



What is the Meaning of the Circumferential Resection Margin Involvement by Lymph Nodes Detected by Magnetic Resonance?

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Editorial

Sometimes, at the colorectal cancer multidisciplinary meeting, patients with rectal cancer with the Circumferential Resection Margin (CRM) involved by a suspicious metastatic lymph node by magnetic resonance are presented.

The question is: Does this picture have any value in the treatment decision?

On the basis of the results of Dutch trial [1] and German CAO/ARO/AIO-94 trial [2], preoperative radiotherapy (short course radiotherapy or long course radiotherapy plus concomitant chemotherapy) has become a standard treatment for patients with stage II-III rectal cancer located between 0 cm to 15 cm from anal verge. Favourable results from both trials were based on a reduction in local recurrence rates without benefits in overall survival. Similar findings were found in the MRC CR07 and NCIC-CTG C016 trial [3].

Since then, two major issues are present. On the one hand, optimal total mesorectal excision is performed by most surgeons focused in rectal cancer, getting a low local recurrence rate. On the other hand, magnetic resonance can identify factors involved in local recurrence.

Quality of the mesorectum excision, pathological stage, depth of mesorectum invasion, distance of the tumour from de anal verge, extramural venous invasion, need of abdominoperineal resection and above all, CRM involvement [4], are recognized factors involved in local recurrence development. This last factor can be prior to treatment decision surely predicted by magnetic resonance [5]. Moreover, data from MERCURY study show that magnetic resonance-involved CRM was the only preoperative staging parameter that remained significant for local recurrence on multivariate analysis [6].

Since benefit of preoperative radiotherapy is related to local recurrence rather than to overall survival and that we can predict the main factor related to local recurrence, it seems logical to develop more restrictive strategies for the use of preoperative radiotherapy in patients with II-III stage rectal cancer, avoiding unnecessary toxicity, sequels and costs.

A variety of strategies have been proposed for these patients. Dutch and German CAO/ARO/AIO-94 trials included patients with TNM stage I-III adenocarcinoma (German trial excluded TNM stage I tumors) with the inferior margin within 15 cm and 16 cm from the anal verge respectively [1,2]. ESMO Consensus Guidelines propose upfront surgery for upper/middle rectum tumors staged as cT3a/bN0 and free CRM [7]. OCUM trial included patients with stage cT2-4 rectal cancer, any cN and cM0 status. Carcinomas in the middle and lower third that were 1 mm away or less from the mesorectal fascia, all cT4 tumors, and all cT3 tumors of the lower third were treated with neoadjuvant chemoradiotherapy followed by total mesorectal excision. All other patients with rectal cancer underwent total mesorectal excision alone. After a median follow-up of 60 months, the 3- and 5-year local recurrence rates were 1.3 and 2.7 per cent respectively, with no differences between two strategies [8] whatsoever. In the MERCURY study, patients staged as T3 stage tumors with <5 mm extramural spread, regardless of nodal status and free CRM by magnetic resonance had a local recurrence rate of 1.7% after total mesorectal excision without neoadjuvant treatment [9]. In all

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proposal strategies, CRM involvement is an indication for neoadjuvant radiotherapy being the role of the lymph node involvement variable. In the OCUM trial and in the MERCURY study, preoperative lymph node status was not a factor for preoperative radiotherapy.

After recognizing CRM involvement as a pivotal risk factor in rectal cancer, Birbeck described six specific modes of CRM involvement with different prognostic value: direct tumor spread, discontinuous tumor spread, tumor within a lymph node, tumor within blood vessels, and tumor within lymphatic vessels or perineural tumor spread. Local recurrence rate after CRM involvement by tumor within a lymph node could be similar to that found in patients without CRM involvement [10]. These data regarding the prognostic value of CRM involvement by a metastatic lymph node were posteriorly confirmed. Nagtegaal et al. analyzed this topic from Dutch trial data. They found a local recurrence rate of 22.1% if CRM was involved by the primary tumour compared with 12.4% in patients with a positive CRM due to a lymph node ($p=0.06$). This rate was not different from the local recurrence rates of patients with negative margins [11]. Patel and col. found that positive margin due to tumour was associated with a higher 5-year cumulative incidence of local recurrence than due to metastatic lymph node (43.7% vs. 8.8%, $p=0.001$); local recurrence in patients with positive CRM due to lymph node was comparable to that of patients with negative margins (8.8% vs. 8.3%, $p=0.694$). For these authors, CRM due to lymph node is related to systemic recurrence [12]. In the same way, a study of our group shows that after a mean follow-up of 32.9 months, patients with CRM involvement by direct tumour spread suffered a local recurrence rate of 31.5%, in front of 5.2% in patients with CRM involvement by a metastatic lymph node. Local recurrence-free survival was significantly higher these patients (mean 145 vs. 61 months; HR: 0.421; 95% CI: 0.016 to 0.963, $p=0.049$) [13].

Unfortunately, unlike CRM involvement secondary to direct tumour spread, sensibility of magnetic resonance to detect CRM involvement due to metastatic lymph node is smaller. This specific issue has been addressed from the MERCURY study. In a study over 396 patients, 50 had a positive CRM on histopathological analysis. Of among these, in five cases were due to a metastatic lymph node. Four out of the five malignant nodes were not predicted on MRI. This highlights the limitation of MRI to detect micrometastases. Moreover, thirty-one of the 396 MRI studies had suspicious nodes 1 mm or less from the CRM. None of these patients had a positive CRM owing to nodal involvement. Authors suggest that the tumour within a lymph node may be encased by an intact lymph node capsule in many cases [14].

Therefore, in front of the finding of a CRM involved by a suspicious metastatic lymph node, several question we must have in mind:

- Accurate staging for appropriate stratification of rectal cancer is pivotal to guide preoperative treatment strategy and we are unable to detect CRM involvement due to metastatic lymph node by magnetic resonance.

- Impact of CRM involvement due to metastatic lymph node in local recurrence is low. In fact, as mentioned above, local recurrence risk after CRM involvement by lymph node is similar to that founded in patients without CRM involvement.

- In the setting of a selective approach for preoperative treatment, tailored by risk of local recurrence: Is there is another

factor that indicates the need for neoadjuvant radiotherapy? If patient presents any local recurrence risk factor, neoadjuvant treatment will be mandatory.

In our opinion, if there is no other factor for local recurrence, present data suggest that preoperative radiotherapy might not be necessary on the basis solely of a suspicious MRI-detected metastatic lymph node close to the circumferential resection margin.

The majority of known data regarding this specific issue comes from pathological studies by comparing local recurrence rates depending on the type of CRM involvement [10-13]. Investigation on magnetic resonance images at the moment of diagnosis must be carried on to clarify this topic.

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