Contrast-enhanced Intraoperative Ultrasonography: A Valuable and Not Any More Monocentric Diagnostic Technique Performed in Different Ways

To the Editor:

We have read with great interest a recent report published by Leen et al.[1] The authors showed how contrast-enhanced intraoperative ultrasonography (CE-IOUS) could improve detection power of colorectal cancer liver metastases during surgery. For this purpose, they studied a series of 60 patients prospectively enrolled in 2 European centers. In 2004, we have, for the first time in literature, proposed the use of CE-IOUS using the same contrast agent reported by Leen et al (Sonovue, Bracco Imaging, Milan, Italy) during surgery for liver tumors, and we demonstrated its feasibility in 20 consecutive patients.[2] After that, our monocentric experience has increased, and we reported the use of CE-IOUS during surgery for hepatocellular carcinoma,[3] and more recently just for colorectal cancer liver metastases.[4] Focusing on this last aspect, which was studied by Leen et al, it is noteworthy that our rate of modified staging by CE-IOUS alone was 21%, which is very close to the 22.8% reported by Leen et al. These similar results are demonstrating that CE-IOUS is feasible and repeatable, as it could provide information that are not strictly dependent from the operator and the equipment used. Indeed, we used for liver exploration a lower frequency probe than the one used by Leen et al. We did it because in 2002, when we started our experience, we had no dedicated technology. However, we have repeatedly demonstrated[2–4] that, using a conventional convex probe commonly adopted for the percutaneous exploration, CE-IOUS is feasible and accurate, without the need of particular settings such as the pulse inversion harmonic (PIH). Furthermore, some advantages exist using lower-frequency probe: indeed, despite the lower resolution power than the higher frequency ones, lower frequency probe allows longer and stronger contrast enhancement. Longer time of exploration, stronger enhancement obtainable, and lower frequency itself permit better exploration of the deeper portions of the liver, providing for that more panoramicity than that obtainable with higher-frequency probes. Conversely, for superficial lesions, palpation of the liver is often more accurate than ultrasound itself, especially in normal or steatotic liver as they are usually in patients with colorectal cancer liver metastases. Indeed, the main target for surgeons is to find deeply located tiny lesions not visible and not palpable: the lesion shown in the figure of the report of Leen et al seems not that small, is located superficially in the caudate lobe, and therefore was well palpable and detectable. Furthermore, that lesion had no close relationship with vessels for which, as we showed, CE-IOUS could be useful in better disclosing tumor margins and relations with vessels.[4] What I would like to know from the authors is how many of the new lesions they detected with CE-IOUS only were also palpable? Which were the segments where the authors found more frequently additional lesions using CE-IOUS in the way they did?

Certainly, for surgical use, high-frequency probes are anyway needed, and they should be small and stable; but these features are mainly related to their use as indispensable tools for resection guidance as we reported.[5] Furthermore, adopting those convex probes used for percutaneous exploration for CE-IOUS does not represent an additional cost: indeed, every ultrasound machine is basically equipped with them. Inversely, we do not need to get special capabilities (PIH), which limits our possibility to select other ultrasound machines or upgrade those we have.

In conclusion, with an actual experience of 114 CE-IOUS performed for hepatocellular carcinoma and colorectal cancer liver metastases in one center, we would congratulate Leen et al for their nice study, which again confirms the feasibility and effectiveness of CE-IOUS during liver surgery. Furthermore, this study lets the discussion move from the real need of CE-IOUS, which was still the object of debate since there was only our monocentric experience available in the literature, to other topics such as the technical requirements for that.

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Reply:

In response to Dr Torzilli's specific questions in his letter, none of the additional lesions seen on contrast-enhanced intraoperative ultrasonography (CE-IOUS) was palpable, and the right lobar segments were more frequently affected than the left lobar segments.

It is our view that it is still premature to be discussing the merits of which technological requirements to adopt at this stage as this is a rapidly developing field. Dr Torzilli's arguments to justify the usage of a lower- over a higher-frequency probe and his claim that palpation is often more accurate than ultrasound are unfounded. It is also misleading to suggest that no dedicated technology is required to enable CE-IOUS; in fact, the Italian group had used a contrast-specific software, even for a lower-frequency probe, as this is the only way CE-IOUS can be performed in real time with SonoVue. Such technology

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is still not widely available on most of standard ultrasound equipment in the Western world. Furthermore, the 21% alteration in surgical management in his cohort of 24 colorectal cancer patients is noticeably much lower compared with the 29.8% change in the surgical management in our study [the statement of 22.8% in his letter is inaccurate].[1,2] In addition, there was a 35.1% change in the combined IOUS/CT/MRI staging following CE-IOUS in our study. The higher impact of CE-IOUS in our study may be accounted for by the superiority of the dedicated higher frequency probe and software that we used.

While these results are interesting and should encourage others to reproduce, we do need to be cautious as the current technology is still evolving and only long-term outcome studies will determine its true value in clinical practice.

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Is There an Increased Risk of the Vas Deferens Occlusion After Mesh Inguinal Hernioplasty and What Can We Do About It?

To the Editor:

Shin et al, in a recent multicenter study, highlighted the risk of the inguinal vas deferens injury after tension-free hernioplasty.[1] They observed obstructive azoospermia in 14 patients which led to infertility due to simultaneous, but different pathology of the reproductive organs of the contralateral side. The authors attribute the result to a robust fibroblastic process around the mesh, injuring and occluding the vas deferens.[1] In the same issue of *Annals of Surgery*, Fitzgibbons, in an editorial, made many pertinent comments with which we mostly agree.[2] He argues that there may not be a causal relationship between fibrosis around the mesh and vas obstruction since no such correlation was ever proven directly. It is true that obstructive vas deferens azoospermia can be also caused by intraoperative damage of the vas during dissection, suturing, or use of electrocoagulation.[2] As he fairly stated, there is also no doubt that the implantation of mesh in hernia repair surgery is a tremendous breakthrough, significantly reducing the recurrence rate and therefore decreasing the risk of spermatic cord injury during reoperation for recurrences.

However, both articles noted that the problem is the difficulty in clearly defining the extent of unilateral vas deferens occlusion. In most cases, such injury does not give any clinical symptoms and does not compromise fertility due to normal function of the contralateral testis or simply, in many patients, the fertility state is never evaluated after the operation. Patients presented in the multicenter study are those in which fertility was compromised due to bilateral reproductive system pathology, at least on one side due to vas deferens occlusion after hernioplasty. Therefore, it is also possible that these patients with clinical symptoms could be the tip of the iceberg of the patients with asymptomatic unilateral vas injury, which was never diagnosed.

It is very well established that the fibroblastic process around the polypropylene mesh is essential for posterior wall reinforcement but can also be harmful to organs in direct contact with the mesh, especially under pressure. Such fibrosis around the mesh can trap and damage inguinal nerves, intestine, urinary bladder, and can even occlude the urethra after polypropylene tape suspension in treatment of stress urinary incontinence.[3–6] Therefore, there is a very strong rationale that such processes can also involve the inguinal vasa when it is exposed to the mesh after dissection of the spermatic cord, and we should not ignore this situation. However, the reality remains that we do not know the actual complication rate due to rare clinical presentation.

Because of the above rationale and until the true complication rate is assessed, why not offer the option of an operation that limits the potential risk of vas deferens occlusion? This option might be extremely attractive to those with unilateral hernias and impairment of the contralateral testis or even to those patients who do not wish to risk compromise of their reproductive health.

One easy solution could be separation of the spermatic cord from the mesh. In the sutureless tension-free Trabucco technique, preshaped polypropylene mesh is placed on the posterior wall of the inguinal canal and the oblique aponeurosis is reapproximated **below** the spermatic cord, in contrast to other tension-free techniques. In this way, polypropylene mesh is placed flat between 2 fascial layers, the transversalis fascia and the oblique aponeurosis, which limits fibrotic tissue ingrowth into intrafascial space, leading to uniform, solid scar formation and preventing recurrence.[7,8] Oblique passage of the spermatic cord through the inguinal canal is not essential after this reinforcement of the abdominal wall.

With this technique, the spermatic cord is placed in the subcutaneous tissue, free from direct contact with the mesh and avoiding chronic inflammatory tissue. Long-term results of this technique are as superb as other tension-free repairs and are well described.[7–13] For those who prefer the Lichteinstein hernioplasty, reapproximation of the oblique aponeurosis below the spermatic cord, instead of over it, could also solve the problem of the potential vas injury complication. A randomized study could be performed to assess the effectiveness of such modification of the Lichteinstein technique, but in our opinion there is sufficient indirect evidence to support our thesis.

A hole for the spermatic cord in preshaped mesh instead of the shutter-valve effect of mesh tails sutured to-

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gether could also decrease the contact of the mesh and the cord without compromising the effectiveness of the technique. The efficacy of this approach was clearly proven in the Trabucco technique and other repairs with utilization of the preshaped onlay mesh with a hole for the spermatic cord. The proposed surgical techniques comply with principles of the tension-free operation and can be easily implemented.

In summary, although the actual inguinal vas occlusion rate due to fibroblastic inflammation around mesh is not known now, there is a strong suggestion that such a process can take place and there is need to evaluate it. Therefore, in the meantime, all those patients with any compromise to their reproductive health or who are concerned about their fertility could be offered a surgical technique that minimizes the potential risk without compromising all the advantages of the tension-free hernia repair.

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Ductoscopic Biopsy of Papillary Tumors in Women With Nipple Discharge

To the Editor:

We read with great interest the article by Moncrief et al reporting a comparative study on the management of women with nipple discharge with or without ductoscopy-guided excision.[1] Ductoscopy improved the localization of intraductal lesions and the proportion of women with intraductal neoplasia was greater in the group undergoing ductoscopy-guided excisions (88% vs. 81%). Visualization of a luminal lesion correlated significantly with proliferative disease, but reliable distinction between benign and malignant lesions was not possible based on the endoscopic appearance. Of the 49 papillomatous lesions visualized, 36 (73%) were indeed papilloma, 5 (10%) were cancer, 3 were atypical hyperplasia (6%), and 3 were hyperplasia of usual type. Although cytology results were not reported, it is well known from other studies that the specificity of ductoscopic cytology is limited.[2] The authors conclude that new methods such as optical spectroscopy will be required to improve the in situ diagnosis of intraductal lesions.

A method for intraductal tissue sampling would significantly improve the diagnostic potential of ductoscopy and could help to define the appropriate surgical procedure in patients with ductal lesions. However, it has been difficult to establish ductoscopic biopsy techniques, mainly because of the small dimensions of ductoscopes (diameter <1 mm).

We have developed a simple ductoscopic biopsy technique that allows precise tissue sampling from intraductal breast lesions under visual control.[3] The biopsy device consists of a special biopsy needle with an outer diameter of 0.9 mm and a rigid gradient index ductoscope with a diameter of 0.7 mm. The needle has a lateral oval opening located 3 mm from the distal tip. The surface of the opening is designed as a blade to cut off tissue samples from lesions that protrude into the lumen. Usually, the tip of the ductoscope is ending at the tip of the cannula, thus sealing the biopsy chamber. When a neoplastic lesion is found, the ductoscope is withdrawn 4 mm to open the biopsy chamber. Under visual control, the lesion can now be maneuvered into the lumen of the biopsy needle. Then vacuum is applied while the instrument is withdrawn from the duct. Multiple tissue samples can be obtained, and substantial parts of smaller lesions may be removed by repeated biopsies. The size of the biopsy samples is approximately 1 mm and the diagnostic quality is generally good.

With the biopsy device, ductoscopy was performed in 30 patients who presented with pathologic nipple discharge. The examinations were carried out preoperatively using topical anesthesia with an anesthetic cream. The study was approved by the institutional review board and informed consent was obtained from all patients. Papillary tumors or obstructing lesions were identified in 21 patients (70%). The biopsy procedure was technically successful in all cases. On average, 3 tissue specimens (range, 1–5) were sampled from any suspicious lesion. Biopsy specimens in diagnostic quality were obtained in all but 1 patient. Histopathology revealed papilloma in 17 patients (80%), ductal carcinoma in situ in 2 patients (10%), and invasive ductal carcinoma in 1 patient. Histopathologic analysis of the resection specimen confirmed the diagnosis made by ductoscopic biopsy in all cases. The rate of 14% cancerous lesions diagnosed by ductoscopic biopsy in patients with nipple discharge compares favorably to the data of Moncrief et al[1] and others.[4]

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Ductoscopic vacuum-assisted biopsy is a simple and efficient technique that allows targeted tissue sampling of intraductal lesions in women with nipple discharge. This new technique allows differentiation of benign papillary tumors from cancerous lesions and could help to define the indication for surgery and the extent of surgery in women with nipple discharge. In the future, ductoscopic biopsy may provide the basis for minimally invasive therapy for benign intraductal lesions.

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Perioperative Radiation for Rectal Cancer and Sexual Dysfunction after TME: Cause and Effect?

To the Editor:

We have read with great interest the article by Hendren et al.[1] Hendren et al revealed high prevalence of sexual dysfunction among both male and female patients undergoing total mesorectal excision (TME) for rectal cancer. Furthermore, they demonstrated that pelvic radiation, operative procedures, and males were independent risk factors for worsening sexual life after surgery by multivariate analysis. Although their work is excellent, there are two major points that need further discussion.

First, Hendren et al speculated that perioperative radiation could deteriorate sexual function after TME based on the result of multivariate analysis. However, their multivariate analysis included only 2 surgery-related variables, namely, radiation and operative procedures, and no other surgical factors were evaluated. Considering the indication of radiation in rectal cancer, radiation in this study might be an indicator of advanced lesions, or in other words, an indicator of more radical surgery, which is more likely to damage autonomic nerves and cause sexual dysfunction. Indeed, the incidence of sexual dysfunction after TME rises in more complex operations with advanced disease, narrow pelvis, or bleeding.[2–4] Therefore, these indicators of surgical complexity should be also included in the multivariate analysis before concluding that radiation truly has an additive effect on the postoperative sexual dysfunction.

Another aspect that deserves further comment is the statement that "combining less radical surgery with radiation might not spare sexual function." It has been advocated that extended pelvic lymphadenectomy reduces local recurrence as well as prolongs survival of lower rectal cancer.[5] However, we have previously demonstrated, by a randomized controlled study, that preoperative radiation is as curative as extended pelvic lymphadenectomy but effectively decreases sexual dysfunction after surgery.[6,7] This study is a good example that combining less radical surgery with radiation effectively spares sexual function.

We agree with Hendren et al that high frequency of sexual dysfunction after TME should be more explained to patients before operation. However, premature "cause and effect" explanation for perioperative radiation and sexual dysfunction might mislead patients to abandon the appropriate treatments. With acceptance on this point, further study is needed to determine whether radiation truly has an additive effect on the risk of sexual dysfunction after TME.

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Stapled Hemorrhoidopexy Versus Milligan-Morgan Hemorrhoidectomy

To the Editor:

In the published report of Gravié et al,[1] comparing the outcome of stapled hemorrhoidopexy with that of the Milligan-Morgan technique, stapled hemorrhoidopexy is recommended as the preferred technique for hemorrhoidal prolapse. In our opinion, this conclusion is at least questionable. A meta-analysis of 9 studies showed a worse rate of recurrent prolapse after hemorrhoidopexy, concluding that hemorrhoidectomy remains the "gold standard" procedure.[2] A multicenter study has shown that hemorrhoidopexy provided similar control of symptoms than hemorrhoidectomy in patients with third-degree hemorrhoids.[3] Other studies demonstrated that hemorrhoidopexy was more successful in treating third-degree hemorrhoids than in fourth-degree hemorrhoids at the 1-year follow-up.[4] The effectiveness of the hemorrhoidopexy as a definitive cure in patients with fourth-degree hemor-

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rhoids is controversial. Of the 7 randomized trials published in the literature in which patients with fourth-degree hemorrhoids were included,[5–11] in 3 of them[8–10] the results obtained in the resolution of one or various hemorrhoidal symptoms after the stapled technique were worse than after hemorrhoidectomy. Moreover, defecation disturbances, such as urgency, were observed. In this respect, it should be noted that, in the consensus position paper of stapled hemorrhoidopexy, it was stated that these symptoms should be included in the informed consent.[12] Taking into account the significant variation in the distance of the staple line above the dentate line, it appears that the technique is not as easily reproducible as it is claimed in the paper or that results are not dependent on whether or not the technique has been standardized. This is clearly in contrast with the consensus document[12] and the original description of Antonio Longo.[13] Therefore, it seems that the appropriate conclusion would have been that hemorrhoidopexy is an adequate technique for the treatment of third-degree hemorrhoids. Finally, the consensus report cited in the reference list as "in press" was in fact published in 2003.

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Sentinel Node Biopsy for Early-Stage Melanoma: Accuracy and Morbidity in MSLT-1, an International Multicenter Trial

To the Editor:

The report by Morton et al concerning the accuracy and morbidity of sentinel node biopsy (SNB) after wide excision in early melanoma is most welcome.[1] This trial is nicely designed to test the strategy of SNB-guided immediate node dissection versus the strategy of observation only, with later therapeutic node dissection if needed. However, the data they have provided to date seem not to show any advantage of the SNB strategy in these patients.

The authors report that, in the SNB-guided group, 234 patients of 1173 had positive sentinel nodes, leading to completion lymphadenectomy (Table 3).[1] An additional 59 patients in this group had subsequent regional nodal recurrence after negative SNB (p. 306)[1] and also underwent complete lymph node dissection. Thus, after a follow-up of 5 to 6 years, 25% [(234 + 59)/1173] of patients in the SNB group had received regional node dissection.

In the wide excision and observation group, 18% (144 of 800) had required node dissection after the same follow-up period (Discussion, p. 308).[1] None in this latter group had been subjected to the time and expense of the SNB procedure, and proportionally fewer of them underwent regional node dissection. Hence the frequency of short- and long-term morbidity due to complete node dissection should be less in this observation group, although the authors do not provide specific data on this. The excess rate of node dissection in the SNB group (25% vs. 18%) is not likely to be due to chance ($P < 0.01$ by χ^2).

Prior randomized trials in similar melanoma patient groups do not demonstrate an overall benefit in survival or disease-specific survival from routine node dissection.[2–5] Further, unlike the situation with breast cancer, there is no approved adjuvant therapy for these early-stage melanoma patients. Thus, no useful therapeutic decision is guided by SNB in these patients.

The MSLT1 trial reported here is the only randomized controlled clinical trial addressing whether melanoma patients managed using SNB have better clinical outcomes than those managed any other way. Unless there is a compensating benefit to survival or recurrence found in this trial of which we have not been told, the strategy of SNB-guided immediate node dissection appears to involve more surgery, thus more morbidity, and more expense, for no demonstrated gain. Therefore, declarations that SNB is now the "standard of care" in these patients (with all that implies) seem premature.

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Gut Hormone Profiles Following Bariatric Surgery Favor an Anorectic State, Facilitate Weight Loss, and Improve Metabolic Parameters

To the Editor:

We found the article by le Roux et al very interesting.[1] The authors investigated the effect of bariatric surgery on gut hormones secretion, an endocrine response to the bypass of part of the small bowel responsible of glycemic control, appetite reduction, and long-term reduction in body weight.[1]

To investigate the hormonal changes after Roux-en-Y gastric bypass (RYGB), basal and meal-stimulated secretion of peptide YY, glucagon-like peptide-1 (GLP-1), polypeptide, insulin, leptin and ghrelin were compared with a group of patients undergoing gastric banding and with 2 control groups composed, respectively, by lean and obese subjects.

To further investigate the role of the hormonal response observed in humans, a jejuno-intestinal bypass (JIB) was carried out in Wistar rats of 387 ± 11.7 g.[1]

The main goal in the animal experiment was to reproduce hormonal changes observed in humans, postulating that these changes are due to the early arrival of nutrients in the terminal ileum as consequence of the bypass of the jejunum, and to demonstrate the role of PYY in reduction of appetite after bariatric procedures entailing with bypass of part of the small bowel. Comparing JIB rats with sham-operated animals, JIB rats experienced a significant postoperative weight loss with a parallel reduction in food intake. Moreover, the authors excluded the presence of malabsorption in the JIB group using a ballistic bomb calorimeter, therefore referring the modifications in body weight and in food intake solely to the hormonal variations.[1]

We would like to point out some technical obscure aspects of the experimental protocol.

First, if the experiments in the rats aim to reproduce hormonal changes observed in obese humans who underwent RYGB, an obese rat model should be more appropriate.

Differences in gut hormonal secretion were, in fact, described among obese and lean subjects: obese control subjects exhibited an attenuated GLP-1 response to meal and a lack of response to meal of PYY. Fasting ghrelin levels were lower in the obese subjects.[1]

Therefore, an obese rat model would be more realistic to study the hormonal modifications after the bypass of the small bowel in an experimental setting.

Moreover, JIB does not seem so appropriate as surgical model to reproduce hormonal changes after RYGB without inducing malabsorption. It's hard to believe that this operation is not malabsorptive, when resection of part of the small bowel is traditionally used in the rat to induce a short bowel syndrome.[2]

Two reasons may be possible to explain the results obtained with the ballistic bomb calorimetric method: the bypassed small bowel was very short, but no indications are given in the text about the length of the blind loop, or a more detailed stool analysis to determine malabsorption would have been necessary to break down this dogma.[3]

Other methods to induce the hormonal modifications secondary to the early arrival of food in the ileum are well described, and ileal transposition, in our knowledge, seems to be the more effective, reproducing a hormonal pattern similar to that of RYGB without reducing the bowel length.[3–7]

The authors assert that JIB is the only established model of bariatric surgery in rodents, omitting the numerous other experimental models described in the literature.[2]

Another question to the authors is about the technique used to measure GLP-1 plasma levels, which is not mentioned in the paper.

Since GLP-1 is rapidly metabolized in the circulation by the ubiquitous enzyme DPP IV, 2 assays for GLP-1 are available. The former, and most widely used, has been designed for the assay of the intact hormone and its inactive metabolites (total GLP-1), while a second one determines the bioactive form (bioactive GLP-1). The total GLP-1 assay, however, can be used just to trace the secretion rate of the hormone without providing any information about the activity and the amount of circulating bioactive GLP-1. Therefore, antiserum for GLP-$1_{7–37}$ and GLP-$1_{7–36amide}$ (bioactive GLP-1) should be preferred to assay modifications in the secretion of this peptide and to evaluate its effects.[5,8]

Moreover, to verify an effect of JIB on GLP-1 secretion a control group of not operated rats should be necessary. Active GLP-1, indeed, was significantly higher in plasma of rats undergone ileal transposition in respect to sham-operated rats but not to a group of not operated rats during a period of 15 minutes after an oral gavage of glucose 1 g/kg,[5] and data are confirmed in the same surgical model in a period of 120 minutes after glucose load (data not published). Therefore, some factor influencing GLP-1 secretion linked to the small bowel division must be taken into account in this type of research.

The human study probably suffers of a type 2 error and cannot be considered definitive about GLP-1 modifications after RYGB, and once again the form of GLP-1 assayed is not indicated in the text.

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