Prospective Evaluation of Adverse Events Following Lower Gastrointestinal Tract EUS FNA

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OBJECTIVES: **There are virtually no data concerning the risk of adverse events (AEs) following lower gastrointestinal (LGI) endoscopic ultrasound (EUS). Our aim was to determine the incidence and factors associated with AEs following LGI EUS fine needle aspiration (FNA).**

METHODS: **We conducted a prospective cohort study at a tertiary referral center. Five hundred and sixty-three patients underwent LGI EUS FNA between 1 January 2004 and 1 January 2012. We analyzed the 502 patients who had complete follow-up. AE severity was graded (1–5) utilizing Common Terminology Criteria or Visual Analog Scale. AEs were assessed during the procedures, in clinical follow-up, during phone interviews conducted at 7–14 days, and final clinical and/or phone interviews at 2–4 months.**

RESULTS: **AEs developed in 103 (20.5%) patients and were classified as grade 1, 2, 3, or 4 in 34 (6.8%), 41 (8.2%), 23 (4.6%), and 5 (1.0%) patients, respectively. Bleeding and pain were the commonest AEs. No deaths occurred. On multivariate analysis, AEs were associated with prior pain (odds ratio (OR): 3.83, 95% confidence interval (CI): 2.35–6.25), FNA from a site other than a lymph node (LN) or gut wall (OR: 2.26, 95% CI: 1.10–4.70), and malignant FNA cytology (OR: 1.80, 95% CI: 1.10–2.97); serious (grade 3–4) AEs were associated with prior pain (OR: 15.21, 95% CI: 5.04–45.85) and FNA from a site other than a LN or gut wall (OR: 3.25, 95% CI: 1.15–9.20).**

CONCLUSIONS: **LGI EUS FNA is associated with a high rate of serious grades 3–4 AEs. This may reflect the total number of associated interventions and the frequency of underlying pathology and symptoms.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Patients with colorectal pathology routinely undergo sigmoidoscopy or colonoscopy with diagnostic or therapeutic intent. The evaluation is often supplemented by endoscopic ultrasound (EUS), which enhances diagnosis and permits transluminal biopsy. No study has addressed the safety of lower gastrointestinal (LGI) EUS guided fine needle aspiration (FNA) other than a report from our center that prospectively evaluated the risk of bacteremia (1). We found a low bacteremia rate when sampling solid lesions that did not warrant antibiotic prophylaxis. However, the study could not address the risk of abscess or other infectious adverse events (AEs) because antibiotics were routinely administered following acquisition of blood cultures. There are no published data pertaining to the risk of other AEs and no assessment of the factors that may be associated with their occurrence.

The aim of this study was to prospectively evaluate the AE rate following EUS FNA of LGI lesions, in order to aid procedural planning and patient counseling. We also sought to identify specific patient, lesion, and procedural factors associated with AEs and to clarify the role of antibiotics.

METHODS

While conducting the LGI EUS FNA bacteremia study we noted that our group was gradually decreasing the administration of prophylactic antibiotics, a practice that had been standard of care. Owing to concern regarding the appropriateness of this

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practice change and to address our perception of heightened risk of other AEs in this setting, we initiated a Quality Improvement and Safety Study to prospectively follow all patients undergoing LGI EUS FNA. This intended conduct and details of the study were discussed with the Mayo Clinic Institutional Review Board before initiating and the study was deemed to satisfy exemption criteria. Informed consent was obtained for all procedures.

LGI endoscopy and EUS FNA

Patients underwent sigmoidoscopy or colonoscopy to locate and characterize underlying pathology. Patients were then examined with a radial (Olympus GF-UM130; Olympus America, Center Valley, PA) and/or curvilinear echoendoscope (Olympus GF-UC30P, GF-UC140P-AL5, GF-UCT180, or GF-UC160P-AT8) to perform FNA and/or trucut biopsy (Quick-Core, Wilson-Cook Medical, Winston-Salem, NC). Mucosal biopsies and/or polypectomy were performed as indicated. Prophylactic antibiotics were administered by the discretion of the performing endoscopist.

AE monitoring

Vital signs were monitored throughout and following the procedures. Minor self-limited intraprocedural bleeding, discomfort, or hemodynamic fluctuations that did not require post-procedure care were not considered to be AEs. AE reporting was based on definite and probable attributable events. Patients were evaluated in the outpatient clinic following the procedures as a part of standard care. AEs were also assessed during phone interviews conducted 7–14 days later and additionally thereafter as necessary to establish AE severity and the outcome of all resulting interventions. These phone interviews were performed by a physician or nurse who was blinded to the patient's procedure and care. Information concerning patient demographics, presenting symptoms, endoscopic and EUS findings, interventions, cytopathology, clinical course, and outcomes were abstracted from medical records. The medical records were re-reviewed for patients again seen in clinic at 2–4 months. Repeat telephone interviews were conducted for the few patients not seen in direct clinic follow-up within this timeframe. AEs specifically monitored included hypotension requiring therapy, fever, abscess, other infectious sequelae, new or increased from baseline bleeding, new or increased from baseline pain, and other notable events. Baseline symptoms for which the AEs were compared included bleeding, pain, and weight loss (≥10 pounds). AE severity was graded on a scale of 1–5 utilizing strict definitions according to the Common Terminology Criteria for AEs (CTCAE), version 4.0 (2) or Visual Analog Scale (VAS) (3,4). (**Table 1**) In general, medical interventions and/or hospitalization are required for grade 3 AEs, whereas grade 4 AEs are life threatening or require urgent intervention, and grade 5 AEs are fatal. In patients with baseline pain, we considered post-procedure pain as indicative of an AE only when the severity increased by ≥3 points relative to prior pain.

Target enrollment

In the absence of existing data, enrollment was set at 500 patients for whom phone follow-up could be achieved. There was concern that potentially rare complications, such as perirectal abscess, although uncommon would substantially have an impact on patient outcome and may indicate the need for antibiotics despite an infrequent occurrence. We therefore set a high target enrollment to ensure adequate power to capture less common AEs.

Statistical analysis

Variables are reported using descriptive statistics. Continuous variables are expressed as mean (s.d.) or median (range) and compared by using the Student-*t* test or Mann–Whitney *U*-test. Categorical variables were reported as frequency (%) and were compared by either a two-tailed Fisher's exact test or Pearson's χ^2-test, when appropriate. Multivariate analysis (backward stepwise logistic regression analysis) was used to identify factors associated with the occurrence of AEs. Multivariate logistic regression analysis was performed to identify predictors of all and serious (grade 3 and 4) AEs. The multivariate models included significant predictors on univariate analysis and potential confounder, such as demographics and antibiotic use, when possible without overfitting the multivariate model. Odds ratios with 95% confidence intervals (CIs) were reported. For all analyses, a significant two-sided *P* value was set at <0.05. SAS version 9.2 software (SAS Institute, Cary, NC, USA) and JMP Version 9 (SAS Institute) were used for statistical analysis and modeling.

RESULTS

Between 1 January 2004 and 1 January 2012, a total of 2,237 patients underwent LGI EUS with 563 undergoing FNA. The remaining 1,674 patients who did not undergo LGI EUS FNA were excluded from the analysis. Among those who underwent FNA, 526 (93.4%) patients were seen in clinic 1–7 days later as a part of routine clinical care and to identify AEs. (**Supplementary Table S1** online) Phone follow-up was successfully conducted 7–14 days following EUS in 502 (89.2%) patients (198 women; median 58 years; range 16–95), representing the cohort from which the AEs were analyzed. (**Table 2**) All patients were again seen in clinical follow-up ($n=486$) or contacted by phone ($n=16$) 1–4 months following EUS. Indications for EUS included evaluation of rectal adenocarcinoma ($n=408$), rectal polyp ($n=18$), anal squamous cell carcinoma ($n=22$), urogenital indications ($n=13$), neuroendocrine tumor ($n=11$), pelvic metastasis ($n=10$), subepithelial mass ($n=4$), and other ($n=16$) (**Table 2**).

Procedures and interventions

Exams were performed using moderate, no, or monitored anesthesia care in 492 (98.0%), 5 (0.9%), and 5 (0.9%) patients, respectively. Among the 91 (18.1%) patients who received antibiotics, they were administered intravenously and orally ($n=75$) or intravenously alone ($n=16$).

Data are provided for all endoscopic procedures performed on the day of EUS as the risk of EUS FNA cannot be considered in isolation. Procedures included sigmoidoscopy alone ($n=324$; 64.5%), colonoscopy alone ($n=18$; 3.6%), sigmoidoscopy and colonoscopy ($n=164$; 32.7%), radial EUS ($n=416$; 82.3%), and

Table 1. Adverse event severity grading based on CTCAE (version 4.0) and VAS[a]

AE	Grade 1	Grade 2	Grade 3	Grade 4
Hypotension[b]	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
Bleeding[c]	Either of the following: (i) Maintain continence and no intervention required, (ii) Mild hemorrhagic incontinence (spotting or trace bleeding in underpants or control with pads) and no intervention required	Either of the following: (i) Hemorrhagic incontinence (through underpants, not controlled by pads) (ii) Intraprocedural intervention (e.g., injection, hemoclip) during index exam	Any of the following: (i) Hospitalization (ii) Hemodynamic instability (SBP <100 & pulse >100 and symptomatic and treated) (iii) Transfusion required (iv) Anemia (hemoglobin drop ≥2 gm/dl) (v) Subsequent endoscopic intervention (e.g., endoscopy, inject, hemoclip) after index exam	Any of the following: (i) Urgent intervention (for bleeding or hemodynamic support)
Pain[d]	Mild pain (VAS 1–3)	Moderate pain (VAS 4–6)	Severe pain (VAS 7–9)	Excruciating pain (VAS 10)
Fever[b]	38.0 –39.0 °C	39.1–40.0 °C	>40.0 °C for less than 24 h	>40.0 °C for more than 24 h
Perforation[b]	NA	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Appendicitis[b]	NA	NA	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated

CTCAE, Common Terminology Criteria for adverse events; SBP, systolic blood pressure; VAS, Visual Analog Scale.
[a]Grade 5 (death) did not occur.
[b]Adverse events that were graded according to the CTCAE, version 4.0.
[c]Adverse event that was graded according to a modification of the CTCAE, version 4.0.
[d]Adverse event that was graded using the VAS.

Table 2. EUS indications, gender, and age

Indication	Number of patients	Female	Age, median (years)	Age, range (years)
Rectal adenocarcinoma	**408**	**144**	**60**	**16–95**
Primary diagnosis (cancer)[a]	294	98	58	16–95
Prior diagnosis (no cancer)[b]	43	18	59	22–87
Follow-up (no recurrence)[c]	42	19	61	34–88
Recurrent cancer	29	9	63	35–84
Rectal Polyp	**18**	**7**	**64**	**31–87**
Anal cancer	**22**	**18**	**55**	**38–77**
Other	**54**	**29**	**60**	**32–86**
Urogenital	13	6	58	36–85
Neuroendocrine tumor	11	9	62	46–76
Non-pelvic metastasis	10	4	66	51–86
Subepithelial mass	4	3	51	32–74
Other	16	7	48	20–79
Total	502	198	58	16–95

EUS, endoscopic ultrasound.
[a]Patients newly diagnosed with primary rectal cancer (adenocarcinoma).
[b]Patients examined after recent (≤4 months) polypectomy or transanal excision or chemoradiotherapy without evidence of residual cancer.
[c]Patients undergoing surveillance imaging following resection without evidence of rectal cancer.

linear EUS ($n=502$; 100%). Among 87 (17.3%) patients, a total of 192 (median 2; range 1–12) polypectomies were performed. (**Table 3**) A total of 201 patients underwent a median of 8 (range 1–58) mucosal biopsies (**Supplementary Table S2**).

Table 3. Procedures and interventions (same day as EUS)

Procedure	# Patients ($n=502$)
Lower GI	
Sigmoidoscopy alone	324 (64.5%)
Colonoscopy alone	18 (3.6%)
Flexible sigmoidoscopy and colonoscopy	164 (32.7%)
Radial EUS	416 (82.3%)
Linear EUS	502 (100%)
Polypectomy	
Snare polypectomy (with electrocautery)	32 (6.4%)
Forceps polypectomy (with electrocautery)	8 (1.6%)
Snare polypectomy (without electrocautery)	20 (3.9%)
Forceps polypectomy (without electrocautery)	49 (9.9%)
Total number of patients regardless of technique	87 (17.3%)[a]
Polypectomy-associated interventions	
Tattoo	80 (15.9%)
Inject (saline, HPMC, epinephrine)	9 (1.8%)
Argon plasma coagulation	4 (0.8%)
Hemoclip	3 (0.6%)
Endoscopic mucosal resection	2 (0.4%)
Upper GI	
Esophagogastroduodenoscopy	10 (2.0%)
Extended upper endoscopy	3 (0.6%)
Mucosal biopsies	5 (0.9%)[b]
Endoscopic ultrasound	3 (0.6%)
Fine needle aspiration	1 (0.2%)[c]

EUS, endoscopic ultrasound; GI, gastrointestinal; HPMC, hydroxypropyl methylcellulose.
[a]Number of patients who underwent polypectomy with any technique. The value does not equal the sum of all rows because some patients underwent polypectomy utilizing more than one technique.
[b]Thirty-six mucosal biopsies performed among five patients.
[c]Ten fine needles aspirate performed in one patient.

FNA sites included lymph nodes (LNs; 434 patients, 652 sites, median four passes, range 1–19), rectal wall or intramural process (42 patients, 45 sites, median four passes, range 1–13), and a variety of other sites (51 patients, median 3 passes, range 1–8; **Supplementary Tables S3** and **S4**) FNA cytology was positive for malignancy when sampling LNs, rectal wall, or other site in 194 (44.7%), 14 (33.3%), and 19 (37.3%) patients, respectively (**Supplementary Table S5**).

Overall AE risk

A total of 103 (20.5%) patients developed an AE associated with EUS FNA and related procedures (**Table 4**). On the basis of CTCAE and VAS, the severity was deemed grade 1, 2, 3, or 4 in 34 (6.8%), 41 (8.2%), 23 (4.6%), and 5 (1.0%) patients, respectively. Therefore, 28 (5.6%) AEs were grade 3–4 and considered serious. No grade 5 AEs occurred.

Any AE (grade 1–4). On the basis of univariate analysis and confirmed by multivariate analysis, the development of any AE was associated with prior pain (odds ratio (OR): 3.96, 95% CI: 2.47–6. 35), FNA from a site other than a LN or gut wall (OR: 2.0, 95% CI: 1.04–3.80), and FNA cytology positive for malignancy (OR: 2.10, 95% CI: 1.4–3.47). FNA sites other than LN or gut wall were located deep into the wall of the GI tract (**Supplementary Table S4**) All three predictors remained significantly associated with any AEs on multivariate analysis after adjusting for age, EUS indication, antibiotics use, and each other. (**Table 5**) Antibiotic use was neither protective nor associated with any AEs.

Serious AE (grade 3–4). The development of serious (grade 3–4) AEs was associated with recurrent rectal cancer (OR: 3.42, 95% CI: 1.09–10.70), use of IV antibiotics (OR: 2.39, 95% CI: 1.04–5.52), prior pain (OR: 15.58, 95% CI: 5.29–45.93), FNA from a site other than a LN or lumen wall (OR: 3.34, 95% CI: 1.34–8.32), and malignant FNA cytology (OR: 2.48, 95% CI: 1.09–5.64; **Table 6**). On multivariate analysis, only prior pain and FNA of a site other than LN or lumen wall continued to be significantly associated with serious AEs.

On the basis of prior (baseline) manifestations

Prior bleeding. Patients with prior bleeding were more likely to have a primary rectal cancer ($P=0.0001$) that was ulcerated ($P=0.0092$) and distally located ($P=0.0433$). However, the

Table 4. Adverse events: all patients ($n=502$)

Any AE	Serious grade 3–4 AE Total (mean)	Grade 1	Grade 2	Grade 3	Grade 4
103 (20.5%)	28 (5.6%)	34 (6.8%)	41 (8.2%)	23 (4.6%)	5 (1.0%)
		Bleed ($n=20$) Pain ($n=9$) Fever ($n=5$)	Pain ($n=20$) Hypotension ($n=13$) Bleed ($n=8$)	Pain ($n=19$) Bleed ($n=2$) Perforation ($n=1$) Appendicitis ($n=1$)	Pain ($n=4$) Bleed ($n=1$)

Table 5. Risk factors for adverse events: all patients (*n*=502)

Parameters	Univariate analysis	Multivariate analysis
General		
Age	0.90 (0.55–1.37)	1.10 (0.67–1.80)
Indication	0.95 (0.85–1.07)	0.95 (0.84–1.01)
EUS for recurrent rectal cancer	1.90 (0.84–4.69)	
Cystic lesion	0.79 (0.23–2.75)	
Antibiotics (intravenous)	0.95 (0.52–1.73)	1.15 (0.32–4.10)
Antibiotics (oral)	0.84 (0.43–1.63)	0.70 (0.17–2.85)
Baseline (prior) manifestations		
Prior bleed	1.52 (0.94–2.47)	
Prior pain	3.96 (2.47–6.35)	3.83 (2.35–6.25)
Prior weight loss (≥10 lbs)	1.72 (0.98–3.00)	
Procedures and interventions		
Flexible sigmoidoscopy	2.70 (0.35–21.00)	
Colonoscopy	1.24 (0.78–1.97)	
Radial EUS exam	0.80 (0.45–1.43)	
Polypectomy	1.02 (0.56–1.85)	
Hot polypectomy (snare)	1.55 (0.67–3.57)	
Hot polypectomy (biopsy)	0.64 (0.08–5.26)	
Polypectomy cold (snare)	0.49 (0.11–2.15)	
Polypectomy cold (biopsy)	0.56 (0.24–1.42)	
Trucut biopsy	1.00 (0.21–4.73)	
FNA site (lymph node)	0.83 (0.44–1.57)	
FNA site (lumen wall)	0.45 (0.16–1.29)	
FNA site (other)	2.00 (1.04–3.80)	2.26 (1.10–4.70)
FNA (positive for malignancy)	2.10 (1.40–3.47)	1.80 (1.10–2.97)
FNA (number of sites)	1.26 (0.98–1.63)	
FNA (number of passes)	1.06 (0.96–1.16)	

EUS, endoscopic ultrasound; FNA, fine needle aspiration.

Table 6. Risk factors for serious (grade 3–4) adverse events: all patients (*n*=502)

Parameters	Univariate analysis	Multivariate analysis
General		
Age	0.46 (0.19–1.07)	
Indication	0.99 (0.83–1.21)	
EUS for recurrent rectal cancer	3.42 (1.09–10.70)	
Cystic lesion	NA	
Antibiotics (IV)	2.39 (1.04–5.52)	2.27 (0.89–5.78)
Antibiotics (oral)	1.68 (0.66–4.32)	
Baseline (prior) manifestations		
Prior bleed	0.82 (0.38–1.79)	
Prior pain	15.58 (5.29–45.93)	15.21 (5.04–45.85)
Prior weight loss (≥10 lbs)	1.18 (0.43–3.19)	
Procedures and interventions		
Flexible sigmoidoscopy	0.67 (0.08–5.38)	
Colonoscopy	1.42 (0.65–3.11)	
Radial EUS exam	0.71 (0.28–1.81)	
Polypectomy	0.82 (0.28–2.44)	
Hot polypectomy (snare)	0.55 (0.07–4.19)	
Hot polypectomy (biopsy)	NA	
Polypectomy cold (snare)	0.92 (0.12–7.15)	
Polypectomy cold (biopsy)	0.71 (0.16–3.09)	
Trucut biopsy	4.14 (0.85–20.19)	
FNA site (lymph node)	0.42 (0.17–1.04)	
FNA site (lumen wall)	0.41 (0.05–3.07)	
FNA site (other)	3.34 (1.34–8.32)	3.25 (1.15–9.20)
FNA (positive for malignancy)	2.48 (1.09–5.64)	1.93 (0.79–4.66)
FNA (number of sites)	0.92 (0.56–1.51)	
FNA (number of passes)	1.07 (0.93–1.24)	

EUS, endoscopic ultrasound; NA, insufficient data to allow analysis.

presence of baseline bleeding was not associated with overall or individual AE risk.

Prior pain. Patients with prior pain were more likely to have anal cancer ($P=0.0002$). For patients with primary rectal cancer, prior pain was associated with greater tumor length ($P=0.0162$), distal tumors ($P=0.013$), and complex tumors (T3–4, long, and ulcerated; $P=0.0013$). On the basis of multivariate analysis, patients with prior pain were more likely to develop any AEs ($P=0.0001$) and serious AEs ($P=0.0004$). The incremental risk was specifically linked to post-procedure pain of any severity ($P=0.0001$) and grade 3–4 pain ($P=0.0136$).

Prior weight loss. Patients with prior weight loss were more likely to have primary rectal cancer ($P=0.0001$), advanced T stage ($P=0.0009$), greater tumor length ($P=0.0091$), greater circumferential involvement ($P=0.0001$), and complex tumors ($P=0.0001$). However, weight loss was not independently associated with overall or individual AE risk.

On the basis of indications

On univariate analysis, patients with recurrent rectal or anal cancers were more likely to experience pain ($P=0.0247$ and

0.0008, respectively). The pain was classified as serious (grade 3–4) with recurrent rectal cancer.

On the basis of individual AEs

Post-procedural hypotension. A total of 13 (2.6%). patients developed hypotension with hemodynamic instability (systolic blood pressure <100 and pulse >100) that required therapy (**Supplementary Table S6**). On the basis of CTCAE, the severity was grade 2 for each patient. Features predictive of hypotension included prior weight loss ($P=0.0104$) and advanced age (>60 years; $P=0.0449$).

Bleeding (new or increased from baseline). Rectal bleeding was reported before EUS in 302 (60.2%) patients. New or increased bleeding developed in 31 (6.2%) patients, which was not associated with baseline bleeding (**Supplementary Table S7**). The severity was deemed grade 1 in most patients, with only three (0.6%) patients experiencing a serious grade 3–4 bleed (**Supplementary Table S8**). The only factor associated with new or increased bleeding was hot snare polypectomy ($P=0.0098$).

Pain (new or increased from baseline). Whereas baseline pain was present in 151 (30.1%) patients, new or increased pain developed in 52 (10.4%). patients, which included anorectal ($n=43$), abdominal ($n=8$), back ($n=4$), flank ($n=2$), shoulder ($n=1$), vaginal ($n=1$), and testicular ($n=1$) pain (**Supplementary Table S9**). On the basis of the VAS, the severity was grade 1, 2, 3, and 4 in 9 (1.8%), 20 (3.9%), 19 (3.8%), and 4 (0.8%) patients, respectively. Factors associated with new or increased pain included pre-procedure pain ($P=0.0001$), anal cancer ($P=0.0068$), and primary rectal cancers that were advanced T stage ($P=0.0032$), ulcerated ($P=0.0130$), ≥51% annularity ($P=0.0195$), distal location ($P=0.0295$), LN-positive disease ($P=0.0038$), and positive cytology ($P=0.0079$). Serious grade 3–4 pain was reported in 23 (4.6%) patients and was associated with prior pain ($P=0.0247$) and recurrent rectal cancer ($P=0.0270$).

Fever, abscess other infection, and miscellaneous AEs. Five patients developed a fever that was grade 1 based on CTCAE criteria. There was no significant difference in the risk between patients who did and did not receive prophylactic antibiotics (1.1% and 1%, respectively, $P=0.91$). No patient developed an abscess or other infection including patients who underwent EUS FNA of a cystic structure ($n=20$), existing abscess ($n=3$), and ascites ($n=6$), among whom 15 patients received antibiotics. These structures were ultimately diagnosed as indeterminate/inflammatory ($n=13$), ovarian cyst ($n=2$), cystic stromal tumor ($n=2$), tailgut cyst ($n=1$), anal cancer recurrence ($n=1$), and ovarian cancer recurrence ($n=1$) (**Supplementary Tables S8** and **S10**).

On the basis of procedures and interventions

In order to separate AEs related to EUS FNA from AEs related to additional procedures performed on the same day, we performed a subgroup analysis limiting the evaluation to patients undergoing EUS without any other endoscopic interventions. In doing so, we performed the analysis eliminating additional therapeutic procedures performed in 146 (29.1%) patients that included 66 patients who had any polypectomy, 59 with tattooing, and 21 with both. There was no statistically significant association of these additional therapies with the development of all AEs, severe (grade 3–4) AEs, hypotension, bleeding, pain, or infectious AE (**Table 7**). On univariate analysis, only hot snare polypectomy was associated with an increased risk of bleeding ($P=0.0098$).

Table 7. Frequency of adverse events in patients with and without additional therapeutic procedures[a]

	No additional therapy (n=356)	Additional therapy (n=146)	P value
Any adverse event	57 (16%)	34 (23.3%)	0.06
Serious (grade 3–4) adverse event	18 (5.1%)	9 (6.2%)	0.66
Hypotension	8 (2.3%)	5 (3.4%)	0.54
Bleeding	18 (5.1%)	13 (8.9%)	0.11
Pain	35 (9.8%)	17 (11.7)	0.52
Infectious adverse event	4 (1.1%)	1 (0.7%)	0.65

[a]Additional therapeutic procedures were performed in 146 (29.1%) patients that included 66 patients who had any polypectomy, 59 with tattooing, and 21 with both.

Primary rectal cancer patients (n=294)

EUS was performed to evaluate 294 patients with primary rectal cancer. The median tumor length was 4 cm (range 0.5–13 cm), 170 (59.2%) were distally located, 240 (87.9%) were ulcerated, and the median tumor circumference was 60% (**Supplementary Table S11**). The tumors were superficial (T1 or T2) vs. deep (T3 or T4) in 66 (24.7%) and 201 (75.3%) patients, respectively. FNA confirmed locoregional or distant iliac LN metastasis in 149 (54.6%) and 30 (13.3%) patients, respectively. A total of 64 (21.8%) AEs were reported among this cohort that were grade 1, 2, 3, or 4 in 21 (7.1%), 25 (8.5%), 14 (4.8%), and 4 (1.4%) patients, respectively.

Any and serious AEs:. On the basis of univariate analysis, AEs in patients with a primary rectal cancer were associated with prior pain (OR: 3.70, 95% CI: 2.00–6. 7), prior weight loss (OR: 2.23, 95% CI: 1.20–4.20), tumor length (OR: 1.96, 95% CI: 1.09–3.53), tattooing (OR: 2.74, 95% CI: 1.40–5.20), advanced T stage (OR: 3.56, 95% CI: 1.35–9.40), local (OR: 3.30, 95% CI: 1.70 –6.50), or distant positive LNs (OR: 2.60, 95% CI: 1.26–5.40), positive FNA cytology (OR: 2.50, 95% CI: 1.35–4.80), and complex tumors (advanced T stage, long, ulcerated, and LN positive; OR: 4.32, 95% CI: 2.29–8.23). Serious grade 3–4 AEs were only associated with prior pain (**Table 8**).

Table 8. Risk factors for all and serious AEs: rectal cancer patients only (*n*=294)

Parameters	Univariate analysis for all AEs (grade 1–4)	Univariate analysis for serious AEs (grade 3–4)
General		
Age	0.85 (0.47–1.52)	0.27 (0.08–0.97)
Cystic lesion	1.36 (0.14–13.34)	NA
Antibiotics (IV)	0.91 (0.38–2.80)	1.60 (0.40–5.90)
Antibiotics (oral)	0.76 (0.28–2.08)	1.22 (0.25–5.70)
Baseline (prior) manifestations		
Prior bleed	1.53 (0.73–3.20)	0.88 (0.27–2.80)
Prior pain	3.70 (2.00–6.70)	10.0 (2.9–37.0)
Prior weight loss (≥10 lbs)	2.23 (1.20–4.20)	1.65 (0.55–4.90)
Procedures and interventions		
Flexible sigmoidoscopy	2.26 (0.28–18.0)	0.50 (0.06–4.20)
Colonoscopy	1.40 (0.79–2.53)	2.20 (0.80–6.00)
Radial EUS exam	0.35 (0.16–0.80)	0.20 (0.07–0.65)
Polypectomy	0.90 (0.40–1.98)	1.20 (0.32–4.20)
Hot polypectomy (snare)	1.75 (0.59–5.2)	1.01 (0.13–8.76)
Hot polypectomy (biopsy)	1.36 (0.14–13.0)	NA
Polypectomy cold (snare)	0.33 (0.04–2.56)	1.47 (0.18–12.0)
Polypectomy cold (biopsy)	0.31 (0.07–1.37)	0.67 (0.09–5.30)
Trucut biopsy	NA	NA
FNA site (lymph node)	1.24 (0.26–5.80)	0.62 (0.07–5.10)
FNA site (lumen wall)	0.80 (0.09–7.10)	3.64 (0.40–33.0)
FNA site (other)	1.50 (0.46–4.90)	1.25 (0.15–10.0)
FNA (positive for malignancy)	2.50 (1.35–4.80)	2.56 (0.80–8.10)
FNA (number of sites)	1.15 (0.83–1.60)	0.66 (0.30–1.47)
FNA (number of passes)	1.09 (0.97–1.22)	1.06 (0.90–1.28)
Primary rectal cancer patients		
Obstruction	2.10 (0.51–8.60)	2.25 (0.26–19.0)
Ulceration	2.00 (0.70–6.10)	2.10 (0.26–16.0)
Tumor length	1.96 (1.09–3.53)	1.64 (0.60–4.50)
Distal tumor	1.32 (0.70–2.40)	2.10 (0.66–6.70)
Tattoo	2.74 (1.40–5.20)	1.93 (0.64–5.80)
Advanced T stage (stage 3 or 4)	3.56 (1.35–9.40)	NA
Local LN positive	3.30 (1.70–6.50)	3.40 (0.94–12.30)
Distant LN positive	2.60 (1.26–5.40)	1.50 (0.40–5.50)
≥T3, long, ulcerated, node positive	4.32 (2.29–8.23)	NA

AE, adverse event; EUS, endoscopic ultrasound; FNA, fine needle aspiration; LN, lymph node; NA, insufficient data to allow analysis.

DISCUSSION

EUS FNA is an essential tool for managing a diverse spectrum of colorectal pathologies (5). The findings often provide a tissue diagnosis, improve tumor staging accuracy, enhance prognostic capabilities, and guide therapy. Many studies have addressed the risk of colonoscopy (6–11), but EUS safety data have been reported exclusively from upper gastrointestinal tract (UGI) exams (12–15), except for our prior evaluation of LGI EUS FNA bacteremia rates (1). The rate and types of AEs correlate with exam complexity and >85% of serious AEs occur following colonoscopy with polypectomy vs. colonoscopy alone (16,17). Serious AEs including bleeding, perforation, and postpolypectomy syndrome are reported in 0.1–0.87%, 0.01–0.32%, and 0.003–0.1% of patients, respectively (16,18–22).

Most EUS-related AEs are associated with FNA (13,15). EUS FNA bleeding data pertain exclusively to UGI exams. Mild and transient intratumoral, extraluminal, and pancreas intracystic bleeding are reported in ≤4%, ≤2.6%, and ≤6% of procedures, respectively (13,15,23–29). However, clinically significant bleeding that requires therapy is reported in only 0–0.5% of patients (13,15,23–29). Luminal perforation has been reported in only 0.03–0.15% of UGI EUS exams (13–15,23,27,28,30,31). Bacteremia develops in 6% of patients following UGI EUS FNA of solid lesions, which is similar to routine endoscopy (32–34). Given the low rate and lack of reported clinical sequelae, antibiotic prophylaxis is not recommended (13,15,35,36). Our prior study established that bacteremia develops after LGI EUS FNA of solid lesions at a rate similar to diagnostic colonoscopy. Another group experienced pelvic abscesses in two patients (7%) following EUS FNA of a pelvic mass (37). In the current study, none of the 502 patients, including 411 patients who did not receive antibiotics, developed an infectious AE of FNA. The three prior UGI and two LGI EUS FNA studies included too few patients with a cystic lesion to allow risk estimation. However, data suggest that UGI EUS FNA of cystic lesions is associated with an increased risk (0.2–0.6%) of febrile episodes or sepsis (23,38). Infectious complications have also been reported following EUS FNA of other fluid-filled structures including the bile duct and gallbladder (39,40). Although prophylactic antibiotics were often administered before FNA of cystic lesions in our cohort, no infectious sequelae occurred.

Our study demonstrates that LGI EUS FNA is associated with a higher AE rate, and in particular serious grades 3–4 AEs as compared with colonoscopy with or without polypectomy. This risk is similar to a prior report on EUS FNA of pelvic masses. The heightened risk likely results from several factors. First, the risk of EUS FNA cannot be isolated from the other same day endoscopic procedures and interventions performed in support of EUS FNA; rather, the AE rate reflects the cumulative risk. Among our patients, a mean of 3.52 endoscopies (including EUS), 7.59 mucosal biopsies, 4.6 FNAs, 0.38 polypectomies, and 0.2 polypectomy-associated interventions were performed per patient. Although all patients underwent more than one procedure, the AE risk is clearly heighted above that of a

routine endoscopy and the additional procedures were not associated with a statistically significant increased risk (**Table 5**), leaving us to believe that the risk of serious AE following LGI EUS FNA is more than other standard procedures. In addition, the risk was likely influenced by the presence of often extensive pathology and by the frequency of baseline symptoms.

We employed precise definitions and severity grading based on CTCAE and the VAS. We expanded upon the CTCAE bleeding criteria to better reflect the type of bleeding that occurs in this setting. On the basis of these definitions, 103 (20.5%) patients developed an AE associated with EUS FNA or related procedures that were grade 1, 2, 3, or 4 in 34 (6.8%), 41 (8.2%), 23 (4.6%), and 5 (1.0%), respectively. The thresholds for determining whether an outcome represents an AE vary substantially among investigators and medical societies, each providing their own strengths and limitations (2–4,41–46). The term "incidents" is sometimes used to represent unplanned events that do not interfere with completion of the planned procedure or change the plan of care. Some consider incidents as being analogous to grade 1–2 AEs as defined by CTCAE and VAS (46). If adopting this classification, the AE rate in our study would be 5.6%.

The manner in which grade 1–2 AEs or incidents are allocated may lead to an overestimation or underestimation of the AE rate, depending on ones' perspective. For instance, 28 of 31 bleeding AEs were grade 1–2. Although they represent either mild AEs or incidents, many of these patients developed hemorrhagic incontinence, with blood staining of their undergarments, protective pads, and even clothing. This sometimes led to missed clinic appointments and social embarrassment. Although these lower-grade AEs or incidents do not result in hemodynamic instability or need for medical or surgical intervention, they do confer a substantial impact on the patient that is best addressed thoughtfully in the pre-procedure discussion of side effects and risks of LGI EUS.

Equally important as the AE rate is the way the information is handled from a patient, endoscopist, reporting, and medicolegal perspective. We have used the study findings to alter our procedure planning and patient counseling. In particular, we can now more accurately convey the AE risk during consent and inform patients of predisposing factors. We now advise many patients with baseline pain to continue analgesic use in an uninterrupted manner and provide more timely analgesic support for new or exacerbated pain. We are more cognizant to the potential for new or increased bleeding and negative social impact, and encourage use or ready access to additional garments or protective pads. Despite the lack of infectious events or proven benefit of a full colon prep, we continue to emphasize thorough colon preparation for rectal EUS. Given the results of our prior bacteremia study and the absence of any infectious AE in the current study, we consider LGI EUS FNA of solid lesions to be low risk for infectious events and do not administer antibiotics. However, given the paucity of data regarding cystic lesions and the risk reported with UGI EUS FNA, we follow current recommendations to administer antibiotics when sampling cystic or fluid-filled structures (13,15,35,36). As we did before the study, we continue to inform patients that the use of sedation warrants restrictions on post-procedure activities and need for transportation. Patients are provided the names of contact persons and phone numbers in the event of procedure-related AEs.

Finally, our data also suggest patient cohorts that may be targeted in the counseling and consent process. Among all 502 patients, multivariate analysis indicated an independent association between baseline pain, and FNA of a site other than the wall or LN, and positive FNA cytology with development of AEs, with the first two factors also associated with serious AEs. Similarly, among the 294 patients with primary rectal cancer, prior pain, tattooing, LN-positive disease, and complex tumors were associated with AEs, and prior pain also predicted serious AEs.

Some of the findings might have been anticipated, such as the association of prior pain with AEs, especially, new onset or increased pain. However, prior bleeding was not associated with new or recurrent bleeding. The risk of AEs with malignancy and complex tumor morphology (length, ulceration) and stage (T, N) may have been expected. Less clear is the causal link between FNA of a site other than the lumen wall or LN and AEs. Among this cohort, 17 out of 51 (33.3%) patients developed an AE vs. other patients 86 out of 451 (19.1%; $P=0.027$). The association was even stronger for serious grade 3–4 AEs; 8 out of 51 (15.9%) vs. 20 out of 451 (4.4%; $P=0.005$), respectively. For FNA of other sites, the increased AE rate could not be attributed to a specific target lesion, solid vs. fluid structure, benign vs. malignant process, tumor stage, or other known variable. The use of IV antibiotics was associated with an increased risk of serious AE in univariate but not multivariate analysis. Antibiotics were administered at the discretion of the endoscopist and its use may be a reflection of the complexity of the procedure, which would contribute to the increased risk of AE.

The main limitation of our study is that many patients underwent additional procedures at the time of the EUS FNA. Despite these additional procedures, particularly those that involved interventions such as polypectomy and/or tattooing, there was no statistically significant difference in the risk of developing AEs as seen on both direct comparison (**Table 7**) and univariate analysis (**Tables 5** and **6**). However, the manner in which we conducted the study is in keeping with standard clinical care during which other procedures and interventions are often performed. Another limitation may be the timing of phone follow-up 7–14 days after EUS FNA, which may have left late AEs to go undetected. This period was selected to allow sufficient time for patients to manifest delayed AEs, but early enough to enable contact before administration of neoadjuvant therapy routinely used in this setting. The timing follows current recommendations for identifying delayed AEs and ensuring that the events are causally connected (46). However, given that all patients were again evaluated 1–4 months later in clinical follow-up ($n=486$) or by phone ($n=16$), it is unlikely that any notable late AEs escaped detection. We did not collect data concerning use of anticoagulants or antiplatelet therapy and cannot address their association with post-procedure

bleeding. Furthermore, our routine use of a full colon preparation may partially account for the lack of infectious AEs, and our data cannot address the risk of less complete preparations used in some centers.

LGI EUS FNA is associated a higher rate of serious AEs compared with colonoscopy alone. The heightened risk likely reflects the number of other diagnostic and therapeutic procedures and interventions performed, in combination with the target patient population being more likely to have severe underlying pathology and baseline symptoms. Although the risk of serious AE was increased, most were related to increased pain or bleeding, for which the use of hot snare polypectomy was statistically significant for the bleeding alone. Our data also highlight factors that are independently associated with AEs. Information pertaining to the heightened risk and associated factors provides opportunity to improve and tailor procedural planning and post-procedure monitoring and care.

CONFLICT OF INTEREST

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Most endoscopic ultrasound (EUS)-related adverse events (AEs) are related to fine needle aspiration (FNA).
- ✓ Bacteremia occurs infrequently after lower gastrointestinal (LGI) EUS FNA of solid masses.

WHAT IS NEW HERE

- ✓ LGI EUS FNA is associated with a higher AE rate, with severe AEs occurring in 5.6% of patients, which is higher than colonoscopy with or without polypectomy.
- ✓ Risk factors for AEs were baseline pain, FNA at a site other than the lumen wall or lymph nodes (LNs), and positive FNA cytology.
- ✓ LGI EUS FNA of solid lesions seem to be low risk for infectious events, and prophylactic antibiotics are not warranted.

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