COMMUNICATION

International Union Against Cancer TNM Prognostic Factors Project Committee and the American Joint Committee on Cancer TNM Process Subcommittee

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TNM Residual Tumor Classification Revisited

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BACKGROUND. For cancer patients, prognosis is strongly influenced by the completeness of tumor removal at the time of cancer-directed surgery or disease remission after nonsurgical treatment with curative intent. These parameters define the relative success of definitive treatment and can be codified by an additional subclassification within the TNM system, the residual tumor (R) classification. Despite the importance of residual tumor status in designing clinical management after treatment, misinterpretation and inconsistent application of the R classification frequently occur that diminish or abrogate its clinical utility.

METHODS. An analysis of the relevant literature regarding the use and prognostic importance of the R classification was undertaken.

RESULTS. In the current study, the prognostic importance of the R classification for different kinds of tumors is discussed. Problems that arise in using the R classification are described. Special issues regarding the use of the R classification are addressed.

CONCLUSIONS. The R classification is a strong indicator of prognosis and facilitates the comparison of treatment results if applied in a consistent manner. Uniform use and interpretation of this classification is essential for the standardization of posttreatment data collection. Cancer 2002;94:2511–9.

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(AJCC)\(^3\) recommended the use of a residual tumor, or R, classification as an adjunct to staging. In 1987, the International Union Against Cancer (UICC)\(^4,5\) published an expanded residual tumor (R) classification that considered distant as well as locoregional residual tumors and was applicable to all patients irrespective of primary treatment modality. This R classification also was accepted by the AJCC and was published in the 4th and 5th editions of the AJCC Manual for Staging of Cancer.\(^6,7\) The R classification of the Japanese classification of carcinoma of the stomach, colorectum, pancreas, liver, and lung,\(^8-12\) which until 1993 was used to describe the extent of lymph node dissection, was changed to the D (dissection) classification to avoid confusion\(^8\) with the UICC/AJCC R classification. Despite international recognition of the importance of the R classification for patient management and estimation of outcome after treatment, misinterpretation and inconsistent application of the R classification has been reported to occur frequently. The objective of this review is to promote the obligatory and uniform use of the R classification.

### Definitions of the R Classification

The R classification, an auxiliary classification within the TNM system, denotes the absence or presence of residual tumor after treatment and describes residual tumor as macroscopic or microscopic in amount. The R classification considers residual tumor at the primary tumor site, in the regional lymph nodes, and/or at distant sites. As such, it reflects the efficacy of primary treatment, influences the design and institution of additional therapy, and is a strong indicator of prognosis.

The R classification should be distinguished from the r symbol, an additional descriptor in the TNM system, which identifies recurrent tumors occurring after a disease-free interval.

The R classification may be used after surgical treatment alone, after radiotherapy alone, after chemotherapy alone, or after multimodal therapy. In the most recent editions of the staging manuals of the AJCC\(^7\) and the UICC,\(^13\) the R classification categories were defined as follows:

- **RX:** The presence of residual tumor cannot be assessed.
- **R0:** No residual tumor.
- **R1:** Microscopic residual tumor.
- **R2:** Macroscopic residual tumor.

The R0 ("no residual tumor") category applies only to cases in which residual tumor cannot be detected by conventional diagnostic methods. A more exact definition would read "no detectable residual tumor."\(^14\) This category corresponds to surgical resection for cure.

The R1 category is reserved exclusively for cases in which residual tumor is found by histologic examination. This category may apply to biopsy sampling of the regional tissue at the site of resection or of a distant site at the time of surgery. It also applies to microscopic examination of the resection margins of the surgical resection specimen by the pathologist.

R2 applies to cases with macroscopically visible residual tumor that is detected either clinically or pathologically. After surgical treatment, assessment for the R classification requires close cooperation between the surgeon and pathologist in a two-step process that is illustrated in Figure 1.

After nonsurgical treatment, the presence or absence of residual tumor is determined using methods such as radiologic imaging and biopsy.

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In patients with leukemia and lymphoma, R0 corresponds to complete disease remission. R1 is applied to cases with clinical complete disease remission, but with unexpected identification of a tumor on biopsy. R2 applies to all other situations in which disease has responded incompletely to therapy and should be specified further into partial disease remission, no change, or disease progression.

Reporting
The pathology report on a primary tumor resection specimen as well as on resected distant metastasis must include statements concerning the presence or absence of tumor at the resection margins. The margins examined should be specified according to the specimen topography (e.g., circumferential [lateral/radial], distal, proximal margins in rectal carcinoma cases, or retroperitoneal, pancreatic cut surface, and common bile duct in cases of pancreatic carcinoma), and their individual status should be stated. It is widely accepted that tumor present at a surgical resection margin corresponds to residual tumor in the patient at the corresponding locus within the surgical site. Thus, the macroscopic or microscopic presence of tumor at the resection margin corresponds to R2 or R1 status, respectively. In contrast, R0 status cannot be assumed in cases in which the resection margins are free of tumor on pathologic examination because distant tumor disease may exist in the patient without the pathologist’s knowledge.

As a general rule, assignment of the R classification must be performed by a designated individual who has access to the complete data. This person may be a surgeon, medical oncologist, radiation oncologist, tumor registrar, or pathologist.

In several institutions in Germany, the R classification is assigned by the pathologist. The precondition for this is that the submitted specimens are accompanied by a form (Table 1) that is filled out by the responsible surgeon. Without such data, the pathologist cannot assign the R classification for the reason stated earlier. In cases without available clinical information, the pathologist reports only the status of the resection margins and may state whether the locoregional tumor was removed completely. A classification of “RX” should not be substituted for such partial data.

How to Assess the R Categories?
The R classification is based on clinical as well as pathologic findings. It takes both of the following sources of data into account: 1) clinical assessment of treatment results locally and (if applicable) at the site of distant metastases; and 2) histopathologic examination of a) the margins of the surgical resection spec-

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form Required for a Definitive R Classification by the Pathologist which is to Be Filled In by the Surgeon</td>
</tr>
<tr>
<td>Macroscopic evidence of residual tumor</td>
</tr>
<tr>
<td>If residual tumor present</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Specify</td>
</tr>
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</tr>
</tbody>
</table>

Clinical Significance
In the 1997 revisions of the AJCC and UICC TNM classification, the clinical significance of the R classification is described as reflecting the effects of therapy and influencing future treatment procedures and as being a strong prognostic indicator.

Thus, the R classification not only has prognostic significance but also is important with regard to quality assurance in oncologic treatment and for additional treatment planning when the first treatment course does not achieve complete tumor clearance.

Prognostic Significance
There is no doubt that a satisfactory long-term prognosis can be expected only when R0 status is achieved. Therefore, patients classified as R0, R1, and R2 should be analyzed separately in outcome studies.

Although a clear correlation between disease stage and R classification does appear to exist, the difference in the prognosis of patients with R0 disease versus those with R1 and R2 disease cannot be explained by differences in disease stage alone. This difference
TABLE 2
Correlation between Stage and R Classification

<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>No.</th>
<th>R1, 2 No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>179</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>II</td>
<td>182</td>
<td>7 (3.8)</td>
</tr>
<tr>
<td>III</td>
<td>253</td>
<td>15 (5.9)</td>
</tr>
<tr>
<td>IV</td>
<td>91</td>
<td>76 (83.5)</td>
</tr>
</tbody>
</table>


TABLE 3
Outcome of Patients with Rectal Carcinoma Based on the R Classification

<table>
<thead>
<tr>
<th>R classification</th>
<th>No.</th>
<th>Cancer-related survival (with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>603</td>
<td>69.0 (65.0–73.0)</td>
</tr>
<tr>
<td>R1</td>
<td>22</td>
<td>18.2 (7.5–44.1)</td>
</tr>
<tr>
<td>R2</td>
<td>86</td>
<td>4.7 (1.8–12.2)</td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval.


can be illustrated by stratification according to disease stage and is confirmed by multivariate analyses.16,17

The data regarding rectal carcinoma from the German Multicenter Study on Colorectal Carcinoma18 (Table 2) demonstrate the relation between disease stage and R classification. The influence of the R classification on patient outcome is shown in Table 3. The likelihood of residual tumor after cancer-directed therapy increases progressively with increasing disease stage. In general, R1 is associated with better survival than R2 within any given stage grouping. In R2 patients predominantly residual distant metastasis is present whereas in the majority of R1 patients the residual tumor is located locoregionally.

Methodic Developments in R Classification

Because the indications for adjuvant treatment and prognosis strongly depend on the R classification, new methods have been developed to refine the detection of residual tumor. Some of the approaches employed are discussed below.

Imprint cytology has been introduced by Veronesi et al.19 for the examination of the resection margins in breast carcinoma resection specimens, but the method may be applicable to other tumors as well.

Cytologic examination of ascites or abdominal lavage fluid to detect peritoneal metastases that are not apparent macroscopically has been applied to gastric carcinoma,20–22 pancreatic carcinoma,23 and carcinoma of the uterine corpus.24 However, in the last case, abdominal tumor cells are classified as T3a, which includes tumor cells in ascites or peritoneal washings.13 Malignant cells have been found in 5–20% of patients treated with curative intent who lacked macroscopic peritoneal metastases, mainly in those individuals with local serosal involvement.

Flow cytometry after staining with appropriate immunologic reagents has been used to detect minimal residual disease in bone marrow specimens from patients with carcinoma of the breast or lung or those with leukemia.25

Molecular biology techniques such as gene rearrangement or polymerase chain reaction have been used for the detection of residual tumor cells, especially after chemotherapy in patients with leukemia or malignant lymphoma, but these techniques may be applicable in other situations as well.26

However, at the current time, it is recommended that cases in which residual tumor was evaluated using conventional methods should not be compared with those cases that were evaluated using new specialized methods. To prevent stage migration (the so-called Will Rogers phenomenon27) due to refined diagnostic techniques, the methods used for R classification should be recorded and must be considered in the analysis of treatment results. Adding the symbols “conv” for conventional and “spec” for specialized to the R category have been proposed (e.g., R0 [conv] or R1 [spec]).15

R Classification and Isolated Tumor Cells

The recording of isolated tumor cells (ITC) using a modification of the R classification has been suggested.28 In patients without demonstration of residual tumor at primary or distant tumor sites using conventional methods (R0), ITC may be found in bone marrow, blood, or other distant sites (so-called minimal residual disease). For such cases the classification of “R0(i+): no residual tumor, positive morphologic findings for ITC” has been proposed.

R Classification and Tumor Cells in Serosal Cavity Washings

Recent data29–33 regarding peritoneal washings indicate that the adverse effect on prognosis formerly reported in association with positive peritoneal cytology20,22,23,34 may have been overestimated. Thus, it may be important to distinguish such cases and analyze them separately. For the identification of cases with positive cytology from pleural or peritoneal washings as the sole basis for a R1 classification, the addition of “cy+” has been recommended [e.g., R1(cy+)].
Tumor spillage during surgery is considered a criterion in the T classification of tumors of the ovary and fallopian tubes.\textsuperscript{13} For all other tumors, tumor spillage does not affect the TNM classification, stage grouping, or R classification.

**Special Situations in Using the R Classification**

- It has been argued that the R1 category might be justified for tumors that penetrate the visceral peritoneum (e.g., in tumors of the liver [T4/pT4], stomach [T3/pT3], and colon [T4/pT4]) because the seeding of tumor cells within the peritoneal cavity would be possible in this instance. However, this is classified as R0 (provided the primary tumor and lymph nodes have been resected for cure). It has been shown that the prognosis of these patients clearly is better than that of those with microscopic tumor at the resection margin.\textsuperscript{35,36}
- Cases with macroscopic residual tumor (R2) may be subdivided according to the certainty of diagnosis into R2a (without microscopic confirmation) and R2b (microscopically confirmation) categories.\textsuperscript{37}
- In the R0 group, there may be M0 cases as well as M1 cases. In the latter category, the distant metastasis as well as the primary tumor must be removed completely (Fig. 1).
- In tumor resection specimens from patients with lymphadenectomy, the “marginal” lymph node is the one near the resection margin that is most distant from the primary tumor. The involvement of such “marginal” or “apical” lymph nodes or of a sentinel lymph node does not influence the R classification.
- The presence of noninvasive carcinoma at the resection margin should be indicated by the suffix (is). Example: Invasive carcinoma of the breast with an associated in situ component. Breast-conserving surgery, according to the surgeon, was complete with no tumor visible at the surgical margins. Histology demonstrates: a) Invasive carcinoma at the resection margin: R1; b) Invasive carcinoma completely removed, but with an associated in situ component at the resection margin: R1 (is).
- If tumor cells are found in the lumen of a lymph vessel or blood vessel at the resection margin without contact with the endothelium or invasion of the vessel wall, the classification is R0. In the case of an attachment or vessel wall invasion, a classification of R1 is appropriate.
- Although there have been proposals to code a tumor as R1 if it is $\leq 1$ mm from the resection margin, R1 should be used only if the tumor is transected; otherwise R0 applies.\textsuperscript{7,13,16} In studies from Germany (ECC) and Australia, R1 was used only if tumor was demonstrated at the resection margins (tumor transected). In studies from the U.K., Quirke et al.\textsuperscript{36,38} included in the R1 category tumors that could be shown to be $\leq 1$ mm from a resection margin. In the U.S., Compton et al.\textsuperscript{40} also recommended use of the latter definition for the R classification. The German documentation system proposes to follow the strict rule, but to record those cases with tumor within $\leq 1$ mm from the resection margin separately.
- In the R classification, serum levels of tumor markers are not considered.\textsuperscript{16}
- When making the distinction between the R classification versus the r symbol, the R classification should not be confused with the r prefix or recurrent tumor symbol. This optional symbol refers to tumors that have recurred after a disease-free interval (e.g., recurrence of colon carcinoma in the mucosa and submucosa at the line of resection would be coded as rT1). Although a recurrence presumably is the result of residual tumor, the latter, by definition, must have been undetected.
- With regard to the relation between residual tumor after surgery and TNM Stage IV disease, R2 is not necessarily synonymous with M1 (Stage IV) disease. For example, in the absence of distant metastasis (M0), residual macroscopic primary tumor that is not resected by the surgeon is classified as R2. However, a solitary metastasis in the liver from a primary colorectal carcinoma would be classified as pM1 (Stage IV) and R0 if the metastasis was resected completely.

**Aspects of Future Developments in Tumor Classification**

One of the main objectives in classifying tumors is to identify stage-independent prognostic factors and to create mathematic models for the prediction of outcome (i.e., prognostic indices and prognostic groupings).\textsuperscript{41} The residual tumor (R) classification has been shown to be a strong independent prognostic factor for virtually all types of malignant tumors and merits inclusion in any prognostic system.

For the vast majority of malignancies, prognosis differs significantly according to the R classification.\textsuperscript{42} Therefore, for multivariate analyses in prognostic factor investigation, we believe the substratification of tumors within the same stage grouping by the R classification is strongly justified. In addition, prognostic factors should be analyzed separately for the R0, R1, and R2 classifications.

**REFERENCES**
