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MINIREVIEWS

Resection of early esophageal neoplasms: The pendulum swings from surgical to endoscopic management

Vedha Sanghi, Hina Amin, Madhusudhan R Sanaka, Prashanthi N Thota

ORCID number: Vedha Sanghi (0000-0002-6832-8630); Hina Amin (0000-0001-8163-0677); Madhusudhan R Sanaka (0000-0003-2506-8602); Prashanthi N Thota (0000-0001-7179-4774).

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Vedha Sanghi, Department of Internal Medicine, Cleveland Clinic, Cleveland, OH 44195, United States

Hina Amin, Madhusudhan R Sanaka, Prashanthi N Thota, Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH 44195, United States

Corresponding author: Prashanthi N Thota, MD, Staff Physician, Medical Director, Department of Gastroenterology and Hepatology, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, United States. thotap@ccf.org
Telephone: +1-216-4440780
Fax: +1-216-4454222

Abstract

Esophageal cancer is a highly lethal disease and is the sixth leading cause of cancer related mortality in the world. The standard treatment is esophagectomy which is associated with significant morbidity and mortality. This led to development of minimally invasive, organ sparing endoscopic therapies which have comparable outcomes to esophagectomy in early cancer. These include endoscopic mucosal resection and endoscopic submucosal dissection. In early squamous cell cancer, endoscopic submucosal dissection is preferred as it is associated with cause specific 5-year survival rates of 100% for M1 and M2 tumors and 85% for M3 and SM1 tumors and low recurrence rates. In early adenocarcinoma, endoscopic resection of visible abnormalities is followed by ablation of the remaining flat Barrett's mucosa to prevent recurrences. Radiofrequency ablation is the most widely used ablation modality with others being cryotherapy and argon plasma coagulation. Focal endoscopic mucosal resection followed by radiofrequency ablation leads to eradication of neoplasia in 93.4% of patients and eradication of intestinal metaplasia in 73.1% of patients. Innovative techniques such as submucosal tunneling with endoscopic resection are developed for management of submucosal tumors of the esophagus. This review includes a discussion of various endoscopic techniques and their clinical outcomes in early squamous cell cancer, adenocarcinoma and submucosal tumors. An overview of comparison between esophagectomy and endoscopic therapy are also presented.

Key words: Esophageal cancer; Submucosal tumors; Submucosal tunneling; Barrett's esophagus; Dysplasia; Adenocarcinoma; Endoscopic therapy; Radiofrequency ablation; Endoscopic mucosal resection

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Core tip: Advances in endoscopic therapies led to organ preserving endoscopic treatments for early esophageal cancer and submucosal tumors of the esophagus. These techniques include endoscopic mucosal resection, endoscopic submucosal dissection and submucosal tunneling endoscopic resection. Ablative techniques are useful for treatment of residual dysplasia.

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INTRODUCTION

Esophageal neoplasms are mostly malignant with benign tumors accounting for less than 1% esophageal tumors[1]. Globally, esophageal cancer was the seventh leading cancer with 572034 new cases (3.2% of all cancers) and the sixth leading cause of cancer related mortality with 508, 585 cancer related deaths (5.3% of all cancer mortality) in 2018[2]. In the United States alone, about 17650 new esophageal cancer cases will be diagnosed and 16080 deaths from esophageal cancer are estimated to occur in 2019[3]. The major histologic subtypes of esophageal cancer are squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). ESCC is the most common subtype globally accounting for over 88% of esophageal cancers[4]. In Australia, western Europe and United States, the incidence of EAC has increased steadily with a simultaneous decline in ESCC making EAC the predominant subtype[5]. Treatment of esophageal cancer depends on the stage of disease with esophagectomy being the main stay of treatment for localized disease with additional neoadjuvant therapy for regional disease. In the past three decades, endoscopic therapy is increasingly used for treatment of early stage cancers when there is minimal risk of lymph node metastases.

SURGICAL MANAGEMENT OF ESOPHAGEAL NEOPLASMS: ESOPHAGECTOMY

The conventional management of esophageal cancer is esophagectomy and lymph node dissection performed through a transhiatal or transthoracic approach[3]. Transhiatal approach includes laparotomy and left cervical anastomosis typically without a thoracotomy. Transthoracic approach involves either Ivor Lewis (right thoracotomy and laparotomy) or McKeown esophagectomy (right thoracotomy, laparotomy, and cervical anastomosis). Esophagectomy has high curative rates and five year survival rates in early stage cancers[6]. However, it is highly invasive with substantial morbidity and mortality. The overall incidence of adverse events varies between 20%-80% and include pulmonary complications such as pneumonia, respiratory failure and aspiration; myocardial infarction, atrial fibrillation; anastomotic leak and recurrent laryngeal injury[7]. Patients need prolonged hospitalization following esophagectomy with mean intensive care unit and hospital length of stay (LOS) of 3.35 and 13.54 d respectively[8]. Mortality rates after esophagectomy vary depending on where it is performed: low volume hospitals have higher rates of in-hospital mortality [8.48% *vs* 2.82%; pooled odds ratio (OR) = 0.29, $P < 0.0001$] and 30-d mortality (2.09% *vs* 0.73%; pooled OR = 0.31, $P < 0.0001$) compared with high volume hospitals[9].

Minimally invasive esophagectomy (MIE) strategy was developed to decrease the morbidity and mortality associated with standard esophagectomy and to improve quality of life (QOL). MIE is performed *via* laparoscopy or *via* thoracoscopy with or without laparoscopy and simultaneous lymph node sampling or dissection. The operative mortality of MIE is about 1.68% and 30-d mortality is 2.1%[10]. When compared with open esophagectomy, MIE has shorter hospital LOS (14.9 *vs* 19.6 d) and intensive care unit LOS (4.5 *vs* 7.6 d) and fewer complications (relative risk 1.20,

95%CI: 1.08-1.34, P = 0.0009)[11]. MIE, however, requires longer operative time and higher costs compared to standard esophagectomy[12].

ENDOSCOPIC MANAGEMENT OF ESOPHAGEAL NEOPLASMS

Esophagectomy is associated with excellent outcomes in early esophageal cancer localized to mucosa but the risk of considerable morbidity and mortality and decreased QOL led to development of alternative techniques grouped under endoscopic eradication therapy (EET)[13]. In carefully selected patients such as those with T1a cancers, lymph node metastases are rare making EET feasible and curative while preserving the esophagus. The multiple EET modalities can be broadly classified into resection techniques [endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) and submucosal tunneling endoscopic resection (STER)] and ablative techniques which include radiofrequency ablation (RFA), photodynamic therapy (PDT), cryotherapy and argon plasma coagulation (APC). With resection, abnormal areas are removed and assessed histologically for staging. With ablation techniques, the abnormal area is destroyed and hence not available for histological evaluation.

ENDOSCOPIC RESECTION TECHNIQUES

EMR

EMR was pioneered in Japan for the management of early gastric neoplasia and soon gained widespread use (Table 1). EMR in esophagus was first reported by Inoue in 1990[14]. EMR is used to remove sessile, flat or discrete mucosal lesions < 2 cm in size and involving less than two-thirds of the circumference of esophageal wall. EMR helps to determine local stage, degree of differentiation and lymphovascular invasion[15]. In injection-assisted EMR, saline or dilute epinephrine is injected in the submucosa of the visible lesion to lift the mucosa away from muscularis propria. This fluid cushion protects the deeper layer from injury during removal of the lesion by electrocautery. In cap-assisted EMR, a plastic cap (Olympus, Tokyo, Japan) is fitted over the tip of the endoscope along with a snare that is located along the internal circumferential groove of the cap. After submucosal injection, the mucosa is suctioned into the cap, the snare is closed around the target site and the lesion is resected using electrocautery. In ligation-assisted EMR, a band ligation device (Duette Kit, Cook Medical Inc., Winston-Salem, NC or Captivator EMR device, Boston Scientific, Marlborough, Mass) is fitted on the tip of the endoscope. The lesion is suctioned into the device and a band is deployed at the base of the tissue to create a pseudopolyp which is then resected using an electrocautery snare. Ligation allows multiple resections (up to 6) in single intubation. Focal EMR is removal of visible lesions only and is usually followed by ablation of remaining Barrett's esophagus (BE) tissue. Stepwise radical EMR is removal of entire BE segment in single or multiple sessions. EMR is safe, quick and has few complications (Table 2). In a study on 1000 patients who underwent EMR, major complications occurred in 1.5% which included major bleeding in 14 patients and perforation in 1 patient[13]. Minor complications included stenosis requiring endoscopic dilation in 13 patients. With stepwise radical EMR, early complications include perforation (1%) and bleeding(1.0%) which can be managed endoscopically[16]. Later, symptomatic stricture formation can occur in over 49.7% of patients and requires endoscopic dilation, stent placement or incision therapy[16].

ESD

ESD was introduced in 1988 in Japan to treat gastric neoplasia and subsequently, its use was extended to treat superficial esophageal cancer[17] (Table 1). ESD allows *en-bloc* resection of lesions irrespective of the size. Lugol's solution is applied to highlight abnormal areas and mucosal markings are made with a needle knife or with APC about 5 to 10 mm away in EAC and close to the margins in ESCC to avoid stenosis. An initial mucosotomy is made with a needle knife to expose the submucosal layer, and then the incision is extended circumferentially around the lesion with a needle knife or insulated tip knife about 5 mm outside of the marking leaving 10 mm of normal tissue between incision and tumor. Hydroxymethylcellulose is injected to lift the submucosa and then dissected with ESD knife parallel to the muscular layer to remove the tumor. ESD is a technically demanding and time consuming procedure. Complications include bleeding in 1.5% to 1.8%, perforation in 1.5% to 4.6% and

Table 1 Summary of the history and role of all endoscopic therapies

Technique	History	Indications/role
EMR	EMR was introduced in Japan to treat early gastric cancer and its use in esophagus was first reported by Inoue in 1990[14]. EMR use determines local stage, degree of differentiation and lymphovascular invasion[15]	EMR is indicated to remove sessile, flat or discrete mucosal lesions < 2 cm in size and involving less than two-thirds of the circumference of esophageal wall[14] Focal EMR is removal of visible lesions only. Stepwise radical EMR is removal of entire Barrett's segment in single or multiple sessions
ESD	ESD was introduced in 1988 in Japan to treat gastric cancer and subsequently, its use was extended to treat superficial esophageal cancer[17]	ESD is indicated for *en-bloc* resection of lesions irrespective of the size. ESD is a technically demanding and time consuming procedure
STER	STER was introduced in 2011 and is based on the principles of peroral endoscopic myotomy and ESD[21]	STER is used to resect submucosal tumors[21]. The advantage of STER is preservation of mucosal integrity that lowers adverse outcomes[23]
RFA	RFA was introduced in 2005 and is now a well-established modality for early esophageal cancer which utilizes high frequency alternating electrical current to generate thermal energy for ablation[25]	RFA is the standard of care in flat mucosal lesions[25]. In RFA, a circumferential catheter is used to ablate ≥ 3 cm Barrett's segment or a focal catheter for shorter segments
PDT	PDT was one of the first techniques described for treatment of Barrett's associated neoplasia	PDT is associated with many complications and is not commonly used in the United States any more
Cryotherapy	Cryotherapy was introduced in 1851 by James Arnott to freeze tumors[27]. The application of Cryotherapy was extended to the esophagus in 1997 using an endoscope	Cryotherapy circumvents the need for mucosal contact making ablation of an uneven or nodular surface feasible[27]. CbFAS uses cryogenic fluid and overcomes the challenges of unequal distribution and need for decompression tube
Hybrid-APC	APC was introduced in the early 1990s to perform thermal coagulation of tissue[25]. More recently, Hybrid APC in which a submucosal cushion is created before APC is being used[28]	Hybrid APC is indicated in Barrett's esophagus up to 3-5 cm in length and the cushion controls the depth of ablation[28]

APC: Argon plasma coagulation; CbFAS: Cryoballoon focal ablation system; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; PDT: Photodynamic therapy; RFA: Radiofrequency ablation; STER: Submucosal tunneling endoscopic resection.

strictures in 6.5% to 11.6% that is treated endoscopically without long-term complications[18,19] (Table 2). Prophylactic use of steroids has been suggested to decrease the stricture rate and frequency of endoscopic balloon dilations[20].

STER

STER was introduced in 2011 and is based on the principles of peroral endoscopic myotomy and ESD[21]. STER is used to resect gastrointestinal submucosal tumors (SMT) by creating a tunnel between submucosa and muscularis propria. About 3-5 cm proximal to the tumor, a submucosal cushion is raised[22]. The mucosa is incised to create an entrance to the tunnel and the submucosa is dissected to form a tunnel advancing towards the tumor. Then the tumor along with its capsule is dissected and removed. Endoscopic clips are used to close the tunnel. The advantage of this process is that the mucosal integrity is maintained which lowers adverse outcomes[23] (Table 2). The most common complications are subcutaneous emphysema and pneumomediastinum in 14.8%, pneumothorax in 6.1% and pneumoperitoneum in 6.8%[24]. Less common complications include pleural effusion (16.9%), mucosal injury (5.6%), esophageal fistula and diverticulum[24]. Majority of STER-related complications can be treated conservatively.

ABLATION TECHNIQUES

Ablation is performed to eradicate abnormal tissue either by thermal injury (heat in RFA and cold in cryotherapy) or photochemical injury (PDT). The underlying principle is that the destruction abnormal neoplastic tissue leads to regrowth of normal squamous epithelium in an environment of maximum acid suppression either by proton pump inhibitors or antireflux surgery. Optimal dosimetry (number of applications and time of exposure) aims to limit tissue damage beyond the mucosal layer to avoid complications.

RFA

RFA is a well-established ablation modality which utilizes high frequency alternating electrical current to generate thermal energy[25] (Table 1). Commercially available RFA

Table 2 Summary of the efficacy and complications of all endoscopic therapies

Technique	Efficacy	Complications
Focal EMR and ablation	CE in EAC: 96.3%[13] and ESCC: 90%[54]	Major bleeding: 1.4%[13] Perforation: 0.1% Strictures: 1.3%
Stepwise radical EMR	CE-N: 94.9%[42] CE-IM: 79.6%	Bleeding: 1.0%[16] Perforation: 1.0% Strictures: 49.7%
ESD	*En-bloc* resection rate in EAC: 92.9%[18] and ESCC: 90%-100%[55-57] Complete resection rate in EAC: 74.5%[18] Curative resection rate in EAC: 64.9%[18] and ESCC: 88%-97%[55-57]	Bleeding: 1.5%-1.8%[18,19] Perforation: 1.5%-4.6% Strictures: 6.5%-11.6%
STER	Complete Resection rates in SMTs: 100%[24]*En-bloc* resection rates in SMTs: 98.6%	Subcutaneous emphysema and pneumomediastinum: 14.8%[24] Pleural effusion: 16.9% Pneumoperitoneum: 6.8% Pneumothorax: 6.1% Mucosal injury: 5.6%
RFA	CE-D: 81%[44] CE-IM: 77.4%[44] CE in ESCC: 84%[61]	Strictures: 6%[25] Chest pain: 2% Bleeding: 1%
PDT	Discontinued in the United States	Photosensitivity reactions: 69%[25] Esophageal strictures: 36% Chest pain: 20%
Cryotherapy	CE-HGD: 98%[46] CE-D: 94% CE-IM: 82%	Abdominal pain: 19.3%[27] Dysphagia: 10.2% Sore throat: 9% Chest pain: 8% Strictures: 0-12.5%
Hybrid-APC	CE-IM:78%[28]	Strictures: 2%[28]

APC: Argon plasma coagulation; CE-D: Complete eradication of dysplasia; CE-HGD: Complete eradication of high grade dysplasia; CE-IM: Complete eradication of intestinal metaplasia; EAC: Esophageal adenocarcinoma; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; ESCC: Esophageal squamous cell carcinoma; PDT: Photodynamic therapy; RFA: Radiofrequency ablation; SMT: Submucosal tumors; STER: Submucosal tunneling endoscopic resection.

devices include the Barrx™360 express RFA balloon catheter, Barrx™ RFA 90 catheter, Barrx™ 60 RFA focal catheter, Barrx™ ultra long RFA focal catheter Barrx™ and channel RFA endoscopic catheter (Medtronic, Sunnyvale, CA, United States)[25]. Circumferential catheter is used for ablation of BE segments ≥ 3 cm whereas focal catheters are used for ablation of shorter segments. Before performing circumferential RFA, the mucosa is sprayed with 1% N-acetyl cysteine to remove the mucus and balloon catheter is introduced over a guidewire. The balloon is inflated and energy is delivered by one application of 10 J/cm^2 followed by cleaning and second application. Focal catheters are mounted on the endoscope or passed through the accessory channel and 2 applications of 12 J/cm^2 are delivered followed by cleaning and second application. RFA is safe with very rare complications making direct RFA the standard of care in flat mucosal lesions (Table 2). Stricture formation is reported in 6% after RFA alone and in 13% when RFA is preceded by EMR[25]. Additionally, chest pain requiring hospitalization (2%), bleeding (1%), esophageal mucosal tears and perforation were reported[25].

PDT

PDT was one of the first techniques described for treatment of BE associated neoplasia (Table 1). In PDT, a photosensitizing drug such as porfimer sodium intravenously or 5-aminolevulinic acid orally is administered. It localizes to the esophagus and is activated by a certain wavelength of light. A photochemical reaction then leads to the generation of oxygen radicals which induce neoplastic tissue damage. Complications were many including photosensitivity reactions (69%), esophageal strictures (36%) and chest pain (20%)[25] (Table 2). Even though effective, PDT was largely replaced by RFA in view of severe adverse effects.

Cryotherapy

In cryotherapy, the esophageal mucosa is exposed to repeated cycles of rapid freezing and slow thawing which cause tissue damage of the cells and their organelles by apoptosis (Table 1). Commercially available cryotherapy options include cryospray and cryoballoon. In cryospray (CryoSpray Ablation Medical, Lexington, Mass, United States), the cryogen (liquid nitrogen) is sprayed onto the mucosa at low pressure (2-4 PSI) for 10 to 20 s. A decompression tube is used to evacuate large quantities of expanded gas released into the stomach. This is followed by thawing of mucosa and repeating the freezing for 2-3 cycles at each site. Cryospray circumvents the need for mucosal contact making ablation of an uneven or nodular surface feasible. Recently, cryoballoon focal ablation system (CbFAS) was introduced in which the cryogenic fluid (liquid nitrous oxide) is delivered by direct mucosal contact through an inflated balloon catheter (Pentax Medical, Montvale, NJ, United States)[25,26]. CbFAS overcomes

the challenges of cryospray such as unequal distribution and need for decompression tube. Cryotherapy is generally safe and well tolerated[27]. Abdominal pain (19.3%), dysphagia (10.2%), sore throat (9%), chest pain (8%) and strictures (0-12.5%) are the most common post-procedural side effects[27] (Table 2). Cryotherapy allows deeper ablation than RFA with fewer complications; hence cryotherapy is often considered when RFA cannot be used.

APC

APC was introduced in the early 1990s and employs high frequency current for thermal coagulation of tissue carried through ionized argon gas[25] (Table 1). Heat generated in the process desiccates and shrinks the tissue to a limited depth that depends upon the application time and operative distance between the probe and tissue. A power setting of 30-90 W is used. In Hybrid APC, a submucosal cushion is created before APC is delivered to the mucosa to control the depth of ablation and this leads to decreased stricture formation (2%)[28] (Table 2).

OUTCOMES: EET VERSUS ESOPHAGECTOMY

Standard esophagectomy, MIE and EET have been employed for the management of early esophageal cancer and have similar survival outcomes that are sustained over long term follow up. However, EET is associated with lower morbidity, mortality and costs and easier availability making the pendulum swing from surgical to endoscopic management in early esophageal neoplasms. In a Surveillance, Epidemiology and End Results database study of 2661 patients with early esophageal cancer treated by either esophagectomy or EET, no significant difference in overall survival [hazard ratio (HR) = 1.216, 0.854-1.731, P = 0.279] or esophageal cancer specific survival (HR = 0.692, 0.404-1.184, P = 0.179) was noted between the two groups[29]. In another study on 114 patients with T1a EAC, complete eradication was achieved in 100% patients who underwent esophagectomy (n = 38) and in 98.7% who underwent EET (n = 75) and these rates were maintained even after about 4-years follow up[30]. Despite the comparable survival rates, esophagectomy is associated with major complications (32%) and high 90-d mortality (2.6%) compared to EET (0% for both). Esophagectomy also carries the risk of substantial morbidity, high overall mortality (> 2%) and higher costs ($53849 *vs* $22640 for EET, $P < 0.001$)[31,32]. While EET is associated with a higher recurrence rate of 6.6%, recurrences can be treated endoscopically[30]. To overcome the drawbacks of standard esophagectomy, MIE was introduced which had comparable outcomes to EET. One study compared the two treatment modalities and found similar rates in the treatment of early esophageal cancer (R0 resection rate 94.9% *vs* 97.5%, $P > 0.05$), 3-year survival (96.6% *vs* 97.5%, $P > 0.05$), 4-year survival (91.5% *vs* 90%, $P > 0.05$) and local recurrence ($P > 0.05$)[33]. However, EET was superior with fewer complications (11.8% *vs* 32.5%, $P > 0.05$), shorter operative time (74 ± 23 min *vs* 298 ± 46 min), hospital LOS ($P < 0.001$) and recovery time compared to MIE[33]. Therefore, EET is increasingly used as it is cost effective, has minimal morbidity and mortality with excellent long-term survival comparable to esophagectomy.

ROLE OF ENDOSCOPIC ULTRASOUND IN EARLY ESOPHAGEAL CANCER

Staging of the tumor is an essential step before determining the approach to management. Staging includes establishing the extent of the tumor by depth of invasion (T-staging), lymph node invasion (N-staging) and metastases (M). The imaging modalities used for staging include computerized tomography/positron emission tomography and endoscopic ultrasound (EUS). EUS is the most accurate tool for evaluating locoregional spread with accuracy of T-staging varying from 81.6% to 92.4%[34]. In a meta-analysis of studies involving EUS-based staging of pre-operative ESCC compared with pathological staging, the pooled sensitivity for T1a was 84%, T1b was 83% and T4 84%[35]. The overall accuracy of EUS for T-staging in ESCC was 79%, and for N-staging was 71%. However, it's utility in management of superficial EAC has been questioned as it is suboptimal in differentiating T1a and T1b cancers[36]. In a recent meta-analysis of 895 patients with BE associated neoplasia, the false positive rate for advanced disease was 9.1% and false negative rate was 9.2% with an overall accuracy of 74.6%[37]. This implies that about 1 in 4 patients will be misstaged with EUS. Rather, careful inspection and endoscopic therapy has been proposed for accurate staging as this approach provides histological specimen for examining depth of invasion and features of lymphovascular spread. For N-staging of regional lymph

nodes, EUS helps in identifying abnormal nodes and by facilitating fine needle aspiration (FNA). The sensitivity and specificity of EUS for N- staging is 84.7% and 84.6% respectively which increased to 96.7% and 95.5% respectively with the addition of FNA[34].

EET IN BE AND EAC

Patient selection

EET is indicated in early EAC with negligible risk of lymph node metastases. T1a cancers are associated with low risk of lymph node metastasis (< 2%) and hence amenable for EET[31]. The risk of lymph node metastases increases with depth of tumor infiltration, lymphatic vessel infiltration, tumor differentiation (well differentiated or moderately differentiated versus poorly differentiated) and vascular infiltration[38]. In T1b cancers, surgical resection is preferred as lymph node metastases have been reported in up to 50% of patients[39]. However, recent studies show that in well differentiated T1b tumors with submucosal invasion ≤ 500 μm and lack of lymphovascular invasion, the risk of lymph node metastasis is 0% to 2% and hence, EET can be safely employed[40]. The indications for esophageal ESD include visible lesions ≥ 15 mm (not amenable to enbloc resection by EMR) and patients with BE with the following features: Large or bulky area of nodularity, equivocal preprocedure histology, T1a tumors, suspected superficial submucosal invasion, recurrent dysplasia or EMR specimen showing invasive carcinoma with positive margins[41].

Outcomes

EMR is very effective in the management of T1a tumors. The largest experience of EMR in esophageal cancer comes from a series of 1000 patients with T1a tumors[13]. After a mean follow up period of 56.6 mo, 963 patients (96.3%) achieved a complete response and surgery was necessary in 12 patients (3.7%) after EET failed (Table 2). Metachronous lesions developed during the follow up period in 140 patients (14.5%) but endoscopic retreatment was successful in 115, resulting in a long term complete remission rate of 93.8%. The calculated 10-year survival rate of patients who underwent EET of T1a tumors was 75%. In a meta-analysis, focal EMR followed by RFA and stepwise radical EMR were found to be equally effective for the treatment of BE-high grade dysplasia (HGD) and T1a tumors[42]. Focal EMR followed by RFA showed complete eradication of neoplasia in 93.4% of patients and complete eradication of intestinal metaplasia (CE-IM) in 73.1% of patients. The recurrence rates of EAC, dysplasia and IM were 1.4%, 2.6% and 16.1% respectively. Stepwise radical EMR showed CE of neoplasia in 94.9% of patients and CE-IM in 79.6% of patients with recurrence rates for EAC, dysplasia and IM of 0.7%, 3.3% and 12.1% respectively (Table 2).

Studies also found ESD to be effective in the management of early EAC with high resection rates and low recurrence rates. A meta-analysis evaluated the efficacy of ESD in early BE neoplasia[18]. The pooled estimate for enbloc resection was 92.9%, complete resection rate was 74.5% and curative resection rate was 64.9% respectively (Table 2). Recurrence after curative resection was 0.17% at a mean follow up 22.9 mo. In a randomized control trial comparing ESD to EMR, R0 resection was achieved more frequently with ESD (10/17 *vs* 2/17, $P = 0.01$), but there was no difference in complete remission from neoplasia at 3 mo (ESD 15/16 *vs* EMR 16/17, $P = 1.0$)[43]. ESD is, however, more time consuming and may cause severe adverse events and hence should be reserved for larger lesions which are amenable for EMR.

The goal of EET in EAC is enbloc resection of cancer with negative margins followed by ablation of residual BE. Therefore, CE-IM is the goal. RFA is the most widely used ablation technique. The efficacy of RFA to eradicate dysplastic BE was evaluated in a multicenter, randomized sham-controlled trial[44]. Complete eradication of dysplasia (CE-D) occurred in 81% of patients with HGD (*vs* 19% in sham arm) and CE-IM in 77.4% of patients with HGD (*vs* 2.3% in sham arm) (Table 2). RFA also lowered the risk of progression to EAC (1.2% *vs* 9.3%, $P = 0.045$). In a comparative model analysis, RFA treatment for BE-HGD decreased the incidence of EAC by 51%, EAC mortality by 44% and the number of treatments needed to avert one EAC death was 44[45]. The strategy was resource intensive with an incremental cost effectiveness ratio of $182093-$422256/quality adjusted life year (QALY) that is above a $100000/QALY willingness-to-pay threshold[45].

In a study evaluating the outcomes of cryotherapy on patients with BE-HGD and T1a tumors, initial CE-HGD, CE-D and CE-IM occurred in 98%, 90% and 60% of the patients respectively[46] (Table 2). This effect was durable with overall CE-HGD, CE-D and CE-IM of 96%, 94%, 82% respectively at 3 years and 93%, 88% and 75%

respectively at 5 years[46]. After initial eradication, the recurrence rates of IM, dysplasia and HGD/EAC per person-year of follow up was 12.2%, 4.0% and 1.4% per person-year for the 5-year cohort. In a study on patients with BE associated dysplasia or T1a tumors who underwent cryotherapy or RFA, CE-IM was achieved in 52.6%, CE-D in 86.4% and persistent dysplasia or cancer in 12.3%[47]. Compared to cryotherapy, patients who underwent RFA had 3-fold higher CE-IM (OR 2.9, 1.4-6.0, P = 0.004) but the odds for CE-D was similar between the two treatments (OR 1.7, 0.66-4.3, P=0.28). CbFAS is effective for primary or rescue therapy for BE-HGD or IM. In a recent study evaluating the efficacy of CbFAS in 41 patients with BE associated neoplasia, the overall 1-year CE-D and CE-IM were 95% and 88% respectively[26].

Risk of recurrence after EET in EAC

The recurrence rates after EET for IM, dysplastic BE, and HGD/EAC are 7.1% (95%CI: 5.6-8.6), 1.3% (95%CI: 0.8-1.7), and 0.8% (95%CI: 0.5-1.1) per patient-year, respectively[48]. After RFA alone, the recurrence rates of IM, dysplastic BE, and HGD/EAC after RFA are 9.5% (95%CI: 6.7-12.3), 2.0% (95%CI: 1.3-2.7), and 1.2% (95%CI: 0.8-1.6) per patient-year, respectively[48]. Any persistence of IM is associated with an increased risk of recurrence; therefore, CE-IM is the goal. Recurrence after EET is treated by repeat EET until complete eradication and infrequently may require surgical intervention.

EET IN ESSC

Patient selection

ESSC is a more aggressive cancer compared to EAC and the risk of lymph node metastases according to the depth of invasion is higher in ESSC. In ESCC, the risk of lymph node metastasis is 0% for M1 (disease confined to epithelium), 3.3% for M2 (disease confined to lamina propria mucosa), 10.2% for M3 (tumors involving muscularis mucosae) and 26.5% for SM1 (disease extending to superficial third of submucosa)[49]. However, lymph node involvement is absent in M3 and SM1 lesions if depth of invasion is < 200 μm, tumors are well to moderately differentiated and there is no lymphovascular invasion[50]. Absolute indications for EET are high grade intraepithelial neoplasms, including M1 and M2 without lymphovascular infiltration, lymph node or distant metastases[51]. Relative indications for EET includes lesions at a depth of invasion < 200 μm in the submucosa (M3 and SM1). ESD is preferred over EMR in tumors large enough to prevent enbloc resection by EMR such as those ≥ 15 mm or for lesions with poor lifting and for better assessment of the depth of invasion in case of suspicion for submucosal invasion[52].

Outcomes

EET in ESCC is associated with excellent outcomes but carries a minimal risk of recurrence. In a Japanese study on 204 patients with early ESCC treated by EMR, the 5-year survival was 75.9% with recurrence of 11% when followed for median of 36 mo[53]. In a European study on 39 patients with superficial ESCC, EMR was curative in 90% patients[54] (Table 2).

ESD in ESCC has enbloc resection rates of 90% to 100% and curative resection rates of 88% to 97%[55-57] (Table 2). In a study on 102 patients treated by ESD, there was no local recurrence when followed over 21 mo[58]. The cause specific 5-year survival rates after ESD are 100% for M1 and M2 tumors and 85% for M3 and SM1[57]. Perioperative mortality following ESD in T1a and T1b ESCC tumors was lower (0.3%) when compared with esophagectomy (1.5%, P = 0.186) and morbidity was also lower (15.2% *vs* 27.7%, P = 0.001)[59]. After a median follow up of 21 mo, there was no significant difference between treatments in all-cause mortality (7.4% *vs* 10.9%, P = 0.209) or rate of cancer recurrence or metastasis (9.1% *vs* 8.9%, P = 0.948).

In a meta-analysis that compared the efficacy of ESD with EMR in ESCC[60]. ESD was found to have higher enbloc resection rates when compared to EMR (314/319 lesions *vs* 299/476 lesions, OR 27.3) and higher complete resection rates (289/297 lesions with ESD *vs* 307/463 lesions with EMR, OR 18.4). The local recurrence rate was also lower with ESD compared to EMR (1/306 lesions *vs* 31/459 lesions, OR 0.13). In view of higher curative rates and lower risk of recurrences, ESD is preferred over EMR for treated of ESSC. Use of RFA for treatment of squamous dysplasia and early ESCC have been reported with over 84% complete response over 12 mo[61] (Table 2). However, even in flat ESCC, there is a chance of lymphovascular invasion and undertreatment with RFA, hence, ESD is preferred.

EET IN RARE ESOPHAGEAL CANCERS

Rare histological types of esophageal cancer include epithelial tumors such as mucoepidermoid carcinoma, adenoid cystic carcinoma, small cell carcinoma, undifferentiated carcinoma, carcinoid and non-epithelial tumors such as leiomyosarcoma, rhabdomyosarcoma, Kaposi sarcoma and malignant melanoma[62]. Treatment depends on the size of the lesion, depth of invasion and presence or absence of metastases. Small cell carcinoma or neuroendocrine tumors account for 0.3% to 3.8% of all esophageal cancers[63]. EET may be considered when tumor size is < 1.0 cm, pathology is not poorly differentiated and in the absence of local lymph node metastasis, lymphovascular invasion or perineural invasion and tumor is completely resectable as the survival rate is high without recurrence on long-term follow up[63]. One case is reported on the successful use of ESD to remove esophageal submucosal NET that showed no recurrence on 22 mo follow up[64].

EET IN BENIGN ESOPHAGEAL TUMORS

Benign esophageal tumors are rare and account for < 1% of esophageal tumors[1]. According to the WHO Classification, benign epithelial tumors are squamous papilloma and non-epithelial tumors are leiomyoma, lipoma, gastrointestinal stromal tumor (GIST) and granular cell tumors[62]. The most common SMT in esophagus are leiomyoma (95%) followed by GIST (4.2%) and granular cell tumors (0.8%)[22]. Esophageal GISTs mimic the appearance of leiomyomas, but can be differentiated following EUS-guided FNA[65]. GIST is KIT-positive with immunohistochemical staining while leiomyomas are KIT-negative and positive for smooth muscle actin, desmin, and h-caldesmon.

Benign tumors are encountered during routine endoscopy as they are usually asymptomatic and are managed by periodic surveillance[66]. Removal is indicated when they become symptomatic or have a risk for malignant transformation (large diameter or origin from muscularis propria). Removal should be attempted in leiomyomas ≥ 2 cm and all granular cell tumors and GIST in view of malignant potential[67]. EMR is performed in SMT ≤ 50 mm. Other endoscopic alternatives include ESD and more recently, STER.

Outcomes

EET can be safely performed in small SMTs. In a study with 36 patients and mean tumor size of 0.6 mm, the overall enbloc and complete resection rates were 100% and 80.6% respectively[68]. There was no local recurrence during follow up of 6 to 82 mo. Some studies evaluated ESD for SMTs and found that an optimal size of 1 to 2 cm and submucosal location instead of muscularis propria or deeper made ESD feasible[69]. In these studies, complete resection rate of ESD was 93% and of STER about 100%. The use of STER for esophageal SMT was also studied in a meta-analysis of 16 studies[24]. Complete resection and enbloc resection rates were 100% and 98.6% respectively (Table 2). STER was most effective in tumors < 3 cm. A study on 180 patients with SMTs of which 69% (n = 124) were esophageal in location with a median tumor size of 2.6 cm, STER had an enbloc resection rate of 90.6%. No recurrence or distant metastasis was noted on median follow up of 36 mo[70]. STER requires longer procedure time than ESD but is relatively safe and preserves mucosal integrity[22,23].

For esophageal GIST, molecular targeted therapy and surgical resection are the main stay of treatment. However, EET is being increasing utilized. The available data on GIST comes from small, retrospective studies with limited follow up[71,72]. In a study of 224 patients with SMTs of which 34.4% were GIST and 41.1% werelocated in esophagus, 92.9% were successfully treated with ESD[71]. The mean size was 13.6 mm and no recurrence was reported during 12 mo follow up. STER was successfully employed in a 69 year old male patient with 4 cm GIST in the lower esophagus who was not a surgical candidate and no recurrence, dysphagia or reflux was reported on 1 month follow up[72].

PALLIATIVE THERAPY

Palliative therapy is considered in patients with esophageal cancer when curative therapy is not achievable[73]. The goals of care at this stage are improved QOL by restoration of the ability to swallow and adequate control of pain and bleeding if any, from the cancer. Dysphagia is treated with endoscopic stent placement or tumor destruction by APC, PDT, Nd:YAG laser therapy, brachytherapy or cryotherapy.

Cryotherapy has been shown to improve mean dysphagia score from 2.4 to 1.7 with lower scores indicating better swallowing function[74]. Bleeding can be controlled by endoscopic hemostatic methods such as injection of epinephrine clipping or APC. Locally advanced esophageal cancer may sometimes lead to tracheoesophageal fistulas that can be covered with an esophageal stent.

CONCLUSION

The role of esophagus preserving EET in management of esophageal tumors is ever expanding. EET is the standard of care in early esophageal cancers with minimal risk of lymph node metastases and low risk features. In ESSC, ESD is preferred over EMR due to low risk of recurrence. In EAC, focal EMR is followed by ablation of residual BE mucosa to prevent recurrences. RFA is suitable for ablation of flat mucosa in esophagus whereas lesions with scarring and distorted anatomy are better approached with cryoablation. In general, the use of PDT has declined because of its side effects. Multidisciplinary assessment and determination of a treatment plan involving endoscopists, pathologists, medical oncologists, radiation therapists and surgeons are necessary for decision making in management of esophageal cancer. Treatment plans depend on clinical tumor stage, subsite, and histology of tumor, performance status, physical fitness and co-morbidities. Currently, studies are undergoing to assess role of second generation PDT and ESD followed by chemoradiation therapy in patients at risk for lymph node metastases. The technologic advances are likely to increase the application of the endoscopic management and high quality studies will guide appropriate candidate selection.

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ORIGINAL ARTICLE

Retrospective Study

Secondary angiodysplasia-associated gastrointestinal bleeding in end-stage renal disease: Results from the nationwide inpatient sample

Tooba Tariq, Patrick Karabon, Furqan B Irfan, Sachin Goyal, Matthew Masaru Mayeda, Austin Parsons, Stephanie Judd, Murray Ehrinpreis

ORCID number: Tooba Tariq (0000-0003-4303-086X); Patrick Karabon (0000-0002-8420-1373); Furqan B Irfan (0000-0002-9684-5168); Sachin Goyal (0000-0001-6672-8537); Matthew Masaru Mayeda (0000-0001-8286-0845); Austin Parsons (0000-0003-2921-5753); Stephanie Judd (0000-0001-7296-5694); Murray Ehrinpreis (0000-0002-8138-8152).

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Tooba Tariq, Department of Internal Medicine, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI 49008, United States

Patrick Karabon, Oakland University William Beaumont School of Medicine, Oakland University, Detroit, MI 48309, United States

Furqan B Irfan, Matthew Masaru Mayeda, Austin Parsons, College of Osteopathic Medicine, Michigan State University, East Lansing, MI 48824, United States

Sachin Goyal, Murray Ehrinpreis, Department of Internal Medicine, Division of Gastroenterology, Detroit Medical Center/Wayne State University, Detroit, MI 48201, United States

Stephanie Judd, Department of Internal Medicine, Division of Gastroenterology, Detroit Medical Center/Wayne State University and John D Dingell VA Medical Center, Detroit, MI 48201, United States

Corresponding author: Tooba Tariq, MD, Instructor, Resident Physician, Department of Internal Medicine, Western Michigan University Homer Stryker M.D. School of Medicine, 1000 Oakland Drive, Kalamazoo, MI 49008, United States. toobatariq31@gmail.com
Telephone: +1-217-9045659
Fax: +1-269-3376222

Abstract

BACKGROUND

Chronic kidney disease is associated with angiodysplasia of gastrointestinal tract leading to increased risk of gastrointestinal bleeding.

AIM

To determine the nationwide prevalence, trends, predictors and resource utilization of angiodysplasia-associated gastrointestinal bleeding in end-stage renal disease hospitalizations.

METHODS

The Nationwide Inpatient Sample database from 2009 to 2014, was utilized to conduct a retrospective study on patients with angiodysplasia associated-gastrointestinal bleeding and end-stage renal disease. Hospitalizations with end-

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stage renal disease were included in the Nationwide Inpatient Sample database and a subset of hospitalizations with end-stage renal disease and angiodysplasia-associated gastrointestinal bleeding were identified with International Classification of Diseases, 9th revision, Clinical Modification codes for both end-stage renal disease (585.6) and Angiodysplasia (569.85, 537.83).

RESULTS

The prevalence of angiodysplasia-associated gastrointestinal bleeding was 0.45% (n = 24709) among all end-stage renal disease patients (n = 5505252) that were hospitalized. Multivariate analysis indicated that the following were significant factors associated with higher odds of angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease patients: an increasing trend from 2009-2014 ($P < 0.01$), increasing age ($P < 0.0001$); African American race ($P = 0.0206$); increasing Charlson-Deyo Comorbidity Index ($P < 0.01$); hypertension ($P < 0.0001$); and tobacco use ($P < 0.0001$). Diabetes mellitus ($P < 0.0001$) was associated with lower odds of angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease patients. In comparison with urban teaching hospitals, rural and urban nonteaching hospitals were associated with decreased odds of angiodysplasia associated-gastrointestinal hemorrhage.

CONCLUSION

Angiodysplasia-associated gastrointestinal bleeding in end-stage renal disease patients showed an increasing trend from 2009-2014. Advanced age, African American race, overall high comorbidities, hypertension and smoking were significant factors for angiodysplasia-associated gastrointestinal bleeding in end-stage renal disease hospitalized patients.

Key words: Angiodysplasia; Renal; Gastrointestinal; Hemorrhage

Core tip: There was an increasing trend of angiodysplasia associated-gastrointestinal bleeding among end-stage renal disease patients over the study period of 2009-2014. The likelihood of angiodysplasia associated-gastrointestinal bleeding significantly increased with advanced age with the highest likelihood occurring in patients above the age of 75 years. African American race, increased co-morbidities, hypertension and tobacco use were independent predictors of angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease hospitalized patients.

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INTRODUCTION

Angiodysplasias, the most common vascular malformations of the gastrointestinal (GI) tract are vascular ectasias with an estimated prevalence of 0.82% in the general population[1]. GI Angiodysplasia are the underlying cause for nearly 6% of lower GI hemorrhage and 1.2%-8% of upper GI hemorrhage[1].

In the United States, the prevalence of chronic kidney disease (CKD) and subsequently end-stage renal disease (ESRD) has been on the rise. The United States Renal Data System 2018 Annual Data Report, showed that the prevalence of CKD was around 15% among adults[2]. CKD is associated with an increased risk of GI bleeding, mainly secondary to angiodysplasias and erosive esophagitis[2]. Suspected pathophysiological mechanisms include uremic platelet dysfunction and intermittent use of anticoagulants in dialysis[3,4].

Prior studies have shown that gastric and small bowel angiodysplasia are found to be the most common cause of obscure GI bleeds in patients with chronic renal

failure[5]. A study by Kalman *et al*[6] showed that angioectasia caused upper GI bleeding in 13% of the patients with CKD, however in comparison, 1.3% of patients with normal renal function were found to have angiodysplasia as a source of bleeding. Another study by Holleran *et al*[7] showed that 47% of CKD patients had small bowel angiodysplasia as compared to 17% of controls. The association between renal failure and angiodysplasia was first reported in 1981 and it remains a common cause of initial and recurrent upper GI bleeding in hemodialysis patients[8,9].

Angiodysplasia can be identified in any part of the GI tract but are particularly common in the cecum and ascending colon[10]. Endoscopic techniques (upper endoscopy, double-balloon enteroscopy, wireless capsule endoscopy, colonoscopy) remain the gold standard in the diagnosis of angiodysplasia[10]. The typical endoscopic appearance of an angiodysplastic lesion is that of an isolated, sub-centimeter, flat or raised bright red fernlike pattern of small dilated veins radiating from a central vessel[11]. Limited epidemiological data exists on the annual number of hospitalizations, patient characteristics and outcomes of angiodysplasia-associated GI bleeding in ESRD. The aim of this study was to determine nationwide prevalence, trends in inpatient hospitalizations, and predictors of hospitalization for patients with angiodysplasia-related GI bleeding in ESRD.

MATERIALS AND METHODS

This retrospective study utilized the Nationwide Inpatient Sample (NIS), 2009 to 2014[12,13]. Patients in the NIS database hospitalized during the study period with ESRD were included and a subset of ESRD hospitalizations with Angiodysplasia related GI bleeding hospitalizations were identified using International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes classified diseases according to primary diagnosis for inpatient admission. ESRD hospitalizations were identified based on the ICD-9 CM code - 585.6, and angiodysplasia associated-GI bleeding hospitalizations were identified based on the ICD-9 CM code 569.85 (Angiodysplasia of intestine with hemorrhage) or ICD-9 CM code 537.83 (Angiodysplasia of stomach and duodenum with hemorrhage). Other ICD-9 CM codes utilized in the study included: Hypertension ICD-9 code – 401.x-405.x, 642.0, 642.1, 642.2, 642.7, 642.9; Diabetes Mellitus (DM) ICD-9 code - 250.x (Includes Type 1 and Type II DM); and Tobacco use ICD-9 code - 305.1, V15.82.

Primary outcome was to estimate the prevalence, and predictors of hospitalization for ESRD patients with Angiodysplasia associated-GI bleeding. The secondary outcome was to examine the inpatient hospital-related total cost of care, length of stay (LOS), and inpatient mortality of Angiodysplasia-associated GI bleeding in patients with end stage renal disease hospitalizations. Inpatient hospital-related total cost of care was defined as, the amount the hospital received for the entire hospital stay. In-hospital cost was calculated using total weighted hospital charges and cost to charge ratios reported for participating hospitals. LOS was defined as the number of days the patient remained in the hospital with inpatient status. Inpatient mortality was defined as a binary (yes/no) variable. Other variables included age in years at admission (18 to ≤ 45, 45 to 65, > 65 to 75, and > 75), gender, race (Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian Pacific Islander, Native American, Other), primary payer (Self-payer, Private payer, Medicaid, Medicare, Others), Charlson-Deyo Comorbidity Index (0, 1-2, 3-4, ≥ 5), presence of hypertension, DM, Obesity (Elixhauser comorbidity), tobacco use, Hospital location/teaching status (rural, Urban teaching, Urban non-teaching), Hospital region (Northeast, Midwest, South, West), and median household income quartile defined as: 1 ($1-$38999), 2 ($39000-$47 999), 3 ($48000-$62 999), 4 (≥ $63000).

Statistical analysis

All statistical analysis was done in SAS 9.4 (SAS Institute Inc., Cary, NC, United States) and utilized the SAS/STAT Survey Sampling and Analysis procedures. Univariate comparisons were made using the Rao-Scott Chi-Square test. The Rao-Scott Chi-Square test is similar to a Pearson Chi-Square tests and adjusts for the complex sampling design of the NIS. Multivariate predictive modeling was done using Logistic Regression for complex sampling data. Differences in LOS and total charges were computed using *t*-tests for complex sampling data. Proper variance estimation (strata, clustering, and domain analysis) were handled based on the recommendations provided by AHRQ[12,13].

All frequencies are displayed as weighted hospitalizations. Since data from both before and after 2012 was utilized, the data was weighted by the NIS Trend Weights. Pediatric cases (< 18 years at time of admission) were excluded from this analysis. The

Charlson-Deyo score was used to compute comorbidities[14]. A small proportion of patients were missing data on race, primary payer, median household income quartile, or hospital location/teaching status. These missing data points were either analyzed as their own "Unknown" group or were grouped with the "Other" group, whatever was most appropriate.

RESULTS

During the 2009-2014 study period, a total of 5505252 hospitalizations with an ESRD diagnoses were recorded in United States, hospitals. Angiodysplasia associated-GI bleeds were found in 24709 (0.45%) of ESRD hospitalizations. Baseline characteristics, demographics, risk factors, and complications comparisons of ESRD with and without GI angiodysplasia are displayed in Table 1. The prevalence of ESRD with GI angiodysplasia varied by year with the lowest annual rate in 2009 and the highest annual rate in 2013, respectively representing 0.33% and 0.52% of all ESRD hospitalizations ($P < 0.0001$). The greatest proportion of ESRD hospitalizations were in patients between ages 45-65 (40.25%) and the majority of hospitalizations were Non-Hispanic White (39.58%), followed by African Americans (32.26%). Medicare was the primary payor for the vast majority of ESRD hospitalizations (74.74%).

Age was associated with angiodysplasia associated-GI bleeding, where the highest rate occurred in those 75 years and older (0.69% of ESRD hospitalizations) ($P < 0.0001$). Non-Hispanic White patients had the highest rate of angiodysplasia associated-GI bleeding (0.48% of ESRD hospitalizations) while Medicare had the highest rate of Angiodysplasia associated-GI bleeding (0.50% of ESRD hospitalizations) (both $P < 0.05$).

The Charlson-Deyo Comorbidity Index score was predictive of angiodysplasia associated-GI bleeding with 0.35% of ESRD hospitalizations with a Charlson-Deyo Comorbidity Score of 1-2, 0.46% of ESRD hospitalizations with a Score of 3-4, and 0.50% of hospitalizations with a Score of 5 or more ($P \leq 0.0001$). Analyzed separately, hypertension and tobacco use were associated with angiodysplasia associated-GI bleeding (both $P < 0.0001$). Sex of the patient, DM, obesity, hospital location/teaching status, and hospital region all failed to demonstrate a statistically significant association with GI angiodysplasia (all $P \geq 0.05$).

Multivariate analysis of factors associated with ESRD and angiodysplasia associated-GI bleeding are reported in Table 2. From 2009 to 2014 for all ESRD hospitalizations, there were significantly increasing trend in the odds of concomitant angiodysplasia associated-GI bleeding with an ESRD hospitalization ($P < 0.0001$). Age independently influenced the odds of Angiodysplasia associated-GI bleeding. Compared to hospitalizations in patients between 18-44 years old, hospitalizations for 75+ patients had approximately 8 times greater odds of GI angiodysplasia (OR: 8.22, 95%CI: 5.87-11.5), followed by 7 times greater odds in those aged 65-74 (OR: 7.42, 95%CI: 5.27-10.4), and 4 times greater odds in those aged 45-65 (OR: 4.12, 95%CI: 3.05-5.57) (all $P < 0.0001$). The odds of angiodysplasia associated-GI bleeding were significantly greater for hospitalizations of African American patients (OR: 1.12, 95%CI: 1.02-1.23, $P = 0.0206$), but less for Asian Pacific Islander patients (OR: 0.77, 95%CI: 0.62-0.96, $P = 0.0194$) as compared to hospitalizations of Non-Hispanic White patients. While median household income quartile was not an independently predictive factor, Self-Pay hospitalizations had significantly lower odds of angiodysplasia associated-GI bleeding (OR: 0.32, 95%CI: 0.20-0.51, $P < 0.0001$) than Medicare patients.

The odds of angiodyslasia associated-GI bleeding increased with higher Charlson-Deyo Comorbidity Scores on multivariate analysis. When compared to Charlson-Deyo Scores between 1-2, Charlson-Deyo Scores of 5 or more represented the highest risk group for angiodysplasia associated GI-bleeding (OR: 1.26, 95%CI: 1.12-1.43, $P = 0.0002$), then followed by those with Charlson-Deyo Scores of 3-4 (OR: 1.15, 95%CI: 1.04-1.27, $P = 0.0047$). A DM co-morbidity decreased odds of having angiodysplasia associated-GI bleeding (OR: 0.79, 95%CI: 0.73-0.85, $P < 0.0001$); however, there were increased odds for Hypertension (OR: 2.01, 95%CI: 1.79-2.26) and tobacco use (OR: 1.26, 95%CI: 1.17-1.36) (both $P < 0.0001$). Rural (OR: 0.78, 95%CI: 0.66-0.93, $P = 0.0057$) and urban nonteaching hospitals (OR: 0.89, 95%CI: 0.80-0.98, $P = 0.0160$) had decreased odds of angiodysplasia associated-GI bleeds as compared to urban teaching hospitals. Hospital Region was not independently predictive of angiodysplasia associated-GI bleeds under multivariate analysis (all $P \geq 0.05$).

During the 2009-2014 study period, ESRD hospitalizations with angiodysplasia associated-GI bleeding had a significantly longer average LOS (8.71 d) than hospitalizations without angiodysplasia associated-GI bleeding (6.85 d) ($p < 0.0001$).

Table 1 Prevalence and distribution of demographics, severity of disease, and covariate of patients hospitalized with a diagnosis of end-stage renal disease and angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease hospitalizations, 2009-2014

	End-stage renal disease hospitalizations (*n* = 5505252), *n* (%)	End-stage renal disease with angiodysplasia associated-gastrointestinal bleeding (*n* = 24709), *n* (%)	End-stage renal disease withoutangiodysplasia (*n* = 5480543), *n* (%)	*P* value
Year				
2009	876373 (15.92)	2886 (0.33)	873488 (99.67)	< 0.0001
2010	905614 (16.45)	3845 (0.42)	901768 (99.58)	
2011	975245 (17.72)	4273 (0.44)	970972 (99.56)	
2012	911325 (16.55)	4450 (0.49)	906875 (99.51)	
2013	909080 (16.51)	4715 (0.52)	904365 (99.48)	
2014	927615 (16.85)	4540 (0.49)	923075 (99.51)	
Sex				
Female	2598705 (47.20)	11792 (0.45)	2586913 (99.55)	0.5452
Male	2906547 (52.80)	12917 (0.44)	2893630 (99.56)	
Age category				
18-44	805556 (14.63)	646 (0.08)	804909 (99.92)	< 0.0001
45-64	2215958 (40.25)	7632 (0.34)	2208326 (99.66)	
65-74	1266923 (23.02)	7996 (0.63)	1258927 (99.37)	
75+	1216815 (22.10)	8435 (0.69)	1208381 (99.31)	
Race/ethnicity				
Caucasian	2179234 (39.58)	10509 (0.48)	2168725 (99.52)	0.0149
African American	1776081 (32.26)	8051 (0.45)	1768030 (99.55)	
Hispanic	796930 (14.48)	3240 (0.41)	793690 (99.59)	
Asian Pacific Islander	174118 (3.16)	610 (0.35)	173507 (99.65)	
Native American	53624 (0.98)	188 (0.35)	53436 (99.65)	
Others/Unknown	525265 (9.54)	2111 (0.40)	523155 (99.60)	
Primary payor				
Self-Payor	86637 (1.58)	78 (0.09)	86559 (99.91)	< 0.0001
Private Payor	606394 (11.01)	2114 (0.35)	604280 (99.65)	
Medicaid	595160 (10.81)	1528 (0.26)	593632 (99.74)	
Medicare	4114876 (74.74)	20728 (0.50)	4094148 (99.50)	
Others/Unknown	102185 (1.86)	261 (0.26)	101924 (99.74)	
Median Household Income Quartile				
1st Quartile (Lowest)	2042427 (37.10)	9105 (0.45)	2033322 (99.55)	0.2426
2nd Quartile	1344796 (24.43)	5844 (0.43)	1338952 (99.57)	
3rd Quartile	1147171 (20.84)	5170 (0.45)	1142001 (99.55)	
4th Quartile (Highest)	831706 (15.11)	4052 (0.49)	827653 (99.51)	
Unknown	139152 (2.52)	538 (0.39)	138615 (99.61)	
Charlson-Deyo Comorbidity Index				
Score 1-2	1024375 (18.61)	3617 (0.35)	1020758 (99.65)	< 0.0001
Score 3-4	2918273 (53.01)	13289 (0.46)	2904984 (99.54)	
Score 5+	1562604 (28.38)	7803 (0.50)	1554801 (99.50)	
Hypertension				
Yes	4234181 (76.91)	21756 (0.51)	4212425 (99.49)	< 0.0001
No	1271071 (23.09)	2953 (0.23)	1268118 (99.77)	
Diabetes mellitus				
Yes	3119720 (56.67)	13648 (0.44)	3106072 (99.56)	0.1309
No	2385532 (43.33)	11061 (0.46)	2374471 (99.54)	
Tobacco use				
Yes	1124816 (20.43)	6004 (0.53)	1118812 (99.47)	< 0.0001
No	4380436 (79.57)	18705 (0.43)	4361731 (99.57)	
Obesity				

Yes	642352 (11.67)	2569 (0.40)	639783 (99.60)	0.1030
No	4862900 (88.33)	22140 (0.46)	4840760 (99.54)	
Hospital location/teaching status				
Rural	362509 (6.58)	1419 (0.39)	361090 (99.61)	0.1437
Urban Nonteaching	2047397 (37.19)	8858 (0.43)	2038539 (99.57)	
Urban Teaching	3053214 (55.46)	14248 (0.47)	3038965 (99.53)	
Unknown	42132 (0.77)	184 (0.44)	41949 (99.56)	
Hospital region				
Northeast	993923 (18.06)	4742 (0.48)	989181 (99.52)	0.1104
Midwest	1149456 (20.88)	5388 (0.47)	1144068 (99.53)	
South	2289246 (41.58)	10245 (0.45)	2279002 (99.55)	
West	1072627 (19.48)	4334 (0.40)	1068292 (99.60)	

Similarly, angiodysplasia associated-GI bleeding hospitalizations also had higher average total charges ($82340 *vs* $64579) ($P < 0.0001$). The mortality rate in ESRD hospitalizations with angiodysplasia associated-GI bleeding was 3.41% while the mortality rate in ESRD hospitalizations without angiodysplasia associated-GI bleeding was 5.01% ($P < 0.0001$). The comparison of hospitalization mortality, total charges, and LOS averages between ESRD hospitalizations with and without Angiodysplasia-associated GI bleeding is shown in Table 3.

DISCUSSION

A significant number of patients with ESRD develop GI angiodysplasia during the disease course and hence our study renders valuable information about an important patient cohort. To our knowledge, this is the first population-based study that looks at hospitalization rates, associated factors and outcomes of angiodysplasia related GI bleeding in renal failure patients. Our study showed that over a 5-year period from 2009-2014, there were a total of 5505252 hospitalizations with the diagnoses of ESRD. Of these 0.45% (24709) had angiodysplasia associated-GI hemorrhage. The incidence of Dieulafoy lesions, angiodysplasia and cancers as etiology of upper GI bleeding has been on the rise. Our study also showed a similar trend towards increasing hospitalizations for angiodysplasia related bleeding in ESRD patients from 2009-2014. During the study period, the hospitalization rate of angiodysplasia related hemorrhage in renal failure patients increased by 6.7%. This finding mirrors that of the study by Abougergi *et al*[15], who showed that the hospitalization rate of angiodysplasia in general increased by 32% from 2002-2012. Despite the introduction of newer and innovative treatment options which are successful in achieving short-term hemostasis, recurrent hemorrhage still remains an important problem in angiodysplasia and neoplasm induced hemorrhage[15].

The results of our study showed that elderly patients had a higher tendency of having bleeding angiodysplastic lesions and hence advanced age was noted to be a significant risk factor in our study[16]. This is compatible with the previously known epidemiology of the angiodysplastic lesions[17,18]. No sex differences in patients with angiodysplasia related GI bleeding and ESRD were seen in our study. However, it was found that hypertension was one of the comorbidities associated with increased risk of GI bleeding in patients with ESRD. Holleran *et al*[7] (2013) on multivariate analysis demonstrated that hypertension was positively associated with small bowel angiodysplasia. One possible reason for it might be that old age is associated with increased prevalence of hypertension as a result of decreased arterial compliance[19] and old age was noted to be the single, strongest and independent risk factor for GI angiodysplasia. It is speculated that aging causes vascular fragility which may lead to dysplastic changes of blood vessels and subsequent bleeding.

Results of our multivariate analysis showed that African-American population is associated with an increased risk of developing angiodysplasia related GI bleeding. This finding may reflect a higher prevalence of CKD among African-Americans[20]. Choi *et al*[21], in his study demonstrated higher risk of ESRD and associated mortality among African American individuals when compared to whites. Plausible reasons for this disparity include inadequately controlled diabetes, hypertension and proteinuria in African Americans compared to their white counterparts[21].

Previous studies by Kim *et al*[17] (2015) and Nishimura *et al*[22] (2016) demonstrated that the DM was not associated with bleeding from GI angiodysplasia. Our analysis

Table 2 Multivariable analyses of factors associated with Angiodysplasia associated-gastrointestinal bleeding in end-stage renal disease hospitalizations, 2009-2014

	Adjusted odds ratio (95%CI)	*P* value
Year		
2010	1.27 (1.07, 1.52)	0.0071
2011	1.28 (1.08, 1.53)	0.0045
2012	1.43 (1.23, 1.66)	< 0.0001
2013	1.51 (1.30, 1.76)	< 0.0001
2014	1.39 (1.19, 1.61)	< 0.0001
2009	Reference	
Sex		
Male	0.99 (0.93, 1.06)	0.8053
Female	Reference	
Age category		
45-64	4.12 (3.05, 5.57)	< 0.0001
65-74	7.42 (5.27, 10.4)	< 0.0001
75+	8.22 (5.87, 11.5)	< 0.0001
18-44	Reference	
Race/ethnicity		
African American	1.12 (1.02, 1.23)	0.0206
Asian Pacific Islander	0.77 (0.62, 0.96)	0.0194
Hispanic	1.08 (0.89, 1.30)	0.4459
Native American	0.93 (0.61, 1.42)	0.7335
Others/unknown	0.98 (0.86, 1.12)	0.7289
Caucasian	Reference	
Primary payor		
Others/Unknown	0.69 (0.52, 0.90)	0.0072
Medicaid	0.84 (0.69, 1.01)	0.0669
Private Payor	0.96 (0.83, 1.10)	0.5551
Self-Payor	0.32 (0.20, 0.51)	< 0.0001
Medicare	Reference	
Median Household Income Quartile		
2nd Quartile	0.96 (0.86, 1.06)	0.4205
3rd Quartile	0.97 (0.88, 1.08)	0.6124
4th Quartile (Highest)	1.00 (0.89, 1.12)	0.9335
Unknown	0.96 (0.76, 1.20)	0.7065
1st Quartile (Lowest)	Reference	
Charlson-Deyo Comorbidity Index		
Score 3-4	1.15 (1.04, 1.27)	0.0047
Score 5+	1.26 (1.12, 1.43)	0.0002
Score 1-2	Reference	
Hypertension		
Yes	2.01 (1.79, 2.26)	< 0.0001
No	Reference	
Diabetes mellitus		
Yes	0.79 (0.73, 0.85)	< 0.0001
No	Reference	
Tobacco use		
Yes	1.26 (1.17, 1.36)	< 0.0001
No	Reference	
Hospital location/teaching status		
Rural	0.78 (0.66, 0.93)	0.0057
Unknown	1.20 (0.77, 1.86)	0.4205
Urban Nonteaching	0.89 (0.80, 0.98)	0.0160
Urban Teaching	Reference	

Hospital region		
Midwest	0.99 (0.89, 1.10)	0.8082
Northeast	0.97 (0.85, 1.10)	0.6453
West	0.93 (0.80, 1.09)	0.3770
South	Reference	

suggested that diabetes was associated with reduced risk of bleeding from angiodysplastic lesions[17,22]. However, it is unknown whether glycemic control was a contributory factor to bleeding from angiodysplasia. Hypothetically, hyperglycemia could be important because of reactive oxygen species mediated oxidative stress[23]. It is essential to elucidate whether DM affects the risk of hemorrhage from angiodysplasia and whether strict glycemic control can lower the bleeding risk. Hence, further studies are required before any definitive conclusions can be drawn.

Our study found smoking to be a significant risk factor promoting angiodysplasia related bleeding in renal failure patients. Kaplan *et al*[24], in his study reported that smokers had a high risk of hospitalizations for upper GI bleed compared to non-smokers. Proposed mechanism involves inhibition of prostaglandins in the upper GI tract induced by smoking. This leads to vasoconstriction of the overlying mucosa and possible ischemia. This effect may be aggravated in ESRD patients who have pre-existing microvascular disease and hence are at increased risk of developing GI bleeding compared to the general population[25,26].

It was also noted in our study that presence of other comorbidities was also significantly associated with bleeding from angiodysplasia in ESRD patients. These comorbidities included peripheral vascular disease, cerebrovascular disease, chronic lung disease, rheumatological disease, peptic ulcer disease, liver disease, DM, cancer and AIDS. We utilized the Charlson Comorbidity Index because it is a well validated score for measuring comorbidity in many different contexts[14]. Many potential mechanisms for this observed association are hypothesized for example decreased oxygen levels in chronic lung disease, malnutrition in many diseases (such as chronic liver disease) or micro-and macrovascular complications in diabetes. Hence, a cumulative effect rather than a single mechanism is involved. This highlights the fact that it is imperative to know the burden of comorbidities of the patient since early recognition will help guide management particularly in cases where modifiable GI risk factors are absent[27].

In-hospital mortality of ESRD patients with angiodysplasia related GI bleeding was found to be lower compared to inpatient mortality of population with end stage renal disease without angiodysplasia (3.41% *vs* 5.01%). This particular finding can potentially be explained by the fact that the reduction in mortality rate could be due to improvements in treatment modalities which include not only medications such as proton pump inhibitors (PPI) and octreotide, but also various hemostatic techniques utilized during endoscopy as well as surgical interventions. This is supported by a study published in 2015, which showed that at the same time that the in-hospital mortality rates have been declining, the rate of in-hospital endoscopy, endoscopy within 24 h of admission and endoscopic therapy for patients with non-variceal upper GI bleeding increased during 1989-2009[28]. There has also been advances in diagnostic testing, provision of better care in the intensive care units and general health care delivery. Effective nonsurgical therapies are currently in place for patients undergoing dialysis and hence they have better chances of survival even in cases of massive, acute upper GI bleeding. Better outpatient management and treatment with erythropoiesis stimulating agents and intravenous iron therapy might have translated into the observed better outcomes as a result of higher hemoglobin targets and an increased "hematocrit reserve"[29]. Yang *et al*[29], by utilizing the NIS database from 2002-2012 similarly showed that the mortality rate for all of the different causes of non-variceal upper GI hemorrhage declined over the study period. Prior studies have demonstrated that the in-hospital mortality of upper GI hemorrhage has been gradually decreasing since 1989.

The total length of hospital stay and hospital charges were noted to be higher in patients with angiodysplasia related bleeding compared to those patients who had only ESRD without angiodysplasia, as a result of more complicated disease course in the former group. This is in line with another study published in 2015, which showed that healthcare burden as well as the median individual hospital charges have increased sharply for upper non-variceal GI hemorrhage, over the past 20 years. The cause for this increase is possibly multifold and include not only more frequent use of expensive therapies such as medications, blood transfusions and endoscopic techniques but also possibly due to changes in reimbursement models[28].

Table 3 Comparison between inpatient mortality, mean hospitalization cost of care, and mean length of stay between end-stage renal disease and angiodysplasia associated-gastrointestinal bleeding, and end-stage renal disease hospitalizations, 2009-2014

	Mortality		Total charges		Length of stay	
	Odds ratio (95%CI)	*P* value	Difference (95%CI)	*P* value	Difference (95%CI)	*P* value
Angiodysplasia	0.67 (0.58, 0.78)	< 0.0001	$17761 ($12550, $22973)	< 0.0001	1.86 (1.40, 2.32)	< 0.0001
No Angiodysplasia	Reference		Reference		Reference	

The NIS is an administrative database hence coding errors and selection bias are unavoidable. In our study the diagnosis of GI hemorrhage related to angiodysplasia and ESRD might be limited by the accuracy and comprehension of the ICD-9 codes. Laboratory parameters are unavailable which is a significant limitation since it is not possible to determine the severity of anemia or CKD without hemoglobin and creatinine[30]. Similarly, the use of medications (PPI, octreotide) during the hospital stay is not included in the NIS.

Information regarding outpatient follow-up, readmission, and the bleeding rates cannot be estimated after hospitalizations since the data is limited to only inpatient stay. For the same reason overall mortality rates cannot be measured due to unavailability of out of hospital mortality rates. Despite these limitations, the NIS database has many strengths including its unprecedented size and the fact that it is a uniform, inpatient administrative database. Due to these reasons, the epidemiological data and outcomes obtained by utilizing it are comprehensive and generalizable[31].

This study highlighted a clear trend in the rising number of hospitalizations of patients with ESRD-related GI angiodysplasia. Advanced age, African American race, overall comorbidities and specifically hypertension and smoking were significantly associated with angiodysplasia-related GI hemorrhage. In addition, patients admitted with GI bleed in the setting of angiodysplasia experienced an increase in their LOS and hospital charges. A unique finding of this study was that compared to ESRD patients without angiodysplasia related bleeding, patients with angiodysplasia related GI hemorrhage were noted to have lower inpatient mortality rate which may reflect better outpatient care and availability of advanced endoscopic hemostatic techniques.

Nonetheless, recurrent hemorrhage remains an important problem in ESRD patients with angiodysplasia leading to increased inpatient encounters. Hence, further studies must continue to identify and formulate long term management plans which aim to stop and prevent repeated episodes of GI bleeding in this particular patient population.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal (GI) angiodysplasia are commonly occurring vascular malformations in the GI tract and account for approximately 6% of lower GI bleeding and up to 8% of upper GI bleeds. Chronic kidney disease and subsequent end-stage renal disease (ESRD) have been associated with increased development and risk of hemorrhage from GI Angiodysplasia.

Research motivation

There are few epidemiology studies exploring the association between angiodysplasia-related GI bleeding in renal disease patients. With increasing burden of chronic kidney disease, prevalence of nearly 15% in United States adults, the proportion of GI bleeding attributed to Angiodysplasia in renal disease patients is expected to increase. Studies need to be carried out to determine the burden and epidemiology, clinical presentation, diagnosis, management and outcomes of angiodysplasia-associated GI bleeding in renal disease patients. Such efforts would help guide clinicians to be watchful and prevent major bleeding in susceptible renal disease patients, improve outcomes and reduce hospitalization costs, especially in the elderly and chronic disease patients.

Research objectives

The main objectives of this study were to determine nationwide prevalence, hospitalization trends, and risk factors of hospitalization for angiodysplasia-associated GI hemorrhage in ESRD patients in the United States. Secondary objectives that were realized included length of stay, average total inpatient charges and mortality rate. The nationwide objectives achieved in this study provide baseline estimates for future research, the prevalence and risk factors identified should guide prevention and lead to improved management and outcomes in such patients.

Research methods
This retrospective study utilized the Nationwide Inpatient Sample, database from 2009 to 2014. International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes, were used to identify all patients nationwide with ESRD hospitalizations during the study period, and a subset of ESRD hospitalizations with angiodysplasia associated-GI bleeding were identified and compared. Independent variables (risk factors) included hospitalization year (2009-2014), gender, age category, race, primary payor, median household income quartile, Charlson Deyo-comorbidity index, hypertension, diabetes mellitus, tobacco use, obesity, hospital location (rural, urban, urban teaching), and hospital region. Multivariable regression modelling was performed to determine the risk factors associated with angiodysplasia associated-GI hemorrhage in ESRD hospitalized patients.

Research results
Angiodysplasia-associated GI hemorrhage in ESRD patients had a prevalence of 0.45% (n = 24709) among all ESRD hospitalizations (n = 5505252). Multivariable regression analysis showed that higher odds of angiodysplasia associated-GI hemorrhage in ESRD hospitalized patients occurred with increasing year trend from 2009-2014; increasing age; African American race; increasing Charlson-Deyo Comorbidity Index; hypertension; and tobacco use. And lower odds were associated with rural and urban nonteaching hospitals in comparison to urban teaching hospitals. ESRD hospitalizations with Angiodysplasia associated-GI bleeding had mean length of stay of 8.71 d, total average inpatient charges of $82340, and mortality rate of 3.41%.

Research conclusions
To our knowledge this is the first nationwide study that has determined baseline epidemiology estimates, hospitalization trends, risk factors and outcomes of angiodysplasia-associated GI bleeding in renal failure (ESRD) hospitalized patients. During the study period of 2009-2014, the hospitalization rate of angiodysplasia-associated GI bleeding in (ESRD) hospitalized patients increased by 6.7%, which indicates that recurrent hemorrhage in such patients should be expected. Clinical implications include patient communication to ESRD patients to immediately seek medical care if they have any signs of GI bleeding. Elderly ESRD patients had the strongest association for angiodysplasia-associated GI bleeding and such patients should be carefully observed for any signs and symptoms of GI bleeding. Hypertensive ESRD patients also had high risk and since elderly patients are frequently hypertensive, the risk for angiodysplasia-associated GI bleeding gets compounded. African American ESRD patients also had increased odds of angiodysplasia-associated GI bleeding that could be attributed to inadequate control of chronic conditions (e.g. hypertension, diabetes mellitus). Further studies need to be carried out to determine if there is a genetic predisposition in ESRD African American patients for angiodysplasia-associated GI bleeding. This study is the first one to report that Diabetes mellitus in ESRD patients was associated with decreased odds of angiodysplasia-associated GI bleeding. The biological mechanisms of diabetes mellitus and glycemic control being a protective factor for angiodysplasia-associated GI bleeding in renal disease patients needs to be elucidated in future studies.

Research perspectives
With increasing burden of renal disease, angiodysplasia-associated GI bleeding in ESRD patients has shown a rising trend. Elderly age group, African American race, overall co-morbidities, hypertension and smoking were significant risk factors for angiodysplasia-associated GI bleeding in ESRD patients. The role of diabetes mellitus in this study showed decreased odds of angiodysplasia-associated GI bleeding in renal disease patients. Future translational studies should look at the underlying biological mechanisms of hyperglycemia being a protective factor for angiodysplasia-associated GI bleeding in renal disease patients.

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ORIGINAL ARTICLE

Retrospective Study

Risk factors for the development of post-endoscopic retrograde cholangiopancreatography pancreatitis in patients with asymptomatic common bile duct stones

Hirokazu Saito, Tatsuyuki Kakuma, Ikuo Matsushita

ORCID number: Hirokazu Saito (0000-0001-8729-9604); Tatsuyuki Kakuma (0000-0002-3713-3099); Ikuo Matsushita (0000-0001-5160-8823).

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Hirokazu Saito, Ikuo Matsushita, Department of Gastroenterology, Kumamoto Chuo Hospital, 1-5-1, Tainoshima, Minami-ku, Kumamoto City, Kumamoto 862-0965, Japan

Tatsuyuki Kakuma, Department of Biostatics Center, Medical School, Kurume University, 67, Asahimachi, Kurume City, Fukuoka 830-0011, Japan

Corresponding author: Hirokazu Saito, MD, Chief Doctor, Department of Gastroenterology, Kumamoto Chuo Hospital, 1-5-1, Tainoshima, Minami-ku, Kumamoto City, Kumamoto 862-0965, Japan. arnestwest@yahoo.co.jp
Telephone: +81-96-3703111
Fax: +81-96-3704017

Abstract

BACKGROUND

Previous studies have revealed that patients with asymptomatic common bile duct (CBD) stones are at a high risk of developing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). However, no studies to date have addressed the risk factors for PEP in patients with asymptomatic CBD stones.

AIM

To examine the risk factors for PEP in patients with asymptomatic CBD stones.

METHODS

Using medical records of three institutions in Japan for 6 years, we identified a total of 1135 patients with choledocholithiasis including 967 symptomatic patients and 168 asymptomatic patients with native papilla who underwent therapeutic ERCP. We performed univariate and multivariate analyses to examine the risk factors for PEP in the 168 patients with asymptomatic CBD stones.

RESULTS

The overall incidence rate of PEP in all the patients with during study period was 4.7% (53/1135). Of the 168 patients with asymptomatic CBD stones, 24 (14.3%) developed PEP. In univariate analysis, precut sphincterotomy (P = 0.009) and biliary balloon sphincter dilation (P = 0.043) were significant risk factors for PEP. In multivariate analysis, precut sphincterotomy (P = 0.002, 95%CI: 2.2-27.8, odds

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ratio = 7.7), biliary balloon sphincter dilation (P = 0.015, 95%CI: 1.4-17.3, odds ratio = 4.9), and trainee endoscopists (P = 0.048, 95%CI: 1.01-8.1, odds ratio = 2.9) were significant risk factors for PEP.

CONCLUSION
ERCP for asymptomatic CBD stones should be performed by experienced endoscopists. When performing precut sphincterotomy or biliary balloon sphincter dilation in patients with asymptomatic CBD stones, the placement of a prophylactic pancreatic stent is strongly recommended to prevent PEP.

Key words: Endoscopic retrograde cholangiopancreatography; Post- endoscopic retrograde cholangiopancreatography pancreatitis; Risk factor; Asymptomatic common bile duct stone

Core tip: The objective of this study was to examine the risk factors for the development of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) in patients with asymptomatic common bile duct (CBD) stones. In multivariate analysis, precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were significant risk factors for PEP. ERCP for asymptomatic CBD stones should be performed by experienced endoscopists. When performing precut sphincterotomy or biliary balloon sphincter dilation in patients with asymptomatic CBD stones, prophylactic pancreatic stent placement is strongly recommended to prevent PEP.

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INTRODUCTION

Endoscopic stone removal through endoscopic retrograde cholangiopancreatography (ERCP) is an effective treatment for common bile duct (CBD) stones. Nevertheless, ERCP is associated with a high risk of treatment-related complications. Post-ERCP pancreatitis (PEP) is the most commonly observed ERCP-related complication, potentially leading to patient mortality[1,2].

The presence of asymptomatic CBD stones is associated with complications, such as obstructive jaundice, acute cholangitis, or biliary pancreatitis. Therefore, available guidelines recommend endoscopic CBD stone removal through ERCP in this setting[3-6].

However, ERCP for asymptomatic CBD stones is associated with a high risk of PEP development[7-9]. In our previous study, we performed a propensity-matched analysis including 949 symptomatic CBD patients and 164 asymptomatic CBD patients and revealed that the incidence of PEP was significantly higher in patients with asymptomatic CBD stones than in those with symptomatic CBD stones [24/164 (14.6%) *vs* 28/949 (3.0%), P < 0.001, odds ratio: 5.6]. In another propensity-matched analysis of 158 matched pairs, a similar result was obtained [24/158 (15.2%) *vs* 5/158 (3.2%), respectively, P < 0.001, odds ratio: 5.5][7]. These findings were corroborated by those of other retrospective studies[8,9].

Treatment for asymptomatic CBD stones through ERCP aims at the prevention of possible complications associated with the presence of CBD stones. Furthermore, this disease is benign and asymptomatic. Therefore, complete removal of stones through ERCP with a low risk of PEP development is important, particularly in patients with asymptomatic CBD stones.

Based on this evidence, risk factors for the development of PEP in patients with stones asymptomatic CBD stones must be identified. Currently, however, there are no studies addressing this topic. Therefore, in the present study, we examined the risk factors for PEP development in patients with asymptomatic CBD stones.

MATERIALS AND METHODS

Patients and study design

We reviewed the medical records of three Japanese hospital from April 2012 to March 2018 and identified 1135 patients with choledocholithiasis–including acute cholangitis, biliary pancreatitis, obstructive jaundice or elevated liver test results without cholangitis, and asymptomatic CBD stones-who were diagnosed with native papilla and gastrointestinal tract without a surgical history or Billroth I reconstruction and who underwent endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), or endoscopic papillary large balloon dilation (EPLBD). Of these, 168 patients with asymptomatic CBD stones were enrolled in this study. Of the 168 enrolled patients, 164 and 4 underwent successful and unsuccessful cannulation, respectively. Those 164 patients in whom successful cannulation was performed were included in our previous study examining the incidence of PEP in patients with asymptomatic CBD stones[7]. We performed univariate and multivariate analyses to identify the risk factors for PEP development in patients with asymptomatic CBD stones. This study was approved by the institutional review boards of the participating hospitals.

Examination and pretreatment

Side-viewing duodenoscopes (Olympus JF-260, TJF-260V; Olympus Medical Systems, Tokyo, Japan) were used to examine all patients. Midazolam and/or pethidine hydrochloride and scopolamine butylbromide or glucagon was intravenously injected for sedation and duodenal relaxation, respectively.

Endoscopists

A total of 23 endoscopists participated in this study. Among those, 10 endoscopists were trainees who were supervised by experienced endoscopists.

Study definitions

Asymptomatic CBD stones: Asymptomatic CBD stones were defined as CBD stones without symptoms and with normal blood examination results (total bilirubin, direct bilirubin, aspartate aminotransferase/alanine aminotransferase, γ- glutamyltransferase, alkaline phosphatase, white blood count, and C-reactive protein) during ERCP.

Trainee endoscopists: Endoscopists were classified as trainees if they had performed < 200 ERCP procedures or were only able to perform Grade 1 biliary procedures (including standard sphincterotomy, removal of stones < 10 mm, and placement of a biliary stent) based on a grading scale for ERCP[10].

EST, EPBD and EPLBD: For patients in whom EST, EPBD, or EPLBD was additionally performed at the second session of ERCP after performing any of these procedures at the first session of ERCP, we selected the procedure that was performed at the first session of ERCP. Biliary balloon sphincter dilation included EPBD and EPLBD without EST. A small balloon (diameter, 8 mm) was used to perform EPBD. EPLBD was defined as the procedure for biliary orifice dilation using a large balloon (diameter, ≥ 12 mm)[11].

PEP: The consensus criteria established by Cotton *et al*[12] were used for PEP diagnosis and grading. The diagnostic criteria for PEP were as follows: newly onset or worsened abdominal pain and > 3-fold elevated serum amylase level from normal 24 h after ERCP. Mild PEP cases included those who required new hospitalization or prolongation of hospitalization by 2-3 d. Moderate PEP cases included those who required hospitalization of 4-10 d. Severe PEP cases included those who required prolonged hospitalization (> 10 d), percutaneous drainage, or surgery.

Cut-off time for cannulation duration

In this study, we used 10 min as the cut-off time for a risk factor for PEP development. This value was selected based on a guideline stating that a duration of biliary cannulation > 10 min is a procedure-related risk factor for PEP development[2].

Statistical analysis

Initially, we performed univariate analyses using chi-squared test, Fisher's exact test, or *t*-test to examine differences in clinical risk factors for PEP development between patients with or without PEP. Subsequently, we performed multivariate analysis using a logistic regression model to examine the associations between PEP incidence and risk factors with $P < 0.10$ in univariate analysis. A $P < 0.05$ denoted statistical significance. JMP® Pro 13 (SAS Institute, Cary, NC, United States) and R version 3.5.1 (http://www.R-project.org) were used for all statistical analyses.

RESULTS

Patient characteristics

Table 1 presents patient characteristics. Among the four patients who underwent EPLBD, three underwent EPLBD with EST and one underwent EPLBD without EST.

Diagnostic modality for CBD stones

For the diagnosis of CBD stones, one or more imaging examinations (*i.e.*, ultrasonography, endoscopic ultrasound, computed tomography, and/or magnetic resonance cholangiopancreatography) were performed in all the patients. In patients in whom CBD stones were not detected through the aforementioned examinations, the diagnosis was confirmed based on dilated CBD on imaging examination, elevated serum bilirubin levels, and/or abnormal liver test findings.

Rate of successful cannulation

The rate of successful cannulation in this study was 97.6% (164/168 patients).

Incidence rate of PEP in patients with choledocholithiasis

Among the 1135 patients with choledocholithiasis-including acute cholangitis, biliary pancreatitis, obstructive jaundice or elevated liver test results without cholangitis, and asymptomatic CBD stones-who were diagnosed with native papilla and gastrointestinal tract without a surgical history or Billroth I reconstruction and who underwent EST, EPBD, or EPLBD, the incidence rate of PEP was 4.7% (53/1135 patients).

Incidence rates and risk factors for PEP development in patients with asymptomatic CBD stones

Of the 168 patients with asymptomatic CBD stones, 24 (14.3%) developed PEP. The results of univariate and multivariate analyses are listed in Tables 2 and 3, respectively. In univariate analysis, precut sphincterotomy and biliary balloon sphincter dilation were identified as significant risk factors for PEP development. In multivariate analysis, precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were identified as significant risk factors for PEP development (precut sphincterotomy: P = 0.002, 95%CI: 2.2-27.8, odds ratio = 7.7; biliary balloon sphincter dilation: P = 0.015, 95%CI: 1.4-17.3, odds ratio = 4.9; trainee endoscopists; P = 0.048, 95%CI: 1.01-8.1, odds ratio = 2.9).

Severity and mortality rate of PEP in patients with asymptomatic CBD stones

Among the 24 patients who developed PEP, 10 (41.7%), 10 (41.7%), and 4 (16.7%) showed mild, moderate, and severe PEP, respectively. In this study, one death (0.60% of the total population) was reported among severe PEP cases.

DISCUSSION

The present study showed that precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were significant risk factors for PEP development in patients with asymptomatic CBD stones.

According to the European Society of Gastrointestinal Endoscopy guidelines, PEP incidence was 3.5% and PEP severity was mild, moderate, and severe (potentially fatal) in 45%, 44, and 11% of the cases, respectively[2]. Among 1,135 patients with native papilla who underwent ERCP for choledocholithiasis in our institution during the study period, the overall PEP incidence was 4.7% and PEP severity was mild in 58.5% (31/53), moderate in 30.2% (16/53), and severe in 11.3% (6/53) of the cases. These results are consistent with previously reported results.

For patients with asymptomatic CBD stones, the current guidelines recommend endoscopic stone removal through ERCP[3-6]. However, when determining the indication for ERCP in patients with asymptomatic CBD stones, risks associated with ERCP and no treatment for asymptomatic CBD stones should be compared[13].

Although the natural history of asymptomatic CBD stones is unclear because of the lack of data on long-term follow-up outcomes, some studies have investigated the natural history of asymptomatic CBD stones. The rate of spontaneous passage of CBD stones through the major papilla within 4-6 wk after diagnosis is approximately 20%-30%[14,15]. A previous study involving 59 patients with asymptomatic CBD stones incidentally diagnosed during cholecystectomy demonstrated that these patients did not develop any complications associated with CBD stones during a follow-up period of > 5 years[16]. Conversely, a study involving 3828 patients with CBD stones diagnosed *via* intraoperative cholangiography during cholecystectomy showed that

Table 1 The characteristics of 168 asymptomatic patients

Characteristics	*n* (%)
Age [mean (SD)], yr	72.6 (11.2)
Sex, female	77 (45.8)
Billroth I reconstruction	9 (5.4)
Non-dilated CBD (< 10 mm)	99 (58.9)
Pharmacological prevention	82 (48.8)
Protease inhibitor	67 (39.9)
Rectal NSAIDs	15 (8.9)
Trainee endoscopist	39 (23.2)
Pancreatic injections	88 (52.4)
PGW-assisted cannulation	33 (19.6)
Precut sphincterotomy	15 (8.9)
Cannulation time > 10 min	64 (38.1)
Unsuccessful cannulation	4 (2.4)
EST	146 (86.9)
EPBD	14 (8.3)
EPLBD	4 (2.4)
Prophylactic pancreatic stent	27 (16.1)
Procedure time [mean (SD)], min	31.1 (16.4)

CBD: Common bile duct; NSAIDs: Nonsteroidal anti-inflammatory drugs; PGW: Pancreatic guide wire; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation.

approximately a quarter of the patients who did not undergo intraoperative treatment for CBD stones showed unfavorable outcomes[17].

Meanwhile, the risk of procedure-related complications, particularly PEP, should be considered when performing ERCP in patients with asymptomatic CBD stones. The overall incidence rate of ERCP for asymptomatic CBD stone was approximately 20% and the incidence rate of PEP was reportedly between 12.5% and 14.6%[7,8]. This high incidence rate of PEP in patients with asymptomatic CBD stones may be attributed to the presence of multiple patient- and procedure-related risk factors, such as normal serum bilirubin levels, non-dilated CBD, and difficult biliary cannulation. In our previous study, we concluded that endoscopists should explain in detail the risk of PEP to patients with asymptomatic CBD stones prior to ERCP[7].

In this study, we showed that precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were significant risk factors for PEP development in patients with asymptomatic CBD stones. In the present study, precut sphincterotomy was performed by expert endoscopists in cases with difficult cannulation.

The current guidelines recommend the placement of a prophylactic pancreatic stent, specifically in patients at a high risk of PEP development[1,2]. Therefore, endoscopists should strongly consider this option when performing precut sphincterotomy or biliary balloon sphincter dilation in this population. Several studies have examined the safety of ERCP when performed by trainee endoscopists. Some prospective studies have demonstrated that involvement of trainee endoscopists was not a significant risk factor for PEP development[18,19]. However, a multicenter prospective study has reported contrasting results[20]. There may be a notion that trainees must gain experience of ERCP. However, ERCP in patients with asymptomatic CBD stones is associated a high risk of PEP development, and ERCP performed by trainee endoscopists is a risk factor for PEP regardless of supervision by an experienced endoscopist. Therefore, ERCP for asymptomatic CBD stones should be performed by experienced endoscopists.

There were several limitations in this study. First, this study was a retrospective study with small cohort. Second, a participating institution in this study suffered tremendous damage due to the Kumamoto earthquake that occurred in April 2016. Thus, ERCP could not be performed after the earthquake, and data obtained from this institution covered only 4 years (April 2012 to April 2016).

In conclusion, precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were identified as significant risk factors for PEP development in patients with asymptomatic CBD stones. Placement of a prophylactic pancreatic stent

Table 2 Univariate analyses of risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis development in patients with asymptomatic common bile duct stones, *n* (%)

	Without post-ERCP pancreatitis (*n* = 144)	With post-ERCP pancreatitis (*n* = 24)	*P* value
Significant risk factors			
Precut sphincterotomy	9 (6.3)	6 (25.0)	0.009
Biliary balloon sphincter dilation	10 (6.9)	5 (20.8)	0.043
Not significant risk factors			
Procedure time ≥ 30 min	66 (45.8)	16 (66.7)	0.059
Trainee endoscopist	30 (20.8)	9 (37.5)	0.073
Cannulation time > 10 min	51 (35.4)	13 (54.2)	0.080
Administration of a protease inhibitor	54 (37.5)	13 (54.2)	0.12
Rectal NSAIDs	15 (10.4)	0 (0)	0.13
Female sex	63 (43.8)	14 (58.3)	0.18
PGW-assist cannulation	26 (18.1)	7 (29.2)	0.26
Pancreatic injections	73 (50.7)	15 (62.5)	0.28
Endoscopic sphincterotomy	127 (88.2)	19 (79.2)	0.32
Age [mean (SD)], yr	72.3 (10.8)	74.7 (13.0)	0.33
Absence of pancreatic stent	122 (84.7)	19 (79.2)	0.55
Non-dilated CBD (<10 mm)	86 (59.7)	13 (54.2)	0.61
Unsuccessful cannulation	4 (2.8)	0 (0)	1.0

ERCP: Endoscopic retrograde cholangiopancreatography; NSAIDs: Nonsteroidal anti-inflammatory drugs; PGW: Pancreatic guide wire; CBD: Common bile duct.

should be strongly considered in patients with asymptomatic CBD stones undergoing precut sphincterotomy or biliary balloon sphincter dilation. ERCP for asymptomatic CBD stones should be performed by experienced endoscopists.

Table 3 Multivariate analysis of risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis development in patients with asymptomatic common bile duct stones

	P value	95%CI	Odds ratio
Precut sphincterotomy	0.002	2.2-27.8	7.7
Biliary balloon sphincter dilation	0.015	1.4-17.3	4.9
Trainee endoscopist	0.048	1.01-8.1	2.9
Procedure time ≥ 30 min	0.55	0.45-4.5	
Cannulation time > 10 min	0.57	0.46-4.1	

ARTICLE HIGHLIGHTS

Research background

Previous studies have revealed that patients with asymptomatic common bile duct (CBD) stones are at a high risk of developing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP). However, no studies to date have addressed the risk factors for PEP in patients with asymptomatic CBD stones.

Research motivation

Treatment for asymptomatic CBD stones through ERCP aims at the prevention of possible complications associated with the presence of CBD stones. Furthermore, this disease is benign and asymptomatic. Therefore, complete removal of stones through ERCP with a low risk of PEP development is important, particularly in patients with asymptomatic CBD stones. We identified the risk factors for PEP in this population to reduce the incidence of PEP.

Research objectives

The objective of this study was to examine the risk factors for the development of PEP in patients with asymptomatic CBD stones.

Research methods

We reviewed the medical records of three Japanese hospital from April 2012 to March 2018 and identified 1135 patients with choledocholithiasis–including acute cholangitis, biliary pancreatitis, obstructive jaundice or elevated liver test results without cholangitis, and asymptomatic CBD stones-who were diagnosed with native papilla and gastrointestinal tract without a surgical history or Billroth I reconstruction and who underwent endoscopic sphincterotomy, endoscopic papillary balloon dilation, or endoscopic papillary large balloon dilation. Of these, 168 patients with asymptomatic CBD stones were enrolled in this study. We performed univariate and multivariate analyses to identify the risk factors for PEP development in patients with asymptomatic CBD stones.

Research results

Among all the 1135 patients with choledocholithiasis including 967 symptomatic patients and 168 asymptomatic patients, the incidence rate of PEP was 4.7% (53/1135). Of the 168 patients with asymptomatic CBD stones, 24 (14.3%) developed PEP. In univariate analysis, precut sphincterotomy and biliary balloon sphincter dilation were identified as significant risk factors for PEP development in patients with asymptomatic CBD stones. In multivariate analysis, precut sphincterotomy, biliary balloon sphincter dilation, and trainee endoscopists were identified as significant risk factors for PEP development in this population.

Research conclusions

ERCP for asymptomatic CBD stones should be performed by experienced endoscopists. When performing precut sphincterotomy or biliary balloon sphincter dilation in patients with asymptomatic CBD stones, prophylactic pancreatic stent placement is strongly recommended to prevent PEP.

Research perspectives

An important limitation of this study was that this was a retrospective study with small cohort. Prospective studies with a large number of patients are warranted to further identify the risk factors associated with the development of PEP in patients with asymptomatic CBD stones.

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