THE IDENTIFICATION "EX VIVO" OF THE SENTINEL LYMPHNODE IN THE COLON CANCER: PHESABILITY STUDY

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Abstract: *The purpose of this study is to evaluate the feasibility and reliability of the "ex vivo" technique in mapping the sentinel lymph node (SLN) in patients with colorectal cancer. In the period between January 2008 and May 2011, 45 patients of the Surgery 1 Department of the Emergency County Hospital Sibiu and of the Surgery Department of the Military Emergency Hospital Sibiu underwent this technique when undergoing curative surgery for colon cancer. The identification quote of the sentinel lymph node was 93,33%, a sensitivity degree of 92,85%, while the false negative SLN was 13,33%. This data suggest that "ex vivo" SLN biopsy is feasible in colorectal cancer. Although ex vivo SLN biopsy does not alter the lymphatic dissection, it may upstage a subset of patients. The technique of ex vivo sentinel lymph node mapping is technically feasible with high sensitivity, high negative predictive value and a high rate of upstaging.*

Cuvinte cheie: *nodul limfatic santinelă, colon, cancer, ex vivo*

Rezumat: *Scopul acestui studiu este să evalueze fezabilitatea tehnicii "ex vivo" de punere în evidență a nodulului limfatic santinelă în cancerul de colon. În intervalul ianuarie 2008 – mai 2011 în Clinica de Chirurgie I a Spitalului Clinic Județean de Urgență Sibiu și Secția de Chirurgie a Spitalului Militar de Urgență Sibiu, am aplicat această tehnică la 45 dintre pacienții operați pentru cancer de colon. Rata de identificare a nodulilor santinelă a fost de 93,33%, acuratețea de 92,85%, iar rata de rezultate fals negative de 13,33%. Cartografierea limfatică a bazinului limfatic prin metoda "ex vivo" este o tehnică fezabilă în cancerul colorectal. Deși această tehnică nu modifică disecția limfatică, ajută la o stadializare mai corectă a pacienților operați.*

INTRODUCTION

The treatment of the colon cancer (CC) should be done by surgery, imposing the total resection of the colon segment containing the primary tumor with regional lymphadenectomy (1,2). The main indicator of recurrent disease and of disease survival is the presence of the lymph nodes metastasis. In this case, chemotherapy is recommended, leading to only 40% recurrence and improvement of the survival quote with 33% (3). Chemotherapy is not a routine treatment for CC without metastic disease because it is a very toxic and expensive therapy, without major benefits regarding the recurrence and survival quote (3,4). However, recurrence is reported in 25% of the patients classified in the II-nd stage of the disease (4,5). This can be explained either by inappropriate anatomicopathological examination, insufficient surgical resection (2), secondary venal or peritoneal determinations (6) or inadequacy of the tumor staging system.

Nodes in a resected specimen have traditionally been identified by a combination of visualization and palpation, which often leads to the identification of a limited number of lymph nodes (7). This method is inadequate because metastasis frequently targets nodes smaller than 0.5 cm in diameter (4,8). Moreover, by examining a single section of a 5mm node, less than 1% of its entire volume is being evaluated (2,8). By standard examination of a positive node, in 33% of the cases metastases cannot be detected (4).

Techniques such as multilevel sectioning, cytokeratin immunohistochemistry (IHC), and reversed transcription polymerase chain reaction (RT-PCR) can identify missed tumor cells in nodes (4), although their impact on staging is unclear. However, applying these techniques to all resected nodes cannot be done because of its high costs and of the human medical resources they imply (6,9).

The sentinel lymph node (SLN) is the first node to receive lymphatic drainage from a primary tumor, so being the most likely site for a metastasis (10). The mapping, dissection and detailed examination of a SLN can identify undetected metastases which may increase the risk of recurrence of the neoplasic disease (4).

These techniques proved their utility in the diagnosis of breast cancer and melanoma for almost 20 years (11). Foremost, for these two types of neoplasic sites, if the SLN proves to be negative, the magnitude of the lymphadenoctomy and of its implicit morbidity can be limited (2,12). Regarding digestive cancer, lymphadenectomy remains a major component of the surgery, applying the SLN method can be used for increasing the accuracy of the staging system (13,14).

By using this method, the pathologist can point to the first 4 lymph nodes having the highest probability of secondary determinations (15). In case that the metastatic disease cannot be identified by standard examinations, the above mentioned techniques can also be used (4). In the case of colorectal cancer, the "in vivo" technique implies the injection of a dye or of radioactive solutions before the mobilization and the resection of the tumor. Alternatively, the "ex vivo" technique can be used, when the mapping is done on the resected part (3, 16-18).

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THE AIM OF THE STUDY

Our study's aim is to analyze the feasibility of the usage of the ex vivo mapping technique in colorectal cancer by means of vital dye.

MATERIAL AND METHOD

In the period between January 2008 and May 2011, the "ex vivo" technique for diagnosing an SLN has been applied to 45 patients of the Surgery 1 Department of the Emergency County Hospital Sibiu and of the Surgery Department of the Military Emergency Hospital Sibiu, suffering from colon cancer. The patient selection criteria was presented in a previous article (19), most of these patients were suffering mainly from primary colon tumors (including rectosigmoidian junction). While still respecting all standard oncological criteria, radical interventions have been practiced on these patients.

The mapping method used is the one suggested by Dr. WONG in 2001 (20), with a few adjustments. After gross examination of the specimen and within 30 minutes of removal, the colon was incised longitudinally on the antimesenteric border. In opening the colon, no attempt was made to avoid the tumor if it involved the antimesenteric wall of the colon. By means of an insulin syringe, four submucosal injections of approximately 1 or 2 ml of a blue dye were performed in four quadrants around the tumor. The quantity used varies according to the dimension of the tumor (Figure 1). The injection points have been gently massaged for 2 to 5 minutes. The mesenter was then examined by incising the peritoneum at the base of the tumor. Stained lymphatic canals and a varying array of blue-stained nodes have been searched for by means of digitoclasy (Figure 2). The first four stained nodes have been resected (Figure 3). The sentinel nodes and the rest of the resected specimen were delivered to the Department of Pathology.

Figure no. 1. Process of injection

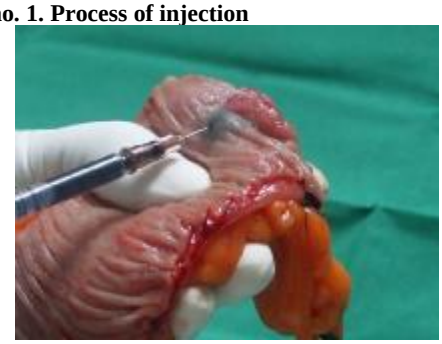
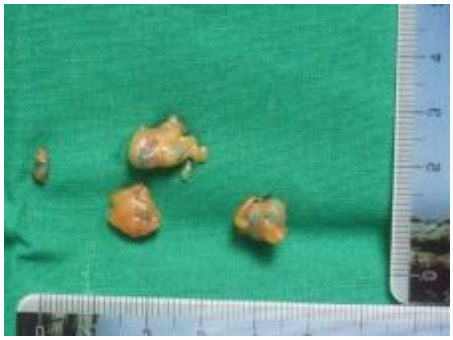


Figure no. 2. Resection of the blue-stained lymph nodes

Out of all studied cases, 13 were suffering from ascending colon tumors, 3 of the transverse colon, 5 of the descending colon, 15 of the sigmoid colon and 9 at the rectosigmoidian junction. The preoperational staging of the tumor was the following: 4 patients in T1, 8 patients in T2 and 33 patients in T3.

Figure no. 3. Sentinel nodes



RESULTS

The identification quota has been 93,33% (that is with 42 patients being identified with at least one SLN).

The average identified number of SLNs was 2 (2,5±1,2).

The accuracy rate means the ability to evaluate the status of the lymph nodes at the lymph basin. In our case it has been 92,85% (39 of the 42 patients had SLNs identified).

The false negative quota was 13,33% (2 patients had false negative results out of 15 patients with lymph node metastases).

DISCUSSIONS

No standard method has been established yet for SLN mapping. However, different colored dyes (visible or invisible with free eye) or even radioactive agents have been used, as well as other time intervals between the injection and the SLN highlighting; different injection sites such as submucosal, subseral and peritumoral, ex vivo or in vivo injections (1,6,8) make up other varieties of establishing the SLN mapping. This variability between methods of study makes the results difficult to compare and interpret.

The main critics of the "ex vivo" technique imply the fact that it is less physiological than the "in vivo" procedure (3) and that it does not highlight the largely affected lymph drain. The dye is being moved through the lymphatic vessels due to the gently manual massage of the specimen. However, by means of this massage, the lymphatic vessels can be disrupted, involving a change of the lymphatic flow and ending in false negative results (3).

For technical variation for the "ex vivo" technique, instead of using the blue dye, there have been reported uses of lymphoscintigraphy (21). After having injected the blue dye, in a few minutes' time, the SLN identification can be visualized on the fresh specimen, but also on the one preserved in formaldehyde.

The "ex vivo" technique has some advantages compared to the "in vivo" procedure. First, the injection is a simple and easy method, not needing too much practice (3). The injection is done into the submucosa, at the point where lymphatic vessels originate. All surgery specimens can be examined and mapped by a single dedicated person, either a surgeon or a pathologist. The peritumoral-localized SLNs can be easier identified because the dissection is carefully done and the injection does not lead to the staining of the mesenter (3). The blue-dye injection does not prolong the duration of the surgery, does not imply any anafilactic risk (16), does not interfere with the pulse oximetry determinations and does not imply the intraoperative manipulation of the tumor, causing possible tumor cell shedding and thus not increasing the risk of local tumor recurrence (3). The technique can be used as a first choice, but also when the "in vivo" technique fails (1, 22).

The results of these two techniques can be compared (5).

The global sensitivity and specificity quote of the lymphatic mapping is 70%, respectively 81%. The cause of the false negative results (an average of 9%) is not completely known, which represents the major problem when introducing this technique in the management of colon cancer (11). There are different possible explanations of the false negative results. A massive invaded or adipose engulfed node behaves as an obstacle in the progression of the dye (23), as well as technique errors (13), insufficient quantity of dye, or bulky sized tumors.

By multiserial analisys of the SLN sections dyed with hematoxilin-eozin, the staging of the disease increases from stage II to stage III in 7-19% of the patients (2). When using IHC the upgrading increases to 7-31%, and for RT-PCR to 30-40% (5).

The prognostic implication of micrometastases found in SLNs requires further evaluation. Even so, their presence was included in the last edition of the TNM classification (4).

CONCLUSIONS

The lymphatic mapping by means of the "ex vivo" technique is a feasible method in colorectal cancer.

The technique is simple, fast, inexpensive and does not prolong the surgery time. Even if this technique does not modify the lymphatic dissection, it helps to correct staging of the involved patients.

However, additional, randomized, prospective trials and long-term follow-up studies are needed to assess the prognostic value of staging, because the follow-up of the previous literature is relative.

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