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# UNIVERSITÀ DEGLI STUDI DI TORINO

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## **The EURO-NOTES clinical registry for natural orifice transluminal endoscopic surgery: a 2-year activity report**

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## Abstract

### Background

The EURO-NOTES Clinical Registry (ECR) was established as a European database to allow the monitoring and safe introduction of Natural Orifice Transluminal Endoscopic Surgery (NOTES). The aim of this study was to analyze different techniques applied and relative results during the first 2 years of the ECR.

### Methods

The ECR was designed as a voluntary database with online access. All members of the European Society for Gastrointestinal Endoscopy and the European Association for Endoscopic Surgery were requested to participate in the registry. Demographic and therapy data as well as data on the postoperative course are recorded in the ECR in an anonymous way.

### Results

A total of 533 patients who underwent NOTES procedures were included in the study. Four different hybrid techniques for 435 cholecystectomies were described, registering postoperative complications in 2.8 % of patients, addition of a single trocar in 5.3 %, and conversions to laparoscopy in 0.5 %. Both flexible endoscopic and rigid laparoscopic cholecystectomy techniques proved to be safe and effective with minor differences. There was a shorter operative time in the rigid laparoscopic group. Thirty-three appendectomies were reported by transgastric and transvaginal techniques, with transvaginal techniques scoring shorter operative time and hospital stay, but with a frequent need to add more trocars. Overall complications occurred in 14.7 % of patients but they did not differ significantly among the different techniques. One transvaginal and 31 transanal sigmoidectomies were included for prolapse and diverticulitis, with four postoperative complications (12.5 %), but none needing further treatment. Twenty peroral esophageal myotomies were included with three postoperative complications (15.0 %), but none needing further treatment.

### Conclusions

Five years since the introduction of NOTES into clinical practice, hybrid techniques have gained considerable clinical application. Several NOTES hybrid cholecystectomy and appendectomy techniques are practicable and safe alternatives to laparoscopic procedures. Also, sigmoidectomies and peroral esophageal myotomies were described, proving feasibility and safety. Nevertheless, the real benefit of NOTES for patients still needs to be assessed.

### Keywords

#### Achalasia Appendix Bowel Cholecystectomy NOTES

Since the widespread introduction of laparoscopy, major advancements in the practice of minimally invasive abdominal surgery have revolutionized the way surgical operations are conceived and performed throughout the world. Lay literature and media focused attention on Natural Orifice Transluminal Endoscopic Surgery (NOTES) at the beginning of 2007 after the first clinical reports, with the concept and feasibility of NOTES having been tested in animal experiments since 2004 [1]. The initial experience of transgastric and transvaginal peritoneal access demonstrated both safety and feasibility in the animal model and has been used as the basis to further evaluate and develop the technology of natural orifice surgery [1–8]. Later, other possible access routes were described: transrectal, transvesical, and transesophageal.

NOTES is a new type of surgical procedure currently being studied at research hospitals and facilities around the world. The NOTES was developed several years ago in response to the ideas that patients would (1) realize the benefits of less invasive surgery by reducing the recovery time, (2) experience less physical discomfort associated with traditional procedures, and (3) have virtually no visible scarring following this type of surgery. All of these advantages have spurred research and investigation, encouraging physicians and researchers to develop new equipment and techniques for use in NOTES procedures. The growing interest in and safe introduction of these novel techniques led to the creation of new scientific societies and committees with the declared aim of regulating research activity through sponsorships and registries [9].

We present an interim report of the EURO-NOTES Clinical Registry (ECR). The EURO-NOTES Foundation, sponsor of the registry, was founded as a joint initiative of the European Society for Gastrointestinal Endoscopy (ESGE) and the European Association for Endoscopic Surgery (EAES) in 2008. The ECR includes mainly cholecystectomies, but it also includes appendectomies, colonic resections, and peroral myotomies, and discusses the pros and cons of the different techniques proposed.

## **Materials and methods**

The ECR is available online to all ESGE and EAES members and has been developed to compile safety data to be used by ethical committees in order to authorize human trials and to implement the interface between medical societies, industry, and regulatory offices. All members of the EAES and ESGE were contacted by e-mail. Every member performing NOTES or planning to do so was asked to participate in the ECR. The registry was also announced at several congresses since 2008. Continuous information was provided through newsletters and announcements on the registry website. Participation in the registry was voluntary and not limited to any society membership.

NOTES is difficult to clearly define; it has been argued that even transumbilical procedures should be included in this group. We preferred to exclude transumbilical procedures, even when performed with the aid of a flexible endoscope. We are also aware that transanal endoscopic microsurgery (TEM) [10, 11] represents the true beginning of the NOTES clinical experience, but inclusion of the data from these procedures would have altered the meaning of the registry so we preferred to exclude these cases. Similarly, we know that gastric GIST is often performed as a laparoendoscopic technique, so we selected only those cases in which dissection was performed by means of flexible endoscopy tools, although a full endoscopic technique has also been described but it does not include resection and specimen retrieval [12].

The data presented in this article were entered into the ECR between May 2010 and August 2012, although data could have been inserted retrospectively. Data were stored in an online database (<http://www.euronotes.world.it>). The software was specifically developed for the purpose of the ECR. It consists of a web 2.0 platform that stores the data of included patients in an anonymous way so that neither the identity of the patient nor the identity of the center is known, so the data can be retrieved while fully respecting privacy regulations. After verification of identity, registered participants have access to the entire database. Each participating center was assigned an account. Each dataset consists of five sections (general data, procedure, technique, postoperative course, and media). The software includes automated statistics, which provides an overview of all the data and is a benefit for participation in the registry.

## **Statistics**

The data of the registry was exported to statistical software. Data of continuous variables are expressed as mean and range. Conversion to standard laparoscopy was defined as the addition of more than one transabdominal trocar. Binary and categorical variables are reported as counts and percentages. Fisher's exact test was used for categorical variables and the Wilcoxon test was used for continuous variables. All reported P values were obtained by the two-sided exact method at the conventional 5 % significance level. Only significant P values were indicated for better comprehension. A subgroup analysis for each procedure was planned as long as there were more than 20 procedures performed on the respective target organ.

## Role of the funding source

The creation of the online registry was supported by the EURO-NOTES Foundation. We had full access to all the data used in this study and had the responsibility of deciding to submit this article for publication.

## Results

### Registry participants

Sixty-two accounts were created, of which 14 were actively used for the input of patient data. The date of the procedures ranged between April 2007 and August 2012. Each center included two or three physicians as a standard, including at least one surgeon or gastroenterologist with advanced training in endoscopy. A total of 542 patients were entered into the ECR. Two centers contributed nine cases of transumbilical cholecystectomy with the aid of a flexible endoscope [13]. We did not consider this procedure a true NOTES procedure and therefore these nine cases were excluded from the analysis.

### Procedural data

No combined procedures are present in the registry. The complete list of procedures is given in Table 1. The most frequently performed procedure was cholecystectomy [435 cases (81.6 %)], followed by appendectomy in 33 patients (6.2 %). Colonic resection was performed in 32 cases (6.0 %), peroral myotomy in 20 (3.8 %), gastric resection in 6 (1.1 %), bilateral adnexectomy in 2 (0.4 %), and 1 each (0.2 %) of a liver resection, liver cyst fenestration, mediastinal necrosectomy, peritoneal adhesiolysis, and a small bowel resection.

Table 1

Characteristics of patients and procedures included in the ECR

Procedure	n	%	Age (years)	BMI (kg/m <sup>2</sup> )	Operative time (min)
Cholecystectomy	435	81.6	45.3 (16–76)	25.3 (16–50)	60.5 (15–270)
Stones	429		45.5 (16–76)	25.6 (16–50)	60.3 (15–270)
Cholecystitis	6		42.3 (18–72)	29.3 (21–42)	72.8 (60–100)
Appendectomy	33	6.2	31.0 (16–73)	25.5 (17–45)	93.5 (40–170)
Colorectal resection	32	6.0	60.5 (27–87)	25.0 (19–30)	134.5 (55–184)
Sigmoid diverticulitis	18		60.0 (30–73)	25.4 (21–30)	134.8 (95–179)
Prolapse	12		64.2 (28–87)	25.1 (21–27)	125.6 (55–184)
Slow transit constipation	2		42.5 (27–58)	20.3 (19–21)	185 (185–185)
Peroral esophageal myotomy	20	3.8	45.0 (15–87)	23.2 (17–32)	99.6 (60–185)
Gastric resection	6	1.1	64.5 (54–73)	27.5 (22–31)	109.2 (61–155)
Bilateral adnexectomy	2	0.4	52 (42–63)	28.5 (27–30)	205 (170–240)
Liver resection	1	0.2	61	22.0	180
Liver cyst fenestration	1	0.2	62	25.7	140
Peritoneal adhesiolysis	1	0.2	76	22.1	45
Ileal resection	1	0.2	64	32.0	195
Necrosectomy	1	0.2	68	30.3	15

Procedure	n	%	Age (years)	BMI (kg/m <sup>2</sup> )	Operative time (min)
Total	533	100	45.7 (15–87)	25.2 (16–50)	70.2 (15–270)

## Cholecystectomies

The registry enrolls patients treated in many different ways which can be summarized into four different techniques:

- A hybrid technique consisting of transvaginal and transumbilical access, with the aid of a flexible endoscope [14], as reported by nine centers.
- A hybrid technique consisting of transvaginal and transumbilical access, with the aid of a rigid laparoscope [15], as reported by two centers.
- A hybrid technique consisting of transgastric and transumbilical access, with the aid of a flexible endoscope [16, 17], as reported by two centers.
- A hybrid NOTES transvaginal technique using modified TEM equipment [18] combined with transumbilical access, as reported by one center.

In all cases in which transvaginal access was used, visualization was obtained through optics inserted transvaginally. The consistent number of cholecystectomies performed by different techniques allows a comparative analysis in terms of morbidity and perioperative results.

Table 2 gives the perioperative characteristics of patients and techniques. Of the 435 patients who underwent a cholecystectomy, the transvaginal approach was preferred in 423 cases (97.2 %), while 12 patients underwent a transgastric hybrid approach. The transvaginal cases were all hybrid, consisting of 138 cases performed with the aid of a flexible endoscope, 279 with the aid of a rigid laparoscope, and 6 hybrid transvaginal procedures using modified TEM equipment. Age varied consistently among groups but not in a statistically significant way. BMI among the groups did not differ significantly.

Table 2

NOTES cholecystectomies included in the ECR divided per technique

Procedure	n	%	Centers	Age (years)	BMI (kg/m <sup>2</sup> )	Additional trocar	Conversion to laparoscopy <sup>a</sup>	Operative time (min)
Transvaginal and transumbilical access, with flexible endoscope	138	31.7	9	45.7 (20–75)	27.1 (17–50)	8 (5.8 %)	1 (0.7 %)	76.6 (15 – 270)
Transvaginal and transumbilical access, with rigid laparoscope	279	64.1	2	45.3 (16–76)	24.8 (16–39)	13 (4.7 %)	3 (1.2 %)	49.4 (23–125)**
Transgastric and transumbilical access, with flexible endoscope	12	2.8	2	48.2 (27–67)	24.8 (21–37)	3 (25.0 %)*	0	125.4 (90–180)
Transvaginal and transumbilical access, by modified TEM	6	1.4	1	36.8 (27–59)	N/A	0	0	80 (40–115)
Total	435	100	12 <sup>b</sup>	45.3	25.3	24 (5.5 %)	4 (0.9 %)	60.5 (15–

Procedure	n	%	Centers	Age (years)	BMI (kg/m <sup>2</sup> )	Additional trocar	Conversion to laparoscopy <sup>a</sup>	Operative time (min)
				(16–76)	(16–50)			270)

\* P = 0.003 vs. overall transvaginal techniques; \*\* P < 0.001 vs. each of the other techniques

<sup>a</sup>Meant as the addition of more than one trocar, plus the one routinely used in the hybrid techniques

<sup>b</sup>Two centers used more than one technique

In all cases transvaginal access was obtained by direct surgical opening after establishing the pneumoperitoneum via transumbilical access (Veress needle or open laparoscopy technique), except for 24 cases in the group that had a hybrid transvaginal approach with the aid of a rigid laparoscope in whom access was obtained by direct insertion of a 12-mm trocar transvaginally without previously established pneumoperitoneum. All 24 cases were performed at the same center. In all cases the transvaginal access incision was sutured by means of a standard colposcope.

In all cases the transabdominal trocar that transformed the procedure into a hybrid NOTES was used for dissection, except in the transvaginal technique by modified TEM, in which case the trocar was used only for visualizing a safe transvaginal access. In this series, a 50-cm-long and 33-mm-large in diameter dedicated colposcope was introduced under vision through the vagina into the peritoneal cavity, and cholecystectomy was performed by means of dedicated instruments through the colposcope only, similar to TEM. In 3 of 12 cases (25 %), a hybrid transgastric technique necessitated the addition of an additional trocar, which also occurred in 21 cases (5.0 %) out of all the transvaginal techniques (P = 0.002). Among the transvaginal techniques there was no statistical difference between groups.

Four procedures performed by transvaginal technique were converted to standard laparoscopy, meaning the addition of more than one transabdominal trocar, in addition to the trocar routinely used in the hybrid technique. One case was in the group in which a flexible endoscope was used, and three cases were in the group in which a rigid laparoscope was used (P = 0.99).

Reasons for adding one or more transabdominal trocars included “bleeding control” in two cases, “uncertain anatomy” in two cases, “large cystic duct” in one case, and the “need for better manipulation by means of a laparoscopic dissecting and retracting device” in the remaining 23 cases.

The mean operative time of all transvaginal techniques was significantly shorter than that of the transgastric approach (60.7 vs. 125.4 min, P < 0.001). Operative time was significantly shorter for the transvaginal technique with the aid of a rigid laparoscope compared to each of the other techniques (P < 0.001). Also, the transvaginal technique with the aid of a flexible endoscope had a significantly shorter operative time than the transgastric technique (P < 0.001). Similarly, the transvaginal technique with modified TEM instrumentation had a significantly shorter operative time than the transgastric technique (P = 0.005). No other statistical significance was observed.

Table 3 lists the complications and hospital stay of the different techniques for cholecystectomy. Two patients in the transvaginal approach with the aid of a rigid laparoscope group had an intraoperative complication. The first consisted of significant bleeding from an inadequately clipped cystic artery branch, which required an additional trocar for safe control of hemostasis. The second consisted of the perforation of the urinary bladder during surgical transvaginal access in a patient who had undergone a previous hysterectomy. The complication was managed with a transurethral catheter for 3 days. No statistical significance was observed.

Table 3

Complications of NOTES cholecystectomies included in the ECR divided per technique



Procedure	n	Intraoperative	Postoperative	Overall	Hospital stay (days)
Transvaginal and transumbilical access, with flexible endoscope	138	0	2 (1.4 %)	2 (1.4 %)	2.1 (0–11)
Transvaginal and transumbilical access, with rigid laparoscope	279	2 (0.7 %)	5 (1.8 %)	7 (2.5 %)	2.0 (0–7)
Transgastric and transumbilical access, with flexible endoscope	12	0	0	0	2.4 (2–4)
Transvaginal and transumbilical access, by modified TEM	6	0	1 (16.7 %)*	1 (16.7 %)**	2.5 (2–4)
Total	435	2 (0.3 %)	8 (1.8 %)	10 (2.1 %)	2.1 (0–11)

\* P < 0.001 vs. each of the other techniques; \*\* P < 0.01 vs. transvaginal and transumbilical access with flexible endoscope and P < 0.05 vs. transvaginal and transumbilical access with rigid laparoscope

Postoperative complications were observed in 8 patients overall (2.5 %). Two complications (1.4 %) occurred after transvaginal and transumbilical access with a flexible endoscope. One complication was a hematoma due to the probable dislodgement of the endoscopic clip on the cystic artery, and the second complication consisted of minimal vaginal bleeding in a patient with surgical transvaginal access; it was controlled with an external suture at the end of surgery. Five complications (2.8 %) occurred after transvaginal and transumbilical access with rigid laparoscope. There was one bile leak and one pelvic abscess, both requiring further surgery. Two other complications required ERCP under sedation for a bile leak. One patient required prolonged use of analgesics for persistent significant abdominal pain in the absence of any imaging or biochemical evidence of alteration. Pain resolved after 6 days and the patient was discharged. Finally, one case of postoperative complication (16.7 %) occurred after the transvaginal technique by modified TEM and consisted of a hemorrhagic fluid collection in the pelvis that was drained surgically by reopening the umbilical port site under local anesthesia. Complications are also classified according to Dindo–Clavien [19] in Table 4. The incidence of complications between the two transvaginal hybrid techniques was not statistically significant (P = 0.80), whereas each of the two groups had significantly fewer complications compared to the transvaginal technique by modified TEM instrumentation (P = 0.01). No other statistical significance was observed.

Table 4

Dindo–Clavien classification of complications of NOTES cholecystectomies included in the ECR divided per technique

Procedure	n	Dindo–Clavien classification						
		I	II	IIIa	IIIb	IVa	IVb	V
Transvaginal and transumbilical access, with flexible endoscope	138	0	0	2 (1.4 %)	0	0	0	0
Transvaginal and transumbilical access, with rigid laparoscope	279	0	1 (0.4 %)	2 (0.7 %)	2 (0.7 %)	0	0	0
Transgastric and transumbilical access, with flexible endoscope	12	0	0	0	0	0	0	0
Transvaginal and transumbilical access, by modified TEM	6	0	0	1 (16.7 %)	0	0	0	0
Total	435	0	1 (0.2 %)	5 (1.1 %)	2 (0.5 %)	0	0	0

CN central nervous system, IC intermediate care, ICU intensive care unit

Grade I any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside

Grade II requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included

Grade III requiring surgical, endoscopic, or radiological intervention, IIIa intervention not under general anesthesia, IIIb intervention under general anesthesia

Grade IV life-threatening complication (including CNS complications such as brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks) requiring IC/ICU management, IVa single-organ dysfunction (including dialysis), IVb multiorgan dysfunction

Grade V death of patient

Suffix “d” if the patient suffers from a complication at the time of discharge, the suffix ‘d’ (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

The overall hospital stay was 2.1 days (range = 0–11 days). The length of hospital stay after the two transvaginal hybrid techniques did not differ in a statistically significant way ( $P = 0.80$ ), whereas the transvaginal hybrid technique with rigid laparoscope registered a significantly shorter hospital stay compared to that of the transgastric and transumbilical access technique with flexible endoscope ( $P = 0.02$ ), but not compared to that of the transvaginal technique by modified TEM ( $P = 0.051$ ). No other statistical significance was observed.

## Appendectomies

Thirty-three cases of appendectomy were included in the ECR, all for acute appendicitis, as reported by three centers. Age varied consistently among groups, but not in a statistically significant way. BMI among the groups did not differ significantly. In 28 cases the access was transgastric with the aid of a flexible endoscope, in 3 patients the access was transvaginal with the aid of a flexible endoscope [20], and in two cases the access was transvaginal with the aid of a rigid laparoscope [21].

The transgastric procedures were performed by puncturing the gastric wall with a needle knife and dilating the incision by balloon inflation under vision of a transumbilical 5-mm laparoscope only for safety reasons. Appendectomy was then performed by monopolar flexible forceps introduced through the working channel of the endoscope. The appendix was resected using a HF loop after positioning an endoscopic loop at the base of the appendix.

Among the transvaginal techniques, the two cases performed with only rigid instruments and laparoscope had direct insertion of a 12-mm transvaginal trocar, while the other three cases had the posterior vaginal fornix surgically opened. All were hybrid procedures that needed a transabdominal trocar. Laparoscopic stapler or knots were used at the base of the appendix in the transvaginal approach. In two of the three (67 %) transvaginal cases performed with the aid of a flexible endoscope another transabdominal trocar was added for better tissue manipulation, while two procedures (7.1 %) performed by transgastric techniques were converted to standard laparoscopy for the same reason.

The mean duration of the appendectomies was 93.5 min (range = 40–170). The mean duration was 99.8 min (range = 59–170) in the transgastric group and 59 min (range = 40–90) in the transvaginal groups ( $P = 0.002$ ). Among the transvaginal cases, mean operative time was 42.5 min (range = 40–45) for those cases performed with the aid of a rigid laparoscope and 70 min (range = 60–90) for those performed with the aid of a flexible endoscope, with no statistically significant difference.

Tables 5 and 6 give hospital stay and complications of the different techniques used for appendectomy. Two procedures (7.1 %) in the transgastric group were converted to laparotomy

because of a tear on the cecum serosa. Over-the-scope clip (OTSC) closure of the gastric access was effective in all but one patient (3.5 %) who required further laparoscopic suturing. Two postoperative abscesses (7.1 %) in the Douglas pouch were also observed after the transgastric technique, the result of persistent septic fluid collection, and were treated by laparoscopic drainage. No complications were observed in any transvaginal technique cases. There was no statistically significant difference among the groups. Complications are classified according to the Dindo–Clavien classification scheme [19] in Table 7.

Table 5

NOTES appendectomies included in the ECR divided per technique

Procedure	n	%	Centers	Age (years)	BMI (kg/m <sup>2</sup> )	Additional trocar	Conversion to laparoscopy <sup>a</sup>	Conversion to laparotomy	Operative time (min)
Transgastric and transumbilical access, with flexible endoscope	28	84.8	1	30.1 (16–73)	25.9 (17–45)	0	2 (7.1 %)	2 (7.1 %)	99.8 (59–170)*
Transvaginal and transumbilical access, with rigid laparoscope	2	6.1	1	23.0 (23–23)	18.9 (18–19)	0	0	0	42.5 (40–45)
Transvaginal and transumbilical access, with flexible endoscope	3	9.1	1	36.7 (31–42)	18.9 (18–19)	2 (67 %)**	0	0	70 (60–90)
Total	33	100	3	31.0 (16–73)	25.5 (17–45)	2 (6.1 %)	2 (6.1 %)	2 (6.1 %)	93.5 (40–170)

\* P = 0.002 vs. overall transvaginal techniques; \*\* P < 0.001 vs. every other technique

<sup>a</sup>Meant as the addition of more than one trocar, plus the one routinely used in the hybrid techniques

Table 6

Complications of NOTES appendectomies included in the ECR divided per technique

Procedure	n	Intraoperative	Postoperative	Overall	Hospital stay (days)
Transgastric and transumbilical access, with flexible endoscope	28	2 (7.1 %)	3 (10.7 %)	5 (17.8 %)	3.9 (1–9)*
Transvaginal and transumbilical access, with rigid laparoscope	2	0	0	0	1.5 (1–2)
Transvaginal and transumbilical access, with flexible endoscope	3	0	0	0	1.3 (1–2)
Total	33	2 (6.1 %)	3 (9.1 %)	5 (15.2 %)	3.5 (1–9)

\* P = 0.003 vs. overall transvaginal techniques

Table 7

Dindo–Clavien classification of complications of NOTES appendectomies included in the ECR divided per technique

Procedure	n	Dindo–Clavien classification						
		I	II	IIIa	IIIb	IVa	IVb	V
Transgastric and transumbilical access, with flexible endoscope	28	0	0	0	3 (10.6 %)	0	0	0
Transvaginal and transumbilical access, with rigid laparoscope	2	0	0	0	0	0	0	0
Transvaginal and transumbilical access, with flexible endoscope	3	0	0	0	0	0	0	0
Total	33	0	0	0	3 (9.1 %)	0	0	0

For definitions of grades, see footnotes to Table 4

The overall mean length of hospital stay was 3.5 days (range = 1–9). The length of hospital stay after the transgastric technique was 3.9 days (range = 1–9), significantly longer than after the transvaginal techniques for which the mean length of stay was 1.4 days (range = 1–2) ( $P = 0.003$ ).

### Colorectal surgery

Thirty-two cases of colorectal surgery were included in the ECR by two different centers. In 12 cases the indication was rectal prolapse and in 18 cases it was diverticulitis; all had a sigmoidectomy, and in one case a sacropexy was combined with the sigmoidectomy. The other two cases were a subtotal colectomy for slow transit constipation [22].

All but one case was performed through the rectum itself under vision with a 5- or 10-mm rigid laparoscope, with the intentional addition of two 5-mm trocars at the beginning of the procedure [23]. The colon-lumen was clamped at the level of the descending segment. Then a 28-mm anvil of a circular stapler was advanced transanally up to the descending colon to the future anastomotic site. This was followed by an incision of the colon at the distal anastomotic site. Here, a transanally introduced linear stapler exited the colon into the abdominal cavity and was used to transect the proximal end of the sigmoid segment. The central pin of the anvil penetrated through the bowel wall at the stapled line to be available for later anastomosis. Once the sigmoid segment was resected and detached, a grasper was advanced transanally to grasp the specimen in the abdomen and pull it through the luminal opening at the distal rectosigmoid stump via the rectal lumen and bring it outside. A purse-string suture was placed at the distal rectosigmoid stump to complete the anastomosis with the circular stapling device inserted transanally [22]. Mean operative time was 134.5 min (range = 55–184). One case was converted to laparoscopic surgery. In four cases a postoperative complication was observed, including one case of bleeding, one case of minor leakage, and two cases of subileus; all recovered spontaneously with no need for further treatment. Hospital stay was 9.9 days (range = 6–17).

The second technique, used in one case, began with a transvaginal approach created surgically and three trocars were added under vision of a 5-mm rigid laparoscope or a flexible endoscope alternatively [24]. The anastomosis was hand-sutured. The intervention was described as a left hemicolectomy. The operative time for this case was 120 min, there were no intraoperative or postoperative complications, and the patient was discharged 3 days later.

### Peroral esophageal myotomy

Twenty peroral esophageal myotomies from two different centers were included in the ECR. In 18 cases the indication was achalasia, while there were two cases of diffuse esophageal spasm. In all

cases an 11-mm operative gastroscope with a large but single operative channel was used. Mean operative time was 99.6 min (range = 60–185). A postoperative complication was observed in three cases, including two cases of emphysema and one case of pneumothorax; all recovered spontaneously with no need for further treatment. Mean hospital stay was 7.4 days (range = 4–13).

## **Gastric resection**

Six cases of gastric resection for gastrointestinal stromal tumors (GIST) were included in the ECR, all from a single center. The transluminal access and gastric resection were performed with a flexible needle knife inserted through the flexible endoscope's working channel under the vision of a 10-mm laparoscope [25]. All were hybrid procedures that included two transabdominal trocars to allow suturing of the defect at the end of resection. The mean operative time was 109.2 min (range = 61–155). No intraoperative or postoperative complications were observed. The mean hospital stay was 7.5 days (range = 7–9).

## **Other procedures**

Other procedures reported in the ECR were as follows:

- Two cases of bilateral adnexectomy for a BRCA-1 mutation and ovarian cysts, respectively. The procedures were performed via flexible endoscopy through the gastric wall and the vagina and lasted 170 and 240 min, respectively, with no complications. Hospital stay was 3 days in both cases.
- One case of transesophageal necrosectomy for a mediastinitis due to a surgical leak after esophageal resection. The leak hole was widened and treated by transmural endoscopic mediastinal necrosectomy. This was performed with a flexible endoscope and a needle knife inserted through the single working channel. The procedure lasted 15 min and there were no complications. Hospital stay was 25 days due to the primary disease.
- One case of liver resection, consisting of a V segment atypical resection, performed transvaginally via a surgical opening and in a hybrid fashion by adding a 5-mm transumbilical port and alternately using a 12-mm double-channel flexible endoscope and a 5-mm rigid laparoscope. An additional abdominal 5-mm trocar was added for better manipulation. The specimen retrieved was 10 × 5 × 5 cm. Operative time was 180 min. No complications were reported and the patient was discharged the next day.
- One case of liver cyst fenestration, performed transvaginally via a surgical opening in a hybrid fashion by adding a 5-mm transumbilical port and using a 12-mm double-channel flexible endoscope. Operative time was 140 min and there were no complications reported. The patient was discharged 7 days later.
- One case of peritoneal adhesiolysis for acute obstruction, performed transvaginally via a surgical opening in a hybrid fashion by adding a 5-mm transumbilical port and alternately using a 12-mm double-channel flexible endoscope and a 5-mm rigid laparoscope. Operative time was 45 min and there were no complications reported. The patient was discharged the next day.
- One case of small bowel resection, performed transgastrically via a needle knife opening and alternately using an 11-mm single-channel flexible endoscope and a 10-mm rigid laparoscope. An additional abdominal 10-mm trocar was added for better manipulation and the use of a laparoscopic stapler. Operative time was 195 min since the operation had to be converted to laparoscopic surgery because of malignancy.

We compared the distribution and safety of the different transluminal approaches included in ECR (Table 8). Transvaginal access was the most common, having been used in 435 cases, with 10

complications (2.3 %) reported (2 intraoperative and 8 postoperative) and a statistically significant difference versus each other group ( $P < 0.001$ ). Transgastric access was the second most used within the ECR, with 46 cases and 5 complications (10.6 %) reported (2 intraoperative and 3 postoperative). Transrectal access was used in 31 patients, with 4 complications (12.9 %), all postoperative. The transesophageal approach is in fact the only pure NOTES technique included in the ECR. It was used in 21 patients, with 3 complications (14.3 %), all postoperative. No other statistical significance was observed.

Table 8

Dindo–Clavien classification of complications of NOTES procedures included in the ECR divided per site of transluminal access

Procedure	n	Dindo–Clavien classification						
		I	II	IIIa	IIIb	IVa	IVb	V
Transgastric and transumbilical access, with either flexible or rigid laparoscope	46	0	0	0	3 (6.5 %)	0	0	0
Transvaginal and transumbilical access, with either flexible or rigid laparoscope	435	0	1 (0.2 %)	5 (1.1 %)	2 (0.4 %)	0	0	0
Transrectal and transumbilical access	31	2 (6.4 %)	2 (6.4 %)	0	0	0	0	0
Transesophageal	21	0	3 (14.3 %)	0	0	0	0	0
Total	533	2 (0.4 %)	6 (1.1 %)	5 (0.9 %)	5 (0.9 %)	0	0	0

For definitions of grades, see footnotes to Table 4

No Dindo–Clavien complication grade IV or V was registered in any group.

## Discussion

The EURO-NOTES Clinical Registry (ECR) is a combined platform of the EAES and the ESGE (<http://www.euro-notes.org>). NOTES is developing in a way that is neither purely surgery nor purely therapeutic endoscopy. As such, collaboration between the two leading societies is essential. NOTES is just a small part of the scope of these organizations. Neither EAES nor ESGE alone could likely have galvanized the NOTES effort as the EURO-NOTES Foundation has. Yet, the EURO-NOTES Foundation is a bridge between the two parental organizations that has served all parties well to this point.

After experiencing a true paradigm shift that significantly changed patient management, such as the introduction of laparoscopic surgery, we are likely to be on the verge of another paradigm shift with NOTES [26]. The registry was developed to compile safety data to be used by ethical committees in order to authorize human trials and to implement the interface between medical societies, industry, and regulatory offices. Within its first 2 years of activity, 533 cases were enrolled from different centers, encompassing transvaginal, transgastric, transanal, and transesophageal procedures. This study of the ECR represents only a cross section of the actual implementation of NOTES techniques in Europe, but it is still apparently representative of the variety of techniques described. Not surprisingly, cholecystectomy is the most performed procedure; however, appendectomy, bowel resection, necrosectomy and others are also reported.

Based on an extremely flexible and expandable architecture, the ECR registry has several features, including the uploading and streaming of videos related to each procedure. It contains online statistical analysis by Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables, comparing selected groups of patients.

The importance of a registry is indicated by the amplitude of the different activities proposed and performed, although in an embryonic phase. The existence of a registry would help the clinical challenge to proceed by avoiding repeating errors and exchanging fruitful experiences. To our knowledge the ECR is one of the largest registries worldwide.

As one of the goals of such a registry, the general impression is that the overall safety of NOTES procedures performed in selected patients at centers where there has been adequate training is guaranteed. It is interesting to observe that as with the introduction of laparoscopy, cholecystectomy is the procedure used while developing and testing a novel surgical technique. For this reason cholecystectomy comprises the vast majority of procedures included in the registry so far, with more than 85 %.

To our knowledge this is the only registry that includes all four NOTES techniques for cholecystectomy described so far. Of course, each has its own pros and cons, which we tried to statistically analyze. Undoubtedly, results are influenced by the learning curve of each technique and probably also by the step-by-step modifications to the technique that occur while learning it. This is even more relevant when, despite the consistency of the series, as many as nine centers contributed to the group of transvaginal cholecystectomies with the aid of a flexible endoscope, fragmenting the experience, while only two centers contributed to the group of transvaginal cholecystectomies with the aid of a rigid laparoscope, thus probably achieving better standardization.

All techniques, except peroral myotomy, are, in fact, hybrid because of the addition of at least one transabdominal trocar, generally for better tissue manipulation. In two cases the hybrid technique was adopted for safely monitoring the creation of colpotomy; they included a transvaginal cholecystectomy by modified TEM instrumentation and a transgastric appendectomy by flexible endoscopy. It should be mentioned that a pure NOTES technique is the goal but the principles of safety must be respected, at least during the initial experience. The fact that very few pure NOTES techniques are described in the ECR reflects the lack of dedicated platforms for NOTES if not the modified TEM instrumentation.

In regard to cholecystectomy techniques, the two most common, i.e., hybrid transvaginal with the aid of either a flexible endoscope or a rigid laparoscope, showed a need of adding a transabdominal trocar in only about 5 % of the cases, with no difference between the two techniques. Similarly, the observation of intraoperative complications and the need to convert to laparoscopy was negligible. The overall incidence of postoperative complications was extremely low. No statistically significant difference between the two main groups was observed in terms of complications, number of trocars used, and number of trocars added. The lower operative time in the hybrid transvaginal technique with the aid of a rigid laparoscope might reflect its similarity to a standard multiport laparoscopic technique as well as the standardization of a consistent series of only two centers compared to the fragmented data reported by many different centers. This has probably increased confidence in the procedure and reduced the duration of the learning curve.

Among the other cholecystectomy techniques, the transvaginal technique by means of a modified TEM instrumentation scored a relatively low operative time. Hospital stay was also short and homogeneous among the different cholecystectomy techniques; this was probably related to local policies. The hybrid transgastric cholecystectomy technique was found to be safe, with a fast recovery time and a shorter hospital stay than expected. Despite the lack of a proper platform, it requires the aid of two transabdominal trocars compared to the one for transvaginal procedures, and the time to complete the procedure is almost double. The absence of any complications reported in this group might be related not only to patient selection and the expertise of the operators, but also to the high incidence of trocar addition and conversion to standard laparoscopy.

Unfortunately, no data about dyspareunia are available. These data would be interesting especially for comparing the different techniques used to create the transvaginal access, i.e., surgical incision or direct insertion of a trocar. It is interesting to note that despite the safety of the procedures proposed, these series account for only about 20 % of all the cholecystectomies performed by the

centers contributing to the registry [27], which shows a high selectivity of cases and extreme caution when proposing these novel techniques.

The analysis of appendectomy cases also offers a variety of techniques, including transgastric and transvaginal approaches. The attempt to perform a pure NOTES technique by means of a transgastric approach allows assessment of the feasibility and safety of the procedure, with two conversions to laparotomy and the safety of the gastrotomy closure by OTSC as already reported [17, 28, 29], and only one case of incomplete success that required further laparoscopic surgery. In fact, OTSC has also proven to be extremely reliable and a success in clinical practice when used to close digestive dehiscence and fistulas [30–32].

Finally, the relatively long hospital stay reported for all of the other procedures described, when compared to the hospital stay for standard laparoscopic techniques, even in the absence of significant complications, reflects the caution used when introducing any novel technique into clinical practice.

The analysis of the database allowed us to realize that in the lack of any really dedicated platform for NOTES procedures, the more similar the technique is to standard laparoscopy, the easier it is to score in terms of operative time, although, in general, complications were very low, thus impeding any group analysis. The continuing assessment and validation of the proposed techniques cannot allow us to confirm that the proposed benefits, the real motivation for performing NOTES, could be seen. On the contrary, while the operative time and hospital stay for any transvaginal cholecystectomy technique seems reasonable compared to standard laparoscopy, this is not the case for any of the other techniques proposed, probably because of the inevitable caution that the introduction of any novel technique entails.

The general impression is that after the initial burst of enthusiasm for NOTES techniques, the slower development of dedicated platforms and instruments and the ongoing diffusion of single-access techniques [33] has mitigated the diffusion and use of NOTES. Dedicated platforms comprising all surgical instruments needed for visualization, dissection, manipulation, and retraction will probably bring the advantage of reproducing a surgical environment through a single transluminal access, thus avoiding the need for transabdominal trocars, so-called hybrid procedures. It is difficult to predict what the new barriers will be. At the same time, once the techniques are validated, appropriate training and accreditation should be provided by scientific societies through certified experts in the field. Despite this, NOTES implementation into clinical activity is ongoing, with excellent results although in extremely selected cases. What benefits NOTES would have for the patient is still too early to be assessed, but research on the topic should go on to provide new solutions to technical problems before a real validation is performed.

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