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Combinations of Tumor and Treatment Parameters Are More Discriminative for Prognosis Than the Present TNM System in Rectal Cancer

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The treatment of rectal cancer has changed radically during the last decade. The introduction of the surgical technique total mesorectal excision (TME) worldwide has resulted in a decline of local recurrence rate because more tumors were excised completely, along with the excision of regional metastatic disease in the mesorectal fat. In addition, the role of neoadjuvant treatment either by radiotherapy or by radiochemotherapy has been established during the last 10 years. In Europe, overwhelming evidence has been gathered from large randomized trials (Total Mesorectal Excision trial [TME], Swedish Rectal Cancer Trial, and Cancer Research UK [CR07]),¹⁻³ with a total number of 4,427 patients, showing that for primarily resectable rectal cancer, short-term preoperative radiotherapy (5 Gy daily for 5 days) resulted in local recurrence rates lower than 5%, especially in combination with TME surgery. For locally advanced tumors, long-term radiotherapy (approximately 50 Gy) in combination with neoadjuvant chemotherapy is the treatment of choice.^{4,5}

The combination of the above-mentioned changes in therapy results in improved prognosis of patients with rectal cancer, especially with respect to local recurrence, but these advances have not yet been included in staging of rectal carcinoma. In fact, these innovations in therapy call for a change in the approach of staging. Because of the application of neoadjuvant therapy, both the function of staging systems and the factors used for staging have changed, which complicates the current practice.

Initially, postoperative pathologic staging was used for the prediction of prognosis as well as for the indication of adjuvant therapy. At present, clinical staging determines whether and which preoperative therapy should be applied, and postoperative staging is used to evaluate the effects of therapy in addition to the above-mentioned goals. The consequence of these changes is a divergence between clinical TNM and pathologic (p) TNM. Moreover, the current pTNM is essentially different from the pTNM of the last century. Still, the staging system for rectal cancer uses the same rules as Cuthbert Dukes proposed in 1932.⁶

IMPACT OF NEOADJUVANT THERAPY

Long-term radiotherapy and chemoradiotherapy schemes are aimed at tumor downstaging to facilitate complete surgical removal. Pronounced changes in tumor histology are observed in the operation specimen, and are indicative of tumor response or regression. In many of these cases, the pT stage is lowered compared with the initial cT stage, but it is not clear which of these two is the best predictor for prognosis. The current guidelines of the American Joint Committee on Cancer TNM staging systems^{7,8} acknowledge preoperative treatment by adding the prefix *y*, but the clinical consequences are not clear.

The ypT stage can be used as a measurement for tumor downstaging, however, after locally advanced tumors are removed, tumor remnants might be left behind in the surrounding tissue, resulting in inadequate determination of T stage. Moreover, there is a large variability between the pT3 tumors with regard to tumor load. Alternatively, response can be indicated by determining the grade of tumor regression. Various systems have been suggested to grade tumor regression,⁹⁻¹¹ but the majority are not able to demonstrate a relation with prognosis. In addition, reproducibility of regression grading is poor.^{11,12}

Given that the goal of long-term neoadjuvant therapy is the facilitation of surgical removal, we suggest inclusion of surgery-related factors in the staging after this kind of treatment.

SURGICAL FACTORS IN THE 21st CENTURY

The recognition of TME as a superior surgical technique is preceded by the recognition of circumferential margin (CRM) involvement as the best prognostic factor, not only for local recurrence, but also for development of metastases and for survival. A recent review with data of more than 17,500 patients (unpublished data: Nagtegaal ID and Quirke P, "What role for the circumferential margin in the modern treatment of rectal cancer," 2007) demonstrated that the prognostic

value of an involved CRM for local recurrence is even stronger after neoadjuvant therapy (hazard ratio, 6.3; 95% CI, 3.6 to 16.7 versus hazard ratio, 2.2; 95% CI, 1.5 to 3.2 without neoadjuvant therapy).

A positive CRM after surgery can be caused by various factors, the most important of which are suboptimal quality of surgery, aggressive tumor growth, therapy resistance, and inadequate preoperative imaging. The quality of surgery is analyzed by the assessment of plane of resection. This is correlated with both local recurrence and overall survival, and its value has been confirmed recently in another large multicenter trial.¹³ The finding that CRM involvement can predict the development of distant metastases as well as survival may suggest that aggressive tumor growth is most important.¹⁴ However, the fact that a positive CRM due to poor-quality surgery also is correlated with survival¹⁴ indicates that for prognosis, the cause of margin involvement does not seem to matter.¹⁴

STAGING SYSTEMS: WHERE SHOULD WE GO?

In the era of neoadjuvant therapy, the existing staging systems are suboptimal. There is a need for the implementation of treatment-related factors, which will improve both staging and prediction of prognosis.¹⁵ The result of treatment is one of the most relevant features for predicting final outcome; therefore, modern staging systems should take both tumor and treatment factors into account. The incorporation of these factors, of course, should be based on evidence. Before we can propose a new staging system, we have to address the following questions: Which factors can predict prognosis reliably? Are these factors generally applicable? Can these factors be assessed in a reliable and simple way? Is there a combination of factors that divides patients adequately in large, homogeneous groups with highly divergent survival curves?

Which Factors Can Predict Prognosis Reliably?

First, we have to question the value and reliability of established tumor factors such as invasion depth and lymph node status in the current situation. As mentioned, the reliability and relevance of ypT is questionable. The presence of lymph node metastases after neoadjuvant therapy is still a major prognostic factor.¹⁶⁻¹⁸ However, an unknown number of node-negative patients will have had positive nodes that are sterilized by neoadjuvant therapy. Therefore, ypN0 consists of a heterogeneous group of patients who were initially node negative and patients whose metastatic tumors responded well to treatment. Although the meaning of ypN0 might be different from that of pN0, the prognostic impact is still applicable. However, a multivariate analysis of 182 patients¹⁸ suggests that after neoadjuvant therapy, CRM is more important for prognosis than lymph node involvement. Given that neoadjuvant therapy is mainly aimed on local control, at present, we can leave the presence of metastatic disease (TNM IV) out of this discussion.

Treatment-related factors are CRM, tumor regression, and quality of surgery. The results of tumor regression grading are variable and no consistent relation with prognosis has been demonstrated. Moreover, four different studies including a total of 490 patients demonstrated the superiority of CRM assessment above regression grading.^{12,19-21} Quality of surgery evaluation in two independent randomized trials demonstrates prognostic value for both local recur-

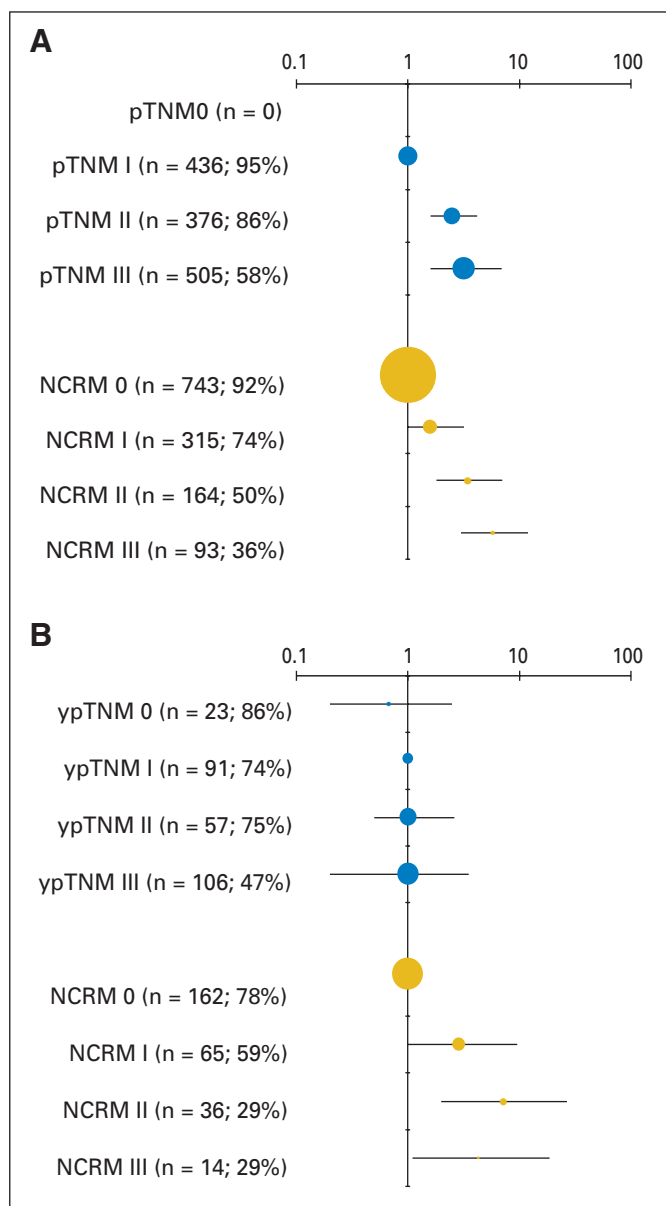


Fig 1. Hazard ratio and 95% confidence interval of TNM staging versus a new staging method based on nodal and circumferential margin status (NCRM). (A) TME trial (n = 1530; follow-up 67 months). (B) Polish rectal cancer trial (n = 316; follow-up 48 months). y, preoperative treatment; p, pathologic.

rence and survival.^{13,14} However, CRM involvement is more important than plane of surgery.¹⁴

Finally, there are many biomarkers described, but none of them have reached the standard assessment of rectal cancer specimens and therefore remain beyond the scope of this commentary.

Are These Factors Generally Applicable?

Although preoperative neoadjuvant therapy will be applied in most occurrences of rectal cancer, some patients will undergo surgery right away. The new staging should be applicable in all situations. Tumor invasion, lymph node metastases, CRM involvement, and quality of surgery can be evaluated with and without neoadjuvant therapy and in any laboratory of pathology. One could argue that this is the case for tumor regression as well, and that without therapy there

will be no regression. As a result, although the absence of regression after therapy may indicate poor prognosis, the absence of regression without therapy has no meaning at all.

Can These Factors Be Determined in a Reliable and Simple Way?

The stage of the tumor is relatively simple to determine provided that an adequate sampling of the tumor area is performed. Especially for the determination of ypT0 (complete regression), a standardized protocol is required. Careful examination of the resection specimen will reveal possible involvement of the circumferential margin and presence of lymph node metastasis. Detailed protocols are available.^{22,23}

Determination of tumor regression is much more difficult and reproducibility studies show κ values as low as 0.30.¹² One of the reasons is that there is no consensus about the definitions that should be used, apart from the definition of complete response. It is disappointing that to date, none of the reported studies used this definition.

Is There a Combination of Factors That Adequately Divides Patients in Large, Homogeneous Groups With Highly Divergent Survival Curves?

In a recent study²⁴ based on the data from a randomized clinical trial,¹ we demonstrated in a multivariate model that CRM rather than pT stage is important for the prognosis of rectal cancer. This is true for patients without preoperative treatment as well as for patients treated with short-term preoperative radiotherapy. On the basis of these findings, we designed a staging system including both CRM (treatment-related factor) and nodal status (tumor-related factor; Fig 1). Using this system, we created highly divergent survival curves, with a small group of patients with a poor prognosis ($n = 93$; 7%; 37% 5-year survival) and a large group of patients with a good prognosis ($n = 753$; 57%; 92% 5-year survival). We confirmed our findings in an independent data set derived from another randomized trial²⁵ (Fig 1B). In this group of patients (with short-term and long-term neoadjuvant therapy) the new staging system performed significantly better than TNM.

In conclusion, in modern staging of cancer there should be an important place for treatment-related factors, given that the result of treatment is one of the most important prognostic factors. For rectal cancer we demonstrated that in the era of neoadjuvant therapy, free circumferential resection margins are more important than the classic factor of invasion depth, and that incorporation of this factor in staging systems leads to better prediction of prognosis and selection of patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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