Observational cohort of patients treated with stereotactic radiotherapy for Oligo LYMPh nOde and other soft tissue metastasiS

Published: 06-03-2018
Last updated: 12-04-2024

Purpose of this studyThe main clinical challenge remains to identify patients who may benefit from aggressive local treatment (SBRT) of lymph nodesoft tissue oligometastases: for which patients can systemic treatment be postponed? Patients who are...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Observational non invasive

Summary

ID

NL-OMON48987

Source
ToetsingOnline

Brief title
OLYMPOS cohort

Condition

- Metastases

Synonym
metastases, soft tissue oligometastases

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W,KWF subsidie (grant 2015-0848)

Intervention

Keyword: Cohort, Oligometastasis, SBRT, Soft tissue

Outcome measures

Primary outcome

5.1.1 Main study parameters

Clinical study parameters that will be collected:

Baseline demographics

• Gender

• Date of birth

Oncological history

• Primary tumor

• Date of diagnosis primary tumor

• TNM-stage at date diagnosis primary tumor

• Previous oncological treatments

• Date of last oncological treatment

• Previous or current diagnosis of metastases other than lymph nodesoft tissue target metastases

• Date of diagnosis of metastases other than soft tissue target lymph node metastases

• Type of metastases other than soft tissue target lymph node metastases (bone,

liver, brain, lung, visceral)

• Previous or current treatment for metastases other than soft tissue target lymph node metastases

• Date of diagnosis first soft tissue target lymph node metastases

• Imaging modalities used for diagnosis soft tissue target lymph node metastases

• Location of all present soft tissue target lymph node metastases

• In case of prostate cancer: PSA values since diagnosis primary tumor

Symptoms at baseline

• Existence of symptoms from soft tissue target lymph node metastases

• Numeric Rating Score (NRS) pain score

• Karnofsky performance status

Treatment data

• Starting date of radiotherapy treatment

• Dose, fractions and technique of radiotherapy treatment, type of radiotherapy treatment facility, type of online position verification imaging, treatment margins used, re-irradiation*

5.1.2 Main study endpoints

Clinical registration of toxicity:

For all participants in the study, toxicity will be registered by the treating radiation oncologist according to Common Terminology Criteria for Adverse Events (CTCAE version 4).

Registration in the electronic patient medical file (Hix) will be done at 1 and

4 weeks and 3 months after treatment.

The following side effects will be scored, depending on nodal location:

For pelvic soft tissue targetslymph nodes:

• Fatigue

• Fractures

• Lymphedema

• Neuralgia

• Pain

• Paresthesia

• Diarrhea

• Gastrointestinal fistula

• Hematuria

• Lower gastrointestinal hemorrhage

• Small intestinal stenosis

• Urinary tract obstruction

For abdominal soft tissue targetslymph nodes:

• Fatigue

• Lymphedema

• Neuralgia

• Pain

• Anorexia

• Diarrhea

• Nausea

• Small intestinal stenosis

• Upper gastrointestinal hemorrhage

• Vomiting

• Gastrointestinal fistula

For thoracic soft tissue targetslymph nodes:

• Fatigue

• Lymphedema

• Pain

• Anorexia

• Bronchopulmonary hemorrhage

• Cough

• Dysphagia

• Dyspnea

• Nausea

• Pneumonitis

• Upper gastrointestinal hemorrhage

• Vomiting

• Esophageal fistula

For head and neck soft tissue targetslymph nodes:

• Fatigue

• Neuralgia

• Pain

• Paresthesia

• Aspiration

• Cough

• Dysphagia

• Hoarseness

• Laryngeal edema

• Laryngeal mucositis

• Pharyngeal hemorrhage

Survival, time until progression and time until start of systemic treatment

Survival of participating patients will be recorded using the Municipal Personal Records Database (in Dutch: Gemeentelijke Basisadministratie, GBA), with access to these records from the UMC Utrecht hospital information system. Time until progression of disease, as well as time until start of systemic treatment will be investigated by periodically requesting follow up data from the treating physician who referred the patient to the Radiotherapy Department, until 5 years after radiotherapy.

Quality of life (patient reported outcomes)

Patients will be asked to fill in quality of life questionnaires before the

start of treatment, and after 1 and 4 weeks, 3 and 6 months after radiotherapy, and then every 6 months until 5 years after radiotherapy or until a next oncological treatment other than radiotherapy is initiated.

Patients will be invited to fill in three different quality of life questionnaires, see section 5.2.3:

• General quality of life questionnaire (F1. EORTC_C30_Dutch_version3), which encompasses amongst others pain, diarrhea, general functioning

• General quality of life questionnaire (F1. EQ5D_Dutch), for assessing cost effectiveness of interventions

• Specific questionnaire for fatigue (F1. Fatigue_MVI_Dutch)

Secondary outcome

Not applicable

Study description

Background summary

Population: patients with lymph node, adrenal, liver, muscle and other soft tissue oligometastases
With technological improvements in the fields of radiology and nuclear medicine, metastases can be diagnosed in an earlier stage [1]. The improved diagnostic tools have boosted interest in the oligometastatic paradigm: the existence of a clinical state between localized and wide-spread metastatic disease [2-4]. When patients are diagnosed with (very) limited metastatic disease, it remains unknown what is the most appropriate therapy for these patients. The current trend is to treat patients with oligometastases locally whenever possible, aiming for local control and for postponement of the start of potentially toxic systemic therapy, such as chemotherapy or androgen deprivation therapy (ADT). By postponing systemic therapies, local treatment may help maintain optimal quality of life [5]. Without treatment, soft tissue metastases will continue to grow and can eventually cause complaints such as pain, lymph edema, dyspnea, hoarseness, plexopathy, ureter obstruction and biliary obstruction [6-9].

Local treatment of soft tissue oligometastases
Surgery has long been the treatment modality of first choice for local treatment of oligometastases in liver, lung and adrenal gland [10-15]. New, minimally invasive therapies such as stereotactic body radiotherapy (SBRT) [16] now provide established alternative treatment options for patients with liver and lung oligometastases, mainly used for inoperable patients [17-20]. More recently, SBRT has also been introduced for patients with lymph node or adrenal oligometastases [21,22-24]. Especially for small target structures as lymph node oligometastases, the minimal invasive nature of SBRT is may be an important advantage, compared with surgical resection.

Previous research from literature
Most studies have investigated SBRT for lymph node oligometastases after treatment with curative intent for prostate cancer [2325-3133]. This is a patient population with the best diagnostic tools available for early diagnosis of oligometastases. With prostate specific antigen (PSA) as a sensitive biomarker for biochemical recurrence and with prostate specific membrane antigen positron emission tomography (PSMA-PET) imaging as very sensitive imaging modality [1], it is now possible to identify (very) small pathologic lymph nodes.

With local treatment of these lymph node oligometastases, the goal is to gain local control, defer ADT and thereby keep quality of life as good as possible [3234,3335]. It has been shown that SBRT for patients with prostate cancer lymph node oligometastases can achieve high rates of local control (ranging 84% - 100%) [2325,2527,2729,2931], with progression free survival rates at 24 months ranging 30% - 44% [2628,2729,2931]. Median time to ADT initiation was 17-24 months after SBRT [2426,2628,3133]. Furthermore, in the study of Bouman-Wammes time to castration resistance was found to be prolonged for patients treated with SBRT compared with a control group who were started on ADT after a median of 4 months (time to progression under ADT mean 66.6, 95% CI, 53.5 - 79.8, vs. 36.41, 95% CI, 26.0 - 46.8 months, $p = 0.020$).

SBRT for lymph node oligometastases from other primary tumors than prostate cancer has also been investigated [3436-4139]. The patient groups in these retrospective reports are very heterogeneous, but the potential of safely obtaining local control with SBRT has been established. For most of these patients, SBRT is a non-invasive alternative to surgery; again the aim is to postpone potentially toxic systemic treatments such as palliative chemotherapy [4042,4143].
Three randomized controlled trials investigating the benefit of SBRT for the treatment of oligometastases have been set up recently: the SABR-COMET, STOMP and ORIOLE trials [4244-4446]. All three trials include both lymph node and bone oligometastases; the STOMP and ORIOLE trials focus exclusively on patients with prostate cancer as primary tumor.

Literature regarding SBRT for liver metastases has been evolving for a longer

period of time, with 5 years of follow-up being completed for a phase II trial [47] and with systematic reviews and reviews on future indications being available [48,49]. Some studies on patient reported quality of life have been published [50,51].
Adrenal gland metastases SBRT has been described in several recent publications [52-57], including a report on video-assisted, respiration-gated, MR-guided SBRT with daily plan adaptation [57].

As described, research into SBRT for soft tissue oligometastases is mounting. However, almost all previously published studies suffer from small sample sizes, especially considering the heterogeneous patient population, and from heterogeneity in treatment strategies, such as SBRT fractionation schedules and administration of adjuvant systemic therapy after SBRT. Patient reported quality of life has only been described in a few studies to this date, mainly for liver metastases SBRT.

Study objective

Purpose of this study
The main clinical challenge remains to identify patients who may benefit from aggressive local treatment (SBRT) of lymph nodesoft tissue oligometastases: for which patients can systemic treatment be postponed? Patients who are diagnosed with additional metastases in <6 months after the radiotherapy treatment, could have been spared the radiotherapy treatment: achieving local control has little clinical relevance in the palliative setting that follows. Patients who experience complaints from lymph nodesoft tissue metastases, such as pain or neurological symptoms, may be treated with a true palliative intention with more appropriate radiotherapy treatment schedules.

By embracing the cohort multiple Randomized Clinical Trial (cmRCT) design [45,4658,59], we want to facilitate future intervention studies within the OLYMPOS cohort study. Such future intervention studies may shed light on other challenges in SBRT for lymph nodesoft tissue oligometastases. One of these lacunas is the optimal radiotherapy treatment schedule for SBRT. Currently, in our department we treat patients with lymph node oligometastases with 5 fractions of 7 gray (Gy), but various treatment schedules have been reported in literature [17,2325-3941]. The administration of radiation dose on the target volume is very precise in SBRT, but the dose received by surrounding healthy organs may show important variations between the different treatment sessions. Currently this limits us in choices regarding the radiotherapy treatment schedule; it has been advocated that a higher biological effective dose may be needed for achieving optimal long-term local control [17]. With better knowledge of the radiation dose that will be received by surrounding healthy organs, and improved sparing of these organs at risk (OAR), it may be possible to safely increase the radiation dose per fraction (dose escalation). Furthermore, it may be possible to decrease the number of treatment sessions (hypofractionation).

Investigating the potential for dose escalation and hypofractionation in nodal SBRT are goals for future studies that we want to facilitate in the OLYMPOS cohort. The cmRCT design provides an efficient way to study multiple different interventions (or treatment schedules) simultaneously.

2. OBJECTIVES

The prospective OLYMPOS cohort will serve the following purposes:

1. Providing detailed information about treatment response, toxicity, complications, postponement of systemic treatment, quality of life and survival.
2. Multi-trial facility for efficient (partly simultaneous) evaluation of innovative interventions according to the cohort multiple Randomized Controlled Trial (cmRCT) design.

Study design

3. STUDY DESIGN

The OLYMPOS cohort is a prospective study, which allows for systematic registration of clinical data of patients with lymph nodesoft tissue oligometastases. It allows for systematic registration of clinical data and will serve as a facility for efficient, systematic and simultaneous evaluation of new radiotherapy interventions. Patients will be followed prospectively and information on survival, quality of life (including fatigue), toxicity and postponement of systemic treatment in relation to radiotherapy treatment will be prospectively collected. By adopting the cmRCT design, we can efficiently facilitate multiple new intervention studies (Figure 1).

3.1 Inclusion
All patients who are referred to the UMC Utrecht Department of Radiotherapy for stereotactic radiotherapy of soft tissue oligometastases, such as lymph node, adrenal, liver or muscle metastases are eligible for participation in the prospective arm of the OLYMPOS cohort. Patients will be included preferably before the start of the treatment, but when patients are missed, inclusion can also take place during or after treatment. If patients are included during or after the treatment, this may influence the eligibility of a patient to be approached for or serve as control in intervention studies.

3.2 Informed consent
Patients can sign informed consent for four separate parts of the study:
1. Use of routinely collected clinical data for research purposes (including follow up data in other hospitals) and willing to participate in a short biannual questionnaire to adequately register (serious) adverse events ((S)AEs).
2. Prospective registration of patient reported outcome measures (QoL, fatigue).
3. Approval to be approached for participation in future (intervention) studies.
4. Approval to share data with industry

Only informed consent for the first study part (Use of routinely collected clinical data for research purposes and participation in short biannual SAE questionnaire) is mandatory for participation in the OLYMPOS cohort. Patients can only be approached for participation in or serve as control in future studies (study part 3) if they also gave informed consent for prospective registration of patient reported outcome measures (QoL and fatigue, study part 2).

If, after signing informed consent, the patient will not receive SBRT treatment (this equals a minimum radiation dose of 5 Gy per treatment session), the patient will only be able to continue with the first study part (Use of routinely collected clinical data for research purposes). These patients will not receive the biannual SAE questionnaire and will not be taken into account for prospective registration of patient reported outcome measures (QoL and fatigue, study part 2). Study part 3 is also not applicable for these patients.
By keeping these patients in the OLYMPOS cohort, we will be able to monitor why these patients did not receive SBRT treatment. With the lower radiation dose per treatment session, these patients are unsuitable for the SAE and patient reported outcome measures study analyses, as they focus solely on the prescribed treatment schedules with a minimum radiation dose of 5 Gy per treatment session.

Besides the OLYMPOS study parts, patients can also consent to participation in the MOMENTUM study.
Then they do not need to sign a separate informed consent form, they can be included based on the combined information letter.
They will only be able to participate in the MOMENTUM study if they will undergo treatment on the MR-linac, otherwise they will just continue participation in only OLYMPOS.

Study burden and risks

Risks and extent of burden associated with participation
Patients are not exposed to any intervention or alternative treatment as part of the OLYMPOS cohort study. Data will be captured/used that has been collected as part of standard clinical care, with the Quality of Life (QoL) questionnaires as additional information that will be collected especially for this study. No (additional) risks are known from participation in this cohort study. Any risks associated with future intervention studies within the OLYMPOS cohort study will be described separately in the application process for each specific (intervention) study.
The burden for patients will be the time it takes to fill in the QoL questionnaires, ~10 minutes at each time point and ~120 minutes in total. Questionnaire sending will be terminated when the patient will undergo a next oncological treatment, this limits the burden for patients.

Benefits and risks assessment, group relatedness

Patients will not experience direct benefit from participation in the OLYMPOS cohort. By participating, patients will contribute to the evidence on clinical and environmental factors associated with treatment outcome, QoL and survival. This will lead to better and a more personalized cancer care for future patients. Risks associated by participating in the OLYMPOS cohort study are negligible since it is observational.

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

- Is referred for, or will receive, stereotactic radiotherapy of a soft tissue metastasis with a localization other than brain or lung.
- Informed consent - at least - for use of routinely collected clinical data

for research purposes (including follow up data in other hospitals).

Exclusion criteria

• Age <18 years
• Mentally incompetent patients

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-07-2018
Enrollment:	700
Type:	Actual

Ethics review

Approved WMO Date:	06-03-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-09-2019

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-07-2020
Application type:	Amendment
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	NL62804.041.17