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TOPIC HIGHLIGHT

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Natural orifice translumenal endoscopic surgery applications in clinical practice

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Abstract

To review natural orifice translumenal endoscopic surgery (NOTES) applications in clinical practice and assess the evidence base for each application as reported in the literature. An electronic literature search was performed. Inclusion criteria were publications relating to NOTES applications in humans. For each type of operation the highest level of evidence available for clinical NOTES publications was evaluated. Morbidity and short-term operative outcomes were compared with gold standard published evidence where available. Finally, registered trials recruiting patients for NOTES applications were identified. Human NOTES publications with the highest level of evidence in each application are identified. There were no RCTs in the literature to date. The strongest evidence came in the form of large, multi-centre trials with 300-500 patients. The results are encouraging, comparable with gold standard techniques on morbidity and mortality. While short-term operative outcomes were also similar when compared to the gold standard techniques, other than improved cosmesis little else can definitely be concluded as a clear benefit of a NOTES procedure. The most common procedures are cholecystectomy, appendicectomy and peritoneoscopy mainly performed *via* transvaginal access. It is evident that morbidity appears to be higher when the transgastric route is used. The safety profile of hybrid NOTES transvaginal procedures is beginning to be confirmed as is evident from the large number of procedures presented in this review. A number of authors have presented work on pure NOTES procedures but the results are inconsistent and thus the vast majority of NOTES procedures worldwide are performed in a hybrid fashion with a variable amount of laparoscopy. This review of the clinical applications of NOTES summarises the growing evidence behind this surgical discipline and highlights NOTES procedures with an acceptable safety profile.

Key words: Natural orifice translumenal endoscopic surgery; Humans; Clinical practice

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INTRODUCTION

Natural orifice translumenal endoscopic surgery (NOTES) in general surgery has been performed clinically for the

past 4 years now and there has been an exponential increase in reports of NOTES procedures as the concept moves from experimental to the clinical arena. Given the established safety profile of the colpotomy[1] transvaginal applications have been the first to be adopted clinically, with the proposed benefits of reduced surgical trauma and improved cosmesis compared with standard laparoscopic approaches.

There is a cautious movement in the NOTES community as we move towards pure NOTES procedures without any trans-abdominal assistance and as evidence gathers on the safety of the transgastric approach. This is in the context of numerous multi-centre, international, randomized controlled trials comparing NOTES with standard laparoscopic approaches due to report their results in the near future.

There have however been some significant issues highlighted by the introduction of NOTES into clinical practice. The flexible endoscope has proven inadequate as an operating platform to independently perform intermediate intra-abdominal surgical procedures and industry has not provided us with a viable alternative. There appears to be a hesitation from industry to enter into this market, perhaps due to the significant investment required in the context of estimated initial low volume sales, but sceptics may comment that many companies have large investments in the single-incision laparoscopy market and have chosen to focus on this in the short term.

Nevertheless the initial clinical data on morbidity and outcome appear promising and clinical trials and feasibility studies are on the whole being conducted appropriately under the scrutiny of IRB protocols at centres with suitable experience. It is important to reflect on progress frequently, particularly during the early years of the introduction of NOTES into clinical practice.

The aim of the present study is to review NOTES applications in clinical practice and assess the evidence base for each application as well as define the morbidity and peri-operative outcomes of as reported in the literature.

LITERATURE SEARCH

An electronic keyword literature search using PubMed of the US National Library of Medicine and The Cochrane Library (CENTRAL) of the Cochrane Collaboration as well as Science Direct databases was performed. Inclusion criteria were publications relating to NOTES applications in humans. For each type of operation the highest level of evidence available for clinical NOTES publications was evaluated using the Oxford Level of Evidence guide[2]. Reference lists of all identified publications were manually searched to ensure completeness. Trials were excluded from detailed examination when they were not one of the highest levels of evidence for that category of NOTES procedure.

Morbidity and short-term operative outcomes were compared with gold standard published evidence where available. Finally, registered trials recruiting patients for NOTES applications were identified through EU clinical trials, US clinical trials, UK trials and the medical research council.

The results of this review are summarised in Table 1: NOTES clinical papers.

CHOLECYSTECTOMY

Transvaginal cholecystectomy

This is the most reported organ resected *via* a NOTES procedure. There are now in excess of 26 different authors publishing their results on NOTES cholecystectomies. There is a huge range in patient number with the majority of reports either single cases or less than ten cases in a series. The majority of these cases, especially within the large, multi-centre studies were performed in a hybrid fashion with a variable amount of laparoscopic assistance.

There are 961 cases of transvaginal cholecystectomy reported in the literature with the highest level of evidence being the studies by Zorron *et al* and Lehmann *et al*[3,4] which represents level 3. In these case-controlled, international/national, multicentre studies short term morbidity was 6.67% in the smaller of the trials[3] and in the trial reported by Lehmann *et al*[4] morbidity was reported as 3.3%. This is at the very least equivalent to the 6%-12% morbidity quoted in large series in the literature for the gold standard laparoscopic cholecystectomy[5,6].

The Lehmann group consisted of an analysis of the German NOTES registry. The authors invited all surgeons performing NOTES procedures in Germany to take part on a voluntary basis to allow the monitoring and safe introduction of the technique. Although 64 different institutions registered, only 28 treatment centres entered data, perhaps introducing a degree of publication bias. Over 14 mo 551 patients were operated on using a NOTES technique, the majority were cholecystectomy, all were female and the transvaginal route was invariably used. They report an overall complication rate of 3.1% and a conversion rate of 4.9%. In this study most procedures were performed in a hybrid fashion, however they report that much of their dissection for their Hybrid-NOTES Cholecystectomies was performed through the umbilical laparoscopic port and they used a rigid endoscope in the majority of cases. An average of 1.2 abdominal trocars was used in this series.

A multitude of surgical techniques have been described in the literature. The most common surgical technique described is a hybrid approach, with umbilical laparoscopic assistance. Additionally, both rigid and dual channel flexible endoscopes have been used and between 1 and 3 abdominal trocars for laparoscopic assistance.

Numerous other authors report the use of laparoscopic assistance to dissect calots triangle and the gall bladder bed[3,7,8]. Laparoscopic clips are considered "absolutely necessary" for patient safety as the endoscopic clips are not fully occlusive[7].

Table 1 Natural orifice translumenal endoscopic surgery clinical papers

Author	Yr	Operation	No. of patients	Operative time (min)	Route of access	Hybrid/pure	Morbidity	Level of evidence
Cholecystectomy								
Marescaux[11]	2007	Cholecystectomy	1	180	Transvaginal	Pure	Nil	4
Bessler[51]	2007	Cholecystectomy	1	NA	Transvaginal	Hybrid	NA	4
Dolz[52]	2007	Cholecystectomy	1	95	Transvaginal	Hybrid	Nil	4
Zornig[53]	2007	Cholecystectomy	20	63	Transvaginal	Hybrid	Nil	3b
Forgione[7]	2007	Cholecystectomy	3	136	Transvaginal	Hybrid	Nil	3b
Zorron[54]	2007	Cholecystectomy	1	81	Transvaginal	Hybrid	Nil	4
Ramos[55]	2008	Cholecystectomy	32	38	Transvaginal	Hybrid	Nil	3b
Zornig[56]	2009	Cholecystectomy	68	51	Transvaginal	Hybrid	Douglas pouch abscess, conserv. Mx	3b
Dallemagne[15]	2009	Cholecystectomy	5	150	Transgastric	Hybrid	Nil	3b
Decarli[57]	2008	Cholecystectomy	1	85	Transvaginal	Hybrid	Nil	4
Decarli[58]	2009	Cholecystectomy	12	125.8	Transvaginal	Hybrid	Vulval lac, Nil post-op	3b
Gumbs[12]	2009	Cholecystectomy	4	209 (hybrid) 185 (pure)	Transvaginal	3 hybrid/ 1 pure	Nil	3b
Auyang[59]	2009	Cholecystectomy	1		Transgastric	Hybrid	Nil	4
Horgan[60]	2009	Cholecystectomy	1	96	Transvaginal	Hybrid	Nil	4
Seven[61]	2009	Cholecystectomy	2	130	Transvaginal	Hybrid	Nil	4
Castro-Perez[62]	2009	Cholecystectomy	7	72.4	Transvaginal	Hybrid	Nil	3b
Horgan[8]	2009	Cholecystectomy	9	114	Transvaginal	Hybrid	Nil	3b
De Sousa[13]	2009	Cholecystectomy	4	45-115	Transvaginal	Pure	Nil	3b
Navarra[63]	2009	Cholecystectomy	6	NA	Transvaginal	Hybrid	Nil	3b
Noguera[10]	2009	Cholecystectomy	15	NA	Transvaginal	Hybrid	Haematuria no intervention	3b
Noguera[64]	2009	Cholecystectomy	20	66.5	Transvaginal	Hybrid	UTI	3b
Palanivelu[65]	2009	Cholecystectomy	6	148.5	Transvaginal	Hybrid	Subhepatic collection USS drainage	3b
Pugliese[66]	2010	Cholecystectomy	18	75	Transvaginal	Hybrid	1 biliary leak, healed 7 d	3b
Zorron[3]	2010	Cholecystectomy	240	96	Transvaginal	Hybrid/pure	6.67%	3a
Zorron[3]	2010	Cholecystectomy	29	111	Transgastric	Hybrid	24.14%	3a
Lehmann[4]	2010	Cholecystectomy	488	61.9	Transvaginal	Hybrid	17 bladder/bowel injuries/ vaginal bleeding/UTI/ wound infection	3a
Appendicectomy								
Palanivelu[19]	2008	Appendicectomy	3	103.5	Transvaginal	2 hybrid/ 1 pure	Nil	4
Bernhart[20]	2008	Appendicectomy	1	NA	Transvaginal	Pure	Nil	4
Rao[22]	2008	Appendicectomy	8	NA	Transgastric	Pure	2 converted out of 10 attempted	3b
Horgan[60]	2009	Appendicectomy	1	78	Transvaginal	Hybrid	Nil	4
Horgan[60]	2009	Appendicectomy	1	150	Transgastric	Hybrid	Nil	4
Tabutsadze[21]	2009	Appendicectomy	2	82	Transvaginal	Hybrid	Nil	4
Shin[67]	2010	Appendicectomy	1	60	Transvaginal	Hybrid	Nil	4
Park[23]	2010	Appendicectomy	3	NA	Transgastric	Pure	1 converted to lap / 1 converted to open + pneumonthorax	4
Zorron[3]	2010	Appendicectomy	37	60.5	Transvaginal	Hybrid	8.10%	3a
Zorron[3]	2010	Appendicectomy	14	135.5	Transgastric	Hybrid	21.42%	3a
Lehmann[4]	2010	Appendicectomy	42	47.1	Transvaginal	41 hybrid / 1 Pure	Nil	3a
Peritonoscopy								
Gettman[36]	2007	Peritonoscopy	1	40	Transvesical	Hybrid	Nil	4
Pearl[68]	2007	Peritonoscopy	4	NA	Transgastric	Hybrid	NA	4
Hazey[33]	2008	Peritonoscopy	10	24.8	Transgastric	Hybrid	Nil	3b
Zorron[34]	2008	Peritonoscopy	1	105	Transvaginal	Pure	Nil	4
Nikfarjam[32]	2010	Peritonoscopy	9	NA	Transgastric	Hybrid	1	4
Nau[30]	2011	Peritonoscopy	130	NA	Transgastric	Hybrid	NA	3b
Memark[31]	2010	Peritonoscopy	40	19.5	Transgastric	Hybrid	Nil	3b
Zorron[3]	2010	Peritonoscopy	8	35	Transvaginal	Hybrid	Nil	3a
Zheng[35]	2011	Peritonoscopy	5	NA	Transgastric	Pure	Nil	3b
Sleeve Gastrectomy								

Ramos[28]	2008	Sleeve Gastrectomy	1	95	Transvaginal	Hybrid	Nil	4
Fischer[69]	2009	Sleeve Gastrectomy	1	NA	Transvaginal	Hybrid	NA	4
Lacy[70]	2009	Sleeve Gastrectomy	1	150	Transvaginal	Hybrid	Nil	4
Chouillard[27]	2010	Sleeve Gastrectomy	20	116	Transvaginal	Hybrid	1 pneumonia	3b
Buesing[71]	2010	Sleeve Gastrectomy	14	NA	Transvaginal	Hybrid	Nil	3a
Zorron[3]	2010	Sleeve Gastrectomy	5	NA	Transvaginal	Hybrid	NA	3a
Lehmann[4]	2010	Sleeve Gastrectomy	6	103.9	Transvaginal	Hybrid	Nil	3a
Nephrectomy								
Kaouk[45]	2009	Nephrectomy	1	420	Transvaginal	Pure	Nil	4
Zorron[3]	2010	Nephrectomy	4	NA	Transvaginal	Hybrid	NA	3a
Sigmoidectomy / Colectomy								
Lacy[38]	2008	Sigmoidectomy	1	150	Transvaginal	Hybrid	Nil	4
Zorron[3]	2010	Sigmoidectomy	12	192	Transvaginal	Hybrid	1 UTI	3a
Lehmann[4]	2010	Sigmoidectomy	14	122.6	Transvaginal	Hybrid	Nil	3a
Leroy[39]	2011	Sigmoidectomy	1	105	Transanal	Hybrid	Nil	4

NA: Not available.

Zornig *et al*[9] compared 200 case matched cholecystectomies undergoing conventional laparoscopy and hybrid NOTES. They used a 5 mm, deep umbilical port for laparoscopic dissection and clipping of the artery and duct. The operative time for the NOTES cholecystectomies was longer (52 min *vs* 35 min; $P < 0.001$) than the conventional laparoscopic operation. However, there was no difference between the groups in relation to intra/post operative complications, length of stay, consumption of analgesia or sick leave. The authors conclude, the only difference other than operative time, was that the NOTES procedure produced no visible scar. Noguera *et al*[10] 2009 performed a much smaller comparative analysis between laparoscopy and NOTES for cholecystectomies and report similar results to Zornig.

Pure NOTES procedures have been described in at least 6 cases[3,11-13]. Prof Marescaux performed a pure (other than using a 2 mm insuflator, no laparoscopic assistance was required) NOTES tranvaginal cholecystectomy, operative time was 3 h and there were no intra/post-operative complications[11]. Gumbs *et al*[12] performed a pure NOTES cholecystectomy using a 15 mm port placed transvaginally to maintain pneumoperitoneum, with an additional 5 mm port to allow for the placement of a retractor. Calot's triangle was dissected using a dual-channel endoscope, the duct and artery were clipped endoscopically with extraction transvaginally and the colpotomy was closed with absorbable sutures. Interestingly, they had to surgically modify the endoscopic clips by manually straightening the tips to ensure they were fully occlusive. De Sousa *et al*[13] report 4 pure NOTES cholecystectomies, performing the procedure with 2 endoscopes, one for insufflation and retraction and one for dissection, clipping and resection of the gall bladder. Operative time was wide ranging from 45-115 min. Similarly to Gumbs et al they report no post-operative complications, with patients discharged on day 1 or 2 of surgery. Totally NOTES cholecystectomies were found to have a significantly longer operative time compared to hybrid NOTES > 120 *vs* < 60 min respectively[3]. Although Zorron *et al*[3] in 2010 describe two techniques for pure NOTES cholecystectomies they do not report how many of their large number of operations were performed in this pure fashion. The first technique they describe employs a dual scope technique with a single channel gastroscope which is used for insufflation and retraction and a double-channel colonoscope used for dissection, endoscopic clipping and resection of the specimen, removing the need for laparoscopic assistance. The second approach to pure NOTES Zorron *et al*[3] describe, utilises a transvaginal multi-port with an insufflation device attached negating the need for a second endoscope. Dissection was once again performed with hot biopsy forceps and polypectomy snares along with transvaginal laparoscopic clips. In both cases pneumoperitoneum was aspirated transvaginally before withdrawal of the scope.

There are 15 registered trials for cholecystectomy. One of these trials represents a prospective, multi-centre randomized controlled trial comparing conventional laparoscopic cholecystectomy to NOTES cholecystectomy. This trial is supported by NOSCAR with the American Society of gastrointestinal endoscopy. The authors are recruiting from multiple centres across the United States, aiming to recruit 200 patients to randomise[14]. There are also comparative analysis between NOTES and conventional laparoscopy to add strength to the trials by Zornig and Noguera, including a cost effectiveness analysis[9,10]. Notably, there is a large multi-centre international study of NOTES cholecystectomy registered[14].

Transgastric cholecystectomy

There are 35 cases of transgastric cholecystecomy reported in the literature with the highest level of evidence being the study by Zorron *et al*[3] which represents level 3. In this case-controlled, international, multicentre study short term morbidity was 24.14%; significantly higher than the same procedure using the transvaginal route. This is greater than the 6%-12% quoted in large series in the literature for the gold standard laparoscopic cholecystectomy[5,6].

The most common surgical technique described is a

hybrid approach, using umbilical laparoscopic assistance. The 29 transgastric cholecystectomies performed by Zorron *et al*[3] used a laparoscopic port for the safe formation and closure of the gastrotomy. If the specimen was too large for the oesophagus the umbilical incision was extended to allow extraction of the gallbladder. This group performed a variable amount of the operation using laparoscopic assistance. To close the gastrotomy safely required the addition of between 1 and 3 abdominal ports. While this group reported a significantly shorter hospital stay in their transgastric cholecystectomies compared to their transvaginal cholecystectomies (38 h *vs* 46 h respectively), there was a vast difference in complications with 24.14% in the transgastric group compared to 6.67% in the transvaginal group[3].

Dallemagne *et al*[15] performed 5 transgastric cholecystectomies using laparoscopic assistance in all cases to enable safe gastrotomy and closure, exposure of the gallbladder and to clip the cystic pedicle. They report that a variable amount of laparoscopic assistance was required, with an average operative time of 150 min and no intra or post-operative complications.

APPENDICECTOMY

Transvaginal appendicectomy

This is the second most reported of the human NOTES operations performed, with over 11 different centres reporting clinical results on 113 patients. To date there are no randomised controlled trials or systematic reviews comparing NOTES appendicectomies to either open or laparoscopic appendicectomies (D'Souza clinical evidence[16] and Sodergren *et al*[17]).

There are 87 cases of transvaginal appendicectomy reported in the literature with the highest level of evidence being the studies by Zorron *et al* and Lehmann *et al*[3,4] which represents level 3. In these case-controlled, international/national, multicentre studies short term morbidity was 0%-8% compared to 4.13% quoted in large series in the literature for the gold standard laparoscopic appendicectomy or 6.39% for open appendicectomy in the same series[18].

The publication by Zorron *et al*[3] included 16 centres in 9 different countries whose NOTES protocols were approved to participate in their international, multi-centred study. They report NOTES procedures on 362 patients with an overall complication rate of 8.84%. They additionally report a wide range of procedures including right hemicolectomy, nephrectomy, hepatic cyst excision, sleeve gastrectomy, gynaecological surgery and rectosigmoidectomy. There were 51 appendicectomies in the Zorron group in total, 37 were performed transvaginally, with a reported complication rate of 8%, resulting from intra-operative bleeding from the appendiceal artery.

The most common surgical technique described is a hybrid approach, using umbilical laparoscopic assistance with a left iliac fossa port for retraction. The appendix was dissected in most cases in the large trials with endoscopic dissection using hot-biopsy forceps and a polypectomy snare. Coagulation forceps and a needleknife have also commonly been used in the dissection of the mesoappendix, with endoloops to secure the base of the appendix. The use of a dual channel endoscope is utilised, which allows the left channel to be used for traction and the right for dissection.

There are only 3 cases of pure NOTES transvaginal appendicectomies, reported by three different authors[4,19,20]. NOTES appendicectomies were found to have a significantly longer operative time compared to hybrid NOTES > 90 *vs* < 60 min respectively[3].

Palanivelu *et al*[19] performed 2 hybrid and 1 pure NOTES appendicectomies. A laparoscope was used for the first two cases to aid colpotomy and a double channel endoscope was used to retract and dissect the appendix. In one case the appendicectomy was complicated by a bleed from the appendicular artery but this was controlled endoscopically. Post-operatively 2 out of 3 patients complained of vaginal discomfort, nevertheless, all patients were discharged after 48 h. The operative time was 103.5 min. Other small studies have noted that operative time can average 78 min[21].

Interestingly Palanivelu *et al*[19] attempted to perform 6 pure NOTES appendicectomies but were only able to perform one due to technical difficulties resulting in the other 5 cases being converted to hybrid NOTES or pure laparoscopy.

There are 5 registered trials for appendicectomy, one of these is a single centre study assessing the transrectal route, from Northwestern University in the United States, aiming to recruit 10 patients. None of these are randomized controlled trials or large, multi-centre international studies[14].

Transgastric appendicectomy

There are 26 cases of transgastric appendicectomy reported in the literature with the highest level of evidence being the study by Zorron *et al*[3] which represents level 3. In this case-controlled, international, multicentre study short-term morbidity was 21.42%, compared to 4%-6% quoted in large series in the literature for the gold standard laparoscopic appendicectomy[18].

The most common surgical technique described employs a hybrid approach, with umbilical laparoscopic assistance with a 3 mm or 5 mm port. This port allows direct vision of the endoscope's entry into the abdominal cavity, to enable retraction of the appendix and to assist with closure of the gastrotomy.

Pure NOTES procedures have been described in 11 cases. Rao et al attempted 10 transgastric appendicectomies. A double-channel endoscope was employed using rat toothed forceps to retract the appendix. Dissection, as with the majority of NOTES appendicectomies, was with hot biopsy forceps, an endoloop and polypectomy snare. They used multiple endoscopic staples to close the gastrotomy. They report no infectious complications, but do report a needle-knife injury to the anterior abdominal

wall, 2 conversions to laparoscopy due to a retrocaecal appendix and one post-operative ileus[22]. Park *et al*[23] reported 3 attempts at pure NOTES with one conversion to laparoscopy and one conversion to open with a pneumothorax complicating the open case.

SLEEVE GASTRECTOMY

Transvaginal sleeve gastrectomy

Laparoscopic sleeve gastrectomy has been widely reported as a safe and improved treatment for morbid obesity [24]. More recently NOTES sleeve gastrectomy has been reported in 48 patients, invariably using a hybrid technique although the number of laparoscopic ports and assistance does vary between the studies.

The majority are single case reports performed using the transvaginal approach. Once again the Zorron and Lehmann papers represent the highest level of evidence[3,4]. However, other than using a transvaginal, hybrid approach with a rigid endoscope in the Lehmann cases there is very little additional operative detail described in either paper. In these case-controlled, national/international, multicentre studies short term morbidity was 0% compared with 12.1% quoted in the large series in the literature for the gold standard laparoscopic sleeve gastrectomy[25,26].

Chouillard *et al*[27] in 2010 reports the highest number of NOTES sleeve gastrectomies in the literature. They describe 20 cases using one or two abdominal ports. The mean operative time was 116 min. The only morbidity was one patient with pneumonia and there were no reported leaks. However, 30% were converted to more formal laparoscopic sleeve gastrectomy, most of these were in the first batch of patients suggesting a learning curve to the procedure, although no cases were converted to open.

Ramos *et al*[28] also describe 4 cases of hybrid transvaginal NOTES sleeve gastrectomy by using 3 abdominal trocars (umbilical/right upper quadrant/left upper quadrant). They report no post-operative complications and an operative time of 95 min.

At the time of writing there were no further registered trials, specifically assessing NOTES sleeve gastrectomy. Pure NOTES sleeve gastrectomy has not been described in the literature.

PERITONEOSCOPY

This has been attempted through a more varied route with transvaginal, transvesical and transgastric routes in a total of 208 cases. The indication for peritoneoscopy is wide-ranging from diagnostic in cancer patients to gastric bypass to visceral biopsy.

Transgastric peritoneoscopy

There are 198 cases of NOTES transgastric peritoneoscopy reported in the literature. Once again the Zorron and Lehmann papers represent the highest level of evidence, with no reported complications[3,4]. In comparison, Camacho *et al*[29] assessed 115 patients for pancreatic cancer staging *via* laparoscopy and then laparotomy to confirm stage/findings, reporting no complications in any of the laparoscopies.

The largest is the study by Nau *et al*[30] which included 130 patients assessed through 3 different arms. They retrospectively evaluated the bacterial load in the peritoneal cavity before and after open gastrotomy, open endoscopic gastrotomy and pure NOTES gastrotomy. They found there was no significant increase in clinical manifestations of peritoneal infection.

Other than Memark *et al*[31] who reported 40 cases of hybrid transgastric peritneoscopy, with no abscesses or anastomotic leaks but one port-site infection, the other trials involving NOTES peritoneoscopy are small ranging from 1-10 patients. Interestingly, Nikfarjam *et al*[32] report that in only one of their prospective series of 9 patients was NOTES peritoneoscopy satisfactory, with difficulty viewing the left upper quadrant. The single case where peritoneoscopy was satisfactory was achieved with entry through the greater curve.

Hazey *et al*[33] in 2008 compared transgastric NOTES peritoneoscopy to laparoscopic peritoneoscopy for pancreatic masses. They assessed differences in operative findings, operative times and clinical course in 10 patients. Laparoscopy was faster (12.3 min *vs* 24.8 min) than NOTES and in 9 out of 10 patients the decision to proceed with laparotomy was confirmed by NOTES as with laparoscopy.

Transvaginal peritoneoscopy

There are 9 reported cases of transvaginal peritoneoscopy, including one case report and a small series of 8 by Zorron *et al*[3,34]. The series does not describe operative details, other than an operative time of 35 min and report no complications.

Pure NOTES peritoneoscopy has been described by Zorron *et al*[34] who report 1 transvaginal case and Zheng *et al*[35] who report 5 transgastric cases. Neither author report any complication from their method of peritoneoscopy and operative time was reported at 105 min[34].

Transvesical peritoneoscopy

There is one reported case in the literature by Gettman and Blute in 2007[36]. They present a case report of a 56 year old gentleman who underwent robotic prostatectomy for cancer. The case proceeded in the usual fashion with the abdominal laparoscopic ports inserted. Under laparoscopic guidance a portal was created in the bladder and a flexible ureteroscope was used to view all intraperitoneal structures. The patient went on to have a successful prostatectomy, the cystotomy was closed with vicryl and the patient suffered no complications.

At the time of writing there were two small registered trials, specifically assessing NOTES peritoneoscopy. One is a 10 participant trial by ethicon and the second is from Ohio State University comparing laparoscopy to

NOTES peritoneoscopy in 40 patients[14].

SIGMOIDECTOMY/RECTAL EXCISION/ HEMICOLECTOMY

Transvaginal sigmoidectomy

There are 27 cases of transvaginal sigmoidectomy reported in the literature with the highest level of evidence being the studies by Zorron *et al* and Lehmann *et al*[3,4] which represents level 3. In these studies short term morbidity was 0%-10% compared to the 11.5% quoted in large series in the literature for the gold standard sigmoidectomy[37].

There are two papers to highlight here, one case report of a single patient undergoing a sigmoidectomy and the large Lehmann trial. The single case report is by Lacy *et al*[38] who report a hybrid NOTES sigmoidectomy in a 78 year old female for sigmoid adenocarcinoma. While performing the dissection and stapling of the inferior mesenteric vessels and upper rectum endoscopically the colonic resection was performed extracorporeally with an intra-abdominal endoscopically assisted stapled anastomosis. The outcome was a successful resection, no complications and discharge on the fourth post-operative day.

The German Registry paper reports 3 cases of hybrid NOTES sigmoidectomy for diverticulitis and 11 cases of colonic resection for which there is no indication and we have very little published detail on the operative technique. They do however, report no complications in any of their cases[4]. Moreover, Zorron *et al*[3] present 12 cases of rectosigmoidectomy, once again with no operative details and just one case complicated by a urinary tract infection.

More recently Leroy *et al*[39] in 2011 has reported a hybrid sigmoidectomy with transanal extraction of the specimen. They took 105 min to perform the procedure and report no complications. There are other reports of similar work, where the majority of the procedure is performed laparoscopically and the natural orifice is used simply for extraction of the specimen. This may be classed as natural orifice specimen extraction rather than NOTES[40].

Rectal excision

The first reported human case of a hybrid NOTES rectal cancer (CA) transanal excision was by Sylla *et al*[41]. They used TEM and laparoscopic assistance to resect a rectal CA. Operative time was under five hours, the tumour was resected with negative margins and an intact mesorectum. The patient was discharged on the fifth post-operative day with no complications recorded.

Tarantino *et al*[42] present 40 patients who underwent a transvaginal hybrid NOTES anterior resection for diverticulitis. They report 4 conversions to minilaparotomy and 2 conversions to laparotomy, with 5% major morbidity and 25% minor morbidity. However the operative procedure was performed almost entirely laparoscopically, with the transvaginal access to allow extraction and resection of the distal segment.

Zorron[43] in 2011 report 5 cases of transcolonic endoscopic NOTES TME with laparoscopic assistance. They performed the mesorectal dissection in a down to up fashion, the opposite to the laparoscopic technique. Their operative time was 350-360 min, one conversion and one complication of bilateral foot parasthesia which resolved spontaneously after 10 d.

Other NOTES colorectal resections include a right hemicolectomy by Burghardt who performed a laparoscopic procedure with transvaginal extraction of the specimen with no intra/post-operative complications[44]. There are no reported cases of pure NOTES colonic resections. There is 1 registered trial for NOTES rectosigmoidectomy from the University of Leuven, Belgium[14]. This trial represents a randomized controlled trial comparing laparoscopic rectosigmoid resection with a hybrid NOTES procedure with laparoscopic assistance but specimen removal through the colon rather than extending the umbilical incision for retrieval.

NEPHRECTOMY

Transvaginal nephrectomy

Zorron *et al*[3] report 4 transvaginal NOTES nephrectomies in their group but fail to give any further operative details, other than an operative time of 170 min. However, they did report a complication in one of their nephrectomies, of subcutaneous and mediastinal surgical emphysema which was managed conservatively.

Kaouk *et al*[45] 2009 present the first NOTES transvaginal nephrectomy. This was performed in a 57 year old woman for an atrophic right kidney. Although all of the dissection and resection of the procedure was performed in a pure NOTES fashion the authors used an umbilical port for direct vision when placing the vaginal port, necessitated by dense adhesions from a previous hysterectomy and for retraction of the colon. The procedure took 307 min, there were no complications and the patient was discharged within 24 h. Of note the visual analogue pain score during the admission was 5.6 and on day two post-operatively was 1 out of 10.

To date there are no reported pure NOTES or transgastric NOTES nephrectomies. In addition there are no registered trials specifically assessing NOTES nephrectomy.

LIVER BIOPSY/RESECTION

Transvaginal/gastric liver biopsy or resection

Lehmann *et al*[4] report 5 cases of liver resection with minimal detail but no reported complications. Noguera *et al*[46] in 2008 report a NOTES transvaginal liver resection including cholecystectomy. They used two abdominal ports for retraction and laparoscopic assistance. They removed the specimen transvaginally, operative time was 110 minutes and they reported no complications, with a short hospital stay (48 h).

Steele *et al*[47] performed a hybrid transgastric peri-

toneoscopy and liver biopsy at the time of performing laparoscopic gastric bypass surgery. They achieved an adequate biopsy and good visualisation.

There are 3 reported cases of pure NOTES liver biopsies by Rao *et al*[22]. They performed pure NOTES transgastric peritoneoscopy and liver biopsy. The peritoneoscopy was performed using retro-flexion of the endoscope, aided by patient positioning on the table to move the bowel out of sight as necessary. The biopsy was performed using jumbo biopsy forceps and haemostasis was achieved using hot biopsy forceps. Endoscopic clips were used to close the gastrotomy. The authors report that the gastrotomy spontaneously closes once the balloon is removed and it becomes difficult to locate the defect.

To date there are no new registered trials which are specifically assessing NOTES liver biopsies or liver resections.

SPLENECTOMY

Transvaginal Splenectomy

Targarona *et al*[48] in 2009 is the only author to date to publish NOTES splenectomies. They report two transvaginal, hybrid NOTES splenectomies, using three laparoscopic ports. Mobilisation of the spleen was performed transabdominally, the pedicle was stapled transvaginally with laparoscopic guidance and the specimen extracted through the vagina. Operative time was 180 min and there were no reported intra or post-operative complications.

To date there are no pure NOTES splenectomies reported and no new registered trials which are specifically assessing NOTES splenectomies.

DISCUSSION

This review represents an up to date summary of human NOTES procedures reported in the literature. It is not inclusive of all human NOTES procedures, but does include those trials demonstrating the highest level of evidence for each application. Evidence of surgical outcome and morbidity for all organs targeted by NOTES has been evaluated.

Overall, considering the volume of procedures performed, the multitude of techniques used, the variety of centres/countries performing NOTES and even different specialties performing the procedures the morbidity and mortality appears acceptable, often comparing favourably to the gold standard techniques. The most commonly performed application is transvaginal cholecystectomy with acceptable reported outcomes and complications reported through trials producing level 3 evidence.

There are however some reports of high morbidity for certain applications, almost exclusively related to the transgastric approach. The large number of cases performed in the multicentre studies has enabled us to broadly compare the transvaginal and transgastric techniques[3,4]. The main issue relating to transgastric (and transcolonic) NOTES is closure of the enterotomy. Although several methods have been proposed, to date there is no robust evidence for a reliable method of closure of the gastrotomy[49].

As a product of the concern over the associated morbidity and safety of transgastric NOTES the majority of human NOTES cases have been performed in females via the transvaginal route which has a proven safety profile[1]. This raises the issue of acceptability to the general public, which is an area which has not been extensively explored. Strickland *et al*[50] surveyed 300 women asking their views on NOTES. Interestingly, they report that three quarters of the women they questioned were either neutral or unhappy about the prospect of NOTES. Most of the concern was in relation to sexual function post transvaginal surgery and only a minority were concerned about the cosmetic effect of conventional laparoscopic surgery. Although the sample size was small in this study and just one un-validated questionnaire was used, it does raise some important questions. If the procedures are deemed unacceptable to the general public then should we pursue the advancement of this technique with such vigour?

The true benefits of NOTES, such as improved cosmesis, reduced hospital stay as a proxy marker of recovery, reduced incidence of hernia and post-operative pain may not be well demonstrated until it is practised in a pure fashion. Even then, due to the low morbidity and complications associated with the laparoscopic approach for many procedures, randomized controlled trials of very large numbers may be required to prove any difference between the techniques.

What is certain is that available technology is limiting the current applicability of NOTES and whilst we wait for a better toolbox hybrid procedures will be necessary to ensure patient safety. It may be that hybrid NOTES procedures are the optimal for certain applications and patient groups. Ultimately NOTES is likely to complement laparoscopy for specific patient groups and procedures and as technology evolves specific NOTES procedures will enter mainstream clinical practice. As a result of this we have not yet identified a "target" procedure from which maximum patient benefit can be demonstrated using the NOTES technique. Bariatric surgery seems promising for NOTES approaches and the next few years are not only crucial in the development of NOTES as a concept but have the potential to revolutionise minimally invasive surgery with the rapid potential for technological innovation and further fusion of the boundaries between laparoscopy and endoscopy.

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