Prognostic value of tumor deposits in rectal cancer: A monocentric series of 505 patients

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Synopsis for table of Contents: Tumor deposits (TDs) were included in TNM staging in 2010 with creation of N1c category. In this study with 505 patients operated for rectal cancer, specimens with tumor deposits had a metastatic risk comparable to a pN2 stage which may lead to changes in adjuvant treatment.

ABSTRACT

Background and Objectives: It has been suggested that tumor deposits (TD) may have a worse prognosis in rectal cancer compared to colonic cancer. The aim of this study was to assess TDs prognosis in rectal cancer.

Methods: Patients who underwent total mesorectum excision for rectal adenocarcinoma (2011-2016) were included. A case-matched analysis was performed to assess the accurate impact of TDs for each pN category after exclusion of synchronous metastasis.

Results: 505 patients were included. TDs were observed in 99 (19.6%) patients, (pN1c=37 (7.3%)). TDs were associated with pT3-T4 stage (p=0.037), synchronous metastasis (p=0.003), LN invasion (p=0.041), VI (p=0.001) and PNI (p<0.001). TD was associated with a worse 3-year DFS among pN0 (51.2% vs 79.8%; p<0.001); pN1 patients (35.2% vs 70.1%; p=0.004) but not among pN2 patients (37.5% vs. 44.7%; p=0.499). After matching, pN1c patients had a worse 3-year DFS compared with pN0 patients (58.6% vs 82.4%; p=0.035) and a tendency towards a worse DFS among N1 patients (40.1% vs 64.2%; p=0.153). DFS was worse when one TD was compared to one invaded LN (40.8% vs 81.3%; p<0.001).

Conclusion: In rectal cancer, TDs have a metastatic risk comparable to a pN2 stage which may lead to changes in adjuvant treatment.

INTRODUCTION

Rectal cancer accounts for around 30% of all colorectal cancer (CRC) with a significant improvement in prognosis and management seen when neoadjuvant chemoradiotherapy is used. [1-3] Adjuvant treatment is guided by pathological prognostic factors including lymph node metastasis (LNM), vascular invasion (VI), perineural invasion (PNI) and tumor deposits (TD). [4]

Tumor deposits were first described in 1935 as nodules of tumor cells in pericolic or perirectal fat tissue without lymph node architecture. [5] They were first included in AJCC/TNM 5th classification in 1997 and considered as lymph nodes (LN) if their size was > 3mm in diameter or as a tumor extension when they measured < 3 mm. Then the 6th edition of TNM staging differentiated round-shaped tumor deposits as lymph nodes and spiculated ones as a tumor extension. Finally the 7th edition in 2010 created a new pN category (i.e. pN1c) for adenocarcinoma with TD without concomitant LNM (N0). [6]

N1c category represent 5 to 10 % of rectal cancers [4,7] with TDs seen in around 20% of all adenocarcinomas. [8] TDs are associated with poor prognostic markers such as a high T stage (T3-T4 stage) [7,9] and a higher N stage. [10,11] 60% of patients with stage IV disease have TDs [12] with a further 72% of colorectal cancer with PNI having TDs also. [7] Nagtegaal et *al*. previously reported in a meta-analysis that N1c tumors are associated with a worse disease-free survival and overall survival. [8] However, most of these studies were retrospective, based on pathological specimens from pre 2010 prior to the reclassification of the TNM stage. [8] It has been suggested that TDs may have worse prognosis in rectal cancer compared to colon cancer [9], although there a limited number of studies purely examining rectal cancer alone. Moreover, TDs identification after radiotherapy remains controversial. Although there are some arguments for lower survival due to TDs after neoadjuvant radiotherapy, [13] small number of studies have reported a poor prognosis in TD positive tumors after neoadjuvant radiotherapy [7] while others showed no difference. [14] The aim of this study was to assess TD and N1c stage tumor prognosis in rectal cancer.

MATERIAL AND METHODS

Study population

All consecutive patients who underwent total mesorectum excision (TME) for rectal adenocarcinoma in our Department between 2011 and 2016 were included from a prospective database. In order to select only true rectal cancers and avoid confusion with rectosigmoid cancers, all colorectal anastomosis not diverted by ileostomy were excluded. The primary endpoint of this study was to compare prognosis in tumor deposit positive tumors and N1c patients using the new TNM staging. The secondary endpoint was to assess TDs impact in a case-control setting.

Data collection

Clinical information concerning tumor, neoadjuvant treatment and surgical procedure was retrieved from patient charts. Histological data concerning TNM stage, TDs, vascular invasion, perineural invasion, tumor grade or differentiation were included from standardized pathological reports according to the 7th edition of AJCC classification. [6] TDs were defined as tumor nodules in the fatty tissue of the mesorectum without lymph node (LN) structure. Local recurrence was defined as pelvic or anastomotic recurrence diagnosed by imaging or endoscopy. In cases with synchronous metastasis, distant recurrence was considered when new lesions appeared, or progression of existing disease occurred. Global recurrence was defined by the occurrence of local and/or metastatic recurrence.

Neoadjuvant therapy and surgical procedure

According to French and ESMO guidelines [1,3] preoperative radiotherapy was always discussed in multidisciplinary meetings for patients with mid and low rectal cancer. Patients with a cT3, cT4 or cN+ tumor were eligible for neoadjuvant radiotherapy. Patient with locally advanced cancer received either a 50.4 Gy radiotherapy associated with oral Capecitabine (CAP-50 protocol) or a short course protocol with 25 Gy radiotherapy. CAP-50 was preferred when a downsizing of tumor was expected to enhance circumferential resection margin. Surgery was performed 6-8 weeks after CAP-50 protocol or 1 week after short course protocol. A total mesorectum excision (TME) was always performed as previously described. [15] Most patients had a primary anastomosis, with intersphincteric resection if needed. In cases of anal sphincter invasion, an abdominoperineal excision was performed. All patients had a low anastomosis and so a diverting stoma to protect the anastomosis. Patients with stage III tumor on pathological exam received adjuvant chemotherapy based on multidisciplinary decision. Patients with N1c stage were considered as stage III.

Outcomes

Data concerning local recurrence, distant metastasis or death were collected from patient charts. Disease-free survival was defined as the time without local and/or metastatic recurrence and analyzed using the date of local and/or distant metastasis. When patients had initial metastatic disease, recurrence was considered when disease progression was observed.

Case-control study

In the case-control study, patients with synchronous metastatic disease were excluded. In each pN category, patients were matched according to sex, BMI, neoadjuvant radiotherapy, surgical procedure, pT stage, VI and PNI presence. A 2 for 1 pairing among pN0 patients and a 1 for 1 pairing in pN1 and pN2 patients was performed.

Statistical analysis

Statistical analysis was performed using SPSS Statistic 20 software (IBM, Armonk, NY; USA). Continuous variables were expressed as mean +/- standard deviation and compared using Mann-Whitney U test. Nominal variables were expressed with percentage and compared using Chi-square test or Fisher test. Multivariate analysis included variables with statistical difference in univariate analysis with p value <0.1. Survival analysis was performed with Kaplan-Meyer curves and compared with log-rank test.

RESULTS

Population

A total of 505 patients were included. Clinical data of the cohort is summarized in **table 1**. There were 315 (62.4%) men with a mean age of 63.3±12.7 years. Neoadjuvant radiotherapy was performed in 275 (54.5%) patients with 42 patients receiving a short course protocol. Abdominoperineal excision was performed in 86 (17%) patients. Pathological examination showed a majority of pT3 (N=253; 50.1%) and pN0 (N=272; 53.9%) tumors. TDs were observed in 99 (19.6%) patients, with 37 (7.3%) patients classified as pN1c. Median follow-up was 32 ± 22 months with a total of 49 (9.7%) deaths occurring during that period. Local recurrence was observed in 35 (6.9%) patients. Among patients without synchronous metastasis (n=455), 103 (22.6%) had metastatic progression. In patients with synchronous metastasis (n=50), 32 (64%) had metastatic progression. Among patients with synchronous metastasis, 5 (10%) had hepatic associated surgery and 1 (0.5%) had latero-aortic lymph node clearance.

Patients characteristics according to the presence of TDs

Comparisons between specimen with and without TDs are detailed in table 1. TD positive specimens were more frequently associated with pT3 and pT4 tumors (p<0.001), LN (p<0.001), VI ($p<0.001$) and PNI ($p<0.001$) (**table 1**). In multivariate analysis, TDs were associated with pT3-T4 tumors (p=0.037), synchronous metastasis (p=0.003), LNM (p=0.041), VI (p=0.025) and PNI ($p<0.001$). We didn't include neoadjuvant radiotherapy in the variable as it is correlated with the T and N stages. Multivariate analysis did not show any statistical association with R1 resections. After exclusion of synchronous metastasis, TD positive tumors were also associated with pT3 and pT4 tumors ($p<0.001$), LN invasion ($p<0.001$), VI and PNI ($p<0.001$).

Relationship between TDs and nodal stage

pN1c tumors were seen in 37 (7.3%) patients and were associated with pT3 and pT4 tumors ($p<0,001$) and synchronous metastasis ($p<0.001$). There was significantly more VI (p=0.003) and PNI ($p<0.001$) in pN1c patients. Among pN1 patients, the presence of TDs was associated with pT3 tumors (p=0.011), VI (p=0.004) and PNI (p=0.001). Within pN2 tumors, there was no difference in pT stage between TD positive and TD negative specimens. There was significantly more PNI involvement but no difference in VI (**table 2**).

Oncological outcomes

In the overall population, three-year overall survival (OS) was 90.5% and disease-free survival (DFS) was 66.4% **(Table 3)**. pN1c patients had a worse DFS compared to pN0 patients (51.2% vs 79.8%; $p<0.001$), although there was no significant difference in in 3-year OS (**figure 1**). pN0 patients were associated with a worse DFS when synchronous metastasis (n=283) was excluded (58.5% vs 82.3%; p=0.001). Among pN1 patients, there was no difference in OS, however, a worse DFS due to TDs was noted (35.2% vs 70.1%; p=0.004). A significantly worse 3-year DFS was seen in TD positive pN1 patients (40.1% vs 74.6%; p=0.007) when synchronous metastasis was excluded (n=101), however, this was not seen in the pN2 patients (37.5% vs 44.7%; p = 0.499). There was no significant difference in 3-year OS (**figure 2**).

Following exclusion of synchronous metastasis (n=71), DFS was comparable (41.1% vs 51.4%; p=0.65). There was no difference in adjuvant therapy among pN1 and pN2 patients due to TDs presence (**table 2**)

Impact of TD numbers

Patients with ≥4 TDs (N=14) had a worse 3-year DFS, however, this was not statistically significant. (20.6% vs. 44.1%; p=0.098). Furthermore, a worse 3-year OS was seen in patient with ≥4 TDs compared with those with 1- 3 TDs (62.2% vs 82.2%; p=0.087). Again, this was not statistically significant. Specimens with one TD versus one positive LN with TDs were examined. A worse DFS was noted in the TD group (40.8% vs 81.3%; p<0.001).

Case-control study

After matching, 22 TD-positive specimens were compared with 44 TD-negative patients among the pN0 population. There was 33 and 20 TD-positive specimens in pN1 and pN2 groups respectively matched with a 1:1 ratio. Patient characteristics after matching are reported in **supplementary table 1**. pN1c patients had a worse 3-year DFS compared with pN0 patients (58.6% vs 82.4%; p=0.035), with no difference in 3-year OS seen. Worse DFS was observed in the pN1 group although this was not significant (respectively 40.1% vs 64.2%; p=0.153). There was no difference in DFS among pN2 patients (32.9% vs 46.5%; p=0.858) (**figure 3**)

Addition of TDs with LN metastasis count

Restaging of N stage was seen when the sum of TDs was added to LN positive patients. 19 patients changed from N1 to N2 and 2 N1c patients changed to N2 stage disease. These 21 new N2 patients had a worse DFS that was not statistically significant to the old N2 classification (28.7% vs 42.7%; p=0.644) and was significantly different to the previous N1 classification (28.7% vs 58.9%; p=0.003).

Neoadjuvant chemoradiotherapy

Among TD positive patients, 50 received CAP-50 neoadjuvant protocol and 36 did not have radiotherapy. There was no difference in 3-year OS (87.1% vs 75%; p=0.447), local recurrence (12.7% vs 3.7%; p=0.188) or DFS (35.7% vs 39.9%; p=0.158) between patient that did and did not receive neoadjuvant chemoradiotherapy.

DISCUSSION

The present study found that TDs were present in nearly 20% of the 505 specimens examined, with N1c status counting for 7.3% of the patients. TDs were statistically associated with larger tumors, pT3-pT4, LN invasion, VI, PNI and, most importantly, synchronous metastasis. TDs had an important impact on DFS among N0 and N1 patients. TD prognosis was comparable to pN2 stage and did not impact N2 DFS which is associated with a poor outcome.

The incidence of TDs in the present study was similar to previous studies [8,9,16,17], however, it was higher than a recently published review on TDs and N1c [18]. The results in the present study are supported by the use of standardized pathological reports that systematically mentioned TDs and other poor prognostic factors. Moreover, the present study included only patient operated after 2010 so the use of N1c status was systematically used for specimens with TDs and no lymph node invasion. The presence of TDs is different in rectal cancers and may be more frequent compared to colon cancer (roughly 15-18% in colon cancer). [9,10] However, some reports have shown the proportion to be as high as 30%, with a 29% rate of TDs in right sided colon tumors [19,20], although these studies only included patients prior to 2010 and discrepancies in TDs definition may explain such a difference. The present study has shown that a number of poor prognostic factors were associated with TDs, notably vascular invasion, perineural invasion and synchronous metastasis. These poor prognostic factors have been demonstrated in previous studies [8,9,16,19,21,22] and suggest the cancer cells ability to disseminate.

The following study has shown that TDs were associated with a worse DFS due to distant metastasis, which is comparable to a pN2 stage. Significantly worse DFS was observed in N0 and N1 patients but not in pN2 patients, probably due to the worse prognosis encountered in pN2 stage disease. A worse DFS among N0 and N1 patients was confirmed after exclusion of patients with synchronous metastasis. After matching on poor prognostic parameters, the present study still observed a significantly worse DFS (24%) due to TDs in pN0 patients (i.e N1c). Furthermore, this study has shown a 24% decrease in DFS due to TDs specifically in N1 patients, however, due to small sample sizes after matching, a non-significant difference in pN1 patients was seen. These studies results differs slightly from previous studies that showed a decrease in DFS and OS among LN-negative patient following chemoradiotherapy [7,21] but not in LN-positive patients. [21] While previous data showed a decrease in OS due to TDs [8], the present study did not observe any difference in OS due to TDs. This observation might be explain by a 3-year OS of more than 80% even in N2 patients, although, such a high OS has already been reported in previous studies. [16,19]

Jin et *al*. have shown an impact of TD numbers on OS with a cut-off of ≥4 TDs. [20] The present study showed a trend towards a worse OS and DFS with the number of TDs, although, this was not significant. While Jin et al only studied N1c patients, the present study included both N1c and LN positive patients which may impact on survival. This may be further supported by the finding in the present study that TDs alone have a poorer prognosis than a positive LN alone, with a 40% decrease in DFS. This can be explained by the fact that the pathway involved in cellular dissemination might be different for each modality. Some authors have demonstrated that TDs are due to *twist* mutation while LN spread is due to *snail* mutations. [23]

N1c status is a peculiar status as it represents patients only with TDs and no LN invasion. N1c patients have a worse DFS of 51.2% in this study. N1c cancers were also associated with larger tumors and poor prognostic factors as previously suggested. [9] Compared to N0 or N1 patients without TDs, DFS was worse among N1c patients and comparable to N2 disease. It has already been proven that N1c status has a poor impact on DFS and OS in colorectal cancer. [9,24]

The present study has shown that TDs did not impact prognosis following neoadjuvant chemoradiotherapy. However, in rectal cancer, it remains uncertain if N1c status is useful after radiotherapy. While some authors suggest that patients with N1c grade have a poor prognosis after radiotherapy [7,21] other studies have failed to show a prognostic difference due to confusion between TDs and residual tumor. [14] There are still a number of difficulties in evaluating TDs prognosis after neoadjuvant treatment. Furthermore, neoadjuvant chemoradiotherapy is indicated for advanced tumors or N positive tumors, that have a high risk for TD presence but TDs are not easily diagnosed on MRI with great difficulties to assess their presence preoperatively.

Distinction between TD and invaded LN remains a challenge and is still debated among pathologists. [25] TDs may be confused for a completely replaced LN, venous invasion or even tumor spread. [18] The present study suggests that TDs must be mentioned in pathological reports and confusion between TDs and LN may lead to a lack of metastatic risk evaluation. Current TNM staging is suboptimal in its definition of TDs. A lot of pathologists do not support practices such as excluding nodules with evidence of underlying EMVI, LI or PNI from the pN1c category and thus downstaging a patient from stage III to stage II if reclassifying them according to the TNM 8 rather than the TNM 7 edition. Currently, French and European guidelines recommended post-operative chemotherapy for patients with stage III and IV rectal cancer. [1,3] However, these recommendations are based on expert consensus and protocols used in colon cancer. Recently, it has been suggested that in colon cancer, a longer duration of adjuvant chemotherapy may improve prognosis for high risk cancer. [26] With this in mind, the authors suggest that the presence of TDs should be considered when implementing adjuvant treatment regimens and protocols. Chavali et *al*. suggest that adjuvant radiotherapy improves prognosis for patients with TDs who did not receive neoadjuvant radiotherapy. [27]

The results in the present study are strengthened by a large sample size and standardized pathological reports. Furthermore, patients were only included after 2010 which corresponded to the introduction of the 7th edition of TNM staging. However, there are still several limitations. It is a retrospective study with the majority of patients having N0 disease. TDs were present in almost 20% of the population, however, only 37 patients were classified as N1c which lead to a lack of statistical strength for this sub-group. Due to the small numbers of N1 patients after matching, a significant impact on DFS due to TDs could not be ascertained. Furthermore, the majority of patients had <4 TDs, again limiting the true impact of TD numbers on DFS outcomes.

CONCLUSION

In rectal cancer, TDs are a poor prognostic factor with a higher risk of metastatic recurrence comparable to N2 disease. Adjustments in chemotherapy protocols must be discussed for patients classified as N1c or N1 with TDs. Further large scale, multicentre, prospective studies are required to ascertain the prognostic implications of TDs.

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Availability of data

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

FIGURES LEGEND

Figure 1: Survival curves between pN0 and pN1c patients. A: OS; B: DFS

Figure 2: Survival curves within LN invasion positive specimen. A: N1; B: N2. TD neg: No TDs; TD pos: TD presence

Figure 3: Survival curves after matching. A: pN0; B: pN1; C: pN2. TD neg: No TDs; TD pos: TDs presence

			Total (N=505)	TD pos (N= 99)	TD neg(N=406)	p	Multivariate		
							OR	IC[95%]	p
Age (years)			63.3 (± 12.7)	63.8 (±12.5)	63.2 (±12.8)	**0.647**	NI		
Sex	**M**		315 (62.4)	56 (56.6)	259 (63.8)	**0.203**	NI		
BMI (kg/m2)			25.4 (+/-4.8)	25.2 (±4.6)	25.5 (± 4.9)	**0.634**	NI		
Synchronous M+			48 (9.5)				NI		
Neoadjuvant TTT	**RCT**		233 (46.1)	50 (50.5)	183 (45.1)	**0.099**	NI		
	RT		42 (8.3)	13 (13.1)	29 (7.1)				
	Chemotherapy		12 (2.4)	3 (3)	9 (2.2)				
	TEM		16 (3.2)	1 (1)	15 (3.7)				
Surgery	**CRA**		38 (7.5)	8 (8.1)	30 (7.4)	**0.226**	NI		
	CAA		358 (70.9)	65 (65.7)	293 (72.2)				
	APE		86 (17)	23 (23.2)	63 (15.5)				
	IPAA		18 (3.6)	1 (1)	17 (4.2)				
	Hartman		5 (1)	2 (2)	3 (0.7)				
pT	**0**		11 (2.2)	0	11 (2.7)	**<0.001***	2.24	1.05-4.79	**0.037**
	1		43 (8.5)	2 (2)	41 (10.1)				
	2		140 (27.7)	11 (11)	129 (31.8)				
	3		253 (50.1)	69 (69.7)	184 (45.3)				
	4		58 (11.5)	17 (17.2)	41 (10.1)				
pN	**0**		272 (53.9)	37 (37.4)	272 (67)	**<0.001****	1.83	1.02-3.28	**0.041**
	1		110 (21.8)	37 (37.4)	73 (18)				
	2		86 (17)	25 (25.3)	61 (15)				
M1 pathological			50 (9.9)	23 (23.2)	27 (6.7)	**<0.001**	3.17	1.49-6.78	**0.003**
Resection status	**R1**		69 (13.7)	28 (28.3)	41 (10.1)	**<0.001**	NS		
	R2		1 (0.2)	0	1 (0.2)				
VI			234 (46.3)	72 (72.7)	162 (39.9)	**<0.001**	2.07	1.10-3.90	**0.025**
PNI			152 (30.1)	64 (64.6)	88 (21.7)	**<0.001**	2.70	1.48-4.92	**<0.001**
Grade		**Low**	394 (78)	70 (84.3)	324 (96.1)	**<0.001**	2.99	1.16-7.72	**0.023**
		High	26 (5.1)	13 (15.7)	13 (3.9)				
Adjuvant TTT			223 (44.2)	85 (85.9)	138 (34)	**<0.001**	NI		

Table 1: Patients characteristics. *: in multivariate analysis comparison concerned pT0-1-2 vs pT3-4; **: for multivariate analysis comparison concerned pN+ vs pN-

TD: Tumor deposit; CRT: Chemoradiotherapy (CAP-50 protocol); RT: Short course radiotherapy; CRA : Colo-rectal anastomosis; CAA: Colo-anal anastomosis; IPAA: Ileal pouch anal anastomosis; APE: Abdominoperineal excision; VI: Vascular invasion; PNI: Perineural invasion; TTT : treatment.

		N0				N1				N2			
		Total (N=309)	**N1c (N= 37)**	**TD neg (N= 272)**	**p**	**Total (N=110)**	**TD pos (N= 37)**	**TD neg (N= 73)**	**p**	**Total (N= 86)**	**TD pos (N= 25)**	**TD neg (N= 61)**	**p**
Neoadjuvant	**0**	117 (37 .9)	8 (21.6)	109 (40.1)	**0.099**	47 (42.7)	14 (37.8)	33 (45.2)	**0.323**	36 (41.9)	10 (40.0)	26 (42.6)	**0.752**
radiotherapy	**CRT**	156 (50.2)	26 (70.2)	130 (47.8)		44 (40)	16 (43.2)	28 (38.4)		33 (38.4)	8 (32.0)	25 (41.0)	
	RT	19 (6.1)	2 (5.4)	17 (6.2)		14 (12.7)	7 (18.9)	7 (9.6)		9 (10.5)	4 (16.0)	5 (8.2)	
Surgery	**CRA**	19 (6.1%)	1 (2.7)	18 (6.6)	**0.274**	9 (8.2%)	3 (8.1)	6 (8.2)	**0.275**	10 (11.6)	4 (16.0)	6 (9.8)	**0.263**
	CAA	221 (71.5)	24 (64.9)	197 (72.4)		77 (70)	26 (70.3)	51 (69.9)		60 (69.8)	15 (60.0)	45 (73.8)	
	APE	59 (19.1)	12 (32.4)	47 (17.3)		15 (13.6)	5 (13.5)	10 (13.7)		12 (14.0)	5 (13.5)	10 (13.7)	
pT	**0**	10 (3.2)	0	6 (2.2)	**<0.001**	2 (1.8)	0	2 (2.7)	**0.011**	3 (3.5)	0	3 (4.9)	**0.636**
	1	31 (10.0)	0	34 (12.5)		5 (4.5)	1 (2.7)	4 (5.5)		4 (4.7)	1 (4.0)	3 (4.9)	
	2	101 (32.7)	4 (10.8)	98 (36)		30 (27.3)	5 (13.5)	25 (34.2)		8 (9.3)	2 (8.0)	6 (9.8)	
	3	142 (46)	26 (70.3)	116 (42.6)		60 (54.5)	29 (78.4)	31 (42.5)		51 (59.3)	14 (56.0)	37 (60.7)	
	4	25 (8.1)	7 (18.9)	18 (6.6)		13 (11.8)	2 (5.4)	11 (15.1)		20 (23.3)	8 (32.0)	12 (19.7)	
pM1		26 (8.4)	14 (37.8)	12 (4.4)	**<0.001**	9 (8.2)	4 (10.8)	5 (6.8)	**0.481**	15 (17.4)	5 (20.0)	10 (16.4)	**0.689**
Resection	**R1**	31 (10.0)	9 (24.3)	22 (8.1)	**0.008**	20 (18.2)	26 (70.3)	64 (87.7)	**0.036**	18 (20.9)	8 (32.0)	10 (16.4)	**0.144**
status	**R2**	1 (0.3)	0	1 (0.4)		0	0	0		0	0	0	
VI		106 (34.3)	21 (56.8)	85 (31.2)	**0.003**	65 (59.1)	29 (78.4)	36 (49.3)	**0.004**	63 (73.3)	22 (88.0)	41 (67.2)	**0.062**
PNI		53 (17.2)	18 (48.6)	35 (12.9)	**<0.001**	46 (41.8)	24 (64.9)	22 (30.1)	**0.001**	53 (61.6)	22 (88.0)	31 (50.8)	**0.001**
Grade	**Low**	250 (80.9)	28 (90.3)	222 (97.8)	**0.058**	82 (74.5)	26 (86.7)	56 (91.8)	**0.470**	62 (72.1)	16 (72.7)	46 (93.9)	**0.021**
	High	8 (2.6)	3 (9.7)	5 (2.2)		9 (8.2)	4 (13.3)	5 (8.2)		9 (10.5)	6 (27.3)	3 (6.1)	
Adjuvant TTT		53 (17.2)	30 (81.1)	23 (8.5)	**<0.001**	95 (86.4)	33 (88.2)	62 (84.9)	**0.77**	75 (87.2)	22 (88.0)	53 (86.9)	**1**

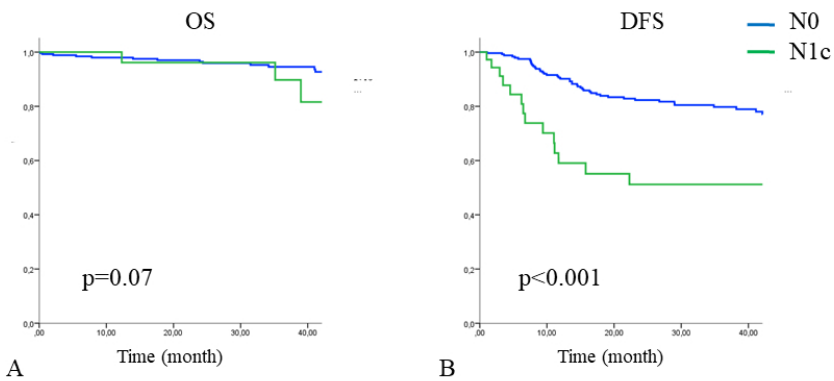
Table 2. Comparison between TD positives and negatives specimen according to LN involvement.

TD: Tumor deposit; CRT: Chemoradiotherapy (CAP-50); RT: Short course Radiotherap; VI: Vascular invasion; PNI: Perineural invasion; TTT : Treatment.

	OS (%)	p	DFS (%)	p	LR (%)	p	DM (%)	p
Population	90.5		66.4		92.3		68.9	
pN0	94.6		79.8		92.4		83.1	
pN1c	89.7		51.2		87.1		55.1	
pN1	90		58.9		92.4		60	
pN1/TD pos	80.8	**0.389**	35.2	**0.004**	93.1	**0.737**	35	**0.003**
pN1/TD neg	93.2		70.1		92.1		72	
pN2	80.6		42.7		94		44.1	
pN2/TD pos	76.4	**0.438**	37.5	**0.499**	100	**0.234**	37.5	**0.375**
pN2/TD neg	82.1		44.7		92		46.6	
M0								
TD pos	89.5	**0.422**	46.7	**<0.001**	92.7	**0.825**	47.8	**<0.001**
TD neg	92.5		76.5		93.4		76.8	
1 TD	82	**0.053**	40.8	**<0.001**	79.1	**0.220**	47.6	**0.001**
N1a/TD ng	95.2		81.3		93.4		81.3	
TD number								
≥4	62.2	**0.087**	20.6	**0.098**	83.3	**0.444**	20.6	**0.96**
<4	86		44.1		93.3		45.3	

Table 3: Three-year survival.

OS: Overall survival; DFS: Disease-free survival; LR: Local recurrence free survival; DM: Distant metastasis free survival



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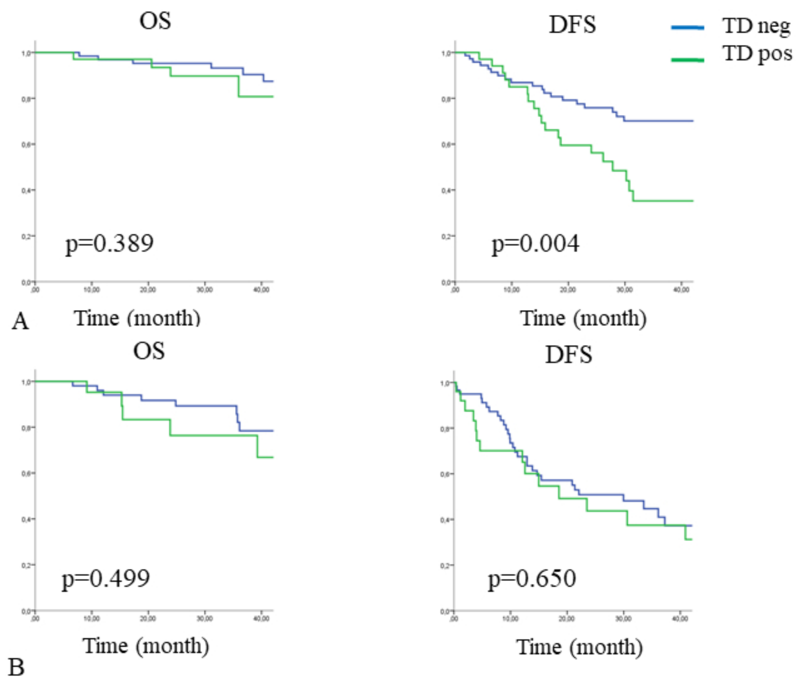

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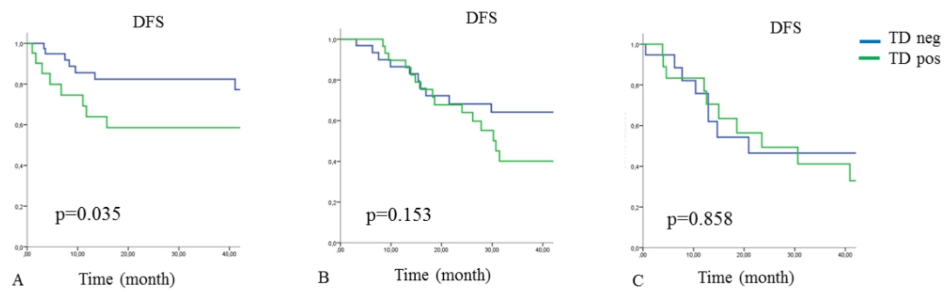

319x203mm (96 x 96 DPI)

		N0			N1			N2		
		TD pos (N=22)	**TD neg (N=44)**	**p**	**TD pos (N=33)**	**TD neg (N=33)**	**p**	**TD pos (N= 20)**	**TD neg (N=20)**	**p**
Age* (years)		64.9 (±10.5)	65.3 (±14.3)	**0.914**	63.6 (±14.4)	59.9 (±14.0)	**0.296**	65.7 (±10.7)	60.2 (±11.4)	**0.128**
Sex*	**M**	11 (50)	22 (50)	**1**	17 (51.5)	17 (51.7)	**1**	13 (65)	13 (65)	**1**
BMI* (kg/m²)		25.3 (±4.5)	25.7 (± 4.7)	**0.764**	24.9 (±5.3)	24.3 (±5.8)	**0.722**	26.6 (±4.1)	26.5 (±6.3)	**0.961**
Neoadjuvant	**0**	8 (36.4)	16 (36.4)	**0.331**	11 (33.3)	13 (39.4)	**0.601**	10 (50)	10 (50)	**0,896**
radiotherapy *	**CRT**	14 (63.6)	24 (54.5)		15 (45.5)	16 (48.5)		7 (35)	6 (30)	
	RT	0	4 (9.1)		7 (21.2)	4 (12.1)		3 (15)	4 (20)	
Surgery*	**CRA**	1 (4.5)	3 (6.8)	**0.905**	2 (6.1)	2 (6.1)	**0.907**	2 (10)	2 (10)	**1**
	CAA	16 (72.7)	30 (68.2)		24 (72.7)	25 (75.8)		13 (65)	13 (65)	
	APE	5 (22.7)	11 (25)		5 (15.2)	5 (15.2)		5 (25)	5 (25)	
pT *	**1**	0	0	**1**	1 (3)	1 (3)	**1**	1 (5)	1 (5)	**1**
	2	4 (18.2)	8 (18.2)		5 (15.2)	5 (15.2)		2 (10)	2 (10)	
	3	13 (59.1)	26 (59.1)		25 (75.8)	25 (75.8)		11 (55)	11 (55)	
	4	5 (22.7)	10 (22.7)		2 (6.1)	2 (6.1)		6 (30)	6 (30)	
Resection status	**R1**	6 (27.3)	8 (18.2)	**0.524**	11 (33.3)	5 (15.2)	**0.150**	7 (35)	5 (25)	**0,731**
VI*		12 (54.5)	2 3 (52.3)	**1**	25 (75.8)	21 (63.6)	**0.422**	17 (85)	17 (85)	**1**
PNI*		12 (54.5)	16 (36.4)	**0.192**	20 (60.6)	13 (39.4)	**0.139**	17 (85)	12 (60)	**0.155**
Adjuvant TTT		16 (72.7)	4 (9.1)	**<0.001**	29 (87.9)	28 (84.8)	**1**	17 (85)	17 (85)	**1**

Supplementary table 1. Patients characteristics after matching.

*: pairing factors.

TD: Tumor deposit; CRT: Chemoradiotherapy (CAP-50); RT: Short course Radiotherap; VI: Vascular invasion; PNI: Perineural invasion;TTT : Treatment.