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# A New Device for Sentinel Node Detection in Laparoscopic Colon Resection

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## ABSTRACT

**Objective:** To test the feasibility of using a newly developed device for laparoscopic lymphatic mapping of the colon by simultaneous and quantitative detection of both tissue coloration and radioactivity.

**Methods:** Four pigs were used in this study. In each animal, both blue dye and radioisotope injections were utilized. Lymphatic mapping was performed laparoscopically in the sigmoid mesocolon and in the right mesocolon. A solution containing a mix of 35 microcuries of Technetium Tc-99 sulfur Colloid and 1 mL of a vital blue dye was administered subserosally by percutaneous insertion of a 25 gauge needle under laparoscopic control. The new device for automated sentinel-node detection consists of a gamma-probe coupled with a laser device and can be passed through a regular 10-mm trocar. The device detects simultaneously both radioactivity and quantitative tissue coloration. Nodes showing a radioactivity at least 5 times higher than that of the background or that had a blue colorant concentration were considered our sentinel nodes.

**Results:** Laparoscopic simultaneous and quantitative detection of sentinel nodes was feasible in all pigs. One or more sentinel nodes were identified by either the blue dye or radioisotopic technique in both the sigmoid and right mesocolon. Quantitative tissue coloration detection led to the recognition of additional nodes that were not apparently colored to the naked eye.

**Conclusion:** Laparoscopic sentinel node detection using a device combining gamma and color detection is feasible in the porcine model. The significance of nodes apparently clear but positive with the quantitative detection technique should be further evaluated.

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**Key Words:** Colorectal carcinoma, Sentinel node, Laparoscopic colon resection, Lymphatic mapping.

## INTRODUCTION

The sentinel lymph node is the first node relay receiving direct drainage from a primary tumor. This concept is based on the premise that lymphatic drainage of tumors initially occurs through dedicated lymph nodes prior to drainage to the regional lymphatic basin. Metastatic tumor cells progress in this way in an orderly sequential fashion following lymphatic channels. Because the sentinel lymph node is the first stage of metastatic nodal involvement, it is thought that its histological status reflects the status of the whole lymph node basin.

The sentinel lymph node concept has been validated in studies of melanoma and breast cancer, and in these cases, the intraoperative sentinel lymph node harvesting of a primary melanoma or a breast cancer was found to be an accurate staging procedure. The application of the sentinel node concept to malignant melanoma has been able to limit the indications of lymphadenectomy in this pathology, thus reducing the morbidities related to it. In breast cancer, this possibility is being explored, as well as the possible upstaging of in situ breast cancer. However, concerns about a fairly high false-negative rate, ranging from 5.1% to 7.6% in a metaanalysis,[1] remain. Nevertheless, no strong evidence exists that extended lymph node dissection in colorectal cancer has any impact on cancer management. Concerning gastrointestinal malignancy, the literature remains contradictory. For several authors,[2] the sentinel node status accurately reflects the regional node status. Nevertheless, for other authors,[3] the concept of lymphatic mapping and sentinel node identification is not valid for colorectal cancer because a false-negative rate of 60% was observed in patients. The key methodological factors for the assessment of sentinel nodes are the techniques of detection of the nodes. Two sentinel lymph node detection techniques are commonly used. The first involves blue dye injection and detection of blue color in the node. The second involves a radiotracer injection and gamma probe detection of the node. Ideally, simultaneous

injection and detection of both markers has been shown to increase detection rates to 99%. Furthermore, reliability and variability at different segments of the gastrointestinal tract as well as the variability between individuals may limit the quality of node detection. The purpose of our study was to evaluate a new device for the detection of sentinel nodes, applied to laparoscopic colorectal surgery, that can simultaneously detect blue dye and radiotracer.

## METHODS

An original probe was developed allowing simultaneous detection of radiotracers and blue dye markers **(Figure 1)**. This probe combines a standard gamma probe to a laser probe able to identify low blue dye injected nodes. This probe is able to perform an automatic measurement of the color of the node as well as its radioactivity.

The dual opto-nuclear probe is designed for the preoperative sentinel lymph node localization based on radiation and tissue coloration detection (French patent N°2 823 092, USA extension N°10/119219).

This probe allows for simultaneous detection of radiotracers and blue dye concentrated in tissues. For radio detection, the probe relies on a high efficiency small-sized CdTe semiconductor detector mounted with its close electronics at the tip of a stainless steel shaft of about 40 cm in length and 12 mm in diameter **(Figure 2)**. It is designed for low to mid energy radiation detection (I-125, Tc-99m, etc.) and operates under low bias voltage. The tip is shielded with tungsten; an epoxy window (diameter 7 mm x 0.3 mm) is placed in front of the detector and offers a frontal field of view (in line with the tube).

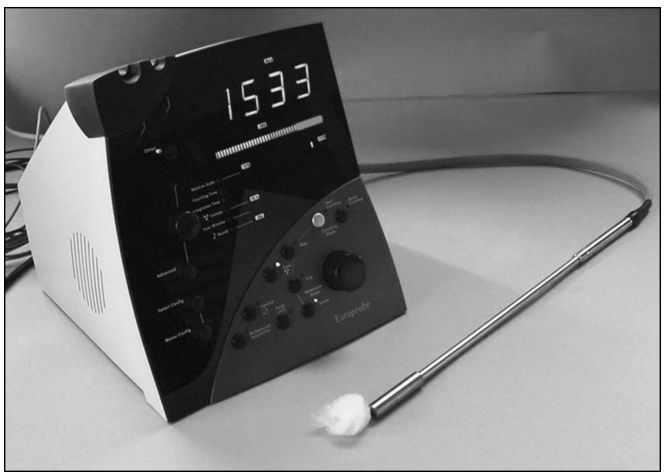


**Figure 1.** Eurorad's opto-nuclear endoscopic probe and readout module.

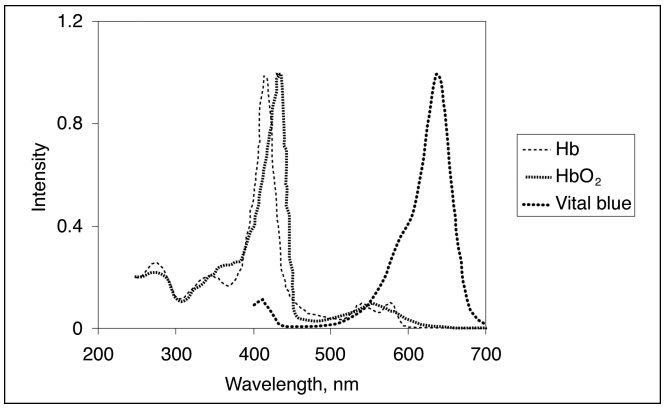


**Figure 2.** Absorption spectra of hemoglobin, hemoglobin oxide, and vital blue.

The probe is also designed to detect the slightest quantity of blue dye coloration in tissues. The principle on which automatic color detection is based is the following: the maximum of the absorption spectrum of the blue dye is located outside the absorption range of main chromophores (a chemical group that absorbs light at a specific frequency and imparts color to a molecule) present in the tissue in this wavelength region, ie hemoglobin and hemoglobin oxide **(Figure 3)**. An optic fiber coupled with a 635 nm laser diode and a photodiode are used for light diffusion and detection in tissue, respectively. When a minute quantity of blue dye, even invisible to the naked eye, is absorbed by a sentinel node, the light diffusion in this node is attenuated.

The probe is equipped with optic fibers for the detection of attenuation of diffusion in tissues. The probe is connected to the read-out module through a 3.5-m flexible cable and operates in 2 modes: radiation detection and optical detection. In the radiation detection mode, the emissions from tissue gamma rays (photons) are detected by a CdTe detector, which transforms each photon into an electrical signal. These signals are amplified through the preamplifier, which is located in the probe. The signals are then transferred to the read-out module where they are processed, counted, and displayed.

An audible alarm, proportional to the detected activity, allows the surgeon to localize the areas of higher activity by "sound" without requiring visual monitoring of the display.

A foot switch connected to the system allows the start of acquisition without touching the module. The same foot switch is used for changing the operating mode from radiation to optical configuration. In the optical mode,

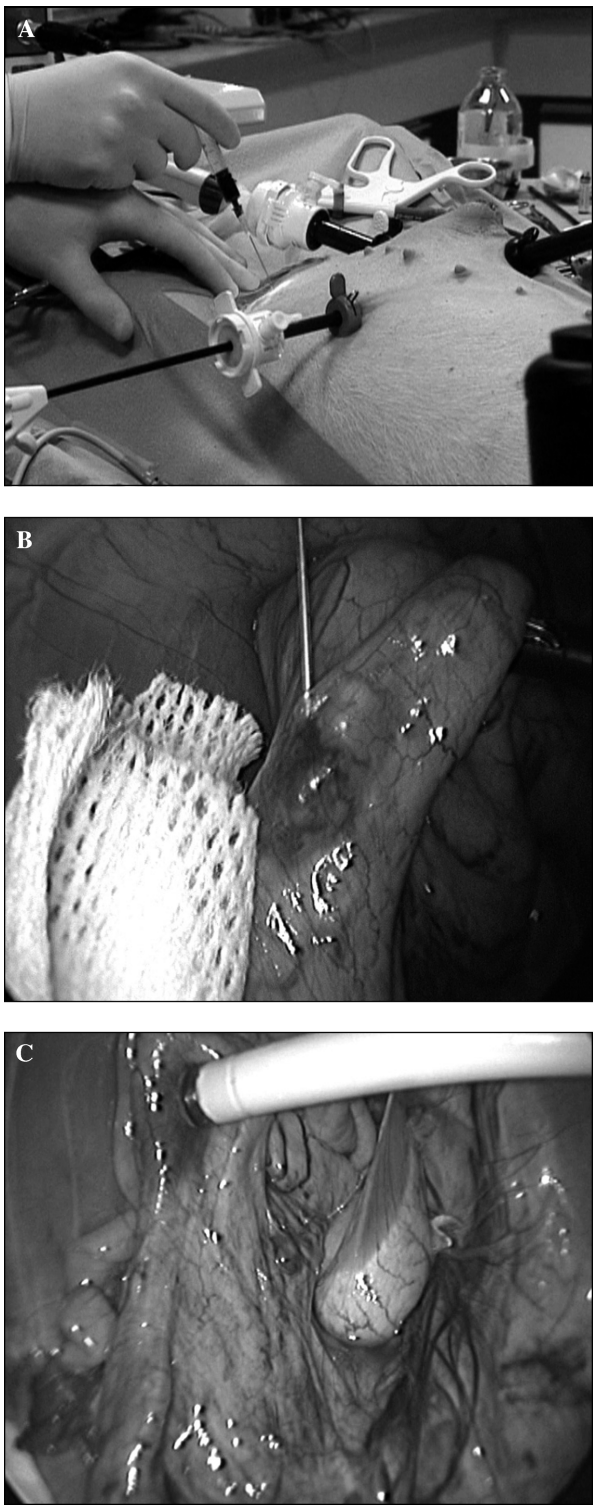


**Figure 3.** The figure shows our experimental model for sentinel node detection: laparoscopic approach (A); subserosal injection of dye (B); detection by our newly developed probe (C).

blue dye tissue coloration is also displayed on the read-out module, and similarly, an audible signal proportional to a tissue coloration degree can be heard.

### Animal Preparation

Animals were fasted overnight. On the morning of the experiment, they were premedicated intramuscularly with 15 mg/kg of ketamine hydrogen chloride and 0.5 mg atropine.

General anesthesia was induced with 20 mg/kg of pentobarbital intravenously. Orotracheal intubation was done using a 5.5-mm endotracheal tube, and anesthesia was maintained with 2% isoflurane and air:oxygen (FiO2:0.50). Muscle paralysis was induced with intravenous pancuronium bromide (0.1 mg/kg) and saline solution administered intravenously at 100 mL/h.

### Operative Technique

Four pigs were used for the study. All pigs were operated on by laparoscopy. Three trocars were used. The sigmoid colon and mesocolon were exposed and studied. Then the same method was used on the right colon a few centimeters distal from its junction with the small bowel. A mix of patent V blue dye (Laboratoire Guerbet, Aunay-Sous-Bois, France) and of unfiltered 99-Tc sulfur colloid was used. The wall of the viscera was injected subserosally with a 25 gauge needle. Spillage of the mixture was avoided by careful swabbing during injection to avoid contamination by radioactivity or coloring at untouched sites. Nodes were searched for in the mesocolon or the draining lymphatic bed of the stomach. With the use of a gamma probe, the level of radioactivity was measured in the mesocolic fat and in all visible lymph nodes, and gamma counts were recorded. The same probe was used for colorimetric measurements, which were made simultaneously. When sentinel nodes were identified, they were marked with a suture or a clip. At the end of the procedure, the animals were sacrificed while still under general anesthesia.

## RESULTS

### Sigmoid Colon

In 100% of cases, one or more (1 to 3) sentinel nodes were identified after injection of the sigmoid colon. In all cases, the sentinel nodes were identified by the blue dye technique; the radioactive technique failed to detect a sentinel node in 3 animals.

In 1 pig, the use of the opto-nuclear probe detected blue dye in occult sentinel nodes.

### Right Colon

One or more sentinel nodes were identified in the right mesocolon in 3 of 4 pigs. The sentinel nodes were identified by the blue dye technique directly. In 1 pig, in which no blue nodes were initially found, the optic probe detected an area of greater colorimetric activity. Dissection of this region led to the discovery of a blue node deep in the mesocolic fat.

## DISCUSSION

In colorectal cancer, the presence of histologically cancer-involved lymph node metastases has been shown to be an independent prognostic indicator of survival.[4] No strong evidence exists that extended lymph node dissection in colorectal cancer has any impact on survival or local recurrence rates, but lymph node metastases are indicators of systemic disease. It is therefore important to identify these nodes in order to accurately stage the disease and to identify patients who may benefit from adjuvant therapy. Studies show that this adjuvant therapy provides survival benefits for American Joint Committee on Cancer (AJCC) stage III patients. Unfortunately, up to 30% of patients with negative lymph nodes (Stage II) will have a recurrence of their disease.[5] Whether it is because of inaccurate initial staging or because of other factors of a poor prognosis is not known. A more precise way to stage these patients might have an impact on these numbers. The selective analysis of sentinel nodes may offer the possibility to do so. Studies show that both in vivo and ex vivo techniques can lead to the detection of sentinel nodes in cases of colon and rectal cancer.[6] Moreover, the identification of sentinel nodes by a method using either blue dye or radioisotopes alone is less accurate than detection performed with the combination of both methods. In melanoma and breast cancer, the detection rate is around 80% for blue dye, 95% for radioisotopes, and 97% to 99% with both methods.[7] Therefore, the combined gamma and laser probe may be more sensitive in the detection of sentinel lymph nodes undetectable by the naked eye or gamma count. Furthermore, as this new probe is designed for laparoscopic application, and as studies tend to validate the oncological safety of treatment of cancer by laparoscopy,[8] it might apply to in vivo laparoscopic as well as ex vivo cases. The in or ex vivo detection technique could furthermore increase the sample size that could improve the reliability of the results as demonstrated in our study by identification of noneye-detected sentinel nodes. In our study, 2 of 4 animals in which sentinel lymph nodes were invisible to the naked eye were detected through the laser probe, so-called occult sentinel lymph nodes. The automatic colorimetric probe using laser might, in clinical cases, obviate the need to rely solely on eye detection and may increase the number of colored sentinel nodes that are detected, which might in turn allow revealing more nodes involved with tumor cells. Whether this would translate into clinical benefits of survival for patients however remains to be demonstrated.

For sentinel node biopsy to be clinically useful, the false-negative rate (proportion of negative sentinel nodes in the presence of tumoral invasion of other nodes) has to be reduced to the lowest percentage possible. Although most authors report sentinel node detection rates of more than 90% for colorectal cancer,[2,9,10] others have reported detection rates of 58% to 71%.[3,11,12] For several authors,[13] the false-negative sentinel nodes have been proposed to originate from a variety of causes, such as the site and volume of the dye or the diversion of lymph flow caused by occlusion of lymphatic channels caused by gross tumoral replacement of nodes. We hypothesize that technological assistance might help to reduce these cases where a sentinel node cannot be found.

Furthermore, nodes that are not located in the classical area but in an alternate drainage area could be detected. Some of these nodes could account for skip metastases, which are reported in 2% to 14% of cases.[11] The possibility of using an intraoperative detection probe would increase the capacity to detect these nodes located in alternate pathways. In these cases, these metastases would be detected, resected, and analyzed separately.

These elements could contribute to causing the search for the sentinel lymph node in colorectal cancer to be accurate as it is in melanoma or breast cancer. Our experimental model in animals and our ex vivo model on a human being confirm the need for better training in the injection technique allowing laparoscopic detection of sentinel lymph node. It also illustrates the necessity to test such new devices before regular clinical use. Merrie et al[14] have shown that the use of combined dye and the radiocolloid injection technique and detection in colorectal cancer may improve the quality of sentinel lymph node detection. The simultaneous automated colorimetric and gamma probe detection of the sentinel node may increase the detection of the invaded nodes and may increase the correlation

between sentinel node status and local-regional lymphatic spread.

## CONCLUSION

The role of sentinel lymph node detection in colorectal malignancies remains to be established, but the integration of new devices combining radiotracer and dye detection may render sentinel lymph node harvesting more sensitive and a more accurate predictor of lymph node status. The prognostic significance and clinical relevance of lymphatic mapping in patients with carcinoma of the colon and rectum could play an important role in upstaging patients and therefore increase the number of patients who may benefit from adjuvant chemotherapy.

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