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ORIGINAL ARTICLE

Predicting factors of postoperative relapse in $T_{2\text{-}4}N_0M_0$ colorectal cancer patients via harvesting a minimum of 12 lymph nodes

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Abstract
Background and aim The aim of this retrospective study was to determine which clinicopathological factors influenced the incidence of postoperative relapse and overall survival rates after radical resection of $T_{2\text{-}4}N_0M_0$ colorectal cancer (CRC) patients via harvesting a minimum of 12 lymph nodes.
Materials and methods Between January 2001 and June 2006, a total of 342 $T_{2\text{-}4}N_0M_0$ CRC patients who underwent radical resection were retrospectively analyzed in Kaohsiung Medical University Hospital. Of these 342 patients, 155 were observed by harvesting a minimum of 12 lymph nodes. These 155 patients were followed up intensively, and their outcomes were investigated retrospectively.
Results Of 155 patients, 83 were men (53.5%) and 72 (46.5%) were women. The mean age was 65.5±11.1 years (range, 24–89 years). The median follow-up period was 49 months (range, 19–80 months). The present data showed invasive depth (P=0.012), vascular invasion (P<0.001), and perineural invasion (P=0.009) as significantly prognostic factors for postoperative 5-year relapse rate by Kaplan–Meier analysis. Likewise, invasive depth (P=0.013), vascular invasion (P<0.001), and perineural invasion (P=0.008) were significant factors for postoperative 5-year survival rate. Meanwhile, using a Cox proportional hazards analysis, depth of tumor invasion (P=0.026) and vascular invasion (P=0.001) were the independent predictors for postoperative relapse. Furthermore, the presence of vascular invasion was considerably correlated to the higher postoperative relapse rate and the poorer overall survival rates by survival analyses (P<0.0001).
Conclusions Besides the conventional depth of tumor invasion, this study highlights the potential for using vascular invasion as a means of identifying a subgroup of $T_{2\text{-}4}N_0M_0$ CRC patients with adequate lymph node harvest at higher risk who would potential benefit from adjuvant therapy after surgery.

Keywords Predicting factors · Postoperative relapse · $T_{2\text{-}4}N_0M_0$ colorectal cancer · Adequate lymph node retrieval

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Introduction

Colorectal cancer (CRC) is one of the most frequent malignancies and is also the third major cause of cancer-related death in Taiwan, with more than 9,000 new cases and 4,000 deaths per year (http://www.doh.gov.tw/statistic/

index.htm;accessed in August 2008). The presence or absence of lymph node metastasis is pivotal in predicting the clinical outcome of patients who have undergone radical surgery for CRC, often determining the use of adjuvant therapy and providing important prognostic information [1]. There is a consistent risk of substaging tumors and under-staging patients when insufficient lymph nodes are retrieved. Therefore, an accurate assessment of pathologic status of the tumor lymph nodes in the resected specimen is essential for reducing the risk of under-staging. To date, the International Union against Cancer staging system remains the most important determinant of the decision to institute postoperative chemotherapy in both colonic and rectal cancer [2]. However, some investigators report that this is insufficient and emphasize the need to develop variables related to tumor growth characteristics [3]. The selection of patients for individualized follow-up and adjuvant therapy after radical resection of CRC depends on finding reliable prognostic criteria for recurrence. However, such criteria are not universally accepted, and follow-up is often standardized for all patients without regard for each individual level of risk of recurrence. Such a system of follow-up is not cost-effective.

As in our previous study [4], an increase in the number of tumor-free lymph nodes has been suggested as clinically important, and this parameter should be taken into consideration in $T_{2\text{-}4}N_0M_0$ CRC patients. In 1990, the Working Party Report to the World Congress of Gastroenterology in Sydney recommended that a minimum of 12 lymph nodes should be recovered for CRC patients [5]. The aim of this study was to investigate the clinical or pathologic variables that could be used to identify a subgroup with a high risk of postoperative 5-year relapse rate and 5-year survival rate among those $T_{2\text{-}4}N_0M_0$ CRC patients who had had a minimum of 12 lymph nodes retrieval.

Materials and methods

Between January 2001 and June 2006, a total of 342 consecutive patients who underwent radical surgery for $T_{2\text{-}4}N_0M_0$ CRC at Kaohsiung Medical University Hospital were reviewed. Clinical stage and pathological features of primary tumors were defined according to the criteria of the American Joint Commission on Cancer [2]. Tumors were classified as $T_{2\text{-}4}N_0M_0$ CRC, that is, tumors that have invaded between the muscularis propria and the pericolic–perirectal tissue of the large bowel wall without lymph node metastases. Radical (R_0) resection is defined as any gross residual tumor that did not remain in the surgical bed, and the surgical resection margin is pathologically negative for tumor invasion [4]. Total mesorectal excision was performed in all patients with tumors of the middle and lower rectum and a distal clearance of at least 2 cm from the edge of the tumor. Of these, 62 $T_{2\text{-}4}N_0M_0$ CRC patients who had received postoperative adjuvant chemotherapy were excluded to prevent the possible chemotherapeutic effects on patients' prognosis, and the remaining 280 were enrolled into this study. The range of lymph node count for 280 $T_{2\text{-}4}N_0M_0$ CRC patients was from three to 66, with the median of ten lymph nodes. Of these 280 patients, 125 patients with lymph node retrieval of less than 12 were excluded from the study, leaving a final total of 155 study patients (155/280, 55.4%) who had tumors classified as $T_{2\text{-}4}N_0M_0$ through harvesting a minimum of 12 lymph nodes. The development of new recurrent or metastatic lesions after operation was defined as a postoperative relapse. The type of postoperative relapse was designated as local recurrence (tumor growth restricted to the anastomosis or the region of primary operation) or distant metastases (distant metastases or diffuse peritoneal seeding).

All surgical specimens were fixed in 10% formalin solution for at least 48 h and routinely processed for paraffin embedding. The tumor was cut serially, and several representative sections were taken for microscopic examination by a senior pathologist. Care was taken to ensure that sections from the deepest area of tumor penetration were included. All lymph nodes were retrieved only by means of sight and palpation. The cut sections were stained with hematoxylin–eosin and bivalving. Information regarding gender, age, depth of tumor invasion, vascular invasion, perineural invasion, tumor location, size, histology, and type were recorded. The following histopathologic features were assessed for each tumor specimen including invasive depth (classified as T2, T3, and T4) and tumor grade (classified as well, moderately, and poorly differentiated). Vascular inva-

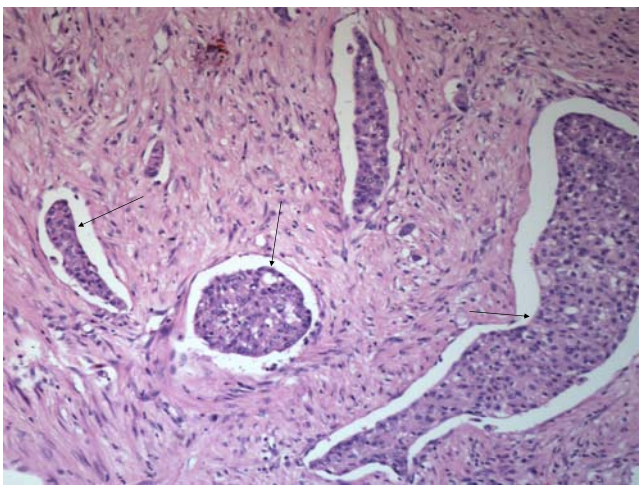

Fig. 1 Histologic diagnostic criteria for vascular invasion: a positive judgment was made when prominent vascular permeation of cancer cells was identified (*arrows*). Hematoxylin–eosin stain, original magnification, 20×

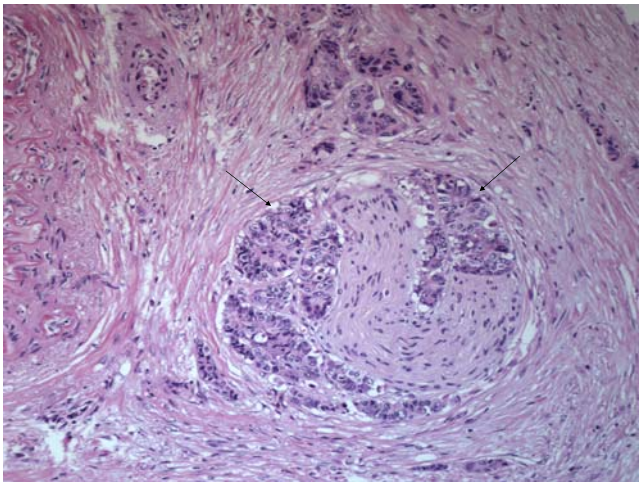

Fig. 2 Histologic diagnostic criteria for perineural invasion: a positive judgemnt was made when cancer cells were observed inside the perineurium. This photomicrograph shows the marked perineural infiltration of cancer cells (*arrows*). Hematoxylin–eosin stain, original magnification, 20×

sion was classified as one or more of the followings: tumor cells lining the venous endothelial surface, tumor cell thrombi inside the lumen of the vein, or destruction of the vein wall by tumor cells (Fig. 1). Perineural invasion was defined when a positive judgment was made when cancer cells were observed extraneurally (Fig. 2).

The median follow-up period was 49 months (range, 19–80 months). The median follow-up for patients with relapse and without relapse was 32 months and 54 months, respectively. All 155 patients were routinely followed up on until their deaths. Patients were followed up routinely at quarterly intervals for the first 2 years, six-monthly intervals for the next 2 years, and yearly thereafter. At each visit, carcinoembryonic antigen levels were assayed. Colonoscopy was performed within 1 year following surgery and yearly thereafter. Ultrasound of the liver and chest radiographs were performed at 6 months and then at yearly intervals or when the patient was symptomatic. Computed tomography scans were performed once per year. The development of new local recurrent or distal metastatic lesions after operation was defined as a postoperative relapse. The median time to postoperative relapse of these patients was 30.8±11.0 months.

All data were analyzed by the Statistical Package for the Social Sciences, version 11.5 (SPSS, Chicago, IL, USA). Results were expressed as mean±SD. For the univariate statistical analysis, chi-square test was used where applicable. A Cox proportional hazards model with forward stepwise variable selection was used for multivariate testing

Table 1 Clinicopathologic characteristics of 155 $T_{2\text{-}4}$NoMo (lymph node retrieval ≥12) colorectal cancer patients

Variables	Number (%)
Gender	
Male	83 (53.5)
Female	72 (46.5)
Age (years)	
<60	49 (31.6)
≥60	106 (68.4)
Maximum size of tumor (cm)	
<5	75 (48.4)
≥5	80 (51.6)
Location	
Colon	113 (72.9)
Rectum	42 (27.1)
Depth of tumor invasion	
T2	29 (18.7)
T3	122 (78.7)
T4	4 (2.6)
Vascular invasion	
Yes	39 (25.2)
No	116 (74.8)
Perineural invasion	
Yes	42 (27.1)
No	113 (72.9)
Histology	
Well-differentiated	17 (10.9)
Moderately differentiated	123 (79.3)
Poorly differentiated	15 (9.8)

Table 2 Correlation between postoperative 5-year relapse rate and clinicopathologic features of 155 $T_{2\text{-}4}$NoMo (lymph node retrieval ≥12) colorectal cancer patients using Kaplan–Meier analysis and differences were compared by log-rank test

	Postoperative 5-year relapse rate (%)	*P*
Gender		
Male	19.1	0.594
Female	18.7	
Age (years)		
<60	14.3	0.870
≥60	14.2	
Maximum size (cm)		
<5	12	0.542
≥5	16.3	
Location		
Colon	15.0	0.579
Rectum	11.9	
Depth of tumor invasion		
T2	0	0.012
T3+T4	23.4	
Vascular invasion		
Yes	37.3	<0.001
No	8.5	
Perineural invasion		
Yes	26.2	0.009
No	10.6	
Histology		
Well + moderately differentiated	13.6	0.712
Poorly differentiated	20.0	

Table 3 Correlation between postoperative 5-year survival rate and clinicopathologic features of 155 $T_{2\text{-}4}$NoMo (lymph node retrieval ≥12) colorectal cancer patients using Kaplan–Meier analysis and differences were compared by log-rank test

	Postoperative 5-year survival rate (%)	*P*
Gender		
Male	81.9	0.338
Female	80.2	
Age (years)		
<60	81.2	0.886
≥60	81.8	
Maximum size (cm)		
<5	83	0.301
≥5	79.5	
Location		
Colon	79.3	0.304
Rectum	87.5	
Depth of tumor invasion		
T2	100	0.013
T3+T4	76.7	
Vascular invasion		
Yes	55.7	<0.001
No	87.3	
Perineural invasion		
Yes	68.0	0.008
No	88.8	
Histology		
Well + Moderately differentiated	81.8	0.712
Poorly differentiated	78.8	

of those factors found to be significant by univariate analysis (the inclusion factors were those with *P* value less than 0.05 by univariate analysis). The cumulative survival and overall relapse rates were calculated by the Kaplan–Meier method, and the differences in survival rates were analyzed by the log-rank test. A *P* value less than 0.05 was considered to be statistically significant.

Results

The clinical and pathologic data regarding the 155 $T_{2\text{-}4}N_0M_0$ CRC patients by recovery of a minimum of 12 lymph nodes are summarized in Table 1. Eighty-three men (53.5%) and 72 women (46.5%) were recorded. The mean age was 65.5±11.1 years (range, 24–89 years). The number of sites where the tumor was at the colon was 113 (72.9%) and 42 (27.1%) at the rectum. One hundred twenty-two patients (78.7%) were classified as T3 tumor invasion, 29 patients (18.7%) as T2, and only four patients (2.6%) as T4. Thirty-nine patients (25.2%) and 42 (27.1%) were found to have vascular and perineural invasion, respectively. With regard to histological types of these tumors, 17 (10.9%) were well-differentiated carcinoma, 123 (79.3%) were moderately differentiated carcinoma, and 15 (9.8%) were poorly differentiated carcinoma. Twenty-two patients were found to develop postoperative relapse in the follow-up period. Of 22 patients, six cases ultimately developed local recurrence (27.3%) and the other 16 cases (72.7%) found with distant metastases.

Using Kaplan–Meier analysis for 5-year relapse rate of 155 $T_{2\text{-}4}N_0M_0$ CRC patients with 12 lymph node retrievals, we found that depth of tumor invasion (P=0.012), vascular invasion (P<0.001), and perineural invasion (P=0.009) were statistically significant. However, no significant differences regarding gender, age, tumor size, tumor location, tumor grade, and tumor type were observed (Table 2). Moreover, using Kaplan–Meier analysis for 5-year survival rate of 155 $T_{2\text{-}4}N_0M_0$ CRC patients with 12 lymph node retrievals, we found that only depth of tumor invasion (P=0.013), vascular invasion (P<0.001), and perineural invasion (P=0.008) were statistically significant (Table 3). Using the Cox proportional hazards analysis, both depth of tumor invasion (P=0.026) and vascular invasion (P=0.001) were demonstrated to be independent predictors for postoperative relapse in $T_{2\text{-}4}N_0M_0$ CRC patients with lymph node retrieval at a minimum of 12 (Table 4). The overall 5-year relapse rate and 5-year survival rate in 155 $T_{2\text{-}4}N_0M_0$ CRC was 14.2% (22/155) and 86.5% (132/155), respectively. Figures 3 and 4 depict the overall relapse rate and overall survival rate of $T_{2\text{-}4}N_0M_0$ CRC patients with lymph node retrieval at a minimum of 12 according to the classification of vascular invasion (negative or positive), respectively. Both overall relapse rate and survival rate of those patients who had vascular invasion was significantly inferior to that of those who had no vascular invasion using a log-rank test. The overall 5-year relapse rate for $T_{2\text{-}4}N_0M_0$ CRC patients with vascular invasion or without vascular invasion was 37.3% and 8.5%, respectively (P<0.0001). Furthermore, the overall 5-year survival rate for $T_{2\text{-}4}N_0M_0$ CRC patients

Table 4 Correlation between postoperative relapse and clinicopathologic features of 155 $T_{2\text{-}4}$NoMo (lymph node retrieval ≥12) colorectal cancer patients using Cox proportional hazards analysis

Variables	β	Standard error	*P*	Hazard ratio	95% Confidence interval
Depth (T3+T4/T2)	1.278	0.547	0.026	2.108	1.401–3.795
Vascular invasion (Yes/No)	1.663	0.478	0.001	5.273	2.065–13.462
Perineural invasion (Yes/No)	0.216	0.459	0.637	1.242	0.505–3.050

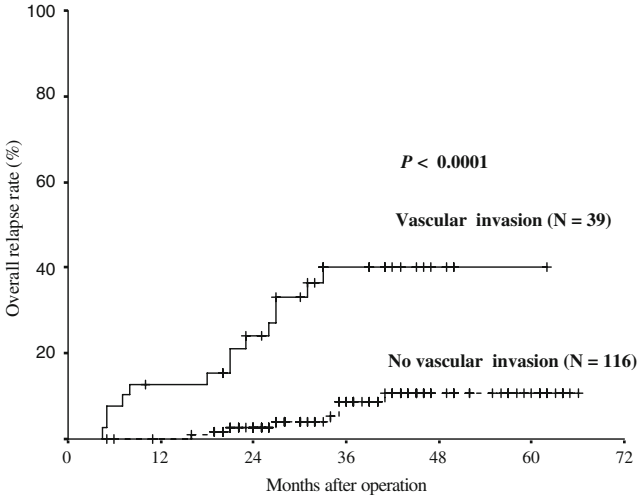

Fig. 3 Cumulative overall postoperative relapse rates of $T_{2\text{-}4}N_0M_0$ colorectal cancer patients with lymph node retrieval at a minimum of 12 were analyzed by the Kaplan–Meier method with the differences compared by a log-rank test. Patients with no vascular invasion had a lower postoperative relapse rate than those with vascular invasion ($P<0.0001$)

with vascular invasion or without vascular invasion was 55.7% and 87.3%, respectively ($P<0.0001$). Additionally, the survival rate of those patients with postoperative relapse was significantly lower than that of those who had no postoperative relapse (Fig. 5; $P<0.0001$).

Discussion

Numerous studies during the past 60 years have shown that long-term survival following CRC resection is inversely

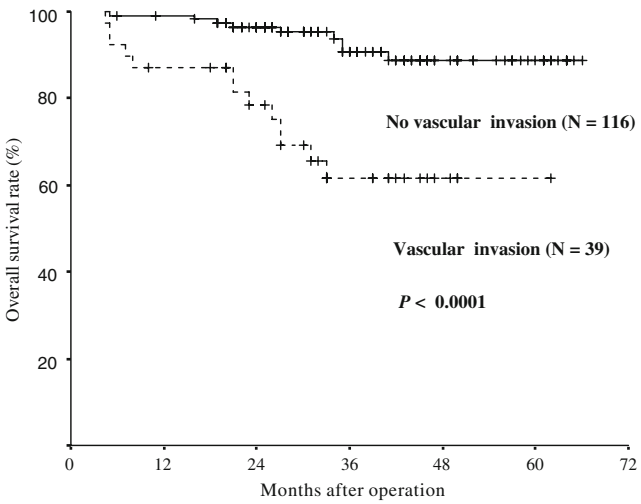

Fig. 4 Cumulative overall 5-year survival rates of $T_{2\text{-}4}N_0M_0$ colorectal cancer patients with lymph node retrieval at a minimum of 12 were analyzed by the Kaplan–Meier method with the differences compared by a log-rank test. Patients without vascular invasion had a better survival rate than those with vascular invasion ($P<0.0001$)

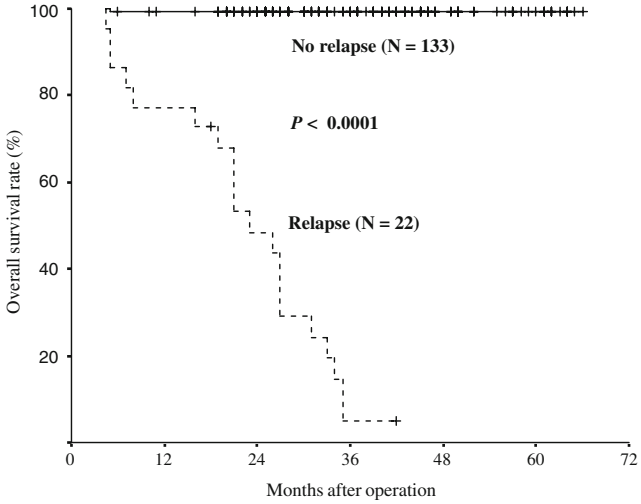

Fig. 5 Patients with postoperative relapse had a prominently poor overall 5-year survival rates than without postoperative relapse ($P<0.0001$)

related to the degree of penetration of the primary tumor through the bowel wall and presence of metastases in adjacent lymph nodes [6–8]. In our previous study [4], we have suggested that the increase of examined numbers of tumor-free lymph nodes would probably decrease the incidence of under-staging or alter further therapies for $T_{2\text{-}4}N_0M_0$ CRC patients and relates to the postoperative relapse or overall survival. The American Joint Committee on Cancer also recommends assessment of 12 nodes or more for accurate staging [9]. Consequently, a further effort to identify $T_{2\text{-}4}N_0M_0$ CRC patients at high risk of tumor recurrence and metastasis is of utmost importance for patients who have had a minimum of 12 lymph nodes identified and studied.

Fujita et al. [10] reported that depth of tumor invasion was a significant prognostic factor of postoperative relapse and survival rate in CRC patients undergoing curative resection. As per our previous report [4], depth of tumor invasion was a significant prognostic factor of postoperative relapse for $T_{2\text{-}4}N_0M_0$ CRC patient. Similarly, it was found that depth of tumor invasion was a significant prognostic factor in postoperative relapse for $T_{2\text{-}4}N_0M_0$ CRC patients with a minimum of 12 lymph nodes in this present observation. From this viewpoint, identifying the predictors of postoperative relapse for $T_{2\text{-}4}N_0M_0$ CRC patients who have accurate staging and adequate lymph node retrieval is a crucial issue.

Consistent with previous reports [11, 12], the incidence of vascular invasion in our current investigation was 25.2%. Information concerning vascular invasion is easily accessible and may be used to enhance the power of existing staging systems to develop a more accurate prognostic profile. Some authors have reported that the odds ratio of lymph node metastasis increased 18-fold for CRC patients who had venous invasion compared with patients who did

not [13]. It was reported that vascular invasion may be useful in characterizing high-risk patients with Dukes' B CRC disease who had a minimum of 12 lymph nodes to be identified [14]. Similarly, our data showed that vascular invasion was not only an independent predictor of postoperative 5-year relapse but also a significant factor of postoperative 5-year survival rate for $T_{2\text{-}4}N_0M_0$ CRC patients in spite of adequate lymph node dissection. By multivariate analyses, it seems that the vascular invasion is probably more important for the prediction of postoperative relapse and the prognosis of these patients. Regarding the sites of postoperative relapse in this study, among 14 patients with vascular invasion, nine patients (64.3%) were found to have liver metastases. Krasna et al. [11] also found that risk of developing liver metastasis was significantly increased when vascular involvement was present (60% vs. 17%). Meanwhile, some authors have reported a close relationship between venous invasion and distant metastases [15–17]. The presence of vascular invasion in tumor tissues may lead to distant metastasis via circulating cancer cells. Conversely, Tsuchiya et al. [18] showed blood vessel involvement in 70% of 124 patients with surgically cured CRC, and their multivariate analysis did not show a statistically significant impact on survival, though most of the previous studies have shown a decreased overall survival in CRC patients in whom vascular invasion has been demonstrated [11, 19]. The possible reason may be that vascular invasion is not an important prognostic factor among patients with Dukes' B CRC or rectal cancer [20, 21] because they claimed that the intermediate stage of vascular invasion and loading by tumor cells dose not always precede or predispose lymph node metastases, nor would it unequivocally serve as an important independent prognostic factor. However, Horn et al. [12] showed that 5-year actuarial survival was reduced when vascular invasion was demonstrated in rectal cancer (29.8% vs. 68.9%). In our current study, the 5-year survival rate was reduced when vascular invasion was found in those $T_{2\text{-}4}N_0M_0$ CRC patients who had a minimum of 12 lymph nodes retrieved (55.7% vs. 87.3%). Clearly, it shows that vascular invasion might influence the overall survival rates of CRC patients when lymph nodes were harvested adequately. Therefore, the introduction of more aggressive adjuvant chemotherapy would be a potentially vital topic to improve clinical outcome of these patients.

Perineural invasion was found in 27.1% of our current study, which is similar to the 30% found by Seefeld and Bargen [22] who were the first to study perineural invasion in CRC in depth. Several investigators have shown that perineural invasion is a vital prognostic factor in patients with rectal cancer [23] or CRC [7]. Moreover, Bruinvels et al. [24] disclosed that perineural invasion had an impact on the 5-year survival rate in CRC patients without lymph node metastasis. Shin et al. [10] reported that perineural invasion status can be used to facilitate the selection of CRC patients for adjuvant chemotherapy and should be described in routine pathology reports. Furthermore, they defined the perineural invasion as the finding of cancer cells inside the perineurium intraneurally and extraneurally. In this study, perineural invasion was a significant prognostic factor in univariate analysis, but not in multivariate analysis. The results of our study differed from those of some investigators because pathologically, we only examined extraneurally perineural invasion. Consequently, it may be necessary to establish diagnostic guidelines for the definition of perineural invasion.

In summary, the present investigation highlights the potential for using vascular invasion as a means of identifying a subgroup of $T_{2\text{-}4}N_0M_0$ CRC patients at a higher risk who may benefit from aggressive adjuvant therapy after surgery. However, additional work in larger patient populations by means of long-term follow-up studies is mandatory for confirming this hypothesis.

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