

# Radioguided localization of occult colonic lesions during open or laparoscopic surgery

## An update



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Roberto Spisni\*, Marco Biricotti\*, Giuseppe Boni\*\*, Giampiero Manca\*\*, Giuliano Mariani\*\*, Paolo Miccoli\*.

University of Pisa, Italy

\*Department of Surgery

\*\*Department of Oncology Medicine

### Radioguided localization of occult colonic lesions during open or laparoscopic surgery. An update

*The applications of radioguided surgery, an approach to oncologic surgery involving a multidisciplinary team, are expanding at a rapid pace. The technique of radioguided occult lesion localization (ROLL) was originally introduced in the mid-90s for applications in breast surgery, and later adapted also to other tumor lesions such as solitary pulmonary nodules (during either open or laparoscopic surgery) and colonic lesions. Concerning the latter, in particular, the technique called radioguided occult colonic lesion identification (ROCLI) consists of identifying, with the aid of intraoperative gamma-probe counts, small lesions that may escape colic intraoperative palpation, after prior tagging of the lesions performed endoscopically through peri- or intra-lesional injection of Technetium-99m-labeled human albumin macroaggregates (<sup>99m</sup>Tc-MAA), a particulate radiopharmaceutical (25-100 μm) that does not migrate from the site of interstitial administration. Since September 2001, ROCLI has been employed in 12 patients, using a collimated gamma-probe measuring 11 mm in external diameter (Scintiprobe MR100 Pol.Hi.Tech.). All patients underwent preoperative colonoscopy in order to inject 0.2 mL of a <sup>99m</sup>Tc-MAA suspension (10-20 MBq) into the submucosa or intra-perilesionally; such tagging required only a few minutes.*

*Eight of the 12 patients were then submitted to open laparotomy, while laparoscopic access was utilized in the remaining 4 patients. In all 12 patients, localization of the lesion with the ROCLI technique was technically feasible, safe, efficient and highly accurate, enabling quick detection of the lesion during surgery, with a 100% success rate. No complications occurred, and there was no risk of contamination by ionizing radiation.*

KEY WORDS: Colon Cancer, Radioguided Surgery, ROCLI

### Introduction

The concept of radioguided surgery (whose beginnings date back to nearly 60 years ago, but which has only undergone its true development over the last 20 years)

involves the use of a portable probe for intraoperative detection of the radiation emitted by the radioactive decay of isotopes, which identify the “in vivo” site of any lesion targeted for surgical excision.

In recent years, radioguided surgery has undergone considerable evolution, especially with regard to the use of radiopharmaceuticals, which have been employed and modified more and more frequently. During the first years of gamma probe use in radioguided surgery, the most frequently adopted radiopharmaceuticals were tagged monoclonal antibodies (generally with radio-iodine). More recently, with the advent of radioguided sentinel lymph node (SLN) biopsy and its application in numerous neoplastic pathologies (though especially in mammary carcinoma and cutaneous melanoma), there has been an exponential increase in the use of radio-

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Correspondence to: Prof. Roberto Spisni, Department of Surgery, University of Pisa, Italy (e-mail: [roberto.spisni@med.unipi.it](mailto:roberto.spisni@med.unipi.it))

pharmaceuticals tagged with  $^{99m}\text{Tc}$ , the radionuclide currently used in the great majority of radioguided surgical procedures. Nevertheless, the future prospects for radioguided surgery with gamma probes also include the use of radiopharmaceuticals such as [ $^{18}\text{F}$ ]fluoro-deoxyglucose ([ $^{18}\text{F}$ ]FDG) and other radiopharmaceuticals tagged with positron emitting radionuclides.

Beginning with the earliest applications <sup>1-3</sup>, the use of the gamma probe in radioguided surgery has broadened enormously and has evolved into what is now considered a discipline that is in all effects an integral part of surgical practice, revolutionizing the diagnostic-therapeutic approach to many neoplastic pathologies, amongst which breast carcinoma <sup>4-19</sup>, parathyroid lesions <sup>20-24</sup>, melanoma <sup>25,26</sup>, and tumors of the colon-rectum.

Radio-immuno-guided surgery (or RIGS) for tumors of the colon-rectum <sup>27</sup> was first introduced in 1984 through the work of Aitken and colleagues <sup>28-29</sup> at Ohio State University. They showed the feasibility in laboratory mice of detecting gamma radiation emitted by polyclonal anti-CEA antibodies tagged with  $^{131}\text{I}$ , moreover revealing the gamma probe's greater sensitivity for small tumors in comparison to imaging with gamma-cameras <sup>28-29</sup>. The Aitken team then performed the first clinical application of RIGS in a 59 year-old male patient with rectal carcinoma <sup>29</sup>. In this patient, the gamma probe detected significantly greater uptake of the polyclonal  $^{131}\text{I}$ -anti-CEA antibodies by the rectal tumor (135 counts/minutes) in comparison to the sigmoid, taken as the normal "background" (111 counts/minutes).

Shortly thereafter, Martin et al. <sup>30-31</sup> reported the results of the first RIGSs in a study on 28 patients with primary (n = 12) and relapsed (n = 16) colorectal tumors. Each patient was administered an intravenous injection of 2.2 mCi (81.4 MBq)  $^{131}\text{I}$ -tagged polyclonal anti-CEA antibodies about 48/72 hours before surgery (23 patients also underwent preoperative scintigraphy scans). In all patients, intraoperative detection of the radiation emissions of the tumor and adjacent tissues was achieved via a portable prototype gamma probe and a commercial control unit. The preoperative scintigraphy furnished correct results in 33% and 64% of the patients with primary illness and relapse, respectively. This clinical study was the first to demonstrate the capacity of RIGS technology to furnish immediate information intraoperatively for evaluating a tumor of the colon-rectum. The study moreover showed for the first time that probe sensitivity and specificity are considerably greater the smaller the distance is between the detector and the source. Indeed, because of its proximity to the radiation source, the intraoperative gamma probe enables identifying a tumor with higher probability.

In all subsequent clinical studies  $^{125}\text{I}$  has been preferred over  $^{131}\text{I}$  <sup>31-33</sup>, given that the gamma probe is more efficient in detecting the  $^{125}\text{I}$  gamma emissions (with an energy of 35 KeV) than the gamma photons emitted by  $^{131}\text{I}$  (364 KeV). For this reason, most clinical trials of

RIGS methodology for the identification of colorectal tumors specifically employ  $^{125}\text{I}$ -tagged monoclonal antibodies.

In 1996 the Radioguided Occult Lesion Localization (ROLL) technique was introduced. This is a new method that entails endoscopic submucosal perilesional injection of  $^{99m}\text{Tc}$ -MAA and offers the possibility of radical treatment in cases of both primary tumors as well as relapses or metastases, guiding the surgeon in the execution of macroscopically targeted, curative excisions.

The ROLL technique, conceived and developed at the European Institute of Oncology in Milan for the intraoperative localization of non-palpable mammary lesions, involves the injection of a suspension of macroaggregates of human albumin tagged with Technetium-99m ( $^{99m}\text{Tc}$ ) in and around the lesion of surgical interest. Through use of the special gamma probe, proper ablation of non-palpable neoplasias has been successfully demonstrated in 99.5% of cases, while moreover avoiding the potential problem of detachment and displacement of the metal marker and enabling extremely precise resection of the tumorous mass. A systematic, detailed literature review has concluded the ROLL technique to be better than traditional wire localization for non-palpable lesions of the breast <sup>4-19</sup>.

The use of the ROLL technique for localization of occult colorectal lesions is termed Radioguided Occult Colonic Lesion Identification (ROCLI). Prospective studies are however still necessary to evaluate the effectiveness, in terms of survival, of ROCLI followed by radioguided surgery on such lesions.

## Materials and methods

Since September 2001 the ROCLI technique has been used on 12 patients, 8 males and 4 females, using a collimated 11 mm-diameter probe (Scintiprobe MR100 Pol.Hi.Tech.) as the gamma ray detector interfaced with a laptop computer for numerical processing of the radiation signal, and a suspension of human albumin macroaggregates tagged with Technetium-99m ( $^{99m}\text{Tc}$ -MAA) as tracer.

The patients included 3 cases of severe dysplasia and 9 cases of carcinoma, amongst which 6 revealed the presence of synchronous carcinoma, that is, a carcinomatous lesion associated with a second neoplastic mass (in these cases severe dysplasia) found within six months of confirmed diagnosis of the first neoplasia. The topographical distribution of the lesions was as follows: 1 carcinomatous lesion of the right colon, treated with right-side hemicolectomy; 1 carcinomatous lesion of the transverse and descending colon, treated with resection of the transverse colon and atypical resection of the descending; 5 carcinomatous lesions in the descending colon, treated with left hemicolectomy; 2 carcinomatous lesions in the descending and sigmoid colon, treated with left hemi-

Table I - Site of lesion e Treatment

N° and site of lesion	Treatment
1 Ca right colon	Right hemicolectomy
1 Ca transverse + descending colon	Resection trans. + atypical resect. of descending colon
5 Ca descending colon	Left hemicolectomy
2 Ca descending colon + Ca Sigmoid	Left hemicolectomy + resect. ant. middle-high rectum
3 Dysplastic lesions of descending colon	Left hemicolectomy

colectomy associated with anterior resection of the mid-high rectum, and lastly 3 dysplastic lesions of the descending colon treated with left hemicolectomy (Tab. I). All patients underwent preoperative colonoscopy 24 hours prior to surgery, with the purpose of injecting the radiopharmaceutical into the submucosa within or around the lesion, through a disposable sclerosing syringe. A minimum of two injections were performed for each lesion to administer doses of 0.2 ml of  $^{99m}\text{Tc}$ -MAA (10-20 MBq). In the event of contemporaneous multiple lesions, the administrations were repeated accordingly.

Immediately after tagging, proper localization was checked through plane scintigraphy with a gamma-camera and/or through external radiation counts with the gamma probe positioned on the cutaneous projection of the injection site.

The time necessary for endoscopy varied between 15 and 30 minutes, including injection of the radiotracer, probe localization of the signal, as well as evacuation of the air present in the colon due to insufflation during the endoscopy procedure.

No special position of the patient on the operating table was necessary during the intraoperative stage of radioguided lesion localization and the gamma probe was used to obtain the intraoperative counts under sterile conditions (during both laparotomy and laparoscopy) (Fig.1).

Laparotomic access was gained through a median supraumbilicopubic incision. Then, after exploration of the abdominal cavity and parenchymatous organs to reveal any metastasis or lymphadenopathy, the Scintiprobe was used to locate the previously tagged lesion.

The left colon, sigmoid, and mesosigmoid were mobilized and liberated by first separating the colon from the peritoneal wall through an incision in the wall of the left parietocolic groove and subsequently detaching the colon from the omentum, which provided access to the posterior cavity of the epiploon, where the spleno-colic ligament was sectioned with consequent liberation of the left colic flexure.

The inferior mesenteric peduncle was isolated, clamped and sectioned near its origin via double ligature with Vicryl 2/0. The proximal colon was sectioned with a linear mechanical stapler and a tobacco pouch fashioned with positioning of the head for the circular stapler.

The next steps were posterior, anterior and lateral detachment of the rectum and mesorectum enveloped in the fascia propria of the rectum, while preserving the nerves of the hypogastric plexus, and consequent resection of the rectum with the linear stapler.

Betadine lavage was then performed of the rectal stump, and anastomosis fashioned via transanal access. The integrity of the anastomosis was verified by hydro-pneumatic test, and temporary protective ileostomy performed as necessary, followed by lavage of the abdominal cavity, positioning of drainages, and layer-by-layer closure of the wall.

For laparoscopic access, pneumoperitoneum was induced with a Verres needle or the Hasson open access technique and a trocar positioned supraumbilically; three more trocars were positioned visually: one in the right hypochondrium (10-12 mm), one in the right iliac fossa (10-12 mm) and one in the left iliac fossa (10-12

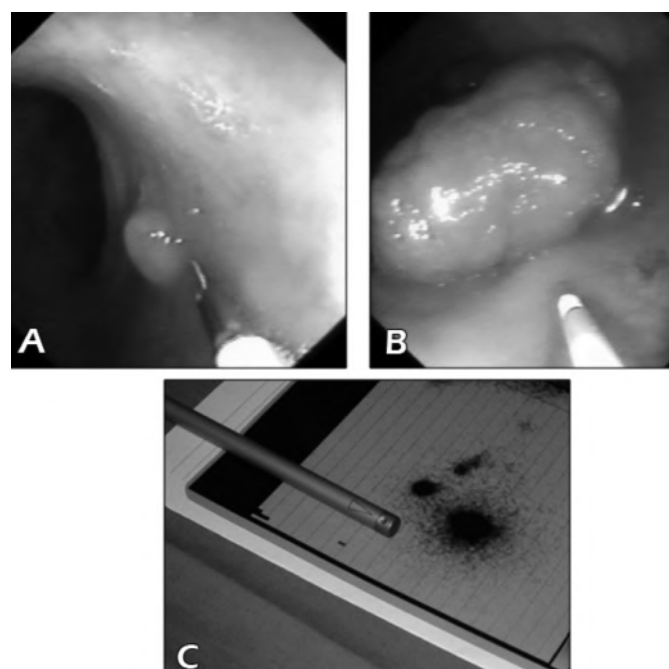


Fig. 1: A-B: Patient with colon neoplasm and perilesional injection of tracer via laparoscopy; C: Laparoscopic Scintiprobe with diagram of the uptake.

mm). The patient was placed in the Trendelenburg position with rightwards rotation and exploration of the abdominal cavity as per the open technique. The endoscopic probe (Scintiprobe) was inserted and the previously tagged lesion(s) localized, after which the borders oncologically free of infiltration were determined. Mobilization of the left colic flexure was performed through left-to-right sectioning of the gastrocolic ligament beginning in the middle of the transverse colon up to the splenocolic and frenocolic ligaments so as to allow depression of the left colic flexure. The inferior mesenteric vessels were then sectioned followed by the mesocolon, as per the open technique. Mobilization of the left colon and sigmoid was finally completed by sectioning the peritoneal reflection of the left parietocolic groove up to the promontory and then separating the rectum and mesorectum anteriorly and laterally, sparing the nerves, as per the laparotomic technique. The colon-rectum was then closed and sectioned with a mechanical stapler after endoluminal betadine lavage. A mini-laparotomy was performed in order to extract the colon-rectum and the colon was sectioned proximally to the neoplasia, and the head for the circular stapler intro-

duced. Anastomosis was performed transanally following the Knight-Griffin method. The integrity of the anastomosis was checked via the hydro-pneumatic test and a temporary protective ileostomy fashioned as needed.

During the procedure, the surgeon used the gamma probe to externally scan along the colon axis to search for the injection sites. In all 8 cases treated with the laparotomic surgical approach the time required to localize the lesion was only few minutes (range 2-5 min.), while for the video-laparoscopic approach used instead in 4 cases, the procedure called for slightly longer times (range 3-9 minutes).

The lesion (or in the event of multiple lesions, the intestinal segment to be resected) was then delimited with clips, which were used during resection as reference markers to avoid having to reintroduce the gamma probe. After resecting, checks were made with the gamma probe to confirm the absence of residual radioactivity in both the resection borders and the rest of the abdominal cavity. Moreover, localization was effected of the injection sites *ex-vivo* by measuring the radiation distribution along the resected segment of the colon with the gamma probe (Fig. 2).

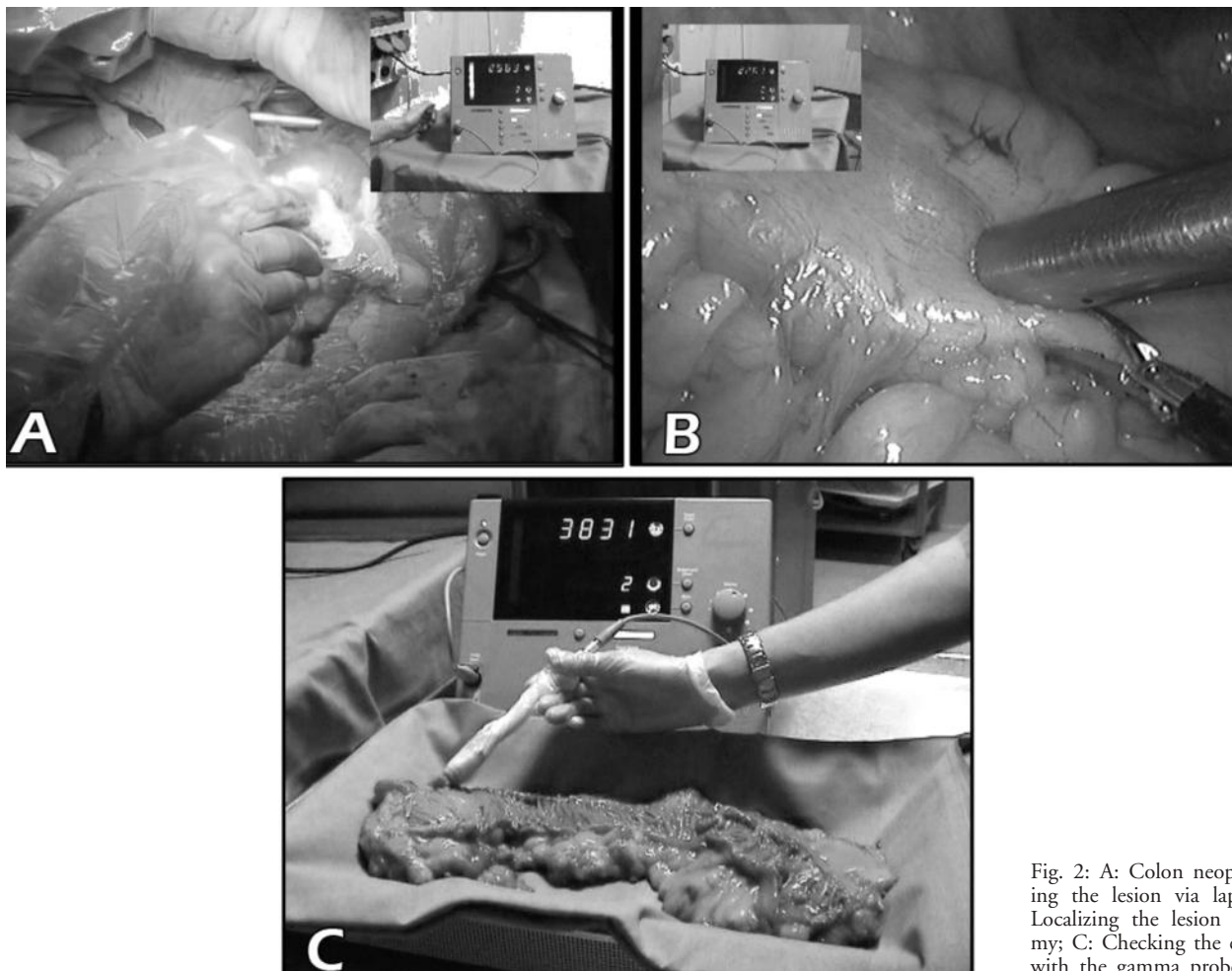


Fig. 2: A: Colon neoplasia, localizing the lesion via laparotomy; B: Localizing the lesion via laparotomy; C: Checking the excised lesion with the gamma probe.



Lastly, as the histological samples drawn from the lesions were to be considered biologically hazardous material until decay of the radiotracer, they were only examined a minimum of 24 hours after the surgical procedure.

## Results

In all 12 patient treated, localization of the lesion through via ROCLI was technically feasible, safe, effective, and highly accurate, enabling timely, 100% successful identification of the lesion during the surgical procedure.

When the distance of the probe from the lesion was maintained within 0.5 cm, the detected radiation counts were very high (8.0-10.0 KCts), though it fell significantly (to about 4.0 KCts) at about 2 cm from the source, to reach 0.1 KCts a distance varying between 5 and 10 cm. In all 12 cases the presence of the lesions was confirmed by pathology examination of the surgical specimen.

## Discussion

The difficulty of detecting small-sized colon lesions or those located in particular areas is well-known to G.I. surgeons. Often polyps, small neoplasias, angiodysplasia and residual neoplastic tissue after incomplete endoscopic ablation are difficult to locate either visually or through palpation. Lesions in the right and left colic flexures, for example, are particularly difficult to identify, especially when they are accompanied by inflammation (peritonitis, diverticulitis). This difficulty in localizing lesions is particularly marked in laparoscopic surgery, during which identification of a lesion or definition of the borders of even large-sized neoformations can be challenging when there is no serous involvement.

Various methods of preoperative localization have been proposed over the years: double-contrast opaque enemas, colonoscopy, tagging techniques with Indian ink or methylene blue and, more recently, tagging with metal clips inserted endoscopically and highlighted intraoperatively through radiological or echographic techniques and the use of a metal detector.

Whether combined with double-contrast enema or not, pre- and intra-operative colonoscopy, which have long been the mostly widely used techniques, do not always enable the distance between the lesion and the anal border to be evaluated accurately. This is due to the relaxation and stretching of the colon that take place during the examination. Planning intraoperative endoscopy during open surgery can be very challenging and at times impracticable, especially in emergency situations. There are inherent difficulties, from positioning the patient, to preparation of a sterile operating field and the necessary surgical timeframe, to which must be added the costs of

sterile materials, antibiotic coverage, and the need for an available operating theater and a gastroenterology team with portable instrumentation<sup>34</sup>.

Preoperative endoscopic tagging (with Indian ink or methylene blue) have moreover not been shown to be safe, reproducible and reliable methods in clinical practice. This is mainly due to the instability of the stains and the near impossibility of repeatedly administering precise submucosal injections. The method is quite unreliable, involves the risk of serious complications, and has a high rate of failure due to various factors, amongst which the risks of injecting the stain into the peritoneal cavity, chemical reactions caused by the dye at the injection site, diffusion of the stain in time, the instability of some stains and the intraoperative difficulty of finding the "colored" site in areas of complex anatomy such as the left flexure of the colon. The method is moreover contraindicated in patients with diverticulitis.

Recently, a technique has been proposed that involves tagging with metal clips, which are then detected by radiology or echography. Such technique has however revealed to suffer from some major drawbacks: the clips may be displaced, the radiographs are often difficult to interpret, and radiation shielding is required. Finally, metal detectors are not easily available for laparoscopic applications and moreover require the application of a large number of clips to be effective *in situ*.

Ecograph detection also presents a number of drawbacks: the colon must be clamped and a saline solution administered rectally in order to guarantee optimal ecograph performance. Lastly, as with the radiograph method, the clips may simply detach or move. For these reasons, ultrasound techniques for the detection of such clip markers can only be used effectively at the level of the sigmoid and rectum.

Radioguided surgery in patients suffering from colon cancer furnishes real-time information to the surgeon regarding the localization and extension of the lesion and enables more precise evaluation of the boundaries for surgical resection. Moreover, such technique has enabled reducing to a minimum the surgical invasiveness of many diagnostic and therapeutic procedures of enormous benefit to oncology patients.

The main advantage of radioguided techniques over other methods is the extremely precise localization they afford of tagged lesions, a process which can moreover be concluded in exceptionally brief times. In addition, they do not call for any extra maneuvers above and beyond those necessitated by surgery, involve lower costs and are faithfully reproducible.

Radioguided localization of occult lesions moreover enables identification of lesions that the surgeon can neither palpate nor see, and limits the area to be resected to the lesion alone, at least in cases where radical resection is not made necessary by clinical or oncological reasons. This technique makes it possible to combine intestinal resection with surgical ablation of a lesion else-

where, such as for instance a right hemicolectomy with the excision of a sessile polyp in the left colon. A further advantage is that it can be performed via limited surgical access through accurate transcutaneous localization followed by precise intraoperative localization.

Regarding video-laparoscopic surgery, which is based on a safe and sure method for lesion localization, the ROCLI technique is clearly of fundamental importance, as it provides fast, precise localization of the lesion, thereby allowing the surgeon to correctly determine the borders of the resection under absolutely safe conditions, without however unduly prolonging the procedure.

In our experience, applying this technique enables locating even the most difficult lesions to identify, whether due to their size, structure or anatomical site. Lesion detection is moreover performed without imposing any additional stress on the patient. The technique boasts a good costs-to-benefits ratio, is consistently replicable and without significant risk of complications. It has moreover enabled safe, effective execution of laparoscopic surgery in 4 patients without having to proceed to laparotomic access – a necessity that used to arise in the event of inaccurate localization of a lesion. In no case were intraluminal effusions of the radiopharmaceutical encountered, though in such event, it is possible to eliminate the radioactivity present in the lumen via prompt lavage of the intestinal tract.

Other possible applications of the technique are currently in the stages of clinical validation, such as localization of occult gastric lesions and sentinel lymph node identification in cancer of the colon-rectum-anus.

In conclusion, our experience with ROCLI has shown, in accord with the conclusions reached in three other important Italian literature reports<sup>35-37</sup>, that the technique provides for 100% successful identification of occult lesions of the colon. It engenders neither complications nor the risk of contamination from ionizing radiation. The radiation exposure risk for the surgeon and hospital personnel involved in the procedure is very low and in any event comparable, if not inferior, to that of a radioguided sentinel lymph node biopsy during treatment of melanoma or mammary carcinoma.

### Riassunto

La chirurgia radioguidata è una disciplina che presenta numerosi campi di applicazione, soprattutto in ambito oncologico; è caratterizzata dall'approccio multidisciplinare diagnostico-terapeutico tra medico nucleare e chirurgo. Dalla metà degli anni '90 è stata introdotta la tecnica ROLL, ideata e messa a punto per il trattamento del carcinoma della mammella, successivamente adattata anche ad altre patologie, come il nodulo polmonare solitario (durante chirurgia a cielo aperto oppure durante toracosopia video-assistita) e le lesioni coliche. Tale tecnica, denominata ROCLI, consiste nell'individuazione, tramite

una sonda per il conteggio intra-operatorio delle radiazioni gamma (sonda gamma), di piccole lesioni coliche che potrebbero sfuggire all'esame palpatorio intraoperatorio, dopo marcatura delle lesioni stesse per via endoscopica tramite iniezioni peri- o intra-lesionali di macroaggregati di albumina umana marcati con Tecnezio-99m (<sup>99m</sup>Tc-MAA), radiofarmaco costituito da particelle di dimensioni tali (25-100 µm) da impedirne la migrazione dalla sede di somministrazione interstiziale.

Dal settembre del 2001, la tecnica ROCLI (sigla che indica la "radioguided occult colonic lesion identification") è stata utilizzata in 12 pazienti, utilizzando una sonda gamma collimata con diametro esterno di 11 mm (Scintiprobe MR100 Pol.Hi.Tech.). Tutti i pazienti sono stati sottoposti a colonscopia preoperatoria al fine di iniettare in sede sottomucosa intra o perilesionale aliquote di 0.2 mL di <sup>99m</sup>Tc-MAA (10-20 MBq). Questa metodica di "marcatura" pre-operatoria della lesione ha richiesto in genere pochi minuti.

In 8 pazienti è stato effettuato un intervento per via laparotomica, mentre nei restanti 4 è stato possibile procedere con un accesso laparoscopico. In tutti i 12 pazienti trattati la localizzazione della lesione mediante tecnica ROCLI è stata tecnicamente fattibile, sicura, efficace ed altamente accurata, consentendo l'individuazione tempestiva della lesione durante l'intervento chirurgico, con tasso di successo pari al 100%; non si sono inoltre verificate complicanze, e non c'è stato rischio di contaminazione da radiazioni ionizzanti.

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