





# BMJ Open Postneoadjuvant surveillance and surgery as needed compared with postneoadjuvant surgery on principle in multimodal treatment for oesophageal cancer: a scoping review protocol

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## ABSTRACT

**Introduction** In current medical practice of curative treatment for non-metastatic oesophageal cancer, surgery on principle is carried out by oesophagectomy after neoadjuvant treatment. However, oesophagectomy is often associated with postoperative morbidity and mortality. Taking into account that modern neoadjuvant therapy is effective and many of patients show no vital tumour cells in the operative specimens, we aim to perform a scoping review as part of the development phase for a prospectively planned multicentre randomised controlled trial investigating ‘surgery as needed vs surgery on principle in patients with postneoadjuvant complete response of oesophageal cancer’ (Prospective trial registration number DRKS00022801). This scoping approach will allow us to finally define and/or adapt the research question including the design and methodology of the randomised controlled trial taking into account the findings for example, research gaps and/or pitfalls in the currently available study pool addressing this or very similar questions.

**Methods and analysis** To identify relevant research, we will conduct searches in the electronic databases Medline, Web of Science Core Collection, Cochrane Library and Science Direct. We will also check references of relevant studies and perform a cited reference research (forward citation tracking). Titles and abstracts of the records identified by the searches will be screened and full texts of all potentially relevant articles will be obtained. We will consider randomised trials and non-randomised controlled studies. Data extraction tables will be set up, including study and patients’ characteristics, aim of study and reported outcomes. We will summarise the data using tables and figures (eg, bubble plots) to present the research landscape and to describe potential clusters and/or gaps to support the planning of a randomised trial in this patient population.

**Ethics and dissemination** Ethical approval is not required for this scoping review. Study findings will be shared by publication in a peer-reviewed journal and by presentation to key stakeholders on scientific meetings.

## INTRODUCTION

Neoadjuvant chemoradiation (nCRT) and neoadjuvant chemotherapy (nCTX)

## Strengths and limitations of this study

- The scoping review is part of the development phase for a prospectively planned multicentre randomised trial, addressing ‘Surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of oesophageal cancer’ (Prospective trial registration number DRKS00022801).
- The scoping review will allow us to finally define and/or adapt the research question, the design and methodology of the following randomised trial.
- The scoping review protocol is guided by validated methodological frameworks and the scoping review will be reported according to the preferred reporting items for systematic review and meta-analysis statement for scoping reviews, and therefore, will be conducted in line with ‘the state-of-the-art’ criteria.
- We will conduct comprehensive literature searches and map the current ongoing and published studies by extracting and cluster key data such as neoadjuvant treatment protocols, diagnostic methods of response evaluation and surveillance, and therapeutic outcomes.
- The final scoping review will be limited to English and German language studies.

improve patients’ survival in curative treatment of non-metastatic oesophageal cancer and have become the standard of care in Western Europe.<sup>1</sup> In these multimodal oncological protocols, curative surgery is carried out after neoadjuvant treatment by oesophagectomy. However, oesophagectomy implicates postoperative mortality rates between 6% and 11% and postoperative morbidity rates range from 60% to 80%.<sup>2–4</sup> In recent years, neoadjuvant therapy has become increasingly effective, with 16%–49% of patients showing no tumour cells in the operative specimens.<sup>5–7</sup> This high locoregional histopathological

complete response rate imposes a need to identify complete responder and avoid potentially unnecessary and harmful surgery in this population. Considering that neoadjuvant treatment without surgery is effective for a large proportion of patients, more individual/personalised treatment options based on surveillance and surgery only if needed are highly relevant for patients with non-metastatic oesophageal cancer.

## OBJECTIVES

We aim to perform a scoping review as part of the development phase for a prospectively planned multicentre randomised controlled trial, addressing ‘Surgery as needed vs surgery on principle in patients with post-neoadjuvant complete response of oesophageal cancer’ (Prospective registration identifier of the clinical trial will be DRKS00022801. Registration is currently in process and will be completed after we have incorporated the results of the scoping review). The scoping review will allow us to finally define and adapt the research question and methodology of the following randomised trial taking into account the findings (such as research gaps and/or methodological pitfalls) in the currently available pool of primary studies addressing this or very similar questions.

The objectives of the scoping review are as follows:

1. What specific neoadjuvant protocols of nCRT and nCTX have been studied for surveillance and surgery as needed?
2. In what populations or settings have these protocols been studied?
3. Which diagnostic methods have been used for post-neoadjuvant tumour staging and surveillance of tumour response?
4. Which outcomes have been addressed in the clinical studies on surveillance and surgery as needed in oesophageal cancer?
5. What results were observed with respect to survival rates?

## METHODS AND ANALYSIS

This protocol is written with reference to the preferred reporting items for systematic review and meta-analysis protocols statement<sup>8</sup> and ‘a priori’ defines the methodology on which the scoping review will be based on:

### Eligibility criteria

#### Participants/population

We will focus on studies including adults with non-metastatic oesophageal cancer (after receiving neoadjuvant treatment). Studies including patients with distant metastases of oesophageal cancer, presence of gastric cancer; and/or participants younger than 18 years of age will be excluded.

## Box 1 Outcome variables.

Outcomes (list will be completed depending on outcomes reported in the available study pool)

- ▶ Overall survival.
- ▶ Progression-free survival.
- ▶ Proportion of radical resection margin.
- ▶ Postoperative complications. (frequency and severity).
- ▶ Rate and timing of distant dissemination.
- ▶ Disease recurrence rate.

### Intervention and comparator treatment

We will consider surveillance after neoadjuvant therapy as eligible intervention. Surgery on principle after neoadjuvant therapy will be the comparator treatment.

### Context

We will consider all nCTX and nCRT interventions implemented and evaluated in the context of non-metastatic oesophageal cancer.

### Relevant outcomes

We will capture any outcomes reported in the eligible study pool. Highly important outcomes are displayed in [box 1](#). This table is non-exhaustive and will be completed depending on the outcomes reported in the identified study pool.

### Study types

Randomised controlled trials; non-randomised controlled studies (using strategies of non-random allocation for assigning interventions) and observational studies (with control group) will be eligible for the scoping review. We will not consider single arm studies. Due to a missing control group within this study design. The reason for this exclusion is that studies without a control group provide no reliable data to estimate comparative effectiveness and will, therefore, not be useful for the planned randomised trial. Furthermore, review articles, clinical guidelines and work that has not been peer-reviewed (eg, thesis, editorials, letters, comments) will be excluded.

We will not apply any exclusion criteria regarding study duration and/or the study setting.

### Information sources

The searches for this scoping review will be performed and conducted by following the recommendation of PRESS (Peer Review of Electronic Search Strategies)<sup>9</sup>; that is, a medical sciences librarian will develop the search strategies; in addition, search strategies will be validated by checking whether they identified studies already known. We will not use any date restrictions in the electronic searches. For each database, the date of the search, the search strategy and the number of search results will be documented.

Systematic searches for relevant published trials will be conducted in the following electronic data sources

**Table 1** Preliminary search strategy for Medline (Ovid).

#	Searches
1	((esophag* or oesophag*) adj5 (cancer* or neoplas* or carcino* or tumor* or tumour* or malign* or adenocarcin* or adeno-carcin*)).ti,ab,kf.
2	esophageal neoplasms/ or esophageal squamous cell carcinoma/
3	1 or 2
4	(chemoradi* or radiochemo* or chemo-radi* or radio-chemo* or chemotherap* or Radiation or radiotherap*).ti,ab,kf.
5	exp Chemoradiotherapy/ or (Chemotherapy, Adjuvant/ and Radiotherapy,Adjuvant/)
6	4 or 5
7	((watch* or see) adj3 wait*) or (active* adj3 surveil*) or ((selective* or needed or necessar* or unnecessar* or declin* or avoid* or on-demand) adj6 (resect* or surg* or esophagectom* or oesophagectom*)) or (chemoradiation alone or chemoradiation only or chemo-radiation alone or chemo-radiation only).ti,ab,kf.
8	Watchful Waiting/
9	7 or 8
10	(surg* or standard treatment or standard therapy or standard surgical resection or tri-modal* or trimodal* or esophagectom* or oesophagectom*).ti,ab,kf.
11	exp Esophagectomy/
12	10 or 11
13	3 and 6 and 9 and 12
14	exp animals/ not exp humans/
15	editorial/ or letter/ or Congress/
16	13 not 14
17	16 not 15
18	limit 17 to (english or german)
19	randomized controlled trial.pt.
20	controlled clinical trial.pt.
21	randomized.ab.
22	placebo.ab.
23	drug therapy.fs.
24	randomly.ab.
25	trial.ab.
26	groups.ab.
27	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	3 and 9 and 27
29	28 not 14
30	28 not 15
31	limit 30 to (english or german)
32	18 or 31

- ▶ Medline, Medline Daily Update, Medline In Process & Other Non-Indexed Citations, Medline Epub Ahead of Print (via Ovid) (a preliminary search strategy is displayed in [table 1](#)).
- ▶ Web of Science Core Collection: Science Citation Index-EXPANDED (SCI-EXPANDED) (via Clarivate Analytics).
- ▶ Cochrane Library (via Wiley).
- ▶ Science Direct (via Elsevier).

Searches for unpublished and ongoing studies will be performed in ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), WHO International Clinical Trials Registry Platform (<http://www.who.int/ictrp/search/en>) and the German study register ([www.drks.de](http://www.drks.de)).

We will use relevant studies and/or systematic reviews to search for additional references via the PubMed similar articles function ([https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/020\\_190.html](https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/020_190.html)), and forward citation tracking. Reference lists of relevant studies and systematic reviews will also be reviewed manually.

#### Identification of relevant Studies

Titles and abstracts of the records identified by the searches will be screened and full texts of all potentially relevant articles will be obtained. Full texts will be checked for eligibility, by two reviewers and reasons for exclusions will be documented (full-text screening). The

complete screening process will be conducted in Covidence (<https://www.covidence.org>).

### Extraction of study data/data items

The following study data will be extracted and relevant information tabulated and/or described descriptively:

- ▶ Study characteristics, that is, author, year of publication, study type (randomised trial, non-randomised study) and design (superiority, non-inferiority trial), study status (eg, planned, ongoing, completed, prematurely discontinued), start and end of study.
- ▶ Details regarding sample size calculation.
- ▶ Details on sample size (number of participants screened and randomised/finally included; reasons for screening failures and number and reasons for drop-offs and compliance).
- ▶ Aim of the study.
- ▶ Setting, that is, geographical and organisational setting.
- ▶ Characteristics and definition of participants (age, gender, tumour histology and tumour stage).
- ▶ Details on neoadjuvant therapy (drug names, dose).
- ▶ Details on the diagnostic methods used for post-neoadjuvant tumour staging and surveillance of tumour response.
- ▶ Definition of complete responders.
- ▶ Characteristics of intervention/surveillance group (definition of surveillance).
- ▶ Characteristics of comparator/surgery group (type of surgery and time between neoadjuvant therapy and surgery).
- ▶ Pathohistological complete response rate after neoadjuvant therapy (surgery group).
- ▶ On-demand surgery rate (surveillance group).
- ▶ All reported outcomes and their exact definitions, that is, how and when the outcome measures were assessed.
- ▶ Recruitment and follow-up time (planned and actual time).

Data from each included study will be extracted by one reviewer and checked by a second. Disagreements will be resolved through discussion until consensus will be reached.

### Risk of bias

Risk of bias assessment is not part of a scoping review and will not be assessed accordingly.<sup>10 11</sup>

The methodology of the scoping review may be adapted minimally during the review process itself in terms of eligibility criteria, data extraction and outcome variables.<sup>12 13</sup>

### Data analyses/summary

We will summarise the collected study data using tables and figures (eg, bubble plots) to present the research landscape and to describe potential clusters and/or gaps to support the planning of the proposed randomised trial in this patient population.

### Perspective/discussion

Currently in Western Europe the majority of patients with non-metastatic resectable oesophageal cancer are treated with nCTX or nCRT plus consecutive surgery. Despite postneoadjuvant pathological complete response rates between 16% and 49%, surgery is carried out in all patients and independent of the results of postneoadjuvant response evaluation.<sup>5–7</sup> The ‘Nationale Dekade gegen Krebs’ programme of the German national government (<https://www.dekade-gegen-krebs.de/de/praxisveraendernde-studien-fuer-eine-bessere-patientenversorgung-2018.html>) is supporting a multicentre randomised trial (which will be conducted by our study group) challenging this ‘sometimes potentially harmful’ algorithm by comparing postneoadjuvant surgery on principle versus surveillance (with surgery only if needed in the event of a persisting or recurring local tumour). Using a randomised study design, we aim to optimise therapeutic outcomes by personalisation of the therapeutic sequence. According to the current evidence and also supported by our clinical experience, it is likely that a subgroup of pathological complete responders (with consecutive omission of potentially harmful surgery) will be identified.<sup>14</sup> A survival disadvantage of delayed surgery in case of local tumour relapse is likely to be excluded in a protocol of close surveillance in complete responder.<sup>15</sup>

Although the scoping review may not provide effect estimates including an evaluation of the certainty of evidence, it will be of great value to crystallise research questions, and the extent of available evidence by highlighting areas where evidence is lacking. The scoping review will support us to map the existing primary research for potential duplications. Furthermore, it will provide an overview of the (1) characteristics and definitions of patient populations (included in available studies) and settings, (2) details on the interventions (including type of neoadjuvant therapy, time between neoadjuvant therapy and surgery, definition of surveillance), (3) details on the diagnostic methods used for postneoadjuvant tumour staging, (4) definition of complete responders, (5) outcome measures and (6) follow-up times. Hence the scoping process will allow us to systematically develop the concept of the randomised trial based on current knowledge (including pitfalls) in this newly emerging treatment area.

By searching the literature in different databases (ie, behind Medline) and also study registers (eg, ClinicalTrials.gov), all relevant completed but also ongoing studies comparing surveillance with surgery on demand in esophageal cancer will be identified. Finally the results of the scoping review will reveal (1) whether the diagnostic methods used and the definition for complete responders were appropriate and homogeneous, (2) whether the included sample sizes were sufficient to draw conclusions on benefits and harms, (3) what interventions were considered (eg, nCRT and/or chemotherapeutic protocols), (4) what outcomes of interest were covered, (5) whether follow-up times were sufficient and (6) whether clinical results across studies are

homogeneous. We believe that the planned randomised trial will benefit from this state-of-the art research approach, and therefore, will provide patients, clinicians and other stakeholders with high evidence considering various patient-relevant outcomes when comparing these two treatment approaches.

Furthermore, parallel to the scoping review patient's values and perspectives towards choice of treatment will be analysed (DRKS00022050) prior to the start of the randomised trial and patient oriented information material for the trial will be developed and provided.

Overall, the final goal will be the development and verification of a protocol to identify patients with pathological complete response (based on reliable diagnostic methods and definitions for complete responders) who would not need to undergo high-risk surgery in the increasing subgroup of postneoadjuvant complete responders. This treatment procedure is expected to reduce morbidity and mortality rates, and increase quality of life. Regarding the socioeconomic impact, omission of oesophagectomy reduces treatment duration, complication rates and time of hospital stay. This results in reduced treatment costs and a faster return to normal life for this patient population.

## ETHICS AND DISSEMINATION

Formal ethical approval is not required, as primary patient data will not be collected in this scoping review. We plan to publish the full scoping review in a peer-reviewed journal and to present the results at national and international scientific conferences.

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**Contributors** All authors of the manuscript meet the ICMJE criteria for authorship: ChS, BN and JM designed the scoping review protocol. ChS and BN designed the preliminary search strategy. JeH and JuH contributed as experts for surgical and multimodal treatment of oesophageal cancer and provided scientific knowledge. ChS and JH wrote the scoping review protocol. JuH and CS are guarantors of the manuscript.

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