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### ► To cite this version:

Jean François Delattre, Ayse Selcen Oguz Erdogan, Romain Cohen, Qian Shi, Jean François J.F. Emile, et al.. A comprehensive overview of tumour deposits in colorectal cancer: Towards a next TNM classification. *Cancer Treatment Reviews*, 2022, 103, 10.1016/j.ctrv.2021.102325 . hal-03579488

**HAL Id: hal-03579488**

**<https://hal.science/hal-03579488v1>**

Submitted on 8 Jan 2024

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## **A comprehensive overview of tumour deposits in colorectal cancer: towards a next TNM classification**

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**A comprehensive overview of tumour deposits in colorectal cancer: towards a next TNM classification**

## **ABSTRACT**

The management of colorectal cancer (CRC) highly relies on the TNM staging system. Tumour deposits (TDs), important histoprognostic factors, are detected in approximately 20% of CRCs and associated with poor prognosis. Integration of TDs in the TNM staging remains a subject of lively debate and differs over the successive TNM classifications. Currently TDs, whatever their number, are considered in pathologic staging only in the absence of lymph node metastasis (LNM; subcategory pN1c). However, the medical community is divided over this way of integrating TDs in the TNM staging system. Considering the personalization of the type and duration of adjuvant chemotherapy in stage III colon cancer according to the number of LNM, this issue has become of growing importance. Thus, ignoring TDs in the presence of LNM represents a major prognostic underestimation and leads to wrong therapeutic decisions. Hence, considering the growing significance of prognostic role, the scientific complexity, and a potential therapeutic effect of TDs, we provide an overview of current knowledge about TDs. Based on the results from recent publications, we also provide plausible scenarios of integration of TDs into the next TNM classification system.

**KEY WORDS:** Tumour deposit, colorectal cancer, histoprognostic factor, TNM classification, lymph node metastasis, extra-mural vascular invasion, perineural invasion

## INTRODUCTION

Colorectal cancer (CRC) is currently the third most common cancer worldwide and the second leading cause of cancer deaths, with more than 1,800,000 new cases and nearly 900,000 deaths each year, worldwide [1]. Its management is based on the TNM staging system, developed in the 1950s, which has been constantly evolving throughout the history of scientific advances [2–6]. The latest 8th edition of the TNM classification has been published in 2017 [7]. Yet, it is essential to identify new histological markers to further improve the classification and to define more relevant subgroups of patients. In CRC, several markers of interest are thought to bear a prognostic impact, including vascular emboli (particularly extramural i.e., located beyond the muscularis, within the colonic subserosa or perirectal fat), perineural invasion, and tumour deposits (TDs).

TDs are defined as tumour foci in the pericolic or perirectal fat, distant from the tumour invasion front, in the lymphatic drainage territory of the tumour, without recognizable residual lymph node tissue [7]. TDs, observed in approximately 20% of CRCs, have been shown to be associated with poor prognosis in several cohort studies [8]. Thus, they constitute a prognostic marker of interest and have therefore been included in the 7th edition TNM classification (TNM7) node status of CRC as a pN1c subcategory [6]. In pN1c subcategory, TDs are considered only in the absence of lymph node (LN) metastasis (LNM). Consequently, in the presence of LNM, TDs have no impact on tumour staging. There has been constant debate in the medical community over this specific modality of integration of TDs into TNM7. Firstly, among pathologists, for whom such a consideration does not accurately reflect the physiological and prognostic reality of this marker [8,9]. Secondly, among oncologists, for whom this modification has a concrete therapeutic implication, with a potential indication for adjuvant chemotherapy [10-12]. Moreover, new data on the modalities of adjuvant chemotherapy in colon cancer (CC) have further complicated the debate. The results from the

international collaboration IDEA (International Duration Evaluation of Adjuvant Chemotherapy) have shown that the type and duration of adjuvant chemotherapy can be personalized in stage III CC (i.e., with LNM) according to histological criteria, particularly the number of LNM [13-15]. In the IDEA study, the 3-year disease-free survival (DFS) was 83% in patients with pT1-3 and pN1 tumors (i.e., low-risk stage III) *versus* 64% in those with pT4 and/or pN2 CCs (i.e., high-risk stage III). Importantly, for patients with low-risk tumors, the evidence from this non-inferiority phase III study supports a shortened duration of oxaliplatin-based adjuvant therapy. Thus, it is now widely accepted that the duration of adjuvant chemotherapy in stage III CC should be based on a consideration of pT and pN criteria to best guide the choice of treatment [16]. In this context, overlooking TDs in the presence of LNM in patients with stage III CC could represent an important prognostic underestimation. In addition, accumulate evidence for the recent meta-analysis, randomized trials, the Surveillance, Epidemiology, and End Results (SEER) database, and the National Cancer DataBase (NCDB) data to support an update of the current pN classification of the AJCC staging system by TDs count [17–26].

Therefore, given prognostic importance, biological complexity, and scientific interest of TDs, we discuss the different implications of the variations between their definitions, summarize evidence about their prognostic value, and suggest the potential scenarios to update the current version of the AJCC/TNM staging system.

### **The definition(s) of TDs**

TDs have been initially described in 1935 as “deposits of carcinoma cells at a distance from the primary growth although the lymphatic glands themselves have been free” [27]. This definition has changed in CC over time. TDs were first introduced in the AJCC/TNM5 staging in 1997, in which tumour nodules of > 3 mm in diameter without histological

evidence of a residual LN were classified as regional LNM, while those of < 3 mm were classified in the T category as a discontinuous extension [4]. In 2002, the AJCC/TNM6 staging system defined TDs according to criterion on their contours, with TDs being defined as positive LNs when they have the firm and smooth contour of LN, while irregular TDs remained in the T category [5]. This variation in TDs definition yields the effect of stage migration over time, with CC being considered as stage I, II, or III depending on the chosen AJCC/TNM version [4,5,7]. Another issue is the high inter-observer variability in the diagnosis of TDs partly due to the subjective nature in their definition. For these different reasons, the definition of TDs in CRC has been updated in the AJCC/TNM7 classification [6]. In this revised staging system, TDs were considered as a specific entity and defined as nodules in the pericolic or perirectal fat tissue, distant from the tumour invasion front, without histological evidence of residual LNs in the lymphatic drainage area of the primary tumour. These were no longer classified in the pT category (i.e., tumour extension), but instead in the category pN (i.e., LN). Even so, the presence of TDs was still considered only in the absence of LNM and classified the tumour as pN1c (irrespective of the number of TDs). Importantly, patients with pN1c CC are less likely to receive adjuvant therapy (52% *versus* 74% of patients with LN-positive tumors;  $p < 0.0001$ ) as shown in an analysis of the National Cancer DataBase (NCDB) [22]. This separate category for TDs in TNM7 was mainly intended to highlight the population of patients with only TDs to better appreciate their inherent prognosis. However, this important change in TNM7 did not solve all issues and new modifications have been introduced in the most recent TNM8 classification [7].

Although the way TDs were considered in the AJCC/TNM8 staging system has not been revised, their definition has been changed from tumour nodules with histological aspects of venous emboli, lymphatic emboli, or perineural invasion to venous emboli, lymphatic emboli, or perineural invasion, respectively. The TNM8 has thus potentially downstaged tumors of



some patients from stage III pN1c (TNM7) to stage II pN0. Hence, changes in the definition of TDs may affect therapeutic decisions for adjuvant treatment. The evolution of the diagnostic criteria for TDs through the various AJCC/TNM classifications is summarized in Fig. 1.

### **Origin of TDs and their association with other histoprognostic factors**

To date, the pathogenesis of TDs remains unclear. Early studies of tumor nodules found on pathological analysis, and identified as non-nodes, classified them into four different subtypes: (i) without identifiable underlying origin, (ii) with vascular invasion, (iii) with perineuronal invasion and (iv) diffuse [28]. In the study by Goldstein and Turner [29], tumour nodules were found to have three distinct origins by cross-section analysis: peri-nervous, perivascular, and intravascular. In total, 10% of patients had only one origin (7% peri-nerve, 3% perivascular), 53% two origins, and 37% all three components. Similarly, Ratto et al. [30], in their study of 77 surgical specimens from rectal cancer patients found that TDs had the endovascular (12%), endolymphatic (16%), peri-nervous (20%), and "isolated" (14%; tumour foci with no origin found) origin. Most cases had a single component (59% *versus* 32%, 6%, and 3% with two, three, and four components, respectively). Yet another study found that venous invasion, lymphatic invasion, peri-nerve invasion, and continuous growth were responsible for TDs in 26%, 4%, 9%, and 12% of cases, respectively [31]. In 49% of cases, no morphologically distinct structures were identified in association with the deposits. The current hypothesis is that TDs might result from an invasion of a certain structure, followed by its subsequent destruction. TDs would therefore reflect the different possible invasion routes of the tumour along the lymphatic, venous, or nervous axes. However, these axes usually run parallel, explaining the presence of multiple structures in the larger TD.

This varied origin is to be linked with the frequently found association between TDs and other pejorative histological biomarkers such as LNM, vascular emboli, and perineural invasion.

Firstly, the occurrence of TDs seems to be more frequently associated with the LN involvement [28,32,33]. In 1997, Ueno et al. [28] observed that LN invasion is more frequent in the presence of TDs (19% *versus* 58%,  $p < 0.001$ ). Similarly in 2014, Yabata et al. [32] found that invasion of LN was increased when TDs were present in tumours (70% *versus* 32%;  $p < 0.001$ ). In the meta-analysis of Nagtegaal et al. [8], TDs were found in 8.7% of patients without LNM and 41.6% of patients with LN involvement (HR 4.2,  $p = 0.002$ ). In another study in patients who underwent radical resection for CRC [33], the presence of TDs was associated with LN status ( $p < 0.001$ ).

The presence of TDs also appears to be correlated with the existence of extramural vascular emboli. In the meta-analysis of 2,805 patients from nine studies [8], TDs were present in 20.9% of patients without vascular emboli and in 31.6% (HR 2.6) of these with extramural vascular emboli. Other more recent studies have confirmed the observed trend, with the proportions of tumours presenting extramural vascular emboli ranging from 20.9 to 60.8% in the absence of TDs and from 31.6 to 95.0% in the presence of TDs [32–34]. In addition, there also appears to be an association between TDs and the presence of peri-neural invasion, however still not as clearly demonstrated compared to other histological factors of poor prognosis [35,36].

The association of TDs with other histopathological factors of poor prognosis, not only underlies the questions raised about their pathophysiological origin, but also questions their intrinsic prognostic value.

## **Prognostic impact of TDs**

### *TDs as a qualitative variable*

There is growing body of evidence concerning the negative prognostic impact of the TDs presence in patients with CC. The meta-analysis by Nagtegaal et al. [8] summarizes published data on TDs prior to 2017. The average prevalence of TDs for all included studies was 22.0% (range, 4.9% to 41.8%). Survival data from five studies ( $n = 1246$ ), showed that TDs were associated with poorer DFS (HR = 2.0; 95% CI 1.4-2.8) and overall survival (OS; HR = 2.2; 95% CI 1.7-2.8). However, the parameters included in the prognostic models varied between studies, which may hamper the robustness of this meta-analysis. Patients with pN1c CC (approximately 3-5% of all stage III tumours) experienced similar outcomes than those with pN1a/b tumors; the 3-year DFS was ranging from 60% to 80% [20,21,23].

Several cohort studies confirmed the association between poor survival and the presence of TDs in patients with LN-positive CCs [8]. In Wong-Chong study [23], patients whose tumours had both LNM and TDs (18.4% of the entire population) had significantly worse 5-year OS than those with LN-positive and TD-negative tumors or with pN1c tumors (46.0% *versus* 63.4% or 61.9%). The negative prognostic impact of the presence of TDs was observed regardless of the pN substage ( $\leq 3$  positive LN, or  $\geq 4$  LNM) [22]. Unfortunately, the NCDB data do not provide any information on local recurrence or metastatic disease and therefore DFS could not be estimated. Similar results were reported from analyses of the Surveillance, Epidemiology and End Results (SEER) database [24]. Overall, these studies suggest that the presence of TDs should be considered despite the pN substage and should not be restricted to the pN1c population. However, several limitations preclude to draw any

definitive conclusion, notably the retrospective nature of these studies that are based on cohort or registries with no control on the therapeutic management.

Taking advantage of two recent adjuvant therapy trials with fluoropyrimidine and oxaliplatin in stage III disease, (IDEA France [21] and CALGB/SWOG 80702 [37]) both comparing 3 months to 6 months of therapy, we have recently conducted two distinct *post-hoc* analyses [21, 37] focused on prognostic value of TDs. All pathological reports from patients enrolled on those two trials were reviewed for the presence and number of TDs. In the analysis by Delattre et al. [21], a low frequency of TDs was reported (184 out of 1942 patients; 9.5%), probably because of a lack of standardization of pathological reports. The pN1a/b and pN1c groups had similar 3-year DFS (78.8%, 95% CI 76.6-80.9 and 80.7%, 95% CI 67.0-89.1, respectively). The negative prognostic impact of the presence of TDs was observed regardless of pN substage. In multivariate analysis, TDs were associated with a higher risk of recurrence or death (HR = 1.4; p=0.0201). In the second study (CALGB/SWOG 80702) [37], the incidence of TDs was 26%. Again, the presence of TDs was associated with worse survival outcomes (DFS and OS) for pN1a/b and pN2 groups. Data from these two *post-hoc* analyses in the adjuvant setting further reinforced the necessity for consideration of TDs in the AJCC/TNM staging system for LN-positive CCs that represent most TDs-positive tumours (i.e., pN1c tumours account for only 15.4% to 29.9% of all TDs-positive cases).

Regarding rectal cancer, the impact of TDs remains even more complex, as the pathological analysis often occur after multimodality treatment, including chemotherapy and radiotherapy. Therefore, it has been suggested that the pN1c category cannot be used because it is unclear whether the TDs are true "TDs" or these are just residual tumour cells present in the mesorectum [38]. Moreover, the prognostic value of the TDs in this setting remains controversial, while one studies have found a predictive role of poor response for TDs in case

of preoperative multimodal treatment [39], other have shown no prognostic impact [38]. New data suggested the prognostic importance of TDs in rectal cancer [40–43].

#### *TDs as a quantitative variable*

The number of TDs may provide additional prognostic information for patients with stage III CCs. Goldstein et al., [44] studied 418 patients with pT3 LN-positive colon adenocarcinomas, 18% of which had TDs. Overall, 31, 15, and 35 patients had 1, 2, or more than 3 TDs, respectively. The 5-year DFS was 35%, 24%, and 2% ( $p < 0.01$ ) in these groups. Both the presence and number of TDs were associated with the risk of recurrence, independently of the LN status. Another publication by Jin et al. [45], reported a shorter survival for the pN1c group with a number of TDs greater than three (16.5 months *versus* 32.5 months,  $p=0.025$ ). These results were confirmed in an analysis of the NCDB database [20]. In this study, pN1c patients with  $\geq 3$  TDs experienced worse survival than those with 1 or 2 TDs (the 5-year OS was 51.4% versus 60.6%) but had similar survival to that of patients with pN2 tumours (48.9%) or those with 1 to 3 LNM and TDs (currently staged as pN1a/b; 50.7%). Shi et al. [46] analysed 29 017 stage III CC patients with the known number of TDs from the SEER database. The 5-year cancer-specific survival rates of patients with no TDs, 1-2 TDs, and  $\geq 3$  TDs were 76.3%, 68.9%, and 53.6%, respectively ( $p < 0.0001$ ). These results are in line with those from several cohort studies [26,47] and the CALGB/SWOG 80702 phase III trial [37]. In the latter, an increased number of TDs was associated with a significant increase of the HR for DFS and OS: the higher the count of TDs the worse the survival prognostic [37]. Table 1 summarizes the main studies assessing TDs in cancer patients in the last 4 years.

## **Possible scenarios for the integration of TDs in the AJCC/TNM classification**

The presence and number of TDs have a negative prognostic impact for patients with CC, regardless of the pN substage. This histological feature, however, is considered currently only in the absence of LNM in the AJCC/TNM7 and AJCC/TNM8 classifications. Therefore, a modification of the current pN category in the AJCC/TNM staging system seems warranted, with several conceivable scenarios (Table 2):

### *1/ Combining the number of TDs with the number of LNM*

In this scenario, TDs are considered as a quantitative parameter and one TD is considered as one LNM: pN1 CCs (less than four LNM or the presence of TDs without positive LN) would be restaged as pN2 if the combined number of TDs and LNM would be four or more [26].

This scenario, which is supported by the prognostic impact of TD as a quantitative parameter, was explored in the *post-hoc* analyses of the IDEA France and CALGB/SWOG 80702 studies [21, 37]. In the first study, 35 patients initially classified as pN1 (2.4%) were reclassified as pN2 by adding TDs to the count of LNM. These patients experienced worse DFS than patients whose number of TDs and LNM remained inferior to four (the 3-year DFS: 60.7% *versus* 79.3%;  $p=0.015$ ) and similar prognosis compared to those initially classified as pN2 [21]. These results were confirmed in the CALGB/SWOG 80720 trial for both DFS and OS [37]. Overall, 104 of 1470 (7.1%) patients initially considered as pN1 were restaged as pN2. These restaged patients experienced significantly worse DFS compared to those who remained pN1 (the 3-year DFS: 65.4% *versus* 80.5%,  $p=0.0003$ ) and OS (the 5-year OS: 69.1% *versus* 87.9%,  $p=0.0001$ ). Survival outcomes were not significantly different between patients restaged as pN2 and those initially staged as pN2 (the 3-year DFS: 65.4% *versus* 62.3%, respectively,  $p=0.4895$ ). These results demonstrate that scenario #1 may impact a significant proportion of patients (from 2.4% to 7.1%) and would significantly improve the

prognosis accuracy of the AJCC/TNM classification. Still, although these two IDEA *post-hoc* studies lack an area under the curve analysis to evaluate properly the prognostic discrimination of this modified pN classification, they demonstrate the superiority of this system over the current AJCC/TNM staging system.

### *2/ Creating a pN2c substage*

Other authors proposed to create new categories in the AJCC/TNM classification, which would consider the number of TDs while maintaining a pN1c group. In this modified pN system, tumors with both LNM and TDs, whatever their number, would be restaged as pN2c. Only patients with one or two TDs and no positive LN would remain in the pN1c group. This is supported by data provided by Pricolo et al. [20] showing that pN1c CC patients with more than two TDs have worse survival outcomes than those with only one or two TDs.

The disadvantage of this strategy is that the number of TDs and LNM is ignored when tumours harbour these two pathological features.

### *3/ Integrating the presence of TDs within the pN subgroups*

Several authors evaluated staging systems with TDs as a qualitative parameter. Analysing patients data from the SEER database, Peacock et al. [24] proposed an AJCC reclassification which would incorporate the presence of TDs into each nodal status: pN1c tumours would be integrated to the pN1b substage, TDs-positive pN1a/b tumours would be restaged as pN2a, pN2a TDs-positive tumours would be restaged as pN2b, and a new “pN3” category would be created for pN2b TDs-positive tumours. A similar modified TNM classification was developed by Pei et al. [48] with superior model-fitting compared with pN stage.

Nonetheless, the complexity of such a system might hamper its implementation into daily clinical practice. Besides, the retrospective nature of these two mentioned analyses, which are based on one single dataset, do not permit firm conclusions to be drawn. Finally, this scenario

considers only the presence or absence of TDs, even though the number of TDs has been shown to provide additional prognostic accuracy.

#### *4/ Including TDs in the pM category*

Another proposed scenario is to include TDs in the M category as in-transit melanoma metastases. TDs without lymphocytes and associated with veins and/or nerves would be classified in the M1a category, whereas cases with distant (visceral) metastases in the M1b category [49].

This scenario is also with limitations. It ignores the number of TDs and its potential impact on the prognostic accuracy and therapeutic decisions is unclear since it would induce a stage migration of all TD-positive CCs from stage III to stage IV.

## **Conclusions**

The presence and number of TDs are the major independent prognostic factors for patients with stage III CC. These represent a decisive source of prognostic information and can no longer be ignored either in pathology reports or in evaluation of patients' prognosis. It is crucial that pathologists use a standardized report requesting the presence or absence and the number of TDs. Nonetheless, many questions about their definition and origin and the best way to consider them in the AJCC/TNM staging system remain unanswered. Further studies evaluating the prognostic accuracy of different scenarios for the new TNM classification are warranted.



**ACKNOWLEDGEMENTS:** Editorial support was provided by Magdalena Benetkiewicz, PhD.

**ROLE OF FUNDING SOURCE:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**DECLARATION OF COMPETING INTEREST:**

TA reports consulting/advisory role and/or honoraria from Amgen, Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Chugai, Clovis, Gritstone Oncology, GlaxoSmithKline, Haliodx, Kaleido Biosciences, Merck & Co., Inc., Pierre Fabre, Roche/Ventana, Sanofi, Seagen, Servier (self). QS reports consulting/advisory role from Yiviva Inc, Boehringer Ingelheim Pharmaceuticals, Inc, Regeneron Pharmaceuticals, Inc., Hoosier Cancer Research Network (self), honoraria/speaker role from Chugai Pharmaceutical Co., Ltd, stocks from Johnson & Johnson, Amgen, and Merck & CO. (self), research funds from Celgene/BMS, Roche/Genentech, Janssen, Novartis (institution). All other authors have declared no conflicts of interest.

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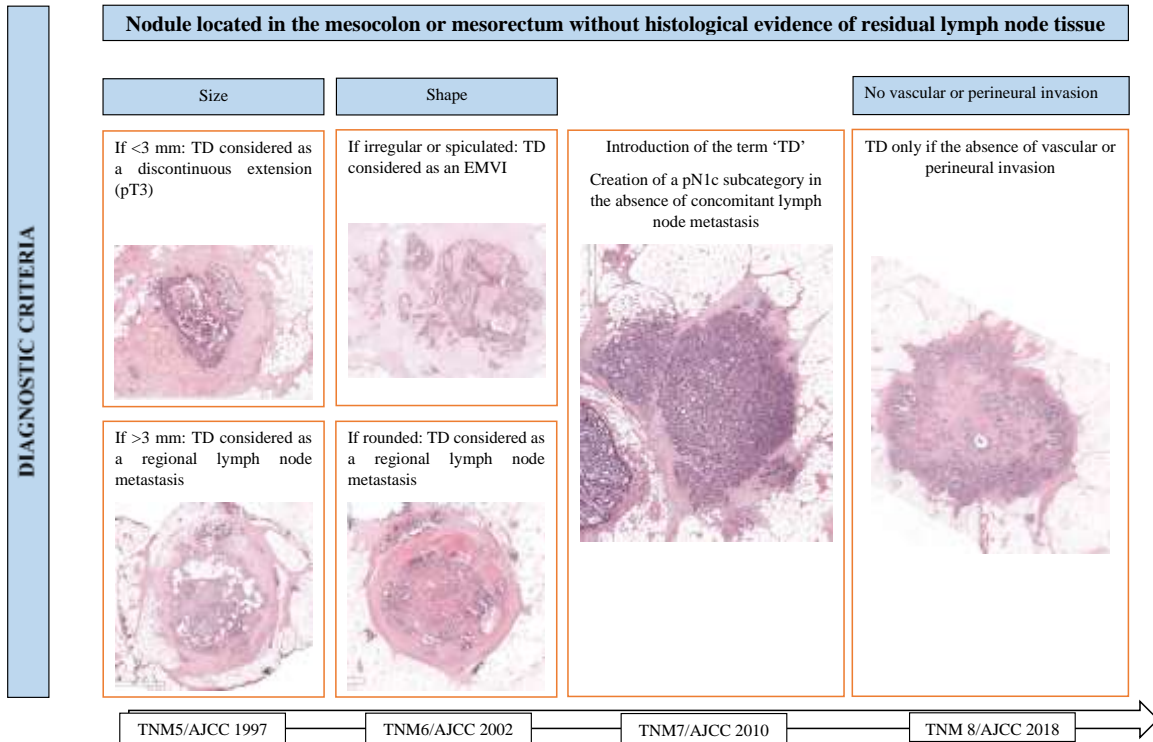


## **FIGURE LEGENDS**

**Figure 1.** The changes in the diagnostic criteria for TDs according to different editions of the AJCC/TNM classification.

TD: tumor deposit, EMVI, EMVI: extramural vascular invasion

**Fig. 1**



**Table 1** Summary information on the main studies assessing tumour deposits in cancer patients reported in the last 4 years.

Reference	Study type/Data	Tumour Stages	Patients (n)	TD (%)	Association with Other Prognostic Factors	Association with Outcome	with	Definition/Classification Related Remarks	Association with ACT
<b>Nagtegaal [8]</b>	Systematic review and individual case meta-analysis	All	10.106	22	LNM, EMVI	DFS: HR 2.0 (1.4-2.8) OS: HR 2.2 (1.7-2.8) CSS: HR 3.3 (2.2-4.7)		No impact of shape or size	NA
<b>Wang [16]</b>	Retrospective/SEER	All	39.155	7.3	Stage, T, N, Grade, Type, Location	CSS: outcome for patients with TD is worse in all groups (N0, N1a/b, N2)		NA	NA
<b>Chen [45]</b>	Retrospective/Monocentric	All	517	11.2	Stage, EMVI, Grade, PNI, T, LNM	OS: 25 months vs 45 months (TD+ vs TD-)		Increased number of TD is associated with poor outcome	NA
<b>Basnet [31]</b>	Retrospective	All	313	16.9	T, N, TNM, EMVI, LNM	DFS: HR 4.3 (2.4-7.8)		NA	NA
<b>Zheng [39]</b>	Retrospective/SEER	All	1252	NA	Grade, M, LNM, PNI	DSS: 41% vs 55.1% (TD 4+ vs TD 1-3)		Increased number of TD is associated with poor outcome	NA
<b>Liu [50]</b>	Retrospective/SEER	All	69178	12.3	Location, T, N, PNI	OS: HR 2.7 (2.6-2.8)		Reclassification has been proposed	NA

<b>Liu [50]</b>	Retrospective/FUSCC		All	3137	14.8	Location, T, N, PNI, EMVI	OS: HR 3.2 (2.6-4.0)	Reclassification has been proposed	NA
<b>Peacock [22]</b>	Retrospective/SEER		I/III	74494	6	Stage, LNM Grade, PNI.	CSS: worse in patients with TD for all groups (N0, N1a/b, N2)	Reclassification has been proposed	NA
<b>Landau [23]</b>	Retrospective review/Monocentric	histological	II/III	256	21	Stage, EMVI PNI	DFS: HR: 2.2 (1.2-4.0); worse in N1a/b patients with TD	No impact of size, Less N1c with new definition	NA
<b>Liu [51]</b>	Retrospective/SEER		III/IV	25868	18.6	T, N, TNM, Location Grade	CSS: worse in N1c patients compared with N0/1a but better than in N2 patients	NA	NA
<b>Bai [52]</b>	Retrospective/SEER		III	10504	15	T, Stage, Location	CSS: worse in N1/2 patients with TD	Increased number of TD is associated with poor outcome	Less ACT in patients with TD (36% vs 39% without TD, p<0.001)
<b>Bai [52]</b>	Retrospective/SEER		III	10802	15.5				
<b>Wong-Chong [21]</b>	Retrospective/Multicenter/NCDB		III	74577	6.8	NA	5-year OS: 46% (TD+LNM) vs 63.4% (LNM alone) vs 61.9% (TD alone)	NA	Less ACT in pN1c patients; p<0.001
<b>Zheng [39]</b>	Retrospective/SEER		III	4623	19.3	NA	OS: HR 1.6 (1.5-1.8) OS TD+LNM worse outcome	NA	NA
<b>Cohen [35]</b>	Post-hoc/Multicenter		III	2028	26	T, LNM, LVI, PNI	DFS: HR 1.6 (1.3-2.0) OS: HR 1.6 (1.2-2.0)	Increased number of TD is associated with poor outcome	NA
<b>Pricolo [18]</b>	Retrospective/NCDB		III	42901	3.9	NA	OS: 41.5% (TD+LNM) vs 59.8% (LNM alone) vs 58.2% (TD alone)	Increased number of TD is poorer outcome. Reclassification has been proposed	NA

<b>Delattre [19]</b>	Post-hoc/Multicenter	III	1932	9.5	PNI	Poorer prognosis in the presence of TD irrespective of N stage	Reclassification has been proposed	NA
<b>Mirkin [20]</b>	Retrospective/NCDB	III	6424	2.5	NA	5-year OS: 40.2% (TD, LNM) vs 68.1% (TD alone) vs 55.4% (LNM alone)	NA	Less ACT in pN1c patients; p=0.003
<b>Pei [46]</b>	Retrospective/SEER	III	14906	13.1	NA	5-year OS: 73.5 (TD+) % vs 54.4% (TD-); p<0.001	Reclassification has been proposed	NA
		III	6384	13.1	NA	5-year OS: 74.5% (TD+) vs 56.8% (TD-); p<0.001	Reclassification has been proposed	NA
<b>Bouquot [32]</b>	Case control/bicentric	pN1c	1122	18.3	Location, T, EMVI, PNI	No difference between pN1a/b and pN1c No effect of TD on pN1a/b	NA	NA
<b>Simon [53]</b>	Retrospective/NCDB	pN1c	5684	1.59	NA	1-year OS: no-ACT vs ACT: 96.2% vs 80%, 3-year OS: no-ACT vs ACT: 67.4% vs 72.9%, 5-year OS: no-ACT vs ACT: 48.5% vs 33.8%; p<0.001	NA	ACT administered in 55% of N1c patients

SEER: Surveillance, Epidemiology and End Results, FUSCC: Fudan University Shanghai Cancer Center, NCDB: National Cancer Data Base, EMVI: extramural vascular invasion; LNM: lymph node metastases, PNI: perineural growth, LVI: lymphatic invasion, TD: tumor deposit, DFS: disease-free survival, OS: overall survival, CSS: cause-specific survival, ACT: adjuvant chemotherapy

**Table 2** Proposed scenarios for the integration of tumour deposits into the AJCC TNM classification.

	<b>AJCC TNM classification 8th edition</b>	<b>Scenario #1</b>	<b>Scenario #2</b>	<b>Scenario #3</b>	<b>Scenario #4</b>
<b>Proposed amendment</b>	-	Combination of the number of TD with the number of LNM	Creation of a pN2c substage for high-risk TD-positive tumors	Integration of the presence or absence of TD into each pN subgroup	Consideration of TD as metastasis
<b>Tumour deposits</b>					
Type of variable	Qualitative	Quantitative	Quantitative and qualitative	Qualitative	Qualitative
Restrictions to integration	Yes - only in the absence of LNM	No	No	No	No
<b>Category</b>	N1a: 1 LNM	N1a: 1 TD or LNM	N1a: 1 LNM and no TD	N1a: 1 LNM and no TD	N1a: 1 LNM and no TD
	N1b: 2-3 LNM	N1b: 2-3 LNM or TD	N1b: 2-3 LNM and no TD	N1b: 2-3 LNM and no TD, or TD and no LNM	N1b: 2-3 LNM and no TD
	N1c: TD and no LNM	-	N1c: 1-2 TD and no LNM	-	-
	N2a: 4-6 LNM	N2a: 4-6 LNM or TD	N2a: 4-6 LNM and no TD	N2a: 4-6 LNM and no TD, or <4 LNM and TD	N2a: 4-6 LNM and no TD
	N2b: $\geq 7$ LNM	N2b: $\geq 7$ LNM or TD	N2b: $\geq 7$ LNM and no TD	N2b: $\geq 7$ LNM and no TD, or 4-6 LNM and TD	N2b: $\geq 7$ LNM and no TD
	-	-	N2c: $\geq 3$ TD and no LNM or LNM and TD	N3: $\geq 7$ LNM and TD	
	M1a	-	-	-	M1a: TD without lymphocytes and associated with veins

M1b

-

-

-

M1b: distant  
visceral  
metastasis

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LNM: lymph node metastasis; TD: tumour deposits