National Institute for Health Research

University of York
Centre for Reviews and Dissemination

Systematic review

*Fields that have an **asterisk (*)** next to them means that they **must be answered. Word limits** are provided for each section. You will be unable to submit the form if the word limits are exceeded for any section. Registrant means the person filling out the form*.

This record cannot be edited because it has been marked as out of scope

1. * Review title.

Give the title of the review in English

Optimal radiation dose for thymic epithelial tumors treated with radiotherapy

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

26/03/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

30/07/2021

5. * Stage of review at time of this submission.

[2*changes]

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Stephanie Peeters

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Peeters

7. * Named contact email.

Give the electronic email address of the named contact.

stephanie.peeters@maastro.nl

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Maastro\Dr. Tanslaan 12\6229 ET Maastricht, The Netherlands

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+31615698511

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Maastro

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Stephanie Peeters. Maastro
Dr Antonio Angrisani. Vanvitelli University
Professor Dirk De Ruysscher. Maastro
Dr Ruud Houben. Maastro

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Dr Florit Marcuse. MUMC+
Dr Monique Hochstenbag. MUMC+
Jos G. Maessen. MUMC+

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

1)How do different radiation doses impact on overall survival of patients with Thymic neoplasms (Thymomas or Thymic carcinoma or TETs) undergoing radiation treatment with curative intent?2)How do different radiation doses impact the recurrences of patients with Thymic neoplasms (Thymomas or Thymic carcinoma or TETs) undergoing radiation treatment with curative intent?3)How do different radiation doses impact the toxicity of patients with Thymic neoplasms (Thymomas or Thymic carcinoma or TETs) undergoing radiation treatment with curative intent?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

A comprehensive search including the following databases: PubMed including MEDLINE (NML), Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov planned to be

performed on April 23rd, 2021. Subject Headings and search terms, adjusted according to the specific Database, are selected prior to performing the search. Search terms must include: 1) Population: patients affected by Thymoma, Thymic cancer, Thymic epithelial tumor, 2) Exposure/Intervention: Radiotherapy, Radiation treatment, proton therapy. The search terms inherent to the outcome(s) were voluntarily omitted in order to obtain a wider selection of studies. Search filters to restrict the search on publications: a)In English language only, b)Involving Humans, c)From 1990 to Apr 2021.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/241826_STRATEGY_20210506.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Thymic epithelial tumors (TETs) are rare thoracic tumors, often requiring a multimodal approach, (Surgery, radiotherapy, and less frequently chemotherapy).

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Patients with a diagnosis of primary TET, or with a diagnosis of recurrence of TET who underwent radiation therapy

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion of studies reporting information regarding:External Beam Radiotherapy with different techniques, dose fractionations, total dose delivered, with curative intent: Before surgery, after surgery, before chemotherapy, concurrent, after chemotherapy, or alone as a definitive treatment, with curative intent.Exclusion of studies reporting information regarding:Any other radiotherapy procedure is different from EBRT (e.g. Intraoperative radiotherapy (IORT), Brachytherapy).Palliative treatments.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Not applicable

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include - Observational studies (including cohort and case-control studies), nRCTs, RCTs- Only studies reporting information regarding RT modality, technique, total dose delivered, dose fractionation.

- Studies with a minimum sample size of 20 patients and a median follow-up time of at least 5 years;

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Studies from Healthcare institutions worldwide, mono- or multi-institutional studies, from public hospitals, private hospitals, of any level (e.g. University hospitals, peripheral medical centers).

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Primary Outcome: 5 years Overall Survival

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Hazard Ratio

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Secondary Outcomes: 10y OS, Recurrence Rate, Toxicity (Cardiac toxicity, lung toxicity)

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Odds Ratio, Hazard Ratio

[1 change]
26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

The selection of the studies will be performed by two reviewers independently.

In case of discrepancies, a third reviewer will be consulted and differences will be solved by consensus.

An Excel workbook will be used to record selected studies and reviewer decisions.

Data collection will include Author(s), Year of publication, type of study, sample size, patients characteristics,

intervention(s), and outcome(s) measured. Data extraction is directed at median survival time, survival probability at 5 and 10 years, recurrence probability, complication probability for different radiation-induced toxicities (such as cardiac and pulmonary toxicity). Two reviewers will independently extract the data. In case of discrepancies, a third person will be consulted and differences will be solved by consensus. Only data that is reported in the publication will be recorded, no additional efforts will be undertaken to collect missing data. Data will be entered in an Excel workbook for each endpoint separately.

[17. *Risk of bias (quality) assessment.] [17. *changed]

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The risk of bias will be assessed using the Revised Cochrane risk of bias tool (for RCTs) or the NOS Newcastle- Ottawa Scale (for Observational studies). This will be performed by two reviewers independently. In case of discrepancies, a third reviewer will be consulted and differences will be solved by consensus. The number of stars will be calculated per each observational study. Studies will be divided into two groups based on the number of stars (according to a median split). Results of the review will first be presented for all studies, after which discrepancies between the top and bottom quality studies will be discussed.
The STROBE (strengthening the reporting of observational studies in epidemiology) checklist will be used to assess the report quality of the selected studies in the case at least one of the reviewers find unclear statements in the reviewing process.

[18. *Strategy for data synthesis.] [18. *changed]

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Data will be synthesized per outcome by reporting the range of the results for the included studies. This includes median survival time or survival probability at a fixed time-point, response probability, complication probability for different toxicities separately. Ratings of study quality will be reported as well, and separate results will be displayed for studies of different quality. Results are presented in text and table formats. No meta-analysis is planned. Heterogeneity among studies will be discussed but not calculated. A Nine Item checklist (SWiM) will be adopted to properly report the analysis of interventions without performing Meta-Analysis.

[19. *Analysis of subgroups or subsets.] [19. *changed]

State any planned investigation of ‘subgroups’. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

A separate investigation will be performed, when possible, in the following subsets of patients according to the Histology (Thymoma or Thymic cancer), completeness of the resection (R0, R1 or R²), the timing of the

radiation treatment: before, after, or alternatively to surgery.An important distinction will be kept, when applicable, between : - Patients with a diagnosis of primary TET- Patients with a diagnosis of TET recurrence

30. * Type and method of review. [no change]

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
Yes

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development

No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Netherlands

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Radiotherapy, TETs, Thymoma, Thymic cancer

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information. [1. Any ad]

Provide any other information relevant to the registration of this review.

This review is being undertaken to summarize the state of the art of current radiation treatment of Thymomas and Thymic cancer (TETs), particularly focused on the comparison between radiation doses delivered.Items #16, #26, #27 were adapted according to some preliminary comments.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.