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Post-neoadjuvant surveillance and surgery as needed compared with post-neoadjuvant surgery on principle in multimodal treatment for esophageal cancer: a scoping review protocol

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ABSTRACT

Introduction

In current medical practice of curative treatment for non-metastatic esophageal cancer, surgery on principle is carried out by esophagectomy after neoadjuvant treatment. However, esophagectomy is often associated with postoperative morbidity and mortality. Taking into account that modern neoadjuvant therapy is effective and many of patients show no vital tumor cells in the operative specimens, wwe aim to perform a scoping review as part of the development phase for a prospectively planned multicenter randomised controlled trial investigating “surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of esophageal cancer”. 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 e.g., 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 include 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 (e.g. bubble plots) to present the research landscape and to describe potential clusters and/or gaps to support the planned 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.

Strengths and limitations of this study

- The scoping review as part of the development phase for a prospectively planned multicenter randomised controlled trial, addressing "*Surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of esophageal cancer*" (DRKS 00022801) and will allow to finally define and/or adapt the research question including the design and methodology of the randomised controlled trial.
- The scoping review is guided by validated methodological frameworks, has a peer-reviewed search strategy, and follows a systematic approach to data analysis
- A comprehensive systematic literature search addressing neoadjuvant protocols, diagnostic methods of response evaluation and surveillance, origin of analyzed cohorts and therapeutic outcome parameters will be performed.
- 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.
- The review will be limited to English and German language studies only.

INTRODUCTION

Neoadjuvant chemoradiation (nCRT) and neoadjuvant chemotherapy (nCTX) improve patients' survival in curative treatment of non-metastatic esophageal cancer and have become the standard of care in Western Europe [1]. In these multimodal oncologic protocols curative surgery is carried out after neoadjuvant treatment by esophagectomy. However, esophagectomy implicates postoperative mortality rates of 6 to 11% and postoperative morbidity rates range between 60 and 80 % [2, 3, 4]. In recent years, neoadjuvant therapy has become increasingly effective, with 16 to 49% of patients showing no tumor cells in the operative specimens [5, 6, 7]. This high locoregional histopathological complete response rate imposes a need to identify complete responder and avoid potentially unnecessary and harmful surgery in this group of patients. Considering that neoadjuvant treatment without surgery is effective for a large proportion of patients, more individual/personalized treatment options based on surveillance and surgery only if needed are highly relevant for patients with non-metastatic esophageal cancer.

OBJECTIVES

We aim to perform a scoping review as part of the development phase for a prospectively planned multicenter randomised controlled trial, addressing "*Surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of esophageal cancer*" (registration identifier of the clinical trial: DRKS 00022801). The scoping review 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 such as, research gaps and/or pitfalls in the currently available study pool addressing this or very similar questions.

The scoping review will address the following questions:

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 tumor staging and surveillance of tumor response?
4. Which outcomes have been addressed in the published studies on surveillance and surgery as needed in esophageal cancer?

METHODS and ANALYSIS

This protocol is written with reference to the preferred reporting items for systematic review and meta-analysis protocols statement [8] 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 esophageal cancer (after receiving neoadjuvant treatment). Studies including patients with distant metastases of esophageal cancer, presence of gastric cancer; and/or participants younger than 18 years of age will be excluded.

Intervention

This review will consider surveillance after neoadjuvant therapy as eligible intervention.

Comparator

Surgery on principle after neoadjuvant therapy will be the comparator treatment.

Context

We will consider all neoadjuvant chemotherapeutic and neoadjuvant chemoradiotherapeutic interventions implemented and evaluated in the context of non-metastatic esophageal cancer.

Relevant Outcomes

We will capture any outcomes reported in the eligible study pool. Outcomes of importance are displayed in Table 1. This table is non-exhaustive and will be completed depending on the outcomes reported in the identified studies.

Table 1. Outcome variables.

Outcomes (this list will be completed in dependence of the findings in the current 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.

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 case reports, case series, review articles, clinical guidelines and work that has not been peer-reviewed (e.g., thesis, editorials, letters, comments).

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) [9]; i.e., 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:

- 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 2);
- 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), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/search/en) and the German study register (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), and forward citation tracking. Reference lists of relevant studies and systematic reviews will also be reviewed manually.

Table 2. 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

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:

- Study characteristics, i.e., author, year of publication, study type and study design (superiority, non-inferiority, randomization), study status (e.g. planned, ongoing, regularly completed, prematurely discontinued), start and

end of study, sample size (number of participants screened and randomized including reasons for screening failures), methods used to plan sample size;

- Aim of the study;
- Setting, i.e., geographical and organizational setting;
- Characteristics of participants (e.g., age, gender, tumor histology and tumor stage);
- Details on the diagnostic methods that have been used for post-neoadjuvant tumor staging and surveillance of tumor response;
- Details on neoadjuvant therapy including drug names and radiation;
- Characteristics of intervention; i.e., definition of surveillance;
- Characteristics of comparator(s), e.g., type of surgery;
- Reported outcomes and their exact definitions, i.e. how and when the outcome measures were assessed;
- Recruitment and follow-up time (planned and actual time);
- Number of patients screened

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 [10, 11].

The methodology may be adapted minimally during the review process itself in terms of eligibility criteria, study characteristics and outcome variables [12, 13].

Patient and public involvement

Patients or public will not be involved.

Perspective / Discussion

Currently in Western Europe the majority of patients with non-metastatic resectable esophageal cancer are treated with nCTX or nCRT plus consecutive surgery. Despite of post-neoadjuvant pathological complete response rates between 16 - 49% surgery

is carried out on principle in all patients and independent of the results of post-neoadjuvant response evaluation [5, 6, 7]. Within the “Nationale Dekade gegen Krebs” program of the german national government (https://www.dekade-gegen-krebs.de/de/praxisveraendernde-studien-fuer-eine-bessere-patientenversorgung-2018.html) a proposed multicenter randomised trial will challenge this algorithm, by comparing post-neoadjuvant surgery on principle versus surveillance (with surgery only if needed in the event of a persisting or recurring local tumor). The randomised trial aims to optimize therapeutic outcomes by personalization of the therapeutic sequence for complete and non-complete responders. According to the known evidence, a reliable clinical identification of a quantitative relevant subgroup of pathological complete responder with consecutive omission of potentially harmful surgery appears most likely. On the other side a survival disadvantage of delayed surgery in case of local tumor relapse appears unlikely in a protocol of close surveillance of clinical complete response. To support the clinical trial, the preceding scoping review will systematically identify and explore published, unpublished and ongoing clinical studies and study protocols comparing surveillance with surgery as needed versus surgery on principle in patients after neoadjuvant treatment for esophaegeal cancer before conducting the randomised controlled trial. It will allow us to finally define and/or adapt the research question including the methodology of the randomised controlled trial taking into account the findings e.g., research gaps, safety issues and/or pitfalls in the currently available study pool addressing similar questions. The randomised trial will add specific high level evidence to answer the research question and will influence the medical practice. Parallel to the scoping review patient`s values and perspectives towards choice of treatment will be analyzed prior to the start of the randomised trial and patient oriented information material for the trial will be developed and provided. The final goal will be the development and verification of a protocol to identify patients with pathological complete response who would not need to undergo high-risk surgery in the growing group of post-neoadjuvant complete responders. This is expected to reduce morbidity and mortality rates, and increase the quality of life in this group of patients. Regarding the socioeconomic impact, omission of esophagectomy reduces length of therapy, complication rates and time of hospital stay resulting 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 scoping review in a peer-reviewed journal and to present the results at national and international scientific conferences.

Contributors

ChS, BN and JM designed the scoping review protocol.

ChS and BN designed the preliminary search strategy.

JH and JuH contributed as experts for surgical and multimodal treatment of esophageal cancer and provided scientific knowledge. ChS and JH wrote the scoping review protocol.

Funding

This work was supported by a research grant (grand number 01KD1908) “Nationale Dekade gegen Krebs” provided to JH by the federal ministry of education and research (BMBF).

Competing interests

None declared.

Patient and public involvement

For the current scoping review protocol patient involvement is not applicable. However, patients will be involved in the design, conduct, reporting, and dissemination of the proposed randomised controlled trial.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
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ABSTRACT

Introduction

In current medical practice of curative treatment for non-metastatic esophageal cancer, surgery on principle is carried out by esophagectomy after neoadjuvant treatment. However, esophagectomy is often associated with postoperative morbidity and mortality. Taking into account that modern neoadjuvant therapy is effective and many of patients show no vital tumor cells in the operative specimens, we aim to perform a scoping review as part of the development phase for a prospectively planned multicenter randomised controlled trial investigating “surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of esophageal cancer”. 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 e.g., 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 (e.g. 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.

Strengths and limitations of this study

- The scoping review is part of the development phase for a prospectively planned multicenter randomised trial, addressing "*Surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of esophageal cancer*" (DRKS 00022801) .
- 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.

INTRODUCTION

Neoadjuvant chemoradiation (nCRT) and neoadjuvant chemotherapy (nCTX) improve patients' survival in curative treatment of non-metastatic esophageal cancer and have become the standard of care in Western Europe [1]. In these multimodal oncologic protocols curative surgery is carried out after neoadjuvant treatment by esophagectomy. However, esophagectomy implicates postoperative mortality rates between 6 and 11% and postoperative morbidity rates range from 60 to 80 % [2-4]. In recent years, neoadjuvant therapy has become increasingly effective, with 16 to 49% of patients showing no tumor cells in the operative specimens [5-7]. 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/personalized treatment options based on surveillance and surgery only if needed are highly relevant for patients with non-metastatic esophageal cancer.

OBJECTIVES

We aim to perform a scoping review as part of the development phase for a prospectively planned multicenter randomised controlled trial, addressing "*Surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of esophageal cancer*" (Prospective registration identifier of the clinical trial will be DRKS 00022801. Registration is currently in process and will be completed after we have incoperated 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 tumor staging and surveillance of tumor response?
4. Which outcomes have been addressed in the clinical studies on surveillance and surgery as needed in esophageal cancer?

METHODS and ANALYSIS

This protocol is written with reference to the preferred reporting items for systematic review and meta-analysis protocols statement [8] 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 esophageal cancer (after receiving neoadjuvant treatment). Studies including patients with distant metastases of esophageal cancer, presence of gastric cancer; and/or participants younger than 18 years of age will be excluded.

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 neoadjuvant chemotherapeutic and neoadjuvant chemoradiotherapeutic interventions implemented and evaluated in the context of non-metastatic esophageal cancer.

Relevant Outcomes

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

Table 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.

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 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 (e.g., 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) [9]; i.e., 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:

- 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 2);
- 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), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/search/en) and the German study register (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), and forward citation tracking. Reference lists of relevant studies and systematic reviews will also be reviewed manually.

Table 2. 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

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:

- Study characteristics, i.e., author, year of publication, study type (randomised trial, non-randomised study) and design (superiority, non-inferiority trial), study status (e.g. planned, ongoing, completed, prematurely discontinued), start and end of study;
- Details regarding sample size calculation;
- Details on sample size (number of participants screened and randomized/finally included; reasons for screening failures and number and reasons for drop-offs and compliance);
- Aim of the study;
- Setting, i.e., geographical and organizational setting;
- Characteristics and definition of participants (age, gender, tumor histology and tumor stage);
- Details on neoadjuvant therapy (drug names, dose);
- Details on the diagnostic methods used for post-neoadjuvant tumor staging and surveillance of tumor 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, i.e. 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 [10, 11].

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 [12, 13].

Data Analyses / Summary

We will summarise the collected study data using tables and figures (e.g. 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 esophageal cancer are treated with nCTX or nCRT plus consecutive surgery. Despite post-neoadjuvant pathological complete response rates between 16 and 49%, surgery is carried out in all patients and independent of the results of post-neoadjuvant response evaluation [5-7]. The “Nationale Dekade gegen Krebs” program of the german national government (https://www.dekade-gegen-krebs.de/de/praxisveraendernde-studien-fuer-eine-bessere-patientenversorgung-2018.html) is supporting a multicenter randomised trial (which will be conducted by our study group) challenging this “sometimes potentially harmful” algorithm by comparing post-neoadjuvant surgery on principle versus surveillance (with surgery only if needed in the event of a persisting or recurring local tumor). Using a randomised study design, we aim to optimize therapeutic outcomes by personalization 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 [14]. A survival disadvantage of delayed surgery in case of local tumor relapse is likely to be excluded in a protocol of close surveillance in complete responder [15].

Although the scoping review may not provide effect estimates including an evaluation of the certainty of evidence, it will be of great value to crystallize 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 (i) characteristics and definitions of patient populations (included in available studies) and settings, (ii) details on the interventions (including type of neoadjuvant therapy, time between neoadjuvant therapy and surgery, definition of surveillance), (iii) details on the diagnostic methods used for post-neoadjuvant tumor staging, (iv) definition of complete responders, (v) outcome measures and (vi) 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 searching the literature in different databases (i.e., behind Medline) and also study registers (e.g., clinicaltrials.gov), all relevant completed but also ongoing studies comparing surveillance with surgery on demand in esophaegeal cancer will be identified. Finally the results of the scoping review will reveal (i) whether the diagnostic methods used and the definition for complete responders were appropriate and homogenous, (ii) whether the included sample sizes were sufficient to draw conclusions on benefits and harms, (iii) what interventions were considered (e.g., neoadjuvant chemoradiation and/or chemotherapeutic protocols), (iv) what outcomes of interest were covered, (v) whether follow-up times were sufficient and (vi) whether clinical results across studies are homogenous. 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 analyzed (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 post-neoadjuvant complete responders. This treatment procedure is expected to reduce morbidity and mortality rates, and increase quality of life. Regarding the socioeconomic impact, omission of esophagectomy 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 scoping review in a peer-reviewed journal and to present the results at national and international scientific conferences.

Contributors

ChS, BN and JM designed the scoping review protocol.
ChS and BN designed the preliminary search strategy.
JH and JuH contributed as experts for surgical and multimodal treatment of esophageal cancer and provided scientific knowledge. ChS and JH wrote the scoping review protocol. JH and CS are guarantors of the manuscript.

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Competing interests

None declared.

Patient and public involvement

For the current scoping review protocol patient involvement is not applicable. Patients or public will not be involved. However, parallel to the scoping review patient`s values and perspectives towards choice of treatment will be analyzed (DRKS00022050) prior to the start of the randomised trial (see above). Moreover, patients will be involved in the design, conduct, reporting, and dissemination of the proposed randomised controlled trial.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	x	☐	3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	x	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	x	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x	☐	6-34
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x	☐	315-320
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	x	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	x	☐	322-325
Sponsor	5b	Provide name for the review funder and/or sponsor	x	☐	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	x	☐	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	x	☐	87-101
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	x	☐	104-122
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	x	☐	129-164

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	x	☐	166-191
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	x	☐	193
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x	☐	195-200
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	x	☐	
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	x	☐	202-231
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	x	☐	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	x	☐	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	x	☐	233-235
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☐	Not applicable, scoping review
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☐	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☐	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x	☐	237-241
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☐	Not applicable, scoping review
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	