

Interest of the Sentinel Node Technique in the Treatment of Colon Cancer

N. SID IDRIS⁽¹⁾, K. HAIL⁽²⁾, S.A BENSARFAR⁽²⁾

¹(Hospital Djillali Belkhenchir, Algiers, Algeria)

²(University hospital Mustapha Pasha of Algiers, Algeria)

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I. Introduction

Optimizing the treatment of colon cancer requires very close collaboration between surgeons, pathologists and oncologists (2). It consists of a colectomy according to the site of the tumor with a lymph node dissection associated or not with an adjuvant treatment according to the tumor stage (TNM). Its prognosis depends on the earliness of care, it is relatively good when it is diagnosed early with overall survival at 5 years which is around 91% and it drops to 11% in a metastatic situation (3).

The prognostic impact of the number of lymph nodes invaded has been demonstrated by several studies which concluded significantly that the number of lymph nodes invaded increased with the number of lymph nodes examined and that overall survival at 5 years was significantly better in patients with at least 15 lymph nodes examined, therefore the number of lymph nodes invaded was an independent prognostic factor (4).

The search for micrometastases whose size will not exceed 2mm (5) by unconventional anatomopathological methods "immuno histochemistry and molecular biology" allows to improve the lymph node status (ultrastaging), but on the practical level they are hardly achievable because of the high number of lymph nodes to be analyzed and the cost it will generate; hence the idea of focusing the search for micrometastases on the sentinel node.

The sentinel node concept is based on the identification and search for tumor infiltration; the latter has been clearly demonstrated in malignant melanomas and breast cancer, thus limiting the extent of lymph node dissection which was sometimes very extensive and provides high morbidity (6). For colon cancer, it is a question of reclassifying a subgroup of patients initially pTN into pTNi + after identification of micrometastases by unconventional anatomopathological methods and therefore will benefit from an adjuvant treatment.

II. Material And Methods

Apart from a contraindication and whatever the site of the tumor, the technique started with the incision of the meso colon opposite the tumor, then injection into the peri-tumor and sub-serous at the 04 cardinal points 0.25 ml of methylene blue (fig. 1), after waiting 5 to 10 minutes, the first nodes colored in blue (fig. 1) were marked with a wire and considered as sentinel nodes, to facilitate identification the pathologist (in vivo detection)



Fig 1: detection technique of invivo sentinel lymph node

After detection of the sentinel lymph nodes, a colectomy was performed with conventional lymph node dissection. If this technique fails, we later carried out the ex vivo detection technique, which consisted of injecting after opening the operating room into the peri-tumor and intra-mucosa at the 4 cardinal points of methylene blue (fig.2), and after a massage of a few minutes, we identified the lymph(s) which was colored blue (fig.2)



Fig. 2: Detection technique of the sentinel exvivo node

At the end of the intervention, the sentinel nodes were removed from the operating room and fixed in formalin and then sent separately with the colectomy specimen for anatomopathological study. All interventions ended with an immediate restoration of digestive continuity.

Sentinel nodes positive in standard staining techniques were classified as pN + and did not benefit from specific techniques; while the rest of the lymph nodes without infiltration benefited from serial sections and an immuno histochemistry complementary staining with the antibody anticytokeratine mnf 116 in order to reveal micro metastases (diameter between > 0.2mm and <2mm) or tumor cells isolated.

Evaluation criteria:

The main evaluation criterion: is the discovery of micrometastases in the sentinel node by the 02 anatomopathological techniques (classic analysis and ultrastaging) performed in the same patient.

Secondary evaluation criteria:

- The location of the sentinel lymph nodes intraoperatively.
- Survival without recurrence and the occurrence of recurrence within 24 months

III. Result

82% of patients (CI = [72.24-91.56]) had a number of lymph nodes removed greater than 12 lymph nodes, among them 65.55% had no lymph node involvement (pN0) during the analysis standard pathology, while 34.45% had pTN1 lymph node involvement. The overall sentinel node detection rate was 98.36% (CI = [95.26-100]). The invivo detection technique was the most used, with a rate of 97.72%; only one patient had benefited from the ex vivo technique.

162 sentinel nodes were removed with an average of 2.65 nodes per patient; among them 8 had micrometastases after immuno histochemical examination representing a detection rate of 4.87% (CI = [1.55-8.19]), which made it possible to reclassify 7 patients initially classified as pN0 (11.48% with an IC = [3.58-19.38]) in PN0i + and therefore the number of patients with lymph node involvement increases to 28 patients (45.90%).

The sensitivity of the micrometastasis test to IHC was 47.62%, the specificity of 100% and the negative predictive value of 75%.

A subgroup of 7 patients initially classified as pTN0 could be identified and reclassified as pTN0i + (ultra-staging) and have benefited from adjuvant chemotherapy for at least 6 months. Recurrence-free survival at 36 months was 100% for the subgroup of patients classified Ptn0i + while it was 79% for patients classified Ptn0i- with a non-significant difference (p = 0.5) and 45.82 % for patints classified pTN +, with a significant difference (p = 0.01), and the mortality rate was zero for the 2 groups of patients classified Ptn0i + and Ptn0i- whereas it was 14.28% for patients classified pTN +.

IV. Discussion

Lymph node involvement in colon cancer, which is an essential element for the indication of a possible adjuvant therapy, requires the study of at least 12 regional lymph nodes (7), in this study we pushed the search for this impairment lymph node at the level of the sentinel node by specific anatomopathological methods (IHC) in order to detect micrometastases not identified by conventional methods (HES).

The sentinel lymph node detection techniques are numerous, we preferred the methylene blue test for its ease of realization compared to the isotopic technique requiring radioactive products and the injection must be done in premises dedicated to this (8).

The sentinel node detection rate in our series was 98.36%. It varies according to the different series published. A literature review published in 2008 by Cahill R.A (9) including 52 studies carried out between 2000 and 2008 with 3390 patients found a detection rate of 100% for the right and transverse colonists and 90% for the left colonist.

The in vivo technique (97.72%) allowed us to identify in all cases at least one sentinel node (164 sentinel nodes), in one case we used the ex vivo method (1.64%), we think that obesity can be a factor hindering the in vivo detection of the sentinel node due to the thickness of the meso colon and this is supported by a study carried out in 2005 (10) which found a significant difference ($p < 0,02$) in favor of patients with a BMI less than or equal to 25.

The discovery of micrometastases after specific anatomopathological study can be influenced by the number of histological sections examined by lymph node and the technique used, it varies between 12.5 to 53% depending on the different series published (in our series: 17.5%). There are several techniques, immunohistochemistry considered to be rapid, inexpensive and used routinely (11), and more sensitive molecular biology techniques (PCR, RT-PCR) supported by the meta-analysis published in 2006 by Douglas DO (12), but require specific and fairly expensive equipment (13).

The prognostic value of micrometastases has been the subject of research for the past ten years, but the results obtained are not unanimous. Several authors consider that the discovery of micrometastases had no statistically significant impact on survival and that they were essentially circulating tumor cells found in the sinus of the lymph node without impact (14) and which were doomed to destruction by the immune system. On the other hand, for other authors, notably Rosenberg et al in 2002 (15), Van Schalik et al (16) found more satisfactory results, these data were supported by a prospective study carried out by Saha et al whose results were published in 2009 (17) including 195 patients, who had found a significant difference ($p = 0.007$) in terms of survival without recurrence at 5 years.

The encouraging results obtained in our study and the various published series do not allow a significant determination of the prognostic impact of micrometastases; due to the small number and retrospective nature of the work as well as the heterogeneity in the samples and in the detection methods.

However, it is likely that the presence of micrometastases will determine a subgroup of patients who will benefit from adjuvant therapy and possibly improve the recurrence-free survival of this group

V. Conclusion

The detection of micrometastases by targeting the sentinel nodes by serial sections with immunohistochemical study allowed ultra staging in a subgroup of patients (pTN0i +) who were initially classified pTN0, and therefore to optimize the indication of adjuvant treatments.

The prognostic significance of these lymph node micrometastases is not statistically well established, but the results obtained despite a reduced number of patients and the monitoring period of 3 years are encouraging and have found a better survival rate for the subgroup of patients classified pTN0i + who have received adjuvant therapy

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