Combination of chemotherapy and adaptive Mr-guidEd Radiotherapy to improve outcomes in patients with esophaGEal adenocarcinoma (MERGE): a phase 1 dose finding trial

Published: 20-01-2025
Last updated: 31-01-2025

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

Summary

ID

NL-OMON57251

Source
ToetsingOnline

Brief title
MERGE

Condition

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

Synonym
esophageal adenocarcinoma, Oesophagus cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: KWF subsidie

Intervention

Keyword: - Dosis escalation, - Esophageal adenocarcinoma, - Hypofractionated, - MR-guided radiotherapy

Outcome measures

Primary outcome

The primary endpoint is the incidence of a dose limiting toxicity (DLT). Early DLT is defined as radiation induced esophageal fistula/ perforation/ hemorrhage/ necrosis or tracheal, bronchial or bronchopleural fistula/tracheal or bronchopulmonary hemorrhage grade >= 3 or any non-hematological grade >= 4 toxicity, assessed clinically significant and related to the radiotherapy, according to Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0 occurring within 16 weeks after the start of radiotherapy and before surgery or postponing of surgery > 16 weeks after the end of radiotherapy due to any grade of treatment-related toxicity. Subacute DLT is defined as peri- and/or postoperative complications occurring within 30 days after surgery, defined as postoperative anastomotic leakage or pneumonitis >= 3b according to Clavien-Dindo.

Secondary outcome

Secondary endpoints are non-DLT toxicity, the technical feasibility of dose delivery, perioperative complications. and oncological outcomes including R0 resection rate, histopathological tumor response, local and regional recurrence

and death from any cause.

Study description

Background summary

Esophageal cancer (EC) is the seventh most frequently diagnosed cancer and the sixth leading cause of cancer-related death worldwide. As a result of the late onset of symptoms, most patients with EC present in an advanced stage with a corresponding poor prognosis. Poor disease outcome after surgery alone (5-yr overall survival between 25-40%) prompted many researchers to explore neoadjuvant chemoradiotherapy (nCRT) or neoadjuvant or perioperative chemotherapy (nCT/pCT) approaches.

In the Netherlands, neoadjuvant chemoradiation has become standard of care for esophageal cancer since publication of the CROSS trial showing a benefit of nCRT over surgery alone for both adenocarcinoma (AC) and squamous cell carcinoma (SCC) (van Hagen et al., 2012). However, the benefit of nCRT was less pronounced in AC, which was also reflected by pathologic complete response (pCR) rates: 23% in AC vs. 49% in SCC. Furthermore, SCC and AC differ in patterns of recurrence after nCRT or chemotherapy. AC is more likely to develop distant metastases while SCC has a predisposition for locoregional recurrences. This difference in response to nCRT and in recurrence pattern indicates that histology-tailored treatment strategies should be explored. In the modern multidisciplinary discussion on the optimal approach to locally advanced adenocarcinoma of the esophagus and junction, both a trimodiality approach or perioperative chemotherapy are acceptable and evidence based. Therefore both are viable options within current guidelines.

As mentioned above, patients with an AC of the esophagus are especially prone to develop distant recurrences. In addition, response to nCRT is only moderate in AC. Therefore, we hypothesize that the ideal neoadjuvant treatment should consist of adding MR-guided radiotherapy to standard pCT in order to achieve maximum systemic control and achieve maximum local control.

Study objective

The main objective of this study is to determine the maximum tolerated dose (MTD) of 5 fractions MRgRT for patients with AC following FLOT therapy. The secondary objectives are feasibility, non-dose limiting toxicity, oncological outcomes and to explore variables for early response evaluation.

Study design

6+3 dose-escalation design with 4 radiotherapy dose levels.

Intervention

5 sequential, homogenous fractions of 4-8 Gy within 2 weeks on the gross tumor volume (GTV) following preoperative FLOT (as part of standard perioperative chemotherapy) using MR-guided online adaptive radiotherapy on the MR-linac. Start in dose level 0, of 5 x 5Gy per patient, and if safe this is increased step-wise to a maximum dose level of 5 x 8Gy per patient.

Study burden and risks

The benefits for the patients may include higher probability of complete primary tumor and lymph node metastases response that initially lead to increased survival and could eventually result in organ-sparing treatment programs. Possible risks are mainly esophageal fistula/perforation and broncho-esophageal fistula or hemorrhage.

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

Patients with adenocarcinoma of the esophagus or gastroesophageal junction (Siewert I or II), potentially resectable tumor , eligible for perioperative FLOT chemotherapy, age >= 18 years, WHO performance status 0-2.

Exclusion criteria

Squamous cell carcinoma, non-resectable, inoperable or metastatic adenocarcinoma of the esophagus or gastroesophageal junction, prior radiotherapy to the mediastinum, pregnant or breastfeeding patients.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2025
Enrollment:	39
Type:	Anticipated

Ethics review

Approved WMO Date:	20-01-2025
Application type:	First submission
Review commission:	METC NedMec

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	NL87824.041.24