ORIGINAL ARTICLE

# Prognostic Significance of Tumor-Infiltrating Lymphocytes for Patients With Colorectal Cancer

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**Objective:** To evaluate the prognostic significance of tumor-infiltrating lymphocytes (TILs) in patients with colorectal cancer.

**Design:** A retrospective review of prospectively collected data.

**Setting:** Tertiary care hospital.

**Patients:** A total of 546 patients who underwent curative surgery for primary nonmetastatic colorectal cancers from May 1, 2004, through December 31, 2007.

**Main Outcome Measures:** The prognostic value of macroscopic ulceration, tumor border configuration, and TILs at the invasive margin was assessed.

**Results:** The low TIL group was significantly correlated with a poorly differentiated status and perineural invasion. During the median 54-month follow-up period, the low TIL group had significantly lower 5-year overall survival and disease-free survival rates than the high TIL group of patients with stage III colorectal cancer ($P=.005$ and $P=.03$, respectively); however, for patients with stage I and II cancers, the survival rates did not differ between the 2 groups. The 5-year overall survival and 5-year disease-free survival rates were significantly different between the high and low TIL groups of patients with rectal cancer ($P=.003$ and $P=.01$, respectively). The multivariate analysis confirmed that the TIL grade was significantly and independently associated with a worse prognosis for overall survival but not for disease-free survival.

**Conclusions:** An inflammatory cell reaction at the tumor invasive border is considered a useful predictor of survival after colorectal cancer surgery, particularly for patients with stage III disease or rectal cancer.

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THE PRESENCE OF INFLAMMATORY cells is a common phenomenon in human colorectal cancer, and the infiltration by various inflammatory cells within the tumor and at the invasive margins tends be regarded as a nonspecific finding. The prognostic effect of tumor-infiltrating lymphocytes (TILs) and tumor-related immune responses has recently become increasingly recognized, and a greater lymphocytic reaction to colorectal cancer has been associated with longer patient survival.[1-5] However, the true nature of this association and the exact mechanisms underlying it remain uncertain, and whether the presence of TILs is a definite prognostic factor remains controversial.[6,7]

*See Invited Critique at end of article*

Therefore, the aim of this study was to evaluate the prognostic value of the TIL counts in patients with colorectal cancer who underwent potentially curative resection. The correlations between the TIL counts and various clinicopathologic variables were also delineated.

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## METHODS

We reviewed consecutive patients who underwent a potentially curative resection for colorectal cancer from May 1, 2004, through December 31, 2007. Patients with synchronous tumors, recurrent disease, or distant metastasis or those who had undergone preoperative chemoradiation for rectal cancer were excluded. Ultimately, 546 patients were eligible for this retrospective review of their prospectively collected data. This study was reviewed and approved by the appropriate institutional review board.

All patients underwent standard colectomy and regional lymphadenectomy according to the tumor location.[8-11] Standard pathologic analysis was performed on all the radical colorectal resection specimens by 2 experienced gastrointestinal pathologists who were masked to the patients' outcomes. After the fi-



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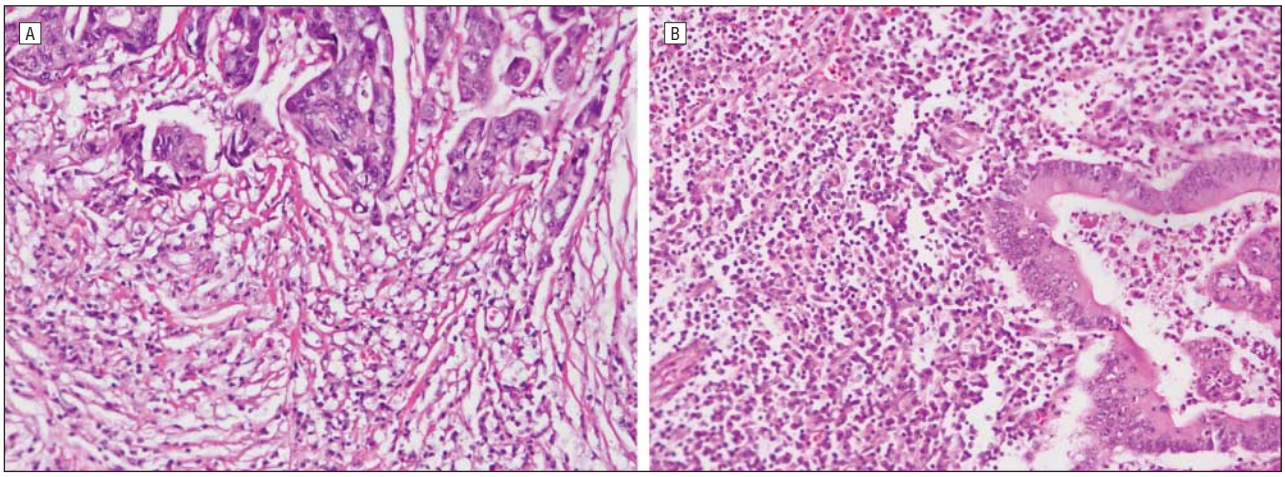


**Figure 1.** Tumor-infiltrating lymphocytes at the invasive margin. A, Low grade; B, high grade.

nal histopathologic examination, the colorectal cancer was staged according to the seventh American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM staging system. The resection specimens were evaluated for the depth of tumor penetration, lymph node involvement, histologic type, lymphovascular invasion, perineural invasion, macroscopic ulceration, tumor border configuration, and TILs.

The tumor border configuration was diagnosed according to the method proposed by Jass et al[12] at low magnification. Briefly, the tumor margins were identified as infiltrating when there was no recognizable margin of growth and a "streaming dissection" between the normal structures of the bowel wall was present. Margins were considered pushing when they were reasonably well circumscribed, and they often were associated with a well-developed inflammatory lamina. The TILs were scored according to the criteria of Klintrup et al.[1] Briefly, tumors were assessed by using a 4-degree scale at the deepest area of the invasive margin. A score of 0 was given when there was no increase in inflammatory cells, 1 denoted a mild and patchy increase in inflammatory cells, 2 denoted a moderate and bandlike inflammatory infiltrate with some destruction of cancer cell islands, and 3 denoted a marked and florid cuplike inflammatory infiltrate with frequent destruction of cancer cell islands. These scores were then subsequently classified as low grade (scores 0 and 1) and high grade (scores 2 and 3) (**Figure 1** A and B).

Postoperative adjuvant treatment was dependent on the patient's general condition or adherence to therapy and the preference of the physician. Postoperative 5-fluorouracil–based chemotherapy was considered for all the patients with T3-4 or node-positive disease.[8,10,11] Of the 546 patients, 398 (72.9%) received adjuvant therapy (355 chemotherapy and 43 chemoradiotherapy). Five chemotherapeutic regimens were used: (1) fluorouracil and leucovorin calcium (6 cycles of a monthly bolus of intravenous fluorouracil, 400-425 mg/m$^2$ daily, on days 1-5 and leucovorin calcium, 20 mg/m$^2$ daily, on days 1-5; n=227), (2) tegafur and uracil (6 cycles of tegafur and uracil, 300 mg/m$^2$ daily, for 28 days; n=35), (3) doxifluridine (6 cycles of 600 mg/m$^2$ daily for 28 days; n=9), (4) capecitabine (8 cycles of 1250 mg/m$^2$ twice daily for 14 days followed by 7 days of rest at the conclusion of each cycle; n=78), and (5) oxaliplatin, fluorouracil, and leucovorin (12 cycles of oxaliplatin, 85 mg/m$^2$, on day 1 and leucovorin calcium, 200 mg/m$^2$, as a 2-hour infusion on day 1 and fluorouracil, 400 mg/m$^2$, as a bolus and a 600-mg/m$^2$ 22-hour infusion on days 1 and 2 bimonthly; n=6). Postoperative radiotherapy consisted of 45 to 50.4 Gy (to convert gray to rad, multiply by 100) in 25 to 28 fractions delivered to the pelvis using a 4-field box technique. Of the 281 patients with rectal cancer, 43 (15.3%) received postoperative chemoradiotherapy. The patients were followed up at 3-month intervals for 2 years, at 6-month intervals for the next 3 years, and annually thereafter. On a semiannual basis or when recurrence was suspected, follow-up examinations were performed, and these included a clinical history, physical examination, serum carcinoembryonic antigen (CEA) assay, chest radiography or computed tomography, abdominopelvic computed tomography or magnetic resonance imaging, colonoscopy, and positron emission tomography scanning, if available.

The statistical evaluation was performed using SPSS statistical software for Windows (version 14.0; SPSS, Inc). Differences between the groups were tested using the $\chi^2$ test and analysis of variance as appropriate. The survival rates were calculated using the Kaplan-Meier method, and the prognostic factors and the survival curves were compared using the log-rank test. The variables with a statistical $P < .20$ were entered into a Cox model of multivariate analysis. $P \leq .05$ was deemed to be statistically significant.

## RESULTS

This analysis included 328 men (60.1%) with a median age of 64 years (range, 23-89 years). Using the seventh AJCC/UICC TNM staging system, 94, 234, and 218 patients had stage I, II, and III cancers, respectively. The distribution of the potential prognostic factors with reference to the TIL subgroups is given in **Table 1**. Tumor location, differentiation, and perineural invasion significantly differed among the 2 TIL groups. However, no correlations were found in TIL grade, patient age, patient sex, tumor size, T category, N category, lymphovascular invasion, preoperative serum CEA level, macroscopic ulceration, and tumor border configuration (Table 1).

On the univariate analysis, the factors associated with poorer overall survival were age, differentiation, T category, N category, lymphovascular invasion, perineural invasion, and TIL grade; moreover, the factors associated with poorer disease-free survival were tumor location, tumor size, T category, N category, lymphovascular invasion, perineural invasion, preoperative serum CEA level, macroscopic ulceration, and tumor border con-



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**Table 1. Correlation Between TIL Group and Clinicopathologic Parameters in 546 Patients**

| Parameter | Low TIL Group (n = 104) | High TIL Group (n = 442) | *P* Value |
|---|---|---|---|
| Age, y | | | .80 |
| <65 | 52 (50.0) | 227 (51.4) | |
| ≥65 | 52 (50.0) | 215 (48.6) | |
| Sex | | | .31 |
| Male | 67 (64.4) | 261 (59.0) | |
| Female | 37 (35.6) | 181 (41.5) | |
| Tumor location | | | .04 |
| Colon | 60 (57.7) | 205 (46.4) | |
| Rectum | 44 (42.3) | 237 (53.6) | |
| Tumor size, cm | | | .87 |
| <4.5 | 48 (46.2) | 200 (45.2) | |
| ≥4.5 | 56 (53.8) | 242 (54.8) | |
| Differentiation | | | .002 |
| Well and moderate | 84 (80.8) | 404 (91.4) | |
| Poor and mucinous | 20 (19.2) | 38 (8.6) | |
| T category | | | .53 |
| T1 and T2 | 19 (18.3) | 93 (21.0) | |
| T3 and T4 | 85 (81.7) | 349 (79.0) | |
| N category | | | .30 |
| Negative | 57 (54.8) | 267 (60.4) | |
| Positive | 47 (45.2) | 175 (39.6) | |
| No. of lymph nodes retrieved | | | .17 |
| <12 | 39 (37.5) | 135 (30.5) | |
| ≥12 | 65 (62.5) | 307 (69.5) | |
| Lymphovascular invasion | | | .22 |
| Negative | 75 (72.1) | 344 (77.8) | |
| Positive | 29 (27.9) | 98 (22.2) | |
| Perineural invasion | | | <.001 |
| Negative | 59 (56.7) | 332 (75.1) | |
| Positive | 45 (43.3) | 110 (24.9) | |
| Preoperative CEA, ng/mL | | | .64 |
| <5 | 63 (60.6) | 260 (58.8) | |
| ≥5 | 35 (33.7) | 144 (32.6) | |
| Not available | 6 (5.7) | 38 (8.6) | |
| Postoperative adjuvant therapy | | | .43 |
| Yes | 79 (76.0) | 319 (72.2) | |
| No | 25 (24.0) | 123 (27.8) | |
| Macroscopic ulceration | | | .66 |
| No | 29 (27.9) | 114 (25.8) | |
| Yes | 75 (72.1) | 328 (74.2) | |
| Tumor border configuration | | | .22 |
| Pushing | 16 (15.4) | 49 (11.1) | |
| Infiltrating | 88 (84.6) | 393 (88.9) | |

Abbreviations: CEA, carcinoembryonic antigen; TIL, tumor-infiltrating lymphocyte.

figuration. Multivariate analysis revealed that age, N category, and TIL grade were the independent prognostic factors for overall survival. In addition, tumor location, tumor size, T category, N category, lymphovascular invasion, and perineural invasion were the independent prognostic factors for disease-free survival (**Table 2**). The multivariate analysis confirmed that the TIL grade was significantly and independently associated with a worse prognosis for overall survival but not for disease-free survival.

The median follow-up period of this cohort was 54 months (range, 4-80 months). When the low and high TIL groups were subdivided according to the TNM stage, the 5-year overall survival rate differed between the 2 groups only for the patients with stage III colorectal cancer (**Figure 2**). For patients with stage I and II cancers, the 5-year overall survival rate did not differ between the 2 groups (Figure 2A and B). However, the low TIL group had a significantly lower 5-year overall survival rate than the high TIL group for the patients with stage III colorectal cancer ($P = .005$; Figure 2C). The prognostic significance of the TIL grade for survival, according to the location of tumor, is also observed. We found that the 5-year overall survival differed as related to the TIL grade for colon cancer and rectal cancer, but a significant difference was only observed for the patients with rectal cancer ($P = .003$), not colon cancer ($P = .10$).

**Table 2. Multivariate Analysis of the Prognostic Factors for 5-Year Overall Survival and Disease-Free Survival**

| Factor | Hazard Ratio (CI) | *P* Value |
|---|---|---|
| Overall survival | | |
| Age | 2.147 (1.373-3.358) | .001 |
| Tumor size | 1.337 (0.839-2.129) | .22 |
| Differentiation | 1.450 (0.815-2.581) | .21 |
| T category | 1.379 (0.610-3.118) | .44 |
| N category | 1.650 (1.033-2.637) | .036 |
| Lymphovascular invasion | 1.494 (0.935-2.388) | .09 |
| Perineural invasion | 1.563 (0.987-2.475) | .06 |
| Preoperative CEA | 1.108 (0.692-1.775) | .67 |
| Macroscopic ulceration | 1.178 (0.672-2.063) | .57 |
| TIL grade | 0.548 (0.334-0.897) | .02 |
| Disease-free survival | | |
| Age | 1.207 (0.839-1.735) | .31 |
| Tumor location | 1.629 (1.112-2.385) | .01 |
| Tumor size | 1.632 (1.108-2.405) | .01 |
| Differentiation | 1.071 (0.619-1.855) | .80 |
| T category | 3.651 (1.435-9.291) | .007 |
| N category | 2.207 (1.450-3.359) | <.001 |
| Lymphovascular invasion | 1.876 (1.290-2.728) | .001 |
| Perineural invasion | 1.693 (1.164-2.461) | .006 |
| Preoperative CEA | 1.118 (0.763-1.636) | .57 |
| Postoperative adjuvant therapy | 1.230 (0.977-3.005) | .06 |
| Macroscopic ulceration | 1.211 (0.731-2.007) | .46 |
| Tumor border configuration | 2.727 (0.984-7.561) | .05 |
| TIL grade | 0.725 (0.472-1.115) | .14 |

Abbreviations: CEA, carcinoembryonic antigen; TIL, tumor-infiltrating lymphocyte.

To determine whether TIL grade predicted survival for the patients with stage III cancer, we performed survival analyses of the 218 patients with node-positive tumors according to the TIL grade and the N category (**Table 3**). For the patients with pN1 tumors, the overall survival, disease-free survival, local recurrence–free survival, and distant metastasis–free survival rates did not significantly differ according to the TIL grade ($P = .73$, $P = .95$, $P = .21$, and $P = .60$, respectively). However, for the patients with pN2 tumors, the overall survival, disease-free survival, local recurrence–free survival, and distant metastasis–free survival rates among the TIL groups significantly differed ($P = .002$, $P = .008$, $P = .04$, and $P = .01$, respectively). We also performed survival analyses according to the TIL grade in the 281 patients with rectal cancer. We found that the TIL grade had a prognostic significance on distant metastasis–free survival (61 patients in the low TIL group and 81 in the high TIL group)



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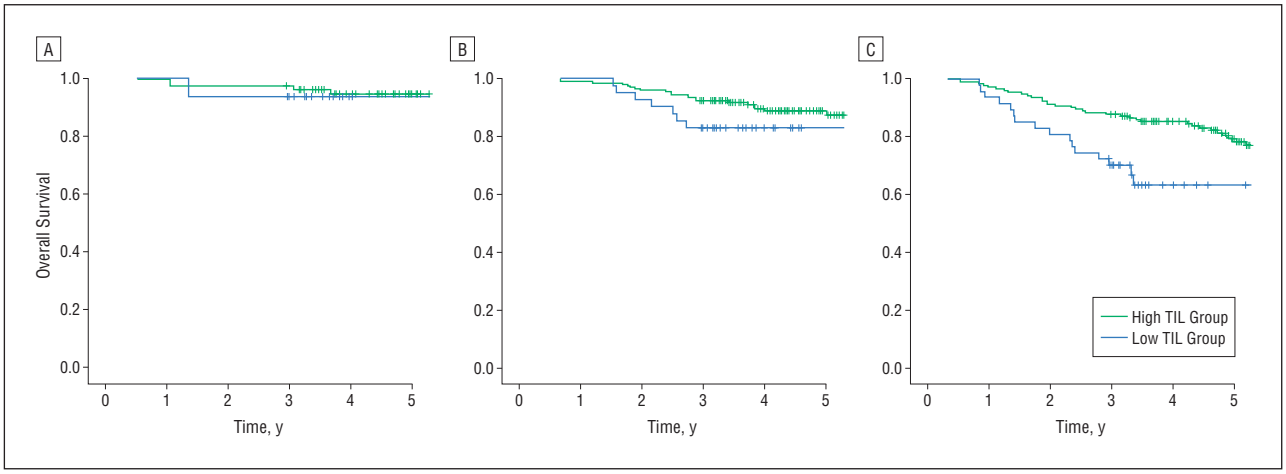


**Figure 2.** Kaplan-Meier curves of overall survival according to the TNM stage and the tumor-infiltrating lymphocyte (TIL) grade. A, Ninety-four patients with stage I disease ($P$=.74); B, 234 patients with stage II disease ($P$=.24); and C, 218 patients with stage III disease ($P$=.005).

**Table 3. Survival Rates of the 218 Patients With Stage III Tumor According to the N Category and TIL Grade**

| Factors | No. of Patients | 5-Year Overall Survival, % | 5-Year Disease-Free Survival, % | 5-Year Local Recurrence–Free Survival, % | 5-Year Distant Metastasis–Free Survival, % |
|---|---|---|---|---|---|
| N1 category | | | | | |
| Low TIL grade | 26 | 80 | 76 | 100 | 76 |
| High TIL grade | 111 | 81 | 75 | 93 | 81 |
| *P* value | | .73 | .95 | .21 | .60 |
| N2 category | | | | | |
| Low TIL grade | 21 | 43 | 19 | 69 | 26 |
| High TIL grade | 60 | 73 | 49 | 90 | 55 |
| *P* value | | .002 | .008 | .04 | .01 |

Abbreviation: TIL, tumor-infiltrating lymphocyte.

and liver metastasis–free survival (83 patients in the low TIL group and 93 in the high TIL group) for the patients with rectal cancer ($P$=.002 and $P$=.04, respectively). However, the 5-year local recurrence–free survival rate was not related to the TIL grade (90 patients in the low TIL group and 91 in the high TIL group; $P$=.81).

## COMMENT

We examined the prognostic significance of a lymphocytic reaction to tumor in a population of patients with stage I to III colorectal cancer who were concurrently assessed for other clinicopathologic predictors of the patient outcome. We observed a significant relation between the TIL grade and patient survival, which was independent of the patient characteristics.

A lymphocytic reaction to colorectal cancer has been associated with longer survival in patients with colorectal cancer,[1-5] and it may be an indicator of a host immune response to tumor cells that leads to improved survival.[13,14] Despite evidence supporting the prognostic value of the TIL grade, the method has not been widely adopted because of the previous controversial results. Ogino et al[6] suggested that for the lymphocytic reaction score using the 4 components of Crohn-like reaction, peritumoral reaction, intratumoral periglandular reaction, and TIL grade, the TIL grade seemed to be less significantly associated with patient survival than the other 3 components. On the other hand, Klintrup et al[1] found a significant relationship between a low-grade inflammatory infiltrate at the invasive margin and poor survival in a study of 372 patients who underwent surgery for colorectal cancer. Roxburgh et al[2] also reported that the TIL grade was independently associated with cancer-specific survival in patients who were undergoing potentially curative resection for colorectal cancer. The results of a Cox regression analysis in our study confirmed that a low TIL grade was the independent predictor of poor overall survival for patients with colorectal cancer, which is consistent with the results of Klintrup et al and Roxburgh et al.

We found a stage-specific prognostic role of the TIL grade. When the categories were broken down according to the TNM stage, the TIL grade was a significant prognostic factor for both the overall survival and disease-free survival only for the patients with stage III tumor (especially in the N2 category) but not for the patients with stage I and II tumors. Morris et al[15] suggested that TIL grade had no prognostic significance in a large cohort of 1306 patients with stage II colon cancer. More recently, using an another cohort of 1156 patients with stage III colon cancer, they showed that TIL grade had



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predictive value for a positive response to chemotherapy.[3] Prall et al[16] also reported that patients with stage III colorectal cancer with high tumor densities of $CD8^+$ cells showed excellent survival compared with those with low densities. Taken together, the TIL grade may have a prognostic role for the patients with a more aggressive phenotype of colorectal cancer.

It is generally known that colon and rectal tumors may be considered as separate entities, and they have different biologic behavior in terms of the recurrence pattern or patient survival. Nagtegaal et al[17] showed that a peritumoral inflammatory cell reaction has a positive influence on the prognosis of patients with rectal cancer. In the analysis of colorectal cancer, previous studies[6,18] have indicated that TILs may be different according to the location of the tumor. Risio et al[19] suggested that in rectal cancer, peritumoral inflammatory cell reaction has been shown to have a positive influence on prognosis, but in colon cancer, these findings have not been corroborated. We concur with this finding and revealed that the TIL grade was a significant prognostic factor for both the overall survival and disease-free survival of patients with rectal cancer but not for patients with colon cancer. In our study, the survival curves differed as related to the TIL grade for the colon cancer, but a significant difference was not observed. Further studies are needed to confirm these prognostic differences according to the location of tumor.

The mechanism underlying the survival advantage associated with a lymphocytic reaction to tumor remains uncertain. Moreover, a few studies have examined the possible correlation between the TIL grade and various cliniopathologic factors. In the current study, we observed that the TIL grade was associated with indolent tumor behavior, such as tumor differentiation and perineural invasion: a low TIL grade was significantly correlated with a poorly differentiated status and perineural invasion. Nakano et al[20] clearly demonstrated that TIL grades were significantly correlated with a dedifferentiated tumor grade in a study of renal cancer, and this finding concurs with our observation. Perez et al[21] suggested that peritumoral inflammatory infiltrate was not associated with both lymphovascular invasion and perineural invasion in radiated rectal cancer. However, the results of the present study are consistent with a previous study[13] in which TIL grade was associated with lymphovascular invasion and/or perineural invasion. Pagès et al[13] demonstrated a relation between the vascular emboli, lymphatic invasion, and perineural invasion (collectively referred to VELIPI) and inflammation, as well as patient survival. They showed that the presence of effector memory T cells within colorectal cancer was significantly associated with VELIPI-negative tumors and a high density of infiltrating $CD45RO^+$ cells was correlated with a good clinical outcome. Some authors[22] have reported that a lymphocytic reaction to colorectal cancer has been associated with an increased lymph node count. However, no association between the TIL grade and the total number of harvested lymph nodes, lymphovascular invasion, and the number of positive lymph nodes was observed in our analysis, which may in part be attributable to differences in the study populations among the various investigations.

We found that the tumor border configuration was a significant prognostic factor for disease-free survival on the univariate analysis but not on multivariate analysis. Zlobec et al[23] suggest that the infiltrating growth pattern at the invasive tumor margin was a significant independent prognostic factor for patients with colorectal cancer. A possible explanation for the discrepant results is the relatively subjective and difficult assessment of the tumor border configuration among the various investigations.

One of the major limitations of the present retrospective study was that tumors with TILs were identified from the pathology reports. Our results will require not only validation by other research groups but also confirmation in a prospective cohort study. In addition, one question that needs to be resolved is whether subtyping of infiltrating lymphocytes provides any additional information beyond the histopathologic evaluation of the lymphocytic reaction patterns. Previous studies[13,24,25] have shown that the presence, degree, or localization of the infiltrates according to a specific subtype of lymphocytes (ie, $CD45RO^+$, $CD8^+$, or $FOXP3^+$) is associated with the clinical outcome in patients with colorectal cancer. However, none of these studies has comprehensively evaluated the distinct histopathologic patterns of the TILs described in the current study. Additional studies are necessary to clarify whether lymphocyte subtyping adds any additional or independent prognostic information beyond the histopathologic evaluation of the TIL grade.

This observation has several implications for clinical practice. First, our results may support the role of the host immune reaction to tumor as an independent prognostic factor among the patients with colorectal cancer. The TIL grade can be assessed on routine histopathologic examination of the resected colorectal cancer, and an evaluation of this may be useful for prognostic stratification of the patients with colorectal cancer. Second, our study also supports the use of immune cells as potential anticancer therapy. The stimulation of the immune response has a number of theoretical advantages over other forms of cancer treatment.[26] Targeting host immune cells may avoid the emergence of resistance mutations, which is commonly observed during targeted therapy against molecules within the cancer cells. Finally, because our study primarily defined the prognostic role of the TIL grade in patients with colorectal cancer, further trials using the stratification by the TIL grade need to be performed.

In conclusion, our study suggests that an inflammatory cell reaction at the tumor invasive border is a useful predictor of survival after colorectal cancer surgery, particularly for patients with stage III disease or rectal cancer. Future studies are needed to confirm these results and to elucidate the exact mechanisms of a lymphocytic reaction to tumor.

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## INVITED CRITIQUE

# Survival Prediction for Patients With Colorectal Carcinoma Incorporating Tumor-Infiltrating Lymphocyte Grade

Huh et al[1] of the Departments of Surgery and Pathology, Chonnam National University Hwasun Hospital and Medical School, Gwangju, Korea, evaluated a population of 546 patients who were retrospectively analyzed after undergoing curative surgery for primary nonmetastatic colorectal cancer (2004-2007). The authors determined the prognostic value of macroscopic ulceration tumor border configuration and tumor-infiltrating lymphocytes (TILs) determined at the invasive margin. Thereafter, the authors differentiated the individual tumor characteristics of high vs low TIL grade and correlated these with commonly identified pathologic tumor characteristics (poorly differentiated vs perineural invasive status). Of interest, with a median 54-month follow-up interval, overall survival and disease-free survival rates were statistically significantly lower for the low TIL group vs the high TIL group of patients with stage III colorectal carcinoma ($P=.005$ and $P=.03$, respectively). The effect on overall and disease-free survival was not evident in patients with stage I and II can-



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