# Prognostic Effect of Nodular and Infiltrating Tumor deposits of colorectal carcinoma and its relation to neoadjuvant therapy; a retrospective study

Mosa NF[1], Hassan HI[2], Shafiq AM[3], Amen MG[1]

[1] Oncologic Pathology Department, South Egypt Cancer Institute, Assiut University, Egypt
[2] Pathology Department, Faculty of Medicine, Assiut University, Egypt
[3] Medical Oncology Department, South Egypt Cancer Institute, Assiut University, Egypt

## Abstract:

**Objective:** This study aimed to assess correlation between tumor deposits and clinicopathological characteristics of colorectal cancer, evaluate the relationship between tumor deposits and prognosis of colorectal cancer (CRC) patient and the relationship between tumor deposits and neoadjuvant chemotherapy.

**Methods**: One hundred and thirty three cases with stage I–IV CRC who underwent primary tumor resection for operable cases in the period between January 2017 and December 2019 and followed up until June 2022 were included in this study. Cases were selected from the registry of the Pathology Department at South Egypt Carcinoma Institute (SECI). The H & E stained slides were examined initially and the tumors were staged according to AJCC TNM classification eighth edition.

**Result**: Tumor deposit (TD) was detected in 39 (29.3%) of the studied cases, while 94 (70.7%) cases were negative for TDs. Statistical significance association was detected between the presence of TDs and tumor invasion and lymph node (LN) metastasis (P=0.004 and P=0.000). There was statistical significance between TDs and prognosis as follow; presence of TDs decreases the overall survival and DFS (associated with poor prognosis). Both are inversely affected (decreased) (P=0.000, P=0.006) respectively

**Conclusion**: this study shows that tumor deposit is an independent prognostic factor in colorectal carcinoma patients that affects negatively both OS and DFS with significant association between it and lymphovascular invasion (LVI), perineural invasion (PNI), LN metastasis, tumor invasion. Furthermore, presence of both TDs and LN metastases confers additive risk.

**Keywords**: Colorectal carcinoma; tumor deposit; lymph node; neoadjuvant therapy; prognosis

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**Authors Information:**

*Naglaa Fatbi Mosa*
Oncologic Pathology Department, South Egypt Cancer Institute, Assiut University, Egypt
email: Naglaafathi600@gmail.com

*Howayda Ismaeel Hassan*
Pathology Department, Faculty of Medicine, Assiut University, Egypt
email: Howydaluxor@gmail.com

*Ahmed Mahran Shafiq*
Medical Oncology Department, South Egypt Cancer Institute, Assiut University, Egypt
email: Mahran_ahmed40@yahoo.com

*Mahmoud Gamal Amen*
Oncologic Pathology Department, South Egypt Cancer Institute, Assiut University, Egypt
email: mahmoudameengamal@aun.edu.eg

**Corresponding Author:**
*Naglaa Fatbi Mosa*
Oncologic Pathology Department, South Egypt Cancer Institute, Assiut University, Egypt
email: Naglaafathi600@gmail.com

## Introduction:

Colorectal cancer (CRC), the most commonly diagnosed gastrointestinal malignancy and the second leading cause of cancer-related death worldwide [1]. According to Globocan 2020 colorectal cancer is the 7th commonest cancer in Egypt, accounting for 5.8% of male cancers and 6.2% of female cancers.

Tumor deposits (TDs) or mesenteric tumor satellites were first described in rectal carcinoma by Gabriel et al at St. Mark's Hospital in 1935 [2]. Subsequently, TDs have been detected in various malignancies other than colorectal carcinoma, including gastric, pancreatic, gallbladder, and bile duct carcinomas [3,4]. Over the years, there is much debate about the genesis, histopathologic characteristics, and prognostic value of TDs [5].

TDs are associated with advanced colorectal carcinoma stage and poor prognosis, with variable outcome due to different definitions of TDs [6].

Before the 5th edition, published in 1997, tumor node metastasis (TNM) classification did not consider microscopic TDs to be lymph node metastases (LNMs),

and they classified them as a discontinuous extension in the T category [7,8]

In the 5th edition of the TNM, the 3 mm rule was introduced; according to which TDs with a diameter of more than 3 mm were LNMs [8].

In the 6th edition published in 2002, TDs were classified based on the contour of the deposit. Smooth contour TD was considered to be LNM, while irregular contour TD was considered to be venous invasion (VI) or lymphatic invasion (LI) [9].

The 8th TNM Edition clarified that the presence of TDs does not change the primary tumor T category, but changes the node status (N) to pN1c if all regional lymph nodes are negative on pathological examination [9,10].

TDs are divided into infiltrating TDs (iTDs: carcinoma cell aggregates with lymphatic or perineural infiltration or carcinoma cell clusters) and nodular TDs (nTDs: smooth or irregularly shaped carcinoma cells without iTDs). Some researchers have identified nTDs as potentially positive lymph nodes that are no longer identifiable due to total substitution by tumor metastasis. Some believe that TDs should be regarded as a systemic disease rather than a local disease as it represents a unique metastasis mode within or along vessels, nerves, or lymphatic channel [11].

In addition, other studies have identified TDs as the fragmentation of advanced tumors following neoadjuvant chemotherapy [6].

## Patients and Methods:

*Cases selection:*

One hundred and thirty three cases with stage I–IV CRC who underwent primary tumor resection for operable cases in the period between January 2017 and December 2019 and followed up until June 2022 were included in this study. Cases were selected from the registry of Pathology Department at South Egypt Carcinoma Institute (SECI). The H & E stained slides were examined initially and the tumors were staged according to AJCC TNM classification eighth edition. Pathological and clinical data were collected and recorded, including survival data (overall survival, disease free survival).

Also post therapy status was evaluated according to Modified Ryan scheme for tumor regression score (only performed on primary tumor) [12].

Examination of sections for tumor deposit evaluation according to the eighth edition of TNM staging system definition (discrete nodule of carcinoma in pericolic/perirectal fat or adjacent mesentery, without histological evidence of residual lymph node or identifiable vascular or neural structures) [13].

Evaluation of number of tumor deposit and its relation to survival with cut off point 3 tumor deposits [14].

*Inclusion criteria:*

1-This retrospective study includes primary invasive colorectal carcinoma samples from Egyptian patients that will be retrieved from the registry of Pathology department, South Egypt Carcinoma Institute and Assiut University Hospital.

2-All patients who underwent resection of colorectal carcinoma will be included in our study.

*Exclusion criteria:*

1- Endoscopic biopsies specimens were excluded in our study.
2- Metastatic tumors
3- Patients with uncomplete medical report.

*Statistical methods:*

All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Quantitative data were statistically described in terms of mean ± SD and median (range) when not normally distributed. Qualitative data were statistically described in terms of frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables was done using one way analysis of variance (ANOVA) test. For comparing categorical data, Chi square ($\chi^2$) test was performed. Fisher Exact test was used instead when the expected frequency is less than 5. Kaplan-Meier's method with log rank test was used for overall and disease free survival analysis. Hazard ratio (HR) with 95% Confidence Interval (CI) and COX regression analysis was calculated to determine significant factors associated with mortality. P-value is always 2 tailed set significant at 0.05 levels.

*Ethical consideration:*

This research was approved by the Committee of Medical Ethics of the Faculty of Medicine, Assiut University under the number of IRB No: 17101467.

## Results:

One hundred and thirty three cases of different histological grade colorectal carcinoma, which had all the required information in the database, were considered eligible and analyzed in the study. The clinicopathological data were obtained from registry of the Pathology Department at South Egypt Cancer Institute.

*Demographic and clinical features of the studied cases:*

This study was carried out on 133 patients. There were 49 (36.8%) patients with an age range from 18-50 years, 37 (27.8%) with age ranges from 51-65 years and 47 (35.3%) with age above 65 years.

The mean age of the cases examined was 56.8 years, with a median age of 60 years. In that study, 59 patients (44.4%) were male while 74 patients (55.6%) were female.

With respect to the tumor site, 65 (48.9%) were at recto-sigmoid, 34 (25.6%) were at right colon and 34 (25.5%) were at left colon as illustrated in Table (I).

*Pathological features of the studied cases:*

Histopathological examination revealed that the majority of samples were adenocarcinoma 111 (83.4%), followed by mucinous adenocarcinoma 19 (14.3%) and signet ring Carcinoma 3 (2.3%). Based on the WHO classification, low-grade adenocarcinoma represents 94 cases (70.7%), while high-grade adenocarcinoma represents 39 cases (29.3%). For lymphovascular and perineural invasion, lymphovascular emboli were detected in 76 (57.1%), whereas 42 (31.6%) showed perineural invasion as shown in Figure (1). There were 59 (44.4%) of patients showing necrosis.

Concerning the level of invasion (T staging), there were 34 (25.6%) cases of early invasion and 99 (74.4%) cases of advanced invasion. Based on LN metastasis (N staging), there were 64 cases (48.1%) of negative lymph nodes, whereas 69 cases (51.9%) showed LN metastasis as shown in Figure (1). According to M staging there were 123 (92.5%) cases were not associated with distant metastasis, while 10 (7.5%) cases had distant metastasis to different organs (liver, lung and bone).

For immune response, 62 (46.6%) showed brisk immune response, while 71 (53.4%) showed a non brisk immune response as illustrated in Table (I).

Among patients who received neoadjuvant therapy, 3 (11.5%) received neoadjuvant radiation therapy, 18 (69.2%) received neoadjuvant chemotherapy, and 5 (19.2%) received combined CTH&RTH. According to Modified Ryan scheme for tumor regression score there were 5(19.2%) TRG0, 3 (11.5%) TRG1, 7 (26.9%) TRG2, 11 (42.3%) TRG3 as illustrated at Table (I).

*Relationship between tumor deposit and clinicopathological data:*

Tumor deposit detected in 39 (29.3%) of the studied cases, while 94 (70.7%) cases were negative for TDs showed in Figure (2).

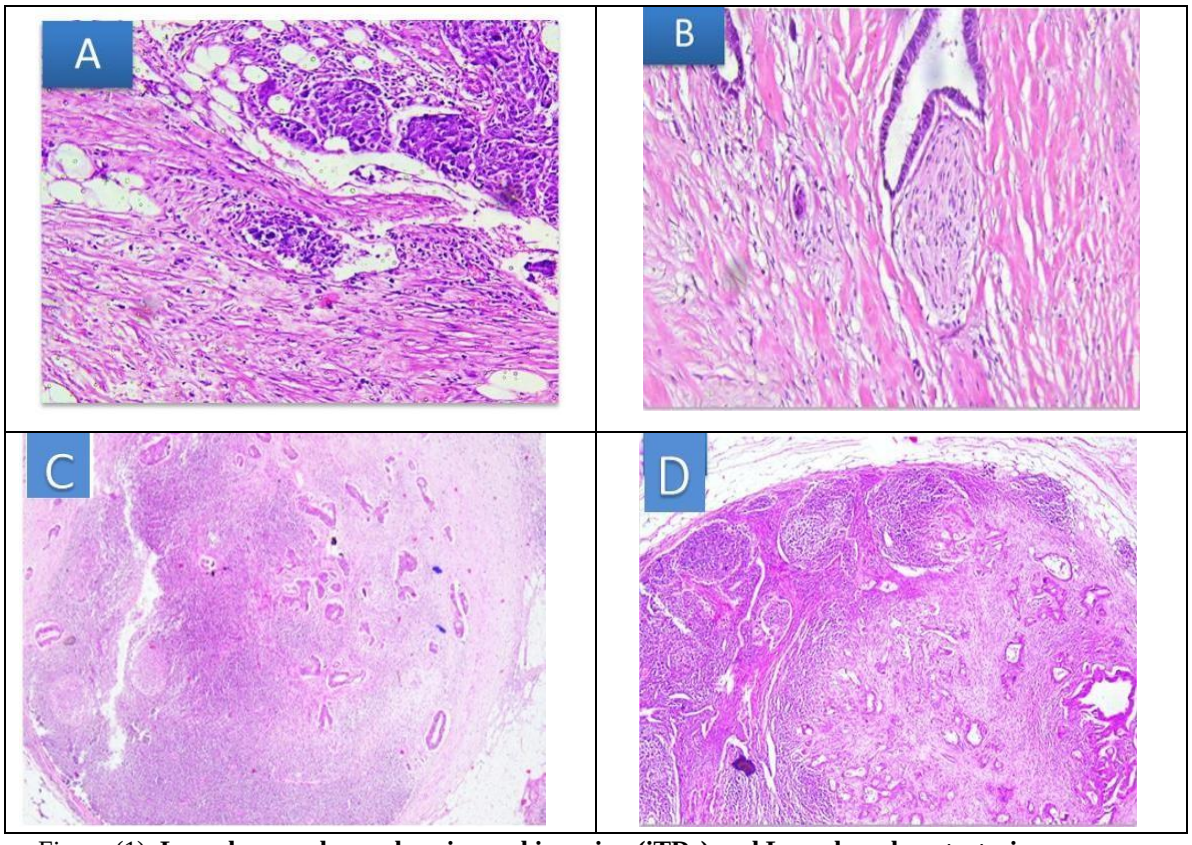


Figure (1): **Lymphovascular and perineural invasion (iTDs) and Lymph nodemetastasis, HE stain, X200 power of magnification**.
(A) Lymphovascular invasion (iTDs): note tumor cells surrounded by endothelial cells with presence of RBCs. (B) Perineural invasion (iTDs): note tumor cells invade perineural sheath. (C) Lymph node metastasis: note metastatic tumour deposits with rim
of lymphatic tissue. (D) Lymph node metastasis with extracapsular extension.

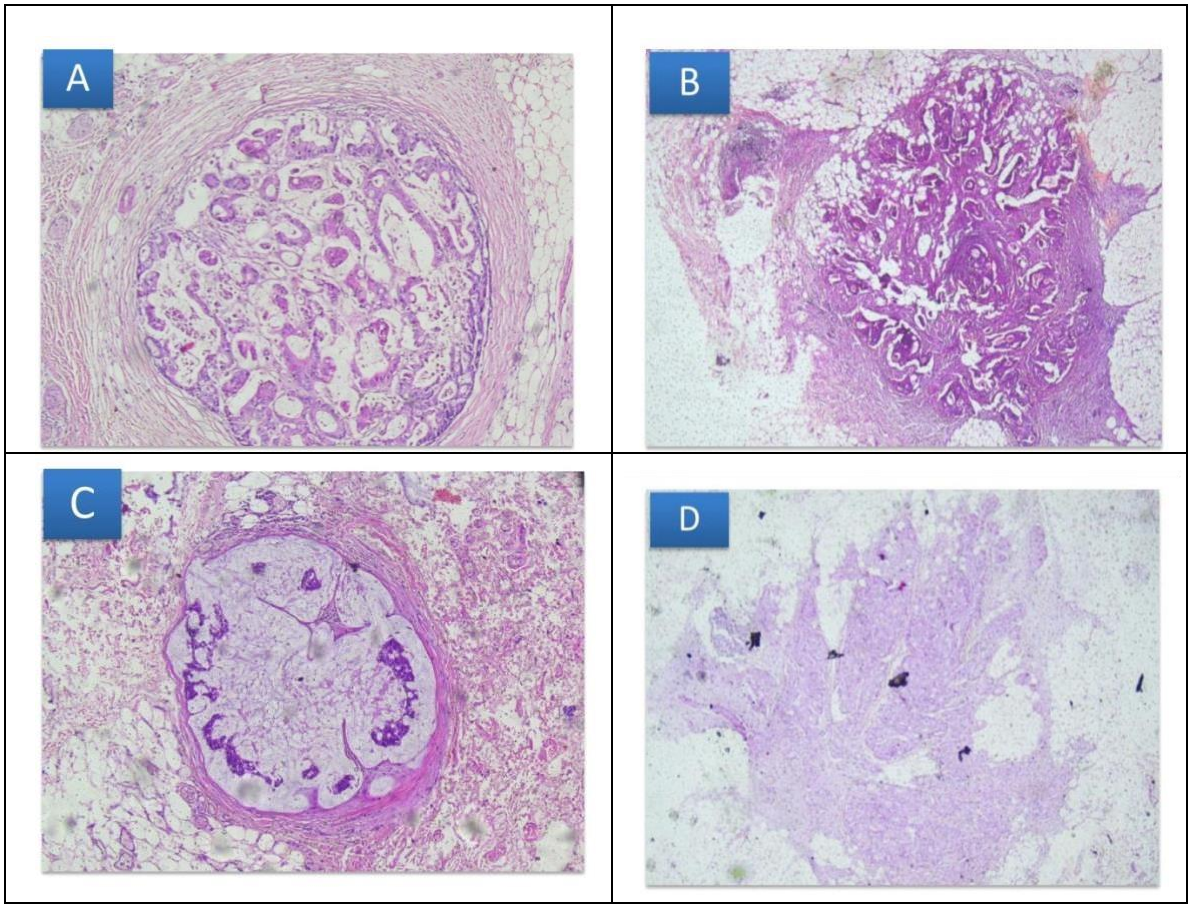


**Figure (2): Nodular tumor deposits (nTDs), HE stain, X100 power of magnification.** (A, B, C) showing nTDs: note the regular contour and absence of lymphatic, neural and vascular structures. Moreover, (C) showing mucinous pools with floating malignant cells.
(D) Showing nTD with irregular contour.

Statistical significance association was detected between presence of TDs and tumor invasion and LN metastasis (P=0.004 and P=0.000). TDs presence associated with increase in tumor invasion and LN metastasis.

No statistical significant correlation was detected between presence of TDs and different histopathologic features including; histologic type, tumor grade, LVI, PNI, necrosis, distant metastasis and immune response (P=0.087, P=0.283, P=0.153, P=0.055, P=0.378, P=0.478 and P=0.110) as illustrated at Table (II).

*Classification of patients according to state of tumor deposits and lymph nodes metastasis:*

Patients who submitted in this study are classified into 4 groups according to the status of LNs and TDs as follow:

1- First group that include patients who was negative for both LN and TD (n=64).

2- Second group that include patients who was positive for both LN and TD (n=25).

3- Third group that include patients who was positive for LN and negative for TD (n=30).

4- Fourth group that include patients who was negative for LN and positive for TD (n=14).

*Association between different groups and clinicopathological data:*

There was no statistical significance between our study groups and (tumor pathology, tumor grade, necrosis, distant metastasis and immune response) (P=0.222, P=0.580, P=0.481, P=0.173, P=0.258).

However, statistical significance was noted with LVI, PNI, tumor invasion and LN metastasis as patient group with LN(+)TD(+) more likely to have LVI, PNI, more advanced tumor invasion and LN metastasis (P=0.000, P=0.006, P=0.005, P=0.000) as illustrated in Table (III)

*Relationship between detectable groups based on tumor deposit status and lymph node status and therapy response:*

There was statistical significance among the study groups and neoadjuvant therapy. This significant relationship could be demonstrated through negative tumor deposit and lymph nodes in patients who

received neoadjuvant treatment, whereas positive tumor deposit and positive lymph node mostly noticed in patients who did not receive neoadjuvant therapy (P=0.014). However, there was no statistical significance between the groups and tumor regression grade (P=0.635) as illustrated at Table (IV).

*Patient's survival analytic data and their relation to TDs status and other clinicopathologic parameters:*
*Clinicopathologic data and TDs:*

Univariate analysis using Kaplan Meier method and log rank test to detect the difference in survival between groups, revealed statistical significance between overall survival and (age group, distant metastasis, neoadjuvant therapy, LVI, PNI, tumor invasion and LN metastasis) (P=0.001, P=0.007, P=0.057, P=0.001, P=0.002, P=0.001, P=0.000) as illustrated in Table (V) Figures (3).

In addition a statistical significance was noted between TDs and prognosis as follow; presence of TDs decrease the overall survival and DFS (associated with poor prognosis). Both are inversely affected (decreased) (P=0.000, P=0.006) respectively as illustrated in Table (V) and in Figures (4).

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*Defined study groups and survival:*

There was statistical significance among the study groups with OS and DFS as follow; patients who are LN(+) TD(+) are more likely to have deteriorating survival period and high mortality and to develop recurrent disease than patients who are LN(-) TD(+) and least in patients with LN(+) TD(-). The best prognosis with highest OS and DFS were patients with LN(-) TD(-) (P=0.000, P=0.000 respectively)as illustrated in Table (V) Figures (5).

Nearly all patients who received neoadjuvant therapy and negative TDs, were alive over 3 years, while only 10% of patients who didn't receive neoadjuvant therapy and positive TDs were alive as illustrated in Table (VI) and Figures (6).

Univariate COX regression analysis for prediction of death among colorectal cancer patients showed that patients with older age, who developed metastasis, LVI, PNI, with advanced stage (TNM staging), those with higher TDs (≥ 3), and patients with either LN +ve TD +ve, LN +ve TD –ve, or LN -ve TD +ve were more likely to have high rate mortality from disease compared to their counterparts. This finding was confirmed in multivariate COX regression analysis after exclusion of independent factors that have multi-colinearity as we observed that patients with LN +ve TD +ve were about 12 times more likely to die compared to patients with LN -ve TD -ve (OR=12.469, 95% CI 4.548 – 34.189, P<0.001), also patients with LN -ve TD +ve were about 15 times more likely to die compared to patients with LN +ve TD -ve (OR=15.132, 95% CI 5.132 – 43.981, P<0.001) as shown in Table VII.

## Discussion:

Colorectal carcinoma is a major health problem worldwide. Several studies have been applied to predict prognostic factors for colorectal carcinoma. The main aim of these studies was to improve patient's overall survival and maintains their physical and social activity in a perfect manner.

Several factors were found to be involved in prediction of the overall survival of colorectal carcinoma patients; one of the important prognostic factors was tumor deposit.

After being defined by several editions of AJCC staging manual, TD was newly defined as isolated tumor foci in the pericolorectal fat or adjacent mesocolic fat away from the leading edge of the tumor without histological evidence of residual lymph node or identifiable vascular or neural structures [15].

Precisely, this study was applied to determine whether TDs are equal to LNMs, in prognostic sense, this would simplify the staging systems as they can be placed in the N category without loss of information; however, if TDs add information to staging, either alone or taking into account their etiology, we need to have specific substaging.

In the present study, Thirty-nine (29.3%) patients with colorectal carcinomas had tumor deposits in the pericolic and/or mesocolic region. The relation between TD status and other clinicopathological data was investigated. A significant relation between tumor deposit and level of tumor invasion and lymph node metastasis was found. This relationship demonstrated that patients have deeper invasion and more LNs metastasis, are more likely to be tumor deposit positive (74.4%, 53.8%). These findings were in agreement with Gopal et al., 2014 who stated that the presence of tumor deposits in patients with rectal adenocarcinoma is associated with a poor prognosis [16]. Tumor deposit patients in our study had larger tumors, higher tumor grade, greater tumor invasion, and higher staging at presentation.

In our study there is no statistical significance between tumor deposit and distant metastasis (P=0.478), although Wu et al., 2022 who compared with patients with negative TDs, CRC patients with positive TDs are more likely to develop distant metastasis [11]. Also he categorized patients as T4aN2bM0 TDs (+) and T4bN2M0 TDs (+), both have a similar prognosis as those with stage IV, and hence these patients should be classified as stage IV. This controversy could be attributed to using larger sample size in their study.

Survival rates among the patients with more than 3 tumor deposits; were significantly lower than those less than 3 and they were lower than those without deposit at all (3-year overall survival: 9.1% vs 25.0% vs 89.4%, p < 0.000 respectively; and 3-year recurrence-free survival: 87.5% vs 79.4% vs 94.2% p < 0.006).

In line with our study, Wei et al., 2016 reported that the cause-specific survival rate of TD-positive CRC patients was significantly worse than those of patients without TDs in the absence of metastatic lymph nodes [18].

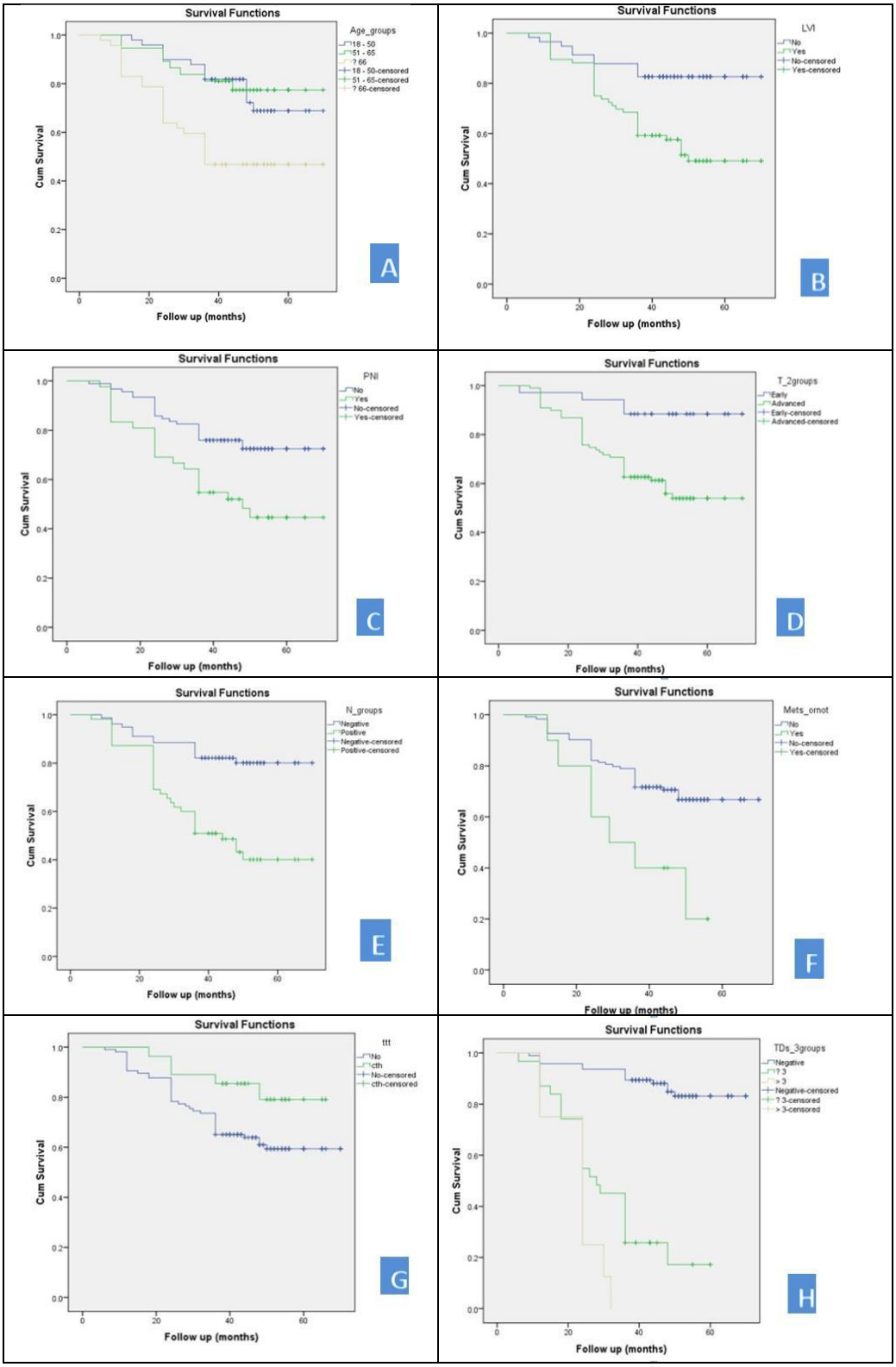


**Figure (3): Overall survival curves of the studied colorectal carcinoma cases according to (A) age, (B) LVI, (C) PNI, (D) level of tumor invasion within colorectal wall, (E) LN metastasis, (F) distant metastasis, (G) neoadjuvant therapy and (H) number of tumordeposits.**

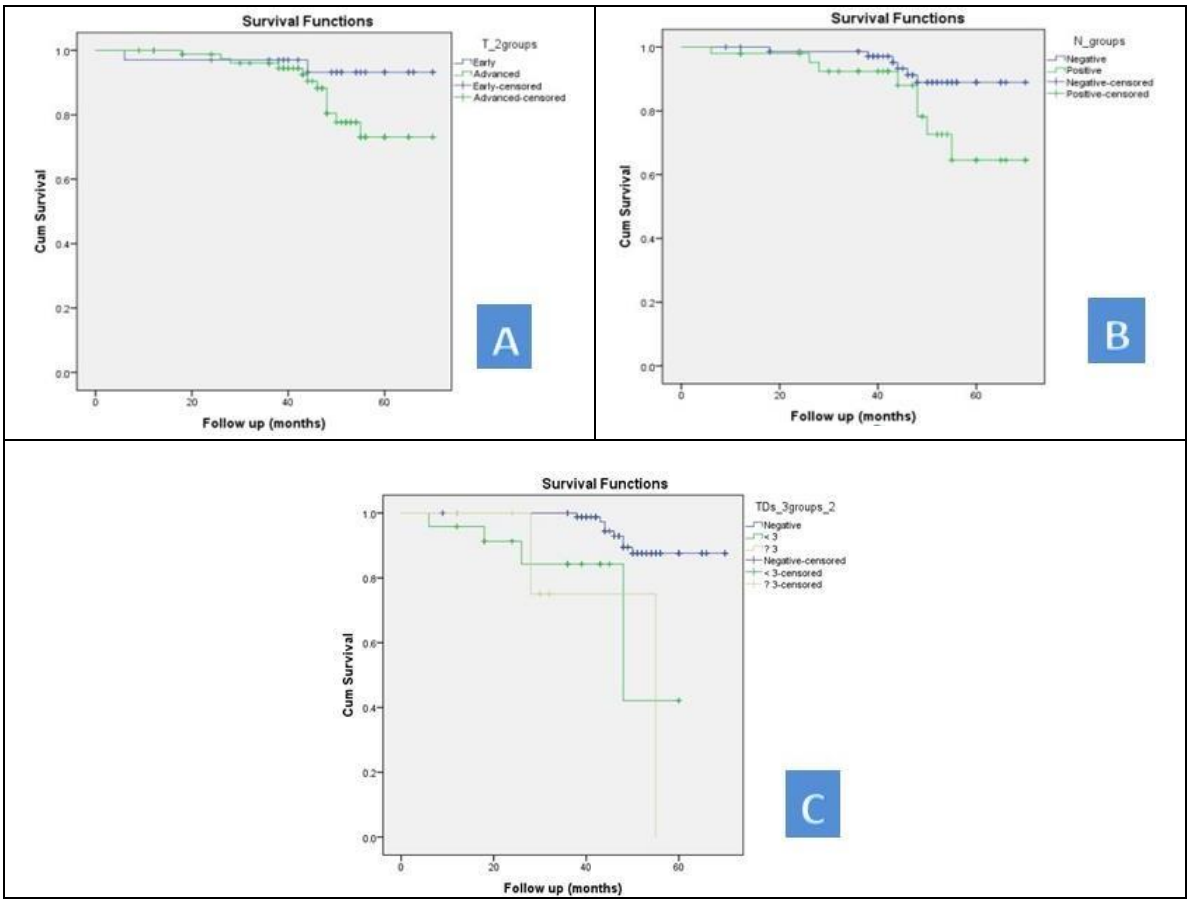


**Figure (4): Disease free survival curves of the studied colorectal cancer cases according to (A) level of tumor invasion within colorectal wall, (B) LN metastasisand (C) number of tumor deposits.**

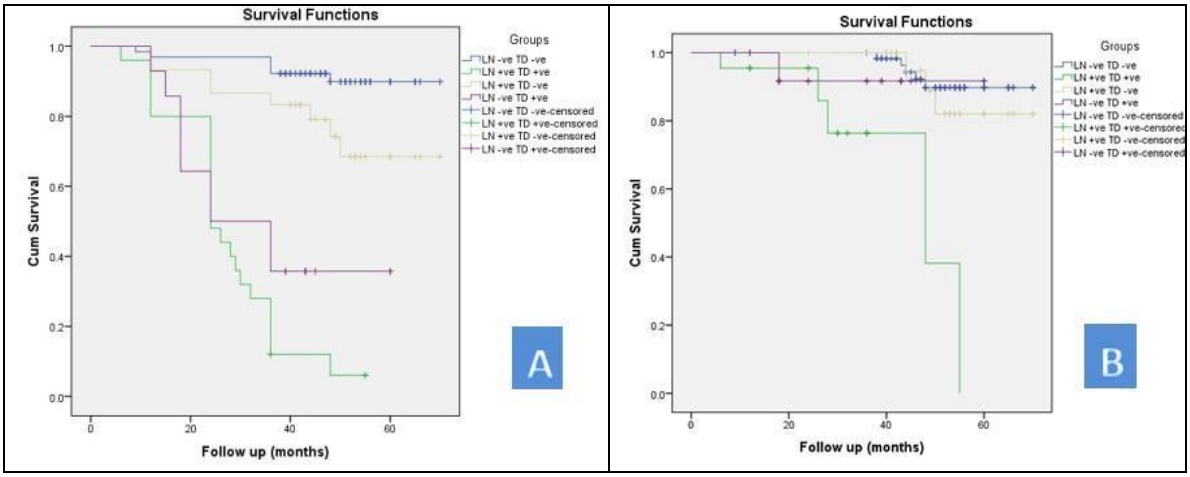


**Figure (5): Survival curves of different study groups, (A) Overall survival curvesand (B) Disease free survival curves.**

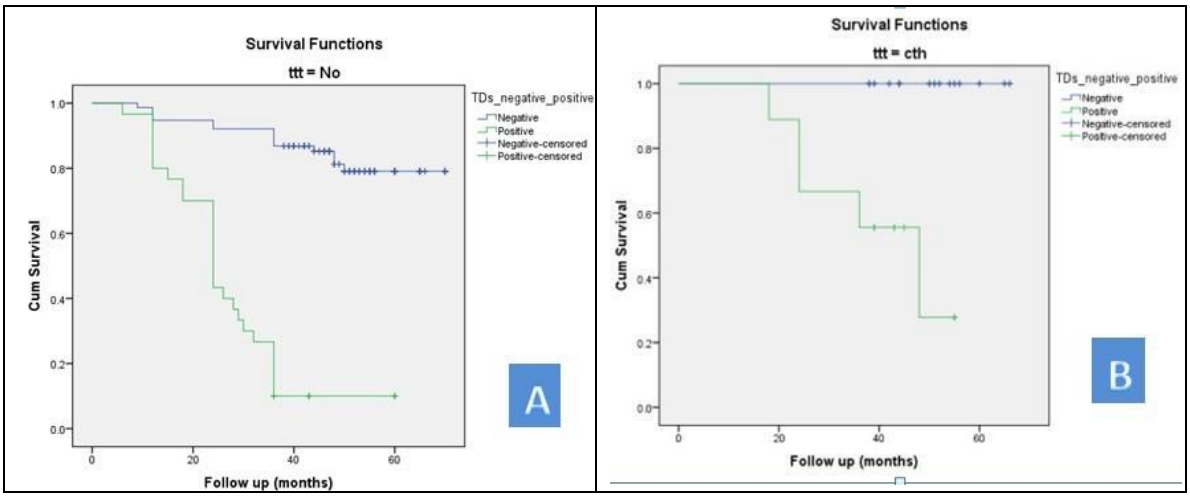


**Figure (6): Overall survival curves among Tumor Deposit positive patients. (A) patients didn't receive neoadjuvant treatment (CTH, RTH, or both) and (B) patients received neoadjuvant treatment (CTH, RTH, or both).**

**Table I Demographic and clinicopathological data of the studied participants (n=267)**

| Variable name | N | (%) |
|---|---|---|
| **Age (years)** | | |
| • Mean ± SD | 56.77 ± 14.71 | |
| • Median (range) | 60 (24 – 82) | |
| **Age groups** | | |
| • 18 – 50 | 49 | (36.8) |
| • 51 – 65 | 37 | (27.8) |
| • ≥ 66 | 47 | (35.3) |
| **Sex** | | |
| • Male | 59 | (44.4) |
| • Female | 74 | (55.6) |
| **Site of tumor** | | |
| • Recto-sigmoid | 65 | (48.9) |
| • Right colon | 34 | (25.6) |
| • Left colon | 34 | (25.5) |
| **Tumor pathology** | | |
| • Adenocarcinoma | 111 | (83.4) |
| • Mucinous adenocarcinoma | 19 | (14.3) |
| • Signet ring carcinoma | 3 | (2.3) |
| **Tumor grade** | | |
| • Low grade | 94 | (70.7) |
| • High grade | 39 | (29.3) |
| **LVI +ve** | 76 | (57.1) |
| **PNI +ve** | 42 | (31.6) |
| **Necrosis +ve** | 59 | (44.4) |
| **TNM staging** | | |
| **Tumor invasion** | | |
| • Early invasion | 34 | (25.6) |
| • Advanced invasion | 99 | (74.4) |
| **Lymph node** | | |
| • Negative | 64 | (48.1) |
| • Positive | 69 | (51.9) |
| **Tumor metastasis** | | |
| • M0 | 123 | (92.5) |
| • M1 | 10 | (7.5) |
| **Immune response** | | |
| • Brisk | 62 | (46.6) |
| • Non-brisk | 71 | (53.4) |
| **Treatment** | | |
| • Radiotherapy | 3 | (11.5) |
| • CTH | 18 | (69.2) |
| • Combined CTH&RTH | 5 | (19.2) |
| **Response grade** | | |
| • TRG0 | 5 | (19.2) |
| • TRG1 | 3 | (11.5) |
| • TRG2 | 7 | (26.9) |
| • TRG3 | 11 | (42.3) |

LVI : Lymphovascular invasion , PNI : Perineural invasion, TNM : Tumor, Node, Metastasis
TRG : Tumor regression grade
Quantitative data are presented as mean ± SD and range; qualitative data are presented as number (percentage).

**Table II Demographic and clinical variables according to Tumor Deposit positivity**

| Variable name | TDs –ve (n=94) | | TDs +ve (n=39) | | P value |
|---|---|---|---|---|---|
| **Histologic type** | | | | | 0.087 |
| • Adenocarcinoma | 82 | (87.2) | 29 | (74.4) | |
| • Mucinous adenocarcinoma | 11 | (11.7) | 9 | (20.5) | |
| • Signet ring carcinoma | 1 | (1.1) | 2 | (5.1) | |
| **Tumor grade** | | | | | 0.283 |
| • Low grade | 69 | (73.1) | 25 | (64.1) | |
| • High grade | 25 | (26.9) | 14 | (35.9) | |
| **LVI** | | | | | 0.153 |
| • Negative | 44 | (46.8) | 13 | (33.3) | |
| • Positive | 50 | (53.2) | 26 | (66.7) | |
| **PNI** | | | | | 0.055 |
| • Negative | 69 | (73.4) | 22 | (56.4) | |
| • Positive | 25 | (26.6) | 17 | (43.6) | |
| **Necrosis** | | | | | 0.378 |
| • Negative | 50 | (53.2) | 24 | (61.5) | |
| • Positive | 44 | (46.8) | 15 | (38.5) | |
| **TNM staging** | | | | | |
| **Tumor invasion** | | | | | **0.004** |
| • Early | 5 | (5.4) | 0 | (0.0) | |
| • Advanced | 3 | (3.2) | 0 | (0.0) | |
| **LN metastasis** | | | | | **<0.001** |
| • Negative | 64 | (68.1) | 14 | (35.9) | |
| • Positive | 30 | (31.9) | 25 | (64.1) | |
| **Distant metastasis** | | | | | 0.478 |
| • M0 | 88 | (93.6) | 35 | (89.7) | |
| • M1 | 6 | (6.4) | 4 | (10.3) | |
| **Immune response** | | | | | 0.110 |
| • Brisk | 48 | (51.1) | 14 | (35.9) | |
| • Non-brisk | 46 | (48.9) | 25 | (64.1) | |

LVI : Lymphovascular invasion , PNI : Perineural invasion, TNM : Tumor, Node, Metastasis
TRG : Tumor regression grade, LN: Lymph node
Chi-square test (Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$).

**Table III Pathological variables comparing LN (-ve) TD (-ve) vs. LN (+ve) TD (+ve) vs. LN (+ve) TD (-ve) and LN (-ve) TD (+ve)**

| Variable name | LN -ve TD–ve (n=129) | | LN +ve TD +ve (n=50) | | LN +ve TD –ve (n=60) | | LN -ve TD +ve (n=28) | | P value |
|---|---|---|---|---|---|---|---|---|---|
| **Histologic type** | | | | | | | | | |
| • Adenocarcinoma | 56 | (87.5) | 18 | (72.0) | 26 | (86.7) | 11 | (78.6) | |
| • Mucinous adenocarcinoma | 8 | (12.5) | 6 | (24.0) | 3 | (10.0) | 2 | (14.3) | |
| • Signet ring carcinoma | 0 | (0.0) | 1 | (4.0) | 1 | (3.3) | 1 | (7.1) | |
| **Tumor grade** | | | | | | | | | 0.566 |
| • Low grade | 48 | (75.0) | 15 | (60.0) | 21 | (70.0) | 10 | (71.4) | |
| • High grade | 16 | (25) | 10 | (40.0) | 9 | (30.0) | 4 | (28.6) | |
| **LVI** | | | | | | | | | **0.000*** |
| • Negative | 44 | (68.8) | 2 | (8.0) | 0 | (0.0) | 11 | (78.6) | |
| • Positive | 20 | (31.2) | 23 | (92.0) | 30 | (100.0) | 3 | (21.4) | |
| **PNI** | | | | | | | | | **0.006*** |
| • Negative | 51 | (79.7) | 11 | (44.0) | 18 | (60.0) | 11 | (78.6) | |
| • Positive | 13 | (20.3) | 14 | (56.0) | 12 | (40.0) | 3 | (21.4) | |
| **Necrosis** | | | | | | | | | 0.481 |
| • Negative | 32 | (50.0) | 14 | (56.0) | 18 | (60.0) | 10 | (71.4) | |
| • Positive | 32 | (50.0) | 11 | (44.0) | 12 | (40.0) | 4 | (28.6) | |
| **TNM staging** | | | | | | | | | |
| **Tumor invasion** | | | | | | | | | **0.005** |
| • Early | 23 | (35.9) | 2 | (8.0) | 9 | (30.0) | 0 | (0.0) | |
| • Advanced | 41 | (64.1) | 23 | (92.0) | 21 | (70.0) | 14 | (100.0) | |
| **Lymph node** | | | | | | | | | **0.000*** |
| • Negative | 64 | (100.0) | 0 | (0.0) | 0 | (0.0) | 14 | (100.0) | |
| • Positive | 0 | (0.0) | 25 | (100.0) | 30 | (100.0) | 0 | (0.0) | |
| **Distant metastasis** | | | | | | | | | 0.173 |
| • M0 | 62 | (96.9) | 22 | (88.0) | 26 | (86.7) | 13 | (92.9) | |
| • M1 | 2 | (3.1) | 3 | (12.0) | 4 | (13.3) | 1 | (7.1) | |
| **Immune response** | | | | | | | | | 0.258 |
| • Brisk | 35 | (54.7) | 8 | (32.0) | 13 | (43.3) | 6 | (42.9) | |
| • Non-brisk | 29 | (45.3) | 17 | (68.0) | 17 | (56.7) | 8 | (57.1) | |

LVI : Lymphovascular invasion , PNI : Perineural invasion, TNM : Tumor, Node, Metastasis , LN: Lymph node, TD: Tumor deposit
Chi-square test (Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$).

**Table IV Comparison of treatment among LN (-ve) TD (-ve) vs. LN (+ve) TD (+ve) vs. LN (+ve) TD (-ve) and LN (-ve) TD (+ve) (n=267)**

| Variable name | LN-veTD–ve (n=129) | | LN+veTD+ve (n=50) | | LN+veTD–ve (n=60) | | LN-veTD+ve (n=28) | | P value |
|---|---|---|---|---|---|---|---|---|---|
| **Received Treatment** | | | | | | | | | **0.014*** |
| • No | 46 | (71.9) | 20 | (80.0) | 30 | (100.0) | 10 | (71.4) | |
| • Yes | 18 | (28.1) | 5 | (20.0) | 0 | (0.0) | 4 | (28.6) | |
| **Response grade** | | | | | | | | | 0.635 |
| • TRG0 | 4 | (22.2) | 1 | (25.0) | 0 | (0.0) | 0 | (0.0) | |
| • TRG1 | 3 | (16.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | |
| • TRG2 | 5 | (27.8) | 0 | (0.0) | 0 | (0.0) | 2 | (50.0) | |
| • TRG3 | 6 | (33.3) | 3 | (75.0) | 0 | (0.0) | 2 | (50.0) | |

TRG: Tumor regression grade
Chi-square test (Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$).

**Table V Overall survival and disease free survival according to clinic-pathological data**

| | OS (3 years) Estimate ± SE | P value | DFS (3 years) Estimate ± SE | P value |
|---|---|---|---|---|
| **Age groups** | | **0.001*** | | 0.678 |
| • 18 – 50 | 87.8 ± 4.3 | | 90.5 ± 4.5 | |
| • 51 – 65 | 81.1 ± 6.4 | | 90.4 ± 5.3 | |
| • ≥ 66 | 46.8 ± 7.3 | | 93.0 ± 3.9 | |
| **Sex** | | 0.344 | | 0.694 |
| • Male | 72.9 ± 5.8 | | 89.6 ± 4.4 | |
| • Female | 66.2 ± 5.5 | | 92.2 ± 3.4 | |
| **Site of tumor** | | 0.757 | | 0.443 |
| • Right colon | 61.8± 8.3 | | 90.2± 5.4 | |
| • Left colon | 64.7± 8.2 | | 93.1 ± 4.8 | |
| • Recto-sigmoid | 75.4± 5.3 | | 90.1 ± 4.2 | |
| **Distant metastasis** | | **0.007*** | | 0.258 |
| • No | 71.5 ± 4.1 | | 90.8 ± 2.8 | |
| • Yes | 40.0 ± 15.5 | | 100.0 ± 0.0 | |
| **Received therapy** | | 0.057 | | 0.979 |
| • No | 65.1 ± 4.6 | | 91.1 ± 3.0 | |
| • Yes | 85.2 ± 6.8 | | 90.9 ± 6.1 | |
| **Tumor grade** | | 0.603 | | 0.746 |
| • Low grade | 53.9 ± 2.3 | | 64.6 ± 1.6 | |
| • High grade | 55.5 ± 3.6 | | 65.0 ± 2.4 | |
| **LVI** | | **0.001*** | | 0.669 |
| • No | 82.5 ± 5.0 | | 90.5 ± 4.0 | |
| • Yes | 59.2 ± 5.6 | | 91.5 ± 3.7 | |
| **PNI** | | **0.002*** | | 0.428 |
| • No | 75.8 ± 4.5 | | 90.1 ± 3.3 | |
| • Yes | 54.8 ± 7.7 | | 93.4 ± 4.6 | |
| **Necrosis** | | 0.964 | | 0.248 |
| • Absent | 70.3 ± 5.3 | | 90.7 ± 3.6 | |
| • Present | 67.8 ± 6.1 | | 91.2 ± 4.2 | |
| **T staging** | | **0.001*** | | 0.167 |
| • Early | 88.2 ± 5.5 | | 93.8 ± 4.2 | |
| • Advanced | 62.6 ± 4.9 | | 89.7 ± 3.5 | |
| **N staging** | | **0.000*** | | 0.140 |
| • Negative | 89.7 ± 3.7 | | 92.3 ± 3.3 | |
| • Positive | 47.7 ± 6.2 | | 90.1 ± 4.3 | |
| **Immune response** | | 0.085 | | 0.244 |
| • Brisk | 77.4 ± 5.3 | | 96.1 ± 2.7 | |
| • Non-brisk | 62.0 ± 5.8 | | 86.2 ± 4.6 | |
| **TDs** | | **0.000*** | | **0.006*** |
| • Negative | 89.4 ± 3.2 | | 94.2 ± 2.5 | |
| • < 3 | 25.0 ± 8.2 | | 79.4 ± 9.6 | |
| • ≥ 3 | 9.1 ± 8.7 | | 87.5 ± 11.7 | |
| **Groups** | | **0.000*** | | **0.001*** |
| • LN -ve TD –ve | 92.2 ± 3.4 | | 91.9 ± 3.5 | |
| • LN +ve TD +ve | 12.0 ± 6.5 | | 70.2 ± 14.6 | |
| • LN +ve TD –ve | 83.3 ± 6.8 | | 100.0 ± 7.0 | |
| • LN -ve TD +ve | 35.7 ± 12.8 | | 92.3 ± 7.4 | |

LVI : Lymphovascular invasion , PNI : Perineural invasion, LN: Lymph node, TD: Tumor deposit
OS: Overall survival DFS: Disease free survival
**Kaplan Meier analysis** Their follow up was ended at 32 months

**Table VI Three years overall survival among patients received treatment (CTH, RTH, or both) according to Tumor Deposit positivity**

| OS (3 years) | Negative TDs Estimate ± SE | Positive TDs Estimate ± SE | P value |
|---|---|---|---|
| **Received treatment** | | | **0.000*** |
| • No | 86.8 ± 3.9 | 10.0 ± 5.5 | |
| • Yes | 100.0 ± 0.0 | 55.6 ± 16.6 | |

TD: Tumor deposit
OS: Overall survival DFS: Disease free survival
**Kaplan Meier analysis** Their follow up was ended at 32 months

**Table VII Results of COX regression analysis for predicting likelihood of death according to clinic-pathological characteristics of the study participants (n=267)**

| | | Univariate COX regression | | | Multivariate COX regression | | |
|---|---|---|---|---|---|---|---|
| **Variable name** | **N** | **HR** | **95% C.I. for HR** | **P value** | **HR** | **95% C.I. for HR** | **P value** |
| **Age groups** | | | | | Not included in the final model | | |
| • 18 – 50 | 99 | Ref | | | | | |
| • 51 – 65 | 74 | 0.852 | 0.353 – 2.056 | 0.721 | | | |
| • ≥ 66 | 94 | 2.547 | 1.301 – 4.984 | **0.006*** | | | |
| **With metastasis** | | | | | Not included in the final model | | |
| • No | 247 | Ref | | | | | |
| • Yes | 20 | 2.786 | 1.243 – 6.245 | **0.013*** | | | |
| **LVI** | | | | | | | |
| • No | 115 | Ref | | | Ref | | |
| • Yes | 152 | 3.064 | 1.519 – 6.182 | **0.002*** | 2.382 | 0.923 – 6.150 | 0.073 |
| **PNI** | | | | | | | |
| • No | 183 | Ref | | | Ref | | |
| • Yes | 84 | 2.333 | 1.307 – 4.163 | **0.004*** | 1.220 | 0.658 – 2.262 | 0.529 |
| **T staging** | | | | | Not included in the final model | | |
| • Early | 69 | Ref | | | | | |
| • Advanced | 198 | 4.440 | 1.589 – 12.407 | **0.004*** | | | |
| **N staging** | | | | | Not included in the final model | | |
| • Negative | 137 | Ref | | | | | |
| • Positive | 130 | 6.797 | 3.159 – 14.626 | **0.000*** | | | |
| **TDs** | | | | | Not included in the final model | | |
| • Negative | 189 | Ref | | | | | |
| • < 3 | 56 | 9.487 | 4.734 – 19.015 | **0.000*** | | | |
| • ≥ 3 | 22 | 14.570 | 6.233 – 34.057 | **0.000*** | | | |
| **Groups** | | | | | | | |
| • LN -ve TD –ve | 129 | Ref | | | ref | | |
| • LN +ve TD +ve | 50 | 20.419 | 8.096 – 51.494 | **0.000*** | 12.469 | 4.548 – 34.189 | **<0.001*** |
| • LN +ve TD –ve | 60 | 3.088 | 1.071 – 8.902 | **0.037*** | 1.792 | 0.569 – 5.644 | 0.319 |
| • LN -ve TD +ve | 28 | 12.693 | 4.446 – 36.238 | **0.000*** | 15.023 | 5.132 – 43.981 | **<0.001*** |

LVI: Lymphovascular invasion, PNI: Perineural invasion, LN: Lymph node, TD: Tumor deposit
B = regression coefficient, SE = standard error, HR= hazard ratio, CI =confidence interval, p value is significant ≤0.05

It was clear that positive TD status was an independent risk factor of poor prognosis of CRC without metastatic lymph nodes, and the classification of N1c has been introduced into AJCC TNM stage system. In the CRC patients with metastatic lymph nodes, the prognostic value of TD status was neglected in AJCC staging system, which aroused worldwide discussion.

X. Li et al., 2018 showed that TDs were associated with worse 3-year OS overall survival in patients of any known and unknown N categories, which suggested that TDs might be associated with a risk of all-cause death or cancer-specific death at least similar to a positive lymph node in all N categories [19]. Basnet et al., 2018 signified that TD was an independent prognostic factor associated with metastatic diseases along with vascular invasion and the number of metastatic lymph nodes among CRC patients (15). All these studies indicated that it might be more reasonable to differentiate prognostic significance of TD status from that of metastatic lymph nodes, and more details of TDs should be explored in CRC patients.

Delattre et al., 2020 reported that the disease-free survival rate was significantly worse for TD-positive patients compared to those without TDs [20].

In agreement with our study a retrospective analysis performed by Pricolo et al., 2020 in stage III colon cancer patients showed how patients included in pN1c staging category with ≥ 3 TDs had a worse overall survival than those with < 3 TDs. Zheng et al., 2020 identified a cutoff of 4 or more TDs to predict poorer disease specific survival using data pooled from SEER database [21].

Also in our study we found that nearly all patients who received neoadjuvant therapy and negative TDs, were alive over 3 years, while only 10% of patients who didn't receive neoadjuvant therapy and positive TDs were alive.

In agreement with our study Gopal et al., 2014 show that the presence of tumor deposits following neoadjuvant chemoradiation is associated with poor prognostic indicators similar to patients with tumor deposits in colorectal adenocarcinoma patients in general and patients with tumor deposits who were treated with neoadjuvant chemoradiation trended toward having a decreased tumor regression grade in response to treatment [16]. Also in line with our study Lord et al., 2019 show that in analogy with untreated patients, the presence of TDs in patients with rectal cancer after neoadjuvant treatment is associated with advanced disease and a poor outcome [22].

In this study the submitted patients were classified into four groups according to status of LNs and TDs as follow:

1- First group that include patients who was negative for both LN and TD (n=64).

2- Second group that include patients who was positive for both LN and TD (n=25).

3- Third group that include patients who was positive for LN and negative for TD (n=30).

4- Fourth group that include patients who was negative for LN and positive for TD (n=14).

According to grouping of the studied patients, 3-year survival rates were nearly similar for LN−ve TD−ve (92.2), LN+ve TD−ve (83.3%), but significantly worse for LN−ve TD+ve (35.7%), LN+ve TD+ve (12.0%) (P<0.001), this means that presence of both TDs and LN metastases confers additive risk. Presence of both elements was, in fact, associated with significantly worse survival than each of these risk factors alone. The presence of LN+ve TD+ve was more often associated with advanced tumor invasion (92%), LN metastasis (96%), PNI+ve (56.0%), and LVI+ve (92.0%), than LN+ve TD−ve or LN−ve TD+ve or LN-ve TD-ve.

This finding was confirmed in multivariate COX regression analysis after exclusion of independent factors that have multi-colinearity as we observed that patients with LN +ve TD +ve were about 12 times more likely to die compared to patients with LN -ve TD -ve (OR=12.469, 95% CI 4.548 – 34.189, P<0.001), also patients with LN -ve TD +ve were about 15 times more likely to die compared to patients with LN -ve TD +ve (OR=15.132, 95% CI 5.132 – 43.981, P<0.001).

In agreement with our study Pricolo et al., 2020 form a comparison of histopathologic variables and different groups showing that LN+TD+ tumors were associated with other adverse features such as T4 status, PD, PNI, LVI, significantly more often than either LN+ve TD− ve or LN−ve TD+ve tumors. Also according to overall and 5-year survival was significantly worse for LN+ve TD+ve patients (41.5%), than either LN+ve TD−ve (59.8%) or LN−ve TD+ve patients (58.2%) (P<0.001) (21).

Also a study formed by P. Zheng et al., 2020 show that patients with tumor deposits only showed similar survival rates to those with lymph node metastases only (P = 0.83). Compared with these, patients with both tumor deposits and lymph node metastases exhibited significantly worse survival (P < 0.01) [23].

As we study the relation between the submitted groups and neoadjuvant therapy, there was a significant relation as follow patients who received neoadjuvant therapy were negative for tumor deposit and lymph nodes, while patients who not received neoadjuvant therapy were positive tumor deposit and positive lymph node (P=0.014), although Gopal et al., 2014 stated that tumor deposits in patients received neoadjuvant chemotherapy were associated with higher rates of lymph node involvement (P=0.035) and distant metastases (P=0.006), and decreased survival (P=0.027) [16]. These patients had a trend toward lower treatment response scores (P=0.285) and higher local recurrence (P=0.092).

## Conclusion:

In conclusion, this study show that tumor deposit is an independent prognostic factor in colorectal carcinoma patients that affect negatively both OS and DFS with significant association between it and LVI,

PNI, LN metastasis, tumor invasion. Also presence of both TDs and LN metastases confers additive risk. Presence of both elements was, in fact, associated with significantly worse survival than each of these risk factors alone.

In addition patients who received neoadjuvant chemotherapy and\or radiotherapy are more likely to be tumor deposit negative and lymph node negative with better OS.

**Conflict of interest**

The authors declared no potential conflicts of interest.

**List of abbreviations:**

| | |
|---|---|
| AJCC | American Joint Committee on Cancer |
| CRC | Colorectal Cancer |
| DFS | Disease Free Survival |
| iTDs | infiltrating Tumor Deposits |
| LN | Lymph Node |
| LNM | Lymph Node Metastasis |
| LVI | Lympho-Vascular Invasion |
| nTDs | nodular Tumor Deposits |
| OS | Overall Survival |
| PNI | Perineural Invasion |
| SPSS | Statistical Package for the Social Science |
| TD | Tumor Deposit |
| TNM | Tumor Node Metastasis |
| TRG | Tumor Regression Grade |

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