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Lord, A, Brown, G, Abulafi, M et al. (17 more authors) (2021) Histopathological Diagnosis of Tumour Deposits in Colorectal Cancer: A Delphi Consensus Study. Histopathology. ISSN 0309-0167

https://doi.org/10.1111/his.14344

Histopathological Diagnosis of Tumour Deposits in Colorectal Cancer: A Delphi Consensus Study

Running title: Defining Tumour Deposits in Colorectal Cancer

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The authors have no conflicts of interest

Word count: 2689

Abstract

Introduction: Tumour deposits (TDs) are an important prognostic marker in colorectal cancer. However, the classification, and inclusion in staging, of TDs has changed significantly in each TNM Edition since their initial description in TNM 5, and terminology remains controversial. Expert consensus is needed to guide the future direction of precision staging.

Methods: A modified Delphi consensus process was used. Statements were formulated and sent to participants as an online survey. Participants were asked to rate their agreement with each statement on a 5-point Likert scale and also to suggest additional statements for discussion. These responses were circulated, together with anonymised comments, and statements were modified prior to carrying out a second online round. Consensus was set at 70%.

Results: Overall, 32 statements reached consensus. There were concerns that TDs were currently incorrectly placed in the TNM system and that their prognostic importance was being underestimated. There were concerns about interobserver variation and it was felt that a clearer, more reproducible definition of TDs was needed.

Conclusions: Our main recommendations are that the number of TDs should be recorded even if LNMs are also present and that nodules with evidence of origin (EMVI, PNI, LI) should still be categorised as TDs and not excluded as TNM 8 specifies. Whether TDs should continue to be included in the N category at all is controversial and did not achieve consensus, however participants agreed that TDs are prognostically worse than LNMs and the N1c category is suboptimal as it does not reflect this.

Keywords: colorectal cancer; staging; tumour deposits; TNM system; histopathology

Introduction

Tumour deposits (TDs) were first mentioned in 1932 by Gabriel et al.[1] but not really pursued as an important part of colorectal cancer staging. Interest in TDs was reignited around the year 2000 when several papers were published reporting a significant adverse effect on prognosis[2–5]. TDs were added for the first time in the 5th Edition of the AJCC/UICC TNM staging system where small TDs were distinguished from lymph node metastases (LNMs) on the basis of size. All nodules of more than 3mm in diameter were classified as LNMs and smaller nodules were included as part of the T stage[6]. In the 6th edition TDs were differentiated from LNMs on the basis of irregular contour , where irregular deposits were again included in the T stage[7]. This definition was heavily criticised both on the basis of the lack of evidence, and biological rationale, as well as the poor reproducibility[8]. In TNM 7 and TNM 8,

TDs were given a separate sub-category: “pN1c”. However, apart from describing TDs as nodules with no evidence of lymph node architecture, the definition in TNM 7 was not very clear[9,10]. In a modification from TNM 7, in the TNM 8 update, non-nodal deposits with evidence of associated extramural venous invasion (EMVI), lymphatic invasion (LI) or perineural invasion (PNI) are also excluded from the N1c category, despite research previously reports confirming that TDs may originate from a variety of origins and can often be seen to exhibit multiple histological associations[11,12].

Recently, a meta-analysis was carried out which showed that TDs have a significantly worse effect on prognosis than LNMs and the presence of both LNMs and TDs was additive[13]. Furthermore, this remains the case in patients who have undergone neoadjuvant therapy[14]. Concerns have been raised that the pN1c category in TNM 8 does not adequately reflect the prognostic effect of TDs, firstly because TDs are only

reported in the absence of LNMs and secondly because the pN1c designation implies that they have a lesser prognostic effect than pN2 which is not in line with the currently available evidence. Given these findings, and the controversy surrounding the recent changes in TNM, a survey of expert opinion is warranted to assess future direction in classifying TDs, determining how TDs should affect staging and utilising this information in aiding treatment decisions. This paper reports a Delphi Consensus study of experts in the field to develop recommendations which could help shape future staging.

Materials and Methods

Expert selection

Pathologists who were known to be experts in the field and/or had previously published research on TDs were approached and asked to participate by email. Overall 15 pathologists from 8 countries agreed to participate and were therefore included in the Delphi process. Following a detailed literature review, a summary of the latest evidence was compiled by the study organisers and sent to all participants before starting the process to standardise knowledge and ensure participants were up to date with the latest published papers in the field[13,15–21].

Delphi Process

A modified Delphi technique was used. The initial statements were formulated after a literature review and discussion between the primary authors. The statements were sent out as an online survey and participants were asked to rate their level of agreement with each statement on a 5-point Likert scale (ranging from strongly agree to strongly disagree). Participants were also encouraged to provide comments to justify their decision where appropriate. As part of round 1, there was an opportunity for participants to suggest further statements that they felt should be included in the round 2. The results were collated and circulated to all participants along with anonymised comments for any statement that had not reached consensus. Consensus was considered to have been reached if >70% of participants selected strongly agree/agree (positive consensus) or strongly disagree/disagree (negative consensus). A second round was then carried out using the same methodology,

including those statements that did not achieve consensus in Round 1 and all new statements proposed by the participants. Some statements were re-worded as a result of feedback during round 1. This process is summarised in figure 1.

Results

In round 1, 35 statements were sent to the participants. The statements were separated into the following categories: origin of TDs, classification of TDs and clinical application. From these 35, 19 statements achieved consensus. The 16 statements which did not achieve consensus were sent again in the second round along with 4 additional statements suggested during round 1. Of these 20 statements, 9 achieved consensus (7 of these being statements which had not achieved consensus in the first round).

Figure 2 shows the level of agreement with each of the statements that achieved consensus. Table 1 outlines all of the statements which achieved consensus during the Delphi Process, with statements achieving negative consensus reworded to improve clarity. The rewording was agreed by all of the participants. The statements which did not achieve consensus are listed in Table 2.

The origin of TDs

The origin of TDs remains topical and debateable. The panel agreed that TDs are a collection of different entities with several potential origins, but it is unclear whether the origin of TDs has differential impact on prognosis (#7). This is probably why the origin is not discussed at multidisciplinary team discussions at participants' institutions (#24). The panel also thinks that the origin should thus not determine the inclusion in cancer staging at the present time based on current evidence (#12). There is a strong correlation of TDs with for example EMVI (#5), however, the panel thinks that once EMVI has outgrown the vessel to form a large TD, it may represent an adverse prognostic feature beyond simple vascular invasion (#6). It is likely that outgrowth from

the perineurium in PNI has a similar effect. From a scientific point of view, it is important to determine the origin of TDs to generate more refined evidence (#1), however there was no agreement on whether there was currently any practical benefit in this (#30). The panel agreed that it might be informative to register both the presence of TDs and any discernible features suggesting their origin in order to document and correlate this information in the future (#8). There was consensus that the size of a TD is not associated with the origin (#4), however there was no agreement about whether the shape of a TD is of similar relevance (#31), and therefore further research is needed.

Classification of TDs

The expert panel of pathologists taking part in this Delphi process were critical of the current TNM staging system with regard to TDs, agreeing that the current definition of TDs was unclear (#14, #16) and did not facilitate good reproducibility (#10, #14). The consensus was that N1c is not the correct terminology for TDs within the TNM system and disagree with the current practice of ignoring TDs if LNMs are also present (#13). The consensus was that the precise number of TDs should be recorded (#11), as is currently done for LNMs, but that adding the number of TDs to the number of LNMs would not be advisable as this is currently not based on strong evidence (#21). There were concerns about excluding TDs with evidence of an origin from EMVI, LI or PNI from the pN1c category as, although these pathological features could be recorded as "additional factors affecting clinical care", they do not affect the stage grouping of a tumour and would be too readily overlooked in clinical decision making (#20). Overall, the consensus was that greater standardisation was needed in the definition of TDs

(#18), even if this did mean sacrificing some precision about their origin (#19). The panel felt that the size and shape of TDs should not be used to determine their inclusion in TNM (#12, #17) as this is not evidence based, and indeed is counterintuitive given that lymph nodes, veins, nerves and lymphatics are of variable size.

Agreement was not reached as to whether any discontinuous tumour nodules in the mesenteric fat should be recorded as a TDs (#32). Some participants felt that clearly discontinuous EMVI and PNI should be recorded a TD, but others felt that discriminatory features, such as whether the tumour was fully contained within a vessel, were key. The panel did not reach consensus about whether the presence of TDs should lead to a tumour being classified as either AJCC stage II with high risk features (#37, #39) (as with features such as EMVI) or stage III (#38). Comments suggested that both of these categories underestimated prognosis and that a new category may be needed to separate LNMs from TDs to reflect their differing prognostic implications. Similarly, the panel did not reach agreement as to whether TDs should be included in the pN category (#36). Some pathologists felt that adding a new category to TNM would be difficult to achieve and therefore the pN category was the most appropriate place to record TDs. However, several argued that using the pN category was not scientific nor accurate due to differing origins and prognostic implications of TDs and LNMs. The panel could not agree on either a cut off for counting TDs (i.e. whether they should only be counted up to 5 or counted beyond this number)(#33) or on whether there should be a size cut off (#34) to aid standardisation. It was felt that these classification criteria should not be implemented until there is better evidence to support them. There was no consensus on whether different criteria

were needed to define TDs in treated and untreated patients, again due to lack of evidence to support this at present. This highlights important areas for future research.

Clinical impact of TDs

In terms of clinical application, participants felt that TDs were a clear marker of poor prognosis in both patients undergoing primary surgery and those who had been previously treated with neoadjuvant therapy (#22, #23), and that TDs were a strong indication for consideration of adjuvant chemotherapy (#28), although they felt that a clinical trial was needed to provide further evidence of the benefits of adjuvant therapy in this population (#29) as well as neoadjuvant therapy if predicted TDs on imaging could be validated (#25). Participants agreed that presence of TDs were a worse prognostic marker than LNMs (#27) but felt that LNMs in the absence of TDs were still important (#26). Consensus was not achieved as to whether TDs resulting from tumour regression in treated patients would still confer a poor prognosis (#40) and further research in this area is warranted, which will require correlation of imaging with pathology findings.

Discussion

The definition of TDs in the TNM system has improved significantly in recent years, with pathologists now being asked to scrutinise nodules and assess whether they are truly nodal rather than relying on arbitrary and non-evidence-based size or shape criteria to differentiate between TDs and LNMs. Despite this, there are major outstanding issues which must be addressed in order to improve prognostication in light of increasing evidence (and expert consensus as set out in this paper) that TDs are in fact a marker of worse prognosis than LNMs[13].

The first clear recommendation from this consensus study is that TDs should be reported whenever they are seen on pathology and not only in the absence of LNMs as is currently the case using the "N1c" category. Furthermore "N1c" is not the correct position for TDs as it does not reflect where they fit prognostically in comparison to LNMs. If they must be included in the N category, N3 would perhaps be a better position, reflecting the fact that they are prognostically worse than LNMs[13]. Referring to TDs as "N1c" is confusing as they are by definition not nodal. Whether or not TDs should be taken out of the N category completely remains controversial and we were unable to reach consensus on this. We would recommend that regardless of the category TDs are recorded in, the precise number should be recorded as is the case for lymph nodes.

Not including deposits with evidence of underlying EMVI, LI or PNI in the N1c category is not evidence based. Several studies have shown that the majority of TDs have

evidence of associated structures such as vessel wall when carefully scrutinised[22,23] although deeper levels often need to be taken to reveal these. The studies that were responsible for linking TDs with poor prognosis did not subclassify them by origin or exclude those with associated EMVI, PNI or LI. There is not yet sufficient evidence about how these features relate to prognosis and it is therefore not currently justified to take nodules out of the N1c category on this basis. We would therefore recommend that all non-nodal deposits should be categorised together unless definitive evidence emerges that nodules with differing origins have different prognostic effects. This will improve agreement between pathologists by only asking them to decide upon a binary diagnosis (nodal or non-nodal) rather than placing nodules into a multitude of categories without evidence that this affects prognosis. Categorizing nodules as EMVI, PNI or LI rather than TDs or "N1c" means a tumour will be down staged from stage III to stage II. This may result in them not being offered adjuvant chemotherapy despite the fact that according to the literature[13,24,25], they would be in a poor prognostic group.

The participants felt that there were significant problems with an unclear and poorly reproducible definition of TDs in current staging and would strongly recommend that this needs further refinement in the next edition of TNM. This could involve defining which features of lymph node architecture need to be present in order to classify a nodule as a LNM. Features such as a round shape are commonly used to recognise a LNM[21] but this is non-specific and a very poor discriminator[19]. Perhaps pathologists should be given direct guidance about which features are specific and reproducible enough to use as evidence of LN architecture. It may be that some precision needs to be sacrificed in order to reduce complexity, and improve agreement, and the pathologists in this study felt that this would be preferable. Currently poor

reproducibility is likely to be resulting in patients being placed into a multitude of staging categories and receiving different treatment strategies as a result. It is of paramount importance that staging is reproducible in order to accurately stratify patients in clinical trials and determine the best treatment for each homogenous group. It is essential therefore that clinical trial protocols include additional guidance for pathologists reporting trial specimens to ensure that TDs are reported reproducibly across different trial centres.

The main limitation of this study is the relatively small number of participants. In addition, although 8 different countries were represented, all participants were from developed countries which may have led to a lack of diversity in the opinions represented in this study. The strategy of predominantly inviting experts who had previously published on this subject was the limiting factor in both the numbers involved and in geography and feel that this was needed to achieve true expert consensus.

There are difficulties with making any major changes to the TNM system. This method of staging is well accepted due to its relative simplicity and consistency across multiple tumour types. However, by limiting tumour categorization to only three categories, T, N and M, important prognostic information may be missed. TDs appear to be more important in predicting prognosis than LNMs, but due to the limitations of only having three categories, there has been an attempt to compartmentalize them into the pN category where TDs do not really belong, as an interim solution. This has led to controversy but resolving the issue will be problematic. Major alteration or abandoning

the well-established TNM system in favour of a more complex multifactorial model for prediction of prognosis could potentially lead to confusion. Nevertheless, retaining a system which is not fit for purpose, on the grounds of simplicity and historic importance, is also not ideal. The pathology community (and indeed the radiological, oncological and surgical communities by extension) need to carefully consider the future direction of staging in colorectal cancer. There are exciting opportunities to refine staging to improve the management and outcome for patients with advanced colorectal cancer.

Acknowledgements

Amy Lord, Gina Brown and Iris Nagtegaal has overall responsibility for carrying out the study and writing the paper.

Muti Abulafi, Brendan Moran and Shahnawaz Rasheed supervised Amy Lord in writing the manuscript, contributed to the idea for the study and helped to formulate the final manuscript.

Adrian Bateman, Wendy Frankel, Robert Goldin, Purva Gopal, Richard Kirsch, Maurice Loughrey, Bruno Maerkl, Giaccomo Puppa, Yoshifumi Shimada, Petur Snaebjornsson, Magali Svrcek, Kay Washington, Nicholas West and Newton Wong were the expert pathologists taking part in the Delphi process but also contributed to formulating the final manuscript.

This study was partly financed by a grant of the Dutch Cancer Society (KWF 12640).

Nick West is funded by Yorkshire Cancer Research.

Figure and Table Legends

Table 1. Statements that achieved consensus (statements marked with a * were new suggestions from round 1) (TD: tumour deposit, EMVI: extramural venous invasion, LNM: lymph node metastasis, PNI: perineural invasion)

Table 2. Statements that did not achieve consensus (statements marked with a * were new suggestions from round 1) (TD: tumour deposit, CRC: colorectal cancer)

Figure 1. Flowchart illustrating the Delphi process

Figure 2. Level of agreement with statements

Category	No.	Statement	Agreement
Origin of TDs	1	From a scientific point of view, it is important to determine the origin of TDs	93%
	2	TDs may be a result of incomplete tumour regression/fragmentation in patients treated with neoadjuvant therapy	80%
	3	Any non-nodal TD is associated with poor prognosis regardless of origin (e.g. EMVI or PNI related)	87%
	4	The size of a TD is unrelated to its origin	73%
	5	TDs are often related to EMVI	93%
	6*	I believe that when, for example, EMVI has outgrown the vessel to form a large TD, it may represent prognostically something beyond simple vascular invasion	87%
	7	TDs are a group of different entities which have grown out of different histological structures. It is currently unknown whether the origin of a TD has an impact on outcome	80%
	8*	Since there is currently no evidence that the origin of TDs is linked with outcome, it would be informative to register both TDs and any discernible origin in order to obtain this information in the future	80%
Classification in TNM	9	N1c is not the correct position for TDs in TNM as it does not reflect their prognostic effect accurately	73%
	10	There is poor inter-observer variation in the diagnosis of TDs	73%
	11	The precise number of TDs should be included in the report	73%
	12	The shape of a TD should not determine its inclusion in TNM	100%
	13	Ignoring TDs if LNMs are also present is the incorrect approach	100%
	14	The current TNM definition of TDs does not clearly define how to differentiate TDs from LNMs	87%
	15	The current TNM definition of TDs has poor reproducibility	87%
	16	A more specific definition of TDs is needed in TNM	93%
	17	The size of a TD should not determine its inclusion in TNM	75%
	18	Using a classification system which improves standardisation (as indicated by good interobserver agreement) is important	93%

	19	I would prefer a classification system focused on standardisation above a system that focuses on the origin of TDs	80%
	20	Although it is possible to record EMVI and PNI in TNM, these factors do not affect staging.	73%
	21	The number of TDs should <u>not</u> be added to the number of LNMs to determine the pN category	73%
Clinical application	22	TDs are a marker of poor prognosis in patients undergoing primary surgery (i.e. without neoadjuvant treatment)	100%
	23	TDs are a marker of poor prognosis in patients who have undergone neoadjuvant therapy	87%
	24	In the MDT I would report TDs and not discuss their potential origin	73%
	25	A clinical trial is needed to assess the effect of neoadjuvant therapy on patients with TDs	83%
	26	LNMs in the absence of TDs are an adverse prognostic factor	80%
	27	TDs are prognostically worse than LNMs	87%
	28	TDs on histopathology are a strong indication for consideration of adjuvant therapy	73%
	29	A clinical trial is needed to assess the effect of adjuvant therapy in patients with TDs on pathology	80%

Table 1. Statements that achieved consensus (statements marked with a * were new suggestions from round 1) (TD: tumour deposit, EMVI: extramural venous invasion, LNM: lymph node metastasis, PNI: perineural invasion)

Category		Statement	Agreement
Origin of TDs	30	From a practical point of view, it is important to determine the origin of TD	40%
	31	The shape of TD is related to its origin	47%
Classification in TNM	32	Any tumour nodule within the mesenteric fat which is discontinuous from the primary tumour should be recorded as a TD	60%
	33*	TD should be counted up to 5 then recorded as >5 if more numerous	47%
	34	It is important for standardisation to have a size cut off for TD	33%
	35*	There should be different criteria for defining TD in treated and untreated patients	60%
	36	TD should not be recorded in the N category	60%
	37	Given the importance of TD it should not be reported similarly to EMVI and PNI due to their "invisibility" in staging	53%
	38	The presence of TD is sufficient to classify a CRC as stage III	60%
	39	The presence of TD should make a CRC high risk stage II	33%
Clinical application	40	TD which are a result of tumour regression still confer a poor prognosis	53%

Table 2. Statements that did not achieve consensus (statements marked with a * were new suggestions from round 1) (TD: tumour deposit, CRC: colorectal cancer)

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