# Concordance in MRI and Pathology Diagnosis of Extranodal Tumour Deposits

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To prove the accuracy of MRI/CT diagnosis of tumour deposits and their adverse effect on prognosis.

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Malignant and unspecified neoplasms gastrointestinal NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON51107

**Source**
ToetsingOnline

**Brief title**
COMET

### Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

**Synonym**
Colorectal cancer

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** The Royal Marsden NHS Foundation Trust, Clinical Research & Development
**Source(s) of monetary or material Support:** Royal Marsden NHS Foundation Trust

## Intervention

**Keyword:** Colorectal cancer, CT, MRI, Pathology

## Outcome measures

### Primary outcome

The accuracy of diagnosing tumor deposits on MRI/CT by comparing radiologically found tumor deposits withreported tumor deposits and 'equivocal' nodules without evidence of lymph node architecture on pathology.

### Secondary outcome

1. The concordance between MRI/CT and pathology

2. The overall survival, disease free survival at 1, 3 and 5 years as well a time to recurrence. This will be reported in four groups of patients: TD+/LN+, TD+/LN-, TD-/LN+, TD-/LN-, and it will be done seperately for both MRI/CT and pathology diagnosis.

3. The prevalence of EMVI and its association with TD, LN status, LN yield, T stage, CRM status

4. The 'L' and 'E' scores for the nodules indicated on MRI/CT

5. The interobserver agreement between local radiologist and central reviewing radiologist

6. The interobserver agreement in pathology reporting between the local pathologists and the central reviewing pathologist.

7. The presence of TD on the pre-treatment MRI for rectal cancer patients who underwent neoadjuvant therapy

8. The concordance in molecular pathology between primary tumour and TD, LNM, and distant metastases

9. The correlation between the finding of a nodular invasive border on MRI/CT

and pathology findings of tumour budding

# Study description

**Background summary**

Predicting prognosis in colorectal cancer (CRC) and determining indications for neoadjuvant treatment is an ongoing challenge for CRC multidisciplinary teams. Staging is almost universally based on the TNM system which is mainly focused on lymph node status and is still flawed in its ability to stratify patients and predict prognosis.(1-3) Therefore, determining which patients will benefit most from neoadjuvant and adjuvant therapy is still controversial. Recent evidence challenges the focus on lymph node metastases (LNM) as the gateway to distant metastatic disease by showing that 65% of distant metastases were not seeded by LNM.(4) Furthermore, other types of locoregional spread have been proven to influence patient outcome, with extranodal tumour deposits (TD) having the most prognostic impact.(5)

TD are aggregates of tumour cells in the fat surrounding the bowel (figure 1). Although they were first described in 1935(6), there is still ongoing controversy about their prevalence, nature, effect on prognosis and how they should be differentiated from LNM. The definition of TD within the TNM system is one of the major changes to have taken place over the years; They were considered lymph nodes (or not) and stratified according to size, contour or presence of other histological structures.(7-10) Currently, TD have to be classified within the subcategory *N1c*. However, experts have argued that there is not sufficient evidence to include TD as part of the N stage. A recent meta-analysis found a strong link between TD and extramural venous invasion (EMVI).(11) Therefore, it is possible that TD and EMVI are a continuation of the same process where TD represent a more advanced form of EMVI with nodules closely related to vessels but not in continuity with the tumour itself. These nodules could be seen as metastases in transit which would make their association with poorer survival and higher rates of recurrence not surprising.

Radiological diagnosis of tumour deposits
Given the prognostic importance of TD, it is imperative that these lesions are accurately reported on pathology so that their presence can be taken into account when making treatment decisions. Next to this, accurate diagnosis or TD by radiological modalities is also important. Identifying adverse prognostic features before surgery via imaging rather than on pathology has distinct advantages in that it contributes to planning of surgery and can guide decisions regarding neo-adjuvant therapy. MRI can accurately identify

pathological markers of poor prognosis pre-operatively to allow risk stratification and aid decision-making. The group of Prof. Gina Brown at the Royal Marsden Hospital (RMH) is able to accurately diagnose EMVI on MRI.(12-14) Also TD can be diagnosed on MRI as well as on CT when they are defined as nodules arising within venous channels, identified as signal void vessels, in continuity with major venous branches within the mesorectum and discontinuous with the main tumour.(15, 16) However, the diagnosis of TD has not been prospectively validated against that of pathology, which is the gold standard.

Preliminary work within the South West London Cancer Network has shown that MRI can detect TD in up to 51% of the rectal cancer cases, and CT can detect TD in up to 20% of the colon cancer cases. This is higher than the average of 13% of patients that are found to have TD on both pathology and CT/MRI. The ability to visualize the entire mesocolon and -rectum in three dimensions is a great advantage of imaging modalities which leads us to believe that TD can be more easily identified on CT or MRI than on pathology. Therefore, we want to use mapping of the resection specimen based on CT/MRI to accurately correlate radiological findings with pathology. Ultimately, this will provide information regarding the accuracy of radiological diagnosis of TD.

Biological characterization of tumour deposits
Molecular pathology techniques are widely utilised in current practice and can give further information about tumour behaviour (e.g. KRAS testing to determine likely response to certain chemotherapy agents). Knijn et al. have shown very low discordance in KRAS mutation between the primary tumour and distant disease (<5% for liver metastases, 7% for lung metastases) but high discordance between lymph nodes and the primary tumour of 20-40%.(17) The concordance of KRAS mutations and other markers such as EMVI and TD has never been reported. We hypothesize that the profile of EMVI and TD will have a higher concordance with the primary tumour and any metastases that develop than that of lymph nodes because this is the primary route of metastasis. Furthermore, it is likely that the concordance between EMVI and TD will be high. If this hypothesis is correct, it would allow a better understanding of the metastatic process and allow better prediction of those likely to suffer local and distant failure. This would in turn take us a step closer to cancer treatment that can be personalised to each patient taking multiple factors into consideration to determine individual risk.

In this study, we want to prove the accuracy of detection of TD on MRI/CT by correlating these findings with histopathology. Furthermore, this prospective setting enables us to analyse the prognostic value of TD in CRC. This could alter the way we stage patients currently. If we can prove the prognostic importance of this CT/MRI findings, the TNM system will most likely need to be modified in such a way that TD will play a larger role in guiding decisions regarding the use of neoadjuvant therapy.

## Study objective

To prove the accuracy of MRI/CT diagnosis of tumour deposits and their adverse effect on prognosis.

## Study design

This will be a prospective interventional, multi-centre study. Patients will be identified from multidisciplinary team meetings. All patients presenting with primary adenocarcinoma of the colon or rectum and undergoing surgical resection (with or without prior neo-adjuvant treatment) will be eligible for inclusion in the study. Patients will be approached following the MDT at their pre-op clinic and asked to participate in the trial. If they agree, they will be asked to sign a consent form.

1. Radiology:
Local Radiologists will be asked to complete a study imaging CRF for the baseline MRI or CT scan, and post-preoperative treatment MRI scan, if applicable. This CRF will include standard staging information and, additionally, information on the presence of Tumour Deposits (mrTD/ctTD). Prior to surgery, imaging CRFs and pre-operative MRI/CT scans will be sent to the Royal Marsden so that the COMET Chief Investigator (or one of her Radiology Registrars) can create an array of images and complete a central review CRF from the pre-op MRI/CT scan. Each mrTD/ctTD will be labelled (e.g E1, E2, E3). These images will be sent to the site study pathologist prior to histopathology processing of the specimen.

2. Histopathology:
As well as following standard local pathological procedures, sections that are thought to be lymph node metastases or TD will be photographed on a numbered grid and clearly labelled. The pathologist will assess the specimen and report whether TD are present using a proforma. A photograph of the tissue slices on a numbered grid will be sent into the Trial Office and used for mapping purposes. All tissue (including slides, blocks and cassettes) can be sent to the Royal Marsden COMET trial team to allow for further assessment with additional examination, staining and DNA extraction for genetic testing. The slides containing nodules will be scanned after which these images will be used for central review of the nodules. Due to the known problems with inter-observer variability in distinguishing TD from LNM, the Study Pathologist at the Royal Marsden as well as another Pathologist at Radboudumc in the Netherlands will identify whether any features of a lymph node are present for each nodule examined as well as recording the presence of vascular and neural invasion. Features which would be specific to the lesion being a LNM will be given an *L* score and those which suggest a lesion of non-lymphatic origin will be given an *E* score.
After analysis, all tissue samples will be returned to local hospitals and kept

in the long term storage facility, for use in future research. All movement of tissue samples between centres will be logged on a secure database at the Royal Marsden Hospital so an accurate account of where the samples are is available throughout the course of the study.

3. General follow-up:
Patients will undergo standard clinical follow up for a minimum of 5 years from the date of surgery. Clinic visits, imaging, blood tests and endoscopic follow-up will be carried out according to local protocols.

**Intervention**

Correlation of diagnostic tests: MRI/CT scans will be correlated with samples from the resection specimen that are photographed on a numbered grid.

**Study burden and risks**

The proposed intervention will be additional radiological and pathological assessment and the reporting of supplementary diagnostic information which would not otherwise have been available. Pathology is regarded as the gold standard and the information gathered from this modality will therefore not change. There will be extra information gathered during radiological diagnostics regarding TD, but this won't be taken into account when treatment decisions are made. Therefore, this study will ultimately not affect the treatment of patients participating in the study.

The tissue collected for diagnostics will follow an alternative processing route without any risk for the participant. The tissue will be available for diagnostics at all times. After diagnosis, the tissue will be made available for the COMET study.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

- Primary adenocarcinoma of the colon or rectum (proven by biopsy)
- Amenable to surgical resection.
- Disease spread assessed on CT and/or MRI
- Patients having primary surgery and those undergoing neoadjuvant treatment will be included.
- All must have had a baseline staging MRI/CT and those undergoing neoadjuvant therapy must also have had a post-treatment MRI.
- Patients aged 18 years and over

## Exclusion criteria

- Under the age of 18 years
- Unable to give informed consent.
- Recurrent tumours
- Synchronous tumours
- Unable to have an MRI/CT scan (e.g pacemaker, contrast allergy, severe claustrophobia)

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Diagnostic |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 25-02-2022 |
| Enrollment: | 100 |
| Type: | Actual |

# Ethics review

Approved WMO

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| Date: | 10-06-2021 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| ClinicalTrials.gov | NCT03303547 |

| Register | ID |
| --- | --- |
| CCMO | NL75352.091.20 |