

## General Surgery News

ISSUE: MARCH 2011 | VOLUME: 38:3

Natural Orifice Surgery: Is the Thrill Gone?

Excitement Has Waned, but Progress Continues, Experts Say

by Gabriel Miller

Five years ago, natural orifice transluminal endoscopic surgery® (NOTES®) seemed to be on the tip of everyone's tongue, at least in surgical circles. At that time, the first white paper on the topic had come out. Ambitious surgeons worldwide were publishing case studies. And news outlets were heralding "surgery without scars" as "the next great surgical evolution."

In the original white paper, lead author David Rattner, MD, outlined 12 challenges needed to be overcome for NOTES to be feasible and safe (*Surg Endosc* 2006;20:329-333). However, as surgeons worked out the kinks, interest in NOTES appeared to fade.

"The air has kind of gone out of the balloon for NOTES; at least that's the perception," said Dr. Rattner, chief of gastrointestinal and general surgery at Massachusetts General Hospital in Boston. "But I think that if you look at where we started five years ago, we have hit the milestones of the original white paper and now we are really into the hard work of doing a clinical trial. We are at a pivotal point."

Dr. Rattner was one of several panelists who spoke at the 12th World Congress of Endoscopic Surgery in National Harbor, Md., last spring addressing the future of NOTES. This assessment has come at a time when less radical techniques are taking center stage.

"I think the first telltale sign [of the popularity of NOTES] is to look around the room," said Jeffrey Marks, MD, associate professor of surgery at Case Western Reserve University School of Medicine in Cleveland. "We have a big room for this meeting but there are a lot of empty seats. I think four or five years ago, you would have found standing-room only with people lined up out the door. I think a lot of interest in NOTES now is '... well, it had its 15 minutes of fame, but now it's not very interesting.'"

As interest in NOTES cooled, surgeons shifted their gaze to single-port or single-incision surgery, which sidestepped many of the challenges NOTES posed. In the halls at national meetings, surgeons pointed to the fact that single-incision surgery could be done with "off-the-shelf" instruments and that a single-incision through the umbilicus was cosmetically almost as good. It seemed that surgeons collectively had taken a deep breath, stepped back and realized that they may have gotten ahead of themselves.

“I feel very strongly that the NOTES train was at the station, and everybody was also at the station but afraid to get on board,” said Paul Curcillo, MD, vice chairman of surgery at Drexel University School of Medicine in Philadelphia.

## **NOTES Progress**

Although excitement over NOTES appears to be fizzling, by several measures—case series, clinical trials, technological developments and published complications—NOTES is still progressing.

As of spring 2010, surgeons reported approximately 1,500 to 2,000 NOTES cases in humans worldwide. Groups in Europe and Latin and North America have advanced their NOTES to the clinical trial stage. And in the United States, a major trial was launched comparing NOTES with laparoscopic cholecystectomy with enough power to compare transgastric and transvaginal NOTES approaches.

Surgeons are continuing to make “steady progress in the arena of NOTES,” said Eric Hungness, MD, assistant professor of medicine at the Feinberg School of Medicine at Northwestern University in Chicago. “The clearest way of measuring progress is actual human cases. As expected, the transvaginal route has been the most popular, but there have been a surprising number of transgastric cases.”

In the United States, NOTES techniques have been pioneered primarily at Ohio State University, where at least 80 patients have undergone transgastric NOTES procedures, primarily for diagnostic purposes such as peritoneoscopy, and at the University of California, San Diego, where investigators are exploring NOTES approaches to sleeve gastrectomy and incisional hernia, as well as cholecystectomy and appendectomy, all through a transvaginal approach. At least a half-dozen other institutions also have performed NOTES procedures, most of which were enrolled in the first U.S. NOTES clinical trial, launched this past summer.

Research in the United States has been driven largely by Natural Orifice Surgery Consortium for Assessment and Research® (NOSCAR®), a joint working group drawn from the Society of American Gastrointestinal and Endoscopic Surgeons and a group of expert interventional endoscopists representing the American Society for Gastrointestinal Endoscopy.

NOSCAR has taken a more measured approach to developing NOTES techniques, at least in comparison with other organizations and medical centers in Europe and Latin America. For example, the NOTES cholecystectomy trial in the United States requires participating groups to use an extra visualization port for safety and observation.

“The international experience is much broader than what is currently being done in the United States and some of that has been the result of NOSCART appropriately slowing down some of the progress here in the United States,” Dr. Hungness said. But as of last spring, no major complications have been reported in the NOSCART registry of NOTES procedures.

Two newer NOTES procedures involving transesophageal and transanal techniques are another sign that NOTES is continuing to evolve, Dr. Hungness said. One of them is the NOTES esophagomyotomy pioneered in Japan by Haruhiro Inoue, MD, at Showa University; the other is NOTES transanal rectal cancer resection performed at Massachusetts General Hospital.

“These two areas are really going to lead NOTES where single-incision can’t take us,” Dr. Hungness said. “It’s a little too early to tell, but I think it’s very promising.”

One other marker of progress—originally perceived as a major limitation—is new technology. There are at least 11 prototype devices currently being used under the FDA’s Investigational Device Exemption program, many of which add articulation to common surgical instruments.

“The fundamental barriers [to the success of NOTES] originally identified by the NOSCART working group were heavily based on technological innovation and we have already met most of those challenges,” said Yoav Mintz, MD, director of the Center for Innovative Surgery at Hadassah-Hebrew University Medical Center in Jerusalem.

The next generation of instruments will “separate our eyes from our hands” by placing miniature high-definition cameras—some as small as 2.5 mm—in strategic places around the abdomen, Dr. Mintz said. He added that several multitasking platforms are already in clinical development, with the goal being to one day incorporate robotic assistance into NOTES procedures.

## **Evolution of Surgery**

Although NOTES is most commonly associated with transvaginal or transgastric operations, the development of more minimally invasive surgery may be better viewed as a constellation of separate but interrelated techniques that are driving the evolution of surgery. These procedures may be divided into endoluminal and transluminal techniques, single-port or single-incision surgery, and the full Monty—natural orifice surgery.

“All the [new techniques] you see with endoluminal surgery couldn’t have happened without NOTES research,” said Dr. Marks.

Endoluminal approaches to gastrointestinal (GI) diseases have a relatively long history and are generally more acceptable to surgeons. “Endoluminal therapies are far less of a paradigm jump. I think we would all agree that the esophagus, stomach and colon are all easily accessed organs for most of the endoluminal therapies,” said Dr. Marks.

The continuing evolution of endoluminal therapies will likely hinge on two developments, Dr. Marks said—a changing view of GI diseases and the available technology to treat them.

“I think we’ve learned over the last decade that we can change the way we manage GI disease so that it doesn’t require a formal resection of major tissue,” Dr. Marks said. For example, mucosal-based diseases such as GI cancers now can be removed either by endoscopic mucosal or submucosal dissection. Endoluminal full-thickness resection also will be possible as technology advances, Dr. Marks added.

“Just because it is endoluminal, doesn’t mean we can’t make a full-thickness hole and fix it, whether it be with staplers or suturing devices,” he said. Ultimately, this technology will allow submucosal myotomies as well as endoluminal anastomoses. Japanese surgeons, for example, already have treated more than 40 patients with achalasia via endoscopic myotomy (*Nippon Rinsho* 2010;68:1749-1752).

Among techniques considered NOTES procedures, the endoscopic approaches are probably closest to bridging the gap between academic medicine and community surgery. “Let’s be honest, even though we are much more comfortable making holes in organs, the idea of doing it [purposely] is very hard for many people to accept,” Dr. Marks said. “I think the endoluminal therapies are more easily accepted by all of us—patients, industry, the FDA and IRBs [institutional review boards].”

Nevertheless, transluminal approaches continue to evolve, primarily in three areas—experience with the most common approaches, development of new techniques and emergence of new technology, long considered a prerequisite to clinical practice of natural orifice techniques.

### **Cosmetic or Clinical Benefit?**

The major question facing NOTES is whether better cosmesis will be enough to drive wider use. “Probably not,” Dr. Mintz said. Instead, NOTES will have to prove it has significant clinical benefits. “Surgery in the next decade not only will be minimally invasive but also minimalistic, meaning it will be more targeted, less extensive and more organ- and function-preserving,” Dr. Mintz added.

The highly toxic systemic therapies used in cancer are ripe for replacement with an arsenal of localized, highly targeted gene therapies that attack tumors directly and prevent the replication of cancer cells. “The major challenge in gene therapy is drug delivery and this is where NOTES comes in,” Dr. Mintz said. “Rather than dealing with difficult molecular mechanisms, we will use the NOTES platform to inject directly into tumors capsules of siRNA drugs specific to those tumors.”

Similarly, the use of fluorescent antibodies to identify tumor cells combined with vessel mapping may allow surgeons to visualize and locate small metastases and remove them using smaller and smaller segmental resections.

Before these techniques become a reality, however, surgeons will have to come to terms with a fundamental question: Should NOTES replace laparoscopy or is NOTES better suited for completely new procedures not possible with current standard approaches? The elephant in the room with NOTES is whether or not the technique provides measurable benefits in outcomes after clinical trials.

Speaking of the relatively larger body of single-port studies, Dr. Curcillo said, "I'll be the first to say, the only real benefit right now is cosmetic. We are coming out with data showing it's not worse, that we're not hurting anyone, but if someone tells you there's less pain and better recovery you have to ask them to show you the data. It's not out there."

Surgeons who are in favor of NOTES point to the history of laparoscopy. After laparoscopy was widely introduced 20 years ago, within the first three years, 70% of cholecystectomies were done with this approach even though morbidity was higher compared with the open approach.

"The factors that drove the adoption of innovation were patient demand, low cost for the surgeon during the learning period, manufacturers' aggressive promotion and the benefits perceived by stakeholders," Dr. Mintz said. "And unfortunately, like a slap in the face for the medical profession, patient outcome and patient benefit were not factors, so it's up to us, the physicians who deal with NOTES, to make sure that patients will eventually benefit from the procedure."

This transition will determine whether or not NOTES has 15 minutes of fame or is here to stay. "Scientific discovery is one thing but translating that from idea to commercialization is quite another," said Dr. Rattner. "That's really what we are struggling with."