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Review

The significance of tumour deposits in rectal cancer after neoadjuvant therapy: a systematic review and meta-analysis

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Abstract ***Background:*** Tumour deposits (TDs) are a poor prognostic marker in colorectal cancer, but their significance after neoadjuvant chemoradiotherapy is less certain because this group of patients is excluded in most studies. Post-treatment TD might even be a sign of tumour response. No previous reviews have assessed outcomes in this group.
Materials and methods: A systematic review and meta-analysis was undertaken according to Preferred Reporting for Systematic Reviews and Meta-Analyses guidelines to determine the relevance of post-treatment TD. Inclusion criteria were studies assessing TD in patients who had undergone pre-operative treatment with radiotherapy and/or chemotherapy and reporting prevalence and survival outcomes. Studies that did not include histological review of cases were excluded.
Results: Eight studies and 1283 patients were included in the review. Prevalence of TDs varied from 11.8% to 44.2% (mean 23.7%), similar to untreated patients. The presence of TDs after chemoradiotherapy was associated with invasion depth, lymph node involvement, perineural invasion and synchronous metastases. The pooled hazard ratio for 5-year adverse disease–free survival was 2.3 (95% confidence interval [CI]: 1.8–2.9), and that for overall survival was 2.5 (95% CI: 1.9–3.3). One study showed a survival benefit with adjuvant therapy in the TD-positive group.
Conclusions: 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.

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1. Introduction

Tumour deposits (TDs) in colorectal cancer (CRC) have been shown to be a marker of poor prognosis [1,2]. However, there is still controversy as to their correct positioning in the tumour-node-metastasis (TNM) system [3,4]. There is evidence that they supersede lymph node metastasis (LNM) as a poor prognostic indicator, [1] but this is not recognised in the current staging. The origin of TDs has been the subject of speculation by numerous authors, and is still not entirely clear. While some authors have reported that a significant proportion of TDs cannot be traced back to lymph nodes, perineural growth or vascular invasion [5–7], Goldstein *et al*. [8] reported that after carrying out experiments of additional deeper sections, the vast majority of TDs (up to 90%) showed signs of more than one origin. The nature of TDs after neoadjuvant therapy is even more unclear. In some cases, TDs may be a result of tumour fragmentation and regression after treatment, where islands of tumour cells are present within the mesentery as the remnants of a previously larger tumour which has regressed, rather than a primary phenomenon [5].

Accurate diagnosis is necessary to ensure optimal treatment decisions. The key problem is that we currently do not know how to classify TDs in this situation, either as remnants of disease or as a primary phenomenon. We also do not know its prognostic implications. Recent imaging advances have allowed TD detection on magnetic resonance imaging (MRI) [9]. Detection of TDs at an early stage could help elucidate the role they play in tumour regression, thereby clarifying their significance. Ultimately, this would aid in determining the risk profile of a tumour at baseline and therefore will determine the best pre-operative treatment.

The majority of studies reporting the prognostic implications of TDs excluded all patients who had undergone neoadjuvant therapy. Patients with rectal cancer with TDs often present with advanced tumours [1], which have an indication for neoadjuvant therapy. Determination of the significance of TDs in this group is very relevant. A small number of studies have included patients who have undergone neoadjuvant therapy, but the evidence has not yet been synthesised in a systematic review. Here, the aim is to critically appraise the existing evidence surrounding TDs in those patients to elucidate the possible prognostic implications of TDs after therapy.

2. Materials and Methods

A systematic review and meta-analysis was conducted in keeping with the Preferred Reporting for Systematic Reviews and Meta-Analyses guidelines [10] (Fig. 1). A literature search was carried out in PubMed using the search string ‘tumour deposits’ or ‘foci’ or ‘n1c’ or ‘extranodal metastasis’ or ‘extranodal spread’ and ‘radiotherapy’ or ‘neoadjuvant’ or ‘preoperative’ and ‘rectal cancer’ or ‘colorectal cancer’. Reference lists were manually searched to identify further relevant studies for full-text review.

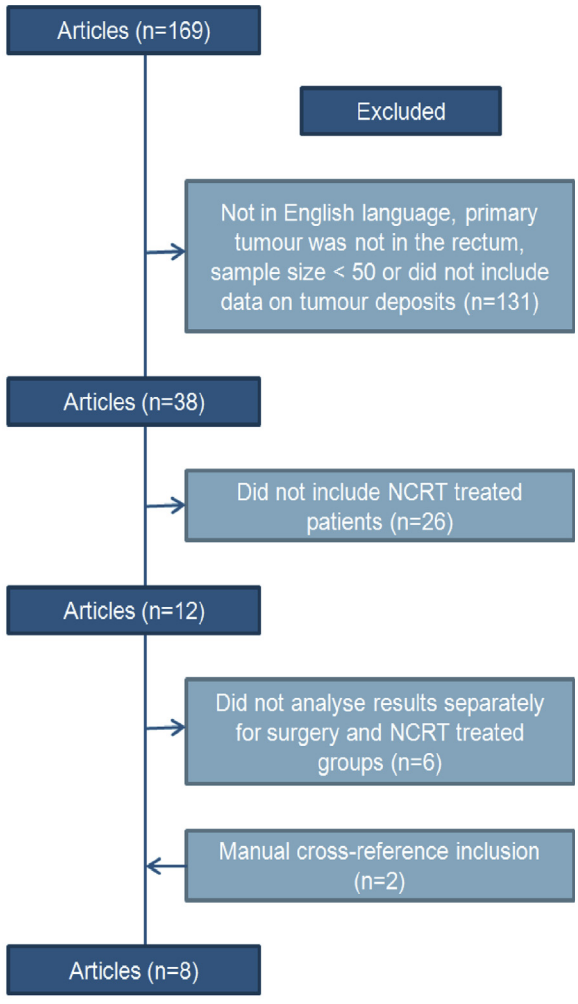

Fig. 1. Flow chart of the article search strategy for systematic review.

Inclusion criteria for the review were studies analysing TDs in patients with rectal cancer who had undergone neoadjuvant therapy and studies reporting the primary outcomes of prevalence, overall survival (OS), disease-free survival (DFS) or recurrence. Studies also including patients who did not undergo neoadjuvant therapy were included in the review, provided that the outcomes in the two groups were reported separately. Studies were excluded if they did not report any of the outcomes of interest, if they were not complete articles or in English or if the number of patients included was <50. Two studies with a small overlap were included because this overlap was limited to the

Table 1
Summary of studies including treatment given and quality score.

Ref. No.	Author	Year	Country	No. patients	No. NCRT	Prevalence of TDs (%)	Percentage reported	Definition of TD	Quality score
[16]	Gopal	2014	USA	205	110	20.9	78.9	TD defined as irregular tumour nodules with infiltrative borders >1 cm from the primary tumour, and lacking a thick fibrous capsule	78.9%
[15]	Hav	2015	Belgium	76	72	13.5	61.1	Assessed first by TNM 5 criteria and second by recording all discontinuous tumour nodules separately to the T and N categories	61.1%
[18]	Zhang	2016	China	310	310	17.4	84.2	TNM 7 definition: TD defined as any nodule without evidence of underlying lymph node architecture and labelled as 'N1c'	84.2%
[7]	Ratto	2002	Italy	77	30	44.2	36.8	Defined as deposits 'discontinuous from the primary tumour, with no evidence of nodal tissue'	36.8%
[17]	Song	2011	Korea	135	135	26.2	57.9	TNM 7 definition: TD defined as any nodule without evidence of underlying LN architecture and labelled as 'N1c'	47.9%
[19]	Swellengrebel	2014	NL	107	107	11.8	78.9	Defined as 'tumour nests discontinuous from the primary tumour, or tumour nest sectioned as a possible LN with no signs of an LN'	78.9%
[11]	Ratto	2007	Italy	68	24	38.2	41.1	Defined as 'mesorectal deposits of adenocarcinoma, discontinuous from the primary tumour, with no evidence of nodal tissue'	41.1%
[12]	Wang	2019	China	495	495	17.8	63.2	TNM 8 definition: TD labelled as 'N1c' and defined as tumour nodules without evidence of LN architecture, EMVI, PNI or LI	63.2%
Mean						23.75	62.8		

Chemo = chemotherapy, No. = number, NL = Netherlands, pre = pre-operative, Ref = reference, RTX = radiotherapy, TD = tumour deposit; PNI = perineural invasion; NCRT = neoadjuvant chemoradiotherapy; EMVI = extramural venous invasion; LI = lymphatic invasion.

comparison of nodal status [7,11]. Studies without histological review (such as surveillance, epidemiology, and end results (SEER) data) were excluded (Fig. 1). Data were extracted independently by three reviewers, and disagreement was resolved via consensus. Study quality was assessed using a 20-point scoring system designed for the evaluation of histopathological studies [12]. Meta-analysis using a random-effects model with weighing according to inverse variance was performed using the Stata software (StataCorp. 2015. College Station, TX) and Review Manager, version 5.3, (The Cochrane Collaboration, Copenhagen: The Nordic Cochrane Centre, 2012). From each study, we extracted the number of patients, TNM stage, risk ratio (RR) or hazard ratio (HR) for OS and DFS with their corresponding confidence interval (CI). If HR data were not available, they were extracted from the Kaplan-Meier curves using Parmar estimation [13]. Heterogeneity was measured with the I^2 statistic to determine the percentage of variation between studies due to heterogeneity and not due to chance. A logistic regression analysis was also performed to investigate the multivariate relationship of pathological risk factors. These results were reported as RRs using the Mantel-Haenszel method in a random-effects model [14], providing pooled ratios across studies with a 95% CI. A p-value < 0.05 was considered statistically significant.

3. Results

The original search returned 169 articles. After review of abstracts, 38 articles were retrieved for full-text review. Twelve studies were found which included the assessment of TDs in patients who had undergone neoadjuvant chemoradiotherapy (NCRT). However, six of these did not analyse the results for patients with NCRT separately and thus were excluded. Of the remaining six studies, four included only those who had undergone NCRT and two included both patients undergoing NCRT and primary surgery but carried out a subgroup analysis comparing these and thus, they were all included. Another two studies [11,15] were found by manual cross-referencing and were included for the multivariate relationship analysis of regression, but only one could be included [12] for the patient outcome comparison as the reporting was not sufficient in the other (Fig. 1).

A total of eight studies, with 1283 patients who had undergone NCRT, were included in the review. All patients in the NCRT groups were treated with radiotherapy, and in six of the eight studies, all patients also underwent pre-operative chemotherapy (Table 1). In the study by Hav *et al.* [16], all 76 patients underwent pre-operative chemotherapy, and in the study by Ratto *et al.* [11], 24 of 68 patients underwent pre-operative

chemotherapy. Despite not all cases having had chemotherapy, for the sake of readability, we refer to all as NCRT.

3.1. Prevalence of TDs

In total, 279 patients had TDs (mean: 23.75%, range: 11.8%–44.2%). Studies by Gopal *et al.* [17] and Ratto *et al.* [11] compared the prevalence in the NCRT and surgery groups. Ratto *et al.* [11] found no significant difference between the two groups with a prevalence of 43.3% in the NCRT group vs 44.7% in the surgery group. These values are very high compared with the reported prevalence of TDs in untreated patients [1,2], which can be explained by their inclusion of vascular invasion as TDs. When vascular invasion cases are excluded, a lower prevalence is seen (32.5%), which falls closer to the reported range. The study by Gopal *et al.* [17] showed a higher prevalence in the surgery group (30.5% vs 20.9%), although this was not significant ($p = 0.12$).

3.2. Correlation with other histological risk factors

With increased post-treatment invasion depth (ypT), there was an increase in cases with TDs (RR: 1.38, 95% CI: 1.10–1.73). The presence of perineural invasion (RR: 2.35, 95% CI: 1.20–4.64) and LNMs (RR: 2.04, 95% CI: 1.67–2.49) also increased the prevalence of TDs. In one of the studies [18], only node-negative patients were selected, and therefore, this study was excluded for the metastatic lymph node calculations. There were no significant associations with the presence of lymphovascular invasion (RR: 1.46, 95% CI: 0.55–3.92) or vascular invasion (RR: 1.04, 95% CI: 0.14–7.98). In the presence of distant metastases, TDs were more frequently present (RR: 1.77, 95% CI: 1.11–2.82) (Table 2).

Table 2
The association with histological risk factors and the presence of tumour deposits.

Histological risk factors	
Invasion depth	
ypT1/T2 vs ypT3/T4	**RR (95% CI)**
Gopal et al., 2014	1.13 (0.96, 1.33)
Ratto et al., 2002	1.31 (1.01, 1.70)
Wang et al., 2019	1.36 (1.16, 1.59)
Zhang et al., 2015	3.08 (1.69, 5.61)
Total	**1.38 (1.10, 1.73)**[b]
Nodal status (ypN + vs ypN-)	**RR (95% CI)**
Ratto et al., 2002	2.11 (1.05, 4.22)
Ratto et al., 2007	1.62 (0.89, 2.92)
Gopal et al., 2014	1.74 (1.08, 2.78)
Wang et al., 2019	2.22 (1.72, 2.87)
Total	**2.04 (1.67, 2.49)**[c]
Lymphatic invasion	**RR (95% CI)**
Gopal et al., 2014	2.32 (0.95, 5.69)
Song et al., 2011	0.84 (0.29, 2.47)
Total	**1.46 (0.55, 3.92)**
Vascular invasion	**RR (95% CI)**
Song et al., 2011	0.22 (0.01, 3.57)
Wang et al., 2019	2.10 (1.03, 4.28)
Total	**1.04 (0.14, 7.98)**
Perineural invasion	**RR (95% CI)**
Gopal et al., 2014	5.54 (1.71, 18.01)
Song et al., 2011	1.23 (0.49, 3.09)
Wang et al., 2019	2.38 (1.41, 4.00)
Total	**2.35 (1.20, 4.64)**[a]
Metastasis	**RR (95% CI)**
Ratto et al., 2002	1.92 (0.59, 6.24)
Gopal et al., 2014	1.75 (1.05, 2.90)
Total	**1.77 (1.11, 2.82)**[a]

Abbreviations: RR: risk ratio, CI: confidence interval, T stage: tumour stage, N stage: nodal status.
[a] Statistically significant (<0.05).
[b] Statistically significant (<0.001).
[c] Statistically significant (<0.0001).

3.3. Effect of TDs on prognosis

TD presence was correlated with poor outcome both for OS (HR: 2.54, 95% CI: 1.95–3.30) and DFS (HR: 2.30, 95% CI: 1.82–2.92) (Fig. 2). Data from 3-year and 5-year survival available from the studies included were pooled together as an assumption of proportional hazards regression is that the HR is constant over time. Heterogeneity measured by the I^2 test was low in all outcome analyses (0.0%, $p < 0.00001$). Funnel plots illustrated no risk of publication bias and are available in Supplementary Figs. 1 and 2.

3.4. Tumour regression

Data regarding tumour regression were obtained from four different studies [11,15,19,20]. Reporting in these studies was carried out using three different grading systems (Mandard's regression grade [21], Dworak regression grade [22] and the American Joint Committee on Cancer (AJCC) tumour regression grade [23]) from which we extracted two groups: intermediate responders and non-responders. Pathologically complete responders (pCRs) were excluded because by definition, they should not have any tumour remnants, although some studies reported pCR cases with TDs (2/75 in the study by Zhang *et al.* [19], 4/21 in the study by Swellengrebel *et al.* [20] & 4/105 in the study by Wang *et al.* [15]). There was more TD presence in cases with regression (TRG1/2) (RR: 1.30 [95% CI: 0.88–1.93]), although this difference was not significant (Supplementary Fig. 3).

4. Discussion

This systematic review and meta-analysis have shown that TDs are a poor prognostic marker in patients who have undergone NCRT, which is similar to the situation in treatment-naive patients. Similar to untreated patients [1], the presence of TDs is associated with higher

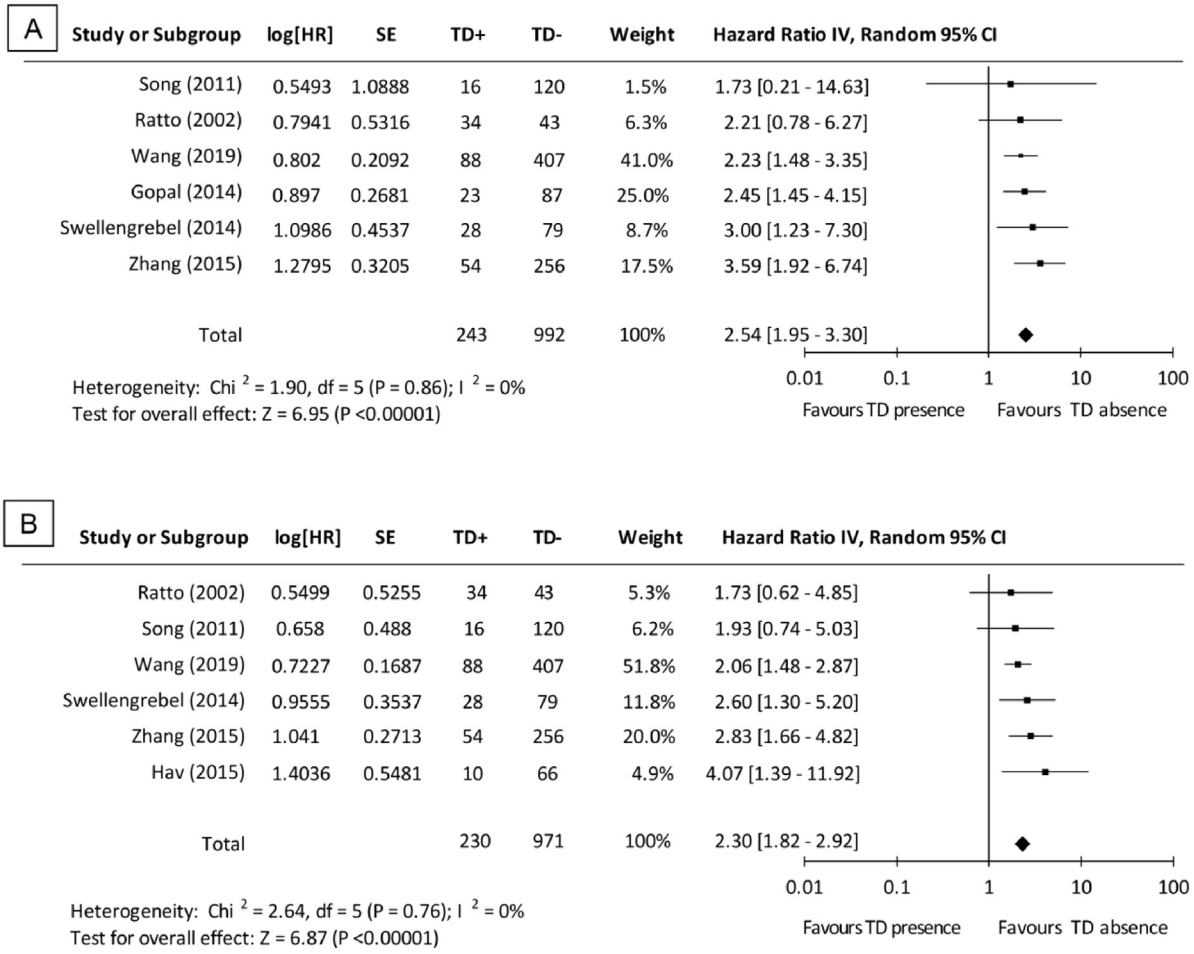

Fig. 2. Prognostic impact of tumour deposits after NCRT: A. overall survival, B. disease-free survival. NCRT = neoadjuvant chemo-radiotherapy; SE = standard error; CI = confidence interval; TD = tumour deposit; HR = hazard ratio.

TNM stage, in particular advanced T stage, LNM and distant metastases. This is also observed in a large database analysis of SEER data (n = 5439) [24]; however, this study was excluded because of the lack of histological review and limited registration of TDs. Their low prevalence of TDs (10.7% versus our average of 21.6%) highlights the problem because only TDs in the absence of LNM (N1c) were included in the analysis.

The great variation in reported prevalence of TDs is consistent with previous meta-analyses of untreated patients [1,2]. This is likely to represent a combination of differences in pathology techniques and classification, high inter-observer variation and differences in case-mix between institutions. The effects of neoadjuvant treatment on the number of TD-positive patients seem minimal as these numbers are comparable with earlier studies [1]; direct comparison within one institution did indeed not show any differences [17]. Very little was found in previous literature on the prognostic importance of TDs in NCRT-treated patients as only two studies [7,17] provided a direct comparison between treated and untreated groups. These were retrospective, non-randomised studies, so there are multiple possible confounding factors. An important confounding factor is patient selection: Patients with advanced cancers are likely to have been preferably selected for NCRT.

In contrast to the situation in untreated patients, there was no correlation of TDs with either lymphatic invasion or vascular invasion, only for perineural invasion. From multiple studies in the untreated setting, we know that extensive investigations into the origin of TDs showed that tumour expansion in these settings can cause TDs and only deeper levels demonstrate likely precursors [5,8]. Owing to the lack of these correlations, we need to examine other explanations. Fragmentation seems a plausible explanation for the origin of TDs in this setting because this form of tumour regression is also associated with poor prognosis [16,25–27]. The

Fig. 3. Origins of tumour deposits and the effects of NCRT. In the untreated setting, the presence of tumour deposits is associated with lymph node metastasis (LNM), vascular invasion (VI) and perineural invasion (PNI). These associations may be more difficult to appreciate after NCRT, which might be explained by the destruction of some tumour deposits and the emergence of new tumour deposits, possibly due to fragmentation as a response mechanism or form of tumour regression. NCRT = neoadjuvant chemoradiotherapy.

comparable prevalence of TDs in treated and untreated patients might be explained by the disappearance of part of the original TDs, for example, those originating from vascular invasion [5], in combination with the appearance of TDs due to tumour fragmentation (Fig. 3). A second explanation is that detection of venous invasion after NCRT can be very challenging because the effects of radiation on vessel walls can make them difficult to recognise on haematoxylin and eosin (H&E) staining. In this setting, vascular invasion may be missed unless elastin staining is used. The comprehensive analysis of Ratto *et al.* [11] showed that at least half of TDs after neoadjuvant therapy have multiple possible origins, although for a significant number of TDs (11.8%), there is no clear evidence of a precursor.

Definite answers to the origin of TDs and their relationship to tumour fragmentation might be established using pre- and post-treatment analysis by MRI. TDs have recently been noted to be visible on MRI [9], and current research is focussing on correlating these findings with pathology [28]. With the use of imaging, we can obtain a clear 3D map of the primary tumour and where TDs were present before the start of neoadjuvant therapy, as opposed to pathology where only a snapshot of the mesorectum, both post-treatment and ex-vivo, is available. Close collaboration between radiologists and pathologists would allow direct correlation of pre- and post-treatment findings to establish whether TDs are a primary or secondary phenomenon in each individual case. We can then distinguish two groups of patients and determine the true value of primary and secondary TDs.

In the study by Zhang *et al.* [19], it was noted that patients with TDs had a survival benefit with the use of adjuvant chemotherapy. This finding is interesting as the survival benefit from adjuvant chemotherapy in patients who have already undergone NCRT is contentious and there is not, as yet, strong evidence defining whether the efficacy of this treatment is highest in any particular TNM stage or other subgroup of patients [29–31]. This requires further assessment with a large randomised controlled trial. In addition to being a potential indication for adjuvant therapy when seen on pathology, radiologically diagnosed TDs may potentially be a similar indication for neoadjuvant therapy.

We have shown that in the neoadjuvant setting, the presence of TDs is associated with a poor outcome, similar to the untreated setting. Our findings suggest that a number of TDs might very well be the result of tumour fragmentation. Tumour fragmentation is a form of tumour regression associated with a poor outcome [16,25–27]. The lack of correlation with potential precursor lesions in the neoadjuvant setting, in contrast to the untreated situation, suggests that this might be the case. Definite proof should be gathered using pre-operative imaging. Until then, our only conclusion can be that TDs are a poor prognostic marker, likely worse than nodal involvement, and as such might prompt consideration of adjuvant therapy.

Conflict of interest statement

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.020.

References

[1] Nagtegaal ID, Knijn N, Hugen N, Marshall HC, Sugihara K, Tot T, et al. Tumor deposits in colorectal cancer: improving the value of modern staging—a systematic review and meta-analysis. J Clin Oncol 2017;34.

[2] Lord AC, D'Souza N, Pucher PH, Moran BJ, Abulafi AM, Wotherspoon A, et al. Significance of extranodal tumour deposits in colorectal cancer: a systematic review and meta-analysis [cited

2017 Jun 27] Eur J Cancer [Internet] 2017 Sep 23;82:92–102. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28651160.

[3] Nagtegaal ID, Quirke P. Tumour deposits in colorectal cancer: the challenge is continuing. Histopathology [Internet] 2008;52(6): 768–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed8&AN=2008204213.

[4] Nagtegaal ID, Tot T, Jayne DG, McShane P, Nihlberg A, Marshall HC, et al. Lymph nodes, tumor deposits, and TNM: are we getting better? [cited 2017 Feb 9] J Clin Oncol [Internet] 2011 Jun 20;29(18). 2487–92. Available from: http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.34.6429.

[5] Wunsch K, Muller J, Jahnig H, Herrmann RA, Arnholdt HM, Markl B. Shape is not associated with the origin of pericolonic tumor deposits. Am J Clin Pathol [Internet 2010;133(3):388–94. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed9&AN=2010234517.

[6] Ueno H, Mochizuki H, Shirouzu K, Kusumi T, Yamada K, Ikegami M, et al. Multicenter study for optimal categorization of extramural tumor deposits for colorectal cancer staging. Ann Surg [Internet 2012;255(4):739–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22395093.

[7] Ratto C, Ricci R, Rossi C, Morelli U, Vecchio FM, Doglietto GB. Mesorectal microfoci adversely affect the prognosis of patients with rectal cancer. Cancer [Internet] 2002;45(6): 733–42. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed5&AN=2002201970.

[8] Goldstein NS, Turner JR. Pericolonic tumor deposits in patients with T3N+M0 colon adenocarcinomas: markers of reduced disease free survival and intra-abdominal metastases and their implications for TNM classification. Cancer 2000;88(10):2228–38.

[9] Balyasnikova S, Brown G. Imaging advances in colorectal cancer [cited 2018 Apr 19]. In: Curr colorectal cancer rep [internet]. vol. 12. Springer; 2016. 162–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27340377.

[10] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration [cited 2016 Aug 12] PLoS Med [Internet] 2009 Jul 21;6(7):e1000100. Available from: http://dx.plos.org/10.1371/journal.pmed.1000100.

[11] Ratto C, Ricci R, Valentini V, Castri F, Parello A, Gambacorta MA, et al. Neoplastic mesorectal microfoci (MMF) following neoadjuvant chemoradiotherapy: clinical and prognostic implications. Ann Surg Oncol [Internet] 2007;14(11): 853–61. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed8&AN=2007059872.

[12] Knijn N, Simmer F, Nagtegaal ID. Recommendations for reporting histopathology studies: a proposal. Springer; 2015 Jun [cited 2019 Jan 16] Virchows arch [internet] 2015;466(6). :611–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25846513.

[13] Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects [cited 2019 Feb 21] Stat Med [Internet] 2002 Aug 15;21(15). 2175–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12210632.

[14] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Oxford University Press; 1959 Apr 1 [cited 2018 Nov 27] JNCI J Natl Cancer Inst [Internet] 1959;22(4). 719–48. Available from: https://academic.oup.com/jnci/article/22/4/719/900746/Statistical-Aspects-of-the-Analysis-of-Data-From.

[15] Wang Y, Zhang J, Zhou M, Yang L, Wan J, Shen L, et al. Poor prognostic and staging value of tumor deposit in locally advanced rectal cancer with neoadjuvant chemoradiotherapy. Cancer Med [Internet] 2019 Apr;8(4):1508–20 [cited 2019 Feb 28]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30790459.

[16] Hav M, Libbrecht L, Geboes K, Ferdinande L, Boterberg T, Ceelen W, et al. Prognostic value of tumor shrinkage versus fragmentation following radiochemotherapy and surgery for rectal cancer. Virchows Arch 2015;466(5):517–23. 2015/02/20.

[17] Gopal P, Lu P, Ayers GD, Herline AJ, Washington MK. Tumor deposits in rectal adenocarcinoma after neoadjuvant chemoradiation are associated with poor prognosis. Mod Pathol [Internet] 2014;27(9):1281–7. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed12&AN=2014587151.

[18] Song JS, Chang HJ, Kim DY, Kim SY, Baek JY, Park JW, et al. Is the N1c category of the new american joint committee on cancer staging system applicable to patients with rectal cancer who receive preoperative chemoradiotherapy? Cancer [Internet] 2011;117(17):3917–24. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed10&AN=2011466748.

[19] Zhang L-NN, Xiao W-WW, Xi S-YY, OuYang P-YY, You K-YY, Zeng Z-FF, et al. Tumor deposits: markers of poor prognosis in patients with locally advanced rectal cancer following neoadjuvant chemoradiotherapy. 2015/12/24. Impact Journals, LLC; 2016 Feb 2 [cited 2016 Jun 13] Oncotarget [Internet] 2016;7(5): 6335–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26695441.

[20] Swellengrebel HAM, Bosch SL, Cats A, Vincent AD, Dewit LGH, Verwaal VJ, et al. Tumour regression grading after chemoradiotherapy for locally advanced rectal cancer: a near pathologic complete response does not translate into good clinical outcome. Radiother Oncol [Internet] 2014;112(1):44–51. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed12&AN=2014715183.

[21] Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations [cited 2018 Nov 27] Cancer [Internet] 1994 Jun 1;73(11). 2680–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8194005.

[22] Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Springer-Verlag; 1997 Mar 24 [cited 2018 Nov 27] Int J colorectal dis [internet] 1997;12(1):19–23. Available from: http://link.springer.com/10.1007/s003840050072.

[23] Edge SB, Compton CC. The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. 2010.

[24] Wei X-L, Qiu M-Z, Zhou Y-X, He M-M, Luo H-Y, Wang F-H, et al. The clinicopathologic relevance and prognostic value of tumor deposits and the applicability of N1c category in rectal cancer with preoperative radiotherapy. Impact Journals, LLC; 2016 Nov 15 [cited 2018 Jan 29] Oncotarget [internet] 2016;7(46). 75094–103. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27655707.

[25] Fernández-Aceñero MJ, Estrada Muñoz L, Sastre Varela J, Corona Sánchez JA, Díaz del Arco C, García Paredes B, et al. Prognostic influence of histopathological regression patterns in rectal adenocarcinoma receiving neoadjuvant therapy [cited 2018 Dec 19] J Gastrointest Oncol [Internet] 2017 Feb;8(1):49–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28280608.

[26] Perez RO, Habr-Gama A, Smith FM, Kosinski L, São Julião GP, Grzona E, et al. Fragmented pattern of tumor regression and lateral intramural spread may influence margin appropriateness after TEM for rectal cancer following neoadjuvant CRT [cited 2018 Dec 19] J Surg Oncol [Internet] 2014 Jun;109(8). 853–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24862927.

[27] Hayden DM, Jakate S, Pinzon MCM, Giusto D, Francescatti AB, Brand MI, et al. Tumor scatter after neoadjuvant therapy for rectal cancer [cited 2018 Dec 19] Dis Colon Rectum [Internet] 2012 Dec;55(12). 1206–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23135577.

[28] Clinicaltrials.gov. Concordance in MRI and pathology diagnosis of extranodal tumour deposits - full text view. Bethesda ClinicalTrials.gov [Internet] 2017 [cited 2017 Dec 11]. Available from: https://clinicaltrials.gov/ct2/show/NCT03303547.

[29] Carvalho C, Glynne-Jones R. Challenges behind proving efficacy of adjuvant chemotherapy after preoperative chemoradiation for rectal cancer. Lancet oncol [internet] 2017. Elsevier; 2017 Jun 1 [cited 2018 Nov 27];vol. 18(6):e354–63. Available from: https://www.sciencedirect.com/science/article/pii/S1470204517303467.

[30] Bosset J-F, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer [cited 2016 Dec 15] N Engl J Med [Internet] 2006 Sep 14;355(11). 1114–23. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa060829.

[31] Breugom AJ, Swets M, Bosset J-F, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data [cited 2018 Jan 3] Lancet Oncol [Internet] 2015 Feb;16(2). 200–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25589192.