International Multicenter Trial on Clinical Natural Orifice Surgery—NOTES IMTN Study: Preliminary Results of 362 Patients


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What is This?
International Multicenter Trial on Clinical Natural Orifice Surgery—NOTES IMTN Study: Preliminary Results of 362 Patients

Ricardo Zorron, MD, PhD,1 Chinnusamy Palanivelu, MD,2 Manoel Passos Galvão Neto, MD,3 Almino Ramos, MD,3 Gustavo Salinas, MD,4 Jens Burghardt, MD,5 Luis DeCarli, MD,6 Luiz Henrique Sousa, MD,7 Antonello Forgione, MD,8,18 Raffaele Pugliese, MD, PhD,8,18 Alcides J Branco, MD,9 T. S. Balashanmugan, MD,10 Camilo Boza, MD,11 Francesco Corcione, MD,12 Fausto D’Ávila Avila, MD,13 Néstor Arturo Gómez, MD,14 Paulo Ayrosa Galvão Ribeiro, MD,3 Susana Martins, MD,15 Marcos Filgueiras, MD,1 Klaus Gellert, MD,5 Aníbal Wood Branco, MD,9 William Kondo, MD,9 Jose Inacio Sanseverino, MD,6 José Américo G. de Sousa, MD,7 Lil Saavedra, MD,4 Edwin Ramírez, MD,4 Josemberg Campos, MD,16 K. Sivakumar, MD,10 Pidigu Seshiyer Rajan, MD,2 Priyadarshan Anand Jategaonkar, MD,2 Muthukumaran Ranagran, MD,2 Ramakrishnan Parthasarathi, MD,2 Palanisamy Senthilnathan, MD,2 Mohan Prasad, MD,2 Diego Cuccurullo, MD,17 and Verena Müller, MD5

Abstract

Objectives: Natural orifice transluminal endoscopic surgery (NOTES) is evolving as a promising alternative for abdominal surgery. IMTN Registry was designed to prospectively document early results of natural orifice surgery among a large group of clinical cases. Methods: Sixteen centers from 9 countries were approved to participate in the study, based on study protocol requirements and local institutional review board approval. Transgastric and transvaginal endoscopic natural orifice surgery was clinically applied in 362 patients. Intraoperative and postoperative parameters were prospectively documented. Results: Mean operative time for transvaginal cholecystectomy was 96 minutes, compared with 111 minute for transgastric cholecystectomy. A general complication rate of 8.84% was recorded (grade I-II representing 5.8%, grade III-IV representing 3.04%). No requirement for any analgesia was found in one fourth of cholecystectomy and appendectomy patients. Conclusions: Results of clinical applications of NOTES in the IMTN Study showed the feasibility of different methods of this new minimally invasive alternative for laparoscopic and open surgery.

Keywords

natural orifice surgery, NOTES, laparoscopy, minimally invasive surgery, natural orifice transluminal endoscopic surgery, prospective study, multicenter study, cholecystectomy, appendectomy

Introduction

Natural orifice transluminal endoscopic surgery (NOTES) is an evolving concept of combination of techniques of minimally invasive surgery with flexible endoscopy, potentially representing a major paradigm shift to scarless surgery. With the aim of avoiding incision-related complications, researchers have made efforts to create even less invasive access by means of transluminal surgery. In the pioneering descriptions on endoscopic transgastric (TG) surgery,
Kalloo, Kantsevoy, and coworkers showed the possibilities of transpassing the gastric wall and operating in an animal model using a perorally introduced flexible endoscope via a sterile overtube in the abdominal cavity.\textsuperscript{1,2} Other researchers described TG cholecystectomy, tubal ligation, oophorectomy, gastroenterostomy, and splenectomy in animal experiments.\textsuperscript{3,4} Human TG appendectomy was also clinically presented in meetings by Rao and Reddy using available endoscopic instruments since 2005.\textsuperscript{7,8} Transvaginal (TV) NOTES provides easy access, direct vision closure, availability of instruments, and a well-known access with reasonable disinfection possibility. In fact, world experience in human, restricted to ethically approved studies, is growing, particularly in the field of TV and TG access.\textsuperscript{9,10}

Although human casuistic of natural orifice surgery is becoming more widely used, isolated studies have still small numbers of patients worldwide, and the design of larger series and comparative studies to evaluate early results and indications of natural orifice surgery techniques is desirable. IMTN Study (International Prospective Multicenter Trial on Clinical NOTES) is designed as a multi-institutional prospective documentation registry started in Brazilian centers in July 2007, and accepting international data since then, aiming to provide information regarding early post-operative results and complications of natural orifice surgery worldwide. Preliminary prospective data collected from 362 patients for TV and TG NOTES are described.

**Methods**

Brazilian and international natural orifice surgery cases were registered in a prospective database. Inclusion criteria for accepting the authorized centers were the following: (a) must prove work as a multidisciplinary team including gastroenterology/endoscopy specialist, (b) must have previous animal research with veterinary facility, (c) flexible endoscopic experience, and (d) local institutional review board approval for human trials in the pretended field of natural orifice surgery. IMTN Registry started accepting NOTES cases from Brazilian centers since July 2007, and since then several international centers were invited and joined the prospective documentation of TV, TG, and transcolonic cases. Latin American research centers joined the IMTN Study in 2007, and other international centers, such as India, Italy, and Germany, were also accepted in the study in 2008. The main reason for not including prospective results from other countries that also actively initiated human NOTES experience is that these centers were reporting their results in their own prospective registry (eg, NOSCAR). The database accepted statements of individually approved human trials and signed informed consent by the institutional ethical committees in each center for natural orifice surgery clinical trials and by personal statement from each study local coordinator; all methods were in accordance with the Helsinki Declaration, revision 1989. The IMTN Clinical Trial database is registered under the Protocol ID 0209.0.314.000-08, ClinicalTrials.gov ID NCT00995735 in a free, publicly accessible, nonprofit electronically searchable database administered by the National Library of Medicine (located at http://www.clinicaltrials.gov).

International centers and responsible coordinators participating in the IMTN Study are listed in Table 1. All participants included their prospective results of new cases every 3 months by electronic input, and late results were

1\textsuperscript{1}University Hospital Teresopolis HCTCO-FESO, Rio de Janeiro, Brazil
2\textsuperscript{2}GEM Hospital and Postgraduate Institute, Coimbatore, India
3\textsuperscript{3}Hospital Santa Rita, São Paulo, Brazil
4\textsuperscript{4}Clínica de Día Avendaño, Lima, Peru
5\textsuperscript{5}Sana Clinical Center Berlin, Berlin, Germany
6\textsuperscript{6}Hospital Irmañade Santa Casa da Misericórdia, Porto Alegre, Brazil
7\textsuperscript{7}SOUSAGROUP Hospital Femina, Goiania, Brazil
8\textsuperscript{8}Niguarda Ca’ Granda Hospital, Milan, Italy
9\textsuperscript{9}Cruz Vermelha Hospital Curitiba, Parana, Brazil
10\textsuperscript{10}PSG Hospital, Coimbatore, India
11\textsuperscript{11}Pontificia Universidad Católica del Chile, Santiago, Chile
12\textsuperscript{12}Hospital UOC General and Laparoscopic Surgery, Naples, Italy
13\textsuperscript{13}Hospital Poza Rica, Poza Rica, Mexico
14\textsuperscript{14}Universidad de Guayaquil, Guayaquil, Ecuador
15\textsuperscript{15}Foster City, CA, USA
16\textsuperscript{16}University Recife, Recife, Brazil
17\textsuperscript{17}NOC Chirurgia Generale e Laparoscopica, Naples, Italy
18\textsuperscript{18}AIMS – Advanced International Mini-invasive Surgery Academy, Milan, Italy

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included before the completion of the statistics. Thirty-day results were the main goal for the study, which included all early postoperative complications. Many participants also sent single-port surgery experiences, but these cases were not computed in the study. Study protocol criteria of inclusion were patients with low ASA risk (I-II), who could

<table>
<thead>
<tr>
<th>Participating Center/Department</th>
<th>Country</th>
<th>Responsible Local Coordinators</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Department of Surgery, University Hospital Teresopolis HCTCO-FSEO, Rio de Janeiro</td>
<td>Brazil</td>
<td>Coordinator: Ricardo Zorron</td>
</tr>
<tr>
<td>2. Department of Surgery, Hospital Irmandade Santa Casa da Misericordia Porto Alegre</td>
<td>Brazil</td>
<td>Coordinator: Luiz DeCarli</td>
</tr>
<tr>
<td>3. Department of Surgery, Cruz Vermelha Hospital Curitiba, Parana</td>
<td>Brazil</td>
<td>Coordinator: Alcides J. Branco</td>
</tr>
<tr>
<td>4. Department of Surgery, Gastrobeso Center, Hospital Santa Rita, São Paulo</td>
<td>Brazil</td>
<td>Coordinator: Manuel Galvao</td>
</tr>
<tr>
<td>5. Department of Surgery and Endoscopy, SOUZAGROUP Hospital Femina, Goiania</td>
<td>Brazil</td>
<td>Coordinator: Luiz Henrique de Sousa</td>
</tr>
<tr>
<td>6. Department of Surgery, Universidade de Recife</td>
<td>Brazil</td>
<td>Coordinator: Josemberg Campos</td>
</tr>
<tr>
<td>7. Clinica de Dia Avendaño, Lima</td>
<td>Peru</td>
<td>Coordinator: Gustavo Salinas</td>
</tr>
<tr>
<td>8. Department of Surgery, PSG Hospital, Coimbatore</td>
<td>India</td>
<td>Coordinator: T. S. Balashanmugan</td>
</tr>
<tr>
<td>9. Department of Surgery, GEM Hospital and Postgraduate Institute, Coimbatore</td>
<td>India</td>
<td>Coordinator: Chinnusamy Palanivelu</td>
</tr>
<tr>
<td>10. Department of General and Emergency Surgery, Niguarda Ca’ Granda Hospital, Milan, Italy and AIMS – Advanced International Mini-invasive Surgery Academy, Milan, Italy</td>
<td>Italy</td>
<td>Coordinator: Antonello Forgione</td>
</tr>
<tr>
<td>11. Department of Surgery, HOSPITAL UOC General and Laparoscopic Surgery, AO Monaldi, Naples</td>
<td>Italy</td>
<td>Coordinator: Francesco Corcione</td>
</tr>
<tr>
<td>12. Department of General Surgery, Sana Clinical Center Berlin (Evangelisch-Freikirchliches Krankenhaus Rüdersdorf, Berlin)</td>
<td>Germany</td>
<td>Coordinator: Jens Burghardt</td>
</tr>
<tr>
<td>13. Department of Surgery, Hospital Poza Rica</td>
<td>Mexico</td>
<td>Coordinator: Fausto D’Ávila Ávila</td>
</tr>
<tr>
<td>14. Hospital “Kennedy,” Policirocro, Facultad de Medicina, Universidad de Guayaquil</td>
<td>Ecuador</td>
<td>Coordinator: Néstor Arturo Gómez</td>
</tr>
<tr>
<td>15. Department of Surgery, Pontificia Universidad Católica del Chile</td>
<td>Chile</td>
<td>Coordinator: Camilo Boza</td>
</tr>
<tr>
<td>16. Hospital Universitario Abel Santamaria Cuadrado, Pinar del Rio</td>
<td>Cuba</td>
<td>Coordinator: Raul Castro Perez</td>
</tr>
</tbody>
</table>
choose natural orifice procedure instead of laparoscopy. Inclusion criteria of the patients in most centers were based on mild preoperative symptoms and short duration of disease. Patients with previous history of hysterectomy were avoided because of possibility of failure of TV access. Patients with previous abdominal surgery were commonly avoided, but some centers accepted a high rate of abdominal operations, not considering previous operations as contra-indication for NOTES. The research groups consisted of multidisciplinary teams of surgeons, gastroenterologists, endoscopists, gynecologists, and veterinary surgeons for the experimental background. Flexible endoscopes were previously submitted to sterilization by ethylene oxide, and in some centers, high-level disinfection was obtained by immersion in glutaraldehyde 2% or peracetic acid 3% solution. A veterinary hospital facility was available, and natural orifice surgery technical possibilities were tested by the study groups in each international participant. At the beginning of recruitment for the study, 2 centers were not approved to join IMTN Study based on absence of 1 or more preconditions.

Intraoperative and postoperative data were prospectively documented until the 30th-day postoperative follow-up. Long-term postoperative data are also collected for future evaluation. Postoperative complications were prospectively recorded based on scores grading initially proposed by Clavien et al in 1992 and modified by Dindo et al in 2004. Mild discomfort, pain, and other postoperative symptoms were recorded as side effects. Conversion from NOTES to laparoscopic surgery was defined as unplanned installation of trocars and use of laparoscopic optic and dissection. Conversion to open surgery was defined of unplanned abdominal incision to perform the operation or specimen extraction. Hybrid NOTES technique was defined as use of 1 or more laparoscopic trocars for assistance, because main dissection and visualization was performed by natural orifice access.

**Surgical Technique**

**Transvaginal Surgery**

Patients were submitted to general anesthesia and installed in a Lloyd–Davies position. Disinfection of the vagina was achieved by topical iodopovidone or chlorhexidine solution, and urinary catheter was installed. Most of the participating centers recommended antibiotic prophylaxis. Usually, a single dose of intravenous bolus of either 2 g cefalexin or a combination of 400 mg metronidazol and 400 mg ciprofloxacin were given at the induction of anesthesia. Some specialists used previous abdominal insufflation with CO₂ performed after introduction of a Veress needle in the left subcostal abdomen or in the umbilicus, to allow a safe entry into the abdominal cavity through the vagina. Other groups in the study achieved good results by accessing directly the cavity through a direct view vaginal access. Incision of vaginal posterior sac was done after traction of the cervix with a conventional instrument. The operator was positioned between the legs of the patient, and the first assistant behind and holding the controls of the endoscope. A second assistant took position on the left side of the patient if laparoscopic assistance was used. Insufflation of the cavity with CO₂ was maintained by most groups using a laparoscopist to provide control of the pressure, either by TV trocar or through a Veress needle. After insufflation, the orientation of the endoscope in the cavity was possible by initial localization of the abdominal wall and abdominal organs using a reverse Trendelenburg position.

**Transvaginal Access and Closure—Method 1: Direct Vision Open Access**

Opening of the posterior vaginal sac was done under direct vision with conventional instruments and facilitated access to the peritoneal cavity. A Sims speculum was inserted in the vagina, and the posterior lip of the cervix was grasped by a Pozzi clamp. The vaginal walls were retracted by 2 lateral retractors, and anterior traction was given to the cervix to stretch the posterior fornix. The vaginal mucosa in the posterior cul-de-sac was opened at the cervico-vaginal junction by a semilunar 2.5-cm incision. The posterior margin was grasped by an Allis forceps, and sharp dissection was performed with scissors. The posterior cul-de-sac peritoneum was identified and opened. CO₂ was insufflated through the smallest working channel of the endoscope using a laparoscopic insufflator. Vaginal wound was closed using absorbable running suture under direct vision.

**Transvaginal Access and Closure—Method 2: Laparoscopic Camera Assistance**

The surgeon was placed standing between the patient’s legs; the first and second assistants stand on the left and right sides of the patient, respectively. In this setting, 2 visualization systems, one for the abdominal laparoscopic camera and the other for the TV flexible endoscope, were used. The procedure started with a Veress puncture through an incision in the umbilicus to avoid a visible scar. Pneumoperitoneum was then induced through the Veress needle. A 5-mm trocar is inserted, and a 5-mm laparoscopic optic used to inspect the abdominal cavity. To avoid the risk of injuring pelvic organs, the team performed a thorough examination of the pelvis, looking for adhesions that might prohibit the TV cul-de-sac puncture. In patients who had
had a previous hysterectomy, or unknown endometriosis, adhesions obliterating the pouch of Douglas contraindicated the further vaginal insertion of the trocar and conversion to formal laparoscopy was usually indicated. After inventory, a longer 10- to 12-mm laparoscopic trocar was inserted in the vaginal posterior cul-de-sac under laparoscopic guidance. The endoscope was progressed after extraction of the laparoscopic trocar. Vaginal wound closure was performed in the same way as described previously, and the diameter of the wound was smaller (1-1.5 cm) than the direct vaginal access (2-3 cm).

Transvaginal Cholecystectomy

Four distinct techniques for NOTES TV cholecystectomy were described by the different centers, regarding pure natural orifice surgery or combined hybrid techniques to allow efficiency and safety for the procedures.

Method 1: Totally NOTES dual scope method. After posterior colpotomy using direct view and conventional instruments, safe open access to the peritoneal cavity was obtained. The ideal final incision diameter was 2.5 cm for the introduction of 2 endoscopes (Figure 1A). The first endoscope (single-channel gastroscope) with the insufflation tube attached was inserted in the orifice created. After pneumoperitoneum with CO₂ was achieved, the second endoscope (double-channel colonoscope) was inserted through the same orifice. Abdominal pressure was maintained between 9 and 10 mm Hg of CO₂ and controlled by a laparoscopic insufflator. There was no use of laparoscopic camera or instruments in any case. The endoscope for retraction and insufflation was situated on the right, and an endoscopic strange body extraction grasper was used to keep the gallbladder retracted under tension, providing triangulation of instruments.

After retraction with the first endoscope, the second operating/visualization 2-channel endoscope was positioned about 4 to 5 cm close to the retracted gallbladder with orientation of the first endoscope. After orientation and after the endoscope passed the pelvic organs, the position of the patient was changed to a reverse Trendelenburg position, allowing visualization of the upper abdomen. Dissection of Calot’s Triangle was performed using endoscopic instruments such as hot-biopsy forceps, polypectomy snare, and endoscopic hook. Cystic duct and artery were dissected and clipped using endoscopic clips, 2 proximal and 1 distal. After transection of the duct and artery with endoscopic scissors, the gallbladder was dissected from the liver bed using polypectomy snare, the instrument also used for vaginal extraction of the specimen. After delivery of the gallbladder, pneumoperitoneum was aspirated before the exit of the second endoscope.

Method 2: Transvaginal multipurpose port with flexible surgery (Figure 1B). In one group, main vaginal access and dissection was obtained by a TV port (local adapted trocar) that permitted independent entry of the flexible endoscope (double-channel colonoscope), insufflation channel from a laparoflator, and semiflexible instruments used for retraction, cutting, and clipping using TV laparoscopic titanium clips. Dissection was accomplished by flexible endoscopic instruments available such as as polypectomy snares and hot-biopsy forceps. After TV extraction of the specimen and port, pneumoperitoneum was aspirated transvaginally, and closure was performed using absorbable sutures.

Method 3: Hybrid NOTES with transvaginal and abdominal laparoscopy. Laparoscopy was used in this technique for purposes such as safe access, visualization, and dissection, usually accomplished by endoscopic instruments or laparoscopy (Figure 1C). Avoiding maximally the difficult endoscopic dissection and instrumentation, this method allowed for faster operations in a similar laparoscopic critical view.

Method 4: Transvaginal trocars (flexible or rigid optic) combined with umbilical minilaparoscopy. Pneumoperitoneum was achieved by umbilical Veress needle puncture, and abdominal pressure was maintained between 8 and 15 mm Hg of CO₂ and controlled by a laparoscopic insufflator. After insufflation, opening of the posterior vaginal cul-de-sac was performed by direct vision and dissection through vaginal speculum and use of monopolar incision and long scissors.

After colpotomy, a 1- or 2-channel gastroscope was introduced in the abdominal cavity. After orientation and after endoscope passed the pelvic organs, the position of the patient was changed to a reverse Trendelenburg, allowing visualization of the upper abdomen. By retroflexed view, a specially designed long trocar (10 mm) was placed in the vagina, parallel to the endoscope. Two 3-mm trocars were placed intra-umbilically under direct endoscopic vision (Figure 1D). Dissection of Calot’s Triangle was performed using endoscopic instruments such as hot-biopsy forceps, polypectomy snares, endoscopic hook, and the umbilical 3-mm instruments. Cystic duct and artery were dissected and clipped using long laparoscopic clipator through the vaginal trocar. After transection of the duct and artery, the gallbladder was dissected from the liver bed using endoscopic hook or polypectomy snare. Extraction of the specimen was achieved by long laparoscopic graspers inserted in the vaginal trocar.

Transvaginal Appendectomy

NOTES appendectomies through vaginal access were performed using direct access to the cavity with or without umbilical laparoscopic assistance. Usually the appendix could be managed without endoscopic retroflection, or using
vaginal rigid camera. Although a simple solution would be performing the dissection through umbilical trocar, most teams used endoscopic dissection with hot-biopsy forceps and polypectomy snare. In case of need for peritoneal lavage due to pus, TV endoscopic aspiration was performed or a laparoscopic irrigator aspirator was used.
Transgastric Surgery

The patient was submitted to general anesthesia and installed in a Lloyd–Davies position. Disinfection of the gastric lumen was achieved by intraoperative washing with chlorhexidine solution, but some centers used no special cleaning besides aspiration. Use of esophageal overtubes usually protected against esophageal trauma due to instrumentation, but they were not widely used. As laparoscopic gastric suture was the method of choice to close the gastric wound after the procedure, insertion of an umbilical laparoscopic optic was the first step of the operations, allowing safe translumenal entrance of the endoscope in the abdominal cavity. Specimens were extracted without special bags, and when the specimen diameter exceeded the diameter of the esophagus, open conversion by umbilical opening and extraction was the solution. Usually 3 trocars were used to close the gastric wound, but in 2 centers, one trocar was used for a 3-mm camera and another 5-mm trocar was used to perform the sutures using external knotting. Endoscopic closure was used early by some of the groups using endoscopic clips for gastric closure in TG cases, but this early casuistic was not included by the study, as it started with prospective registry later. Other TG closure methods and technology were not available for use by any of the contributing centers.

Transgastric cholecystectomies were performed using either endoscopic dissection or by laparoscopic dissection. One 3-mm umbilical trocar was placed at the umbilicus for guiding the endoscope’s safe transgastric exit under vision and, later, for retracting the fundus. At the end of the procedure, one more 3-mm trocar was inserted in the right pararectus region. Two centers reported the use of 2 and 3 trocars. The gastrotomy wound was sutured “single handedly” by inserting a needle holder through this trocar and a 3-mm laparoscope through the umbilical trocar. This closure was also monitored by the endoscope, which was withdrawn and kept in the gastric lumen while the bytes were taken. The use of an additional trocar in the right pararectus region allowed the achievement of a secured gastrotomy closure.

Transgastric appendectomies were performed using initially a 3- or 5-mm umbilical trocar in the beginning of the surgery for guiding the operating endoscope’s TG exit into the peritoneal cavity under vision. The same trocar was later used for retracting the appendix. All the steps were usually performed without using any other extra trocars till the extraction of the specimen. At that juncture, a 5-mm right pararectal trocar was inserted for securely closing the gastrotomy wound by deploying extracorporeal knots.

Special Methods

Transvaginal cases for cancer staging were less complex procedures, usually using only the endoscope without laparoscopic assistance and performing retraction and biopsies using endoscopic hot-biopsy forceps through the working channels. TV nephrectomy, TV sleeve gastrectomy, and more complex cases were performed with significant laparoscopic dissection because of lack of advanced endoscopic technology, such as long and flexible stapler devices and graspers.

International centers reported new cases performed every 3 months, and the prospective database was maintained in the leading center by the main author responsible (RZ). Operative and postoperative data including operative time, blood loss, intraoperative complications, intra-abdominal pressures, end-tidal (expiratory) CO₂, reasons for conversion to laparoscopic or open surgery, length of postoperative hospital stay, morbidity, 30-day morbidity and mortality, general data, and reason for reoperation were also collected. Statistical differences in categorical variables were analyzed by the χ² test, and differences in continuous variables were analyzed by Student’s t test.

Results

A total of 362 patients were prospectively documented until June 30, 2009. Indications for NOTES surgery and the method of access were different between the centers, with the majority performing TV access, and only 4 centers reporting TG procedures also (see Table 2). TV NOTES cholecystectomy was the main indication in the study (240 cases), followed by TV appendectomy (37), TG cholecystectomy (29), TV colectomy (13), TV sleeve gastrectomy (5), TV cancer staging (8), TG appendectomy (14), TV nephrectomy (4), TV hepatic cyst extraction (1), and TV gynecologic surgery (11). Overall, the complication rate

<table>
<thead>
<tr>
<th>Type of Procedure</th>
<th>n</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>TV cholecystectomy</td>
<td>240</td>
<td>66.3</td>
</tr>
<tr>
<td>TV appendectomy</td>
<td>37</td>
<td>10.2</td>
</tr>
<tr>
<td>TG cholecystectomy</td>
<td>29</td>
<td>8.01</td>
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<tr>
<td>TG appendectomy</td>
<td>14</td>
<td>3.87</td>
</tr>
<tr>
<td>TV rectosigmoidectomy</td>
<td>12</td>
<td>3.31</td>
</tr>
<tr>
<td>TV gynecologic surgery</td>
<td>11</td>
<td>3.03</td>
</tr>
<tr>
<td>TV cancer staging</td>
<td>8</td>
<td>2.2</td>
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<tr>
<td>TV sleeve gastrectomy</td>
<td>5</td>
<td>1.38</td>
</tr>
<tr>
<td>TV nephrectomy</td>
<td>4</td>
<td>1.10</td>
</tr>
<tr>
<td>TV right colectomy</td>
<td>1</td>
<td>0.28</td>
</tr>
<tr>
<td>TV hepatic cyst</td>
<td>1</td>
<td>0.28</td>
</tr>
<tr>
<td>Total</td>
<td>362</td>
<td>100</td>
</tr>
</tbody>
</table>

Note: NOTES= natural orifice translumenal endoscopic surgery; TV= transvaginal; TG, transgastric.
was 8.84%, distributed between 6.9% for TV surgery and 23.26% for TG surgery. Mean intra-abdominal CO₂ pressure did not show significant differences between the types of access and surgeries performed. Mean postoperative stay was 46 hours for TV cholecystectomy and 37.7 hours for TG cholecystectomy, and many centers adopted minimum postoperative stay of 3 days because of local study protocol. There were no postoperative deaths reported from the involved centers.

Operative Time

Operative time for NOTES cholecystectomy did not have significant differences between TV access (96.1 minutes) and TG access (110.93 minutes; see Table 3). In comparison to TV appendectomy, TG appendectomy had significant longer operative times (60.5 vs 135.5 minutes; Table 4). Gastric opening and closure were challenging, and also retroflexion generated most difficulty in achieve orientation and restricted dissection possibilities. In one TG cholecystectomy case, the retrieval specimen was too voluminous (and contained a 2.4-cm gallstone) and got aprisionated in the oropharynx for approximately 150 minutes, until it was guided again to the stomach and extracted through an umbilical incision. In 2 other cases where no overtube was used, large specimens also caused esophageal hematoma and laceration and longer operative times. Longest times were recorded for TV cholecystectomy (270 minutes), TV left colectomy (192 minutes), TG cholecystectomy (190 minutes), and TV nephrectomy (170 minutes). Faster procedures were gynecologic procedures such as tubal ligation (25 minutes) and TV diagnostic staging (35 minutes).

Interestingly, if totally NOTES technique was used (without any use of laparoscopic assistance), longer operative times were always recorded. In the case of cholecystectomy, use of laparoscopic assistance—one or more trocars—reduced the operative time from more than 120 minutes to less than 60 minutes, thus approximating from the former laparoscopic approach. Totally NOTES appendectomy times using flexible endoscopy (more than 90 minutes) were also more demanding than hybrid NOTES (less than 60 minutes).

Insufflation and Orientation

Insufflation and spatial orientation were considered satisfactory with the evolution of each surgeon’s experience with endoscopic techniques from experimental lab. Visualization of the cavity was mostly described as of very good quality, and the endoscope allowed regular cleaning of the lenses with sterile water, instead of retrieving the scope from the

Table 3. Prospective Intraoperative and Postoperative Data of NOTES Cholecystectomy, IMTN Study

<table>
<thead>
<tr>
<th>Prospective Data</th>
<th>TV Cholecystectomy (N = 240)</th>
<th>TG Cholecystectomy (N = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (min)</td>
<td>96.08 ± 57.815</td>
<td>110.93 ± 50.461</td>
</tr>
<tr>
<td>Anesthesiology time (min)</td>
<td>145.16 ± 61.980</td>
<td>154.89 ± 36.548</td>
</tr>
<tr>
<td>Intra-abdominal pressure (mm Hg CO₂)</td>
<td>11.55 ± 2.571</td>
<td>12.29 ± 2.156</td>
</tr>
<tr>
<td>Expiratory CO₂</td>
<td>35.2 ± 4.381</td>
<td>33.5 ± 2.121</td>
</tr>
<tr>
<td>Operative bleeding (mL)</td>
<td>12.41 ± 22.424</td>
<td>15.67 ± 13.650</td>
</tr>
<tr>
<td>Complications (%)</td>
<td>6.67b</td>
<td>24.14b</td>
</tr>
<tr>
<td>Postoperative stay (h)</td>
<td>46.04 ± 32.176b</td>
<td>37.76 ± 74.246b</td>
</tr>
</tbody>
</table>

Note: NOTES = natural orifice translumenal endoscopic surgery; TV = transvaginal; TG, transgastric. 
*Mean values expressed with standard deviation. 

Table 4. Prospective Intraoperative and Postoperative Data of NOTES Appendectomy, IMTN Study

<table>
<thead>
<tr>
<th>Prospective Data</th>
<th>TV Appendectomy (N = 37)</th>
<th>TG Appendectomy (N = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (min)</td>
<td>60.50 ± 31.335b</td>
<td>135.50 ± 9.256b</td>
</tr>
<tr>
<td>Anesthesiology time (min)</td>
<td>91.88 ± 29.402b</td>
<td>170.50 ± 7.326b</td>
</tr>
<tr>
<td>Intra-abdominal pressure (mm Hg CO₂)</td>
<td>12.38 ± 1.063</td>
<td>13.75 ± 0.957</td>
</tr>
<tr>
<td>Expiratory CO₂</td>
<td>36.91 ± 4.018b</td>
<td>37.25 ± 3.862b</td>
</tr>
<tr>
<td>Operative bleeding (mL)</td>
<td>26.37 ± 36.193</td>
<td>25.00 ± 3.742b</td>
</tr>
<tr>
<td>Complications (%)</td>
<td>8.10%b</td>
<td>21.42%b</td>
</tr>
<tr>
<td>Postoperative stay (h)</td>
<td>31.31 ± 37.275b</td>
<td>78.00 ± 12.00b</td>
</tr>
</tbody>
</table>

Note: NOTES = natural orifice translumenal endoscopic surgery; TV = transvaginal; TG, transgastric. 
*Mean values expressed with standard deviation. 
	bP < .05.
cavity. Laparoscopic transumbilical camera was used in some instances for TV surgery, and all cases of TG surgery, allowing safety and faster orientation than direct orificial access. TG endoscopic retroreflected visualization was corrected by changing the positioning of the endoscope, changing the positioning of the monitor, or correcting the "mirror effect" by computer software. CO₂ was the gas of choice to insufflate NOTES surgery, and pressures of 5 to 15 mm Hg were used, with no difference between TV and TG cases. Also, mean CO₂ pressures less than 10 mm Hg were not constantly used (Tables 3 and 4). Accidentally, in 2 cases air was insufflated by the operator of the endoscope, leading to abdominal pressures of nearly 30 mm Hg for short periods, with no morbidity associated. In the cases when any abdominal trocar was inserted, insufflation trough the trocar or a Veress needle was preferred. Translumenal endoscopic insufflation was obtained usually by attaching a laparoflator to a working channel of the endoscope, by tying an insufflation tube to the endoscope, by a special vaginal port that allowed insufflation, or by insertion of a vaginal trocar. Of these methods, the method using working channels to insufflate CO₂ was the only to introduce special problems because of low flux and sometimes bad exposition due to obstruction of the channel by fluids and low inflow.

Surgeon Versus Gastroenterologist

Main subjective questioning regarding the multidisciplinary aspect of the team showed predominance of the surgeon performing the operation, with a gastroenterologist responsible for part of dissecting, cutting, and clipping in a few centers. A minority of the NOTES teams were not composed of any gastroenterologist-endoscopist, as the surgeon was a skilled endoscopist or colonoscopist himself in these centers.

Conversion

Conversion to full laparoscopy was defined as insertion of unplanned trocars and significant use of laparoscopic dissection, clipping, or camera, and occurred in 6 patients due to difficult exposure, bleeding of appendiceal or cystic vessels, or adhesions from previous surgery. Conversion to open surgery occurred in 3 cases in the study. In the first, TG access led to important hemorrhage from epiploic vessels and required open conversion and ligature control, with no postoperative morbidity. In 2 other patients submitted to TG cholecystectomy with large stones (>2.4 cm), extraction of the specimen through the mouth was an important issue. In one of them, after an uneventful procedure, the team tried to retrieve the specimen, which was stuck in the proximal esophagus/oropharynx. The gallbladder and stone remained blocked in place, and many methods were tried to solve the problem, such as laringoscopy with tentative transoral grasping, breaking the stone, and variable delivery maneuvers. The solution was to return the gallbladder to the stomach and to the abdominal cavity and then to extract the specimen through an umbilical open incision.

Complications

Intraoperative complications occurred in 5.8% patients, and postoperative complications occurred in 3.04% of the patients (see Tables 5 and 6). The prospective documentation grade of surgical complications followed the scores initially proposed by Clavien in 1992 and modified in 2004 (Clavien–Dindo classification12). Complications were recorded in 32 patients (8.84%) and stratified in grades I to IV according to the Clavien–Dindo classification and were represented by intraoperative and postoperative complications. Reoperations were necessary for 5 patients because of the following: (a) Peritonitis—in 1 case of TG cholecystectomy, the patient was readmitted on the fifth postoperative day due to diffuse abdominal pain and distension. Laparoscopy was performed and diffuse peritonitis due to Streptococcus faecalis was found, but without gastric fistulae and clean cystic duct stump and gastric closure site. Abdominal fluid aspiration and washing with saline solution was performed, with good postoperative course. (b) Esophageal perforation—in 1 patient, the passage of a large calculi with an inflamed gallbladder led to perforation of the proximal esophagus and thoracic operation and longer intensive care unit longer admission (grade IVa). (c) Biliary fistula described below in 2 cases, but in only 1 case leading to laparoscopic reoperation.

Comparing TG and TV surgery, the former had significantly more grade I-II (9.3%) and grade III-IV (13.95%) complications than TV surgery (5.33% and 1.57%, respectively; see Table 7). Nevertheless, smaller numbers of cases for each procedure of TG NOTES were recorded than TV cases.

Intraoperative Bleeding

During NOTES procedures, intraoperative hemorrhage during dissection or direct artery lesion occurred in 5 cases of TV cholecystectomy (treated in 1 case by endoscopic clips and with laparoscopic clips in 4 cases), in 1 case of TG appendectomy, and in 3 cases of TV appendectomy (all treated by laparoscopic clips). One case of intraoperative gastric perforation in a NOTES TV cholecystectomy occurred due to adhesions to the anterior gastric wall of a chronically inflamed gallbladder. TV dissection of the fibrosis caused perforation that was intraoperatively recognized and laparoscopically sutured.
In 2 patients submitted to TV cholecystectomy, biliary leak occurred and no case was related to use of endoscopic clips. In 1 case, the patient was readmitted on the fifth postoperative day and was successfully treated by laparoscopic drainage and antibiotics and dismissed after 8 days. The finding was that the double layers of laparoscopic suturing in the first operation were disrupted. The second patient had 2 proximal laparoscopic clips applied during the NOTES procedure, and biliary leak and biloma was diagnosed on the first postoperative day. The patient was successfully treated by nasobiliary stenting and percutaneous drainage of the fluid collection under tomographic guidance.

No deaths were registered by the centers in this study, and no definitive untreated sequel occurred by the time of closing of these preliminary data.
Despite there being no control from study protocol to unify individual analgesia prescription, analgesia was given by patient’s request, and prospective data were documented. From the patients submitted to NOTES cholecystectomy and appendectomy (N = 320, with 17 missing data), no requirement for any analgesia was found in 23.6% of NOTES cholecystectomy and 23.5% of NOTES appendectomy (see Table 8). About analgesia, there is difficult to compare as there is no control group in the study. Parameters were crossed to identify potential reasons for no pain, and there were no relations with regard to operative times. Most of the cases with no pain medication also used hybrid surgery with at least 1 laparoscopic trocar.

Discussion

Natural orifice surgery is an emerging alternative to standard laparoscopy, combining endoscopic flexible techniques to diagnose and treat abdominal pathology. NOTES surgery is promising in achieving no scar surgery; completely avoiding incision-related complications such as hernias, postoperative pain, wound infection, adherences, and intestinal obstruction; and providing good cosmetic result and possibly with less postoperative pain. More than this, the adoption of future flexible platforms to perform therapeutic procedures, with many surgeons becoming skilled in flexible endoscopy and gastroenterologists replacing complex procedures by simple endoscopic ones, may change the current system of care, separated into compartments by skill sets rather than target organs.

Early experimental studies, mostly using TG access, evidenced technical difficulties, infection, and orientation issues related to the lack of adequate flexible platform and instruments for these specific procedures. Because of limitations of technology for TG access there is need for industry to develop new devices, especially endoscopic suture devices to avoid danger of postoperative leakage and peritonitis. Transcolonic, transurethral, and transesophageal accesses were described, currently still restricted to experimental animal experience.

To discuss the needs and possibilities of the emerging translumenal flexible procedures, a working group representing societies ASGE (American Society of Gastrointestinal Endoscopy) and SAGES (Society of American Gastrointestinal and Endoscopic Surgeons) met in New York in 2005. The group named NOSCAR (Natural Orifice Consortium for Assessment and Research) identified barriers that needed to be transposed for the development of translumenal surgery and suggested a list of steps and guidelines. This consortium of surgical endoscopists has established taxonomy, delineated the current limitations to NOTES, and motivated a unified plan of research to propel NOTES into human practice. Important aspect from this early discussion identified several inherent technical challenges to natural orifice surgery, including creating a viscerotomy, orientation, insufflation, infection, manipulating intra-abdominal organs, and safely closing the viscerotomy. Following the directives, safe process of gaining experience with translumenal access, allied to safe closure by new devices, should be the natural way to slowly apply NOTES to clinical use.

Instead of other NOTES proposal accesses, however, TV natural orifice surgery may be a potentially less hazardous alternative for diagnostic and therapeutic purposes. Although TV NOTES can possibly benefit only around 50% of human population, it is now the preferred access published by most researchers in clinical series. Also, TV NOTES access allows the passage of endoscope and instruments through the natural orifice without retroflection or closure issues and has been performed for abdominal therapeutic purposes for many years. Culdoscopy was described by Decker and Cherry in the 1940s, and with its evolution to TV hydrolaparoscopy, procedures usually performed
for investigation and treatment of infertility.28 Bueno described in 1949 the first case of successful performance of incidental vaginal appendectomy at the time of vaginal hysterectomy,29 and Reiner, in 1980, presented his experience with 100 consecutive appendectomies done incidentally at the time of vaginal surgery30; and currently, many operations have been described for open TV surgery, including larger series of appendectomy. Laparoscopic extraction of specimens through the vagina (such as gall-bladder, colon, spleen, and kidney) has also been previously described.31-33 Using a hybrid procedure, Tsai and coworkers described vaginal cholecystectomy and other operations after simultaneous hysterectomy with a vaginal trocar and formal laparoscopic instruments through the anterior abdominal wall, naming the procedures as “culdolaparoscopy.”34 These previous clinical experiences using vaginal (contaminated) access to perform abdominal (sterile) operations showed small rates of infectious complications and few concerns about compromising fertility due to the access. TV NOTES may possibly represent the safest and most applicable way for natural orifice routes, relatively independent development of technology, with a potential benefit of controllable access and easy closure.

Recent publications and presentations in scientific meetings described the first clinical human applications of the new method, after institutional review board approval, for human trials on NOTES in different countries. Since the publication of successful NOTES TV cholecystectomy in early 2007,35-38 other groups published their initial clinical results of the technique, sometimes conjoined with laparoscopy for retraction or for camera purposes.39-49 TG appendectomy was also clinically presented in meetings by Rao and coworkers using available endoscopic instruments since 2005,5 and the first TV NOTES appendectomy was first described by Palanivelu et al,50 and later by Bernhardt et al.51 Lacy et al first described a case of hybrid TV sigmoidectomy for cancer (MA-NOS),52 Burghardt et al for right colectomy,53 and Ramos et al presented a first series of TV NOTES sleeve gastrectomy.54 Successful TG PEG rescue was described by Marks et al,55 and initial human application for TG pancreatic cancer staging and TV cancer staging has also been reported.9,56,57 Only 5 groups previously reported clinical TG surgery for cholecystectomy, appendectomy, and cancer staging with good results in a small number of cases.3,4,43,56,58,59 Frequently, procedures such as TG pancreatic debridement by Seifert et al60 and transanally endoscopic microsurgery performed by Bues et al61 were correctly referred as pioneering NOTES techniques.

The International Prospective Multicenter Trial on Clinical NOTES Registry started accepting participant centers from July 2007 as there was a need to understand technique improvements and postoperative results of NOTES cases. Inclusion was conditioned to centers having institutional research committee approval, adequate experimental lab and resources, endoscopic experience, and availability of a multidisciplinary team. The preliminary results reported here will be followed for a minimum period of 6 years, and partial results will be published in intervals of 2 years.

Before adequate NOTES platforms become available, postoperative time will remain longer than when standard laparoscopic techniques are used. Despite lack of adequate technology for natural orifice surgery, totally NOTES surgery was first described in the literature by Sousa et al,46 using a technique with 2 vaginal endoscopes, and by Gumbs et al43 and Davila et al,49 using rigid TV retraction. In the present study, TG and TV NOTES cholecystectomy took a mean of 96.1 and 110.9 minutes, respectively, and TG and TV NOTES appendectomy, respectively, 135.5 and 60.5 minutes. This time was significantly decreased in the case of introduction of 1 or more trocars for retraction or dissection, clearly showing that technical and instrumental development is needed for NOTES procedures. Orientation and visualization were not significant issues, as all the multidisciplinary groups have had previous NOTES techniques tested in the animal experimental set. Laparoscopic assistance representing hybrid surgery was necessary in many cases of advanced procedures, in all cases of TG surgery, and always represented economy in operative and anesthesiology time, if compared with totally NOTES cases. The performance of first entrance by gastrotomy using the endoscope was accompanied by laparoscopic visualization for safety and allowed low incidence of puncture accidents. Gastrotomy closure was always performed by laparoscopic suture, sometimes with innovative methods using only 2 trocars (one for 3-mm optic and one 5-mm for one-hand suture by external knotting), ensuring safe recovery without compromising on cosmesis, until reliable, universally approved, safe, and cost-effective methods of closure will be available. Although 1 episode of postoperative peritonitis occurred after TG surgery, it was not related to inadequate closure or fistulae, and no TV cases became infected. Vaginal opening was accompanied by laparoscopic umbilical guidance in a few centers, and most centers using direct vision vaginal access did not report access-related complications. Vaginal wound was effectively closed transvaginally in all cases using absorbable sutures under direct view.

Analgesic requirement is an important field of research for NOTES clinical trials, as it may indicate better results than standard laparoscopic and open therapy. Studies comparing laparoscopic with open cholecystectomy demonstrated less pain scores and less analgesic needs for laparoscopic surgery.62-64 Laparoscopic surgery has also shown to have lower stress response and less impaired immune functions when compared with open surgery in the past65,66 and improvements in immunologic function.
in natural orifice surgery is at least expected to approximate these results, but early experimental research does not support it yet. A prospective study comparing NOTES cholecystectomy and standard laparoscopic cholecystectomy in 46 patients registered less need for analgesia, although further prospective randomized trials should be performed to better compare postoperative pain. The expectation is that an expressive percentage of NOTES patients may not need any postoperative pain medication, as shown in our preliminary multicenter study results. Absorption of CO\textsubscript{2} measured by end-tidal CO\textsubscript{2} may also represent a trend and differences in further studies. Although collected from a few patients in this study, significant increase in end-tidal CO\textsubscript{2} can be seen in the laparoscopic group when compared with natural orifice surgery patients, as well as higher CO\textsubscript{2} intra-abdominal pressure for laparoscopy when compared with the NOTES group. Other unpublished reports suggested lower intra-abdominal pressures needed for NOTES compared with laparoscopy; in some cases the procedure was possible using 5 to 6 mm Hg CO\textsubscript{2}, possibly because of less need of exposure and insufflation. Although these findings could also contribute to lower analgesia needs in natural orifice surgery, these suggestions were not confirmed in the present IMTN study, because the centers reported mostly same pressures used at laparoscopy. Recent experimental studies provided initial information for understanding the physiologic issues of insufflation and infection in natural orifice surgery.

The intraoperative complications rate was 5.48%, and the postoperative complication rate was 2.87%. In larger series of laparoscopic cholecystectomy, biliary duct iatrogenic lesions are encountered in 0.2% to 3% of the cases, but most individual centers reported a rate of 0.3%. Major complications are reported in 2% to 4% of the cases, and minor complications range from 5% to 7% for laparoscopic cholecystectomy. The mortality rate for laparoscopic cholecystectomy is estimated to be as low as 0.1%. TV NOTES procedures had less grade I-II and grade III-IV complication rates than TG NOTES operations in this study, although the small number of cases might bias statistical significance analysis. Although there were no reports of deaths in the IMTN registry, at least 1 patient had a possibility of fatal postoperative course due to esophageal perforation and mediastinitis. Grade III-IV complications occurred in 10 patients (2.76%), represented by intraoperative bleeding, bowel injury (intraoperatively recognized and treated), biliary fistula, and esophageal injury. Postoperative peritonitis by \textit{S. faecalis} occurred after 1 case of TG cholecystectomy, although with no gastric closure site leak. Biliary leaks occurred in 2 patients after TV surgery, but were not due to endoscopic clip failure, which were not used in the cases. Failures were due to cystic duct inefficient closure by laparoscopic clips or sutures. There was no iatrogenic biliary injury reported. Infection is a concern from the very beginning of the natural orifice concept, but was rarely reported in this study. With the exception of 1 peritonitis case reported, established means of gastric and vaginal disinfection, sterilization of the instruments, and high-level disinfection of the flexible endoscopes proved to be satisfactory in this casuistic in avoiding surgical infection.

The choice of the orifice access showed significant differences in operative complication rates. TG surgery reported significantly higher rates of grade I-II (9.3%) and grade III-IV (13.95%) complications than TV surgery (5.33% and 1.57%, respectively). A longer learning curve for TG surgery is expected. Because of the lack of instruments to perform adequate dissection and retraction, the need for retroflexion, the need for flexible endoscopy skills, and the small size of the esophageal lumen surely contribute to higher operative times and complications than TV NOTES. The use of gastroesophageal overtures could prevent esophageal injuries, as well as avoiding technical difficulties for specimen retrieval, but still the instrumental and ports to be invented by industry will have more restrictions in size and shape than vaginal and colonic NOTES access.

The preliminary results of the IMTN Study represent the first large series application of NOTES in the literature. In most clinical cases, the access was easily created and intra-abdominal procedure was performed without technical or orientation difficulty, even in cases in which retroflexion visualization from the endoscope was needed. Operative time was longer than a standard laparoscopic operation, but possibly might be shortened with more adequate instruments in the future. Interestingly, if “pure NOTES” (totally NOTES) is used, without laparoscopic assistance, operative time is significantly longer than with any laparoscopic assistance for retraction or visualization. The desired triangulation was not possible using the endoscope, and more in-line dissection technique was frequently described by the centers for dissection. The difficulties in applying traction, lack of multiplanar instrumentation, and limited size of the working channels of the endoscope are other obstacles. Closure of the vaginal wound was not a problematic issue of the approach and was done externally under direct vision using conventional instruments. Closure of TG access, however, was still an issue, and the procedures could only be performed using laparoscopic closure of gastric access using 1 or 2 laparoscopic trocars. As the experienced surgeon knows, a hostile pelvis due to adhesions, previous pelvic infections, and endometriosis is more common than a hostile upper abdomen, possibly making TG access more attractive, especially for the general surgeon with upper endoscopy experience. However, large specimen retrivals are not expected to be solved by the TG approach, as the
esophagus allows only a maximal instrumental (or specimen) diameter of around 2 cm. TV NOTES approaches have less potential for complications such as fistula and peritonitis when compared with other transluminal accesses. Potential disadvantages of NOTES surgery are the necessary use of antibiotics and bladder catheterization and risk of infection and morbidity of gastric, vaginal, and colonic access, even with longer operative times.

Based on the preliminary results of the study, initial general recommendations of the IMTN NOTES Study Group are the following:

1. **Suggested taxonomy for NOTES procedures.**

   Totally NOTES (T-NOTES) are procedures performed through any natural orifice without percutaneous assistance. Hybrid NOTES implies use of laparoscopy for retraction and visualization, but with significant dissection performed through the natural orifice. NOTES-assisted laparoscopy means operations performed by laparoscopy with low natural orifice instrumentation contribution (retraction or visualization), such as culdolaparoscopy. NOSE refers to natural orifice specimen extraction, as previously published. A differentiation between NOTES performed by flexible endoscopy (FLEX-NOTES) and those performed by rigid instruments (RIG-NOTES) seems important, as flexible instruments are not accepted everywhere for intra-abdominal surgical arsenal and because of difficulties in reliable device sterilization.

2. **Choice of the natural orifice access.** The group recommends that all further clinical trials for TG and TV approaches, under institutional review board approval, be performed by a multidisciplinary team with a skilled endoscopist and with previous extensive animal experience in transluminal techniques before human series. Transcolonic, transesophageal, and transurethral accesses are not suitable yet for clinical studies, as there is a lack of experimental data and technical development for its safe use in trials.

3. **Single access surgery.** Umbilical laparoscopic surgery (laparoendoscopic single site surgery [LESS], single access surgery [SAS], single port access [SPA], or transumbilical endoscopic surgery [TUES]) is not natural orifice surgery, as the umbilicus is a natural scar, not orifice, and produces somatic pain rather than visceral pain. Regarding this evolving concept, potential advantages in NOTES regarding avoidance of incision-related complications and somatic pain are absent in SAS. As it is recognized as laparoscopy performed through a single trocar, there is, in our view, no restriction for its use in clinical trials.

4. **Feasibility and safety.** Basic TG and TV NOTES procedures are feasible with the available instruments, taking possibly longer operative times than laparoscopy until new endoscopic technology arises. TV surgery is feasible and safe for uncomplicated indications, although TG surgery needs evolution of technology for more wide clinical applications. Gastric opening wound still needs laparoscopic closure and preoperative gastric lavage with antisepsics for patient’s safety. The use of overtubes to perform TG NOTES could minimize esophageal complications. The determination of safety of each procedure can only be assured after the next steps of IMTN Study with larger numbers of patients per procedure and longer follow-up times.

5. **Learning curve.** TG NOTES showed a more hazardous learning curve and more initial complications than TV surgery, due to the difficulty in navigation, spatial orientation, small size of the viscera (esophagus) allowed for operative work, and need for a safe entry and closure of the gastric wall. These barriers possibly will slow the acceptance and development of clinical TG surgery, as the access has a limitation for instruments and specimen extraction sizes.

6. **Sterilization and preparation.** Although the occurrence of postoperative infectious complications was relatively low in the study, efforts have to be directed to produce flexible endoscopes able to be sterilized under available and cost-effective methods. Intraoperative gastric lavage with chlorhexidine and traditional vaginal disinfection can minimize infection.

7. **Contraindications.** Cases shall be well selected and performed by a skilled team in flexible endoscopy to avoid long operative times and misorientation. Previous abdominal and pelvic surgeries as well as adhesions are no longer contraindications. Advanced and emergency procedures should be avoided in the early phase of technological development. For TV access, previous hysterectomy, vaginal infection, pregnancy, endometriosis, and virgin patients constitutes contraindications. Oncologic NOTES procedures are not supported yet by the literature, but possibly will follow the same pattern of acceptance as laparoscopy. Natural orifice tumor implant possibilities are issues for future research.

8. **Indications.** None of the procedures performed worldwide in the study showed evidence of being
superior to laparoscopic surgery. Advantages suggested in this study, such as lower intra-abdominal pressures, less pain demonstrated by a percentage of patients showing no use of postoperative analgesia, and less incision complications, may be considered for future research.

NOTES seems to be evolving as a feasible, safe, and reasonable option for transabdominal surgery, with the potential to avoid incision-related complications completely. However, caution is necessary, as complications faced during the early days of laparoscopic surgery should not be repeated. Despite long operative times, these preliminary results of the IMTN Trial showed acceptable complication rates in all international centers, low postoperative hospital stay, and good cosmetic and pain requirement results, especially for TV surgery. Future prospective clinical trials comparing NOTES with laparoscopy may be needed. More important than this and perhaps crucial to indicate widespread use translumenal surgery will again be the ability of surgeons and endoscopists to replace complex surgical procedures with simple endoscopic ones and the identification of novel therapeutic targets. Therefore, it is expected that more clinical studies may reproduce the study results, thus stimulating also the call for prospective randomized studies comparing natural orifice surgery with standard laparoscopy.

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