Colorectal tumour deposits in the mesorectum and pericolon; a critical review

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Although tumour deposits (TD) in the pericolic and mesorectal fat have been recognized since 1935, incorporation in the Tumour Node Metastasis (TNM)/American Joint Committee on Cancer (AJCC) system took place in 1997. The 3-mm rule classified TD as lymph node metastases. This rule was changed in 2002, when the contour of the deposit became the diagnostic feature. This review has evaluated the 3714 patients described in the literature. The incidence of TD varies from 5 to 45%. Their origin has been shown to be heterogeneous; however, their presence indicates a poorer survival. The hazard ratio for death due to disease is 1.96. Various studies have tried to determine the importance of types of TD, based on contour, size and origin, but all fail to provide an evidence base to substantiate its use in the TNM system. To classify TD as positive lymph nodes after neoadjuvant therapy is a misconception, since the presence of tumour microfoci after therapy can be a sign of good response to treatment and indicative of a good prognosis. In conclusion, we did not find adequate evidence for the inclusion of TD in TNM/AJCC staging systems. Moreover, the current directives are confusing, and the definitions should not be used after neoadjuvant therapy.

Keywords: colorectal cancer, lymph nodes, staging, tumour deposits

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; MF, microfoci; TD, tumour deposits; TNM, Tumour Node Metastasis

Introduction

Tumour deposits (TD) in the pericolic and mesorectal fat have been recognized since 1935, when they were attributed to vascular invasion. Further studies have examined the origin and importance of TD, which were first incorporated in the Tumour Node Metastasis (TNM)/American Joint Committee on Cancer (AJCC) staging manuals in 1997. The 3-mm rule classified TD as lymph node metastases. This rule was changed in 2002, when the contour of the deposit became the diagnostic feature. This review has evaluated the 3714 patients described in the literature. The incidence of TD varies from 5 to 45%. Their origin has been shown to be heterogeneous; however, their presence indicates a poorer survival. The hazard ratio for death due to disease is 1.96. Various studies have tried to determine the importance of types of TD, based on contour, size and origin, but all fail to provide an evidence base to substantiate its use in the TNM system. To classify TD as positive lymph nodes after neoadjuvant therapy is a misconception, since the presence of tumour microfoci after therapy can be a sign of good response to treatment and indicative of a good prognosis. In conclusion, we did not find adequate evidence for the inclusion of TD in TNM/AJCC staging systems. Moreover, the current directives are confusing, and the definitions should not be used after neoadjuvant therapy.

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Table 1. Definitions of tumour deposits in staging manuals

AJCC 5th edn, 1997
Metastatic nodules or foci found in the pericolic or perirectal fat or in adjacent mesentery (mesocolic fat) without evidence of residual lymph node tissue are equivalent to regional lymph node metastasis. Multiple metastatic foci seen microscopically only in the pericolic fat should be considered as metastasis in a single lymph node for classification. A tumour nodule > 3 mm in diameter in the perirectal or pericolic fat without histological evidence of a residual node in the nodule is classified as regional perirectal or pericolic lymph node metastasis. However, a tumour nodule < 3 mm in diameter is classified in the T category as a discontinuous extension, i.e. T3.

TNM 5th edn, 1997
A tumour nodule > 3 mm in diameter in perirectal or pericolic adipose tissue without histological evidence of a residual lymph node in the nodule is classified as regional lymph node metastasis. However, a tumour nodule up to 3 mm in diameter is classified in the T category as discontinuous extension, i.e. T3.

TNM 6th edn, 2002
A tumour nodule in the pericolic/perirectal adipose tissue without histological evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis, as the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or V2, if it was grossly evident, because there is a strong likelihood that it represents venous invasion.

AJCC 6th edn, 2002
Metastatic nodules or foci found in the pericolic or perirectal fat or in the adjacent mesentery (mesocolic fat) without evidence of lymph node tissue are considered equivalent to regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If a nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or V2 (if it was grossly evident), because of the likelihood that it represents venous invasion. Multiple metastatic foci seen microscopically only in the pericolic fat should be considered lymph node metastases for classification.

such patients. These papers are all single-centre retrospective case reviews on < 400 patients dating from the 1960s and 1970s, prior to modern pathology, surgery and chemotherapy. They have not been independently reproduced. Thus the evidence on which TNM6 is based is poor and, like the N3 and 3-mm rules, leads to the need for multiple revisions. Moreover, due to the fundamental changes in definitions in the different versions of the staging systems, it becomes nearly impossible to compare large series of patients and trial populations over time. In this review, we evaluate the evidence in the current literature.

Methods

A literature search was performed using PubMed, with a combination of the following keywords: tumour nodule, tumour deposit, microfoci, neoplastic foci, tumour aggregate, discontinuous carcinoma, metastatic, non-nodal, nodal-independent, extranodal, peri-colonic, mesorectal. A total of 24 relevant papers were identified and are evaluated in the current review. Only published papers in the English literature were included.

The Importance of Tumour Deposits

Incidence

Dependent on the method of examination and the selection of cases, there is a large variation in the incidence of TD. Large section techniques show TD in virtually all cases. However, no distinction between microscopically and macroscopically visible deposits is made. Only single-centre studies are reported and the percentages vary from 4.5% to 45% of cases in the colon and rectum (27.3% versus 25.5% and 17.3% versus 17.6%, respectively). Microscopic deposits (≤ 1 mm) were observed in 22.5% of the cases, whereas in the same series (n = 427) ‘macroscopic’ deposits (defined as > 1 mm) are observed in 31.1% of cases.

Location

In rectal carcinoma, more TD were present in low tumours (mean number six versus two, P = 0.02). Most of the TD (48.7%) were located in the posterior rectum, where most lymph nodes are found. Whole mount sections revealed that although the majority of deposits were present in the middle layers of the mesorectal fat column, a significant percentage (25.8–38.7%) were present in the outer layer of the mesorectum, justifying once again total mesorectal excision as the preferred surgical technique.

Relation with positive lymph nodes

When evaluating cases with TD, the percentage of lymph node-negative patients varied between 28 and
59% (Table 2). However, when reviewing the other series (all single-centre studies), TD were present in the absence of lymph node metastases in only 3–25% (mean 8%, Table 2). Only one of the studies gives information about the number of lymph nodes retrieved, which is an indicator of the quality of pathology. In the study of Tocchi et al.,14 the mean number of lymph nodes is 19.3 (± 8.8) and they find TD in 15% of cases without positive lymph nodes. This suggests that the percentage of ‘TMN II’ cases with TD might be higher than 8% with careful pathological examination. In 18%, TD were present together with lymph node metastases.

However, it is clear that TD can be present in early tumour stages. Ratto et al.12 show that deposits were found in 18.8% of TNM stage I tumours and 46.9% of TNM stage II tumours.

**Prognosis**

Local recurrence of rectal carcinoma was significantly higher in patients with TD (35.8% versus 14.9%, \( P < 0.01 \), 30.3% versus 15.7%, \( P < 0.05 \)). A similar difference, although not significant, was also observed in a case–control study:18 17.2% versus 3.8%. In the other case–control study,15 a local failure rate as high as 50% was observed in a case with TD, with 78% distant recurrences. The study of Tocchi et al.14 also showed a significantly lower local recurrence rate in the absence of TD (\( P < 0.03 \)). This increased risk of local recurrence is probably due to the increased risk of circumferential margin involvement due to the presence of TD22 and the increased risk of stage III disease that is linked with the presence of TD.

Other studies have evaluated the presence of TD in relation to survival. The results are shown in Figure 2. Not included is the study of Tocchi et al.14 who demonstrate a significantly worse survival in the presence of TD, on both univariate and multivariate

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**Table 2. Relation of tumour deposits with positive lymph nodes**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>No tumour deposits or positive lymph nodes</th>
<th>Tumour deposits only</th>
<th>Positive lymph nodes only</th>
<th>Positive lymph nodes and tumour deposits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocchi</td>
<td>53</td>
<td>18 (34%)</td>
<td>8 (15%)</td>
<td>11 (21%)</td>
<td>16 (30%)</td>
</tr>
<tr>
<td>Ratto</td>
<td>77</td>
<td>34 (44%)</td>
<td>19 (25%)</td>
<td>9 (12%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Tateishi (colon)</td>
<td>307</td>
<td>151 (49%)</td>
<td>31 (10%)</td>
<td>102 (33%)</td>
<td>23 (7%)</td>
</tr>
<tr>
<td>Tateishi (rectum)</td>
<td>237</td>
<td>122 (51%)</td>
<td>19 (8%)</td>
<td>74 (31%)</td>
<td>22 (9%)</td>
</tr>
<tr>
<td>Ueno 1997</td>
<td>369</td>
<td>149 (40%)</td>
<td>22 (6%)</td>
<td>90 (24%)</td>
<td>108 (29%)</td>
</tr>
<tr>
<td>Ueno 1998*</td>
<td>427</td>
<td>199 (47%)</td>
<td>11 (3%)</td>
<td>133 (31%)</td>
<td>84 (20%)</td>
</tr>
<tr>
<td>Reynolds</td>
<td>50</td>
<td>22 (44%)</td>
<td>5 (10%)</td>
<td>11 (22%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Total</td>
<td>1520</td>
<td>695 (46%)</td>
<td>115 (8%)</td>
<td>430 (28%)</td>
<td>280 (18%)</td>
</tr>
<tr>
<td>Singh†</td>
<td>18</td>
<td>5 (28%)</td>
<td>1 (8%)</td>
<td>13 (72%)</td>
<td></td>
</tr>
<tr>
<td>Prabhudesait†</td>
<td>29</td>
<td>17 (59%)</td>
<td></td>
<td>12 (41%)</td>
<td></td>
</tr>
</tbody>
</table>

*< 1 mm.
†Case–control studies.
analysis (P < 0.001). Figure 2 shows that all studies point in the same direction, proving without doubt the adverse prognostic value of TD. In all cases, the hazard ratio (HR) for survival in the presence of TD is > 1, indicating an increased risk of death due to disease. In all patients (n = 3714), the HR is 1.96 [95% confidence interval (CI) 1.6–2.6]. There are differences in HRs between the different studies, probably due to selection biases seen in single-centre studies. No difference is shown between colon (n = 1051; HR 1.93, 95% CI 1.6, 2.5) and rectum (n = 2663; HR 2.0, 95% CI 1.6, 2.7).

Two studies performed multivariate regression analysis, including, respectively, TD, T-, N-stage, lymphoid infiltrate and N-stage and tumour grade. Both studies demonstrate a significant prognostic value of TD in the colon. The latter finding is curious, since this study was limited to node-positive patients. Similar analysis in the rectum did not prove the prognostic value of TD, although its presence was strongly correlated with the selected variables: T-stage, Crohn’s-like lymphoid reaction and extramural vascular invasion. However, failure to consider the circumferential resection margin status invalidates the assessment of the independent value of TD for predicting local recurrence and survival in rectal cancer.

Increasing numbers of TD are associated with a poor prognosis in one study, but not in others.

In TNM stage IV patients, the presence of TD in the area of the primary tumour is also reported to have a significant effect on disease-specific survival (HR 4.5, CI 1.5, 13.9).

Development of metastases
Goldstein and Turner suggest that the site of distant metastases might be different in patients with TD. Most tumours initially metastasize to the liver (47%). TD patients develop liver metastases only in 24%, with 59% developing non-hepatic intra-abdominal metastases, compared with 12% in patients without TD (P < 0.01). The heterogeneity observed in metastatic pathways of patients with TD might reflect the different origins of the deposits.

The origin of tumour deposits
One can speculate about the origin of TD in the pericolic and mesorectal fat. They might be derived from tumour growing inside or along lymphatic or vascular structures or nerves. Some of them will be lymph node metastases, in which the pre-existing node is no longer recognizable. Strong correlations have been demonstrated between the presence or number of TD with intramural vascular invasion, extramural vascular invasion, lymphatic invasion and lymph node metastases. Ueno et al. demonstrate that the incidence of TD is higher in cases with extracapsular growth of lymph node metastases, compared with cases with lymph node metastases with an intact capsule.

Using step sectioning, Goldstein and Turner investigated the origin of TD and divided them into three groups: perineural, perivascular and intravascular. Only 10% of patients showed only one pattern (7% perineural, 3% perivascular), 53% showed two patterns and in 37% all three components were present.

Another type of grouping is used by Ratto et al. finding: 12% endovascular (cancer deposits in blood vessels), 16% endolymphatic (foci in lymphatic non-nodal vessels), 20% perineural and 14% isolated (tumour foci without evidence of origin). One pattern was present in 59%, two in 32%, three in 6% and four patterns in 3% of the patients.

Although different methods and categories are used, making comparison difficult, it is clear that the determination of the origin of TD is not particularly useful, since in a large number of patients more than one pattern is present. Moreover, in a number of cases the origin cannot be determined. Step sectioning might give the answer in a number of cases, but outside the research setting this is not feasible. No analyses have
been performed with regards to the prognostic value of the different types of TD.

THE SIZE CRITERION

Although in some studies a distinction has been made between different types of TD based on size, none of these gives a definite answer. In general, a difference is made between macro- and microtumour deposits, the latter being an additional finding in the microscopy. Macro tumour deposits are tumour nodules, which are macroscopically visible and taken out of the resection specimen, to investigate their origin. Often they are macroscopically taken for lymph nodes. The cut-off point for macroscopically visible TD is not clear, but based on lymph node studies, very few nodes found with the use of clearing technique after thorough manual dissection are larger than 2 mm.25 In a number of cases there is a desmoplastic reaction around the TD. Its presence will make the macroscopic visibility of the deposit clearer. Whether this should be included in the determination of the maximal diameter is not clear. In the paper of Goldstein and Turner,9 the desmoplastic reaction is included, but other studies do not mention this feature.

One study11 tried to address the 3-mm rule. In 95 patients with TD, 32 showed TD < 3 mm in size. In addition, 27 of these patients also had larger TD and the remaining five patients did have positive lymph nodes. The coincidence of small and larger TD has also been observed by Ueno17 and Wang.21 These data suggest that although the 3-mm rule might be easy to use, its usefulness is doubtful.

Only one study9 shows that an increasing size of TD is indeed significantly associated with the development of distant metastases (P = 0.034). However, no cut-off point is given.

One argument in favour of the 3-mm rule is the multidisciplinary approach to rectal cancer. Imaging, using magnetic resonance imaging, can detect lymph nodes or tumour nodules reliably with a diameter of ≥3 mm26 and measurements are more reproducible than other forms of assessment. Moreover, all practising pathologists exercise some kind of subconscious form of quantification. Alternatively, a 2-mm rule might be used, as seen in the light of another TNM rule distinguishing micro- and macrometastases;4 however, there is little published evidence to support this either.

THE CONTOUR CRITERION

In 1997 a description of four different types of TD (or extrabowel skipped cancer infiltration, as it is called in this paper) in 369 patients was published.16 The four patterns were distinguished based on histology (Figure 3):

1 Scattering pattern: microscopic clusters of undifferentiated or microtubular cancer cells.
2 Vessel invasion outside the adventitial.
3 Neural invasion: spread between the fasciculus and perineurium.
4 Nodular pattern: unknown origin. might be the end stage of one of the other patterns or a replaced lymph node.

The distribution of these patterns was, respectively, 5, 16, 6 and 30% in patients with TD. An overlap in patterns was present in a number of patients. The survival of patients with TD was significantly worse compared with those without TD. However, there was no difference in prognosis when the different patterns were tested, although all patients with the scattered pattern were dead after 4 years. This group was very small. Tateishi et al.11 confirms these results in 544 patients.

No other studies were found using contour or morphology as a criterion. The study by Goldstein and Turner9 excludes the nodular pattern from analysis, presuming the lymph node origin of these deposits.

The reproducibility of the new TNM guidelines based on contour was tested in a series of 80 cases, reviewed by 23 pathologists.27 Overall agreement on the form and contour of nodules was only fair (κ = 0.36). The new classification led to upstaging of 4/80 cases from stage II to III. This was confirmed in an unpublished series by 20 Dutch pathologists (κ = 0.13). Difficulties with the definition based on contour are illustrated in Figure 4.

TUMOUR DEPOSITS AFTER NEOADJUVANT THERAPY

With the widespread introduction of neoadjuvant therapy in rectal carcinoma, radiation- and chemoradiation-induced changes are becoming a major feature in histopathological reporting. Residual ‘microfoci’ (MF) or tumour deposits are reported after neoadjuvant therapy28–31 in percentages varying from 17% to 48% of patients (also called ‘near complete response’). We prefer to call these tumour remnants MF rather than TD, since they constitute a different type of deposit.

MF are found in all layers of the bowel wall, most often associated with chronic inflammation, fibrosis and other radiation-induced changes.29 They vary in size from 0.6 to 4 mm. Since these are the remains of advanced tumours, there has been a good response to therapy and this phenomenon is, in general, associated
with a good prognosis. It is clear that these MF are of an entirely different origin than the TD discussed above and that special care is thus required in staging patients treated with neoadjuvant therapy.

Moreover, Kinoshita et al. describe a long course of preoperative radiotherapy (50 Gy) delivered to half of the patients, without the induction of downstaging. TD (≤ 1 mm) were reported to be present only in the non-irradiated patients, suggesting that small TD may preferentially disappear due to neoadjuvant therapy. Thus the TNM changes cannot be applied to ypT cases, since it would again have implications for postoperative chemotherapy in rectal cancer.

**Discussion**

TD are a phenomenon which has been recognized since early in the 20th century. In the last decade of that century, TD have been included in universally applied staging systems. The evidence behind this inclusion is poor.

It is clear that TD arise through a number of invasive mechanisms that themselves have prognostic importance, i.e. vascular, lymphatic and neural spread. If these are properly recognized by good pathology, what is the prognostic relevance of TD then? Is the value of finding a TD only important with poor pathology, where the above factors have not been identified? The incidence of TD is variable, depending on the definitions and selection criteria applied by the various authors. The variation is reflected by the numerous names by which the deposits are described: tumour nodules, tumour deposits, extranodal foci, neoplastic foci, non-nodal metastatic foci, extranodal cancer deposits, extrabowel skipped cancer infiltration, mesorectal microfoci, to name a few.

Based on the data of 1520 patients, we can conclude that in 8% TD are present without lymph node metastases, in 28% only lymph node metastases are present and in 18% a combination of lymph node metastases and TD is present. No metastases are present in 46% of cases. The influence on tumour
Stage in the cases with lymph node metastases is limited; there might be migration from N1 to N2, but this has no impact on treatment. In 8% of the cases there might be consequences, when TD are included in the N stage, upstaging these patients from TNM stage II to TNM stage III. When evaluating prognosis, all studies (n = 3714) indicate a worse prognosis for patients with TD: increased local recurrence rates, increased development of distant metastases and decreased survival. Whether this also holds true for patients without positive lymph nodes is still unknown, although one study has shown that the presence of TD has independent prognostic value next to N staging.  

Figure 4. Illustrations of the contour criterion. A, Smooth contour of vascular invasion. B, C, Irregular contour of a lymph node with extracapsular growth; outgrowth will give rise to an irregular tumour deposit.

Figure 5. Tumour deposit or not? Although the initial slide (A) suggests the presence of tumour deposits, deeper levels (B) suggest continuous growth.
The HR for death due to disease is 1.96 (95% CI 1.6, 2.6), comparable to ratios commonly reported for invasion depth through the bowel wall (1.2, 1.3, 1.4), lymph node metastases (1.8, 2.3), extracapsular spread of lymph node metastases (1.4), lymphovascular invasion (1.6, 2.8), extramural vascular invasion (1.8), and perineural invasion (1.5, 1.5–2.6, 2.0, 2.9).

We believe that both the size and the contour criteria that form the basis of different editions of staging systems have, as yet, no scientific background. Due to the lack of proper and more extensive guidelines, reproducibility is poor. Difficulties arise when determining whether a TD is really a deposit or just a continuous finger of tumour growth that is not represented in the area sampled (Figure 5). The frequency of this lesion will depend on the number and size of blocks taken, with high volume sampling pathologists likely to have a greater frequency of these lesions leading to more frequent upstaging.

Nowadays, many patients are eligible for either short-course or long-course radio(chemo)therapy, and special care should be taken with a rectal cancer specimen after neoadjuvant treatment. In cases of tumour regression the presence of (residual) TD is an indication of a better prognosis than no response, invalidating the use of this factor in such patients.

**Conclusion**

A TD is the end product of a variety of processes and frequently the process that gave rise to the individual lesion will be unknown, since the deposits become indistinguishable. However, careful searching elsewhere may identify the likely cause(s). Lymph node metastases, lymphatic invasion, perineural invasion and vascular invasion can all result in TD and all these processes are (independently) associated with a poor prognosis. The continuing changes in definitions and non-specific nature of TD in universally applied staging systems do not help in providing evidence necessary for decision making in modern medicine. Prior to their introduction into a widely used classification such as TNM, carefully designed studies in which the different definitions are tested were required. They were not performed. In the current situation the presence of TD should lead to a careful search for evidence of lymphatic, neural or vascular invasion. If these are not seen on further blocks, then comment on their presence may be valuable. Further studies are needed to determine whether they should be considered as high-risk stage II tumours, but these are warranted based on the current literature. The inclusion of TD in TNM6 as lymph node involvement is not supported by the literature or recent studies on reproducibility.

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**References**
