A Randomized Phase III Trial of Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of 4-10 Oligometastatic Tumors (SABR-COMET 10)

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To assess the impact of SABR, compared to standard of care treatment, on overall survival, oncologic outcomes, and quality of life in patients with a controlled primary tumor and 4-10 metastatic lesions.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON52850

Source
ToetsingOnline

Brief title
SABR-COMET 10

Condition

- Metastases

Synonym
metastases, oligometastases

Research involving
Human

Sponsors and support

Primary sponsor: London Health Sciences Center- Lawson Health Research Institute
Source(s) of monetary or material Support: persoonlijke gift aan hoofdonderzoeker dr Palma te Canada

Intervention

Keyword: oligometastases, radiotherapy, SABR, SBRT

Outcome measures

Primary outcome

Primary Endpoint

• Overall Survival

o Defined as time from randomization to death from any cause

Secondary outcome

Secondary endpoints:

• Progression-free survival

o Time from randomization to disease progression at any site or death

• Time to development of new metastatic lesions

• Quality of life

o Assessed with the Functional Assessment of Cancer Therapy: General (FACT-G)

and the EQ-5D-5L

• Toxicity

o Assessed by the National Cancer Institute Common Toxicity Criteria (NCI-CTC)

version 4 for each organ treated (e.g. liver, lung, bone)]

Translational endpoints (see section 12)

• Assessment of circulating tumor cells, cell-free DNA, and tumor DNA as

prognostic and predictive markers of survival, and for early detection of

progression

• Assessment of immunological predictors of response and long-term survival

Study description

Background summary

The oligometastatic state refers to a stage of disease where a cancer has spread beyond the site of the primary tumor, but is not yet widely metastatic.1 In patients with a limited oligometastatic burden, emerging evidence suggests that treatment of all sites of disease with ablative therapies (such as surgery or stereotactic radiation) can improve patient outcomes, including overall- and progression-free survival.

Historically, evidence to support the oligometastatic state has consisted of single-arm, non-randomized studies without controls. One classic study reported on over 5000 patients with lung metastases from a variety of primary tumors. In patients who achieved a complete resection of their lung metastases, 5-year overall survival (OS) was 36%, better than might be expected for a cohort of patients with metastatic disease.2 Similarly, after radiation, a recent pooled analysis of 361 patients with oligometastatic lesions treated with radiation demonstrated a 3-year OS of 56%.3

It has been suggested the long-term survivals achieved in patients with oligometastases after ablative therapies is merely due to the selection of very fit patients with slow growing tumors, since randomized evidence to support the oligometastatic paradigm has been lacking.4,5 However, at least four recent randomized phase II trials now provide some supporting evidence of an oligometastatic state.

1.1 Randomized Evidence Supporting the Oligometastatic State

Two of these four randomized trials were done in the setting of oligometastatic non-small cell lung cancer (NSCLC). In both, patients presented with a primary lung tumor and a limited number of metastatic lesions (1-3 in one trial, 1-5 in the other), and after initial systemic therapy, patients were randomly assigned to standard palliative treatments vs. consolidative ablative treatments to all sites of disease. Both trials were stopped early due to evidence of efficacy, with the ablative treatments achieving a ~3-fold improvement in progression-free survival (PFS).6,7 Based on these results, the phase III NRG LU-002 trial is assessing the impact of consolidative ablative therapies on

OS.

A third trial, EORTC 40004, examined the impact of an ablative therapy (radiofrequency ablation [RFA]) in patients with colorectal cancer metastatic to the liver. In this trial, patients with a controlled primary tumor and fewer than 10 hepatic metastases not amenable to resection, and with no extra-hepatic disease, were randomized to systemic therapy +/- RFA to all sites of disease.8 When initially reported,9 the trial showed no difference in OS between arms, but with long-term follow-up (median 9.7 years), a significant difference in OS emerged, with an 8-year OS of 36% in the RFA arm and only 9% in the systemic therapy arm.8

The fourth trial, Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Disease (SABR-COMET) enrolled 99 patients who had controlled primary solid tumors and up to 5 metastatic lesions. Patients were randomized in a 1:2 ratio between standard of care (SOC) palliative treatments (Arm 1) vs. SOC + SABR to all sites of disease (Arm 2). The primary endpoint was OS, and the trial employed a randomized phase II screening design, with an alpha of 0.20, in order to provide an initial comparison between arms. More than 90% of patients enrolled had 1-3 metastases. OS was 28 months in Arm 1 and 41 months in Arm 2 (p=0.09), meeting the primary endpoint of the trial. PFS was doubled: 6 months in Arm 1 and 12 months in Arm 2 (p=0.001). SABR was generally well tolerated, with a 29% rate of grade 2 or higher toxicity, although the rate of treatment-related grade 5 toxicity was 4.5%.

Despite this new evidence, many uncertainties remain regarding the oligometastatic state.

1.2 Defining the Oligometastatic State

A major unanswered clinical question is the precise definition of the oligometastatic state, namely, how many metastatic lesions are amenable to ablative therapies that may benefit the patient.

Many studies have defined *oligometastatic* as 1-3, or 1-5, metastatic lesions, although some have used broader definitions, including the EORTC 40004 trial described above that allowed up to 9. For example, one single-arm phase II trial in patients with NSCLC enrolled 24 patients with up to 6 active sites of extracranial disease, and treated patients with SABR to all active sites along with erlotinib. The treatment was well-tolerated, with only two grade 3 toxicities. Median OS was 20.4 months, and median PFS was 14.7 months. A second study included NSCLC patients with up to 8 lesions, as long as all could be treated within established dose constraints.10

In the setting of brain metastases, recent non-randomized evidence suggests that patients may benefit from stereotactic radiotherapy to 4-10 metastatic lesions. The prospective JLGK0901 trial treated 1194 patients who had 1-10

metastatic lesions, with a total cumulative volume of <=15 mL, and treated all with stereotactic radiosurgery. The study used a non-inferiority design with a primary endpoint was OS, comparing patients with 5-10 lesions vs. those with 2-4. Median OS in both groups was 10.8 months, meeting the primary endpoint of non-inferiority ($p<0.0001$). Treatment was well-tolerated, with only 9% of patients in either group experiencing adverse events of any grade. A separate retrospective study examined stereotactic radiation in patients with more than 10 brain metastases (where 64% had received prior brain radiotherapy), and concluded that it could be delivered safely, with no episodes of symptomatic necrosis and a 13% rate of radiographic necrosis.11

The toxicity of SABR may not depend on the overall number of lesions, but moreso the doses delivered to organs at risk. For serial organs, such as the spinal cord, bronchi, and great vessels, reduction of the maximum dose of radiation is expected to reduce the risk of toxicity. For parallel organs, such as the lung, liver and renal cortex, the risk of toxicity may be mitigated by ensuring that a critical volume of the organ is spared from substantial doses of radiation.12 The typical critical volume to be spared is about 1/3 of the volume of the organ. Therefore, this trial will employ dose constraints for serial structures that ensure minimization of high-dose volumes, constraints for parallel structures that ensure critical volume sparing, and constraints for dose spillage, to ensure that all SABR plans are highly conformal.

The application of ablative therapies for patients with 4-10 metastatic deposits appears promising, based on the encouraging results from randomized trials mostly enrolling patients with 1-3 lesions and the single-arm studies evaluating ablative therapies patients with a larger burden of disease. However, it is likely that as the number of metastases increases, the risk of further distant failure (i.e. development of additional metastases after SABR) will increase, and the risk of toxicity from SABR will likely increase. As a result, the use of SABR in such patients might be best in a scenario where the doses of SABR are lowered to reduce the risk of toxicity, pre-planning of SABR is required before enrollment, and SABR is given immediately prior to systemic therapy that will help to address the risk of occult micrometastases.

Study objective

To assess the impact of SABR, compared to standard of care treatment, on overall survival, oncologic outcomes, and quality of life in patients with a controlled primary tumor and 4-10 metastatic lesions.

Study design

This study is a phase III multicentre randomized trial. Patients will be randomized in a 1:2 ratio between current standard of care treatment (Arm 1) vs. standard of care treatment + SABR (Arm 2) to sites of known disease.

Patients will be stratified by two of the strongest prognostic factors, based on a large multi-institutional analysis3: histology (Group 1: prostate, breast, or renal; Group 2: all others), and type of pre-specified systemic therapy (Group 1: immunotherapy/targeted/hormones; Group 2: cytotoxic; Group 3: observation)

Intervention

Standard Arm (Arm 1)

Radiotherapy for patients in the standard arm should follow the principles of palliative radiotherapy as per the individual institution, with the goal of alleviating symptoms or preventing imminent complications. Recommended dose fractionations in this arm will include 8 Gy in 1 fractions, 20 Gy in 5 fractions, and 30 Gy in 10 fractions. Patients in this arm should not receive stereotactic doses or radiotherapy boosts, unless there is a clearly known clinical benefit (e.g. stereotactic radiation to a new brain metastases when all disease is controlled on systemic therapy).

Systemic therapy will be pre-specified based on the standard of care approach for that patient, and it may include systemic therapy (cytotoxic, targeted, hormonal, or immunotherapy) or observation. See section 6.3 for the timing of systemic therapy.

Experimental Arm (Arm 2)

Stereotactic radiation in Arm 2 will be delivered with three major guiding principles:

• Minimization of Toxicity: The SABR doses used herein are lower than those used for radical treatments, and normal tissue tolerance doses will never be exceeded. Concurrent chemotherapy or targeted therapy at the time of radiotherapy is not permitted

• Minimization of Treatment Time. To avoid delays in proceeding to systemic therapy, all SABR will be delivered over the course of two weeks.

• Pre-planning required before enrollment: To ensure safety, all patients require a pre-plan of their SABR treatments before enrollment. If a patient undergoes pre-planning but cannot be randomized due to failure to generate an acceptable plan, the centre will receive modest compensation to cover pre-planning costs. The baseline information of such patients will be captured (i.e. the Eligibility Checklist and Baseline Form), but they will not be followed for outcomes.

Study burden and risks

Quality Assurance (Arm 2)

In order to ensure patient safety and effective treatment delivery, a robust quality assurance protocol is incorporated. The following requirements must be completed for each patient:

• Prior to treatment, plans for each patient must be peer-reviewed, either by discussion at quality assurance (QA) rounds or by another individual radiation oncologist.

• All radiotherapy plans must meet target dose levels for organs at risk (Appendix 1). Prior to plan approval, the dose to each organ at risk must be verified by the physicist or treating physician.

• All dose delivery for intensity-modulated plans (including arc-based treatments) will be confirmed before treatment by physics staff.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Age 18 or older
• Willing to provide informed consent
• Karnofsky performance score >60
• Life expectancy >6 months
• Histologically confirmed malignancy with metastatic disease detected on imaging. Biopsy of metastasis is preferred, but not required.
• Restaging within 12 weeks prior to randomization:

o Brain: CT or MRI for tumor sites with propensity for brain metastasis. All patients with brain metastases (at enrollment or previously treated) require an MRI.

o Body: 18-FDG PET/CT imaging is recommended, except for tumors where FDG uptake is not expected (e.g. prostate, renal cell carcinoma). PSMA-PET or choline-PET is recommended for prostate cancer. In situations where a PET scan is unavailable, or for tumors that do not take up radiotracer, CT neck/chest/abdomen/pelvis with bone scan required.

o Spine: MRI required for patients with vertebral or paraspinal metastases. The MRI needs to image the area being treated and one vertebrae above and below as a minimum, but does not need to be a whole spine MRI unless clinically indicated.
•
• Controlled primary tumor
o defined as: at least 3 months since original tumor treated definitively, with no progression at primary site
• Total number of metastases 4-10
• All sites of disease can be safely treated based on a pre-plan

Exclusion criteria

• Serious medical comorbidities precluding radiotherapy. These include interstitial lung disease in patients requiring thoracic radiation, Crohn*s disease in patients where the GI tract will receive radiotherapy, or ulcerative colitis where the bowel will receive radiotherapy and connective tissue disorders such as lupus or scleroderma.
• For patients with liver metastases, moderate/severe liver dysfunction (Child Pugh B or C)
• Substantial overlap with a previously treated radiation volume. Prior

radiotherapy in general is allowed, as long as the composite plan meets dose constraints herein. For patients treated with radiation previously, biological effective dose calculations should be used to equate previous doses to the tolerance doses listed in Appendix 1. All such cases must be discussed with one of the study PIs.
• Malignant pleural effusion
• Inability to treat all sites of disease
• Any single metastasis >5 cm in size. Bone metastases larger than 5 cm may be included if, in the opinion of one of the study PIs, it can be treated safely.
• Any brain metastasis >3 cm in size or a total volume of brain metastases greater than 30 cc.
• Metastasis in the brainstem
• Clinical or radiologic evidence of spinal cord compression
• Dominant brain metastasis requiring surgical decompression
• Metastatic disease that invades any of the following: GI tract (including esophagus, stomach, small or large bowel), mesenteric lymph nodes, or skin
• Pregnant or lactating women

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-03-2023
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	15-04-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NCT03721341
CCMO	NL70693.029.19