A Review of Natural Orifice Translumenal Endoscopic Surgery (NOTES) for Intra-abdominal Surgery

Experimental Models, Techniques, and Applicability to the Clinical Setting

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Objective: Evaluation of models, techniques, outcomes, pitfalls, and applicability to the clinical setting of natural orifice translumenal endoscopic surgery (NOTES) for performing intra-abdominal surgery through a systematic review of the literature.

Summary Background Data: NOTES has attracted much recent attention for its potential to allow traditional surgical procedures to be performed entirely through a natural orifice. Amid the excitement for potentially scar-free surgery and abolishment of dermal incision-related complications, the safety and efficacy of this new surgical technology must be evaluated.

Methods: Studies were identified by searching MEDLINE, EMBASE, CINAHL, Current Contents, Cochrane Library, Entrez PubMed, Clinical Trials Database, National Health Services Centre for Reviews and Dissemination (NHS CRD) databases, and National Research Register from 2000 to June 2007. Studies identified in September 2007 were included if they were performed in live human subjects.

Results: Of the 34 studies included for review, 30 were experimental studies conducted in animals, thus the evidence base was very limited. Although intra-abdominal access could be achieved reliably via oral, anal, or urethral orifices, the optimal access route and method could not be established. Viscerotomy closure could not be achieved reliably in all cases and risk of peritoneal infection has not been adequately minimized. Although the majority of interventions could be performed in animals using NOTES, a number of technical problems were encountered that need to be resolved.

Conclusions: NOTES is still in early stages of development and more robust technologies will be needed to achieve reliable closure and overcome technical challenges. Well-managed human studies need to be conducted to determine the safety and efficacy of NOTES in a clinical setting.

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The objectives of this article are evaluation of models, techniques, outcomes, pitfalls, and applicability to the clinical setting of natural orifice translumenal endoscopic surgery (NOTES) for performing intra-abdominal surgery through a systematic review of the literature.

Intra-Abdominal Surgery

For many years surgical procedures have been performed for the diagnosis and/or treatment of diseases affecting the organs of the abdominal cavity. These procedures may be performed for diagnostic purposes or they can involve tissue repair or resection of diseased tissue or whole organs. Common examples include appendectomy, cholecystectomy, gastrojejunostomy, colon surgery, splenectomy, abdominal lymphadenectomy, hysterectomy, oophorectomy, tubal ligation, and antireflux surgery.

To perform surgery on the abdominal organs, access must first be gained to the peritoneal cavity. Surgical section of the abdominal wall has traditionally been used to access the abdominal cavity and is commonly referred to as open abdominal surgery or laparotomy, a technique that is still widely used today to perform a host of surgical procedures.[1] More recently, less invasive methods for accessing the abdominal cavity have been developed, including laparoscopic procedures in which one or more small incisions are made in the abdominal wall and a pneumoperitoneum is created to provide a working space.

Laparotomy

Methods for performing laparotomy have been optimized and well researched so that long-term consequences

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are known and the learning curve for implementing new open abdominal and procedures is not steep.[1] Many of the complications of laparotomy are related to incision of the abdominal wall. Wound infections and incisional hernias can be problematic, with surgical site infections occurring in 2% to 25% of patients undergoing laparotomy in the United States[2,3] and incisional hernias experienced by 4% to 18% of US patients.[2] Postoperative pain at the incision site can be quite severe for some patients and slow wound healing and scarring are also a major concern. Extended convalescence periods after surgery can place a large burden on patients and the healthcare system. Other complications related to the procedure include laceration of organs, intra-abdominal abscesses and adhesions, and complications related to general anesthesia.[3]

Laparoscopy

As laparoscopic incisions are much smaller than those created during laparotomy, incision-related complications are greatly reduced.[4,5] A trend toward a faster recovery, decrease in wound-related infections, and reduction in postoperative pain after laparoscopic surgery has been noted in clinical trials comparing laparoscopic with open procedures.[6–8] This has allowed laparoscopic cholecystectomy and appendectomy to now be performed as outpatient procedures.[6–10] In addition to some of the risks associated with open surgery, laparoscopic surgery carries further, technique-specific risks. Procedural complications can occur as a result of a combination of difficulties with visibility and maneuverability, as well as the learning and optimization of this relatively new procedure. Laparoscopic procedures requiring precise hand-eye coordination are performed with awkwardly long instruments lacking in tactile feedback and limited, 2-dimensional vision.[9,11] Complications can include intra-abdominal abscesses and adhesions, the development of CO_2 gas emboli resulting from the creation of the pneumoperitoneum and injuries to vascular structures from needles, trochars, and electrical arching of instruments. Injury rates are up to 3 times those of laparotomy.[3,6,7,10,12,13] Although the rates of these complications have been reduced in recent years, the high incidence of injury after the hasty introduction of laparoscopic surgery should be remembered when developing and introducing other new surgical procedures.

Natural Orifice Transluminal Endoscopic Surgery (NOTES)

Historically, endoscopic technology has been limited by the barrier of the luminal wall (gastrointestinal or vaginal). The idea of using endoscopic procedures to perform intra-abdominal surgery via a natural orifice started to become viable when endoscopy researchers noted no apparent ill effects after accidental punctures of the stomach wall during removal of large stomach tumors or the colonic wall during endoscopic polypectomies.[2,14] This led to the exciting new concept of puncturing the luminal wall to access intraperitoneal organs such as the liver, appendix, gallbladder, spleen or fallopian tubes without making incisions through the body surface. Thus, access to the abdominal cavity could potentially be gained via natural orifices such as the mouth, vagina, anus, or urethra. Today, endoscopic ultrasound (EUS)-guided pancreatic pseudocyst or abscess drainage is standard practice[2,15] and complete removal of a necrotic spleen by transgastric debridement has also been reported by Seifert et al in 2000.[16,17] Kantsevoy et al[18] reported that the first description of surgery via a natural orifice was in 2000 in a presentation at Digestive Disease Week and since then there have been many reports of human transgastric appendectomies being conducted in India.[4,19,20]

The use of flexible endoscopy to perform transluminal surgery via a natural orifice has been referred to by a number of terms, such as "incisionless surgery," but the most commonly used is natural orifice transluminal endoscopic surgery (NOTES).[19] Essentially, NOTES involves the insertion of a flexible endoscopic device through a natural orifice (mouth, anus, vagina, urethra), followed by a transvisceral incision to gain access to transluminal organs (ie, those in the peritoneal cavity, where surgery is performed). Although this concept is not complex, the reality of performing these procedures is fraught with many challenges.[12]

There are a number of potential benefits to using NOTES over traditional surgical techniques that are associated with the lack of surface incision, including the elimination of surgical site infections[2,15,21] and any visible scarring,[2,15] and a reduction in pain[2,15,21] and the need for anesthesia and analgesia,[2] recovery time,[2,15,21] hernia formation[2,15,21] and adhesions,[2,15,21] and the ability to perform procedures in patients where an abdominal incision is not feasible, such as in the morbidly obese.[4] NOTES shares the potential for many of the complications associated with laparoscopic surgery: difficulties with poor visibility, maneuverability, and grasping are likely to be increased as distances are further and the equipment required is more specialized. However, it is expected that technological advances in laparoscopic and endoscopic devices will lead to the advancement of NOTES, reducing the expected difficulties with visualization and maneuverability. Although NOTES procedures may be technically feasible and challenges can be theoretically addressed, the reality is more complex, with initial studies in animals revealing a series of complications that need to be addressed in order for these procedures to become viable.[12,22]

METHODS

This review is a summary and an update of an assessment carried out for the Australasian Safety and Efficacy Register of New Interventional Procedures (www.surgeons.org/asernip-s).

Search Strategy

Studies were identified by performing electronic searches of MEDLINE, EMBASE, CINAHL, Current Contents, the Cochrane Library and Entrez PubMed from 2000 to June 2007. Pubmed and Medline were researched in September 2007 to identify any additional studies performed in human subjects. The clinical trials database (United States), NHS CRD databases, and National Research Register (United Kingdom) were also searched in September 2007. The search terms used for MEDLINE, EMBASE, and Current Contents were "natural orifice" or [(peritoneal cavity/su [Surgery] [MeSH] or abdominal cavity/[MeSH] or abdominal cavity or transgastric or trans gastric or transluminal or translumenal) and (orifice or peroral or per-oral or transoral or endoscopy[MeSH] or endoscop$ or transvaginal or trans vaginal or transurethral or trans urethral or transanal or trans anal or transrectal or trans rectal or transcolonic or trans colonic or transvesical or trans vesical)]. The search terms used for the Cochrane Library, CINAHL, NHS CRD, The National Research Register, Clinicaltrials.gov, Meta-Register, and the Australian Clinical Trials Registry were transgastric; transluminal (Cochrane Library only); natural orifice; endoscopic surgery (nor NRR).

Selection Criteria

Studies of any level of evidence conducted in humans or animals were included for evaluation as NOTES procedures are still in the early stages of development. Studies in cadavers were excluded as they do not provide relevant safety or efficacy outcomes. Additional studies identified by searching Medline and Pubmed in September 2007 were only included if performed in live human subjects. Survival and nonsurvival studies involving transluminal surgical procedures in the abdominal region where access was gained via a natural orifice were included. Studies reporting established extraperitoneal endoscopic procedures and those that do not traverse the luminal wall such as abscess or cyst drainage or debridement and transvaginal gynecological procedures were not included, as they are standard practice and are not considered to be NOTES procedures. English language articles were included for review and foreign language articles were included if they added any additional, relevant information. The bibliographies of all publications retrieved were manually searched for relevant references that may have been missed in the database search (pearling).

Validity Assessment

The methodological quality of the included studies was assessed according to the National Health and Medical Research Council (NHMRC) hierarchies of evidence.[23] However, as NOTES technology is still in early stages of development, all studies were included; quality could not be critically appraised in a traditional manner as all of these studies were in animals to which the NHMRC levels of evidence cannot be applied.

Data Collection and Analysis

Data from the included studies were extracted by the Australasian Safety and Efficacy Register of New Interventional Procedures-S researcher using standard data extraction tables developed a priori and checked by a second researcher. If the data was suitable for statistical pooling, meta-analysis was performed. Where possible, the data was stratified into clinically relevant groups. Otherwise, data for the main outcomes was reported narratively.

RESULTS

A total of 34 studies that reported NOTES procedures (intra-abdominal) were included in this review, including 3 human studies identified in September 2007[24–26] (Tables 1 and 2). Only 4 of the included studies were performed in humans[24–27] and only 1 of these studies was comparative. This internal comparative study, designated level III-2 evidence, compared NOTES peritoneoscopy with diagnostic laparoscopy in 10 patients with a pancreatic mass requiring staging laparosocpy.[24] One of the included human studies was a case series of 100 patients treated for benign surgical conditions using minilaparoscopy-assisted natural orifice surgery (MANOS).[25] Although not strictly NOTES, MANOS is a precursor to NOTES that provides a solution to practicing NOTES in a clinical setting although techniques are still being optimized.[25] In this case study 3 transvaginal appendectomies were performed; however, the other 97 procedures were gynecological so will not be discussed in this review. The other 2 human studies were single case reports, one reporting on transgastric NOTES peritoneoscopy and "percutaneous endoscopic gastrostomy (PEG) resucue"[27] and the other describing NOTES transvesical peritoneoscopy.[26]

All other 30 included studies18,28–56 were noncomparative, animal studies. All of the included studies were essentially experimental pilot/feasibility studies, although animals were observed for a short survival period following NOTES procedures in 20 of the studies. As only one comparative study was included in this review, it was difficult to compare NOTES procedures with current intra-abdominal surgery alternatives.

A summary of instrumentation used for performing NOTES is listed in Table 3.

TABLE 1. Ongoing Trials

ID	Title	Principal Investigator(s)	Location	N	Investigation	Expected Completion
NCT00427752	Abdominal Exploration Without Incisions	J.W. Hazey, MD; W.S. Melvin, MD	Ohio State University Center for Minimally invasive Surgery, Ohio	20	Efficacy of transgastric endoscopic peritoneoscopy with biopsy	July 2007
NCT00486655	NOTES-Assisted Laparoscopic Cholecystectomy surgery	L. Swanstrom, MD	Oregon Clinic, Oregon	25	Ability of orally inserted flexible endoscopic instruments to reduce the size and number of laparoscopic incisions required for cholecystectomy	June 2007
NCT00484783	Transluminal Flexible Endoscopic Procedure in Foregut and Urologic Surgery (NOTES)	J. M. Marks, MD	University Hospitals of Cleveland Case Medical Center, Ohio	20	Feasibility of obtaining peritoneal access from NOTES during combined laparoscopic-endoscopic foregut surgery	August 2007

TABLE 2. Summary of Included Studies

Human Studies

Authors	Year	N	Population F/M	Population Age	Orifice	Intervention (N*)	Sedation	Follow-Up Period
Gettman et al[26]	2007	1	0/1	56	U	PER (1)	NR	2 mo
Hazey et al[24]	2007	10	NR	67.6 (49–79)†	O	PER (10)	General anesthesia	NR
Marks et al[27]	2007	1	0/1	70	O	PER, PEG (1)	Conscious sedation	30 d
Tsin et al[25]	2007	3‡	3/0	NR	V	APP (3)‡	General anesthesia	Up to 2 mo

Animal Studies

Authors	Year	N	Population W (kg)	Population F/M	Population Pig Breed	Orifice	Intervention (N*)	Survival§ Study (N*)	Survival§ Period (d)
Bergstrom et al[31]	2006	12	27–38	NR	NR	O	ANA (12)	Y (6)	7–10
Fong et al[28]	2007	6	25–30	NR	YOR	A	PER (6)	Y (6)	14
Fritscher-Ravens et al[32]	2003	16	NR	NR	WHI	O	ANA (12)	Y (16)	28
Fritscher-Ravens et al[29]	2006	6	27–35	NR	WHI	O	LYM (6)	Y (4)	21–28
Jagannath et al[33]	2005	6	50	6/0	SSD	O	FAL (6)	Y (6)	14–21
Kalloo et al[34]	2004	17	50	NR	SSD	O	BIO (5)	Y (5)	14
Kantsevoy et al[35]	2005	2	50	NR	SSD	O	ANA (2)	Y (2)	14
Kantsevoy et al[18]	2006	6	50	NR	SSD	O	SPL (6)	N	—
Kantsevoy et al[36]	2006	11	55	NR	SSD	O	ANA (11)	N	—
Kantsevoy et al[37]	2007	12	50	NR	SSD	O	PER (12)	N	—
Lima et al[38]	2006	8	35–45	NR	SSD	U	BIO (8)	Y (5)	15
McGee et al[40]	2007	4	25 [5]	4/0	SSD	O	IAPM (4)	N	—
Merrifield et al[42]	2006	5	25	5/0	YOR	O	OOP, TUB, HYS (5)	Y (5)	14
Onders et al[30]	2007	4	25 [5]	4/0	NR	O	DP (4)	N	—
Onders et al[41]	2007	8	25 [5]	8/0	SSD	O	BIO (8)	N	—
Pai et al[45]	2006	5	27–33	NR	YOR	A	CHO (5)	Y (5)	14
Park et al[49]	2005	16	27–35	NR	N	O	ANA (3); CHO (5)	Y (8)	14–28
Pham et al[47]	2006	10	NR	10/0	YOR	A	CC (10)	Y (8)	7
Raju et al[46]	2005	5	50	5/0	NR	A	CC (5)	Y (4)	7
Rentschler[86]	2007	1	27	NR	NR	O	PER (1)	N	—
Fritscher-Ravens et al[39]	2007	15	15–25	15/0	SSD	O and U	CHO (7)	N	—
Sumiyama et al[50]	2006	5	40–50	5/0	NR	O	APP (2)	Y (5)	1–2
Sumiyama et al[51]	2007	6	43.2 [3.82]	NR	SSD	O	MGC (6)	Y (5)	7
Sumiyama et al[52]	2007	4	42.1 [2.71]	NR	SSD	O	SEMF (4)	Y (4)	7
Sumiyama et al[53]	2007	6	30–40	NR	SSD	O	CHO (6)	Y (6)	7
Swanstrom et al[54¶]	2005	10	50	NR	NR	O	CHO (3); BIO (10)	N	—
Von Delius et al[55]	2007	5	35–40	5/0	LR	O	IVH (5)	N	—
Wagh et al[44]	2005	8‖	25–30	8/0	YOR	O	OOP, TUB, HYS (6)	Y (3)	≥1
Wagh et al[43]	2006	6	25–30	6/0	YOR	O	OOP, TUB, HYS (6)	Y (6)	14
Wilhelm et al[56]	2007	8	NR	NR	NR	A	PER (8)	Y (5)	10

*Number of subjects receiving this treatment.
†Mean (range).
‡Only 3 appendectomies out of case series of 100 patients will be considered for this review.
§Survival refers to monitoring of animals postprocedure for signs of morbidity, mortality and recovery.
¶Endoscopic devices were inserted via oesophagectomy, but does not affect any other part of procedure or results.
‖1 cadaver also used.
A indicates anal; ANA, anastomosis; APP, appendectomy; BIO, biopsy; CC, colotomy closure; CHO, cholecystectomy; DP, diaphragm pacing; FAL, fallopian tube ligation; HYS, hysterectomy; IAPM, intra-abdominal pressure monitoring; IVH, in vivo histology; LR: land-race; LYM, lymphadenectomy; MGC, multiple gastrotomy closure; MON, mongrel; NR, not reported; O, oral; OOP, oophorectomy; PEG, "PEG rescue"; PER, peritoneoscopy; SEMF, submucosal endoscopy with mucosal flap; SPL, splenectomy; SSD, sus scrofus domesticus; Tub, tubectomy; U, urethral; WHI, White; YOR, Yorkshire.

Subject Characteristics

Only 4 of the included studies used human subjects[24–27] and all of the animal studies used pigs, with the exception of 1 study, which used 4 mongrel dogs in addition to 6 pigs[54] (Table 2). The patient in the study by Marks et al[27] was in the intensive care unit (ICU) after tracheostomy and had been

TABLE 3. Endoscopic Instrumentation Used During NOTES

Model	Manufacturer	Description	Channels (endoscopes)	Studies
13806PKS	Karl Storz	Gastroscope	Double-channel	55
2 New FES devices	Swanstrom et al[54]	2 new FES devices based on ShapeLock technology (USGI Med). Imaging with prototype digital, "chip-on-a-stick" flexible scope (4 mm, 160 cm length with 2-way tip deflection; Pentax); Full flexible including retroflection in 2 planes and 4-way maneuverability at tip. Second device designed with 3 independent arms at tip permitting optimal positioning of optics and complex independent maneuvers with endoscopic instrumentation. Rigid locking shaft of devices can be used to leverage and hold solid organs anteriorly	FES Guides ≤18 mm and tip slightly tapered to allow easy insertion	54
A2281; Oly	Olympus	Cystoscope		38
A2942A	Olympus	Ureteroscope		38,39
CF-1T100L	Olympus	Adult colonoscope		36,45
CF2T-160L	Olympus	Therapeutic colonoscope with transparent cap at tip	Double-channel	50,51
DUR-8	Gyrus ACMI	Flexible uteroscope		26
ECSD	Apollo Group/ Olympus[47]	Over-the-scope suture device consisting of control arm, mounting bracket and functioning tip		47
EndoEye 50021A	Olympus	Video telescope with 5 mm diameter, chip-on-the-tip and 0° view direction (normally used as laparoscope)		38,39
Endoscopic transilluminator	Olympus			36
EUB6000	Hitachi	Hitachi ultrasound console		29
EVIS Type 100 Q140	Olympus	Standard forward-viewing video endoscope	Single-channel	30,40,41
FG 38 UX	Pentax	Linear array echoendoscope	Single-channel	29,32
Gastroflex "type S" and "type Z"	Mauna Kea Technologies	Confocal Miniprobes for *in vivo* histology		55
GIF 130	Olympus	Standard Gastroscope	Single-channel	27
GIF 140	Olympus	Upper endoscope	Single-channel	28
GIF-160	Olympus	Standard forward-viewing upper endoscope	Single-channel	34–37
GIF 2T100	Olympus	Gastroduodenoscope	Double-channel	28,42,43,45
GIF 2T100B	Olympus	Standard endoscope with 19 mm EMR cap	Double-channel	52,53
GIF 2T160	Olympus	Adult Forward-viewing endoscope		18,31,33,39,49
GIF Q140	Olympus	Gastroduodenoscope	Single-channel	42,43,49
GIF Q160	Olympus	Standard flexible sigmoidoscope	Single-channel	
GIF-QX240	Olympus	Standard upper endoscope	Single-channel	47
Hitachi 525	Hitachi	2.5 mm image processor		32
	Richard Wolf Med Ins Corp.	Standard rigid cytoscope with injection mechanism		26
TEM	Storz	Modified device for transanal microsurgery		56
XGIF-2TQ260ZMY	Olympus	R-Scope—multibending endoscope	Double-channel (actuated)	53

Some studies did not specify instrumentation used, so they are not listed in this table.[24,25,29,46,48]

receiving enteral nutritional support via PEG and the patient in the study by Gettman et al[26] was scheduled to undergo robotic prostatectomy using a new technique using suprapubic catheter placement to limit the duration of the indwelling urethral catheter postoperatively. Many studies reported outcomes for a group of animals, where the first few animals were used to trial and optimize the novel procedure and learn new surgical techniques. One study used a cadaver for the development and learning of NOTES techniques that were used in 8 subsequent live animals.[44] In this study, outcomes using the cadaver were often reported along with in the 9 live animals and were not distinguished from them. We have noted where this was the case.

Results of Human Studies

In the study by Hazey et al[24] findings of traditional laparoscopy to determine evidence of metastatic disease and respectability were recorded by abdominal quadrant and then compared with the findings of NOTES peritoneoscopy subsequently performed by an endoscopist blinded to the laparoscopy results in each patient. NOTES peritoneoscopy was performed using laparoscopic visualization to ensure safety.

Peritoneal access was obtained using a per-orally inserted needle knife to puncture the anterior wall of the stomach, followed by dilation with a pyloric dilating balloon to allow the passage of the gastroscope into the peritoneal cavity.

In the study by Tsin et al[25] transvaginal appendectomies were performed in 3 patients with the assistance of a minilaparoscope introduced through an infraumbilical port and a pneumoperitoneum induced with Veress needle inserted in the infraumbilical area. The mesoappendix was cut with monopolar scissors, stapled, and transected then placed into an endoscopic bag and removed via the vagina, followed by irrigation and suctioning of the surgical area, and closure of the incision in the posterior fornix with an absorbable suture.

In the study by Marks et al, transgastric peritoneoscopy and PEG "rescue" was performed as an alternative to conventional surgery in an ICU patient whose PEG tube had become dislodged.[27] A 12-mm hydrostatic dilating balloon was advanced through the PEG gastrotomy and inflated to allow advancement of the gastroscope into the peritoneal cavity, where peritoneoscopy and PEG "rescue" was performed. In the study by Gettman et al, a transurethrally inserted reusable flexible injection needle on a standard rigid cytoscope was advanced through the bladder wall under laparoscopic and endoscopic guidance. After guidewire placement, a flexible uteroscope was inserted though the vesicotomy and peritoneoscopy was performed.

Efficacy

Mean endoscopic abdominal exploration time using NOTES reported by Hazey et al[24] was 24.8 minutes (range 15–34 minutes) compared with 13.3 minutes (range 4–25 minutes) for laparoscopic examination. The decision to proceed to open abdominal exploration was consistent for both methods in 90% (9 of 10) cases; however, there was some variability in the adequacy of visualization of abdominal structures between the techniques. Although visualization of the anterior abdominal wall, omentum, left lateral segment of the liver, left upper quadrant, left lower quadrant, and right lower quadrant and the need for biopsy was corroborated in 100% or patients, in 40% (4 of 10), visualization of the right lobe of the liver and right upper quadrant structures was inadequate using NOTES. In one patient, an incarcerated umbilical hernia was identified using NOTES that was not identified laproscopically. Hazey et al found that a single-channel therapeutic gastroscope was the most effective during transgastric endoscopic peritoneoscopy; however, a single-channel diagnostic gastroscope was too flexible and a dual-channel therapeutic gastroscope was too cumbersome.

Transvaginal appendectomies were successfully completed in 100% (3 of 3) patients by Tsin et al[25] using MANOS and no technical challenges were reported.

Marks et al reported that visualization during peritoneoscopy was adequate; however, the appendix was not able to be visualized and the right hemidiaphragm and right lobe of the liver were difficult to visualize. PEG "rescue" was successfully completed using a guidewire and endoscopic snare and with no gastric leakage evident 4 days later in a contrast study. Gettman et al were able to successfully perform peritoneoscopy using a transvesical port; however, orientation of the vesicotomy precluded suprapubic tube placement using NOTES, so prostatectomy was performed using a robotic system. Time taken for cytoscopy, transvesical access, peritoneoscopy, and attempted suprapubic bone placement was 40 minutes.

Safety

Two of the patients in the study by Hazey et al[24] experienced postoperative complications unrelated to endoscopic exploration and there were no mortalities during the study period. Tsin et al[25], who administered prophylactic antibiotics to patients before surgery, reported that there were no postoperative complications including infection or mortality in the 2 months after appendectomies. Marks et al reported that tube feeds were instituted after no gastric was leakage determined and the patient recovered uneventfully. After 30 days the patient was tolerating full tube feeds and there was no evidence of complication, apart from rehospitalization for 2 days in the interim for pneumonia. Gettman et al reported that the patient was discharged the day after surgery with return of bowel function, no urine leakage, and minimal pain. No adverse events because of transvesical peritoneoscopy were experienced in the 2 months after surgery.

Ongoing and Unpublished Clinical Trials

Searches of the National Research Register failed to reveal any trials; however, 3 trials of intra-abdominal NOTES procedures were found in the Clinical Trials Database (Table 1). There have been many references to human transgastric appendectomies being conducted in India by V.G. Rao and N. Reddy that was presented at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) 2005 meeting[20] and often cited as personal communication,[4,19,21] however, no details of these trials were uncovered in the published literature. There have also been reports of transvaginal cholecystectomies being conducted in Brazil,[57] France,[58] and the United States,[59,60] however, these were not identified in clinical trials database searches.

Results of Animal Studies

Efficacy

Success of Surgical Techniques. The majority of outcomes were related to the efficacy of individual components of NOTES rather than the efficacy of the NOTES intervention as a whole. This includes efficacy of viscerotomy creation and closure, efficacy and challenges regarding visualization, manoeuvrability and grasping during NOTES, and pneumoperitoneum-related issues. Efficacy of using NOTES to perform intra-abdominal procedures will be discussed in relation to feasibility and ease of performing these interventions; however, as these studies were all performed in animals they can only give some indication of the feasibility of NOTES in future patient studies.

NOTES Viscerotomy Creation. Access routes adopted by animal studies included in this review included the mouth, anus, or urethra, followed by a transgastric, transcolonic, or transvesical incision, respectively.[18,28–39,39–56] All studies reported the method for viscerotomy creation;[18,28–39,39–56] however, only some of these studies made any mention of success or complications encountered.[18,28–31,34,35,37–39,39,41,42,44,45,47,49,52–54,56]

NOTES Viscerotomy Site. In most cases, the visceral incision site was carefully chosen to minimize complications and optimize peritoneal access for the chosen procedure (Table 4). Gastrotomy sites were generally chosen in an anterior location to avoid cutting into blood vessels and to minimize bleeding and spillage of gastric contents. Many studies also reported using external abdominal palpation of the anterior abdominal wall,[31,42,43,49,50,55] sometimes aided by transillumination,[31,39,49,50] EUS,[43] or a transvesically inserted EndoEye or ureteroscope[39] to locate the incision site and to avoid adjacent organs and major vessels. Studies employing transcolonic incisions reported using abdominal palpitation[28,45] or endoluminal ultrasound in addition to direct inspection[56] to identify a suitable colotomy site.

TABLE 4. Sites Chosen for NOTES Viscerotomy (in Animal Studies)

Study	N	Viscerotomy Site
Gastrotomy		
Bergstrom et al[31]	12	Anterior mid-antrum (n:8) or within 2 cm of CEJ, anteriorly (n:4)
Fritscher-Ravens et al[32]	16	Angulus of stomach
Fritscher-Ravens et al[29]	6	Site of thread penetration through stomach wall*
Jagannath et al[33]	6	Stomach wall
Kalloo et al[34]	17	Anterior stomach wall
Kantsevoy et al[35]	2	Border of anterior gastric wall and greater curve at junction of body and antrum of stomach
Kantsevoy et al[18]	6	Stomach wall
Kantsevoy et al[36]	11	Border of anterior stomach wall and greater curve at junction of body and antrum of stomach
Kantsevoy et al[37]	12	Stomach wall
McGee et al[40]	4	Stomach wall
Merrifield et al[42]	5	Anterior site (incision shifted away from a strictly anterior location during 5/5 cases to varying degrees. In 1 case, anterior incision rotated ~180° to posterior orientation)
Onders et al[30]	4	Standard anterior site on abdominal wall
Onders et al[41]	8	Standard anterior site on abdominal wall for PEG. Site would also be used for PEG in ICU patients
Park et al[49]	16	Body of antrum‡
Rentschler et al[48]	1	Stomach wall
Fritscher-Ravens et al[39] †	15	Anterior stomach wall (bodyantrum transition)
Sumiyama et al[50]	5	Anterior abdominal wall
Sumiyama et al[51]	6	Anterior stomach wall and greater curvature of stomach
Sumiyama et al[52]	4	Anterior stomach (n:3), posterior stomach wall (n:1)§
Sumiyama et al[53]	6	Anterior wall of the mid body or the antrum of stomach
Swanstrom et al[54]	10	Anterior stomach wall
Von Delius et al[55]	5	Anterior stomach wall
Wagh et al[44]	8	Anterior stomach wall
Wagh et al[43]	6	Anterior stomach wall, high in proximal stomach, near liver
Colotomy		
Fong et al[28]	6	Anterior colonic wall
Pai et al[45]	5	Anterior colonic wall
Pham et al[47]	10	Colonic wall, 35 cm from anus (n:4¶); 25 cm from anus (n:6)
Raju et al[46]	5	Peritoneal portion of colonic wall, 25 cm from anus
Wilhelm et al[56]	8	Ventral aspect of rectosigmoid junction (~12–15 cm from anal verge)
Vesicotomy		
Lima et al[38]	8	Ventral bladder wall, posterior to bladder dome
Fritscher-Ravens et al[39]	15	Ventral bladder wall, posterior to bladder dome

*See lymphandectomy.
†This study used both transgastric and transvesical access, thus gastrotomy and vesicotomy were both performed.
‡Site a few centimeters away from gallbladder (instead of immediately adjacent) allowed better access to gall bladder in a recurved position and ease anastomosis creation.
§Small bowel injury encountered during gastrotomy creation at posterior location but no complications at anterior location.
¶Site 35 cm from anus led to pancreas damage, so site 25 cm from anus used for subsequent animals.

NOTES Gastrotomy Creation. In 22 of the 24 studies using peroral access, transgastric incisions were created to access the peritoneal cavity after endoscope insertion into the stomach.[18,30,31,33–37,39–44,48–55] In the other 2 studies, a novel tag and thread firing device were used to capture target organs and pull them to the outer gastric wall without gastrotomy creation.[29,32] In one of these studies, gastrotomies were only created at the end of the procedure to create anastomoses.[32] In the other study, the gastric incision was made with a needle knife after a lymph node was captured and pulled back to the exterior stomach wall.[29] In the majority of transgastric studies, gastrotomies were created using a needle knife to make an initial gastric incision,[18,30,31,33–37,40–44,48–51,55] which was usually then enlarged with either a sphincterotome or dilation balloon. Seven studies used a sphincterotome to enlarge the incision to the desired length.[18,31,34,35,37,49,51] Park et al[49] reported that the sphincterotome method is quicker than balloon dilation and as there is no tendency for the hole to spontaneously close because muscle is cut, it is advantageous if speed and repeated gastric crossing are required. Twelve studies used a dilation balloon to enlarge the initial needle-knife incision,[30,33,34,36,39–44,49,50] which Park et al[49] noted had the advantage that after endoscope withdrawal the muscle layers tend to spring back together, partially closing the defect; however, this made it difficult to get back through the defect with the endoscope. Many studies reported that using a guidewire aided gastrotomy creation.[30,31,34,37,39,40,49] In the study employing a mini robot for peritoneal exploration, gastrotomy dilation was not required as the robot was able to fit through the incision.[48] In a study employing a combination of transgastric and transvesical access, the uteroscope inserted through the vesicotomy was found to be very useful in assisting the passage of the gastroscope through the transgastric incision.[39] Gastrotomies were successfully created in all cases using needle knives and where reported, were performed easily and without complications such as bleeding, regardless of incision method.[31,34,35,37,39,41,44,49,54,55]

Two studies used a submucosal endoscopy with mucosal flap safety valve (SEMF) technique in a bid to control peritoneal contamination.[52,53] This involved the creation of a submucosal working space using high-pressure CO_2 injection and balloon dissection to allow resection of the muscle layer while allowing the overlying gastric mucosa to control contamination from a perforating muscle layer resection. In one of the studies using the SEMF technique, 83% (5 of 6) of submucosal dissections were successful using CO_2 injections, except in the last pig where the submucosal space was eventually created using supplemental balloon dissection.[53] All (4 of 4) gastrotomies were successfully created in the other study using the SEMF technique, but complications were encountered in the pig where a posterior site was chosen.[52]

NOTES Colotomy Creation. Wilhelm et al[56] used a modified device for transanal endoscopic microsurgery to create colonotomies by deployment of a purse-string suture around the planned incision site before perforation with the sharp tip of the device. Fong et al[28] used a similar prototype incision and closure device in 4 of their pigs and a standard needle-knife in the other 2 and standard needle-knives were used to create all colonotomies in the other 3 studies.[45–47] Balloon (or sphincterotome) dilation was not required in any of these studies because colonotomies were easily dilated; however, Wilhelm et al[56] and Pai et al[45] advanced a guide tube or catheter, respectively, through the incision before endoscope insertion. Transcolonic incisions were successfully performed without complication in 100% of pigs in all transcolonic studies; however, Wilhelm et al[56] reported accidentally cutting the purse-string suture upon guide tube insertion in one pig, thus requiring extra staples.[56]

NOTES Vesicotomy Creation. Lima et al[38] used 3 acute (nonsurvival study) pigs to acquire the skills necessary to perform transvesical peritoneoscopy and performed the vesicotomy without complication in the remaining 5 pigs. Fritscher-Ravens et al[39] performed the vesicotomy without complication with all pigs, but as they are the same group as Lima et al,[38] most probably acquired necessary skills during the first procedure.

NOTES Viscerotomy Closure. Only 22 of the 30 animal studies reported the method used for viscerotomy closure, if any[28–30,33,34,38,39,41–54,56](Table 5).

NOTES Gastrotomy Closure. Gastrotomy closure was attempted in 14 studies and successfully completed in 95% (84 of 88) of attempted cases;[29,30,34,41–44,48–54] however, procedures involving anastomosis creation did not require closure, as the incision formed part of the anastomosis[31,32,35,36,49] and closure was unnecessary in acute nonsurvival studies.[18,33,39,40] Although Swanstrom et al[54] reported complete closure in 83% (5 of 6) of attempts, they found the closed gastrotomy was watertight on explant testing only in 17% (1 of 6). Most studies did not test the robustness of the gastrotomy closure; however, 2 studies that tested watertightness by filling the stomach with india ink solution and examining leakage through the gastrotomy site on necropsy reported no extraversion of india ink in 100% of subjects.[30,41] Some studies mentioned that it was difficult to locate the incision site after endoscope withdrawal, which was avoided in other studies by leaving a guidewire in place.

NOTES Colotomy Closure. All studies involving transcolonic access reported closure of the colostomy.[28,45–47,56] Fong et al[28] reported that closure was easily achieved in 4 pigs using a prototype purse-string suture closure device; however, although closure with endoscopic or forceps was completed in the other pigs, it was technically demanding and endoscope withdrawal from the peritoneal cavity caused air leakage into the abdomen and affected luminal distention and colotomy visualization. Pham et al[47] reported that 40% (2 of 5) of pigs that had colonotomies closed by a fellow in training were euthanized because of hemodynamic instability resulting from complications during EagleClaw Suturing Device (ECSD) use; however, 100% (5 of 5) of closures by a senior

TABLE 5. NOTES Viscerotomy Closure

Study	n/N	Viscerotomy Closure Method
Gastrotomy closure		
Fritscher-Ravens et al[29]	2/2	Newly developed endoscopic sewing, tag firing, locking, and thread-cutting devices used to close gastrotomy. For removal of a single node, 1 set of stitches sufficient to close defect. Depending on size of defect, process could be repeated with second and/or more stitch pairs and locks. All devices could be used through 2.8 mm accessory channel
Kalloo et al[34]	17/17	Easily closed in all pigs after endoscope withdrawal with 4–6 jumbo clips applied to both ends of incision and then sequentially toward centre. Incision sometimes difficult to locate because of pronounced contraction following endoscope withdrawal
Merrifield et al[42]	4/5*	6.4 endoclips (avg) used to pull incision edges together and close gastrotomy. Guidewire marked gastrotomy site until first clip placed
Onders et al[30]	4/4†	Standard PEG tube attached to guidewire left in place during procedure. PEG withdrawn back through gastrotomy, leaving internal mushroom bumper in gastric lumen
Onders et al[41]	8/8†	Gastrotomy managed by attaching PEG tube to guidewire left in place during NOTES procedure. PEG withdrawn back through gastrotomy, leaving internal mushroom bumper in gastric lumen
Park et al[49]	8/8	Closed with 2–4 stiches placed with new needle, tag thread, and locking method that could be performed through 2.8 mm accessory channel
Rentschler et al[48]	1/1	Closed with endoclips and single endoloop
Fritscher-Ravens et al[39]	NA	Gastrotomy closure not attempted, as it was in preliminary experiments (n:9) using endoscopic clips
Sumiyama et al[50]	5/5‡	Gastric wall on each side of perforation penetrated by dual needle catheters with T tags attached to "Y" suture by deploying tag into peritoneal cavity. Tags deployed into gastric lumen and cinched by sliding a proximal tag with pusher sheath over forceps and grasping proximal free end of suture. Anchors cinched
Sumiyama et al[51]	12/12¶	Perforations closed with 3–5 tissue anchors
Sumiyama et al[52]	4/4‖	Sealed with the overlying mucosal flap then mucosal apposition with metal clips (n:1). If clipping failed, tissue anchors (n:2) or medical acrylate glue (n:1) used
Sumiyama et al[53]	2/4**	Sealed with the overlying mucosal flap then apposed with haemoclips (n:2) or tissue anchors (n:2)
Swanstrom et al[54§]	5/6††	2 different closure devices used; a tissue anchoring system (n:4) and a variation of Bard suturing device (n:2)
Wagh et al[44]	6/6	Endoclips and endoloops used to secure incision edges together and close gastrotomy
Wagh et al[43]	6/6‡‡	Endoclips used to secure incision edges together and close gastrotomy
Total Gastrotomy closure		84/88
Colotomy closure		
Fong et al[28]	6/6	Prototype closure device used where a titanium knot was deployed to secure a previously placed purse string suture and close the incision (n:4); Sequential deployment of endoscopic clips along the incision (n:1); Forceps used to pull the margins of incision into an open endoloop before subsequent closure (n:1)
Pai et al[45]	4/5§§	Incision edges secured together using single endoloop (n:1) or 3–8 endoclips (n:4). Residual air evacuated from peritoneum via external percutaneous catheter
Pham et al[47]	8/10	Prototype ECSD device used to place full-thickness sutures across perforation. Of 2.56 ± 1.13 stiches attempted, 2.11 ± 0.78 were successful (mean ± SD)
Raju et al[46]	5/5	Endoclips—2 pigs: 3–4 clips used; 2 pigs: 1–2 clips used as escape of air prevented application of more; 1 pig (5 cm colotomy): 6 clips used
Wilhelm et al[56]	8/8	Purse-string suture closed and resulting small secured with linear stapler. Closure confirmed with digital rectal examination
Total Colotomy closure		31/34

*In 1 pig gastrotomy not completely closed due to edema at incision site. Necropsy revealed 4 mm hole at incision site.
†No extravasation of india ink at gastrotomy site managed by PEG observed on necropsy.
‡Firmly closed (gastrotomy only closed following model prep).
§Follow-up endoscopy revealed all treated sites closed firmly, with all tissue anchors in place.
¶Two per pig.
‖No water seepage on waterleak testing of stomachs. Mucosal apposition only successful in 1 pig as free mucosal edge had become too edematous to grasp with standard clips.
**Two pigs died in surgery so closure was not attempted. 1 pig, clip mucosal apposition failed, 1 pig, hole on overlying mucosal flap at a different location from the mucosal entry point found.
††Closure completed in 5 of 6 but only watertight on explant testing in 1of 6.
‡‡Mucosal aspect showed presence of well-aligned endoclips on necropsy.
§§Closure not possible in 1 pig (method not reported), and 4 mm residual defect remained at the conclusion of surgery.
ECSD indicates eagle claw endoscopic suturing device.

gastroenterologist were successful, although wound dehiscence was observed in one of these pigs on necropsy.[47]

NOTES vesicotomy closure. Lima et al[39] reported that the cystoscope showed obvious signs of contraction after ureteroscope withdrawal, making the vesicotomy appear like a puncture hole, so it was left unclosed without any apparent adverse effect. There is no mention of any vesicotomy closure in the other study involving transvesical access, but this was a nonsurvival study and the gastrotomy made during this procedure was not closed either.

Success of Visualization Using NOTES

Standard endoscopic techniques such as rotation, torque, and movement of obstructive organs away from others were commonly used to achieve visualization in most studies, but were sometimes aided by external transillumination. Various measures were undertaken to improve visualization in the peritoneal cavity such as the creation of a pneumoperitoneum and positional changes of the animal to move obstructive organs away from others. Most studies did not compare visualization between different devices; however, one study which trialed both a standard double channel endoscope and a multibending R-scope (Table 3) found no difference between scopes in time to visualize the gallbladder.[53] In a study using a mini robot to explore the peritoneal cavity an endoscope was successfully used to observe the robot's movements, but in the future such a robot may be fitted with a camera.[48]

Complications such as bleeding hindered visualization. For example, during cholecystectomy Swanstrom et al[54] found that uncontrolled bleeding from a cystic artery caused loss of visualization in one pig, whereas gallbladder perforation made identification of gallbladder dissection planes impossible in another. Wilhelm et al[56] reported no visual alteration caused by blood-polluted ascites in their study using a fluidoperitonem.

Visualization appeared to vary depending on the access port used and distance of the target region from this port. When the transgastric port was used, visualization was generally good.[37] Using transcolonic access the upper abdominal organs (stomach, liver, spleen, gallbladder) were readily identified[28,45,56]; however, limitations in retraction made visualization of structures in the most posterior and superior aspects more challenging and the uterine and retroperitoneal structures could not be identified by Fong et al[28] or Wilhelm et al.[56] Fritscher-Ravens et al[39] used both transvesical and transgastric ports to monitor all procedures, with a scope positioned through the transvesical port.

Fritscher-Ravens et al (2006)[39] reported that using EUS for visualization of lymph nodes to be selected for removal was useful to identify blood vessels and avoided the requirement for an endoscope in the peritoneal cavity, thus minimizing leakage and negating the need for a pneumoperitoneum. Kantsevoy et al[36] used an endoscopic transilluminator (ET) to direct the endoscope to proximal jejunum and reported that ET placement was completed without any technical problems in 100% (11 of 11) of pigs.

Success of Maneuverability of Equipment During NOTES

Standard endoscopic techniques (torquing, retroflexion, rotation, scope reduction, tip deflection) were adequate in many cases but in others, movement was limited, making completion of procedures difficult. Creation of pneumoperitoneum aided maneuverability in the peritoneal cavity by providing more space in which to move. A variety of different endoscopes were used to perform NOTES procedures including standard endoscopes as well as specially designed prototypes and equipment such as overtube was often used to assist endoscope passage and increase stability. Most studies did not compare devices; however, Sumiyama et al[53] found that the R-scope trialed was able to reach both the gallbladder fundus and cystic duct in 100% (4 of 4) of pigs whereas the double-channel endoscope was only successful in 50% (2 of 4) and 75% (3 of 4) in reaching the gallbladder fundus and cystic duct, respectively. Both scopes were found to be equally effective in performance during gallbladder dissection.

Maneuverability in the upper abdominal quadrants posed few problems when using transgastric access; however, more difficulties were encountered when maneuvering endoscopic devices through a transcolonic port. Von Delius et al[55] reported that additional maneuverability leading to an improved field of application was achieved by advancing the miniprobes through the endoscope; however, spatial orientation in the upper abdomen still needs to be improved. In a study using transcolonic access, limited retraction in the sagital plane made scope control in the most superior and posterior aspects of the upper abdomen difficult.[28] Scope control near the dome of liver, hilum of liver, lesser curvature of stomach and right and left lower abdominal quadrants were also restricted.[28] Using a transvesical port, Lima et al[38] reported that the length of their ureteroscope allowed liver biopsy and falciform ligament section to be performed in all animals without difficulty and the use of an overtube allowed easy introduction of the EndoEye.

One study used an endoluminal robot (12 mm $\times$ 75 mm) capable of transgastric exploration under esophagogastroduodenoscopic control to successfully explore the peritoneal cavity.[48] The robot has forward, backward, and turning capabilities and a tail to prevent counter rotation of its body when the wheels are turning. The robot's wheel design provided sufficient traction to traverse the gastric cavity and its size did not hinder its motion. Following gastric incision, it was challenging, but possible to maneuver the robot around the entire peritoneal cavity, including the liver and small bowel, by remote control.

Success of Grasping and Organ Manipulation During NOTES

Although most procedures required grasping to manipulate organs/tissue at some stage, the difficulty and problems depended on the specific procedure and factors such as location of the organ, as organs which were situated further away, or were obstructed, were difficult to grasp. Most of the difficulties with grasping were reported during cholecystectomy or cholecystogastric anastomosis[32,39,45,49,54] and techniques were often described in detail. Grasping forceps were popular for grasping in most studies, but snares and endoscopes were also commonly used in combination. Most articles reported trial and error with different grasping techniques and equipment and the most optimal method is yet to be determined. The access point appeared to effect grasping, as did the proximity of the organ to the access point. As with maneuverability, positional changes aided grasping by moving obstructing organs away from the target organ.

A common challenge in organ manipulation was exposure of the cystic duct for cholecystectomy, as retraction of the floppy porcine hepatic lobes was difficult with most flexible endoscopic instruments.[49,54] Sumiyama et al[53] reported that the multibending endoscope (R scope) trialed was better for accessing the fundus and cystic duct (successful in 100% of cases) than the standard double channel endoscope [unsuccessful reaching the fundus in 25% (1 of 4) of pigs and the cystic duct in 50% (2 of 4) of pigs]. Exposure of the cystic duct was possible using a combination of forceps and graspers, but this was generally difficult and unreliable.[45,49] The novel flexible endoscopic device used by Swanstrom et al[54] was useful in exposing the cystic duct, by holding up the liver with the locking body whereas aggressive graspers were used to retract the infundibulum.[54] Fong et al[28] achieved additional exposure of the gallbladder and cystic duct using blunt-tip probing and retraction of the overlying liver lobes with 2 forceps. Fritscher-Ravens et al[39] found that transvesical gallbladder grasping allowed quick identification of the cystic duct and significant manipulation of the gallbladder in 100% (7 of 7) of pigs, such as retraction of the gallbladder body in the major axis. This was particularly useful in selecting the most appropriate anatomic exposure for gastroscope-guided dissection and small positional adjustments were possible when using forceps introduced by gastroscope.

Success of NOTES Intervention and Techniques

All surgical interventions attempted in the included studies, namely anastomosis (gastrojejunal and cholecystogastric), cholecystectomy, appendectomy (model), splenectomy, lymphadenectomy, female reproductive procedures, diaphragm pacing, and diagnostic procedures including biopsy and in vivo histology, were able to be successfully completed in animal models using NOTES (Table 6). As many of these procedures were completed using trial and error of techniques, they were often tedious and unreliable.

Success of NOTES Anastomosis

A number of methods were successfully used to create anastomoses, 9 of which were cholecystogastric[32,49] and the other 31 were gastrojejunal.[31,32,35,36] In one study, gastrojejunal anastomosis creation was aided using an ET to transilluminate a specific loop of the proximal jejunum.[36] One study used a novel tag and thread firing anastomosis device to create gastrojejunal and cholecystogastric anastomoses with access to only one lumen.[32]

Success of NOTES Cholecystectomy

Dissection and mobilization of the gallbladder from the fossa represented the most fastidious and challenging part of the cholecystectomy and a variety of devices were trialed for this purpose. Park et al[49] successfully performed dissection with a needle knife, but other devices tested such as endoscopic scissors and a suture cutter were not strong enough to be useful during the dissection. Two of the 4 reported unsuccessful cholecystectomies were because of mortality during surgery in a study using a SEMF access technique.[53] The other unsuccessful attempts occurred in a study trialing new flexible endoscopic devices: in one animal, bleeding from the cystic artery was unable to be controlled, causing loss of visualization and in another animal gallbladder perforation made identification of the dissection planes impossible, so the attempts were abandoned.[54] Endoscopic clips were successfully used to control the cystic duct and artery in all other studies.

TABLE 6. Success of NOTES Interventions

Study	Orifice	n/N	%
Anastomosis creation			
Bergstrom et al[31]	O	12/12	100
Fritscher-Ravens et al[32]	O	12/12	100
Kantsevoy et al[35]	O	2/2	100
Kantsevoy et al[36]	O	11/11	100
Park et al[49]	O	3/3	100
Appendectomy			
Sumiyama et al[50‡]	O	2/2	100
Biopsy			
Kalloo et al[34]	O	5/5*	100
Lima et al[38]	U	8/8†	100
Onders et al[41]	O	8/8‡	100
Swanstrom et al[54]	O	9/10§	90
Cholecystectomy			
Pai et al[45]	A	5/5	100
Park et al[49]	O	5/5	100
Fritscher-Ravens et al[39]	O and U	7/7	100
Sumiyama et al[53]	O	4/6	67
Swanstrom et al[54]	O	1/3	33
Diaphragm pacing			
Onders et al[30]	O	4/4	100
Fallopian tube ligation			
Jagannath et al[33]	O	6/6	100
In vivo histology			
Von Delius et al[55]	O	5/5	100
Lymphadenectomy			
Fritscher-Ravens et al[29]	O	2/2¶	100
Oophorectomy and tubectomy			
Wagh et al[44]	O	6/6	100
Wagh et al[43]	O	6/6	100
Partial hysterectomy‖			
Merrifield et al[42]	O	5/5	100
Wagh et al[43]	O	6/6	100
Splenectomy			
Kantsevoy et al[18]	O	6/6	100
Total		140/146	96

*Liver biopsy.
†Liver biopsy and falciform ligament section.
‡Liver and spleen biopsies.
§Wedge liver biopsy.
¶Complete lymphadenectomy, 6 of 6 partial lymphadenectomies performed successfully (up until pulling lymph node to exterior gastric wall).
‖Model appendectomy was essentially a partial hysterectomy, but listed as appendectomy for this review.
A indicates anal; O, oral; U, urethral.

Success of NOTES Diaphragm Pacing

A prototype NOTES diaphragm mapping system was successfully used by Onders et al[30] to provide temporary diaphragm pacing. The diaphragm mapping system was transgastrically inserted into diaphragm muscle using NOTES and the electrode attached to the diaphragm pacing system (DPS) stimulator and the diaphragm paced synchronously with a ventilator. The prototype endoscopic mapping device allowed stimulation of the diaphragm with qualitative assessment of diaphragm contraction in 100% (4 of 4) of pigs. Visualization and stimulation was comparable with laparoscopic visualization of the spinal cord and amyotrophic lateral sclerosis trials, although the view was upside down.

Success of NOTES Diagnostic Procedures

Lima et al[38] reported that the length of their ureteroscope allowed the liver biopsy and falciform ligament section to be performed in all animals without difficulty. Swanstrom et al[54] reported that during wedge liver biopsy significant bleeding, which was not able to be stopped with cautery or endoscopic clips required a laparoscopic "rescue" in one animal, accounting for the only unsuccessful biopsy reported. In a series of ICU diagnostic procedures, Onders et al[41] easily obtained liver and spleen biopsies, lysed intra-abdominal adhesions with needle knife cautery, and drained ascitic fluid (used to represent intra-abdominal abscess) from pelvic gutters via modified suction catheters passed through an endoscopic accessory channel.

Confocal fluorescence microscopy is a recently developed endoscopic diagnostic tool that was used by Von Delius et al[55] to microscopically examine superficial tissue layers during NOTES peritoneoscopy and was technically feasible in 100% (5 of 5) of pigs. This group reported that direct contact of the miniprobe tip with tissue provided adequate stability for reliable image acquisition; however, breathing movements cause artifacts in some images (particularly liver) that did not impede image interpretation.[55] Cellular visualization in different tissues was variable; however, confocal fluorescence microscopy is definitely feasible using NOTES.

Duration of Surgery

Operative times were recorded for different procedures or for different stages of individual procedures and therefore were not comparable between studies (Table 7). Even for similar procedures, duration of surgery varied greatly, because of differing surgical techniques and partially because of the developmental stage of NOTES procedures, which have a very steep learning curve. One trend that could be observed is that operating times generally decreased with experience.

Safety

Mortality

Of the 30 animal studies included for review, only 2 studies reported mortality during NOTES.[47,53] In one study, 2 (of six) pigs died of sudden cardiac arrest and hypoxemia during cholecystectomy performed using transgastric SEMF access. In one of these pigs, microair bubbles were discovered in the coronary veins, right atrium, and ventricles of the heart on necropsy. In the other study, 2 (of 10) pigs were euthanized during immediately because of severe pneumoperitoneum and hemodynamic instability resulting from unsuccessful colotomy closure.[47]

Twenty studies followed a total of 109 (not including 2 pigs who died during transgastric cholecystectomy) animals for survival periods ranging from 1 to 28 days (Table 8).[28,31–35,38,42–47,49–53,56] In 3 of these studies,[42,45,53] an additional 4 mortalities were reported following NOTES procedures and mortality ranged from 0% to 67% (median: 0%) across the 20 studies. The only 3 studies that reported mortality were Pai et al,[45] who reported a 20% (1 of 5 pigs) mortality rate and Sumiyama et al,[53] who reported a mortality rate of 67% (4 of 6 pigs) after transgastric cholecystectomy, and Merrifield et al,[42] who reported a mortality rate of 20% (4 of 5 pigs) after transgastric partial hysterectomy. The mortality rate of all other NOTES procedures reported was 0%.

Of the 5 studies reporting unsuccessful viscerotomy closure, only 3 reported survival outcomes (not including the 2 pigs who were euthanized immediately after unsuccessful colotomy closure).[47] In all of these studies, the pigs with incomplete vesicotomy closure experienced significant infection and did not survive the 7- or 14-day survival periods. These 4 pigs were also the only pigs out of the 109 pigs included in the 20 survival studies, who did not survive their observation period after NOTES. Importantly, the 6 pigs with unclosed gastrotomies in the study by Jagannath et al[33] and the 5 pigs with unclosed vesicotomies in the study by Lima et al[38] survived the entire 14- to 21-day observation periods without any adverse effects including infection; however, all the other 100 surviving pigs had successfully closed viscerotomies or anastomoses that incorporated the gastrotomy.

Postoperative Recovery

General Observations, Appetite, and Weight Gain

No ill effects were noted during the recovery period in 12 studies[28,31,33–35,38,43,44,46,47,50,51] and nor in any of the 4 of 5 surviving pigs in the studies by Merrifield et al[42] and by Pai et al[45] or the 2 of 6 surviving pigs in the study by Sumiyama et al.[53] The only ill effects reported in the study by Fritscher-Raven et al[32] was refusal of 1 pig to eat for 1 day after its gallbladder was punctured repetitively, but it was treated with antibiotics and was well the next day. The study by Wilhelm et al[56] reported 1 pig had delayed recovery for 2 days, but was asymptomatic on the third, and all 4 other pigs showed excellent condition during follow-up. In the study by Sumiyama et al,[52] the 3 (of 4) pigs with anteriorly located SEMF gastrotomies (closed with glue or tissue anchors) exhibited good weight gain averaging 2.5 kg, compared with the pig with a posterior SEMF gastrotomy (closed with clips) who lost 5.4 kg. All animals for which no ill effects were noted generally tolerated a regular diet around 1 day after surgery and exhibited good weight gain. Merrifield et al[42] reported using ranitidine to prevent reflux after surgery; however, the effects of this treatment were not reported.[42]

Viscerotomy Healing

Where reported, most viscerotomies were well healed. Merrifield et al[42] reported that 40% (3 of 5) of gastric incisions were well healed and there were no intra-abdominal adhesions, abscesses, or pathologic evidence of peritonitis and Pai et al[45] reported full colotomy healing in 80% (4 of 5) of pigs, but not in the pig with incomplete closure. Five studies reported complete healing of all incisions on necropsy.[28,34,38,43,56] Pham et al[47] observed dehiscence of the colotomy in 12.5% (1 of 8) of pigs on necropsy and only 1 pig had a healed colotomy scar at

TABLE 7. Duration of Surgery

Study	N	Procedure/Part of Procedure	Time (min)
Bergstrom et al[31]	12	Enter peritoneal cavity from stomach, grasp SI and pull it into peritoneal cavity	<5
	12	Suturing and thread locking to complete anastomosis	30**
Fong et al[28]	6	ID of stomach, liver, gallbladder, spleen, small bowel, colon, and peritoneal surfaces	<3
	6	Total time from insertion to withdrawal from peritoneal cavity	30–45
	6	Closure of colonic incision with endoclips and endoloops	<30
	6	Closure with prototype device	<2
Jagannath et al[33]	6	Gastric-wall incision to completion of surgery	20–25
Kantsevoy et al[35]	2	Completion of anastomosis	90–120
Kantsevoy et al[36]	11	ET placement	10–15
Kantsevoy et al[37]		Operating time	11.4* ± 3.7
Lima et al[38]	8	Cystoscope introduction to completion of surgery	20–40
Merrifield et al[42]	5	Complete procedure	174*†
Pai et al[45]	5	Entrance into peritoneal cavity to removal of gallbladder from anal orifice	68*
	5	Completion of procedure	70–165 (115*)
Park et al[49]	5	Cholecystectomy	40–150††
Pham et al[47]	10	Colotomy closure	<10
Fritscher-Ravens et al[39]	7	Overall procedure, including establishment of transvesical and transgastric ports	120*
Sumiyama et al[50]	5	Model prep	40–160
	2	Pilot appendectomies	30–90
Sumiyama et al[51]	6	Perforation closures¶	15–30
Sumiyama et al[53]	6	Visualization of gallbladder	2.8* ± 1.5
	4	Total operating time‖	1.2–2.1 (1.7*)
Swanstrom et al[54]	10	Esophageal insertion and gastric positioning	2–12 (4*)
	10	Gastrotomy and abdominal insertion	3–8 (5*)
	3	Cecal retraction	2–4 (3*)
	10	Run small bowel	3–16 (11*)
	10	Liver exposure and biopsy	4–13 (7*)
	10	Hiatal exposure	7–22 (9*)
	3	Cholecystectomy**	31* (all 3 attempts); 56 (successful)
Wagh et al[43]	6	Entire procedure§	210–240
	6	Gastric cleansing	45*
	6	Gastric incision	30–45
	6	Incision closure	45–90
Wilhelm et al[56]	8	Incision creation	9.3* ± 1.3
		Withdrawal of scope and colotomy closure	7.8* ± 2.3
		Induction of fluidoperitonem through Verres needle	20–30

*Mean value.
†Gastric lavage, passing scope through gastric wall, and closing stomach represented most time-consuming aspects of procedure and locating and removing portions of uterus accomplished relatively quickly.
§Time for procedure improved with experience.
¶Excluding time for perforating stomach.
‖From insertion of endoscope in peritoneal cavity.
**Gallbladder exposure to placement into stomach.
††Esophageal intubation to gastrotomy closure.

the time of necropsy. On necropsy, Raju et al[46] observed that in the 1 pig (of 4) with a 2.3-cm colotomy, a healed scar was present on both the mucosal and serosal sides; however, in the 3 pigs with ~1.5 cm colonotomies ulceration was observed on the mucosal side, 2 of which had a faecalith over the ulcer. In 2 of these pigs, nodules were present on the serosal side of the colotomy and in the other pig, an adherent white plug of tissue was seen.

Infection-related Complications

Studies reporting infection-related complications including adhesions, infection, abscesses, peritonitis, inflammation, or

TABLE 8. Mortality

Study	Survival Period (d)	Orifice	Intervention	n/N	%
Bergstrom et al[31]	7–10	O	Ana	0/6	0
Fong et al[28]	14	A	Per	0/6	0
Fritscher-Ravens et al[32]	21–28	O	Ana	0/16	0
Jagannath et al[33]	14–21	O	Fall	0/6	0
Kalloo et al[34]	14	O	Per	0/5	0
Kantsevoy et al[35]	14	O	Ana	0/2	0
Lima et al[38]	15	U	Per	0/5	0
Merrifield et al[42]	14	O	Hys	1/5	20
Pai et al[45]	14	A	Chol	1/5	20
Park et al[49]	14–28	O	GC	0/8	0
Pham et al[47]	7	A	CC	0/8	0
Raju et al[46]	7	A	CC	0/4	0
Sumiyama et al[50]	1–2	O	App	0/5	0
Sumiyama et al[51]	7	O	MGC	0/6	0
Sumiyama et al[52]	7	O	SEMF	0/4	0
Sumiyama et al[53]	7	O	Chol	4/6*	67
Wagh et al[44]	≥1	O	Ooph; Hys	0/3	0
Wagh et al[43]	14	O	Ooph; tube	0/6	0
Wilhelm et al[56]	10	A	CC	0/5	0
Total				6/111	5

*Two pigs died from sudden cardiac arrest and hypoxemia during the operation.

ulceration are shown in Table 9. In studies with no adhesions, infection, abscesses, peritonitis, inflammation, or ulceration reported, it is likely that these complications were not encountered, as most complications were generally mentioned, but this cannot be assumed. Six survival studies did not report any of these complications;[29,32,46,49,50,56] however, Raju et al[46] and Pham et al[47] did report the presence of thin fibrous material throughout the peritoneal cavity in 4 of 4 or 8 of 10 pigs, respectively, on necropsy.[46,47] Thirty-three percent (15 of 45) of reported cases had adhesions (range: 0%–100%, median: 0%). Infection, abscesses, peritonitis, or inflammation was present in 25% (14 of 55) of reported cases (range: 0%–100%, median: 0%) and only some minor ulcerations were observed in all reported studies. Some groups examined infection-related complications histopathologically, whereas others only visually inspected for these complications and may have been less likely to report infection.

Animals that were reported as having incomplete viscerotomy closure also had substantial infection, but infections were also noted in other pigs where complete closure was reported. Merrifield et al[42] reported widespread adhesions and frank abdominal pus in the 1 pig with incomplete gastrotomy closure, which was subsequently euthanized 4 days after surgery because of illness. In the pig that was febrile from 2 to 3 days after surgery, copious adhesions and a 1-mm abscess were observed at the gastric incision site and small collections of pus were seen in remaining portion of uterus and scattered throughout abdominal cavity. No intra-abdominal adhesions, abscesses, or pathologic evidence of peritonitis were observed in the other 3 pigs in this study.

Pai et al[45] also reported substantial infection in 20% (1 of 5) of pigs, which was the pig with incomplete colotomy closure. This pig had acute peritonitis, with seepage of bowel contents from the colonic perforation and necrotizing granulomas. External adhesions were observed in 75% (3 of 4) of pigs: salpingocolonic attachments in 2 pigs and colovesical attachments the third. Submucosal and/or serosal microabscesses and ulceration and necrosis at the incision site were seen in 100% (5 of 5) of pigs.

Kalloo et al[34] noted intraperitoneal microabscesses in the 2 pigs not pretreated with antibiotic, so gave prophylactic antibiotics to the subsequent 3 pigs and found no intraperitoneal microabscesses on necropsy. Only 17% (1 of 6) of pigs in that study showed signs of infection on necropsy. That pig was 1 of the 2 not given prophylactic antibiotics.

Fong et al[28] reported salpingocolonic and colovesicular adhesions in 67% (4 of 6) of pigs. No adhesions were seen in 20% (1 of 4) of pigs where prototype closure device used in the pig closed with endoscopic clips. Incision-related adhesions and inflammatory changes restricted to colonic closure site were observed in 100% (6 of 6) of pigs. Inflammatory infiltrates, microscopic abscesses, microscopic mucosal ulcerations, and serositis were seen in all pigs on histopathologic examination, but could not be picked up by visual examination on necropsy. Similarly, although Jagannath et al[33] did not find any infection-related complications upon visual examination, they found chronic inflammatory infiltrates without abscesses on histopathologic examination.

Although Wagh et al[43] did not report any major infection, they did observe follicular hyperplasia of mesenteric and pelvic lymph nodes in 100% (6 of 6) of pigs as well as a body giant-cell reaction secondary to the endoclips and chronic inflammatory changes at gastrotomy site.

TABLE 9. Infection-related Complications

Study	Peritoneal		Vesicotomy Site			Site Preparation	Antibiotics	
	Adhesions	Signs of Infection	Ulcers	Fecalith	Location		Before	After
Bergstrom et al[31]	NR	0/6 (0%)	Some	NA	Stomach	NR		
Fong et al[28]	4/6 (33%)	0/6 (0%)	0/6	NR	Colon	Enemas. Antibiotic irrigation. Rectum lavaged scrubbed	√	√
Jagannath et al[33]	0/6 (0%)	0/6 (0%)	NR	NA	Stomach	Antibiotic irrigation.	√	NR
Kalloo et al[34]	0/5 (0%)	1/5 (20%)	0/5	NA	Stomach	Oral cavity disinfected in all pigs. Antibiotic lavage In 3 pigs	NR	NR
Kantsevoy et al[35]	0/2 (0%)	0/2 (0%)	NR	NA	Stomach	Antibiotic irrigation	√	√
Lima et al[38]	0/5 (0%)	0/5 (0%)	NR	NA	Bladder	Emptied and refilled with saline	√	NR
Merrifield et al[42]	2/5 (40%)	2/5 (40%)	NR	NA	Stomach	Water lavage. Antibiotic instillation	√	NR
Pai et al[45]	3/4 (75%)	5/5 (100%)	Some	NR	Colon	Enemas. Residual stool removed with snares, aggressive washing and suctioning. Antibiotic instillation and external scrub	√	√
Pham et al[47]	NR	0/10*	7/8	4/8	Colon	Pigs fed total of 20 Viscol tables in the 2 d leading up to procedure.	√	√
Raju et al[46]	NR	0/4†	3/4	2/4	Colon	Pigs fed total of 20 Viscol tables in the 2 d leading up to procedure	√	√
Sumiyama et al[51]	0/6 (0%)	0/6 (0%)	NR	NA	Stomach	Lavaged with water and iodine.	√	√
Sumiyama et al[52]	NR	NR	3/4‡	NA	Stomach	Lavaged with water and iodine.	NR	√
Sumiyama et al[53]	NR	2/4	NR	NA	Stomach	Lavaged with water and iodine. (Peritoneal cavity also lavaged with iodine)	NR	√
Wagh et al[44]	NR	0/3 (0%)	NR	NA	Stomach	Lavaged sterile water. Antibiotic instillation	√	NR
Wagh et al[43]	6/6 (100%)	6/6 (100%)	NR	NA	Stomach	Lavaged with water until free of food particles. Antibiotic instillation	√	NR
Wilhelm et al[56]	0/5	0/5§	NR	NR	Colon	Enemas. Sigmoid sealed orally, end bowel decontaminated. Protective decontamination fluid instilled into peritoneal cavity	√	√

*Thin fibrous material noted through peritoneal cavity in 2 pigs.
†Thin fibrous material noted through peritoneal cavity in 4 pigs.
‡Pigs with anteriorly located site.
§Clear thick bubbled foam identified between small bowel segments in 2 pigs (probably result of taurdolin instillation).

In the only transcolonic study that did not report any site preparation no infection-related complications were reported other than minor ulceration.[31] In the study by Wilhelm et al,[56] the peritoneal cavity was instilled with decontamination solution to provide a safe colonic entry site. No infection-related complications were encountered in this study; however, this decontamination method was not compared with other methods.

Procedure-Related Complications

Bleeding

Although minor bleeding during surgery occurred in many cases, it was generally self-limiting or was controlled by methods including electrocauterization, clamping, and tissue anchors. Studies generally reported bleeding narratively, so it is difficult to compare bleeding across studies because some groups have reported minor bleeding,[34] but others have not reported numbers for nonsignificant bleeding. Seven studies reported no significant bleeding.[28,30,31,34,42,55,56] Kalloo et al[34] reported minor bleeding in 2 of 5 pigs which was stopped with electrocoagulation, Kantsevoy et al[35] noted minor bleeding of an intestinal loop stopped with electrocautery, Park et al[49] encountered occasional manageable bleeding from cystic artery during dissection and Kantsevoy et al[37] reported bleeding during gastrotomy creation in 1 pig when pure cutting was used without electrocautery. Fritscher-Ravens et al[39] reported liver-surface bleeding in 14% (1 of 7) of pigs that did not obscure endoscopic visualization and Sumiyama et al[51] were able to manage arterial bleeding at the perforation site in 17% (1 of 6) of pigs. Bleeding which was not able to be controlled was experienced by Swanstrom et al[54] during liver resection, where significant bleeding was able to be stopped with cautery or endoscopic clips in 10%

(1 of 10) of animals and laparoscopic "rescue" was required. During cholecystectomy bleeding from cystic artery was unable to be controlled and visualization was lost in the first animal (of 3).[54]

Organ Injury

Of the studies that examined organ injury, most studies reported no injury to surrounding organs and vessels,[18,28,31,32,34,35,37,39,42–45,55,56] but organ injury was not thoroughly examined in all cases, so may have been unnoticed. Kantsevoy et al[36] reported no injuries as the result of ET use, but did not mention injuries associated with any other part of procedure. Although no organ injury was reported by Fritscher-Ravens et al,[39] secondary bile leakage seriously disturbed endoscopic view during cholecystectomy in 1 pig (of 7). Wilhelm et al did not report any organ injury; however, in some cases herniation of the small bowel occurred during withdrawal of the endoscope, but could be easily avoided by insufflating a small amount of air when withdrawing the endoscope.[56] Wagh et al[43] reported that trauma to the liver during gastric exit may have occurred and in 1 pig the anterior abdominal wall was punctured during gastrotomy and Sumiyama et al[52] reported small bowel injury during SEMF gastrotomy creation in the pig with a posterior site.

Sumiyama et al[51] reported penetration of surrounding organs by 12.5% (3 of 24) of tissue anchors used and Sumiyama et al[52] reported tissue anchor penetration of the liver in 25% (1 of 4) of pigs. During cholecystectomy, Swanstrom et al[54] reported that in the second animal (of 3), perforation of the gallbladder made identification of dissection planes impossible, so the cholecystectomy was abandoned, and in the third animal some gallbladder perforations occurred. Sumiyama et al[53] reported that a small perforation occurred in 50% (2 of 4) of removed gallbladders during dissection from the liver bed. Rentschler et al[48] reported that their mobile robot had sufficient traction to explore the gastric and peritoneal cavities without causing tissue damage.

DISCUSSION

Limitations of the Evidence

With the exception of 4 human studies and 1 study, which used 4 dogs, all procedures were performed in pigs, which may respond differently to surgical procedures when compared with humans, in addition to the obvious differences in surgical technique because of pig anatomy. Three human trials have been registered with the Clinical Trials Register; however, these trials have not yet been completed and only one article has been published from these trials to date.[27] There were numerous references in the literature to peroral transgastric appendectomies performed in humans in India,[4,19–21] but these were cited as personal communications and no published data could be obtained. Additionally, there have been a number of news reports of human transvaginal cholecystectomies being successfully performed without complication by Bessler et al in New York City, (hybrid),[59–62] by Ricardo Zorrón's group in Rio de Janeiro, Brazil,[57,62] and by a group led by Jacques Marescaux in Strasbourg, France.[58,62] These trials were not found in database searches of peer-reviewed literature; however, this omission may be because of the bias for English language articles and time taken for publication.

Only one of the included studies compared NOTES procedures with current intra-abdominal surgical procedures, and most focused primarily on the ability to successfully complete the procedure, rather than on how safe or effective the procedure was. In many studies, the first few animals were used to optimize methods and gain experience with performing various aspects of the procedure; however, outcomes for these animals were often pooled with those of subsequent animals. Additionally, as these procedures were novel, the learning curve was significant, and ability to successfully perform the technique generally increased greatly with experience, which has an obvious impact on outcomes. Furthermore, it is likely that only studies achieving some level of success using NOTES were published, thus outcomes gathered from these studies are probably overly optimistic, as failures are less likely to be published.

Safety and Efficacy Outcomes

The development of NOTES has attracted the attention of many prominent surgeons and gastroenterologists who have formed collaborations to identify concerns and challenges in the development of NOTES. A working group established at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) leadership meeting in Chicago in 2005 developed guidelines for the implementation of NOTES, which were outlined in a resultingöNOTES White Paper."[19] This article outlined important challenges including peritoneal access, viscerotomy closure, prevention of infection, suturing and anastomotic devices, maintenance of spatial orientation, development of a multitasking platform, management of intraperitoneal complications and hemorrhage, adverse events caused by NOTES, education and training. Some of these challenges have been investigated in the included studies and have been further addressed in studies presented at the SAGES 2007 meeting, but have not been satisfactorily resolved at this stage.

It was apparent that although technically possible to perform many of the surgical interventions using NOTES, these procedures have not yet been optimized for maximum effectiveness and minimization of risk, and still require substantial refinement before they can be compared with established procedures in a clinical setting. The positive patient outcomes and lack of postoperative complications experienced by all patients in the included human studies suggest that NOTES procedures may be both safe and viable in a clinical setting. However, it must be noted that safety and effectiveness outcomes were not explored in great detail or for extended follow-up periods in any of these studies, so further investigation is warranted. The only mortalities occurring during surgery in any of the included studies occurred during NOTES cholecystectomy, which was reported to be challenging in all accounts. This highlights the need for optimization techniques for this procedure and the need for peer-reviewed data for adoption of this procedure in a clinical setting. The 100% success rate for other interventions trialed using NOTES, including appendectomy, splenectomy, anastomosis creation, diaphragm pacing, and gynecological procedures indicates little more than feasibility of the use of NOTES in these intra-abdominal procedures because of the small sample size and lack of a human model.

The reported success performing transgastric and transvesical NOTES peritoneoscopy in 2 human case reports and in 1 comparative demonstrates the potential for NOTES in a clinical setting; however, the procedure was not complex and the reporting of outcomes was limited. Importantly, transgastric NOTES peritoneoscopy was comparable to diagnostic laparoscopy for evaluation of pancreatic cancer; however, time taken and visualization during the NOTES procedure was less efficacious than for laparoscopy. The advantages of using NOTES in ICU patients with PEG gastrotomies are clear, as there is no need to create a new gastrotomy and the importance of minimizing invasive procedures is higher for ICU patients, for whom even a small laparoscopic wound can pose potentially dangerous complications; however, outcomes will need to be improved to demonstrate an advantage of using NOTES in other patients.

As proposed in the NOTES White Paper,[19] peritoneal access was easily achieved in all studies without significant complication, via oral, anal or urethral orifices; however, the optimal access route was not compared for any of the procedures and transvaginal access was not used in any of the included studies, also it is being trialed in human studies registered with the Clinical Trials Registry and was employed in studies presented at the 2007 SAGES meeting.[63–65] The combination of transgastric and transvesical access appeared to be advantageous, particularly for organ manipulation and visualization; however, this needs further investigation to be substantiated. Most groups agree that optimization of the viscerotomy creation method and site must be determined to yield better surgical results,[2,19,66,67] but this has not been achieved satisfactorily in the included studies.

Although it was proposed in the NOTES White Paper that a 100% reliable means of viscerotomy closure must be ensured,[19] this remains to be proven. Four of the 6 mortalities that were reported in the included studies were related to incomplete viscerotomy closure. Two mortalities occurred because of complications during SEMF gastrotomy closure and 2 resulted from infections occurring after unsuccessful gastrotomy or colotomy closure. This finding is suggestive of a relationship between unclosed viscerotomy and poor outcome; however, the complication-free survival of 6 pigs with unclosed gastrotomies in one study and 5 with unclosed vesicotomies in another, suggest that viscerotomy closure may not always be crucial, but dependant on incision type and method or survival in these pigs may be because of pig physiology.

Viscerotomy closure was completed in the majority of cases where it was attempted, using a variety of devices, with incomplete closure not consistent for any device and reliability could not be properly assessed because of the very small sample size lack of comparison between closure methods. Furthermore, the failure of a fellow in training to close 40% of colonotomies in one study compared with 100% success by a senior gastroenterologist in the same study, illustrate the difficulty of the techniques and suggest that the reliability of closure may have been reduced in other studies if not performed by expert gastroenterologists, in a carefully controlled environment. Another concern is that although the closure of one viscerotomy is considered to be relatively simple, ensuring the closure of multiple punctures created for multiple working ports is more difficult.[2,19] In one study, 2 gastrotomies per animal were successfully closed, and no subsequent infection-related complications reported, but the closure of multiple viscerotomies needs to be further tested. The novel closure devices presented at the SAGES 2007 meeting such as the Power Medical SurgASSIST[68] and the NDO plicator (NDO Surgical Inc.)[69,70] may help to provide solutions to achieving simple and reliable closure, but again, these devices will need to be further tested.

It is important to measure the robustness of viscerotomy closure when determining reliability of closure, as in some cases dehiscence of closed viscerotomies led to infection. Although 2 animal studies[30,41] and 1 human case report reported no leakage of gastrotomies during testing, leak testing was not conduced in the other studies. Furthermore, the fact that not all successfully closed gastrotomies were watertight on explant testing indicates that ensuring viscerotomy closure does not necessarily ensure protection from contamination. The use of bioprosthetic plugs for viscerotomy closure, as presented at the SAGES 2007 meeting, may speed the viscerotomy healing process.[71]

Other causes of peritoneal infection experienced by some of the pigs with closed viscerotomies may be leakage of intestinal pathogens into the peritoneal cavity during surgery or contamination by equipment passing through pathogen-containing lumens; however, studies have revealed that peritoneal exposure to low levels of bacteria appear to be well tolerated, especially if prophylactic antibiotics were given.[19,22] Additionally, a study presented at the SAGES 2007 meeting demonstrated that although transgastric equipment does contaminate the peritoneal cavity, pathogens are clinically insignificant because of species or bacterial load.[72] Although many studies used measures to reduce peritoneal infection including disinfection and cleansing of the viscerotomy site, instillation of protective decontamination fluid, postprocedural peritoneal lavage, the use of sterile overtubes and administration of prophylactic antibiotics, outcomes for these treatments were not compared, and physiologic effects were not investigated.[4,23] Additionally, it is expected that very low gastric pH[3,4] limits bacterial growth and thus contamination.[23] Thus, excessive cleansing of the stomach or the administration of prophylactic antacids, as was undertaken in some of the included studies, may in fact increase risk of peritoneal contamination.[73]

Visualization was generally adequate to allow the completion of the procedures; however, the inability to identify numerous organs and structures will need to be addressed if NOTES is to be performed in the range of intra-abdominal interventions possible with current surgical techniques and to achieve the same reliability as diagnostic laparoscopy. A better field of view may be achieved using 2 ports, such as a combined transvesical and transgastric approach, or with technological advances providing a multitasking platform or multiple cameras on separate arms of endoscopic devices.[19,54,74] This may reduce adverse events such as organ laceration and if such events do occur, they are more likely to be captured so that consequences could be minimized.

Maneuverability of flexible endoscopic devices through the peritoneal cavity was generally achievable with current devices, but was often tedious and cumbersome. The flexibility of endoscopic equipment that is required to traverse long luminal spaces does not allow for adequate traction and counter traction to be achieved, making organ and tissue manipulation difficult;[2,19] however, the successful peritoneal exploration by a mobile robot, without causing tissue damage, indicates great potential for future use in NOTES. Additionally, most endoscopic devices have limited degrees of freedom, with the lack of maneuverability further hindering tissue manipulation.[2] Grasping and organ manipulation was quite variable, depending on the target organ/tissue, equipment and access port used, and distance of the target organ from that port. Adequate grasping could be achieved to perform all included procedures, but was often difficult and unreliable. Using a combination of transvesical and transgastric ports helped with organ manipulation and should be explored as a possibility.[19] The development of a multitasking platform and physically stable work environment will be critical to the use of NOTES for more complex procedures. Other methods to address these issues include the use of overtubes to stabilize positioning of equipment, the development of surgical robots with flexible arms attached to the end of an endoscope[12,14] and voice activation technology.[19,75]

Importantly, in the human study, where NOTES peritoneoscopy was performed in a patient with a preexisting PEG gastrotomy, only conscious sedation was required, which may be advantageous in the ICU. Good pain management was reported in the other human studies; however, patients were still put under general anesthesia and further studies will be required before it can be determined if NOTES is associated with a reduced need for analgesia and anesthesia.

NOTES Devices

Many of the challenges that have been identified are related to the capacity of devices used to reliably perform procedures with such limited access. Rapidly advancing surgical technology makes this a technical possibility, yet it is unclear if current technology is adequately advanced and if surgeons' skills in using these novel devices may keep up with the technology.[34,76] Flexible video endoscopes and devices which enable suturing, dissecting, grasping, ligating, and anastomosis are being perfected to address issues such as flexibility versus strength/traction, visualization, and lack of tactile feedback.[19,34,66,76–78] At present, most devices are cumbersome and backup is needed in case mechanical closure and anastomoses devices fail, especially for use during complex procedures.[19] The novel tag/thread firing devices used to perform lymphadenectomy in one study[29] and to create anastomoses in another,[32] could potentially reduce complications by eliminating the need for a pneumoperitoneum and minimizing the need for equipment in the peritoneal cavity. The large number of prototype devices that were successfully used in the included studies and in SAGES presentations need to be further developed and evaluated.

Other Considerations

Past experience, especially with the introduction of laparoscopy, has revealed the need for adequate and regulated training. The problems that occurred with the rapid adoption of laparoscopic surgery, such as complications associated with laparoscopic cholecystectomy,[9] need to be avoided with the introduction of NOTES. This signifies a need for good research into NOTES with adequate and transparent reporting to ensure surgeons are provided with up-to-date education on optimal methods of performing the procedures, handling of the latest devices, and complications to avoid.[19]

Surveys presented at the SAGES 2007 meeting where patients were asked their perceptions of NOTES technology indicate what risks are considered acceptable. Complications, recovery time, and postoperative pain were considered to be more important than cosmesis, cost and length of hospital stay, and there was no tolerance for higher risk or worse outcomes for NOTES, regardless of expected benefits.[79] This indicates that safety and efficacy need to be adequately addressed before it is acceptable to perform NOTES in a clinical setting.

Future Research

At the SAGES 2005 meeting it was acknowledged that NOTES has blurred the boundaries between traditional disciplines such as gastroenteroscopy and endoscopic and laparoscopic surgery; however, a general consensus was reached that "NOTES is truly surgery and should be developed and promoted by surgeons knowledgeable in suturing, wound healing, anatomy, and other surgical options."[19,80,81] This group went on to form the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR; http://www.noscar.org/), whose goal is to conduct research into this emerging field and to guide the responsible development of NOTES. In Europe, the New European Surgical Academy has founded the Natural Orifice Surgery working group[62,82] and an association called European Association for Transluminal Surgery has also been formed.[83,84] NOSCAR have identified the following membership criteria, which should be applied to all those developing NOTES must have a multidisciplinary (ie, possesses advanced endoscopic and laparoscopic skills); should be SAGES and/or ASGE members; must have animal laboratory facilities to perform research and training; must agree to share laboratory results with other NOSCAR members; must agree that any and all human procedures be performed only after obtaining Institutional Review Board approval.[19]

Following optimization and refinement of NOTES procedures, it is critical that future studies compare outcomes of NOTES procedures with those of current intra-abdominal surgical procedures. Challenges including achieving adequate visualization/spatial orientation, maneuverability, grasping, and organ manipulation still need to be addressed and will be aided by further development of the many promising devices outlined in the literature.[2,11,19,74,77,78] The method of Failure Mode and Effect Analysis to survey technical problems of NOTES, as presented at the SAGES 2007 meeting, may assist in this development.[85]

Optimization of peritoneal access and a reliable closure method will need to be determined in future studies comparing viscerotomy creation and closure with important outcomes such as organ injury, bleeding, infection, recovery, and survival. Longer and more comprehensive survival studies may help to determine adverse events caused by NOTES and it has also been suggested that better animal models need to be used to account for physiologic differences before moving into human trials.[2]

Hybrid studies in humans (ie, laparoscopic/transgastric) could be used in early human procedures,[19] although the risk seems unnecessary as they would be greater than those for laparoscopy with none of the benefits of NOTES. Alternatively, laparoscopic and laparotomic backup may be enlisted to ensure patient safety when performing NOTES in early human trials.

CONCLUSIONS

As NOTES is still in a developmental stage and no human studies have been published, it is difficult to compare the safety and efficacy of using NOTES to perform intra-abdominal surgery with current surgical interventions. The outcomes obtained from the 34 studies included in this review indicate that NOTES can in fact be used to perform some intra-abdominal procedures. What is more apparent, however, is the need for further development of these procedures and detailed studies comparing NOTES to current surgical alternatives before NOTES may seriously be considered for use in a clinical setting. The development of new devices will speed the development of NOTES and improve outcomes. There is a definite need for further studies to compare surgical methodology of NOTES procedures and to determine optimal methods of performing intra-abdominal surgery via a natural orifice. The safety and efficacy of these optimized procedures will then need to be carefully evaluated and compared with existing surgical interventions.

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