (n = 104) of endoscopists treated their complicated cases surgically because the most frequent ERTs-related complications were procedural bleeding (26.7%), and perforations (17%).

CONCLUSION

A significant deficiency was reported in the knowledge and attitude of Egyptian practitioners caring for patients with SBN toward ERTs. The lack of trained endoscopists in both EMR and ESD in part is due to unsuitable infrastructures of many endoscopy units.

Key Words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Polypectomy; Superficial bowel neoplasia; Egypt

Core Tip: A paradigm shift in the management of superficial bowel neoplasia had been observed over the last few decades with the introduction of new endoscopic resection techniques and the advancements reported in the endoscopes and accessories. These advanced endoscopic resection techniques especially endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) necessitates the insertion of knowledge and improvement of the practice attitude of the practitioners before delivering education and training programs to skilled endoscopists. The current study investigated these aspects among Egyptian practitioners and it revealed a significant deficiency in the knowledge and attitude with lack of trained endoscopists in both EMR and ESD in part is due to unsuitable infrastructures of many endoscopy units.

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INTRODUCTION

The prevalence of bowel cancer is variable around the globe. Colon cancer ranks 3rd among all cancers while cancer stomach which has geographic predilection ranks 6th. Cancer colon ranks 2nd while cancer stomach ranks 4th regarding cancer-related death[1]. In Egypt there is no recent formal prevalence rate, however, early reports showed that colorectal cancer ranks 7th most common cancer among Egyptians [2].

Management of early bowel malignancy has been associated with better treatment outcomes; low morbidity and mortality. Over the last two decades, there was a paradigm shift in the management of early bowel malignancy[3,4]. Surgical resection had been the therapeutic option of choice. However, the major advancements in gastrointestinal (GIT) endoscopy evolved in the development of new endoscopic resection techniques (ERTs) as alternative curative options.

Across the literature, ERTs have been associated with better outcomes and improved quality of life in comparison to conventional surgical techniques[3,5]. Different ERTs are currently known and include the standard snare polypectomy techniques, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). Each method had its indications, techniques, complications as well as training curve defined by many of the current practice guidelines[3,6,7].

In Egypt, there is a growing GIT endoscopy practice. Unfortunately, most of the institutions lack formal training programs for junior gastroenterologists. Consequently, no clear data are evident about the current practice of endoscopic resection techniques. We believe that investigating the current aspects of ERTs would alarm; currently and guide; in the near future, the practice as well as the training of advanced resection techniques among Egyptian practitioners. The current study aimed at investigating the knowledge, attitude, and practice of endoscopic resection techniques among Egyptian practitioners managing patients with SBN as well as the suitability of the infrastructures in the endoscopy units toward these techniques.

MATERIALS AND METHODS

Questionnaire development

An online questionnaire was developed and designed only for Egyptian physicians caring for patients with SBN. Besides the demographic data (gender, age, career specialty, the main hospital of practice, *etc.*) in this questionnaire (Supplementary Material), four domains were investigated: (1) Knowledge about the cancerous process of the bowel and its management options, either from authorized websites as international guidelines or real experience (11 questions); (2) Attitude toward (5 questions) ERTs as an acceptable therapeutic option for management of SBN; (3) Practice of ERTs (6 questions); and (4) infrastructures of the national endoscopy units (manpower, endoscopes, accessories, policy, and procedures): One of the important determinants for performing ERTs are infrastructures of the endoscopy units (14 questions)

For all physicians (non-endoscopists and endoscopists), the knowledge about and attitude toward ERTs were assessed while endoscopists only were surveyed for their practice and the infrastructures of their endoscopy units

The questionnaire dissemination

The survey was disseminated through 3 main channels: First, through 2 WhatsApp groups for national gastroenterology physicians. Second, through emails of the national societies for gastroenterologists, internists, and surgeons. Third, through Facebook accounts of the relevant groups. The survey was disseminated through July 2021. A reminder announcement and emails were sent again one week before the closure of the survey. The responses were collected in an online platform (2 online pages; the first page focused on demographic data, knowledge, and attitude while the second page comprised data for endoscopists; evaluating the skills in practice and the infrastructures of their endoscopy units). The data were exported to an excel sheet and were analyzed later anonymously.

Participants

Egyptian physicians manage patients with gastroenterology problems (gastroenterologists, internists, and surgeons).

Sample size calculation

The primary objective of this study was to measure the knowledge, attitude, and practice among Egyptian physicians caring for patients with SBN. Consequently, we tried to reach as many physicians as we can without fixing a sample size, aiming that a large number of recruited physicians improve the reliability of the results.

Ethical considerations

In this survey form, all participants were informed about the volunteer role to participate. The data were analyzed anonymously and the data of participants were not disclosed. The institutional review board of Kafrelsheikh University approved the questionnaire (approval code MKSU code 36-9-21).

Statistical analysis

The data were collected and analyzed using Statistical Package for Social Sciences (SPSS version 26.0) software (IBM SPSS Inc. Chicago, United States). There were no incomplete responses to be excluded from the analysis. The data were expressed as numbers and proportions.

RESULTS

Study participants

In this survey, about 2300 Egyptian physicians were invited. The complete responses were obtained from 833/2300 with a percentage of 36.2%. There were no missing responses from visitors to the first page of the questionnaire (the measure of knowledge and attitude among endoscopists and non-endoscopists) nor to the second page of the questionnaire (endoscopists). About two-third of the participants were males (560, 67.2%) and the majority were middle-aged between 36-45 years (n = 366, 43.9%), were consultants (n = 464, 55.7%), and were gastroenterologists (n = 678, 81.4%). The majority were experienced in practice; spending more than 15 years in practice (n = 368, 44.2%), and about two-third also were working in university hospitals (n = 569, 68.3%) (Table 1).

Although the respondents represented the 4 major regions of Egyptian practice (Cairo, Alexandria, Nile Delta, Upper Egypt), some regions were not represented in the responses *e.g.* the region of Sinai and Suez Canal. More details are shown in Supplementary Table 1.

Knowledge

Although the current survey demonstrated that 88.4% of the physicians correctly identified the SBN as a cancerous process of the bowel that is limited to the mucosa and submucosa, 34.3% and 36.9%of them missed the correct diagnostic (different endoscopic methods) and therapeutic (ERTs) maneuvers for SBN, respectively. These findings explain why 43.2% of the surveyed practitioners failed to describe the different therapeutic modalities for bowel cancer in general. More details about the correct and incorrect responses are shown in Table 2.

The majority of the surveyed physicians identified what is meant by polypectomy, EMR, and ESD correctly in 92.1%, 90.2%, and 89.1% respectively. However, a substantial proportion of them lacks the correct knowledge about the endoscopic treatment for mucosal lesions and the lack of recognition of the correct answer parallels the complexity of the maneuver. For polypectomy, 26.9% did not recognize that endoscopic treatment of pedunculated polyp is snare polypectomy, compared to 43.2% who did not correctly recognize EMR as the standard endoscopic resection technique for non-pedunculated lesions ≤ 15 mm. Furthermore, the frequency rises to 49.5% when ESD was investigated as the endoscopic resection technique for non-pedunculated lesions ≥ 20 mm. Consequently, 28.5% of the surveyed physicians did not recognize the spectrum of indications of ERTs to involve Barrett's high dysplasia, polyps, and SBN (Table 2).

Attitude

Early diagnosis of SBN necessitates picking up cases so early before even any manifestations develop; consequently, screening of average-risk population and/or surveillance of high-risk patients is necessary. However, the screening policy seems deficient in Egyptian practice. According to the personal attitude toward the SBN measured in the current questionnaire by 5 questions, only 15.1% of physicians refer all candidates of screening for endoscopic surveillance. Furthermore, 12.2% of the physicians did not refer the high-risk patients for endoscopic screening, the main bulk of practitioners (72.6%) invariably refer the candidates for screening (Table 3).

Although 68.1% of physicians are convinced about the ERTs as management for SBN; only 8.9% of them refer all candidate cases for ERTs which represents a sort of reluctance in the decision making. When SBN is suspected/confirmed endoscopically only 14.4% of practitioners refer their patients for surgical resection and surprisingly 17.6% did not refer them for surgical resection at all and the main bulk of the surveyed physicians (68%) prefer the patients to resection with variable frequencies (Table 3).

Table 1 Demographic characteristics of the surveyed physicians

Variable	Frequency (*n* = 833)	Percent (%)
Gender		
Male	560	67.2
Female	273	32.8
Age (yr)		
≤ 35	276	33.1
36-45	366	43.9
> 45	191	22.9
Academic categories		
Consultants	464	55.7
Residents	36	4.3
Specialist	333	40.0
Career specialty		
Gastroenterologist	678	81.4
General medicine	121	14.5
Surgery	34	4.1
Years of practice (yr)		
< 5	145	17.4
5-10	120	14.4
10-15	200	24.0
> 15	368	44.2
Main hospital of practice		
Central	80	9.6
General	111	13.3
Teaching institution	73	8.8
University	569	68.3

It seems that the above-mentioned attitude toward endoscopic detection and endoscopic management of SBN is related to individual opinions and behavior because most of the institutions (62.2%) are lacking for panels discussing the management of SBN.

Practice

About two-third of the surveyed physicians were endoscopists (*n* = 570, 68.4%). More than two-third of the endoscopists had formal training in the basic polypectomy techniques (67.5%), while formal training focusing on the advanced ERTs namely EMR and ESD was encountered only in 31.9% and 7.2% respectively which represents a substantial deficiency in training for the advanced ERTs in the Egyptian community. Although most of the endoscopists (58.1%) are familiar with the Paris classification for reporting SBN, only 34.9% are popular with or using Kudo classification, and only 10.5% of endoscopists use other classification systems in reporting their lesions. About two-third (63.7%) were aware of the causes that increase the submucosal fibrosis which ultimately affect the success rates of advanced ERTs (Table 4).

Regarding the personal/individual skills (Table 5) for ERTs, a substantial number of the surveyed endoscopists (67.4%) did not excise polyps in the last year, although the cause is not clear this probably reflects the low prevalence of bowel neoplasia in the Egyptian community. This seems accepted because 71.6% did not perform EMR in the last year and 88.4% of the endoscopists did not perform ESDs in the last year. Consequently, it is accepted that the complication rate reported by endoscopists was limited to 18.1% (*n* = 103) of endoscopists. An alarm reported in the current survey is the competency in management of ERTs-related complications. Only 25.8% of endoscopists feel confident in the management of complications and nearly half of the surveyed endoscopists (49.9%) are not sure about their competency.

Table 2 Assessment of knowledge among the surveyed physicians

Variable	Number	Percent
What is superficial bowel neoplasia?		
True	736	88.4
False	97	11.6
Superficial bowel neoplasia can be diagnosed with?		
True	547	65.7
False	286	34.3
What is the best option for the treatment of bowel cancer in general?		
True	473	56.8
False	360	43.2
What is the best treatment for superficial bowel neoplasia?		
True	526	63.1
False	307	36.9
What does polypectomy mean?		
True	767	92.1
False	66	7.9
What does EMR stand for?		
True	751	90.2
False	82	9.8
What does ESD stand for?		
True	742	89.1
FalseE	91	10.9
The best endoscopic treatment option for pedunculated polyps		
True	609	73.1
False	224	26.9
The best endoscopic treatment option for non-pedunculated lesions ≤ 15 mm in diameter		
True	473	56.8
False	360	43.2
The best endoscopic treatment option for non-pedunculated lesions ≥ 20 mm		
True	421	50.5
False	412	49.5
Endoscopic resection is a suitable treatment?		
True	596	71.5
False	237	28.5

Infrastructures of the national endoscopy units

One of the important determinants for performing ERTs is infrastructure of the endoscopy units, which was focused in the current survey (Table 6).

Manpower: About 70.2% (n = 400) of the surveyed endoscopists had ≥ 5 independent endoscopists in their units, which means a suitable number of endoscopists to deliver training in each unit. However, most of the nursing staff (52.1%) are not formally trained for advanced resection techniques.

Endoscopes and accessories: About 54.4% of the endoscopists see that the total number of endoscopes in their units is not sufficient to perform the daily endoscopic procedures including the ERTs. Furthermore, the endoscopes with optical enhancements (NBI, i-SCN, FICE) are lacking in 23.7% of

Table 3 Attitude of the surveyed physicians towards superficial bowel neoplasia

Question (%)	Frequency	Percent
How frequently do you refer your patients for endoscopic screening of superficial bowel cancer in high-risk groups? (% of the high-risk patients you see)		
0	102	12.2
25	386	46.3
50	116	13.9
75	103	12.4
100	126	15.1
How convinced you are with endoscopic treatment of superficial bowel cancer?		
Convinced	567	68.1
I don't Know	175	21
Not convinced at all	91	10.9
How frequently do you refer a patient with endoscopic features of superficial bowel cancer for endoscopic resection? (% of the patients you see)		
0	235	28.2
25	301	36.1
50	115	13.8
75	108	13
100	74	8.9
How frequently do you refer a patient with endoscopic features of superficial bowel cancer for surgical management? (% of the patients you see)		
0	147	17.6
25	290	34.8
50	212	25.5
75	64	7.7
100	120	14.4
In your institution do you have a panel to discuss the treatment options for superficial bowel neoplasia?		
No	518	62.2
Yes	315	37.8

endoscopy theaters, and 42.5% had ≤ 25% of the endoscopes with optical enhancement which means a deficiency of magnification facility and diminished probability of accurate diagnosis while only 4.2% of the centers had their endoscopes 100% armed with optical enhancements. More than two-third of the centers had advanced diathermy units (68.2%), meanwhile, argon plasma coagulation and haemoclips available to enable resections and guard against adverse events were available in 89.3% and 86.1%, respectively. Again the probability of diagnosis seems defective if relied on chromoendoscopy because only 20.2% of endoscopists had in their units the dyes for chromoendoscopy and tattooing.

Procedure: Focusing on the procedures, most centers (80.7%) perform ERTs under anesthesiologist observation. Furthermore, 72.5% of endoscopists reported that a surgical back up team is available for management of complications and that is why 54.4% of them decided that their institutions are ready for managing complications following ERTs. Only 18.3% (n = 104) of endoscopists treated their complicated cases surgically, because the most frequent complication during ERTs was procedural bleeding (26.7%), and perforations were the second common complication (17%).

DISCUSSION

In fact, the last 2-3 decades experienced a paradigm shift in the endoscopic management of SBN in particular for the colonic lesions due to the advancements in magnification endoscopy (imaging), introduction of CO_2 insufflation and the advent of modern electrosurgical devices with adoption of new techniques mainly EMR and ESD. Both have been associated with improved patient oriented outcomes

Table 4 Basic endoscopic practice knowledge for endoscopic resection techniques among the surveyed endoscopists

Question	Number (N = 570)	Percentage (%)
Are you trained formally on endoscopic polypectomy?		
No	134	23.5
Yes	436	76.5
Are you trained formally on EMR?		
No	388	68.1
Yes	182	31.9
Are you trained formally on ESD?		
No	528	92.6
Yes	42	7.4
Do you use Paris classification in reporting the lesions?		
No	239	41.9
Yes	331	58.1
Do you use Kudo classification in reporting the lesions?		
No	371	65.1
Yes	199	34.9
Do you use classifications other than Paris and Kudo in reporting the lesions?		
No	510	89.5
Yes	60	10.5
Which of the following practices increase sub-mucosal fibrosis and hence affect the success of advanced endoscopic resection techniques		
All apply	363	63.7
Extensive biopsies	117	20.5
Partial snare polypectomy	24	4.2
Tattoo injection for marking immediately under or close by a lesion	66	11.6

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

with improved quality of life and that is why a growing interest in such techniques became rapidly a global era.

However, these advanced techniques are not widely available in all endoscopy units and need special advanced training. Furthermore, we believe that certain communities may lack the basic knowledge and practice attitude toward these techniques as the currently preferred management for early stages of bowel neoplasia in comparison to the surgical excision and this was the rationale to investigate the Egyptian practice about these high-quality ERTs. To the best of our knowledge, this is the first trial to estimate different aspects of ERTs in the Egyptian community.

In this study, the knowledge among the physicians managing patients with SBN was not sufficient, especially in the area of endoscopic diagnosis and the clear indications of each technique. Furthermore, there was also a deficiency in the knowledge of the spectrum of indications for ERTs, although the description of the proper diagnostic and management approach to SBN and description of such techniques and their indications are defined by many of the published practice guidelines[3,8].

According to the current survey, there was an obvious reluctant attitude at both institutional and individual levels. Most of the Egyptian institutions lack panels discussing the management of SBN. The individual reluctance is obvious not only in the endoscopic screening of high-risk patients and hence early recognition of SBN[9], but also clear in the lack of referring all candidate patients for ERTs although most of the physicians are convinced in ERTs.

In fact, the knowledge and attitude to ERTs have not -to the best of our knowledge- been investigated previously, yet did the current survey and we identified a reasonable deficiency in the knowledge and deviation of the attitude of the surveyed physicians. The barriers to knowledge and attitude vary and are not limited to; lack of sufficient time to access the educational materials[10], lack of funds[11], among others. We believe that delivering educational materials focusing on these techniques and supplying reports with documented efficacy of such techniques in the management of SBN with its

Table 5 Individual competency in endoscopic resection techniques among the surveyed endoscopists

Question	Number (N = 570)	Percentage (%)
How many polyps did you excised in the last year?		
0	384	67.4
11-20	96	16.8
21-30	30	5.3
41-50	36	6.3
Less than 10	12	2.1
More than 50	12	2.1
How many EMRs did you perform in the last year?		
0	408	71.6
10-20	48	8.4
20-30	12	2.1
Less than 10	102	17.9
How many ESDs did you perform in the last year?		
0	504	88.4
10-20	12	2.1
Less than 10	54	9.5
How many complications from endoscopic resection techniques have you had in the last year (% of your total cases)?		
0	329	57.7
0.25	91	16.0
0.5	12	2.1
I don't practice advanced endoscopic techniques	138	24.2
How competent are you in managing the complications of endoscopic resection techniques?		
Competent	147	25.8
I am not sure	284	49.8
Non-competent	139	24.4

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

impact on the quality of life among the patients would improve both the knowledge and attitude among the Egyptian practitioners. This was proved in previous reports in other practice topics, for example, the knowledge and attitude of students and healthcare professionals was effectively improved through the delivery of teaching materials through different means ranging from face-to-face learning seminars, lectures and curricula[12], attending online curriculum[13], sending regular SMS to the practitioners [14], disseminating leaflets and hand-outs[15], and allowing quick *e.g.* through mobile phones, access to online resources[16].

In the current study, the barriers to knowledge and attitude toward ERTs in the management of SBN were not investigated. However, some data from previous reports can be inferred. These barriers are not limited to lack of evidence with limited belief in the value of available tools[17], because 78.1% of physicians are convinced about ERTs, or to lack of effective collaboration and teamwork skills[17], which is a growing interest in our practice, but rather extend to lack of formal education programs, the reluctance of sticking to the application of the guidelines and probably also to lack of continuous clinical audits[18].

The door is then open for the national leaders in the field to deliver these educational materials in the local conferences and meetings that run in the country over the year. In addition, directors of the gastroenterology curricula are responsible to insert these data in the course syllabus to be an integral part of the topic rather than an advancement delivered only to the subgroup of experts performing endoscopy. This has been proved effective per reports from Asia that proved improvement in the knowledge of practitioners toward early diagnosis and management of SBN after delivering structured training programs[8].

Table 6 Parameters of the endoscopy units' infrastructures among the surveyed endoscopists

%	Number (*n* = 570)	Percent
How many independent endoscopists are in your unit?		
Less than 5	170	29.8
5-10	164	28.8
More than 10	236	41.4
The nursing staff in your endoscopy unit are knowledgeable and trained on endoscopic resection techniques		
No	297	52.1
Yes	273	47.9
How sufficient is the number of endoscopes in your unit to perform all endoscopy duties?		
I am not sure	36	6.3
Not- Sufficient	310	54.4
Sufficient	224	39.3
How many endoscopes with optical enhancement (NBI- i-SCAN- FICE) are available in your unit (% of the total scopes in your unit)		
0.00	135	23.7
25.00	242	42.5
50.00	126	22.1
75.00	43	7.5
100.00	24	4.2
Dyes for chromoendoscopy are available in your unit		
No	455	79.8
Yes	115	20.2
Advanced Diathermy unit with different endoscopy modes is available in your unit		
No	181	31.8
Yes	389	68.2
APC is available in your unit		
No	61	10.7
Yes	509	89.3
Haemoclips are available in your unit		
No	79	13.9
Yes	491	86.1
In your endoscopy unit, the endoscopic resection techniques are operated under anesthesiologist's observation		
No	110	19.3
Yes	460	80.7
The most commonly reported complications from endoscopic resection techniques in your unit		
Delayed bleeding	24	4.2
Perforations,	97	17.0
Procedural bleeding	152	26.7
Sedation or anesthesia-related	12	2.1
We do not perform advanced endoscopic resection	285	50.0
Your institution is ready for managing the complications of endoscopic resection techniques?		
I am not sure	218	38.2
No	42	7.4

Yes	310	54.4
The surgical backup team is usually ready to manage complications of your cases		
No	157	27.5
Yes	413	72.5
How many complicated cases following endoscopic resection treated under surgical repair in the last one year within your institution (% from complicated cases)		
0.00	430	75.4
25.00	74	13.0
50.00	30	5.3

Per the current survey, a deficiency was reported not only in training for but also in performing ERTs, especially EMR and ESD. Furthermore, a small number of endoscopists are popular or using endoscopic classification systems and a reasonable number lack the competency in facing ERTs-related complications. The high-quality practice in ERTs relies on many pillars, the most important among it is training. Many endoscopic societies[3,19] formulated stepwise training curves for such procedures. It seems that an endoscopist should pass in the training curve from the basic polypectomy techniques to EMR and later to ESD in parallel with the advanced techniques. This could explain the results of the current survey. In an ascending frequency; polypectomy, EMR, and ESD were performed by Egyptian endoscopists at rates of 32.6%, 28.4%, and 11.6% respectively because this matches the complexity of each. Furthermore, the centers offering training for both EMR and ESD are very limited. However, the standard polypectomy is more popular, less technically demanding, and hence was the commonly practiced technique among the surveyed.

The delivery of high-quality resection techniques needs a recognized skill in delivering the resection and in managing the complications, especially the bleeding and perforation not only at an individual endoscopist level but rather very important at an institutional level. This emphasizes the importance of a teamwork management plan including basically an endoscopist, surgeon, anesthesiologist, and interventional radiologist. Favorably, there is a growing trend in the Egyptian practice toward teamwork activities for many GIT case scenarios including ERTs although in its early milestones.

The availability of skilled endoscopists is the stone cornerstone of performing ERTs. Their availability guarantees not only delivering a high-quality resection, but also a training platform to the possible trainees. Although, the current survey revealed recognized skills in the standard polypectomy, it did reveal a fair experience in EMR and very limited skilled endoscopists in ESD, and it also revealed a lack of competency in the management of ERTs-related complications. This should alarm the stakeholders for the urgent need to establish training centers and exchange experience with worldwide leaders in advanced endoscopy to train a new generation of Egyptian gastroenterologists in ERTs. In Egypt, we have a few endoscopy workshops that usually operate such cases both as hands-on training on models and live transmission of real cases but this seems non-sufficient solely in delivering the desired training, although it is important.

Although EMR was introduced before ESD, the experience in its application still needs training and assurance of competency. This ultimately grantee quality and improved patient outcomes. This needs to be inserted in post-graduate courses and continuing education settings[20].

One recently published report surveyed Korean endoscopists showed that both observation and performing ESD under direct supervision were the most important determinants of ESD training[21]. The authors reported also that, hands-on-courses were implemented by all the training centers. It is worth mentioning that in Korea at least 45 centers implement formal ESD practice and training in comparison to very few centers in Egypt. The problem of delivery of a formal training program for advanced resection techniques such as ESD has its own reasons that vary from the far East to the West and are not limited to trainees' background, differences in the type of the pathology seen, the availability of highly qualified mentors and training centers, availability of high-quality endoscopes among others[22]. Hence, it is expected to have a global shortage in training for ESD and not only in Egypt and Middle East countries.

The infrastructures (both in equipment, procedures, and skilled personnel) of endoscopy units nationwide need improvements. Most of the endoscopy centers are not equipped with enough scopes and specifically, the units lack advanced scopes with optical enhancements. The procedures with the availability of surgical backup teams look accepted, however, there was a shortage in the formal nurse training.

In the Egyptian community, tertiary referral centers (university hospitals, teaching institutions) are rather equipped than the general and central hospitals as per the data from the current survey. Consequently, these centers offer most of the national daycare service and training. However, focusing on EMR and ESD very few centers are currently delivering the service for real cases with a very limited number of trainees. Hence, we can deliver a very important message to the local health authorities for

the necessity to equip endoscopy units nationwide with the required equipment and establish multidisciplinary teams for managing cases of SBN and running formal training programs.

The plan is to deliver lectures in the meetings, conferences to insert the knowledge and improve the attitude among all physicians caring for patients with SBN. Later on, endoscopists can have a rising training curve that begins with hands-on courses[21], on *ex vivo* models[23-25] and *in vivo* on the animals[25,26], then trainee needs to watch videos, attend live cases, observes and assist in cases and finally perform under direct supervision. Implementation of this step-up fashion of training will enable trainees to learn early and to have a great chance to had supervised techniques[27,28]. Both have been associated with trainee satisfaction in previous studies[21]. Although attendance of conferences, meetings, face to face theoretical courses, watching recorded videos, attending live cases demonstrations are essential to improve knowledge and attitude, performing these advanced techniques under direct supervision by experts seems the most important method of training and hence we encourage our local leaders to propose a teaching and training algorithms in certified centers that end with practice and performance of ERTs under direct supervision by experts. This, ultimately fill the missing gaps in Egyptian practice.

This study had some limitations. First, include use of non-gastroenterologists. In fact, evaluation of knowledge and attitude of non-gastroenterologists is very essential because they constitute an integral role of care and sometimes are the first relay in delivering the care for patients with SBN and that is why there was a generalization in the questions of the knowledge domain. Second, lack of coverage for some geographic areas in the country. We distributed the questionnaire aiming at covering the whole country but usually, the response rates from the online questionnaires are limited due to many reasons. Third, the is a non-inclusion of the private sector. Currently, the law is not allowing practicing endoscopy in private clinics. However, endoscopy still running in private hospitals although it is sometimes difficult to assess the private sector due to many reasons including but not limited to the heterogeneity of the working endoscopists. Fourth, we did not investigate the barriers to the deficiency in all aspects focused. These can be focused on future surveys.

CONCLUSION

In conclusion, to the best of our knowledge, this is the first survey to focus ERTs status in Egypt and despite the limitations we have, this survey revealed a significant deficiency not only in the knowledge and attitude of Egyptian practitioners caring for patients with SBN toward ERTs, but it also spotted the light on the lack of trained endoscopists in both EMR and ESD in part due to unsuitable infrastructures of many endoscopy units around the country. These findings would enforce stakeholders for the urgent need to deliver educational and training programs focusing ERTs hand in hand with improving the infrastructures of the endoscopy units. Stakeholders of gastroenterology practice in Egypt are asked to improve all aspects of practice. They should focus on giving basic knowledge, improve the attitude of practitioners before giving the advanced training and supply the required infrastructures.

ARTICLE HIGHLIGHTS

Research background

Stakeholders of gastroenterology practice in Egypt are asked to improve all aspects of practice. They should focus on giving basic knowledge, improve the attitude of practitioners before giving the advanced training and supply the required infrastructures. The barriers to the deficiency in all aspects of primary and secondary outcomes can be focused on in future surveys.

Research motivation

Our study concluded that lack of knowledge towards endoscopic resection techniques (ERTs), reluctant attitude, lack of well-trained endoscopists, and shortage of infrastructures are the main obstacles that hamper performing endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) on wider scale and on a routine basis in Egypt.

Research objectives

Complete responses were 833/2300. The majority correctly identified the definition of superficial bowel neoplasia (SBN), the terms polypectomy, EMR, and ESD (88.4%, 92.1%, 90.2%, and 89.1% respectively). However, 26.9%, 43.2%, and 49.5% did not recognize the clear indications of polypectomy, EMR, and ESD respectively. Although 68.1% are convinced about the ERTs; only 8.9% referred all candidate cases for ERTs. About 76.5% of endoscopists had formal training in the basic polypectomy techniques while formal training for EMR and ESD was encountered only in 31.9% and 7.2% respectively. About 71.6% and 88.4% of endoscopists did not perform EMR or ESD in the last year. Only 25.8% of endoscopists feel confident in the management of ERTs-related complications. Only 4.2% of the centers had their

endoscopes 100% armed with optical enhancements.

Research methods

This observational study began with the development of a questionnaire during May and June 2021, after agreement upon it an online 2-page questionnaire was developed and distributed through July 2021. The questionnaire was distributed through social media including WhatsApp and Facebook as well as emails from the national relevant scientific groups. The study focused on Egyptian physicians caring for patients with gastrointestinal health problems

Research results

The primary aim of our study was to assess the knowledge and attitude of Egyptian physicians caring patients with SBN toward the ERTs as potential curative methods. Furthermore, the practice of Egyptian endoscopists practicing ERTs was also investigated. The secondary endpoint was to assess the infrastructure of the endoscopy units regarding the manpower, scopes, and accessories, as well as policies within.

Research conclusions

In Egypt we have a growing endoscopy practice, however little is known about physician knowledge, attitude, and practice toward ERTs. Furthermore, the nationwide spread of endoscopy units needs to be explored as regards the suitability to run these advanced techniques.

Research perspectives

There is a global era in the management of SBN due to the introduction of advanced ERTs mainly EMR and ESD.

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FOOTNOTES

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Country/Territory of origin: Egypt

ORCID number: Mohamed H Emara 0000-0002-1504-7851; Mariam Zaghloul 0000-0002-4244-5396; Haidi Karam-Allah Ramadan 0000-0003-0627-3985; Salem Youssef Mohamed 0000-0003-2917-4293; Mohammed Tag-Adeen 0000-0001-9813-

3191; Ahmed Alzamzamy 0000-0002-3817-5370; Mohamed Alboraie 0000-0002-8490-9822; Ahmad Madkour 0000-0001-8416-6013; Ahmed Youssef Altonbary 0000-0001-8850-9829; Tarik I Zaher 0000-0002 -3846-0032; Ahmed Abo Elhassan 0000-0003-2282-9891; Nermeen Abdeen 0000-0003-3272-4233; Mohammed Hussien Ahmed 0000-0003-1761-3527.

Corresponding Author's Membership in Professional Societies: WEO Emerging Stars; Egyptian Association for Research and Training in Hepatogastroenterology.

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P-Editor: Liu JH

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