

# Natural orifice transluminal endoscopic surgery (NOTES<sup>®</sup>): a technical review

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## Abstract

**Introduction** The clinical NOTES literature continues to grow. This review quantifies the published human NOTES experience to date, examines instrument use in detail, and compiles available perioperative outcomes data.

**Methods** A PubMed search for all articles describing human NOTES cases was performed. All articles providing a technical description of procedures, excluding cases limited to diagnostic procedures, specimen extraction, fluid drainage or gynecological procedures, were reviewed. Two reviewers systematically cataloged the technical details of each procedure and performed a frequency analysis of instrument use in each type of case. Available outcomes data were also compiled.

**Results** Forty-three discrete articles were reviewed in detail, describing a total of 432 operations consisting of transvaginal ( $n = 355$ ), transgastric ( $n = 58$ ), transesophageal ( $n = 17$ ), and transrectal ( $n = 2$ ) procedures, with 90% of cases performed in hybrid fashion with laparoscopic assistance. Cholecystectomy (84% of cases) was the most common procedure. Analysis of key steps included choice of endoscope, establishment of peritoneal access, dissection, specimen extraction, and closure of the access site. Analysis of instrument use during transvaginal cholecystectomy revealed variation in the choice of endoscope and the technique for establishment of access. A majority of these procedures relied heavily on the use of rigid and transabdominal instrumentation. Closure of the vaginotomy

site was found to be well standardized, performed with an open suturing technique. Similar analysis for transgastric procedures revealed consistency in the choice of flexible endoscope as well as access and closure techniques. Perioperative outcomes from NOTES procedures were reported, but the data are currently limited due to small case numbers.

**Conclusions** NOTES is most commonly performed using a hybrid, transvaginal approach. Although some aspects of these procedures appear to be well standardized, there is still significant variability in technique. More outcomes data with standardized reporting are needed to determine the actual risks and benefits of NOTES.

**Keywords** NOTES · Natural orifice surgery · Transgastric · Transvaginal · Transrectal · Review

Natural orifice transluminal endoscopic surgery (NOTES<sup>™</sup>) is an evolving field of minimally invasive surgery. The goal of NOTES is to access the peritoneum through a transoral, transvaginal or transanal approach, thereby reducing or eliminating abdominal incisions and their associated morbidity. Proposed benefits include decreased wound infections, incisional hernias, and post-operative pain [1].

In 2005 the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the American Society for Gastrointestinal Endoscopy (ASGE) formed the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR<sup>™</sup>), an organization whose primary goal is to oversee and guide research in this field [2]. NOTES research has proceeded exponentially since this time, and in the past 4 years practitioners throughout the world have started performing NOTES procedures on human patients.

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The results of much of this work are finally being published in peer-reviewed literature.

To evaluate the current state of therapeutic human NOTES procedures worldwide, including the types of procedures that have been performed and the techniques and instruments associated with them, we performed a detailed and deconstructed technical review of all human NOTES procedures performed to date. The advantages and disadvantages of the instruments and techniques used for the steps of NOTES procedures, from transluminal access, to dissection, to closure, were evaluated. Additionally, inconsistencies and deficiencies in the publication of human NOTES procedures were examined and technical complications documented.

## Methods

### Literature search

The MEDLINE database was searched using PubMed, attempting to find all articles describing human NOTES cases from January 1, 2004 to June 10, 2010. Search terms included “human natural orifice surgery,” or “human transvaginal,” or “human transrectal” or “human transgastric,” or “human transvaginal,” or “human transrectal,” or “human trans-gastric,” or “human NOTES surgery.” Two reviewers independently sorted through the search results and picked articles providing a detailed technical description of therapeutic NOTES procedures for further review. We excluded cases limited to diagnostic procedures, specimen removal only, transluminal pseudocyst or abscess drainage, and gynecological procedures. We also excluded non-English-language articles to facilitate the review process.

### Data abstraction

After generating a list of articles suitable for technical review, two reviewers carefully read each article and cataloged the technical details of each procedure. Data abstraction was performed with the goal of describing intraoperative techniques from a conceptual level (e.g., vaginotomy creation by open colpotomy versus trocar insertion under laparoscopic visualization), as well as to calculate the overall frequency of instrument use in each type of case. Instruments were cataloged as generic instrument types (e.g., laparoscopic clip applier) rather than by proprietary names.

In addition to obtaining technical data, the reviewers abstracted outcomes data reflecting operative times, perioperative complications, and conversion rates to laparoscopy or open surgery in an intention-to-treat manner.

Different articles published by the same authors or by authors at the same institution were reviewed to reduce reporting of redundant cases.

Disagreements between the reviewers were resolved by discussion until consensus was reached. Data from the review were entered into a Microsoft Excel spreadsheet, and frequency analysis was performed.

## Results

The literature search using the search terms listed above yielded a total of 6,274 articles from PubMed. Of these, 64 articles [3–66] met the inclusion and exclusion criteria of the study and were chosen for further, detailed review. Detailed review of these articles revealed nine studies [6, 10, 13, 16, 34, 57, 58, 60, 66] reporting cases that were included in other series. These redundant cases were accounted for in the final analysis. We also found 12 articles describing cases limited to natural orifice specimen extraction (NOSE) and/or visualization through the natural orifice, cases in which the lumen was not traversed, and cases which considered the umbilicus a natural orifice. These 12 articles [3, 15, 17, 26, 28, 33, 36, 39, 41, 43, 44, 46] were excluded from the final analysis as they were not felt to adequately meet the definition of NOTES. Thus, 43 articles [4, 5, 7–9, 11, 12, 14, 18–25, 27, 29–32, 35, 37, 38, 40, 42, 45, 47–56, 59, 61–65] were included in the final analysis after accounting for articles reporting redundant sets of patients and those failing to adequately meet the definition of NOTES.

A total of 432 NOTES cases meeting these criteria were reported in the literature, the majority of which were transvaginal procedures ( $n = 355$ ), followed in frequency by transgastric ( $n = 58$ ), transesophageal ( $n = 17$ ), and transrectal ( $n = 2$ ) procedures, accounting for 84%, 13%, 4%, and 0.5% of all NOTES procedures, respectively (Table 1). Of all reported NOTES cases, 90% were performed in hybrid fashion with transabdominal laparoscopic assistance. Cholecystectomy was the predominant procedure, accounting for 84% of cases, followed by appendectomy, accounting for 7% of cases. In contrast to transvaginal and transgastric cases, transrectal and transesophageal cases have utilized a pure NOTES approach more frequently (50% and 100% of cases, respectively), but have been limited to colorectal resections and esophageal myotomies, respectively.

Table 2 lists reported NOTES cases by author and year, with the largest overall, single-center experience consisting of 128 hybrid transvaginal cholecystectomies by Federlein et al. [18] in Germany, reported in 2010. The largest single-center transgastric cholecystectomy experience consists of 27 transgastric cholecystectomies reported by Salinas et al.

**Table 1** Published human NOTES cases, from Jan 1, 2004 to June 10, 2010

	Transvaginal ( <i>n</i> = 355)		Transgastric ( <i>n</i> = 58)		Transrectal ( <i>n</i> = 2)		Transesophageal ( <i>n</i> = 17) Pure	Overall ( <i>n</i> = 432) Total
	Pure	Hybrid	Pure	Hybrid	Pure	Hybrid		
Procedure	13	342	11	47	1	1	17	
Cholecystectomy	8	315		42				365
Appendectomy	4	9	10	5				28
Esophageal myotomy							17	17
Nephrectomy	1	6						7
Partial gastrectomy		3						3
Adjustable gastric band		3						3
Sigmoidectomy		2						2
Liver resection		1						1
Splenectomy		1						1
Hernia repair		1						1
Renal cyst resection		1						1
PEG rescue			1					1
Proctosigmoidectomy						1		1
Transanal pull-through					1			1

[49] in 2009. Only two case reports of transrectal NOTES exist, one by Velhote et al. [56] in 2009 and one by Sylla et al. [52] in 2009. Likewise, only one report of transesophageal NOTES was found, with Inoue et al. reporting a series of 17 peroral esophageal myotomy (POEM) cases in 2010 [23].

A detailed deconstruction of the NOTES procedures revealed fundamental steps and elements present in all procedures. These included the choice of endoscope, establishment of peritoneal access, dissection using endoscopic and/or rigid instruments, specimen extraction, and closure of the access site. Within each of these categories, the frequency of instrument use was documented. Although every type of procedure was deconstructed in this way, at the present time it is most useful to limit the analysis to the most frequently performed procedures. Thus, we report the frequency of instrument use during hybrid transvaginal cholecystectomy (Table 3), and compare that with pure transvaginal cholecystectomy (Table 4). The choice of endoscope utilized for hybrid transvaginal cholecystectomy was most often a rigid endoscope, accounting for 64% of all cases. Dual- or single-channel flexible endoscopes were utilized less frequently, accounting for a total of 32% of cases. This is in contrast to pure transvaginal NOTES cases, which most often utilized flexible endoscopes. It is interesting to note that four of the eight pure transvaginal cholecystectomy cases utilized two flexible endoscopes through the vaginal incision: a single-channel endoscope used for insufflation and retraction of the gallbladder, and a dual-channel endoscope used to perform dissection of the cystic duct

and artery [12]. Establishment of peritoneal access was fairly uniform among transvaginal procedures. In approximately 60% of hybrid and pure NOTES procedures, open colpotomy with conventional open instruments was performed. The other frequently used technique was direct trocar insertion through the vaginal wall under laparoscopic guidance (in case of hybrid procedures). Although peritoneal access in five of the eight pure transvaginal cholecystectomies was achieved using an open approach, the remaining three procedures lacked sufficient technical description to classify the method of achieving peritoneal access. In terms of dissection, it is interesting to note that hybrid transvaginal cholecystectomies relied heavily on use of rigid instrumentation; up to 64% of procedures used no flexible endoscopic instruments for dissection and instead relied on a rigid transvaginal instrument along with rigid transabdominal instrument(s). In contrast, the dissection during pure transvaginal cholecystectomies was performed largely using flexible endoscopic instruments with only one case utilizing a transvaginal rigid grasper. Retraction in these cases without rigid instrumentation was provided using a second flexible endoscope. The comparative difficulty of the operative approaches is reflected by the fact that pure transvaginal cholecystectomies took on average almost three times as long (205 min) as hybrid cases, which took 77 min (Table 6, formal statistical analysis limited by inadequate reporting of operative times). Lastly, the closure of the vaginal incision was uniform throughout all the studies examined, with all cases utilizing an open approach with direct suturing, regardless of a pure or hybrid approach.

**Table 2** Clinical NOTES publications, by procedure type

Author (year)	Orifice	Procedure	Type	Cases
De Sousa (2009)	V	Cholecystectomy	Pure	4
Gumbs (2009)	V	Cholecystectomy	Pure	1
Rao (2008)	V	Cholecystectomy	Pure	3
Asakuma (2009)	V	Cholecystectomy	Hybrid	10
Branco (2007)	V	Cholecystectomy	Hybrid	1
Davila (2009)	V	Cholecystectomy	Hybrid	1
DeCarli (2008, 2009)	V	Cholecystectomy	Hybrid	12
Federlein (2010)	V	Cholecystectomy	Hybrid	128
Forgione (2008)	V	Cholecystectomy	Hybrid	3
Dolz (2007), Noguera (2009), Cuadrado-Garcia (2010)	V	Cholecystectomy	Hybrid	25
Bessler (2007), Gumbs (2009)	V	Cholecystectomy	Hybrid	3
Horgan (2009), Horgan (2009)	V	Cholecystectomy	Hybrid	11
Marescaux (2007)	V	Cholecystectomy	Hybrid	1
Palanivelu (2009)	V	Cholecystectomy	Hybrid	8
Pugliese (2009)	V	Cholecystectomy	Hybrid	18
Rossi (2008)	V	Cholecystectomy	Hybrid	3
Rudiman (2009)	V	Cholecystectomy	Hybrid	1
Salinas (2009)	V	Cholecystectomy	Hybrid	12
Tsin (2007)	V	Cholecystectomy	Hybrid	3
Zornig (2007, 2008, 2009)	V	Cholecystectomy	Hybrid	71
Zorron (2007, 2008)	V	Cholecystectomy	Hybrid	4
Bernhardt (2008)	V	Appendectomy	Pure	1
Palanivelu (2008)	V	Appendectomy	Pure	1
Tabutsadze (2009)	V	Appendectomy	Pure	2
Horgan (2009)	V	Appendectomy	Hybrid	1
Palanivelu (2009)	V	Appendectomy	Hybrid	5
Tsin (2007)	V	Appendectomy	Hybrid	3
Branco (2008)	V	Nephrectomy	Hybrid	1
Kaouk (2009)	V	Nephrectomy	Hybrid	1
Sotelo (2009)	V	Nephrectomy	Hybrid	4
Kaouk (2009)	V	Nephrectomy	Pure	1
Nakajima (2009)	V	Partial gastrectomy	Hybrid	2
Fischer (2009)	V	Sleeve gastrectomy	Hybrid	1
Jacobsen (2009)	V	Hernia repair	Hybrid	1
Noguera (2008)	V	Liver resection and cholecystectomy	Hybrid	1
Michalik (2010)	V	Adjustable gastric banding	Hybrid	3
Lacy (2008)	V	Sigmoidectomy	Hybrid	1
Zorron (2009)	V	Renal cyst excision	Hybrid	1
Sanchez (2009)	V	Sigmoidectomy and rectocolpopexy	Hybrid	1
Targarona (2009)	V	Splenectomy	Hybrid	1
Dallemagne (2009), Asakuma (2009)	G	Cholecystectomy	Hybrid	6
Salinas (2009)	G	Cholecystectomy	Hybrid	27
Auyang (2009)	G	Cholecystectomy	Hybrid	4
Ujiki (2009)	G	Cholecystectomy	Hybrid	5
Rao (2008)	G	Appendectomy	Pure	10
Horgan (2009)	G	Appendectomy	Hybrid	2
Park (2009)	G	Appendectomy	Hybrid	3
Marks (2007)	G	PEG rescue	Pure	1
Velhote (2009)	R	Transanal pull-through	Pure	1
Sylla (2010)	R	Proctosigmoidectomy	Hybrid	1
Inoue (2010)	E	Esophageal myotomy	Pure	17

V transvaginal, G transgastric,  
R transrectal, E esophageal

**Table 3** Instrument use (frequency)—hybrid transvaginal cholecystectomy

	% of procedures
Endoscope utilized	
Rigid	64%
Flexible, dual channel	24%
Flexible, NOS	8%
Unknown	3%
Establishment of peritoneal access	
Open	60%
Trocar insertion	38%
Other (needle knife, balloon dilator, etc.)	2%
Dissection—endoscopic instruments, transvaginal	
None (rigid instruments only)	64%
Monopolar cautery	27%
Grasper	23%
Snare	8%
Endoscopic clips	4%
Unknown	4%
Cold scissors	3%
Ligating loop	<1%
Dissection—rigid instruments, transvaginal	
Grasper	79%
None (endoscopic dissection only)	17%
Laparoscopic clips	4–6%
Unknown	3%
Monopolar cautery	1%
Retractor	1%
Specimen extraction	
Rigid graspers	69%
Specimen retrieval bag	52–57%
Unspecified grasper	11%
Endoscopic forceps	9%
Endoscopic snare	8%
Unknown	3%
Closure of access site	
Open	100%

NOS not otherwise specified

After the transvaginal approach, transgastric procedures in general were the second most utilized approach for NOTES. Thus, we felt it would be important to analyze the frequency of instrument use during transgastric procedures. However, given that individual procedures were infrequently reported in the literature, we performed an aggregate analysis of all transgastric NOTES procedures, examining only those elements common to all transgastric procedures: peritoneal access, specimen extraction, and closure (Table 5). We did not include transgastric dissection in our aggregate analysis of all transgastric procedures given that the results of this type of analysis would be

**Table 4** Instrument use (frequency)—pure transvaginal cholecystectomy

	% of procedures
Endoscope utilized	
Flexible, dual channel	63%
Flexible, single channel	50%
Unknown	38%
Establishment of peritoneal access	
Open	63%
Unknown	38%
Dissection—endoscopic instruments, transvaginal	
Grasper	63%
Monopolar cautery	63%
Endoscopic clips	63%
Scissors	50%
Snare	50%
Unknown	37%
Dissection—rigid instruments, transvaginal	
None (endoscopic dissection only)	88%
Grasper	12%
Specimen extraction	
Snare	50%
Unknown	38%
Rigid grasper	12%
Closure of access site	
Open	100%

**Table 5** Instrument use (frequency)—transgastric NOTES (all procedures)

	% of procedures
Endoscope utilized	
Flexible, dual channel	79%
Flexible, single channel	21%
Multichannel operating device	19%
Unknown	2%
Establishment of peritoneal access	
Balloon dilator	100%
Endoscopic needle knife	98%
Specimen extraction	
Snare	56%
Endoscopic grasper	43%
Unknown	3%
None required	2%
Closure of access site	
Laparoscopic	67%
Endoscopic clips	22%
Endoscopic tissue anchors	19%
PEG placement	2%

**Table 6** Perioperative outcomes, by procedure type

Procedure	Total cases No.	OR time (min) Mean (range)	Converted to laparoscopy No. (%)	Complications No. (%)	Complication description
<b>Transvaginal</b>					
<b>Cholecystectomy</b>					
Pure	8	205 (180–240)	0 (0)	0 (0)	
Hybrid	315	77 (22–285)	63 (20)	16 (5)	(See Table 7)
<b>Appendectomy</b>					
Pure	4	89 (76–104)	0 (0)	1 (25)	Intraoperative hemorrhage of appendiceal artery
Hybrid	9	95 (72–135)	3 (33)	0 (0)	
<b>Other</b>					
Nephrectomy	7	280 (170–420) <sup>a</sup>	3 (50)	3 (50)	Rectal injury, upper-pole renal bleeding, intra-abdominal abscess
Partial gastrectomy	2	138 (170–365)	0 (0)	0 (0)	
Sleeve gastrectomy	1	171	0 (0)	0 (0)	
Hernia repair	1	NR	0 (0)	0 (0)	
Liver resection and cholecystectomy	1	110	0 (0)	0 (0)	
Gastric banding	3	110 (80–145)	0 (0)	1 (33)	Right ureteral injury with ureterovaginal fistula
Sigmoidectomy	1	150	0 (0)	0 (0)	
Retroperitoneal cyst removal	1	210	0 (0)	1 (100)	Facial and cervical subcutaneous emphysema
Sigmoidectomy and rectocolpopexy	1	NR	0 (0)	0 (0)	
Splenectomy	1	180	0 (0)	0 (0)	
<b>Transgastric</b>					
Cholecystectomy	42	159 (75–377) <sup>b</sup>	0 (0)	5 (15)	Gastric hematoma, esophageal laceration, esophageal perforation, abdominal sepsis, bile leak or wound infection, pancreatitis requiring relaparoscopy
<b>Appendectomy</b>					
Pure	10	NR	2 (20)	1 (10)	Needle-knife injury, NOS
Hybrid	5	150 (78–150)	3 (60)	1 (20)	Pneumothorax secondary to gastric closure device
PEG rescue	1	NR	0 (0)	0 (0)	
<b>Transrectal</b>					
Pull-through	1	120	0 (0)	0 (0)	
Proctosigmoidectomy	1	270	0 (0)	0 (0)	
<b>Transesophageal</b>					
Esophageal myotomy	17	126 (100–180)	0 (0)	1 (6)	Pneumoperitoneum requiring needle decompression

NR not reported, NOS not otherwise specified

<sup>a</sup> Only 3/6 cases reported OR times

<sup>b</sup> 6 of 42 cases did not report OR times

difficult to interpret due to the heterogeneity of procedures. Transgastric operations utilized primarily two types of flexible endoscopes: 79% of procedures used a dual-channel flexible endoscope, while 19% used a single-channel flexible endoscope combined with a multichannel operating device (Transport<sup>TM</sup>; USGI Medical, San Clemente, CA). Establishment of peritoneal access was also

remarkably uniform, with 98% of procedures utilizing both an endoscopic needle knife and balloon dilator to create a gastrotomy. Specimen extraction most frequently utilized endoscopic snares (59% of cases) and graspers (43%). Closure of the access site was also fairly uniform, with the majority of cases utilizing laparoscopic suturing (67%) or endoscopic clips (22%). The remaining cases (19%)

utilized endoscopic tissue anchors (g-Prox<sup>®</sup>; USGI Medical, San Clemente, CA) either alone or with laparoscopic sutures for reinforcement, or utilized a percutaneous endoscopic gastrostomy (PEG)-type closure (2%).

In addition to the deconstruction of each procedure type, self-reported outcomes data were collected, including operative times, conversion rates to laparoscopy, and perioperative complications (Tables 6, 7). The mean operative times reported ranged from 77 min (range 22–285 min) for hybrid transvaginal cholecystectomy up to 280 min (range 170–420 min) for hybrid transvaginal nephrectomy (Table 6). Conversion rates also appeared significant (50%) for transvaginal nephrectomy and hybrid transgastric appendectomy (60%), although the number of cases was small. Characterization of the learning curve for NOTES procedures based on the reported data was not possible, given the significant heterogeneity of NOTES techniques between centers and the relative scarcity of large series.

Reported complications for transvaginal procedures included rectal injuries, a right ureteral injury with a ureterovaginal fistula, facial and cervical subcutaneous emphysema, a colon injury, vaginal bleeding, a bladder perforation, and a vulvar laceration (Tables 6, 7). In the largest NOTES experience to date (hybrid transvaginal cholecystectomy experience,  $n = 315$ ), however, the only complication occurring more than 1% of the time was bile leak, occurring in 1.4% of cases (Table 7). The complications of transgastric procedures included a gastric hematoma, esophageal laceration and perforation, a pneumothorax secondary to misfiring of a gastric closure device, pancreatitis requiring relaparoscopy, as well as complications usually associated with conventional

laparoscopic techniques (Table 6). No statistical difference in the rate of complications was noted between pure versus hybrid techniques for transvaginal cholecystectomy, transvaginal appendectomy, transgastric appendectomy or transvaginal nephrectomy (Pearson's chi-square,  $p > 0.05$ ).

## Discussion

Clinical application of NOTES is clearly still in its early development phase, as demonstrated by the wide variability of techniques and instruments used in the cases that have been reported to date. Reports of human NOTES cases at scientific meetings and presentations also greatly outnumber the published human NOTES procedures in peer-reviewed literature, though these numbers are gradually converging as manuscript submissions are catching up.

In deconstructing the NOTES literature, we identified that many of the studies in the published literature do not give detailed descriptions of how the procedures are performed and with what specific types of instruments; for example, many articles state that “monopolar cautery” is used. Instead, it would be more specific and beneficial to the scientific community to state that “monopolar biopsy forceps (Model ABC, XYZ company) introduced through the flexible endoscope were used to dissect the gallbladder from the gallbladder fossa.” This lack of specific data introduces reporting bias into our frequency analysis. In a field as rapidly changing as NOTES, we strongly advocate that authors who are publishing their results include as much technical detail about their methods and instruments as possible.

Similarly, when examining the literature and applying our exclusion criteria, there are many perceptions of what the term “NOTES” refers to. It is quite clear that “pure” NOTES involves introduction of instruments through a natural orifice route only, without any transabdominal assistance. This “pure” NOTES approach has alternatively been referred to as “totally NOTES (T-NOTES)” by Zorron et al. [67]. The definition of “hybrid” NOTES, however, is less clear. There are practitioners who consider the introduction of any instrument through a natural orifice, including a single endoscope strictly used for visualization, to be NOTES. Others consider the extraction of a specimen through the natural orifice alone to be NOTES, even while the rest of the dissection is performed completely through transabdominal ports. In agreement with the proposed taxonomy for NOTES procedures suggested by Zorron et al., we would argue that specimen extraction or visualization alone (without dissection) through the natural orifice does not constitute a hybrid NOTES procedure. Rather, these procedures should be referred to as natural orifice

**Table 7** Hybrid transvaginal cholecystectomy complications—combined results from all reported cases ( $n = 315$ )

Complication	No. (%)
Bile leak	4 (1.3)
Urinary tract infection	2 (0.6)
Pouch of Douglas abscess	1 (0.3)
Hematuria	1 (0.3)
Colon injury	1 (0.3)
Wound infection	1 (0.3)
Vaginal bleeding	1 (0.3)
Rectal serosal injury	1 (0.3)
Bladder perforation	1 (0.3)
Gallbladder bed bleeding	1 (0.3)
Umbilical granuloma	1 (0.3)
Vulvar laceration	1 (0.3)
Total complications	16 (5.1)

specimen extraction (NOSE) [36] and natural orifice visualization (NOV), respectively. Either technique in isolation or in combination should be considered “NOTES-assisted laparoscopy” [67]. In contrast, we propose that the term “hybrid” NOTES be used to define procedures in which the dissection is performed primarily through the natural orifice, along with some degree of transabdominal (laparoscopic or percutaneous) assistance. In addition, others have considered the umbilicus a “natural orifice,” a definition which we do not support [15]. Defining “hybrid” NOTES has thus become an area of controversy based on the practitioner’s interpretation. However, for consistency of reporting in the literature, a standardized classification such as the one defined above should be used.

Based on our deconstruction and frequency analysis, there are multiple means by which to perform therapeutic NOTES procedures, each with its own advantages and disadvantages. The major differences in technique are discussed.

### Hybrid versus “pure” NOTES

Most NOTES procedures to date have been hybrid procedures requiring at least one transabdominal port. Thus far, three groups have published pure NOTES transvaginal cholecystectomies [12, 21, 45], three groups have published pure NOTES transvaginal appendectomies [5, 37, 53], one group has published a pure transvaginal nephrectomy [64], and one group has published a series of pure NOTES transgastric appendectomies [45]. Safe access into the peritoneum and inadequate flexible instrumentation are the two primary reasons for the predominance of the hybrid approach.

### Flexible versus rigid endoscopic visualization

Both flexible and rigid endoscopes for NOTES visualization have been used successfully. Many flexible endoscopes have one or two working channels through which additional instruments, such as cautery devices and graspers, may be introduced without the need for additional trocars or increasing the diameter of the natural orifice port. Flexible endoscopes also have the advantage of increased maneuverability within the peritoneal cavity, allowing navigation between and around organ structures. However, the maneuverability comes at a cost, in that platform stability is sacrificed. This results in diminished axial force of instruments that are introduced through channels in the flexible endoscope. Flexible endoscopy also requires an additional skill set with which many surgeons are not currently comfortable. Additionally, the cost of adding a flexible endoscope to an operating room that is not equipped for support of this platform may create an economic disadvantage.

In an attempt to increase the rigidity and stability of flexible endoscopes as a transgastric NOTES platform,

three groups [22, 63, 65] have reported combining a single-channel flexible endoscope with a multichannel operating device that has the ability to alternate between flexible and rigid configurations as needed during the procedure (Transport™; USGI Medical, San Clemente, CA). While useful to provide increased stability, this platform remains dependent on a flexible endoscopic paradigm and currently does not provide additional degrees of freedom in the movement of the flexible endoscopic instruments used through its channels.

In contrast to flexible endoscopes, rigid endoscopes have the advantages of visual platform stability and independence of working instruments from visualization, and are readily available in any institution where laparoscopic surgery is already in practice. Resolution, field of view, and picture quality are currently better with rigid endoscopes compared with flexible endoscopes, though imaging technology is constantly evolving. Brighter light sources and higher-resolution imaging chips are narrowing the gap between flexible and rigid endoscopes [68]. The obvious disadvantage of rigid endoscopes, however, is that their use is limited to access routes where the point of entry into the peritoneum is close to the orifice (vagina, rectum, and urethra) and the direction of dissection is in line with the peritoneal access.

### Transluminal access to the peritoneal space

Transvaginal NOTES has a clear access advantage over transgastric and transrectal routes in that the initial access incision can be achieved more easily under direct visualization without an intra-abdominal scope. “Blind” transvaginal access has a theoretically lower likelihood of collateral injury given direct visualization access techniques established in the gynecology literature [69–72]. However, reports of rectal injuries from blind trocar insertion should serve as a word of caution that complications may still occur. Direct culdoscopic techniques have facilitated the performance of pure transvaginal NOTES procedures that have been reported. Nevertheless, approximately one-third of hybrid transvaginal procedures have utilized laparoscopically visualized trocar insertion through the posterior vaginal wall to gain peritoneal access. A potential benefit of this technique is the ability to directly visualize the entry site and more securely seal the vaginotomy during the procedure (reducing pneumoperitoneum leaks). However, this technique relies on a transabdominal trocar and is not compatible with a pure NOTES approach.

Transgastric access has been achieved using the combination of a monopolar needle knife and balloon dilator to create and dilate a hole on the anterior stomach wall for introduction of the operating platform. However, this cannot be performed currently in a safe fashion without



transabdominal or intraperitoneal visualization of the stomach due to the proximity of surrounding organs and gastric vasculature. The liver can easily be large enough to cross the midline and overlie the anterior wall of the stomach. An additional pitfall with transgastric access is that the gastroepiploic artery and its branches are only visible from an exterior view of the stomach. Therefore, “blind” entry through the stomach wall can result in damage to either of these structures, resulting in serious bleeding complications. Most procedures to date have thus utilized a hybrid transgastric approach with laparoscopic guidance. There have been several proposed techniques to perform blind transgastric access that involve using endoscopic ultrasound or invaginating the gastric wall to distract the stomach away from surrounding organs [65, 73, 74]. These have been attempted in animal studies but have not yet been reported in the human literature.

Transrectal access has been reported in two cases so far, facilitated with a transanal endoscopic microsurgery (TEM) platform or performed through direct transrectal trocar insertion. Access through a transrectal approach allows the use of a rigid or flexible endoscope along with rigid or flexible instruments. The cases performed thus far have utilized either a single rigid endoscope inserted transanally [56] or the rigid endoscope that is part of the TEM device along with laparoscopic visualization once cephalad to the pelvic brim [52].

Transesophageal procedures (POEM) have been performed by a submucosal tunneling technique, allowing a pure NOTES access route with a flexible, single-channel endoscope. A mucosal bleb is made using an injection needle, which is then incised using a monopolar cautery electrode to enter the submucosal space.

## Dissection

The full armamentarium of laparoscopic instruments exists for hybrid NOTES procedures in which any transabdominal port is placed. This includes the multitude of monopolar, bipolar, and ultrasonic energy devices, staplers, clip appliers, and retractors.

Flexible endoscopic instrumentation is currently much more limited. There are several monopolar electrocautery devices that have been available to interventional endoscopists. These include needle-knives, sphincterotomes, L-shaped electrocautery hooks, polypectomy snares, biopsy forceps, and endoscopic scissors made by several manufacturers.

Much of the research work and industry development has been focused on flexible endoscopic instruments to aid with dissection or the development of full operating platforms that can be introduced as a system through the natural orifice [75–80].

## Closure of entry site

Development of devices for reliable and safe transgastric closure is one of the most researched areas of NOTES. Many studies have been published regarding novel techniques or devices for transgastric closure [65, 81–99]. Some of these devices have since been approved for use in human patients, though long-term data are not currently available. Due to the difficulty of endoscopic transgastric closure, laparoscopic closure at the time of transgastric NOTES procedures continues to be the most frequently used closure method. Transgastric surgery in general has lagged behind transvaginal surgery, partially due to difficulties with transgastric closure. Several groups have chosen either not to pursue transgastric surgery or have abandoned transgastric surgery until improved closure devices become available. An alternative to closure of transgastric access sites is conversion to a PEG tube as some have suggested [100], though this is only a valid option for the subset of patients in whom percutaneous feeding is also indicated.

Transvaginal access has the benefit and simplicity of being able to be closed under direct visualization. In addition, the vagina does not normally carry the usual steady stream of caustic or highly contaminated luminal contents that would potentially make a transgastric or transrectal closure leak dangerous. Dissolvable suture placed in a simple interrupted or running continuous fashion using standard handheld instruments has been the most common closure method.

Closure of the rectotomy during the reported transrectal cases has so far been done by incorporating it into a handsewn coloanal anastomosis or transanal pull-through resection, but could presumably be performed with sutures or staples delivered through the TEM device. There is still considerable work, however, that needs to be done to develop a safe, reliable transrectal closure for clinical cases, unless the closure continues to be incorporated into the specimen or anastomosis as has been done previously.

Esophageal closure during transesophageal procedures has been performed using endoscopic clips to close the mucosal incision, combined with a submucosal tunnel separating the entry site from the site of the myotomy. So far, there have been no leaks or infectious complications reported in a series of 17 POEM patients. However, further prospective data will be needed to determine the ultimate safety of this approach.

## Complications

In terms of analyzing the complications from NOTES procedures, for many procedures the low number of cases precludes an accurate estimate of the actual complication

rates. Similarly, an analysis of patient factors and how they may contribute to complications is limited given sparse reporting of basic variables such as inclusion/exclusion criteria, age, body mass index (BMI), and comorbidities. Nevertheless, complications which might otherwise be rare during the corresponding laparoscopic operation are worth noting. In terms of transvaginal procedures, several access-site or closure-related complications have been reported, including rectal injuries, a right ureteral injury with ureterovaginal fistula, a colon injury, vaginal bleeding, a bladder perforation, and a vulvar laceration (Tables 6, 7). These complications serve to emphasize the extreme care that must be taken while obtaining access or closing the posterior vaginal wall given its proximity to the rectum and to the ureters laterally. While these complications are a sobering reminder of the potential risks of transvaginal operations, it should be kept in mind that for the largest NOTES experience to date (hybrid transvaginal cholecystectomy,  $n = 315$ ), the only complication occurring more than 1% of the time was bile leak, occurring in 1.4% of cases (Table 7), similar to rates seen for laparoscopic cholecystectomy. Thus, it remains to be determined whether these serious complications associated with transvaginal NOTES are a result of an early learning curve or whether they indeed occur at unacceptable rates even after the initial learning curve has been overcome. Similarly, the complications of transgastric procedures included a gastric hematoma, esophageal laceration and perforation, pancreatitis requiring relaparoscopy, a pneumothorax secondary to misfiring of a gastric closure device, as well as complications usually associated with conventional laparoscopic techniques (Table 6). While these serious complications may be inherent to the transgastric route, their frequency may also be exaggerated due to the nascent state of transgastric NOTES surgery and its initial learning curve. Although we were able to compile reports of complications related to NOTES, we found a significant lack of standardization in reporting, with heterogeneous outcomes measures and only some manuscripts clearly describing basic outcomes measures such as operative time, conversions to laparoscopy, length of stay, pain scores, and morbidity/mortality. This points out a limitation of our study, which is that the complications we found are likely to be significantly underreported when considering that the articles we analyzed represent only a small portion of the actual NOTES experience performed to date.

Moving forward, not only are more data needed, but the methodology of published research on NOTES needs to improve. Large, prospective, randomized trials will be difficult to conduct given the small numbers of patients willing to be randomized to an approach with largely unknown outcomes. Meta-analyses of smaller NOTES series may be the only feasible way to study these new

techniques. However, consensus needs to be reached on what the important outcomes should be for both intraoperative measures (e.g., operative duration, number of ports used, etc.) as well as postoperative outcomes [e.g., Short Form 36 (SF-36) score at 1 month, visual analog scale (VAS) pain score at 1 week, etc.]. These outcomes should be well defined and agreed upon, so that investigators can better design studies and focus their resources on ensuring the complete reporting of crucial outcomes. In this way, better data will be generated across studies. This type of quality improvement initiative for research methodology has already been done by investigators studying diseases such as atrial fibrillation [101], for example, and is arguably needed to study an intervention as complicated as NOTES. Heterogeneous reporting of pain scores, the use of nonvalidated scales to report patient outcomes, reporting of summary measures (e.g., mean or median) without an adequate measure of dispersion (standard deviation or interquartile range), and sparse reporting of relevant preoperative patient factors are examples of poor reporting practices present in the current literature which will prevent future investigators from being able to conduct high-quality meta-analyses. Only with better data will we be able to weigh the risks and benefits of NOTES, and improve techniques.

## Conclusions

NOTES operations are most commonly performed using hybrid technique and a transvaginal approach. Although we found that some parts of procedures were well standardized, there is still significant variability in NOTES techniques due to technical and instrumentation limitations. In regards to improving the quality of future reports, many of the published NOTES manuscripts do not provide sufficiently detailed descriptions of technique and instruments used, thus hindering technical analysis and dissemination of techniques. Finally, in order for NOTES to remain a potentially promising technique, more standardized reporting of its outcomes, including complications, is necessary. Only then can we gain a better understanding of the potential risks and benefits associated with NOTES.

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