

# Sentinel lymph node in colorectal cancer

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## ABSTRACT

Colorectal cancer represents one of the most encountered malignancies worldwide, with a high capacity of lymphatic spread. Therefore, the lymph node status plays a crucial role in order to tailor the adjuvant treatment and to decrease the recurrence rates. In consequence, performing the sentinel lymph node detection in colorectal cancer patients should orientate the surgeon's attention on the lymphatic basins of drainage and, furthermore to orientate the lymph node dissection. However, the method has certain particularities in colorectal patients depending on the location of tumor, on the size and on the type of associated neoadjuvant therapy. This is a literature review of the most relevant studies conducted on this theme.

**Keywords:** colorectal cancer, sentinel node biopsy, lymphadenectomy, recurrence, neoadjuvant radiotherapy

## INTRODUCTION

Colorectal malignancies represent the second most common carcinomas in developed countries and an important cause of cancer related death worldwide (1). In order to increase the curability rates in such cases, resection with curative intent (involving both the tumor and the surrounding lymphatic stations) remains the gold standard (2). Furthermore, histopathological examination of the specimen as well as of the retrieved nodes is essential in order to identify the cases that could further benefit from adjuvant chemotherapy (1).

It has been widely demonstrated that the lymph node status plays a crucial role for the long-term prognostic in colorectal cancer patients even if the disease is diagnosed in an early stage. Therefore, attention was focused on an adequate determination of the status of the lymphatic stations. Patients diagnosed in stage I of disease are expected to have an overall survival of up to 90%, while those diagnosed in stage II of disease have an estimated 5 year survival rate of 75%; although it is considered that these two groups of patients are node negative

cases, it has been estimated that up to 25% of cases diagnosed in stages I-II of the disease will develop local or distant metastases within five years from the initial diagnostic and will eventually die of disease (3,4). The development of distant metastases can be related to both hematogenous and lymphatic spread of the tumoral cells; it has been stated that the existence of undetected lymph node metastases represents one of the most important prognostic factors for further development of recurrent disease (5). In order to provide a better control of the lymphatic spread as well as an adequate staging of the disease, it has been established that at least 12 lymph nodes should be retrieved in any patient with colon cancer irrespective of the stage of the tumor (6). Moreover, other histopathological studies sustain that in order to affirm the true negativity of the lymphatic basins draining from a colic tumor, at least 40 nodes should be retrieved and examined (7). The number of the harvested nodes seems to be strongly correlated with the overall recurrence and survival rates in such cases (8-14).

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In order to establish which are the lymphatic basins that should be carefully analysed in colorectal cancer patients, the implementation of the sentinel lymph node biopsy technique has been implemented with encouraging results. The technique seems to be able to recognize the lymphatic areas which are at risk of harbouring metastatic cells and, in consequence, to focus the lymph node dissection on these areas. Performing this technique seems to predict the nodal status in more than 90% of cases and to upstage the disease in up to one third of the colorectal patients, leading in this way to an adequate selection of cases which should benefit most from the administration of adjuvant chemotherapy (15-17).

### **Ex vivo sentinel node mapping in colorectal cancer**

Sentinel lymph node identification in colorectal cancer can be performed similarly to other solid malignant tumors, using the *in vivo* technique by injecting radiopharmaceutical substances or different types of dyes (9).

However, the method of sentinel lymph node detection might be sometimes difficult to be applied in rectal cancer patients; the presence of a bulky mesenteric tissue as well as the infraperitoneal location of the viscera represent the most important factors affecting the process of *in vivo* sentinel lymph node detection. Due to these reasons the technique of *ex vivo* detection of the sentinel node has been implemented with satisfactory results (17). However, whenever this technique is performed, it should not be omitted the fact that the results might be influenced by the time between retrieving the specimen, injection of the tracer and histopathological analysis of the specimen. In this respect, a standard protocol should be respected whenever the method is applied. If not, the risk that the dye will wash out from the sentinel nodes and will be concentrated in the second stations of lymphatic drainage will increase, leading to the wrong diagnose of the true sentinel nodes (18).

### **The influence of the preoperative treatment of the rate of detection of the sentinel lymph node in rectal cancer**

Another interesting aspect which should be taken in consideration in rectal cancer patients who are submitted to the technique of sentinel lymph node biopsy is the possible interference with the type of neoadjuvant treatment which had been administrated. It is widely known the fact that an important

number of patients diagnosed with low rectal carcinomas will benefit from neoadjuvant radiation therapy in order to decrease the risk of local recurrence, which might induce the distorsion of the lymphatic channels; therefore, the detection rate of the sentinel lymph node might be affected (19).

In the study conducted by van der Zaag *and co.*, 23 patients diagnosed with rectal cancer were submitted to five fractions of five Gray before surgery, the last administration being performed at five to 10 days before surgery (17). Their results were compared to those reported in a similar study group of nine patients in whom neoadjuvant radiation therapy had not been performed. Finally, the sentinel lymph node was successfully identified in 25 of the 32 cases of rectal cancer patients. The authors underlined the fact that the rate of false negative results was significantly associated with the preoperative administration of the short course radiation therapy. However, overall the per cent of the patients with rectal cancer who were upstaged after performing the sentinel node biopsy was not significantly different when compared to colon cancer patients (17). The lower rate of correct identification of the sentinel lymph nodes in pre-irradiated patients was explained by the fact that the radiotherapy might induce fibrosis and might alter the lymphatic flow; moreover, these alterations might be also responsible for the apparition of false positive staining of the non-sentinel lymph nodes. Therefore, the authors concluded that a special protocol should be created for this subtype of cases.

### **The accuracy of sentinel lymph node detection in colorectal cancer patients**

The study of reference conducted on the theme of sentinel lymph node detection in colorectal cancer patients was conducted by van der Zaag *et al.* and published in 2009 in the European Journal of Surgical Oncology in 2009 (17). The study included 132 patients with colorectal cancer submitted to surgery via laparoscopic or open approach between November 2006 and May 2008. In this study, the *ex vivo* technique was used, 0.5-2 ml of patent blue being injected around the tumor immediately after standard resection. The first one to four coloured lymph nodes were considered as sentinel nodes and were sent for histopathological analysis. The method had an accuracy of 91%, being significantly influenced by the location of the tumor (rectal versus colonic tumor), as well as by the presence of lymphatic invasion. In the meantime, the false negative rates were significantly associated with the increas-

ing number of positive nodes as well as with the tumoral stage (defined by the depth of the tumoral infiltration) (17). The significant differences in terms of sentinel lymph node detection between colon and rectal cancer was explained by the authors by the fact that the mesorectum is hardly to be inspected when compared to the mesocolon, due to the shape and due to the presence of the perirectal fascia which should be kept intact during surgery (17). Contrarily to this study, one of the largest meta-analysis conducted on the issue of sentinel lymph node biopsy in colorectal cancer demonstrated that the stage of the tumor does not significantly affect the rate of detection of the sentinel node (2). Therefore, the theory that a larger and a more infiltrating tumor will conduct to the blockage of the efferent lymphatic vessels leading to a distortion of the channels and a lower rate of detection of the sentinel node does not seem reasonable anymore.

However, the authors of this meta-analysis also stated that the method should be reserved for stage I and II patients, as long as cases presenting more advanced disease will be certainly submitted to adjuvant chemotherapy, and therefore, association of sentinel node detection could not bring any benefit for them in terms of tailoring the adjuvant therapy (2).

In order to diminish the influence of the tumoral size on the rate of sentinel lymph node detection, other authors proposed to tailor the quantity of the injected tracer in accordance with the dimension of the tumor. For example, Viehl *et al.* proposed to inject 0.5 ml of blue/dye per 1 cm of tumor and demonstrated that this amount is associated with a significantly higher rate of sentinel lymph node detection ( $p=0.04$ ) when compared to cases in which a standard amount of dye was injected (20).

One of the largest meta-analyses conducted on the subject of sentinel lymph node biopsy in colorectal cancer patients originates from Amsterdam and was published by van der Pas in 2011 (2). The meta-analysis included 52 studies and 3767 sentinel node procedures for colon cancer and 806 procedures for rectal cancer respectively. The study came to demonstrate the safety of the method, especially if it is an *ex vivo* one (out of the patient) and therefore, not harming the patient. According to these authors, the method should be routinely associated to the conventional resection and to become in this way a part of the standard of care for early stage colorectal cancer; in their opinion, associating this method will provide an upstage of the disease in up to 15% of cases, increasing in this way the chances to correctly identify the patients

who could benefit most from adjuvant chemotherapy. However, the authors underlined the fact that, for the moment, the method is not still well standardised, the different techniques which have been used so far being responsible for the high rates of variations of the overall sensitivity rates between different studies.

Another important issue which was discussed in this meta-analysis was the one related to the learning curve; while other authors consider that the learning curve for this method can be safely resumed at five cases, the current paper underlined the fact that only after performing at least 20 such procedures it can be considered that the learning curve has been realised (2). Therefore, is estimated that the accuracy and sensitivity of the method reach 98% and respectively 96% when performed by a skilled team (8).

### **Indocyanine green (ICG) staining for sentinel lymph node detection in colorectal cancer patients**

Another dye which has been proposed in order to identify the sentinel nodes from various malignancies is represented by indocyanine green, a substance with fluorescent properties in the near infrared spectrum which has been recently approved by FDA (21). Its benefits in terms of sentinel node detection have been clearly demonstrated in breast, endometrial and skin cancer (22-24).

When it comes to the colorectal tumors, the method seems to be safe and effective if performed both in *in vivo* and in *ex vivo* manner, especially for tumors diagnosed in early stages of the disease. Moreover, the method seems to be also effective in obese patients, providing an efficient detection of the sentinel nodes (5,25).

A large study which came to demonstrate the efficacy of the method in colorectal cancer patients comes from A. C. Curie *et al.* and was published in 2017 in the European Journal of Surgical Oncology (26). The paper included 30 patients with T1 and T2 colonic cancer who were submitted to peritumoral submucosal injection of ICG through an endoscopic approach, followed by laparoscopic resection; in terms of surgical technique, in all cases a medial to lateral, vessel first technique was performed. The authors reported a median number of three mesocolic sentinel nodes which were identified after a median time from injection of 7 minutes; among these cases the authors identified three cases with positive sentinel nodes (26).

## CONCLUSIONS

Sentinel lymph node detection in colorectal cancer patients seems to be a feasible and accurate method in order to provide a better staging of the disease and to orientate the adjuvant treatment more efficiently. As demonstrated, performing sentinel lymph node techniques in colorectal cancer

has also some particularities when compared to other malignancies. The accuracy of the method is influenced by the location of the tumor, by the moment of identification (ex vivo versus in vivo) as well as by the association of neoadjuvant therapy such as preoperative therapy.

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