JBUON 2016; 21(6): 1476-1481
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Tumor deposits: Prognostic significance in gastric cancer patients

Bulent Yildiz[1], Durmus Etiz[2], Pinar Dal[1], Bermet Junushova[1], Ozgul Pasaoglu[3], Evrim Yilmaz[3], Serdar Erkasap[4], Murat Dincer[1]

[1]Department of Medical Oncology, [2]Department of Radiation Oncology, [3]Department of Pathology, [4]Department of Surgery, Eskisehir Osmangazi University, Eskisehir, Turkey

Summary

Purpose: *Tumor deposits (TDs) are defined as satellite peritumoral nodules in the peritumoral adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule. We aimed to investigate the relation between TDs and clinicopathological characteristics of gastric cancer and to evaluate the effect of TDs on prognosis.*

Methods: *One hundred and seven non-metastatic gastric cancer patients were enrolled. The relationships between positive and negative TDs with respect to clinicopathological characteristics, as well as disease free survival (DFS) and overall survival (OS), were analyzed.*

Results: *TDs were detected in 28 patients (26.2%). Advanced pT stage and pN stage were significantly higher in TDs-positive compared to TDs-negative patients (p=0.015 and p=0.037, respectively). No significant differences were identified between the groups in other clinicopathological variables such as gender, lymphovascular and perineural invasion. Recurrence and mortality rates were higher in the TDs-positive patients during follow-up of both groups (22/78.6% vs 38/48.1%, p=0.010 for relapse; 20/71.4% vs 3/38%, p=0.005 for mortality). The univariate analysis demonstrated shorter DFS and OS for TDs-positive compared to TDs-negative patients. In multivariate analysis, TDs-positive patients had 1.75-fold higher likelihood to develop recurrence, while the likelihood of death increased 1.99-fold (p=0.041 and p=0.020, respectively).*

Conclusion: *TDs-positive gastric cancers demonstrate a more aggressive clinical course compared to TDs-negative. More effective treatment methods should be necessary for management of this subgroup of gastric cancer.*

Key words: *gastric cancer, prognosis, survival, tumor deposits*

Introduction

Despite the decreasing incidence and mortality rates of gastric cancer in developed countries, this malignancy ranked 4th in the world in 2012. This cancer is the 3th and 5th leading cause of cancer-related deaths in males and females, respectively [1].

TDs are defined as satellite peritumoral nodules in the peritumoral adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule, which may represent discontinuous spread, venous invasion with extravascular spread, or a totally replaced lymph node [2]. After several studies about colorectal cancer had revealed prognostic significance and predictive role of TDs [3,4], TDs were included in AJCC 7 grading system [2]. In recent years, TDs in gastric cancer have been reported by pathologists. Besides colorectal cancer, TDs have also been described in many other neoplasms, such as stomach, biliary duct (cholangiocarcinoma and

Correspondence to: Bulent Yildiz, MD. Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Oncology 26480, Eskisehir, Turkey. Tel: +90 222 2392979, Fax: +90 222 2201363, E-mail: drbulentyildiz@hotmail.com
Received : 08/03/2016; Accepted : 24/03/2016

gallbladder) and pancreatic cancer [5]. The prognostic significance of TDs in colorectal cancer is well understood. However, the role of TDs in gastric cancer is not clear. There are only few articles focused on TDs in gastric cancer in the English literature [6-8].

The aim of this study was to investigate the relationship between TDs and clinicopathological characteristics of gastric cancer and to evaluate the effect of TDs on prognosis.

Methods

One hundred and seven patients with gastric cancer who underwent total or subtotal gastrectomy from 2010-2015 were retrospectively studied and analyzed. Inclusion criteria were gastric surgery (total/subtotal) and no administration of neoadjuvant chemotherapy or radiotherapy. Exclusion criteria were early postoperative mortality (30 days postoperatively), metastatic stage (stage IV), histology other than adenocarcinoma and signet-ring carcinoma (neuroendocrine and adenosquamous carcinoma), and death due to second primary cancer. The present retrospective study was approved by the Institutional Ethics Committee.

Adjuvant chemoradiotherapy (5-fluorouracil/leucovorin for 5 courses concurrent with radiotherapy) was given to all patients with pT2-4b and/or with lymph node metastasis. Post-therapy follow-up consisted of visits at 3-month intervals during the first 2 years and at 6-month intervals during the next 3 years. Each visit included physical examination, complete blood count, routine biochemical tests, and CEA and CA 19.9 tumor markers. Abdominal ultrasonography or computed tomography (CT) of the abdomen and thorax were performed annually and all of the patients were monitored for recurrence/metastasis.

Gastric cancer stage at diagnosis was defined according to the American Joint Committee on Cancer Staging Manual (7th edition) [2].

DFS was defined as the period from the time of diagnosis until the appearance of a local recurrence or metastasis. OS was defined as the period from the time of diagnosis until the last visit or death.

Statistics

Chi-square test was used for comparisons between TDs-positive and TDs-negative groups for relationships with respect to clinicopathological characteristics (gender, localization, lymph node involvement, histological type, stage, etc.), while comparisons of means (age and tumor size) were carried out using the Student's t test. Relationships between the variables to DFS and OS were assessed by the Kaplan-Meier survival analysis and differences were estimated by the log-rank test. For the variables which were statistically significant in univariate analysis, multivariate Cox regression analysis was used. Statistical evaluations were performed using the SPSS 21 (SPSS Inc., Chicago, ILL, USA) statistical software. The level of significance was set at $p<0.05$.

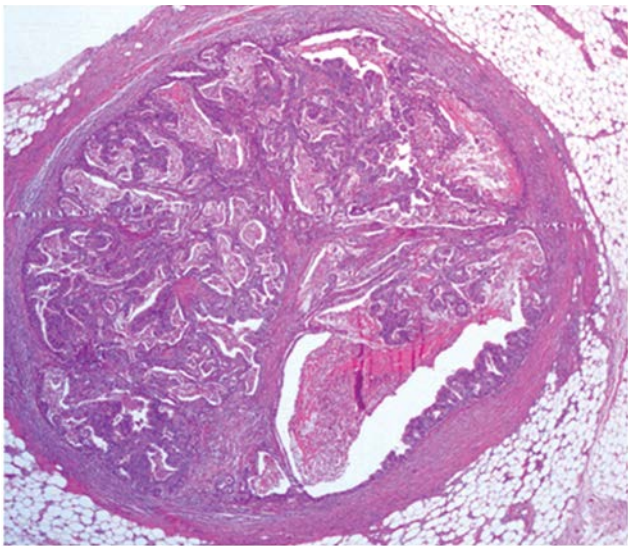

Figure 1. Separate tumor deposit in perigastric soft tissue (H&E, original magnification x 100).

Results

The median patient follow-up was 30 months (range 3-71). Of the 107 patients enrolled, TDs were detected in 28 patients (26.2%) in the peritumoral adipose tissue of the primary carcinoma (Figure 1). The number of TDs ranged from 1 to 5 (median 1).

Clinicopathological characteristics of TDs-positive and negative patients are demonstrated in Table 1. Statistically significant relationships were identified between patients with TDs-positive and negative groups in terms of the studied parameters which included tumor size, localization, surgical margins, depth of invasion, lymph node metastasis and stage. Depth of invasion was significantly higher in TDs-positive patients (p=0.015). Similarly, lymph node metastasis was more common in TDs-positive patients (p=0.037). Both recurrence and mortality rates were higher in the TDs-positive group during the follow-up period (22/78.6% vs 38/48.1%, p=0.010 for recurrence; 20/71.4% vs 3/38%, p=0.005 for mortality).

The impact of the studied variables on DFS and OS according to the univariate analysis is presented in Table 2. TDs-positive patients had shorter DFS and OS compared to TDs-negative patients (p=0.001 and p<0.001) (Figures 2 and 3). Results of the multivariate analysis carried out for variables with p values <0.05 in the univariate analysis are shown in Table 3. There was 1.75-fold higher likehood for recurrence in TDs-positive patients

Table 1. Characteristics of TDs positive and negative patients

Characteristics	*TDs positive, N (%)*	*TDs negative, N (%)*	*Total*	*p value*
Gender				
Male	19 (67.9)	51 (64.6)	70	
Female	9 (32.1)	28 (35.4)	37	0.933
Mean age at diagnosis (y ±SD)	58.04 ± 13.10	60.58 ± 11.17		0.325
Mean tumor size (cm ±SD)	6.91 ± 3.66	5.32 ± 3.63		0.049
Localization				
Upper third	16 (57.1)	19 (24.1)	45	
Middle third	7 (25)	29 (36.7)	36	
Lower third	3 (10.7)	29 (36.7)	32	
Entire	2 (7.1)	2 (2.5)	4	0.003
Histological type				
Adenocarcinoma	24 (85.7)	75 (94.9)	99	
SRCC	4 (14.3)	4 (5.1)	8	0.202
Surgical margins				
Negative	13 (46.4)	63 (79.7)	76	
Positive	15 (53.6)	16 (20.3)	31	0.002
Depth of invasion				
pT1	0 (0)	15 (19)	15	
pT2	1 (3.6)	8 (10.1)	9	
pT3	9 (32.1)	28 (35.4)	37	
pT4	18 (64.3)	28 (35.4)	46	0.015
Lymph node metastasis				
N0	2 (7.1)	25 (31.6)	27	
N1-2	14 (50)	30 (38)	44	
N3	12 (42.9)	24 (30.4)	36	0.037
Number of nodes retrieved				
0-14	7 (25)	33 (41.8)	40	
>15	21 (75)	46 (58.2)	67	0.177
Stage				
I	1 (3.6)	17 (21.5)	18	
II	4 (14.3)	18 (22.8)	22	
III	23 (82.1)	44 (55.7)	67	0.030
Tumor grade				
I-II	14 (50)	40 (50.6)	54	
III-IV	14 (50)	39 (49.4)	53	1.000
Vascular invasion				
Negative	20 (71.4)	51 (64.6)	71	
Positive	8 (28.6)	28 (35.4)	36	0.668
Lymphatic invasion				
Negative	6 (21.4)	29 (36.7)	35	
Positive	22 (78.6)	50 (63.3)	72	0.213
Perineural invasion				
Negative	6 (21.4)	30 (38)	36	
Positive	22 (78.6)	49 (62)	71	0.174
Operation				
Subtotal	7 (25)	32 (40.5)	39	
Total	21 (75)	47 (59.5)	68	0.216
Adjuvant therapy				
No	3 (10.7)	17 (21.5)	20	
Yes	25 (89.3)	62 (78.5)	87	0.328
Recurrence (local and/or distant)				
Absent	6 (21.4)	41 (51.9)	47	
Present	22 (78.6)	38 (48.1)	60	0.010
Mortality				
Absent	8 (28.6)	49 (62)	57	
Present	20 (71.4)	30 (38)	50	0.005

TDs: tumor deposits, SRCC: signet ring cell carcinoma

Table 2. Association between variables and survival in univariate analysis

Variables	*DFS*			*OS*		
	OR	*95% CI*	*p value*	*OR*	*(95% CI)*	*p value*
TDs (presence vs absence)	2.48	1.45-2.24	0.001	3.00	1.68-5.33	<0.001
Gender (male vs female)	0.59	0.34-1.04	0.062	0.49	0.27-0.94	0.028
Age (≤50 vs >50 years)	0.75	0.40-1.38	0.344	0.65	0.34-1.24	0.186
Tumor size (≤5 vs >5cm)	2.29	1.37-3.84	0.001	2.93	1.64-5.23	<0.001
Localization (upper,middle,lower third,entire)	0.88	0.66-1.18	0.367	0.83	0.60-1.14	0.198
Histological type (adeno vs TYHK)	1.96	0.93-4.14	0.068	2.07	0.93-4.61	0.068
Surgical margins (negative vs positive)	3.29	1.96-5.51	<0.001	3.14	1.79-5.51	<0.001
Depth of invasion (pT1,T2,T3,T4)	2.06	1.48-2.87	<0.001	2.55	1.70-3.82	<0.001
Lymph node metastasis (N0,N1-2,N3)	2.86	1.96-4.17	<0.001	3.37	2.17-5.23	<0.001
Number of nodes retrieved (0-14 vs >15)	1.10	0.65-1.85	0.730	1.50	0.82-2.76	0.182
Stage (stage I,II,III)	2.99	1.83-4.88	<0.001	5.43	2.56-11.54	<0.001
Tumor grade (I, II,III,IV)	2.12	1.26--3.58	0.004	2.30	1.29-4.09	0.003
Vascular invasion (negative vs positive)	1.69	0.97-2.92	0.057	1.92	1.03-3.58	0.037
Lymphatic invasion (negative vs positive)	2.88	1.48-5.59	0.001	4.02	1.78-9.01	<0.001
Perineural invasion (negative vs positive)	3.01	1.56-5.83	0.001	3.55	1.66-7.61	<0.001
Operation (subtotal vs total)	1.33	0.77-2.27	0.298	1.41	0.78-2.56	0.254
Adjuvant therapy (yes vs no)	2.82	1.21-6.58	0.012	2.90	1.14-7.35	0.018

OR: odds ratio, TDs: tumor deposits, DFS: dissease-free survival, OS: overall survival, CI: confidence interval

Table 3. The effects of variables on disease-free survival and overall survival in multivariate analysis

Variables	*DFS*			*OS*	
	RR	*95% CI*	*p value*	*RR*	*95% CI*
TDs	1.75	1.02-3.01	0.041	1.99	1.11-3.54
Tumor size	1.46	0.87-2.47	0.155	1.90	1.05-3.45
Depth of invasion	1.52	1.04-2.24	0.032	1.88	1.18-2.99
Lymph node status	2.23	1.45-3.44	<0.001	2.34	1.41-3.90

TDs: tumor deposits, RR: relative risk, DFS: dissease free survival, OS: overall survival

while the likelihood for death was increased 1.99-fold (p=0.041 and p=0.020, respectively).

Discussion

TDs were firstly described by Gabriel et al. in 1935 [9]. The prognostic significance of TDs has mostly been studied in colorectal cancer [4,10-16] and TDs were included in the AJCC staging (7th Edn) in 2010 [2].

In recent years, although TDs are reported in the pathology reports in gastric cancer, there are only few studies about the prognostic impact of TDs in gastric cancer in the literature.

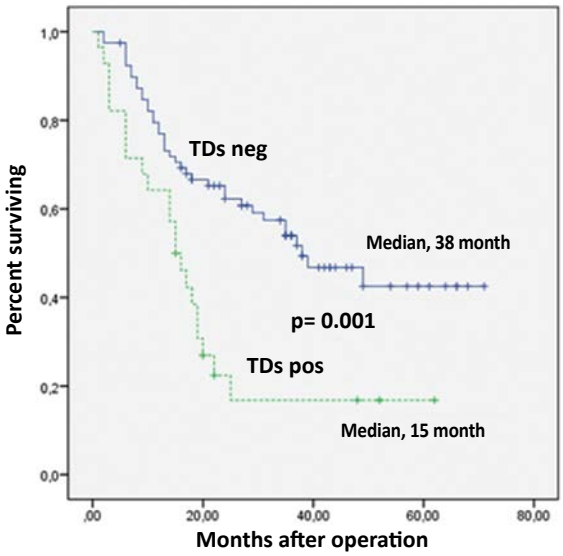

Figure 2. Kaplan-Meier curves for disease-free survival. TDs: tumor deposits.

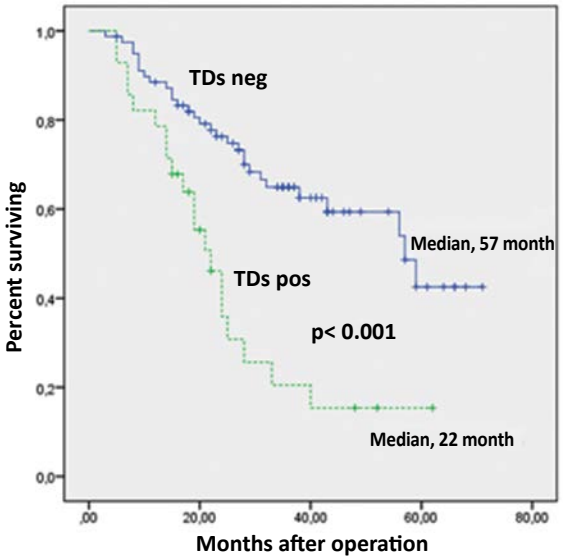

Figure 3. Kaplan-Meier curves for overall survival. TDs: tumor deposits.

Interestingly in gastric cancer, patients with similar pathological stages and prognostic factors have different survival times and TD positivity may be responsible for survival differences found in colorectal cancer patients [3,17].

In this study, TDs positivity was 26.2%. This rate was 17.8% and 23.9% in two studies from China and South Korea, respectively [7,8]. But both of these studies included patients with metastasis and TDs positivity was mostly encountered in patients with metastatic disease. Similarly to our study, Ersen et al. found 24% positivity in the non-metastatic group [6]. This 'similar' higher rate may be due to racial and geographical changes. In the literature, TDs positivity differed widely (5-45%) in different racial and geographical areas [12-19].

In our study, TDs positivity was higher in tumors with larger sizes, with deeper invasion, extended lymph node metastasis and higher stage. Mortality and recurrence rates were higher in the TDs-positive group and these results are comparable with the studies of Sun et al. and Lee et al. [7,8]. In the present study, TDs positivity was not significantly correlated with lymphovascular and perineural invasion. In TDs-positive subgroup, some biochemical and pathological markers (E-cadherin, epiregulin, amphiregulin, BRAF etc) might be responsible for increased recurrence and mortality rates. We recommend that further studies should be necessary for clarifying the relationship between these markers and TDs.

The univariate analysis showed shorter DFS and OS in TDs-positive patients, consistent with the data from previous studies [7,8]. A study by Lee et al. [7] confirmed through multivariate analysis that TDs in gastric cancer were an independent prognostic factor in both DFS and OS. Similarly, in the present study TDs in gastric cancer were identified as independent prognostic factor, increasing the risk of recurrence by 1.75-fold and the risk of death by 1.99-fold in the multivariate analysis.

In conclusion, better insight in clinicopathological characteristics (higher grade, lymphovascular invasion, perineural invasion etc) will provide more accurate prognostic and predictive factors and better guidance to clinicians in developing effective treatment strategies for this subgroup with high rates of recurrence and mortality. We consider that further studies with large numbers of patients may clarify whether TDs should be included in the staging of gastric cancer.

Conflict of interests

The authors declare no conflict of interests.

References

1. American Cancer Society. Global Cancer Facts & Figures (3rd Edn). Atlanta: American Cancer Society; 2015. Available from http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-044738.pdf

2. Edge SB, Byrd DR, Compton CC et al. AJCC cancer staging manual. (7th Edn) New York: Springer; 2010.
3. Puppa G, Maisonneuve P, Sonzogni A et al. Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. Mod Pathol 2007;20:843-855.
4. Lo DS, Pollett A, Siu LL, Gallinger S, Burkes RL. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. Cancer 2008; 112:50-54.
5. Puppa G, Ueno H, Kayahara M et al. Tumor deposits are encountered in advanced colorectal cancer and other adenocarcinomas: an expanded classification with implications for colorectal cancer staging system including a unifying concept of in-transit metastases. Mod Pathol 2009;22:410-415.
6. Ersen A, Unlu MS, Akman T et al. Tumor deposits in gastric carcinomas. Pathol Res Pract 2014;210:565-570.
7. Lee HS, Lee HE, Yang HK, Kim WH. Perigastric tumor deposits in primary gastric cancer: implications for patient prognosis and staging. Ann Surg Oncol 2013;20: 1604-1613.
8. Sun Z, Wang ZN, Xu YY et al. Prognostic significance of tumor deposits in gastric cancer patients who underwent radical surgery. Surgery 2012;151:871-881.
9. Gabriel WB, Dukes C, Bussey HJR. Lymphatic spread in cancer of the rectum. Br J Surg 1935;23:395-413.
10. Ratto C, Ricci R, Rossi C, Morelli U, Vecchio FM, Doglietto GB. Mesorectal microfoci adversely affect the prognosis of patients with rectal cancer. Dis Colon Rectum 2002;45:733-742.
11. Nagayoshi K, Ueki T, Nishioka Y et al. Tumor deposit is a poor prognostic indicator for patients who have stage II and III colorectal cancer with fewer than 4 lymph node metastases but not for those with 4 or more. Dis Colon Rectum 2014;57:467-474.
12. Prabhudesai A, Arif S, Finlayson CJ, Kumar D. Impact of microscopic extranodal tumor deposits on the outcome of patients with rectal cancer. Dis Colon Rectum 2003;46:1531-1537.
13. Nagtegaal ID, Quirke P. Colorectal tumour deposits in the mesorectum and pericolon; a critical review. Histopathology 2007;51:141-149.
14. Zhang LN, Xiao WW, Xi SY et al. Tumor deposits: markers of poor prognosis in patients with locally advanced rectal cancer following neoadjuvant chemoradiotherapy. Oncotarget 2015 Dec 18. doi: 10.18632/oncotarget.6656.
15. Jin M, Roth R, Rock JB, Washington MK, Lehman A, Frankel WL. The impact of tumor deposits on colonic adenocarcinoma AJCC TNM staging and outcome. Am J Surg Pathol 2015;39:109-115.
16. Ueno H, Hashiguchi Y, Shimazaki H et al. Peritumoral deposits as an adverse prognostic indicator of colorectalcancer. Am J Surg 2014;207:70-77.
17. Goldstein NS, Turner JR. Pericolonic tumor deposits in patients with T3N+MO colon adenocarcinomas: markers of reduced disease free survival and intra-abdominal metastases and their implications for TNM classification. Cancer 2000;88:2228-2238.
18. Mayo E, Llanos AA, Yi X, Duan SZ, Zhang L. Prognostic Value of Tumor Deposit and Perineural Invasion Status in Colorectal Cancer Patients: a SEER-Based Population Study. Histopathology 2016 Jan 23. doi: 10.1111/his.12936.
19. Song YX, Gao P, Wang ZN et al. Can the tumor deposits be counted as metastatic lymph nodes in the UICC TNM staging system for colorectal cancer? PloS One 2012;7:e34087. doi: 10.1371/journal.pone.0034087. Epub 2012 Mar 26.