Number of lymph nodes after neoadjuvant therapy for rectal cancer: How many are needed?

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Abstract
Neoadjuvant chemoradiation is the standard treatment for advanced rectal tumor, providing better local control of disease and potentially increasing sphincter preservation surgery [1-3]. Neoadjuvant radiation may affect the number of lymph nodes (LNs) harvested after resection and may thus influence correct staging of the tumor [4,5]. Over the past 10 years, standards for lymph node harvests in colorectal cancer have been proposed. Several studies have recommended examination of at least 12 lymph nodes (LNs) in the specimen and this number is now used as a reflection of surgical quality. Nevertheless, recent reports have identified significantly decreased LN harvests in patients treated with neoadjuvant radiation [11,12]. The real question is whether the number of nodes retrieved in the rectal specimen after chemoradiation actually plays a role in the correct staging of the patients?

Key words: Rectal cancer; Neoadjuvant therapy; Lymphnodes
mens. In the literature, the mean numbers of detected nodes varied between 4 and 14 per specimen\cite{13,14}. Our experience clearly supports the assumption that preoperative long-term CRT reduces the cumulative number of LNs within the rectal specimen. The removal of the entire mesorectal tissue within its intact envelope fascia not only ensures minimal local recurrence rates and functional preservation of pelvic structures but also guarantees a satisfactory regional lymphadenectomy\cite{15}.

Moreover, optimized and extensive macro- and histopathological diagnostic procedures allow the detection of more number of LNs from rectal cancer specimens. Some authors have reported a significant reduction of lymph node count in rectal cancer specimens after long-term radiation (doses ranging from 45 to 50.4 Gy) with different concomitant chemotherapy regimes\cite{16} as well as after short-term radiotherapy\cite{17,18}. Only one investigation failed to find significant differences in mesorectal lymph node retrieval in patients after neoadjuvant treatment compared to patients who underwent primary surgical treatment. However, in this study, only 17% of the study population had neoadjuvant therapy comprising both long-term 5-FU-based CRT as well as short-term radiation\cite{19}. Perez evaluated the number and distribution of mesorectal LNs in rectal specimens from 18 cadavers without evidence of colorectal disease. The author found a mean number of 5.7 nodes per specimen and concluded that the absence of pathological alterations within the rectum might result in a lower lymph node count compared to other investigations\cite{20}. Various authors have failed to find any correlation between mesorectal lymph node numbers and either patient-related factors like gender and age or tumor-related pathological characteristics such as individual stage or therapy-induced tumor regression. The same investigators also found that neoadjuvant CRT appears to have an important effect on mesorectal lymph node size. From anatomical studies, it is clear that the majority of nodes range between 0.1 and 0.2 cm in size. We believe this to be a consequence of applied CRT, in accordance with others who also described a significant reduction of nodal size\cite{21,22}. Changes in morphology of nodes after neoadjuvant therapy have also been described with decreased numbers of CD4+ lymphocytes and other modifications in paracortical areas of the irradiated nodes. As a result, the nodes have a reduced immune and tumor suppressive function as well as reduced mechanical filter function for tumor cells\cite{23,24,25}.

It appears to us that radiation-related reduction of lymph node size might be the main reason for the apparent reduction of lymph node numbers in irradiated specimens worked up with conventional retrieval, given the difficulty in detecting LNs smaller than 0.2 cm. Murphy et al\cite{26} identified lymph node size as an independent prognostic indicator for survival in node-negative rectal cancers after primary surgery, assuming that the small nodes (< 2 mm) less likely to be infiltrated and suggesting a consideration of lymph node size within the staging systems for rectal cancer. Using immuno-histochemistry to determine occult lymph node micrometastases in stage II rectal cancers after neoadjuvant CRT, it is possible to detect a comparatively high incidence of micrometastases compared to conventional evaluation with hematoxylin-eosin\cite{27}. Although their prognostic role has not been clarified, we consider these to be important findings, which need to be investigated further in order to reveal individual tumor biology and distant metastatic potential. We believe that an appreciable number of mesorectal micrometastases in LNs below 0.5 cm are not being detected by manual lymph node recovery and standard pathological diagnostics.

Statistical analyses of the minimum number of LNs needed to stage patients with locally advanced rectal cancer have indicated that the probability of detecting a single lymph node metastasis increases with the number of retrieved nodes and reaches 46% when 18 nodes have been recovered\cite{28}. This resulted in the recommendation that smaller nodes, ranging from 0.1 or 0.2 cm in diameter, should be located. Nevertheless, other investigations revealed that more than 60% of institutions in the USA fail to regularly achieve the controversial benchmark of 12 LNs per specimen\cite{29}. The role of pathologists is very important, as extensive pathological diagnostics with microscopic evaluation of the entire lymph node leads to higher lymph node recovery after preoperative CRT than conventional pathological work-up. This has distinct clinical implications because several investigations have shown the prognostic relevance of enhanced lymph node retrieval in stage II colorectal and rectal cancer patients. Kim et al\cite{30} evaluating 900 node-negative rectal cancer patients, suggested that a minimum number of 23 evaluated nodes was required to stratify patients for low and high risk of cancer-specific survival. As nodal status, particularly after preoperative CRT, is a major criterion in determining the need of adjuvant treatment, this should be based on a sound diagnostic basis\cite{31}. We are very well aware that meticulous lymph node evaluation is scarcely feasible in pathological routine diagnostics in rectal cancer specimens. However, it shows that adequate nodal staging is feasible after applied CRT where there are more than the minimum number of 12 nodes per specimen. In summary, we would underline the key role of the surgeon and, particularly, of the pathologist. These conclusions are further supported by another large prospective investigation on more than 7000 colorectal specimens\cite{32}.

In conclusion, the diligence and accuracy of the pathologist and the correct high-quality total mesorectal excision by surgeon is essential to detect the majority of LNs and to achieve a valid nodal staging after preoperative RCT. Conversely, other authors have reported that the absence of nodes (ypNx) or a decreased number of nodes retrieved in ypN- patients do not represent an inferior oncological outcome. The number of nodes does not seem to impact survival and recurrence in ypN- patients\cite{33}.

At this time we agree that LNs are important for prognosis and probably represent biological factors rather than simply correct staging. However, risk assessment
is an area of ongoing research, as reflected in recent reports concerning genetic profiles and colorectal cancer. In multivariate analyses, lymph node number is an independent predictor of outcome but other measures such as lymph node ratio may eventually prove to be more helpful. Lymph node status is just one part of the risk assessment and physicians are urged to review risk in terms of all pathologic features when making a decision about the use of adjuvant therapy. If fewer than 12 nodes are found in an individual and there is no opportunity to find more (or there really are none to be found), then adjuvant therapy is currently recommended in situations considered to be high risk. Regardless of its validity, failure to achieve the 12 lymph node benchmark is currently being used by oncologists to make chemotherapy decisions. Until such time as it disappears from practice it is important to be aware of its pragmatic importance.

We agree on the urgent need to develop novel prognostic markers also for rectal cancer. The current staging of colorectal cancer is predominantly based on the TNM staging classification. However, colorectal cancer should be regarded as a heterogeneous and multi-pathway disease. This observation is substantiated by the fact that tumors with similar histopathological characteristics may have different clinical outcomes and responsiveness to therapy. This explains why numerous research studies are now being directed towards developing powerful prognostic factors for colorectal cancer. In addition, we concur with the suggestion that individualized therapies tailored to a patient’s genetic composition and test results may be of great value for treating colorectal cancer. Various possible chemosensitivity tests have been studied, but they have not yet been adopted on a worldwide clinical basis. Therefore, developing novel prognostic markers for patient-tailored treatment is essential in the current clinical setting. New research should facilitate evaluation of the stage-specific incidence of different markers and their prognostic role. Such studies need to be controlled for multiple variables and to be comprehensive and validated.

In conclusion, we think that chemoradiation has an important effect on the number of nodes harvested in rectal specimens and that this needs to be taken into consideration. In the future the total number of nodes may become less important than specific biologic markers which detect high-risk patients and improve their prognosis with adjuvant therapy tailored.

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Scabini S et al. Lymphadenectomy after neo-adjuvant therapy for rectal cancer

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