PAPER

Assessment of Criteria and Clinical Significance of Circumferential Resection Margins in Esophageal Cancer

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Objective: To assess the clinical significance of circumferential resection margins according to current criteria of the College of American Pathologists (CAP) and the Royal College of Pathology (RCP) in esophageal and esophagogastric cancer.

Design: Prospective study.

Setting: Single-surgeon database.

Patients: One hundred thirty-five patients (mean age, 64 years) with T3 tumors who underwent esophageal resection for cancer between 1991 and 2006.

Main Outcome Measure: Resection margins criteria and survival.

Results: Three hundred seventy-four consecutive patients were prospectively identified from an institutional review board–approved database between 1991 and 2006. All patients with T3 tumors (n=135) had their original pathologic slides reassessed by a single gastrointestinal pathologist. Operative mortality was 0.7% and mean follow-up was 3.1 years. Follow-up was complete in 81% of patients. Positive margins were identified in 16 cases in the CAP group vs 83 cases in the RCP group. Five-year Kaplan-Meier survival curves in the CAP group demonstrated a significant ($P<.001$) difference in survival, whereas the RCP group showed no difference ($P=.20$). In comparisons of negative vs positive margins, respectively, median survival in the CAP group (29.8 months [95% confidence interval (CI), 22.7-36.9] vs 8.33 months [95% CI, 4.4-12.3]) was significantly different from the RCP group (28.47 months [95% CI, 19.7-37.2] vs 22.23 months [95% CI, 13.6-30.8]). At 60-month follow-up, the positive predictive value with respect to survival was 100% in the CAP group vs 81% in the RCP group. Univariate and multivariate analyses identified R1 margins in the CAP group and lymph node ratio as being directly linked to survival.

Conclusions: Positive circumferential resection margins are prognostically important and the CAP criteria provide a more clinically meaningful assessment. Universal adoption of the CAP system can improve interpretation of international clinical trials and allow more accurate comparisons of outcomes.

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THE 2 CURRENT SYSTEMS FOR staging cancer were last revised in 2002.[1,2] The TNM system in the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre Le Cancer (UICC) staging manuals are currently identical, though the structure and prognostic significance of the present TNM classifications are being questioned.[3-6] Changes were considered prior to the publication of the sixth edition of the AJCC manual[1] but not instituted owing to insufficient published data.[7]

Although not currently a criterion associated with the allocation of tumor stage, the presence of residual tumor (R classification) has been a routine component of data collection for both the AJCC and the UICC. Assessment within the R classification includes analysis of proximal, distal, and radial or circumferential resection margins.

In the assessment of circumferential resection margins in esophageal cancer specimens, the definition currently differs in the R0 and R1 categories between the College of American Pathologists (CAP),[8] which considers circumferential microscopic margins (R1) positive if tumor is found at the cut margin of resection, and the Royal College of Pathologists (RCP),[8] which considers circumferential margins positive when tumor is located within 1 mm of the cut margin (**Figure 1**).

Positive resection margins (proximal, distal, and circumferential) in esophageal cancer have previously been demonstrated to be related to prognosis.[9-13] Esophageal cancer recurs in a locoregional pattern in 50% of cases.[14] As a result, positive resection margins are typically considered when postsurgical treatment decisions are being made. The changes in the current R classification in the *Dataset for Histopathologic Reporting*

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of Esophageal Carcinoma[8] from the RCP was initiated following studies of the surgical treatment of rectal cancer that documented the prognostic significance of circumferential tumor margins less than 1 mm.[15] The current R classification for esophageal cancer was instigated following a publication by Sagar et al,[16] which demonstrates a similar relationship of positive margins within 1 mm of resection margin to prognosis.[17,18] Although the published data are not entirely consistent, multiple studies from the United Kingdom have supported a prognostic link associated with positive circumferential margins within 1 mm of resection margin. Despite this data, both the AJCC TNM Process Subcommittee and the UICC TNM Prognostic Factors Project Committee support the traditional interpretation of R1 classification associated with tumor cells at the margin of resection. This study assesses the prognostic significance of circumferential positive resection margins using both the CAP and RCP criteria while also assessing the effect of other independent factors, such as tumor length, grade, lymph node status, and neoadjuvant therapy.

METHODS

We used an institutional review board–approved, single-surgeon, prospective database to identify all patients who underwent esophageal resection for cancer between 1991 and 2006. Three hundred seventy-four patients were operated on during the study period. All patients found to have pathologic T3 tumors were selected as the primary study population. One hundred thirty-five patients with T3 disease were identified and all of their original slides were rereviewed by a single pathologist (R.D.) with a primary interest in gastrointestinal pathology. Slides were assessed for tumor histology and grade, margin, and lymph node status. Specific measurements were carried out to categorize circumferential resection margins using both the CAP and RCP criteria. Other patient demographics, including endoscopic tumor length, were collected from the database.

TISSUE AND SPECIMEN HANDLING

The methodology for immediate handling and assessing esophageal resectional margins is far from uniform. Although in-depth descriptions exist for the handling and reporting of esophageal cancer specimens,[19,20] there is little standardization within published studies.

The specimens in the current series underwent a variety of resectional approaches, which were matched to individual patient physiology and tumor characteristics. The specimen was delivered fresh to the pathologic laboratory and accompanied by the surgeon, who oriented the pathologists regarding the specimen's anatomic transection locations, close resection margins, and the original location of attached lymph nodes. Lymph nodes in the paraceliac, left gastric pedicle paraesophageal, and subcarinal locations were resected en bloc whenever feasible and were not removed from the specimen prior to fixation but were identified and labeled. Circumferential resection margins were inked fresh and all specimens were opened, avoiding cutting across residual tumors when possible. Frozen section analysis for residual cancer and Barrett's esophagus was carried out on proximal margins in all cases. Specimens were pinned out and fixed in 10% formalin for at least 24 hours. The entire area of the tumor was blocked out, and representative samples from the residual esophagus and stomach, as well as distal and proximal resection margins, were obtained. In cases in which patients had undergone previous neoadjuvant or endoscopic therapy, the entire specimen was often blocked out. Lymph nodes were harvested after fixation, and in cases of neoadjuvant treatment, the degree of residual tumor was assessed.

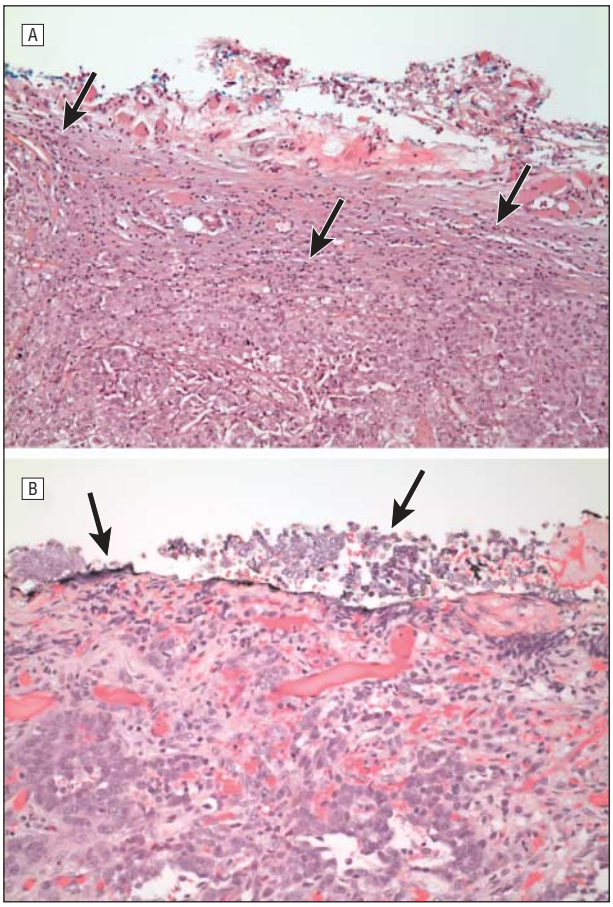

Figure 1. Photomicrographs of resected sections of esophageal cancer. A, Tumor cells within 1 mm of circumferential margin (arrows), R0 according to College of American Pathologists and R1 according to Royal College of Pathology criteria. B, Tumor cells at the circumferential margin (arrows) (cauterized tumor shown in black), R1 according to College of American Pathologists and R1 according to Royal College of Pathology criteria (original magnification, ×200; field of view is approximately 2.0 mm from the cauterized edge).

STATISTICAL METHODS

Data were analyzed using standard statistical software (SPSS, version 16.0; SPSS Inc, Chicago, Illinois). Continuous variables were considered using an independent *t* test; nonparametric χ^2 or Fisher exact tests were used to evaluate categorical variables. Univariate survival analyses were performed using the Kaplan-Meier method, including overall survival as the end point. Tests of significance for Kaplan-Meier survival analyses were performed using the log-rank statistic. Multivariate analysis using the Cox proportional hazards model to identify independent predictors of survival included only statistically significant variables of univariate analysis. In all cases, $P < .05$ was considered statistically significant.

RESULTS

The study population included 135 patients with pathologically staged T3 tumors (115 men and 20 women; mean age, 60.2 years; range, 36-82 years). Cancer histology in-

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Table 1. Median Survival of Patients With Positive and Negative Circumferential Resection Margins

Resection Margin Status	No. of Patients (n=135)	Median Survival (95% CI), mo
CAP criteria		
Negative	119	29.8 (22.71-36.89)
Positive	16	8.33 (4.38-12.29)
RCP criteria		
Negative	52	28.47 (19.70-37.24)
Positive	83	22.23 (13.66-30.81)

Abbreviations: CAP, College of American Pathologists; CI, confidence interval; RCP, Royal College of Pathology.

cluded adenocarcinoma (87%), squamous cell cancer (11%), and others (2%). All tumors were classified as Siewert type I or II. Lymph node staging was N0 in 35 patients (25.9%), N1 in 91 patients (67.4%), and M1a in 9 patients (6.7%). Neoadjuvant therapy was used in 44% of cases, chemotherapy alone in 41%, and chemoradiotherapy in 59%. Operative approach was individualized according to the tumor and patient characteristics and included left thoracoabdominal (n=93 [69%]), Ivor-Lewis (n=38 [28%]), 3-stage (n=3 [2%]), and transhiatal (n=1 [1%]) approaches. Cervical anastomoses were done in 72% of patients. One patient died, giving a 30-day and in-hospital mortality of 0.7%. Mean follow-up was 3.1 years (range, 1-16 years); patients were followed up until death or last-known contact. Follow-up was complete in 81% of cases. All pathologic specimens were reassessed by a single gastrointestinal pathologist. Changes in stage or margin status occurred in 3 patients (2.2%). Using the CAP criteria (R1 tumor positive at cut margin of resection), we found that 16 patients (11.8%) with T3 tumors had positive microscopic margins. Under the RCP criteria (R1 tumor within 1 mm of the cut margin), 83 patients (61.5%) had positive margins. Negative margins under CAP criteria were identified in 354 of all of the 374 patients (94.7%) operated on during the 15 years of study.

Table 1 presents the differences in median survival between the 2 systems based on resection margin status. It demonstrates a marked difference in length of survival under the CAP system, which is not seen with RCP criteria. **Figure 2** illustrates Kaplan-Meier survival analysis at 5 years, demonstrating a significant difference in survival between patients with positive and negative margins using the CAP criteria. No significant difference in survival was noted according to RCP criteria.

Univariate analysis examining the relationship between survival and a variety of other factors (**Table 2**) found a statistically significant relationship with respect to positive resection margins using the APC criteria and the criterion of more than 25% of lymph nodes being positive. The presence or absence of positive lymph nodes was close to being statistically significant ($P=.05$). However, the use of neoadjuvant therapy, tumor length and differentiation, total number of positive lymph nodes, and positive resection margin according to the RCP criteria was not found to be directly related to survival.

Subsequent multivariate analysis of CAP positive resection margins and a positive lymph node ratio of more than

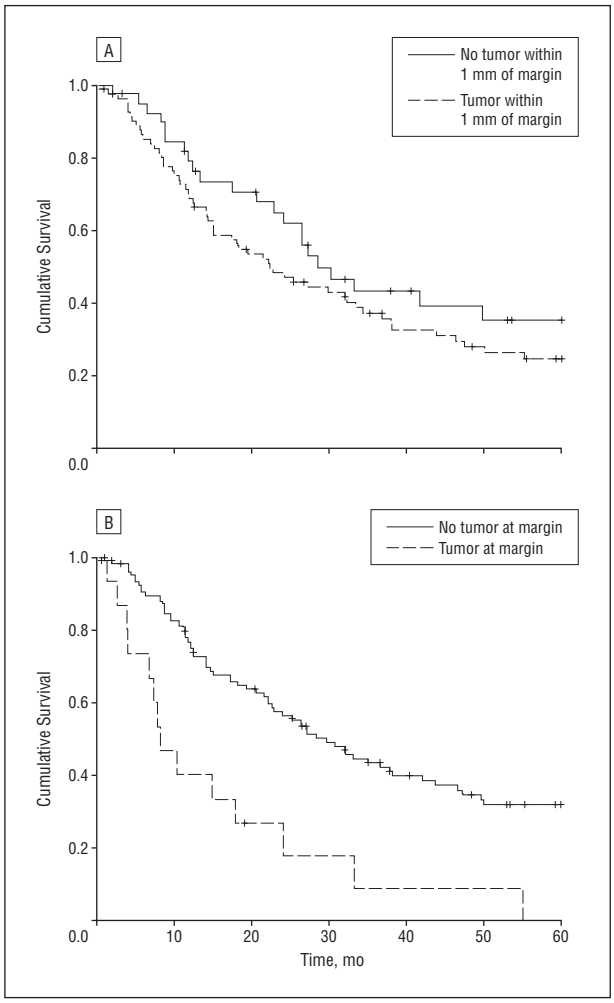

Figure 2. Kaplan-Meier survival curves comparing patients with positive vs negative circumferential resection margin according to College of American Pathologists and Royal College of Pathology criteria. A, No significant difference in survival with Royal College of Pathology criteria ($P=.20$). B, Significant difference in survival with College of American Pathologists' criteria ($P<.001$).

25% confirms that they were independent predictors of survival. Cox hazard ratio for risk of death with CAP positive margins is 3.8 (95% confidence interval, 2.0-7.4 months), and with the positive lymph node ratio of more than 25%, 2.2 (95% confidence interval, 1.3-3.7 months).

At 60-month follow-up, circumferential resection margin assessment of survival comparing CAP with RCP criteria demonstrated a positive predictive value of 100% vs 81.4%, whereas negative predictive value was virtually identical (23.5% vs 24.1%). In patients with positive margins, there were no significant differences between CAP and RCP, respectively, in median number of lymph nodes reviewed (17.48 vs 16.3) or lymph node ratio (0.40 vs 2.7). However, tumor length was found to be significantly shorter in patients with RCP positive margins (5.1 vs 6.4 cm; $P=.03$), though univariate analysis of tumor length did not demonstrate it to be an independent factor related to survival (Table 2). **Table 3** demonstrates the effect on median survival in patients with differing node statuses. The number of positive lymph nodes appears to be a significant prognostic factor in pa-

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Table 2. Univariate Analysis of Various Prognostic Factors and Their Relationship to Survival

Factor	No. of Patients	No. (%) of Events	Median Survival (SE), mo	95% CI	*P* Value
Age, y					
<65		37/59 (63)	24 (2.7)	18.7-29.2	
≥65		37/63 (59)	30 (6.2)	17.6-41.9	.99
Sex					
M	115	65/104 (63)	26 (3.2)	20-32.9	
F	20	9/19 (47)	47	. . .	.34
Chemoradiation					
No	76	43/66 (65)	22 (5.7)	11.5-34.1	
Yes	59	31/57 (54)	27 (12.8)	1.9-52.5	.34
Circumferential resection margin status					
CAP criteria					
Negative	119	58/98 (59)	27 (4.1)	19.2-35.3	
Positive	16	12/14 (86)	8 (0.9)	6.2-9.7	<.001
RCP criteria					
Negative	52	20/37 (54)	28 (9.4)	10-46.8	
Positive	83	50/75 (67)	21 (5.2)	11-31.5	.14
Differentiation					
Good	4	1/3 (33)	59	. . .	
Moderate	43	20/31 (65)	29 (6.7)	16.5-43	
Poor	73	44/76 (58)	24 (3.5)	17-31	.46
Tumor length, cm					
≤3.5	45	24/45 (53)	32 (6.1)	19.8-44.1	
>3.5	78	50/78 (64)	24 (3.6)	16.9-31	.30
Positive lymph nodes					
No	33	13/33 (39)	55	. . .	
Yes	76	53/76 (70)	22 (4.0)	14.8-30.5	.05
% of positive lymph nodes					
≤25	64	30/64 (47)	47 (11.1)	25.4-69.3	
>25	45	36/45 (80)	15 (4.4)	6.4-23.7	.003
No. of lymph nodes involved					
0	33	13/33 (39)	55	. . .	
1-2	21	15/21 (71)	30 (6.8)	16.8-43.5	
>2	55	38/55 (69)	21 (4.5)	12.4-30.2	.15

Abbreviations: CAP, College of American Pathologists; CI, confidence interval; RCP, Royal College of Pathology; ellipses, not available.

Table 3. Median Survival and Lymph Node Involvement in Patients With R1 Positive Margins by CAP and RCP Criteria

No. of Positive Lymph Nodes	No. of Patients	Median Survival (Range), mo	
		CAP Criteria	RCP Criteria
0	33	29.80 (22.70-36.89)	28.46 (19.46-37.23)
1-2	22	7.43 (0.00-15.11)	27.23 (10.00-44.46)
≥3	55	8.33 (0.00-17.14)	21.33 (11.75-30.93)

Abbreviations: CAP, College of American Pathologists; RCP, Royal College of Pathology.

tients with CAP positive margins but not in those with RCP positive margins.

COMMENT

There are multiple criteria that have been potentially linked to prognosis following resection of esophageal cancer. These include tumor stage,[9,10,21,22] tumor grade,[21,22] node status and lymph node ratio,[3-6,9,10,22,23] and degree of tumor response following neoadjuvant therapy.[5,24] Positive resection margins (proximal, distal, and circumferential) have also been associated with survival in multiple studies.[9-12,21] Saha and Dehn[25] reported positive circumferential margins as the most important prognostic criteria on univariate and multivariate analysis.

Circumferential resection margins as a specific prognostic issue have been assessed more regularly in the United Kingdom than elsewhere.[10,16,17,22,25-27] The current reporting data set from the RCP[8] indicates a positive circumferential margin to be within 1 mm of the cut surgical margin, which is not the same as the criteria in other countries using AJCC and UICC guidelines. Considering that the TNM staging systems are identical, the difference in R classification produces a confounding factor when comparing results of international clinical trials or national reports of surgical outcomes.

The current criteria within the RCP data set is, in part, based on data derived from reports on the surgical treatment of rectal cancer in which circumferential margins of less than 1 mm were found to be prognostically significant.[15] The comparison of resectional criteria in esophageal and rectal cancer is likely not appropriate. Despite both viscera being outside the peritoneal reflection and having no serosal covering, the esophagus has no comparable anatomic boundaries, such as the mesorectum or Denonvilliers fascia. In addition, the esophagus lies directly adjacent to organs that cannot be removed with en bloc resection, such as the aorta, spine, heart, and tra-

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Table 4. Incidence of Positive Circumferential Resection Margins by CAP and RCP Criteria

Source (Country of Study)	No. of Patients	% Positive Circumferential Resection Margin: RCP Criteria	% Positive Circumferential Resection Margin: CAP Criteria	% T3 Tumor Only: RCP Criteria	% T3 Tumor Only: CAP Criteria
Sagar et al,[16] 1993 (United Kingdom)	50	40			
Dexter et al,[26] 2001 (United Kingdom)	135	47			
Khan et al,[22] 2003 (United Kingdom)	329	20	12		
Roh et al,[29] 2004 (Korea)	59	44			
Griffiths et al,[17] 2006 (United Kingdom)	249	32		54	
Sujendran et al,[27] 2008 (United Kingdom)	242	22		39	
Barbour et al,[21] 2007 (United States)	505		6		
Current study (United States)	374		5		12

Abbreviations: CAP, College of American Pathologists; RCP, Royal College of Pathology.

cheobronchial tree, and immediately adjacent to the pleura, which can be removed en bloc but does not provide a continuous covering for the esophagus. We tend to agree with previous articles[9,28,29] that suggest that positive circumferential resection margins in esophageal cancer are more likely to represent advanced tumor stage rather than a lack of surgical expertise. As a result, surgical resection of a well-defined cancer will predictably have a much higher instance of positive margins in patients with the current RCP system. Studies from the United Kingdom (**Table 4**) document an incidence of circumferential positive margins between 20% and 47%. Circumferential resection margins have not been routinely assessed in other international studies, but when all patients who were operated on within the present study are included, a positive circumferential resection margin instance of 5% was obtained, which compares well with another large North American study by Barbour et al (n=505),[21] which demonstrated an incidence of positive circumferential margins of 6%. When only T3 tumors are studied, the differences are just as significant. Positive circumferential resection margins according to CAP criteria in the current study were found in 12% compared with 39% to 54% in studies from the United Kingdom using RCP criteria.[17,27] The primary issue remains as to which system provides the most clinically relevant prognostic information. The current study attempts to answer this question specifically and though it has the weakness of being a retrospective study, it does have certain design strengths. The study population includes only T3 tumors, which previous series have confirmed is the most pertinent population for comparison.[17,22,27,30] Most importantly, though retrospective, all pathologic slides were prospectively rereviewed by a single pathologist with special expertise in gastrointestinal pathology. This provided a consistency in interpretation, measurement, and expertise that is typically lacking in other series. Also, because all operations were done by a single surgeon, there was a consistent approach with respect to tumor resection and lymph node dissection.

Our results demonstrate a significant difference in 5-year survival in patients with positive circumferential resection margins measured according to the CAP system. No significant difference in 5-year or median survival was seen in patients with positive margins when using the RCP criteria (Figure 2). This supports a previous assessment by Griffiths et al,[17] which documented no significant difference in 5-year survival using the RCP criteria when T3 tumors were analyzed separately. Both systems demonstrated low negative predictive values. However, positive predictive value favored the CAP criteria 100% to 81.4%.

Previous studies regarding the significance of positive circumferential resection margin are mixed. Some studies have shown positive circumferential margins to have little effect on prognosis.[20,27] Others have documented a direct correlation with locoregional recurrence[16,27,28] and overall survival.[16,25,27] Some studies also suggest that the effect of positive circumferential resection margins on prognosis only occurs when lymph node involvement is limited to less than 25%.[17,26] That by Khan et al[22] is the only current study to compare outcomes using both resection margin criteria. Although 5-year survival was improved in patients with positive margins using RCP criteria (26% vs 20%), the difference was not statistically significant. There was no attempt to compare survival between positive and negative margins between the CAP and RCP criteria.

Neoadjuvant therapy is often used, especially in patients with T3 tumors. However, the question as to whether neoadjuvant therapy affects the incidence of positive circumferential resection margin remains unclear. Studies from England[27] and Ireland[28] noted a decrease in positive resection margins in patients receiving neoadjuvant therapy. Two other studies—one that analyzed T3 tumors as a separate group[17] and the randomized MRC (the British Medical Research Council) trial from the United Kingdom, which compared more than 800 patients who underwent surgery only vs preoperative chemotherapy followed by surgery[31]—saw no difference in the incidence of positive resection margins following neoadjuvant therapy. The current study did not demonstrate that either chemotherapy alone or chemoradiotherapy had any significant effect on median survival in patients with positive or negative resection margins using either the CAP or RCP systems.

The current AJCC and UICC TNM classifications are the same, but there are increasing indications that revision will be required in the near future.[4-7,23] These revi-

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sions will occur, and maintaining international consistency in staging and pathologic assessment is critical. One of the current recommendations for modification of the TNM system is the change of the N classification from categorizing nodes regionally to a system that highlights the overall number of positive nodes.[4] When this new classification is applied to patients with both positive and negative resection margins, as classified by both systems, there is a significant effect on median survival between node-positive and node-negative patients in the CAP system that is not seen in the RCP system (Table 3). However, the number of positive lymph nodes does not seem to affect survival in patients with positive margins categorized by either the CAP or RCP criteria.

The UICC TNM Prognostic Factors Project Committee and the AJCC TNM Process issued a joint communication in 2002, which confirmed that the "R classification is a strong indicator of prognosis and facilitates the comparison of treatment results if applied in a consistent manner."[32] They go on to say that the R classification has been inconsistently reported on and suggest that application should be uniform and obligatory. Our findings support this approach, because positive circumferential resection margins, according to CAP criteria, were 1 of 2 factors directly related to survival on univariate and multivariate analysis. There is limited current information regarding the completeness of residual tumor (R classification) documentation in most countries. However, regional audits of esophageal cancer reporting in the United Kingdom indicate that data on completeness of resection in general and circumferential resection margins in particular are the most commonly omitted data points.[33,34]

To reliably document and compare outcomes in clinical trials and individual studies, we cannot be comparing apples with oranges. Researchers are currently reviewing many issues in an attempt to improve the consistency of international reporting. The AJCC and the UICC use the tumor location with respect to the gastroesophageal junction to distinguish esophageal cancers from gastric cancers.[1,2] This differentiation has historically been done poorly and the Siewert classification[35] has been adopted at a consensus conference of the International Gastric Cancer Association and the International Society of Disease of the Esophagus to provide a consistent venue for reporting esophageal and gastric tumor location.[36]

The same should occur with respect to reporting of the residual tumor (R) classification, especially with respect to circumferential tumor margins. The present study demonstrates that positive resection margins according to the CAP criteria currently recommended by both the UICC and the AJCC is a significant prognostic indicator, while a positive circumferential resection margin according to the current RCP criteria does not demonstrate the same level of prognostic significance. Standardized templates for tissue handling and margin assessment should be developed in conjunction with revisions to the TNM staging systems. International interpretation of margin status should be consistent and reflect the current CAP criteria. Additional assessment on the best methodology of handling esophageal specimens and the appropriate clinical response to R1 resection margins is required.

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REFERENCES

1. Greene FL, Page DL, Fleming ID, Fritz A, Balch CM; American Joint Committee on Cancer. *AJCC Cancer Staging Handbook.* 6th ed. New York, NY: Springer-Verlag; 2002.
2. Union Internationale Contre le Cancer. *TNM Classification of Malignant Tumours.* 6th ed. New York, NY: Wiley-Liss; 2002.
3. Veeramachaneni NK, Zoole JB, Decker PA, Putnam JB Jr, Meyers BF; American College of Surgeons Oncology Group Z0060 Trial. Lymph node analysis in esophageal resection: American College of Surgeons Oncology Group Z0060 trial. *Ann Thorac Surg.* 2008;86(2):418-421.
4. Rice TW, Blackstone EH, Rybicki LA, et al. Refining esophageal cancer staging. *J Thorac Cardiovasc Surg.* 2003;125(5):1103-1113.
5. Rizk NP, Venkatraman E, Bains MS, et al; American Joint Committee on Cancer. American Joint Committee on Cancer staging system does not accurately predict survival in patients receiving multimodality therapy for esophageal adenocarcinoma. *J Clin Oncol.* 2007;25(5):507-512.
6. Hofstetter W, Correa AM, Bekele N, et al. Proposed modification of nodal status in AJCC esophageal cancer staging system. *Ann Thorac Surg.* 2007;84(2):365-375.
7. Rusch VW. Should the esophageal cancer staging system be revised? *J Thorac Cardiovasc Surg.* 2003;125(5):992-993.
8. Royal College of Pathologists. *Dataset for the Histopathological Reporting of Oesophageal Carcinoma.* 2nd ed. London, England: The Royal College of Pathologists; 2006.
9. Griffiths EA, Pritchard SA, Mapstone NP, Welch IM. Emerging aspects of oesophageal and gastro-oesophageal junction cancer histopathology: an update for the surgical oncologist. *World J Surg Oncol.* 2006;4:82.
10. Hölscher AH, Bollschweiler E, Bumm R, Bartels H, Hofler H, Siewert JR. Prognostic factors of resected adenocarcinoma of the esophagus. *Surgery.* 1995;118(5):845-855.
11. Paraf F, Flejou JF, Pignon JP, Fekete F, Potet F. Surgical pathology of adenocarcinoma arising in Barrett's esophagus: analysis of 67 cases. *Am J Surg Pathol.* 1995;19(2):183-191.
12. Roder JD, Busch R, Stein HJ, Fink U, Siewert JR. Ratio of invaded to removed lymph nodes as a predictor of survival in squamous cell carcinoma of the oesophagus. *Br J Surg.* 1994;81(3):410-413.
13. Skinner DB, Dowlatshahi KD, DeMeester TR. Potentially curable cancer of the esophagus. *Cancer.* 1982;50(11)(suppl):2571-2575.
14. Law SY, Fok M, Wong J. Pattern of recurrence after oesophageal resection for cancer: clinical implications. *Br J Surg.* 1996;83(1):107-111.
15. Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg.* 2002;89(3):327-334.
16. Sagar PM, Johnston D, McMahon MJ, Dixon MF, Quirke P. Significance of circumferential resection margin involvement after oesophagectomy for cancer. *Br J Surg.* 1993;80(11):1386-1388.
17. Griffiths EA, Brummell Z, Gorthi G, Pritchard SA, Welch IM. The prognostic value

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of circumferential resection margin involvement in oesophageal malignancy. *Eur J Surg Oncol*. 2006;32(4):413-419.
18. Royal College of Pathologists. *Minimum Dataset for Oesophageal Carcinoma Histopathology Reports*. London, England: Royal College of Pathologists; 1998.
19. Ibrahim NB. ACP. Best Practice No 155: guidelines for handling oesophageal biopsies and resection specimens and their reporting. *J Clin Pathol*. 2000;53 (2):89-94.
20. Association of Directors of Anatomical and Surgical Pathology. Recommendations for the reporting of resected esophageal carcinomas. *Mod Pathol*. 2000; 13(9):1034-1037.
21. Barbour AP, Rizk NP, Gonen M, et al. Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome. *Ann Surg*. 2007;246(1):1-8.
22. Khan OA, Fitzgerald JJ, Soomro I, Beggs FD, Morgan WE, Duffy JP. Prognostic significance of circumferential resection margin involvement following oesophagectomy for cancer. *Br J Cancer*. 2003;88(10):1549-1552.
23. Kunisaki C, Akiyama H, Nomura M, et al. Developing an appropriate staging system for esophageal carcinoma. *J Am Coll Surg*. 2005;201(6):884-890.
24. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer*. 2005;103(7):1347-1355.
25. Saha S, Dehn TC. Ratio of invaded to removed lymph nodes as a prognostic factor in adenocarcinoma of the distal esophagus and esophagogastric junction. *Dis Esophagus*. 2001;14(1):32-36.
26. Dexter SP, Sue-Ling H, McMahon MJ, Quirke P, Mapstone N, Martin IG. Circumferential resection margin involvement: an independent predictor of survival following surgery for oesophageal cancer. *Gut*. 2001;48(5):667-670.
27. Sujendran V, Wheeler J, Baron R, Warren BF, Maynard N. Effect of neoadjuvant chemotherapy on circumferential margin positivity and its impact on prognosis in patients with resectable oesophageal cancer. *Br J Surg*. 2008;95(2):191-194.
28. Mulligan ED, Dunne B, Griffin M, Keeling N, Reynolds JV. Margin involvement and outcome in oesophageal carcinoma: a 10-year experience in a specialist unit. *Eur J Surg Oncol*. 2004;30(3):313-317.
29. Roh MS, Lee JI, Choi PJ. Significance of circumferential resection margin involvement following esophagectomy for esophageal cancer. *Korean J Pathol*. 2004; 38:23-28.
30. Wu TT, Chirieac LR, Abraham SC, et al. Excellent interobserver agreement on grading the extent of residual carcinoma after preoperative chemoradiation in esophageal and esophagogastric junction carcinoma: a reliable predictor for patient outcome. *Am J Surg Pathol*. 2007;31(1):58-64.
31. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet*. 2002;359(9319):1727-1733.
32. Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. *Cancer*. 2002;94(9):2511-2516.
33. Burroughs SH, Biffin AH, Pye JK, Williams GT. Oesophageal and gastric cancer pathology reporting: a regional audit. *J Clin Pathol*. 1999;52(6):435-439.
34. King PM, Blazeby JM, Gupta J, Alderson D, Moorghen M. Upper gastrointestinal cancer pathology reporting: a regional audit to compare standards with minimum datasets. *J Clin Pathol*. 2004;57(7):702-705.
35. Rüdiger Siewert J, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg*. 2000;232(3):353-361.
36. Allum WH, Griffin SM, Watson A, Colin-Jones D; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; British Society of Gastroenterology; British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut*. 2002;50(suppl 5):v1-v23.

DISCUSSION

Elizabeth Peralta, MD, Springfield, Illinois: In this very interesting article, Dr Deeter et al challenges [sic] the prevailing residual tumor classification that has been in use by the Royal College of Pathologists since 2002. The current definition of the negative radial margin in the RCP system was created by analogy to the Norwegian Rectal Cancer Project, which set out to improve the outcome of rectal cancer by improving the radicality of the surgical technique, as distinct from the contribution of radiation or chemotherapy, namely, the total mesorectal excision.

In the current study, a 15-year single-surgeon series of 135 pathologically staged T3 tumors was reviewed for margin status. Although the operative approach and the use of neoadjuvant therapy was individualized for each patient, all cases included a meticulous mediastinal lymph node dissection. Median survivals were then calculated with the cases classified by CAP vs RCP criteria, with 81% complete follow-up.

Results demonstrate that application of the RCP classification did not show a statistically significant difference in median survival between R0 and R1 resections. Similar findings have been reported in another large single-surgeon study cited in this work. In contrast, analyses that include esophageal tumors of all stages, including T1 and T2 tumors that ought never to have involved radial margins, have found that a radial margin less than 1 mm was an independent adverse prognostic feature. (1) Are the preponderance of esophagectomies performed in this country by dedicated specialists who can achieve CAP negative margins as you did 95% of the time, and if not, should the stringent R0 criterion be applied for all T stages, as a surrogate for surgical quality, even though some R1 patients will do as well as R0?

In your study, there were 67 cases designated R1 by the RCP system that became R0 by the CAP system. (2) Did the CAP criterion allow some patients to be spared adjuvant therapy that would have received it under the RCP system?

In the RCP classification, median survival for positive margins was no worse than that for negative margins. This implies that some so-called positive margins are salvageable. (3) Among patients with margins less than 1 mm and with prolonged survival, what percent had been treated with neoadjuvant therapy?

Dr Low: With respect to the current surgical population carrying out esophageal resection in the United States, I believe there has been a modest trend toward concentrating these procedures in high-volume medical centers. However, I still believe that this procedure is carried out by a wide variety of general and thoracic surgeons, which makes it even more important that there is a clear understanding of the assessment criteria for circumferential resection margins, but also we could do better with respect to standardizing the handling of these complex surgical specimens. Pathologic T stage is confirmed only after analysis of the specimen is complete. Therefore, a standardized assessment of proximal, distal, and circumferential resection margins should be part of the assessment in all patients, irrespective of clinical TNM classifications.

Your second question explores one of the key issues in this comparison. In high-volume centers using the CAP criteria in North America, the incidence of positive circumferential margins is 5% to 10%. I believe that this finding would routinely be a major component of the discussion in tumor boards regarding adjuvant therapy. On the other hand, our European and British colleagues, using the RCP system, have a positive circumferential margin between 25% and 55% of the time, making it such a common postoperative issue that it is less likely to figure in routine decisions regarding adjuvant therapy.

The question as to whether the RCP classification system is prognostically important has been assessed in multiple studies from the United Kingdom. The reports are mixed, although there is a trend toward this system being a measurable prognostic factor when patients with any T stage are included in the analysis. Our study assessing only T3 patients clearly demonstrates that the RCP system does not provide any significant difference in median or 5-year survivorship. We also did not notice any significant effect on the incidence of R1 margins in our populations that had neoadjuvant therapy vs those that had not.

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