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Natural orifice transluminal endoscopic surgery (NOTES): initial experimental results

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A B S T R A C T

Introduction: The advent of natural orifice endoscopic surgery (NOTES) and new prototypes for performing this surgical procedure led us to design an experimental animal surgical programme.

Material and method: NOTES was performed over a period of 1 year, in sows, following the European guidelines on the use of experimental animals. Ninety operations were performed with no animals surviving. The following aspects were assessed: *a)* access route complexity (transgastric, transvaginal, transesophageal, and transumbilical); *b)* support measures for temporal/spatial orientation; *c)* technical possibilities for visceral orifice closure (clips, t-bars®, Obesco® clips, and endoscopic suture). Resections of fallopian tubes, ovaries, gallbladder, mediastinal lymph nodes, tail of the pancreas, and gastrojejunal derivations were performed with 1 or 2 endoscopes.

Results: This experience enabled us to highlight a series of technical aspects essential for these techniques: *a)* pneumoperitoneum with CO_2 is safer for entry; *b)* orifice size is important to limit contamination; c) puncture entry and guided dilation is safer; d) good gastric exit location makes it easier to approach viscera to be resected; e) intra-abdominal haemorrhage is difficult to control; f) leak-free closure cannot be guaranteed with clips, but t-bars® and Obesco® clips may be effective; and *g)* endoscopes that permit triangulation may facilitate the dissection and endoscopic suture.

Conclusions: NOTES requires a multidisciplinary team comprising laparoscopic and endoscopic surgeons. Pure NOTES is complex and hybrid forms or transumbilical route could be intermediate steps.

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Cirugía endoscópica transluminal NOTES: resultados experimentales iniciales

Palabras clave:
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R E S U M E N

Introducción: La aparición de la cirugía endoscópica transorificial (NOTES) y de nuevos prototipos para su realización nos llevó a diseñar un programa de cirugía experimental.
Material y métodos: Se ha realizado durante 1 año cirugía de NOTES en cerdas, cumpliendo la normativa europea de experimentación animal. Se han practicado 90 intervenciones sin supervivencia animal. En este estudio se ha evaluado: *a)* complejidad de las vías de acceso (transgástrica, transvaginal, transesofágica y transumbilical); *b)* técnicas de ayuda para la orientación temporoespacial, y *c)* posibilidades técnicas de cierre de los orificios viscerales (clips, t-bars®, clips de Obesco® y sutura por endoscopia). Las intervenciones practicadas mediante uno o dos endoscopios han sido: anexectomía, colecistectomía, biopsia de adenopatías mediastínicas, pancreatectomía distal y gastroyeyunostomía.
Resultados: Esta experiencia nos ha permitido conocer una serie de aspectos técnicos imprescindibles para el desarrollo del NOTES: *a)* el neumoperitoneo con CO_2 es más seguro para la entrada; *b)* el tamaño del orificio es importante para limitar la contaminación; *c)* la entrada con punción y dilatación con guía es más segura; *d)* la buena localización de la salida gástrica facilita el abordaje de las vísceras a disecar; *e)* la hemorragia intrabdominal es de difícil control; *f)* el cierre con garantías absolutas de fuga no existe, los clips no lo garantizan, los t-bars® y clips de Obesco® y la sutura endoscópica pueden funcionar, y *g)* la posibilidad de utilizar endoscopios que triangulan facilita la disección.
Conclusiones: La NOTES requiere de un equipo multidisciplinario con cirujanos laparoscopistas y endoscopistas. La realización de NOTES pura es compleja; posiblemente las formas híbridas o la vía transumbilical sean fases intermedias..

Introduction

Twenty-one years have passed since the first laparoscopic cholecystectomy was performed and the following surgical revolution that took place until the apparition of a new concept midway between the flexible and the rigid endoscopy, called NOTES (natural orifice transluminal endoscopic surgery) that consists of accessing the abdominal or thorax cavity through natural orifices (mouth, vagina, anus, or urethra). Kalloo et al[1] described the first peritoneoscopy in 2004, and afterwards the APOLLO group was formed, composed by gastroenterologists and surgeons interested in the development of NOTES. In these 5 years, different procedures such as the tubal ligation,[2] cholecystectomy,[3,4] access to the abdominal cavity via NOTES[5,6] and visceral resections[7] have been described in experimental models.[8] A White Paper was written in 2006, which is an authentic roadmap with the basic principles and clinical application of NOTES. Reddy et al[10] performed the first intervention in humans (transgastric appendicectomy) in 2006, and later Marescaux et al[11] and Swanström performed the first transvaginal and transgastric cholecystectomy. Currently, many hundreds of hybrid transvaginal or transgastric cholecystectomies have been performed.[12,13] However, this study focuses on the description of the intensive training and development required to perform NOTES.

Material and method

In June 2007, we designed an experimental research project in NOTES. The goal was to learn the routes of transorifice treatment, to evaluate the complexity of opening and closing, and the possibility to intervene in diverse organs. WIDER-Barcelona (World Institute for Digestive Endoscopy Research) was created at the same time, formed by a multidisciplinary team including endoscopists, surgeons, and veterinarians.

A NOTES project was developed in a non-survival porcine model using sows of 35-40 kg. The project was approved by the ethics committee of our hospital and all animal-handling protocols were followed. The animals were kept on a diet 24 h before surgery. The unit has 2 flexible endoscopy devices and 2 laparoscopic device. Two flexible endoscopes with 1 single channel (GIF-1TQ160, GIF-H180) and two 2 channel flexible endoscopes (GIF-2T160, and multiflexor R-scope, Olympus). The experimental design included 4 phases that are shown in Table 1. From July 2007 to July 2008, 90 animals were operated on.

In a first phase, the transvesical route was not performed because of a lack of material and the transrectal route was discarded because of faecal contamination of the abdominal cavity. In the second phase, a transumbilical laparoscope was used to help in the intra-abdominal orientation of the flexible

Table 1 – Description of the 4 phases of the experimental trial

Experimental phases	Objectives	Procedures per animal, No.	Animals, No.
First stage	Access routes with/without CO_2 Transgastric route (14) Transgastric route (10) Transoesophageal route (4) Transumbilical route (2)	1–2	16
Second stage	Space-temporal orientation (50)	1 in the first 50 animals	
Third stage	Orifice closure Haemostasis clips (11) T-bars (19) Obesco clips (10) Laparoscopic sutures (6) Endoscopic sutures (5)	1 procedure per animal 51 gastric routes, 23 vaginal routes	74
Fourth stage	Visceral surgery Oophorectomy (20) Cholecystectomy (54) Distal pancreatectomy (4) Lymphadenectomy (4) Gastrojejunostomy (6)	1–2 88 procedures	74
Total of procedures and animals		More than 150 procedures	90

endoscope. In the third phase, different types of gastric and oesophageal closures were tried; we used the pressure inflation of the stomach and we evaluated it for leaks by immersing in water to visualize escaping air. And in the fourth phase, hybrid, assisted and pure techniques were performed using 1 or 2 fibre-endoscopes with 1 and 2 channels.

Results (Table 1)

First Stage

Access to the abdominal cavity with CO_2 pneumoperitoneum

In the first 5 animals, a direct transgastric entry was performed without pneumoperitoneum causing 2 lesions (spleen and colon). The gastric transluminal technique was used for puncture entry without pneumoperitoneum and the Verres needle for the entry with pneumoperitoneum. The pneumoperitoneum with a Verres needle and inflation with CO_2 increased the access safety margins for the stomach or the vagina.

Transgastric and transvaginal treatment

Eigthy-eight animals were used to evaluate these treatment routes. We needed 24 cases to standardise gastric and vaginal entry. The difficulties of the transgastric or transvaginal access can be summarised as:

Gastric/vaginal exit point. The pylorus should be visualised to evaluate the exit point. The place for gastric puncture is variable depending on the organ to be operated on. The ideal place to treat the liver is the anterior side, 3-4 cm from the pylorus. The hilum can be adequately visualised in retroflection. To access the inframesocolic space, the most adequate point in the greater curvature, in the anterior side, to avoid the omentum. The ideal exit point of the vaginal route is at the front of the uterine horns.

Orifice size. Orifice size should be adjusted to the diameter of the endoscope. Puncture with balloon dilation over guide is the best method.

Haemorrhage. Haemorrhaging may occur due to 2 mechanisms: organ lesion due to blind puncture (spleen or liver) or by injuring the gastric wall when sectioning.

Puncture and dilation or cutting the gastric or vaginal wall. Puncturing the gastric or vaginal wall with a fine needle and previous pneumoperitoneum is the safest technique. The insertion of a guide is indispensable to direct the dilating balloon that makes it possible to open the puncture orifice and the passage of the abdominal cavity for the endoscope. Vaginal access is simpler than gastric access: puncture and dilation should be done in the anterior side to avoid injuring the urinary bladder (Figure 1).

Gastric emptying and leakage of content. Making an orifice at the gastric level adjusted to the diameter of the endoscope decreases abdominal contamination from gastric fluids.

Transoesophageal route

We have performed this procedure in 4 occasions. The oesophageal wall is sectioned using electro-coagulation and mediastinal inflation without pressure control producing pleural breakage and respiratory failure in the animal. The risk of massive haemorrhaging is important when entering blindly with electrocautery.

Transumbilical route

This procedure was performed in 2 cases. Transumbilical access with a flexible endoscope presents more disadvantages than the rigid laparoscope without enhancing visualisation, as the lack of rigidness of the endoscope makes it harder to use.

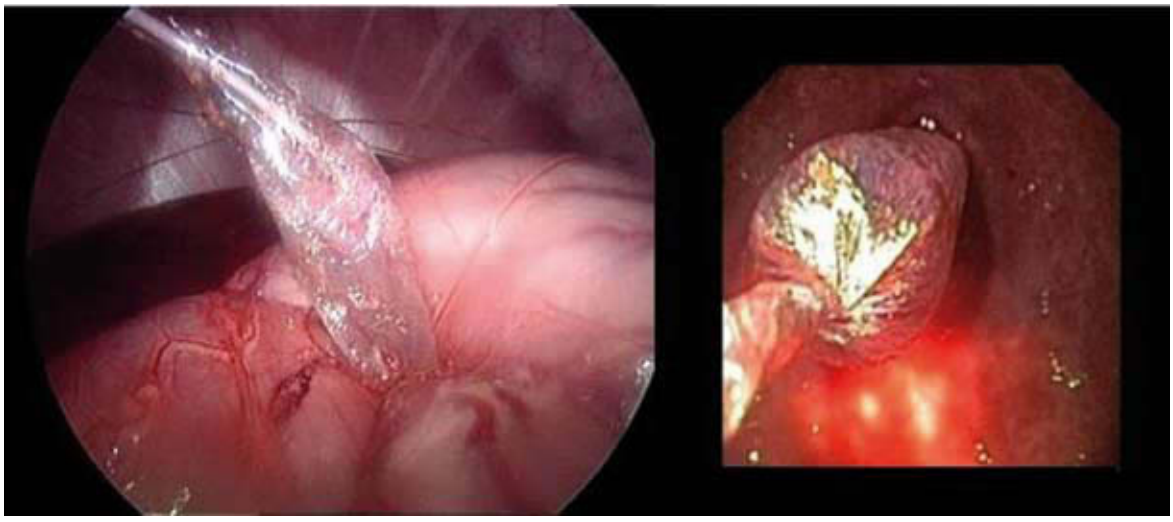

Figure 1 – Transgastric opening with dilation balloon (laparoscopic and endoscopic view).

Second stage

Space-temporal orientation

The flexible endoscope has been designed to be introduced in the digestive tract. Its movable termination allows for limited lateral movements and broader anterior and posterior flexibility. The fish eye's image, designed to visualise the inside of the digestive tract, deforms the intra-abdominal anatomy. Without the support of the luminal wall, the endoscope "falls" into the cavity at the mercy of organs and gravity. At the same time the retroversion of the endoscope inverts the right and left sides, which makes its use more difficult. We used a 10 mm transumbilical optic in the first 50 animals to help us with the intra-abdominal orientation. This manoeuvre helped with the spatial orientation in the abdomen working in retroflection, controlling the entry orifice, the adequate exposure of the organ to be resected, controlling haemorrhaging, in the evaluation of abdominal contamination, controlling the closure of orifices and recording the intervention and revision of errors.

Third stage

Entry orifice closure

This is the technical issue that is least resolved. A safe closure technique will allow for further advances with animal survival studies and to evaluate their possible use in humans. The different methods were used:

Haemostatic clips (20 cases). The principle inconvenience is that they are designed for haemostasis and the amount of tissue clamped is small. They connect the mucosa but not the whole gastric wall, which gives a false image of an adequate closure.

T-bars®/T-tags® (10 cases). They are specifically designed for the closure of the gastric wall, as they penetrate the entire thickness of the wall using a needle for puncturing. They require a pneumoperitoneum and it is carried out with intragastric controlled puncture, but not extragastric puncture which presents a risk of haemorrhage or organ damage. When bringing the t-bars® together to close the orifice, a correct convergence of the mucosa is produced, but the serosa is opened. Currently, it is the most airtight closure than can be performed by endoscope (Figure 2).

Obesco® clips (10 cases). These clips are specifically designed for the closure of orifices. Each side of the perforated wall is pulled with a clamp with 2 openings, and the clip surrounds the perforation, sealing it with its closure. It is easy to use and there are no risks of damaging structures outside of the orifice; it is also very airtight (Figure 3).

Endoscopic sutures (6 cases). Since several months, we have had an Olympus prototype to manually suture with two needle-drivers by endoscope. The goal is to suture with conventional needles and sutures by endoscope. The necessity to work with two instruments parallel, without triangulation capacities, makes it is harder to suture and especially to complete the surgical knots.

Laparoscope-assisted closure (5 cases). Three 5 mm trocars are needed to perform a closure by laparoscope, 2 for instruments and 1 for the 5 mm optic. The needle and sutures can be introduced in a bag using the gastric endoscopic route (Table 2).

Fourth stage

From July 2007 to July 2008, different interventions have been performed on the experimentation animal (Table 3):

Hybrid techniques: flexible endoscopy and umbilical trocar

Initially, all of the treatments were hybrids to facilitate the entry of the endoscope, the space-temporal orientation and the closure of the orifice. It is defined as laparoscope-assisted endoscopic surgery.

Hybrid transgastric treatment. This method is ideal for surgery on inframesocolic organs. The orifice has to be on

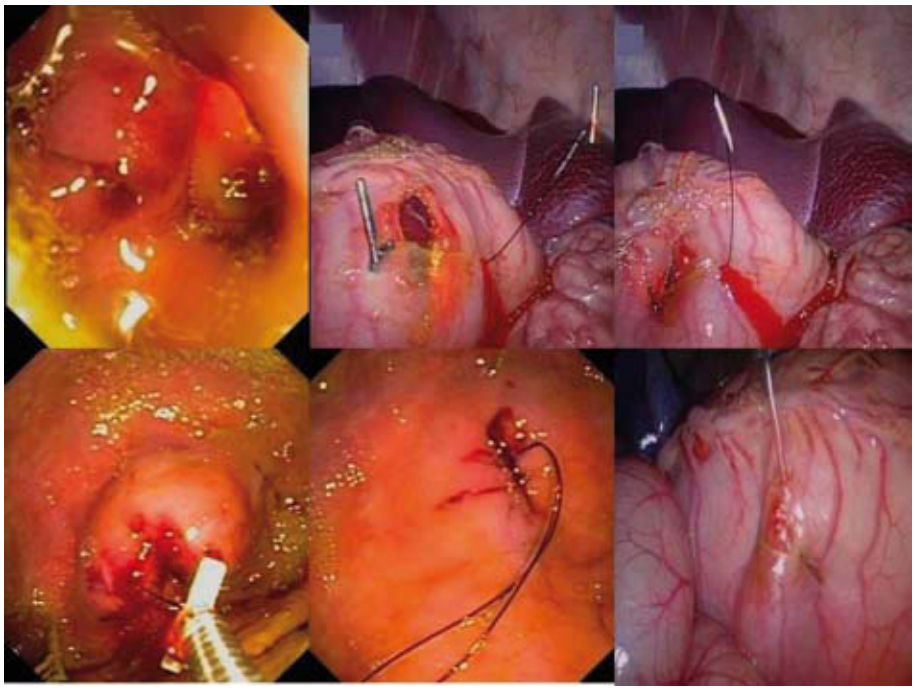

Figure 2 – Closure sequence gastric wall t-bars.

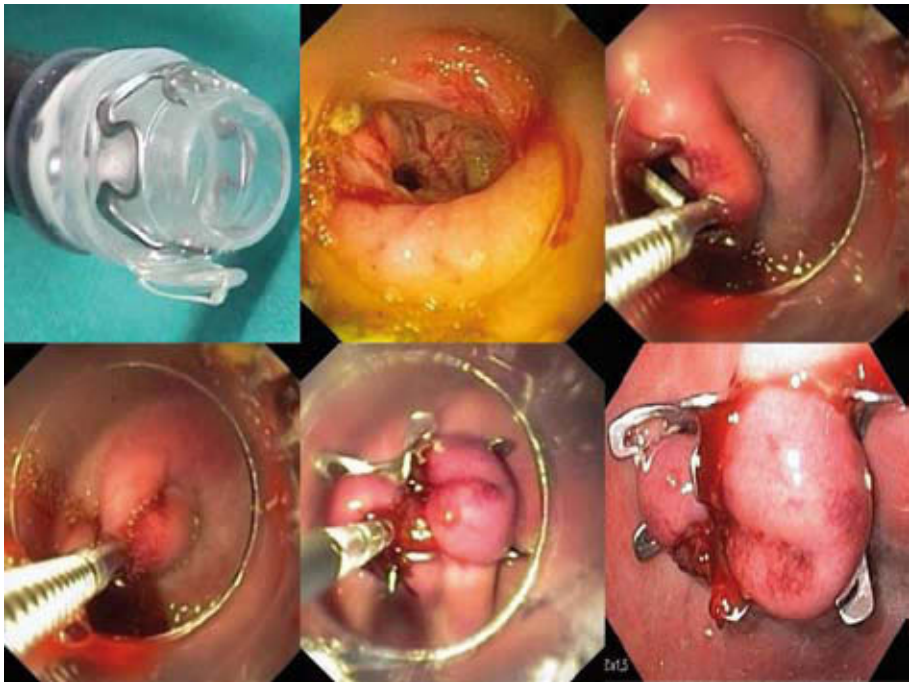

Figure 3 – Closure with obesco clips.

the anterior side and close to the greater curvature of the stomach. The surgeons work from the front. Laparoscopic pincers are needed to help move organs. Endoscopic pincers handled at a distance are not sufficiently rigid to move the abdominal organs.

- Transgastric anexectomy (10 cases). Transgastric anexectomy is an easy technique. With an electrically charged loop, sectioning can be done without causing bleeding.
- Cholecystectomy (22 cases). This is a complex technique as it is performed in retroflection, with the corresponding

Table 2 – Types of orifice closure. Safety from + to +++++

Gastric closure suture	Haemostasis clips	T-bars	Obesco clips	Endoscopic suture	Laparoscopic
Endogastric vision	++	++++	++++	+++++	–
Check for leakage	+	+++	+++	++++	+++++
Technical difficulty	++	++	+	+++++	+
External laparoscopic vision	+	++		–	+++++

Table 3 – Surgical techniques performed

Hybrid techniques with flexible endoscope and rigid laparoscope	Transgastric treatment (42 cases) Transvaginal treatment (17 cases) Transumbilical treatment (2 cases)
Pure techniques with a transgastric or transvaginal endoscope	Transgastric (6 cases) Transvaginal (6 cases)
Pure techniques with 2 simultaneous endoscopic treatments (gastric and vaginal)	3 cases

inversion of the normal image. The gallbladder is lifted up with a laparoscopic pincer for complete visualisation, as the hepatic lobes of the pig make it difficult to see. The endoscope dissects with vertical or transversal movements, but it has a hard time working diagonally. The haemostasis clips are placed to clamp the artery and the cystic duct together or separately. The fine vesicular wall of the pig makes extirpation from the vesicular floor difficult. The endoscopic hook or the coagulation point can be used.

- Distal pancreatectomy (4 cases). The tail of the pancreas in pigs is surrounded by peritoneum and spleen vessels are more centrally located making its dissection possible with an electrically charged loop.
- Gastrojejunostomy (6 cases). The performance of an anterior gastrojejunostomy is feasible.[14] The adequate selection of the proximal loop requires laparoscopic help. Clips or t-bars® are used for fixation to the stomach.

Hybrid transvaginal treatment

- Cholecystectomy (17 cases). Orientation is better than in the superior route. However, the endoscope is farther away from its object and it tends to move spontaneously, altering the fixed view. Help with a trocar to retract the gallbladder is obligatory. Gallbladder dissection is more similar to the classic method without retroflection.

Hybrid transumbilical treatment

- Cholecystectomy (2 cases). There are no advantages to using this method compared to conventional laparoscopic surgery. The flexible endoscope makes stable vision difficult and requires a trocar to retract the liver.

Pure techniques with a transgastric or transvaginal endoscope

Pure NOTES is understood as a procedure performed without the help of any assisting trocars. Pure techniques present various problems:

Organ retraction. We have worked in 2 lines of research: the use of magnets and endoloops. We used external magnets to move the gallbladder. The magnets used must meet various requirements in order to be used: controllable and gradual strength to retract the organ; sufficient strength for contra traction needed to dissect; and a correct size/strength ratio of the magnet. Endoloops for gallbladder retraction and transparietal externalisation have been very helpful to dissect.

Haemorrhage control. Haemostasis methods for endoscopy are limited: argon, electrocautery, and clips. Copious haemorrhages are hard to aspirate with the fine tube of the endoscope.

Cholecystectomies. Six pure cholecystectomies have been performed. External retraction was done with endoloops or magnets. Extirpation time was longer than in the hybrid procedures (Figure 4).

Pure techniques with 2 simultaneous transgastric and transvaginal endoscopes (3 cases). The simultaneous use of 2 endoscopes allows for visibility and aid in gastric opening and closure. In addition, it allows for the retraction of organs with one of the endoscopes.

Cholecystectomy. We have performed 3 cholecystectomies with 2 simultaneous endoscopes. Control of the gastric opening and its closure is better; however, one endoscope loses all of its utility as it is only used for gallbladder retraction.

Discussion

The use of the endoscope by surgeons and the dissection of digestive organs by endoscopists are exceptional in clinical practice. Transorifice surgery requires a multidisciplinary team for its implementation. Teams capable of performing experimental interventions with guaranteed success and safety come from mutual learning. However, from the beginning of this experience there have been numerous

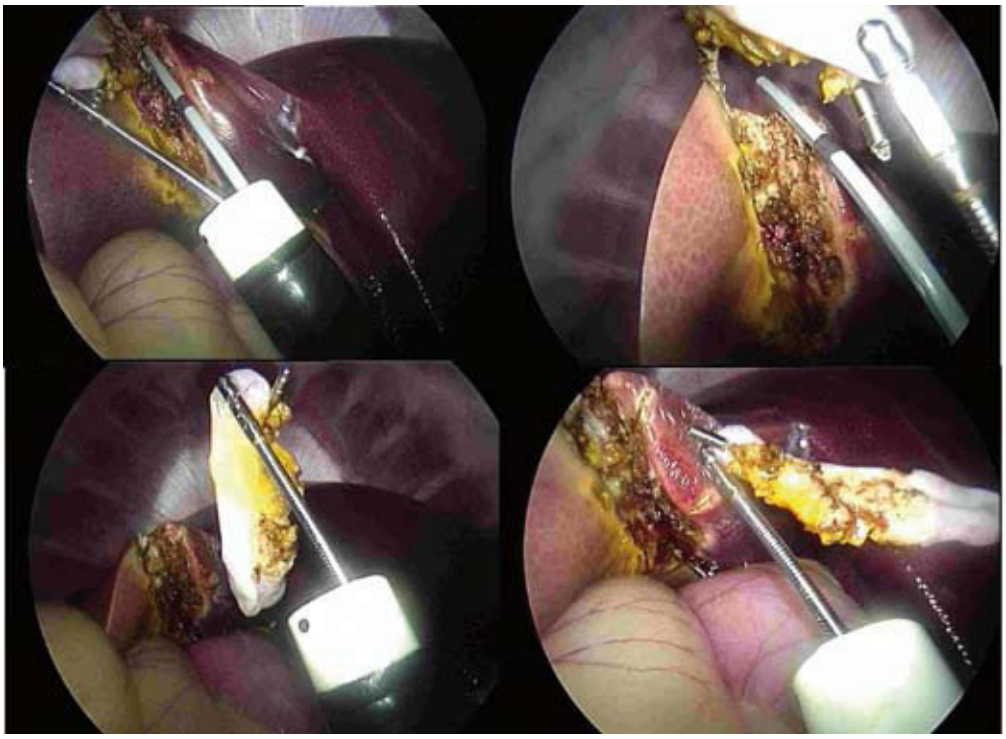

Figure 4 – Cholecystectomy with Rscope.

Table 4 – Controversies and technical difficulties in the development of NOTES

Gastric opening
Pneumoperitoneum
Orientation and navigation
Endoscope characteristics
Sterility
Handling of tissue
Triangulation
Ergonomic work platforms
Haemostasis
Gastric closure

technical and surgical problems that need to be solved and experimental surgery has allowed us to better understand (Table 4).

Gastric or vaginal entry is possibly the smallest problem. Almost all of the authors that perform experimental NOTES[15] recommend dilating over the cut of the wall, as it has a lower rate of haemorrhaging. Another advantage of dilation is the adaptation to the diameter of orifice to the size of the endoscope, to minimize leakage of gastric fluids. One unresolved problem is gastric re-entry without gastric distension by air leakage by the orifice in the wall, which entails a difficult process to locate the foramen again and exit the abdominal cavity a second time. The use of overtubes from the entry orifice helps in this problem.[16]

A pneumoperitoneum is mandatory to carry out intra-abdominal interventions and it is safer for gastric or vaginal entries.

Abdominal orientation and navigation is a difficulty that is usually overcome with experience. Getting used to working in retroversion is possible. Another problem is the poor working stability that the traditional flexible endoscopes offer. To solve this problem, endoscopes have been designed that become rigid once they are introduced, such as the Rscope prototype made by Olympus. Another solution is to use transporters which are semiflexible tubes with 2 to 4 channels where a fine endoscope can be inserted for vision and the other channels are for instruments of greater calibre. Fibre-endoscopes and laparoscopes have different characteristics (Table 5). The ideal endoscope would be a mixture: a semiflexible endoscope with external channels (Table 6).

Depending on the NOTES access route, the risk of infection varies. In the transgastric route, where we have more experience, contamination is produced from the oropharynx towards the abdominal cavity. Stomach germs in an acidic environment have little pathogenicity. Another experimental observation includes the progressive widening of the gastric orifice during its intra-operatory manipulation, and the leakage of fluids. Overtubes are being designed as a type of sterile hose that is placed from the mouth orifice to the gastric orifice to decrease infection by dragging.

Triangulation between pincer and scissors is vital to carry out an optimal and careful dissection. Existing endoscopes only allow working in parallel. Pincers that can be triangulated in their terminations will favour NOTES and allow the

Table 5 – Differences between the flexible and rigid endoscopes in the abdominal cavity

	Flexible endoscope	Rigid endoscope/laparoscope
Vision	Fish eye	Front vision 0º, 30º, or 45º
Vision quality	High definition	High definition
Aspiration	Yes (limited)	No
Zoom	No	Yes
Optic cleaning	Self-cleaning	No
Channels	Yes (1 or 2)	No
Inflation channel	Yes	No
Light	Yes	Yes
Triangulation (2 channels)	No (except Rscope)	No channels
Movable	Very difficult	Easy
Movement controls	Difficult for individual work	Not available
Manoeuvrability (abdomen)	Difficult	Easy
Mobility	+++	–

Table 6 – Characteristics of the ideal endoscope: "semiflexible endo-laparoscope with external channels"

Frontal, high definition vision, light, zoom, and self-cleaning
Various external channels of 3-4 mm diameter
Triangulation of the terminations of the channels
CO_2 inflation and aspiration channel
Changeable rigidness of the body and fixation of the position
Broad distal mobility
Electronic inversion and rotation of the image
Separate ergonomic controls for vision and working

performance of surgical knots. Currently there is one type of endoscope that allows triangulation: the Rscope (Olympus), and there are projects pending to commercialise triangulable pincers.

The robustness and pincer strength of endoscopic material is minimal. The industry is working to change the material, but these changes would require an increase in channel calibre of the endoscopes.

The ergonomics of the controls and channels of the existing endoscopes must change to make their use more comfortable and faster. The monitored platforms have a good future in this field and the manipulation of remote controls as well as of surgical robots will be used in the future.

Haemostasis is not easy with a fibre-endoscope. The small diameter of the instruments do not allow for fast and effective coagulation. Haemostasis clips are voluminous and slow to orient. The placement of one by one makes their application much slower. However, clips that are similar to those used in laparoscopic surgery and with multi-charge and bipolar coagulation pincers are being designed. Another problem added to haemostasis is the lack of effective aspiration and irrigation of coagula, from the limited diameter of the channels.

Gastric closure is the weakest point for NOTES. A safe closure is not guaranteed with any existing technique and laparoscopic aid and traditional suturing are required.[17,18] Currently, suturing in pure NOTES is very technically complex. Therefore, triangulation and manual or mechanic suturing will be the future.

Initiating a project in NOTES requires a multidisciplinary team. A non-survival experimental surgery program enables the analysis of all of the current possibilities of this type of surgery, its technical difficulties, its complications and its successes. It is possible that experimental trails with animal survival will be needed to consolidate the instruments that will later be sold in the market. Furthermore, the design of new endoscopes with larger channels and new pincer material is indispensable to be able to advance in this type of surgery. To do so, the joint efforts of the industry, the design of new instruments and the adaptation of those already existing are necessary. And, the future of transorifice surgery depends on said cooperation.

Scientific ethics requires solid and public experimental surgery before beginning research in human cases. It is possible that in the future NOTES substitutes certain common laparoscopic procedures and it will allow for advanced intraluminal endoscopy to advance. This journey will pass through different phases that include the hybrid procedures and the single port techniques, just as the mini-laparotomy preceded laparoscopic surgery many years ago.

The medical indications of this technique and by whom it will be performed in the future is a path that is yet to be taken and where all speculations are allowed.

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