
Simulation of a colorectal polypoid lesion—a pilot porcine model

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Background: Large sessile polyps almost always contain villous tissue with appreciable premalignant potential and tend to recur locally after colonoscopic resection. Developing new endoscopic techniques for the removal of polyps requires a large animal model of colorectal polypoid lesions. So far, no appropriate large animal model of a colorectal or other GI polyp has been described in the English literature.

Objective: Our purpose was to develop a large animal model simulating large, perfused and viable, sessile colorectal polypoid lesions, with distinct easily detectable histologic features.

Setting: An animal laboratory.

Interventions: Two simulated rectal polyps, using 2 different techniques, were created in each of 10 animals. The polyps were simulated by ovarian tissue that was introduced either intraluminally through the rectal wall or into a dissected submucosal space in the rectal wall. In 2 animals the created polyps were endoscopically resected.

Results: All submucosal lesions were sessile-like polypoid lesions because the base of the polyp was the widest diameter of the lesion. All transmural polypoid lesions had short and thick pedicles. Resection by snaring and cutting was demonstrated to be feasible.

Main Outcome Measurements: The mean measurements of the submucosal-simulated polyps were as follow: 1.74 cm (± 0.32) \times 2.07 cm (± 0.42) \times 1.51 cm (± 0.27). The mean measurements of the transmural-simulated polyps were significantly larger: 2.55 cm (± 0.52) \times 3.57 cm (± 1.1) \times 2.7cm (± 0.64).

Limitation: This model does not simulate a real intestinal neoplasia.

Conclusion: Either method, the submucosal or the transmural, could be helpful in the research and development efforts of surgical and endoscopic treatments of intestinal polyps.

Polyps of the colon and rectum are usually benign. Nonetheless, they may cause rectal bleeding and, over time, adenomatous polyps may develop into colorectal cancer (CRC). Clinical studies have conclusively shown that patients with colorectal adenomas have an increased risk for development of subsequent CRC and that resection of these adenomas substantially decreases this risk.¹ Particularly, polyps larger than 1 cm are associated with a greater cancer risk.

Clearly, colonoscopy is the most accurate method of detecting polyps, and it has the additional obvious advantage over barium enema and CT colonoscopy in that it provides an immediate means of resecting most polyps and obtaining biopsy specimens of other suspicious lesions.^{2,3} Most polyps can be completely removed through

a colonoscopic procedure. Large sessile polyps almost always contain villous tissue with appreciable premalignant potential, and they tend to recur locally after colonoscopic resection. Various removal techniques are available; most involve a cutting instrument or an electrical wire loop or burning the polyp base with an electric current. Usually the resection of larger polyps must be done piecemeal as commonly performed in endoscopic mucosal resection. This may lead to incomplete resection and local recurrences and poses difficulties regarding the accuracy of the histopathologic evaluation of the polyp. It may also be difficult to determine the extent and the invasiveness of a colonoscopically observed malignant lesion or other premalignant condition.^{4,5}

Serious complications of polypectomy include bleeding or bowel perforation. These may require surgery in 0.1% to 0.2% of patients who undergo colonoscopy with polypectomy.⁶ The complete removal of relatively large sessile polyps (over 1 cm in diameter) is a great challenge to the endoscopist. In view of the above difficulties in accurate diagnosis and technical problems, new technologies for

Abbreviation: CRC, colorectal cancer.

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the treatment of colorectal polyps are needed.³ Specifically, development of endoscopic techniques and technologies for the safe removal of GI tumors requires a large animal model of colorectal polypoid lesions that will enable performing endoscopy or colonoscopy with resection of polyps that will simulate the technical details of a similar procedure in humans and will enable evaluation and even long-term follow-up after the procedure. So far, no appropriate large animal model of a colorectal or other GI polyp has been described in the English literature. Therefore, we developed a porcine model simulating large, sessile colorectal polyps.

MATERIAL AND METHODS

Animal care

Ten healthy female pigs, *Sus scrofa domestica*, 3.5 months old, weighing 38 to 42 kg, were used. The study was conducted in full accordance with the principles and authorization of the local Helsinki Institutional Review Board for animal studies (Approval No. 040806). An additional animal was initially used in a pilot experiment to establish the technical aspects of polyp simulation and was killed immediately after the surgical procedure. A restricted commercially available pig mix (dry sow mix, Nir Oz mixture institute, Nir Oz, Israel) was given 48 hours before and 72 hours after surgery, during which solid food was replaced by a liquid diet and sweetened water. The large bowel of the animals was prepared with oral Soffodex solution (Dexxon, Hadera, Israel). Two hours before surgery a cleansing enema was administered. Concomitantly with the induction of anesthesia, a single dose of prophylactic antibiotics, cefazolin sodium (Merck, Darmstadt, Germany) 30 mg/kg and Vetricoxine L.A. Veterinary (Ceva Sante Animale, Libourne, France) 15 mg/kg, was given intravenously. Premedication and induction of anesthesia was achieved by intramuscular injection of diazepam (Hoffmann-La Roche, Nutley, NJ) 2 mg/kg, xylazine (Spectrum Chemicals and Laboratory Products, Gardena, Calif) 1.5 mg/kg and ketamine (Spectrum Chemicals and Laboratory Products) 10 mg/kg, orotracheal intubation, and halothane (Nicholas Piramal, Mumbai, India) 5%. Anesthesia was maintained by halothane 0.8% to 2% and spontaneous breathing of oxygen at 2 L/min. The pigs were infused during the procedure with 10 mL/kg/h sodium chloride.

Surgery

Through a midline laparotomy, the proximal rectum was released of its retroperitoneal attachments, to remain freely mobile on the mesorectum. The adnexa on both sides were mobilized in the same way. The ovaries and tubes on both sides remained attached parallel to the corresponding uterine horn. Two simulated rectal polyps, using 2 different techniques, were created in each animal. The polyps were simulated by ovarian tissue and a distal segment of the uterine horn that were introduced either

Capsule Summary

What is already known on this topic

- Development of endoscopic techniques for safe removal of large sessile polyps requires a large animal model that can simulate the details of a similar procedure in humans.

What this study adds to our knowledge

- Ovarian tissue was introduced into 10 pigs either intraluminally through the rectal wall or into a dissected submucosal space in the rectal wall to simulate exophytic and superficial, but broader-based, polyps.

intraluminally through the rectal wall or into a dissected submucosal space in the rectal wall. In each animal the 2 polyps were created in the antimesenteric aspect of the rectal wall, 5 cm apart from each other.

Transmural intraluminal fixation of ovary and uterine horn. A seromuscular purse-string suture, 3 cm in diameter, with a Vicryl 4/0 round needle suture, was placed on the antimesenteric aspect of the proximal rectum (Fig. 1). Surgical gauze pads were used to isolate the area around the rectum to prevent a potential contamination of the peritoneal cavity by spillage of bowel content. A blunt thin dissector was used to puncture the rectal wall in the center of the purse-string suture. The transmural puncture was then dilated by the dissector to create an opening through which the ovary with an attached 1- to 2-cm segment of the distal uterine horn was introduced into the rectal lumen. The purse-string suture was loosely tied around the created stalk containing the ovarian vessels and the uterine horn to prevent leakage of bowel contents and ovarian ischemia. A Vicryl 4/0 suture secured the ovarian “stalk” to the seromuscular layer of the outer surface of the bowel, 2 cm from the insertion site.

Intramural, submucosal fixation of ovary and uterine horn. The same preparation of a seromuscular purse-string suture as described above was created (Fig. 2). Diathermy was used to create a focal pinpoint burn of the serosa only. A thin sharp dissector was used to carefully dissect the submucosal plane to create a submucosal pocket without puncturing the mucosa. The pocket size was at least 4 cm in diameter and was created 2 cm around the seromuscular penetration point. This seromuscular penetration point was then gently dilated to enable the introduction of the ovary into the submucosal “pocket.” As in the previous technique, the purse-string was loosely tied around the “stalk” containing the ovarian vessels and the uterine horn. In addition, a Vicryl securing suture was applied in this model as well.

Endoscopic resection of the 2 types of simulated polyps. Two additional animals were operated on to

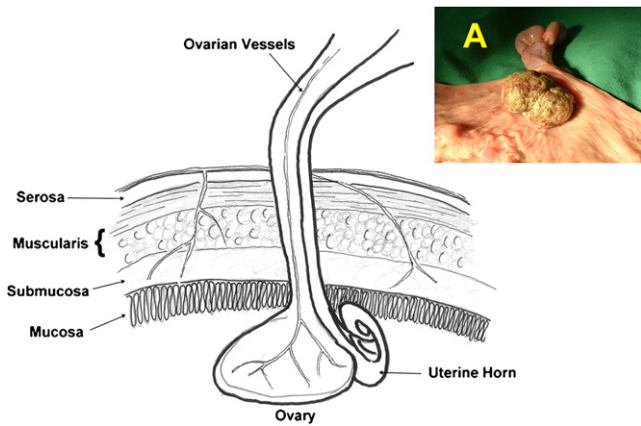


Figure 1. Schematic presentation of the “transmurular” polypoid lesion in the large bowel wall. **A**, A specimen of such lesion. A segment of the large bowel cut open by a longitudinal incision exposing the lesion and its extraluminal stalk above it.

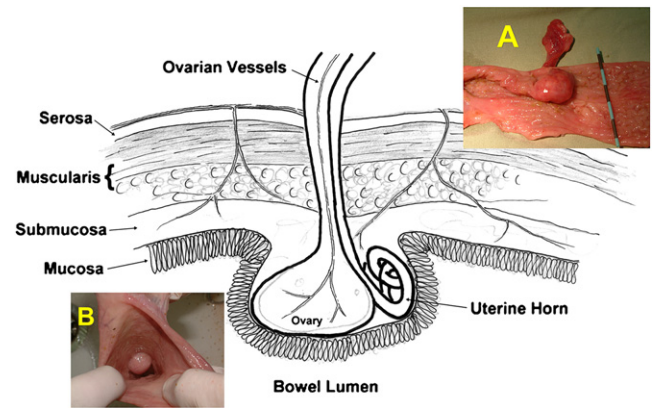


Figure 2. Schematic presentation of the “submucosal” polypoid lesion in the large bowel wall. **A**, A specimen of such lesion. A segment of the large bowel cut open by a longitudinal incision exposing the lesion and its extraluminal stalk above it.

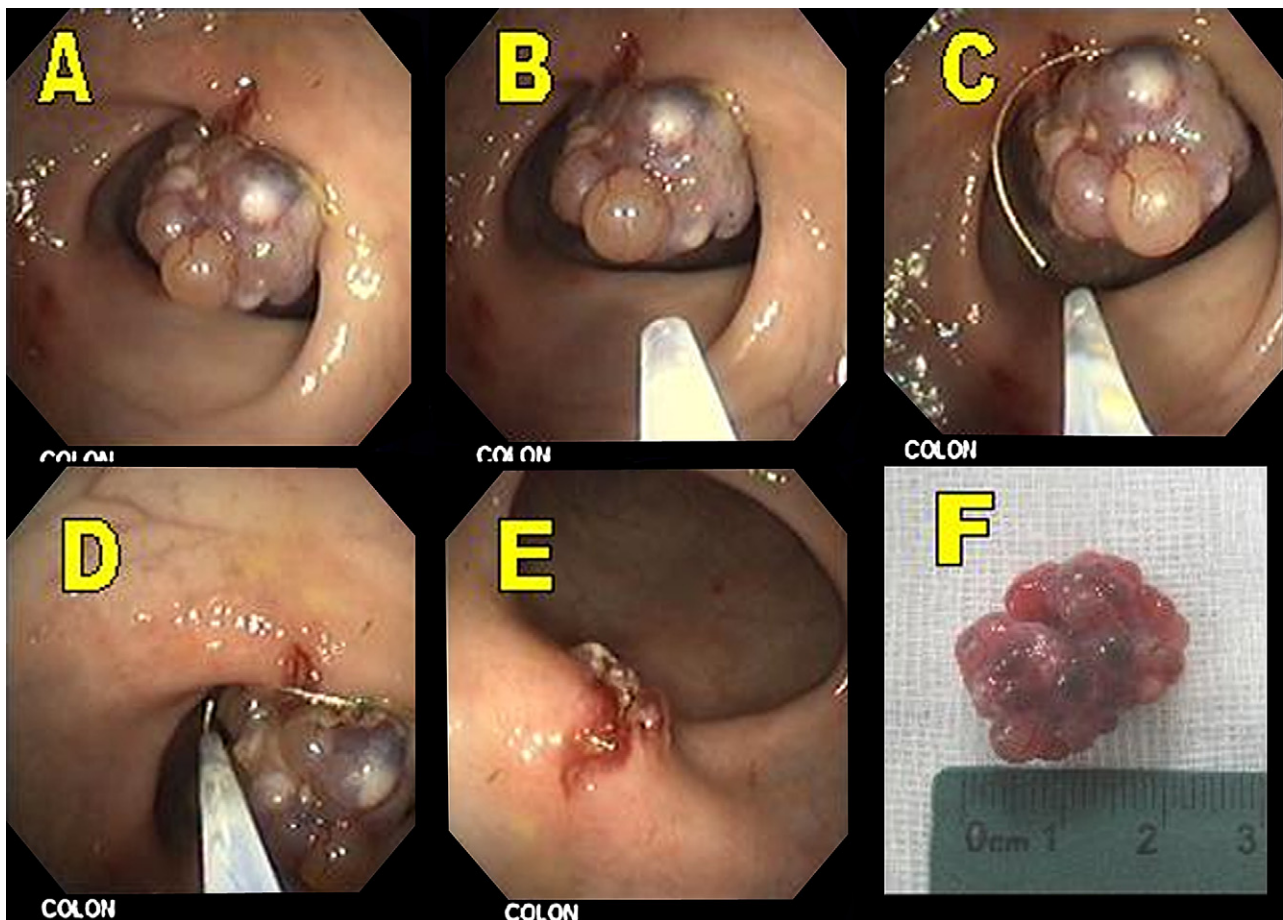


Figure 3. Snare resection of a pedunculated transmurular polypoid lesion (ovary).

create the 2 types of polypoid lesions, 2 polyps in each animal. A trained senior endoscopist resected the lesions by coagulation snaring and cutting (Figs. 3 and 4). The resection site was endoscopically evaluated during a short fol-

low-up period. One hour later, a 30-cm segment of proximal rectum containing both resection sites of the polypoid lesions was excised and tested ex vivo for possible perforation or leakage.

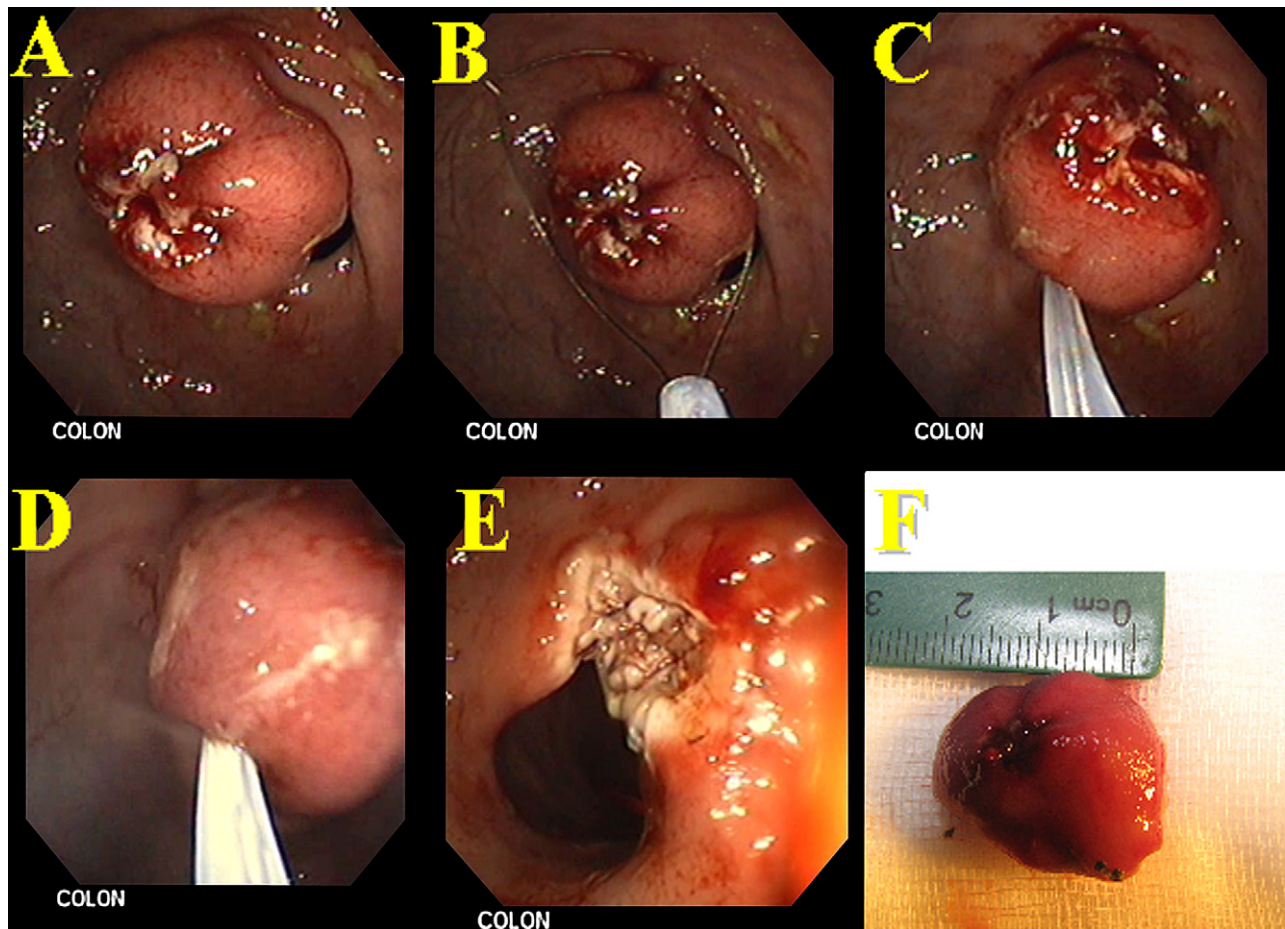


Figure 4. Snare resection of a sessile, broad-based submucosal polypoid lesion.

Follow-up

Eight animals were allowed to recover and were followed up daily by an experienced veterinarian. The clinical follow-up evaluation included the general health status and weight gain. During the 72 hours after the procedure the animals received drinking water and liquid diet only. Regular nutrition dissolved in water was started at the fourth postoperative day. Follow-up included an evaluation of the animals' behavior, GI tract function, blood samples for complete blood cell count, and an abdominal x-ray film on the third and seventh postoperative days. Four pigs were killed after 7 days. Two pigs were killed after 14 days, and the other 2 were killed after 3 weeks. During the second operation, just before the death of the animal, the abdominal cavity was evaluated for signs of possible infection, leakage, or bowel obstruction. A 30-cm segment of the distal colon and proximal rectum, with both adnexa attached to it was visually evaluated and palpated for signs of infection, tissue ischemia, or bowel obstruction. Bowel diameter 5 cm proximal and distal of the newly created polyps was evaluated. The 30-cm segment containing the polyps was resected. All the resected specimens were histopathologically examined (Fig. 5). Each polypoid lesion was measured and photographed.

RESULTS

All animals fully recovered from the surgical procedure and remained healthy during the follow-up period. The animals had normal appetite and normal bowel movements during the follow-up period. Blood cell counts and plain abdominal x-ray films on the third and seventh postoperative days were normal.

Size of the simulated polyp

The size of each polypoid lesion is described in Table 1. In 1 animal (No. 5 in Table 1), no polyp was detected. The ovary and adjacent tissue that were inserted and secured in a submucosal "pocket" had slipped out, and hence there was no polypoid lesion. The puncture site had, however, healed well with no signs of spillage or perforation. The transmural polyp in the same animal was also absent, although the tube and uterine horn were still connected to the serosal surface of the bowel. The finding on the mucosal surface at that site was merely a submucosal bulge 0.5 cm in diameter, unlike any other transmural polyp. The mean measurements of the submucosal simulated polyps were as follow: 1.74 cm (± 0.32) \times 2.07 cm (± 0.42) \times 1.51 cm (± 0.27). The mean measurements of

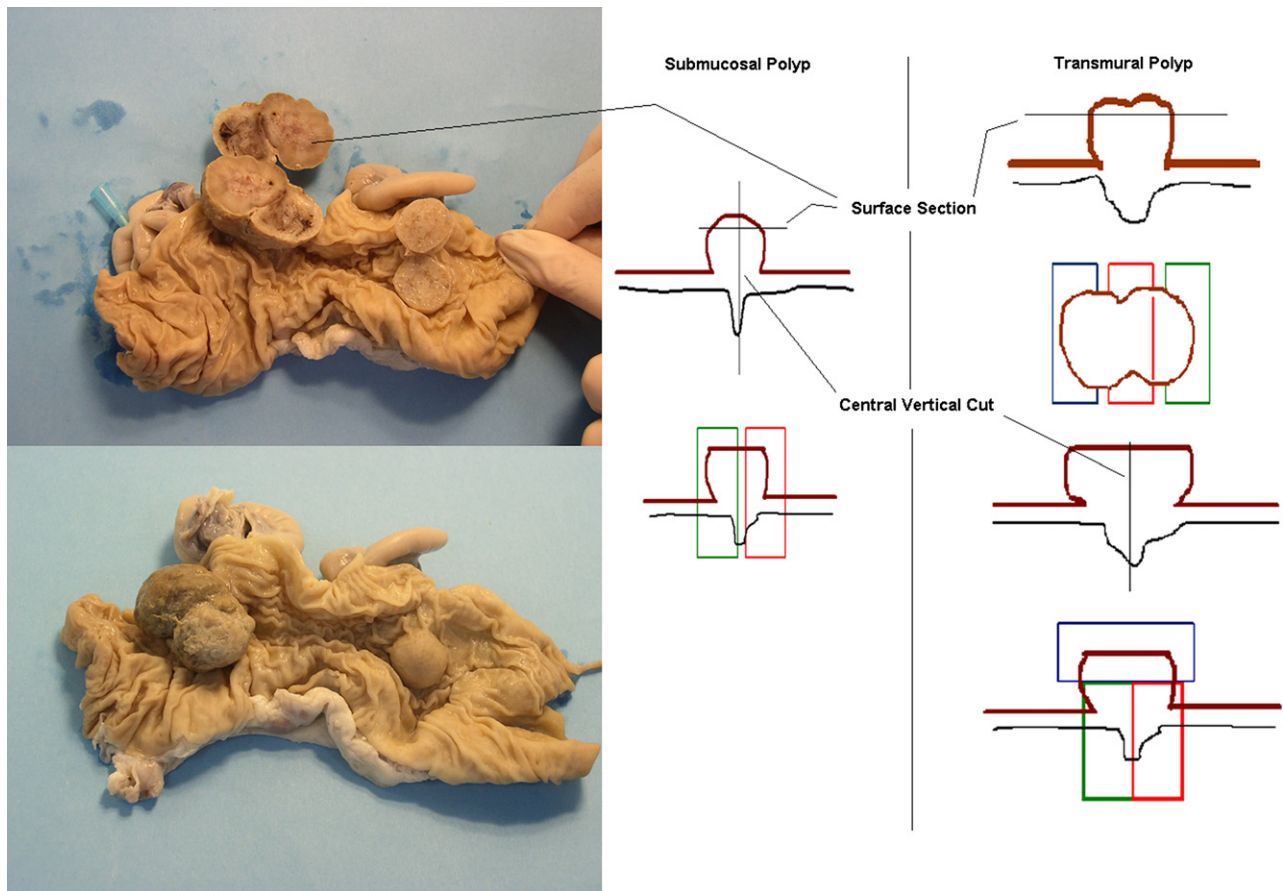


Figure 5. *Left*, Macroscopic pathologic examination of a large bowel segment containing both types of polypoid lesions. *Upper panel*, The cut polyps after a horizontal surface transection. *Right*, A schematic description of the orientation of the macroscopic incisions made in each type of polypoid lesion.

the transmural simulated polyps were significantly larger: 2.55 cm (± 0.52) \times 3.57 cm (± 1.1) \times 2.7 cm (± 0.64).

Visual appearance

The intraluminal surface of the simulated submucosal polyp was smooth with normal-appearing rectal mucosa covering the lesion (Fig. 6). The surface of the transmural polyp was rough and irregular and the lesion itself was lobulated, usually elongated and bilobar (Fig. 7).

Morphologic characteristics

All submucosal lesions were sessile-like polypoid lesions because the base of the polyp was the widest diameter of the lesion. All transmural polypoid lesions had a short (up to 1-2 mm) and thick (range 10-25 mm) pedicle.

Histopathologic evaluation

The base of the transmural polyp consisted of the ovary enveloped on one side by muscularis mucosa and on the other by smooth muscle layers. The ovary was at the base of the polypoid structure covered by colonic mucosa. Thrombus formation was present in the lamina propria

with foci of hemorrhage and interstitial fibrosis. The uterine tubes and uterus were seen in the serosa. The polyp contained large blood vessels that varied in diameter from 80 to 400 μ m.

The ovary in the submucosal space was covered by muscularis mucosa and colonic mucosa. Compared with the transmural polyp, a less prominent inflammatory reaction was noticed. The base of the ovary was enveloped by mucosa and muscularis mucosa on the internal (endoluminal) side and with muscularis on the external aspect. The uterine tube and uterine horn structures were located in the serosa and contained blood vessels, varying in size from 60 to 350 μ m.

Endoscopic resection of polypoid lesions

The conventional endoscopic snare coagulation and cutting was demonstrated to be feasible and successful in the 2 types of polypoid lesions. The snare resection was performed with no special difficulty. There was no bleeding from the resection site during the short follow-up period after the resection. The resection sites did not leak in the immediate ex vivo air and blue dye evaluation.

TABLE 1. Dimensions of simulated polyps, measured immediately after scarification

Pig no.	Days after operation	Submucosal sessile polyp		Transmural polyp	
		Diameter (cm)	Height (cm)	Diameter (cm)	Height (cm)
Preliminary procedure	0	1.5 × 1.5	1.5	2.0 × 2.0	2.0
1	7	1.8 × 2.1	1.9	3.0 × 4.7	3.0
2	7	1.8 × 2.4	1.1	3.0 × 5.3	2.8
3	7	2.1 × 2.6	1.5	1.6 × 2.7	1.5
4	7	1.1 × 1.4	1.3	2.5 × 2.8	3.5
5*	14	—	—	0.5 × 0.5	0.5
6	21	2.1 × 2.2	1.9	2.7 × 3.3	3.0
7	21	1.8 × 2.3	1.4	3.1 × 4.2	3.1
Mean measurements (SD)*		1.74 (0.32) × 2.07 (0.42)	1.51 (0.27)	2.55 (0.52) × 3.57 (1.10)	2.70 (0.64)

*Detailed description of the findings in this animal appears in the text (Results). The measurements of this animal were excluded from the calculation of mean diameters.



Figure 6. An endoscopic view of a submucosal polypoid lesion.

DISCUSSION

The porcine model was selected mainly because of the animal size. The porcine spiral colon is significantly different in its anatomic location and orientation from the human colon, which is why we chose to create the lesion in the porcine rectum, which is much more accessible colonoscopically from the other parts of the porcine colon. The porcine rectal histologic characteristics are very similar to those of the human. We were able to show that ovarian tissue with the distal segment of the uterine horn can be used to simulate both exophytic and more superficial, but broader-based, polyps. The simulated polyps by the 2 different techniques had different characteristics: the transmural lesion was significantly larger than the submucosal. This was because this type of polyp became more edematous, possibly because of the inflammatory reaction of the exposed polypoid tissue to the large bowel content, as was evident from the histopathologic evaluation of the

polyps. Another possible explanation could be a tighter purse-string suture around the full-thickness enterotomy, as a preventive measure against possible leakage, which caused venous congestion of the polypoid tissue, as evidenced by the presence of thrombus formation.

The level of tightness of the serosal purse-string suture was probably the reason for both failures in animal 5. The submucosal polyp failed because of slippage of the tissue from the submucosal space from inadequate closure of the securing purse-string suture. On the other hand, the transmural polyp failed probably from a too-tight closure of the same securing suture. We assume that the tissue of the polyp became ischemic and necrotic and finally detached from the mucosal surface into the bowel lumen. The 2 different types of tissue that were included in the lesion, an ovary along with its adjacent uterine horn, cause the bilobar appearance of the transmural polyp.

The same lesion sizes and histopathologic pattern were noted 7 days and 21 days after the surgical reconstruction of the lesions. The animals did not present any sign or symptom indicating the presence of an infectious focus. In spite of the relatively large diameters of the transmural polyps, up to 5.3 cm, no signs or symptoms of interference with bowel movements or bowel obstruction were noted.

The histologic examination of the created polypoid lesions showed blood vessels ranging from 60 to 400 μm in diameter. Polkowski et al⁷ reported endosonographic examination of large nonpedunculated adenomatous rectal polyps (≥ 20 mm, with median diameter of 30 mm) before endoscopic polypectomy. No significant vessels were found in 80% of the polyps. Vessels measuring 2 to 4 mm, 10 times larger than the vessels detected in our model, were found in 20% of the polyps. Simulations of colonic polyps in an in vitro porcine phantom have been described before.^{8,9} For

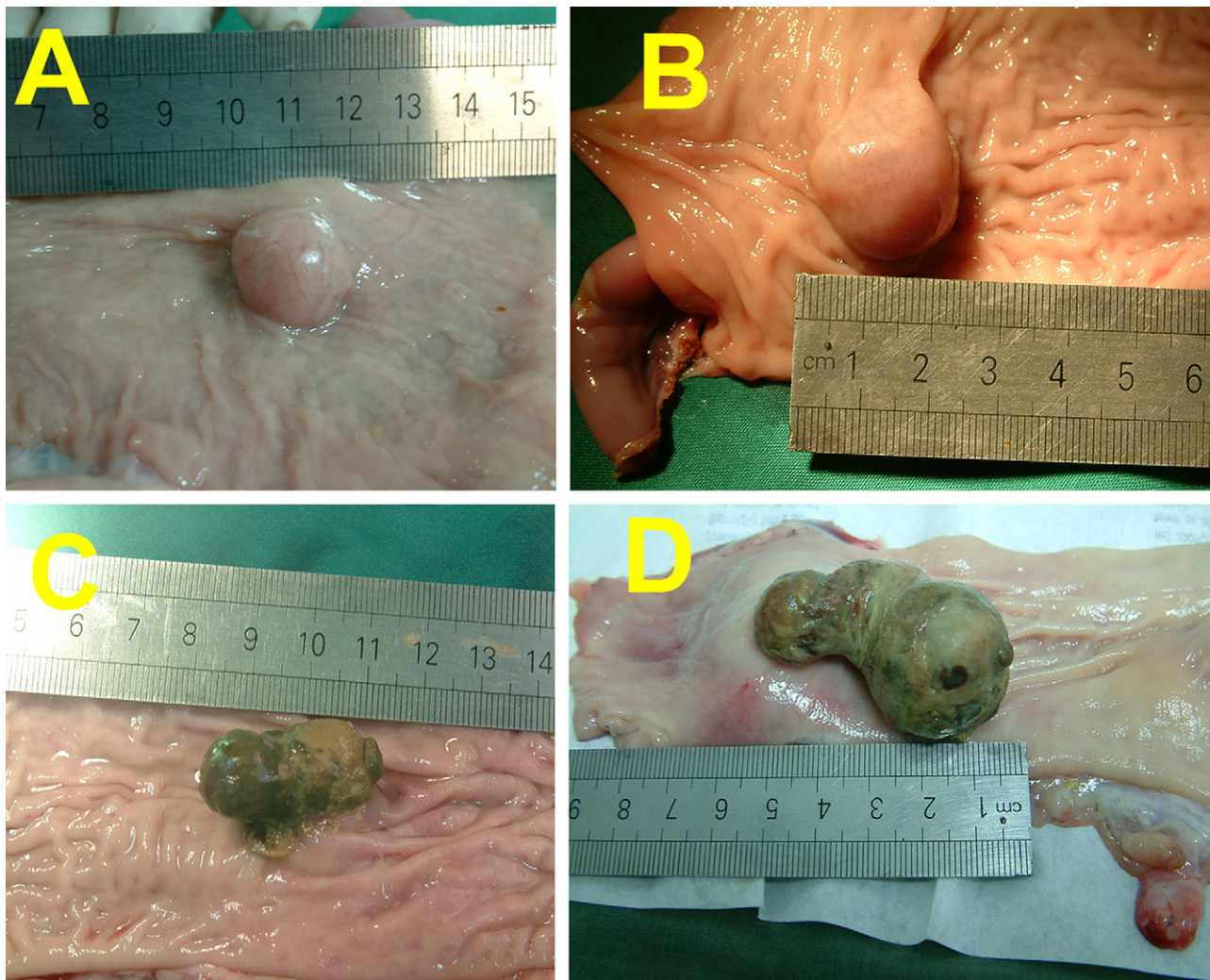


Figure 7. The macroscopic appearance of the 2 types of polypoid lesions. **A** and **B**, The “submucosal” method. **C** and **D**, The “transmural” method.

example, protruding polypoid lesions and flat polyps of 2 to 8 mm in diameter were placed in 3 explanted segments of a thoroughly cleaned porcine colon (overall length, 4.5 m) that was distended with air and submerged in a water phantom. Furthermore, several in vivo polyp models in rodents have been developed. Corpet and Pierre¹⁰ reviewed the results of 2 animal models that are the most widely used for identifying colon cancer–preventive agents, one based on colon carcinogenesis in rats treated with a methylating agent that is a colonic carcinogen¹¹ and the other based on carcinogenesis in mice with a defective *apc* gene, such as Min mice.¹²

Our model for the simulation of colorectal polyps is the only in vivo large animal model. Such a model is suitable to explore novel technologies and devices aiming at surgical or endoscopic resection of either large (≥ 2 cm) or sessile polyps, which represent the most problematic types of colorectal polyp for the surgical endoscopist. The 2 methods described in this article require some surgical experience and a delicate surgical technique but are relatively easy to perform, with the resulting polyps being

reproduced with a low failure rate (6.25%). This model creates a viable polypoid lesion with its own blood supply that is independent of the intestinal vasculature. The histologic features of the simulated polyp are unique and easily differentiated from the histologic patterns of the intestine. This principal method can be used in other segments of the GI tract to create viable polypoid lesions, although achieving this goal may necessitate the use of tissues other than the ovaries and uterus.

A limitation of this model is that it does not simulate in any way the neoplastic proliferative process that is the etiologic basis for real colorectal adenomatous polyps. The tissue of the simulated polyp was that of a healthy-looking ovary and the tip of the ipsilateral uterine horn. Therefore, this model cannot serve in studies aiming at preventing the formation of adenomatous polyps by modulation of their proliferative neoplastic natural history or for investigating systemic medical therapeutic agents for the treatment of such polyps. There are differences between the problematic superficial spreading sessile villous adenoma

and a submucosal lesion with smooth surface. This model will best serve possible future technologies of en bloc complete resection of the polyp, probably along with full-thickness bowel wall. The model will be much less suitable for piecemeal resection techniques.

This polyp model represents a unique surgical technology that has the potential to become instrumental in the research and development of new endoscopic or laparoscopic techniques for the resection of GI polypoid lesions. This model is obviously not a real neoplastic lesion and it has its limitations. This model is not meant to imitate a real adenomatous polyp; therefore, it will not become a useful method to evaluate the oncologic long-term results of any of the existing and future resection techniques. We create intraluminal protruding viable soft tissue lesions that have a unique histologic pattern and that have their own blood supply. The current understanding of the endoscopic resection techniques, which are practiced in so many procedures all over the world, brings forward the issues of completeness of resection and margins. We were able to demonstrate the feasibility of using a conventional resection method by snare coagulation for the resection of the 2 types of polypoid lesions. We chose to demonstrate the feasibility of endoscopic resection immediately after the creation of the polyps, which is the most vulnerable period of the bowel wall in terms of the chances for leakage. There was no evidence of leakage in any of the resection sites; nevertheless, one should bear in mind that longer follow-up may provide different results, especially in the relatively wide coagulated base of the "sessile" submucosal polypoid lesion. In this model we did not evaluate the longer-term postpolypectomy complication rates. Further testing of this model in the setting of new technology will have to explore the postpolypectomy outcome in a larger number of subjects. Future emerging endoscopic technologies may enable safe full-thickness resection of bowel wall with relatively large polyps.¹³⁻¹⁵ Our model, though, is meant to serve such future efforts. We do not currently have in hand the proper mature technology to achieve this goal, yet we expect our model to solve many problems and limitations of the currently existing models of polypoid lesions. We believe that this model contributes to our armamentarium and future research options. While choosing the proper research model, one should take into consideration specific characteristics of the current model such as the scar tissue at the polyp base from transmural or partial-thickness perforation of the intestinal wall; this fact may, with certain technologies, affect the rate of perforations and introduce an artifact when polypectomy is attempted with new techniques.

To date, despite the frequency with which polypectomy is performed, there is a paucity of information on the technical aspects of the procedure.¹⁶ Large animal in vivo studies are an essential step in the research and development process of any novel invasive technology. In spite of this model being somewhat complex, obliging the cost of oper-

ating in the setup of a large animal laboratory and requiring surgical dexterity, we believe that this model with either method, the submucosal or the transmural model, is a useful in vivo model in large animals that could be helpful in the research and development efforts of new surgical and endoscopic techniques and technologies for the treatment of intestinal polyps. This model may also provide a means of providing training in new polypectomy techniques, although cost and ethical considerations would favor development of ex vivo alternatives for training applications.

DISCLOSURE

The following authors report that they have no disclosures relevant to this publication: A. Szold, S. Lelcuk. The following authors report actual or potential conflicts: D. Kopelman has consulting/advisory/speaking relationships with Niti Medical Technologies Ltd, InSightec Ltd, Atria Ltd, Serafix Ltd, Chex healthcare Ltd, and has received research support from Niti Medical Technologies Ltd, InSightec Ltd, and Serafix Ltd. A. Geller has consulting/advisory/speaking relationships with Niti Medical Technologies Ltd. A. Bapaye has consulting/advisory/speaking relationships with Niti Medical Technologies Ltd, and Medigus Ltd. P. D. Siersema has consulting/advisory/speaking relationships with Janssen-Cilag BV, and Niti Medical Technologies Ltd, has received research support from Boston Scientific BV, Astra Zeneca BV, Janssen-Cilag BV, Tramedico BV, and Life Support Technology, and has received travel grants from Astra Zeneca BV, Janssen-Cilag BV, and Alveolus Inc.

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EDITORIAL

Extending our scope to intramural lesions and beyond!

Over the past 40 years, colonoscopic polypectomy has become a routine diagnostic and therapeutic procedure. It is hard to imagine the time when only rectal lesions could be removed endoscopically (by rigid sigmoidoscopy) whereas proximal polyps required surgery. In 1969, Shinya (a surgeon) and colleagues constructed an expandable flexible wire loop that could be passed through the biopsy channel of the colonoscope to snare polyps under visual guidance. Polyps were severed by applying cautery through the loop. That year, they removed the first colonic polyp without laparotomy by using this device, and presented their technique at the 1971 American Gastroenterological Association Meeting.¹ By 1975 they had reported on 2000 polypectomies.² Endoscopic techniques and experience have advanced considerably since then, such that polypectomy is now possible for large mucosal lesions as well as some submucosal lesions.

For the most part, these polypectomy techniques have been developed and used in humans, as there is no adequate large animal model currently available for study. Given the routine application of polypectomy, is there

a need for such a model to evaluate ways to improve polypectomy? The answer is most certainly yes, of course! One use of an animal model would be to train inexperienced as

The ideal animal model should comprise a lesion with distinct histology, its own vascular supply, and normal surrounding mucosa.

well as seasoned endoscopists in new approaches to the "large and/or difficult" polyp, which few are willing to tackle and are often referred for surgical resection.

The ideal animal model should comprise a lesion with distinct histology, its own vascular supply, and normal surrounding mucosa. These characteristics would allow accurate histopathology, which in turn is essential for the assessment of the adequacy of margins for any new (or old) tumor resection technique. The model should provide the setting to address clinically relevant complications, such as bleeding and adjacent organ trauma. In vivo models are clearly superior to ex vivo models or computer simulators since they create the most accurate environmental settings (including peristalsis, organ mobility,