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Original article

Effect of Tumor Deposits on Overall Survival in Colorectal Cancer Patients with Regional Lymph Node Metastases

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Abstract

Objectives: The staging system of the International Union Against Cancer considers tumor deposits to be N1c in patients with no regional lymph node metastasis, but the significance of tumor deposits in patients with regional lymph node metastases is unclear. We investigated the effect of tumor deposits on overall survival in colorectal cancer patients with regional lymph node metastases.

Patients and Methods: From 2000 to 2008, 551 patients underwent resections for colorectal cancer at our medical center. We excluded 87 patients who had distant metastases or had received neoadjuvant chemotherapy or radiotherapy from our study and statistically analyzed the remaining 464 patients.

Results: Stepwise multivariate Cox proportional hazards analysis in patients with regional lymph node metastases showed only tumor deposits to be significant for overall survival (hazard ratio: 2.813; $P = 0.0002$). Recurrence was seen in 49.2% of patients with tumor deposits (30/61) compared with 14.4% of patients without them (58/403; $P < 0.0001$). Tumor deposits did not show the same effect on overall survival as lymph node metastases.

Conclusions: Tumor deposits were significantly associated with poorer overall survival in colorectal cancer patients with regional lymph node metastases. The effect of tumor deposits on overall survival was between that of lymph node metastasis and distant metastasis.

Key words: tumor deposits, overall survival, colorectal cancer, lymph node metastasis

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Introduction

Cancer staging is an important factor in predicting patient survival and deciding the best treatment. In Japanese classifications of colorectal cancer (CRC), tumor deposits (TDs) are described as extramural discontinuous cancer spread without residual lymph node structures. Tumor nodules are incorporated into the category of lymph node metastasis[1]. In contrast, in the Tumor Node Metastasis (TNM) staging system of the International Union Against Cancer (UICC), the place of TDs in the staging system has changed several times. In the 5th edition (1997), tumor nodules > 3 mm in diameter were classified as regional lymph node metastases (RLNMs). Tumor nodules ≤ 3 mm were classified in the T category as discontinuous extensions. In the 6th edition (2002), classification by size was abandoned. Tumor nodules with smooth contours were classified as RLNMs. Tumor nodules with irregular contours were classified in the T category and also coded as V1 (microscopic venous invasion) or V2 (if grossly evident). Nagtegaal and Quirke advocated that inclusion of TDs as lymph node involvement in the 6th edition was not supported by the literature or recent studies on reproducibility[2]. In the 7th edition (2009), classification based on shape was abandoned. TDs (satellites) were defined as macroscopic or microscopic nests or nodules of a primary carcinoma in the lymph drainage area of pericolorectal adipose tissue in the absence of histological evidence of residual lymph node in the nodule[3]. TDs were classified as N1c if they were seen in patients with no lymph node metastasis; the T classification was not changed. If a pathologist confirmed that they had totally replaced lymph nodes, they were recorded as positive lymph nodes. TDs were considered to be N1c in patients with no RLNM, but the significance of TDs in patients with RLNMs is unclear. Here, we investigated the impact of TDs on overall survival (OS) in CRC patients with RLNMs.

Patients and Methods

Between 2000 and 2008, a total of 551 patients underwent tumor resection for CRC at our medical center. We excluded 87 patients who had distant metastases or had

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received neoadjuvant chemotherapy or radiotherapy. The remaining 464 patients were analyzed statistically. We performed possible curative operations for them. Patients with RLNMs or TDs received adjuvant chemotherapy. Our adjuvant chemotherapy had three patterns: tegafur-uracil, tegafur-gimeracil-oteracil, or tegafur-uracil/calcium folinate. Our postoperative follow-up was similar till five years after surgery. The mean follow-up period was 63 months.

We performed autonomic nerve-serving surgery in the rectum, which was defined as the large intestine located between the inferior border of the second sacral vertebra and the superior border of the puborectalis muscle. Tumor depth of invasion was classified based on the UICC TNM 7th edition. Lymph node metastasis was classified as follows: pN0, no evidence of lymph node metastasis; pN1, 1–3 lymph node metastases; and pN2, ≥ 4 lymph node metastases.

After resections, surgeons dissected fresh resected specimens and detected nodules in the fatty tissue macroscopically or by manipulation. Nodules were fixed in formalin solution and stained with hematoxylin and eosin. A pathologist verified the presence of lymph node metastases. When cancer nests were found in nodules with no evidence of residual lymph nodes, they were defined as TDs. They were recorded separately from lymph node metastases.

Relapse-free survival (RFS) and OS were considered based on the following 10 variables: gender, age at surgery, circumferential occupancy, tumor location, tumor depth, histology, lymph node metastasis, TDs, lymphatic invasion, and venous invasion. RFS was defined as time from primary surgery to first documented recurrence or death from any cause. OS was defined as time from primary surgery to death from any cause.

Univariate analysis of survival predictors was assessed by the Kaplan-Meier method. Differences for survival were evaluated by log-rank tests. Variables found to be significant in univariate analysis were tested by the stepwise Cox proportional hazards regression model. For remaining data, significant differences were determined by either chi-square test or Fisher's exact test, as appropriate. A value of $P < 0.05$ was considered to be significant. Statistical calculations were performed using the StatView software (SAS Institute, Cary, NC, USA).

Results

The 464 patients included 280 men and 184 women (male/female ratio: 1.5/1). The mean age of the patients was 69 years (range: 34–99 years). Tumors were located at the colon in 371 patients (80.0%) and at the rectum in 93 patients (20.0%).

In the univariate analysis for RFS in all cases, significant variables were age at surgery, tumor depth, circumferential occupancy, tumor location, lymph node metastasis, TDs, lymphatic invasion, and venous invasion (Table 1).

In the univariate analysis for OS in all the cases, significant variables were age at surgery, circumferential occupancy, tumor depth, lymph node metastasis, TDs, lymphatic invasion, and venous invasion (Table 1). In the stepwise multivariate Cox proportional hazards analysis, TDs, age at surgery, lymphatic invasion, and tumor depth remained significant (Table 2). In patients with RLNMs, the only significantly predictive variable was TDs (Table 3). The hazard ratio of TDs presence versus absence was 2.813 ($P = 0.0002$).

Of the 464 patients, 88 (19.0%) developed recurrence. Recurrence was observed in 49.2% of patients with TDs (30/61) compared with 14.4% of patients without them (58/403) ($P < 0.0001$). In rectal cases, local recurrence occurred in 33.3% (4/12) of patients with TDs compared with 7.4% (6/81) of patients without TDs ($P = 0.0226$). In colon cases, it occurred in 6.1% (3/49) of patients with TDs compared with 2.8% (9/322) of patients without TDs ($P = 0.2019$).

TDs were detected in 13.1% of patients (61/464). They were located at the colon in 13.2% of patients (49/371) and at the rectum in 12.9% of patients (12/93). Sixty-one patients had 171 TDs. The mean number of TDs was 2.8 (2.5 at the colon, 4.1 at the rectum). The range was 1–16 (1–3, 48 patients; >3, 13 patients). Depth of tumor invasion in patients with TDs was pT2 in 1 patient, pT3 in 3 patients, pT4a in 53 patients, and pT4b in 4 patients. Eighteen patients with TDs (18/61; 30.0%) had no lymph node metastasis (pN1c using the UICC TNM 7th edition); their mean number of TDs was 1.2. Of 294 patients without lymph node metastasis, 6.1% (18/ 294) had TDs. OS curves are shown in Figure 1 and Figure 2 by presence of TDs. OS curves of pN(+)TDs(+)M(–) and M(+) are shown in Figure 3.

RLNMs, lymphatic invasion, venous invasion, tumor depth, and circumferential occupancy were significantly associated with the presence of TDs (Table 4). RLNMs were significantly associated with TDs, lymphatic invasion, venous invasion, tumor depth, and circumferential occupancy (Table 5).

Discussion

In the 7th UICC TNM staging system, TDs were considered N1c in patients without RLNM, whereas the significance of TDs in patients with RLNMs remained unclear. Tateishi *et al.* showed that tumor nodules could justifiably be regarded as lymph node metastases with regard to OS[4]. Ueno *et al.* reported that N staging could predict survival outcome with the highest accuracy when both nodal in-

Table 1 Univariate analysis for 5-year relapse-free survival and overall survival for all subjects

Variables	n	RFS (%)	*P* value	OS (%)	*P* value
Gender			0.2736		0.6737
Male	280	73.6		80.7	
Female	184	75.6		81.1	
Age at surgery			**0.0005**		**<0.0001**
≤ 65	176	83.5		89.2	
> 65	288	68.6		75.6	
Circumferential occupancy			**<0.0001**		**0.0035**
≤ 1/2	162	84.1		86.0	
> 1/2	302	69.1		78.0	
Tumor location			**0.0194**		0.0639
Colon	371	77.2		83.8	
Rectum	93	63.7		69.9	
Tumor depth			**<0.0001**		**<0.0001**
≤ pT2	127	88.7		91.2	
≥ pT3	337	68.7		76.7	
Histology			0.1116		0.2629
Well differentiated	423	75.6		81.8	
Others	41	62.0		71.4	
Lymph node metastasis			**<0.0001**		**<0.0001**
Negative	294	83.4		87.4	
Positive	170	58.7		69.4	
Tumor deposits			**<0.0001**		**<0.0001**
Absence	403	79.2		84.8	
Presence	61	41.8		52.9	
Lymphatic invasion			**<0.0001**		**<0.0001**
Negative	329	82.5		86.3	
Positive	135	54.6		66.9	
Venous invasion			**<0.0001**		**0.0085**
Negative	130	84.4		84.9	
Positive	334	70.3		79.3	

RFS, relapse-free survival; OS, overall survival. Bold indicates statistical significance at $P<0.05$.

Table 2 Stepwise multivariate Cox proportional hazards analysis for overall survival for all subjects

Covariates	*P* value	Hazard ratio (95% confidence interval)
Tumor deposits (presence vs. absence)	0.0002	2.493 (1.535–4.048)
Age at surgery (> 65 vs. ≤ 65)	0.0007	2.229 (1.402–3.545)
Lymphatic invasion (positive vs. negative)	0.0033	1.928 (1.245–2.986)
Tumor depth (≥ pT3 vs. ≤ pT2)	0.0158	2.127 (1.152–3.927)

Table 3 Stepwise multivariate Cox proportional hazards analysis for overall survival in patients with regional lymph node metastases

Covariate	*P* value	Hazard ratio (95% confidence interval)
Tumor deposits (presence vs. absence)	0.0002	2.813 (1.644–4.812)

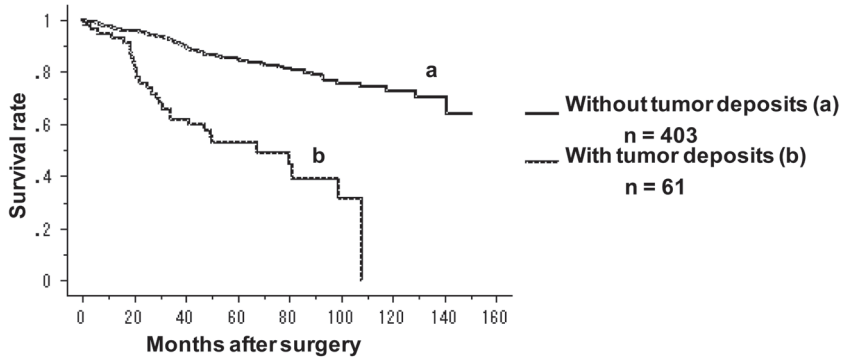

Figure 1 Overall survival curve according to presence of tumor deposits. *P*<0.0001.

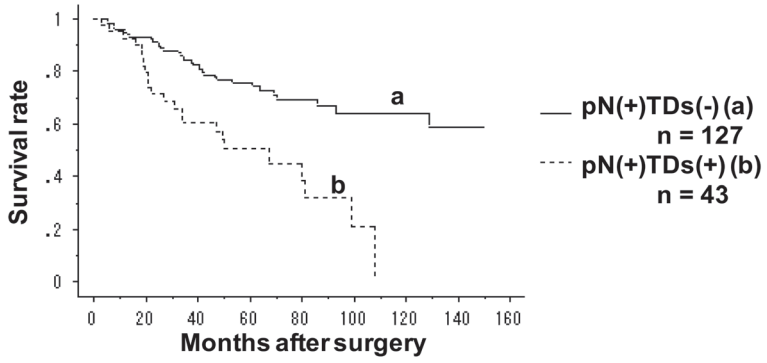

Figure 2 Overall survival curve according to presence of tumor deposits in patients with regional lymph node metastases. N, lymph node metastases; TDs, tumor deposits. *P*<0.0001.

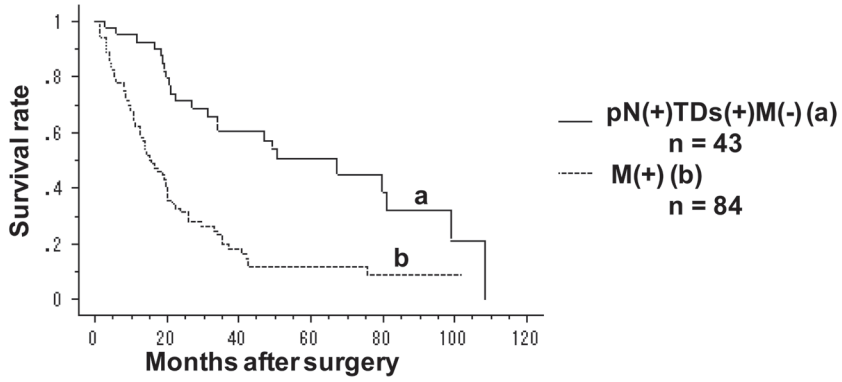

Figure 3 Overall survival curve of pN(+)TDs(+)M(-) and M(+). N, lymph node metastases; TDs, tumor deposits; M, distant metastases. *P*<0.0001.

volvement and nonvascular invasion-type extranodal cancer deposits were treated together as an N factor[5]. Nagtegaal *et al.* showed that the definitions in the 5th edition UICC TMN were the most reproducible when tumor nodules > 3 mm in diameter were considered as lymph node metastases and further noted that many questions remained about the definition, reproducibility, and use of this category in special situations, such as after neoadjuvant treatment[6]. On the other hand, Goldstein *et al.* reported that TDs were distinct from lymph node metastases and suggested that TDs of all sizes

Table 4 Correlation between variables and tumor deposits (TDs)

Variables	No. of TDs (–) patients	No. of TDs (+) patients	*P* value
Gender			0.4299
Male	246	34	
Female	157	27	
Age at surgery			0.7473
≤ 65	154	22	
> 65	249	39	
Circumferential occupancy			**<0.0001**
< 1/2	155	7	
≥ 1/2	248	54	
Tumor location			0.9381
Colon	322	49	
Rectum	81	12	
Tumor depth			**<0.0001**
≤ pT2	126	1	
≥ pT3	277	60	
Histology			0.5010
Well differentiated	366	57	
Others	37	4	
Regional lymph node metastasis			**<0.0001**
Negative	276	18	
Positive	127	43	
Lymphatic invasion			**<0.0001**
Negative	307	22	
Positive	96	39	
Venous invasion			**<0.0001**
Negative	127	3	
Positive	276	58	

Bold indicates statistical significance at $P<0.05$.

should be considered a single entity[7]. Puppa *et al.* advocated that TDs without lymphocytes and in close association with veins and/or nerves could be included in the M1a category for staging purposes[8]. Al Sahaf *et al.* suggested that extramural deposits be classified as metastases[9]. Wünsch *et al.* showed that TDs in which the origin remained unclear should be included in the M subcategory[10]. Ueno *et al.* reported that tumor nodules ≥ 5 mm growing with venous/perineural invasion had a considerable adverse prognostic effect[11]. Tong *et al.* suggested that disease categorized as T3N2bM0TDs (+) and T4N2bM0TDs(–/+) should be reclassified as stage IV[12]. Shimada *et al.* reported that extranodal cancer tissue had a more severe clinical impact than nodally involved tissue[13]. In our stepwise multivariate Cox proportional hazards analysis of patients with RLNMs, only TDs remained significant for OS. The prognosis of patients with RLNMs was not homogeneous according to presence of TDs (Figure 2). The effect of TDs on OS was between that of lymph node metastasis and distant metastasis (Figure 2 and Figure 3).

In Japan, the recurrence rate after curative resection was 17.3% between 1991 and 1996[14]. Of 464 patients, 88 (19.0%) developed recurrence in our study. Recurrence was observed in 49.2% of patients with TDs (30/61) compared with 14.4% of patients without TDs (58/403) ($P < 0.0001$). Heald *et al.* suggested that minute foci in the mesorectum might lead to suture-line or pelvic recurrence[15]. Paty *et al.* reported that mesenteric implants were found in 6 of 13 patients with pelvic recurrence[16]. In our rectal cases, local recurrence occurred in 33.3% (4/12) of patients with TDs compared with 7.4% (6/81) of patients without TDs ($P = 0.0226$). TDs indicated a high risk of local recurrence in rectal cases. In our colon cases, local recurrence occurred in 6.1% (3/49) of patients with TDs compared with 2.8% (9/322) of patients without TDs ($P = 0.2019$). Local recurrence was not significantly associated with the presence of TDs in colon cases. The results regarding correlation between variables and TDs, shown in Table 4, indicate that the presence of TDs was not significantly associated with the location of cancer. Anatomy or autonomic nerve-preserving surgery in the rec-

Table 5 Correlation between variables and regional lymph node metastases (RLNMs)

Variables	No. of RLNMs (–) patients	No. of RLNMs (+) patients	*P* value
Gender			0.6105
Male	180	100	
Female	114	70	
Age at surgery			0.9182
≤ 65	111	65	
> 65	183	105	
Circumferential occupancy			**<0.0001**
< 1/2	126	36	
≥ 1/2	168	134	
Tumor location			0.2357
Colon	240	131	
Rectum	54	39	
Tumor depth			**<0.0001**
≤ pT2	113	14	
≥ pT3	181	156	
Histology			0.1768
Well differentiated	272	151	
Others	22	19	
Tumor deposits			**<0.0001**
Absence	276	127	
Presence	18	43	
Lymphatic invasion			**<0.0001**
Negative	271	58	
Positive	23	112	
Venous invasion			**<0.0001**
Negative	116	14	
Positive	178	156	

Bold indicates statistical significance at $P<0.05$.

tum might increase the risk of local recurrence in patients with TDs.

Many reports have suggested different groupings for TDs. In 1997, Ueno *et al*. reported that extrabowel skipped-cancer infiltration had four patterns: scattering, vessel invasion, neural invasion, and nodular[17]. In 2007, extranodal cancer deposits were classified as vascular and nonvascular invasion types[5]. In 2000, Goldstein *et al.* divided TDs into three groups: perineural, perivascular, or intravascular tumor extension[7]. In 2002 Ratto *et al.* divided mesorectal microfoci into four types: endovasal, endolymphatic, perineural, and isolated[18]. In 2003 Prabhudesai *et al.* reported that a significant proportion of extranodal deposits might represent blood-borne spread[19]. In 2007, Puppa *et al.* divided TDs into two patterns, with or without lymphocytes, and suggested that pericolonic TDs without lymphocytes were a destructive type of venous invasion and different from other types of vessel involvement[20]. In 2010, Shimada et al. reported that extranodal cancer tissue was classifiable into three types: a vascular and perineural invasion type, smooth nodule type, and irregular nodule type[13]. Wünsch *et al*. classified pericolonic TDs as venous invasions, lymphatic invasions, nerve sheath infiltrations, free pericolonic TDs, and continuous growth[10]. The previous reports suggested that TDs arose from various situations. In our study, TDs included vessel invasion, neural invasion, and nodules. Lymph node metastasis, lymphatic invasion, and venous invasion were significantly associated with the presence of TDs (Table 4). TDs could not be incorporated into one category.

Conclusion

In stepwise multivariate Cox proportional hazards analysis of CRC patients with RLNMs, only TDs remained significant for OS (hazard ratio: 2.813; $P = 0.0002$). The prognosis of patients with RLNMs was not homogeneous according to presence of TDs. The effect of TDs on OS was between that of lymph node metastasis and distant metastasis.

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