# PET-CT and DWI-MRI in evaluating and predicting response to neoadjuvant chemoradiotherapy in esophageal cancer patients: PET/MRI-OES-1 study

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Malignant and unspecified neoplasms gastrointestinal NEC |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON41028

**Source**
ToetsingOnline

**Brief title**
PET-CT vs DWI-MRI and response in esophageal ca.

### Condition

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

**Synonym**
esophageal cancer response

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Groningen
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** DWI-MRI, esophagus, PET-CT, response

## Outcome measures

### Primary outcome

Primary endpoint:

Tumor response (complete or partial) during and after neo-adjuvant CRT.

Clinical response will be assessed by PET/CT (SUVmax) and by DWI-MRI (ADC; the stronger the diffusion, the greater the diffusion coefficient) either alone or in a combined approach (PET/MRI) when available. The assessed clinical response (cR) will be correlated to the pathologic response (pR) on the resected specimen according to a standard protocol.

The value of both imaging methods will be determined alone and combined to assess both early (around 2 weeks) and late responses (>= 2 weeks after the end of CRT) .

### Secondary outcome

Secondary endpoints:

Determining disease free survival (DFS) after different response type (clinical complete response =cCR or pathologic complete response = pCR) at T1 (early volumetric and functional response) and at T2 (post CRT=histological response /volumetric and functional) comparing pathologic status with blinded reading of PET/CT and DWI-MRI from two independent radiologists/nuclear medicine

physicians.

Assessment of no response or progression at T1 for a better selection of

patients to early definitive surgery. Moreover, at T1 cCR will be assessed and

at T2 cCR and pCR will be determined.

Determining the changes in radiotherapy target volume delineation by the

additional use of MRI.

# Study description

**Background summary**

PET-CT is currently used as standard method in both staging and determining of treatment response in esophageal cancer patients. For staging and determining response a standard PET-CT will be performed with additional endoscopic ultrasonography (EUS) of suspected nodes seen on PET-CT or during EUS. In 20-36% of the patients with esophageal cancer (EC) treated with neo-adjuvant chemoradiation (CRT), no residual tumor (ypT0N0) can be detected after curative intended surgery. On the other hand nearly 40% of the patients after CRT had locoregional failure in the CROSS trial and our study group found residual tumor in approximately 15% of the patients outside the radiation target volumes (CTV) after CRT.
Although, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT), in particular PET/CT, is able to distinct responders from non-responders, it still misses significant clinical evidence. Recently, whole-body diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) has shown a potential benefit, which might be enhance by combining both imaging methods. In assessing treatment outcome in cancer patients, FDG-PET and whole-body DWI-MRI should be regarded as complementary techniques, as they address complete different biophysical tissue properties (glucose metabolism vs. cellular density and vascularity of the tumor).
PET has limitations similar to CT in distinguishing tumor from inflammatory tissue. The value of adding DWI-MRI (Siemens Healthcare) is an increase in overall sensitivity up to 94% with fused image data sets of PET-CT with a rapid total acquisition time of around 30-40 min for PET/MRI depending on the area of interest. The potential benefit of using both PET/CT and DWI-MRI is a more precise anatomic and metabolic correlation with FDG-avid lesions and better assessment of post-treatment changes with reasonable accuracy, especially regarding nodal staging.
For both techniques it is claimed that they can play an important role in

selection of patients with clinical complete response (cCR) and indirectly with pathologic complete response (pCR) after CRT, and also in patients with no clinically effective response, early during CRT. However, the exact role and complementary effects of both techniques are still unknown.
For an appropriate judgment of nodal response to CRT, secure standard endoscopic ultrasonography (EUS) with fine needle aspiration (FNA) of suspected lesions seen on PET/CT or DWI/MRI or during EUS, will be performed at primary staging and after CRT.
DWI-MRI is based on movement (Brownian motion) of water molecules, which enables identification of tissue with high cellular density, such as in malignant tumors. The apparent diffusion coefficient (ADC), as a measure of water diffusion, is calculated by differences in the rate of changes in signal intensity at various b values. The degree of diffusion-weighting, the so-called b-value, adjusts the strength and duration of the diffusion gradients. The term "apparent" is used because the measured value does not only indicate diffusion, but also reflects capillary perfusion.
The b value parameter requires optimization based on body part, pathology, and radiologist preference. So, the ADC value is influenced by the b value. Perfusion, which is more present at a low b-value, has a larger effect on the ADC value than diffusion. If the b value is zero, there is no diffusion weighting and the images are similar to T2-weighted images. Conversely, if the b value is high, there is heavy diffusion-weighting. At a high b-value the ADC value mainly depends on diffusion, leading to a low ADC.
DWI-MRI can be effective in the pre-treatment prediction of treatment outcome. Tumor hypoxia is known to mediate chemoradiation resistance, leading to selection of aggressive tumor cell clones with their capacity to evade tumor microenvironment by increasing the anaerobic glycolysis and angiogenesis. ADCs can be used to determine the likelihood of tumor response to treatment, in which a high ADC before treatment has shown to predict an unfavorable treatment response, probably because a high ADC reflects the presence of tumor necrosis and low oxygen tensions. On the other hand as ADC indirect measures tissue density, ADC values are low in viable tumor and increase with treatment-induced apoptosis and necrosis.
Tumors presenting with a lower ADC value on presentation generally respond better to treatment. A recent study has shown that an increased ADC in patients during and after CRT could be used to predict early pathological response i.e discrimination of *responders and non-responders* to CRT. So, a low ADC value is predictive of good treatment response, while increased ADC values post CRT suggest reduced cell burden. Response in ADC seems to be more sensitive than the change in tumor volume size.

## Study objective

1. The primary aim of the proposed research is to compare the value of current best available imaging method (PET-CT) with recently evolved functional imaging with DWI-MRI alone or in combination with PET/CT in determining response to neo-adjuvant chemo-radiotherapy (CRT) in potentially curable esophageal cancer

(EC) patients.
Therefore, we will quantified the baseline FDG uptake (max. standardized uptake value; SUVmax), by FDG-PET and SUV changes (*SUV) during and after treatment with CRT. As ADC is an indirect measure of tissue density, DWI-MRI may provide an early marker of response to CRT by detecting both changes in perfusion (anti-angiogenic effect) and changes in tissue diffusivity (necrosis).
We will determine whether DWI-MRI alone or combined with PET/CT performed at staging (pretreatment i.e < 6 weeks before start CRT), early during the course of CRT (i.e 2 weeks after CRT initiation) and late before surgery ( i.e <= 2 weeks before surgery ) can be used to predict early and late persistent/progressive disease or clinical complete response, respectively.

2. The secondary aim is to determine disease free survival (DFS) after different response types (complete or partial and no response) at T1 (early volumetric and functional response at 2 wks after start of CRT) and at T2 (post CRT=histological response / both volumetric and functional) comparing pathologic status with blinded reading from two independent radiologists/nuclear medicine, in order to select patients better for *definitive* surgery or wait and see policy with eventually *salvage* surgery (in case of residual or recurrent disease) in the near future. To answer this question we will need the information obtained by combined PET/CT and DWI-MRI, including clinical responses (complete = cCR and partial = cPR) at the different time periods (T1 and T2). Furthermore secure EUS of suspected lesions on both, PET and DWI or during EUS will be biopsied or punctured for cytological examination.
Moreover, by comparing PET-CT with DWI-MRI, alone or combined, in correlation with the pathological examination of the resected esophageal specimen, according to the RESPECT protocol, we will be able to evaluate the accuracy of the given radiotherapy by examination of the involved target volumes (Gross = GTV and clinical = CTV). Furthermore, incorporation of (DWI)-MRI into the radiotherapy target volume delineation process might improve the accuracy of the delineation. With this respect both imaging modalities will be performed in a radiotherapy treatment position.
We will also assess whether TPV=Total proliferative volume (TPV=SUV x TV) will be a reliable estimation of tumor volume based on the texture features (TF) estimation in TF index. By using texture features,, including repeating pattern of local variations in image intensity and the partition of images into regions of interest in classifying the regions. In this way we can achieve a spatial arrangement of colors and intensities in those images. This can be performed by using static and dynamic scans.

**Study design**

Prospective observational non-randomized single institution, comparison pilot study, that can divide in two main parts.
Part I: consists of a limited exploring study to determine and validate the most appropriate DWI-MRI b-value, both low (0- 100 sec/mm2) and high (800-1000

sec/mm2) in detecting optimal imaging of EC. The b-value identifies measurement's sensitivity to diffusion and determines the strength and duration of the diffusion gradients. This study will be performed in three to five patients.
Part II: In part two, after we have obtained the optimal b-values, we will use DWI-MRI to evaluate the additional effect on staging and response evaluation in 15 to 20 patients (pilot study). Furthermore, we will evaluated the effect of the additional use of DWI-MRI for target volume delineation and radiotherapy planning.
Depending on the results of this pilot study, the study will be continued (Part III) after determining a sample size analysis for the genuine study size (new application or amendment will be submitted at that time ). In this latest study we will determine the adequacy of PET-CT and DWI-MRI in assessing clinical tumor response to pathological response in order to select patients better in a group of early non-responders (early response evaluation; 2 weeks after start of CRT) and a group of clinical incomplete/partial (cPR) and complete responders (cCR) vs. pathological complete responders (pCR). In that way surgery can be planned better in estimating the correlation between DWI-MRI and pathologic outcome more accurately (monitoring tumor response). Moreover, we will evaluate whether DWI-MRI will be of additional clinical value in determining a more accurate radiation (Gross and Clinical) target volumes (GTV and CTV).

**Study burden and risks**

In this study DWI-MRI is added on top of routine work-up and treatment. Adverse events of MRI are not to be expected. Therefore the burden for the patient is an extra diagnostic procedure in a machine with a small bore, which may trigger feelings of claustrophobia.

Relevance
This study will provide insight into the value of response evaluation, both in early
(<= 2 weeks after the start) and late (<= 2 weeks after the end) of CRT. The study will give good insight into the usefulness of DWI/MRI combined with PET-CT as a tool in clinical practice in determining pCR. The responses on these imaging methods can be used as surrogates or translate to objective cCR with pCR and subsequently in selecting patients for an *early resection* or a *wait-see policy*
The additional information of DWI-MRI and PET-CT might also improve target volume delineation (GTV/CTV) and consequently the radiotherapy treatment planning and irradiation. Once the program has been developed, it would be introduced regionally (Managed Clinical Network; MCN esophagus) and nationwide (DUCA).

# 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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. Histologically proven esophageal cancer (SCC and AC).
2. Age 18 years or older.
3. Able to give written informed consent before registration.
4. T2-T4aN0M0 or T1-T4aN1-3M0 esophageal cancer.
5. Potentially curatively (R0) resectable tumor.
6. Tumor should have sufficient FDG-baseline uptake (in case routine baseline FDG-PET/CT shows insufficient uptake no additional MRI will be made).
7. Able to tolerate PET-CT and DWI-MRI as required by protocol.
8. Patients eligible for neo-adjuvant chemoradiotherapy (CRT), including a Karnofsky Performance Score (KPS) >= 70% / WHO>2, adequate renal, hepatic, hematological function.

9. No prior chemotherapy or mediastinal radiotherapy allowed.
10. Written informed consent.

### Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Non-resectable tumours
2. Proven distant metastases
3. Prior malignancy except in-situ cervical lesions and/or non-melanoma skin cancer in the past 5 years.
4. Poorly controlled diabetes
5. Medical comorbidity preventing from surgery/preop CRT
6. General contraindications to MRI:
- implanted pacemaker/serious claustrophobia
- aneurysmal clips/metal implants in field of view
6. Major obesity (BMI > 40)
7. Active esophagitis
8. Breast feeding/Pregnancy

## Study design

### Design

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| Study phase: | 2 |
| Study type: | Observational non invasive |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Diagnostic |

### Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 24-02-2015 |
| Enrollment: | 20 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 25-11-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 28-02-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

# 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 |
|---|---|
| CCMO | NL49621.042.14 |