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# BMJ Open

## 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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3 **Post-neoadjuvant surveillance and surgery as needed compared with post-**  
4 **neoadjuvant surgery on principle in multimodal treatment for esophageal**  
5 **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, 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 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).
<ul style="list-style-type: none"> <li>• Overall survival;</li> <li>• Progression-free survival;</li> <li>• Proportion of radical resection margin;</li> <li>• Postoperative complications. (frequency and severity);</li> <li>• Rate and timing of distant dissemination;</li> <li>• Disease recurrence rate.</li> </ul>

### 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](http://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](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.

**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 adenocarcin*)).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

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3 end of study, sample size (number of participants screened and randomized  
4 including reasons for screening failures), methods used to plan sample size;  
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7 • Aim of the study;  
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9 • Setting, i.e., geographical and organizational setting;  
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11 • Characteristics of participants (e.g., age, gender, tumor histology and tumor  
12 stage);  
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14 • Details on the diagnostic methods that have been used for post-neoadjuvant  
15 tumor staging and surveillance of tumor response;  
16  
17 • Details on neoadjuvant therapy including drug names and radiation;  
18  
19 • Characteristics of intervention; i.e., definition of surveillance;  
20  
21 • Characteristics of comparator(s), e.g., type of surgery;  
22  
23 • Reported outcomes and their exact definitions, i.e. how and when the  
24 outcome measures were assessed;  
25  
26 • Recruitment and follow-up time (planned and actual time);  
27  
28 • Number of patients screened  
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31 Data from each included study will be extracted by one reviewer and checked by a  
32 second. Disagreements will be resolved through discussion until consensus will be  
33 reached.  
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### 36 37 **Risk of Bias**

38 Risk of bias assessment is not part of a scoping review and will not be assessed  
39 accordingly [10, 11].  
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43 The methodology may be adapted minimally during the review process itself in terms  
44 of eligibility criteria, study characteristics and outcome variables [12, 13].  
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### 48 49 **Patient and public involvement**

50 Patients or public will not be involved.  
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### 54 55 **Perspective / Discussion**

56 Currently in Western Europe the majority of patients with non-metastatic resectable  
57 esophageal cancer are treated with nCTX or nCRT plus consecutive surgery. Despite  
58 of post-neoadjuvant pathological complete response rates between 16 - 49% surgery  
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3 is carried out on principle in all patients and independent of the results of post-  
4 neoadjuvant response evaluation [5, 6, 7]. Within the “Nationale Dekade gegen  
5 Krebs” program of the German national government ([https://www.dekade-gegen-](https://www.dekade-gegen-krebs.de/de/praxisveraendernde-studien-fuer-eine-bessere-patientenversorgung-2018.html)  
6 [krebs.de/de/praxisveraendernde-studien-fuer-eine-bessere-patientenversorgung-](https://www.dekade-gegen-krebs.de/de/praxisveraendernde-studien-fuer-eine-bessere-patientenversorgung-2018.html)  
7 [2018.html](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  
8 comparing post-neoadjuvant surgery on principle versus surveillance (with surgery  
9 only if needed in the event of a persisting or recurring local tumor). The randomised  
10 trial aims to optimize therapeutic outcomes by personalization of the therapeutic  
11 sequence for complete and non-complete responders. According to the known  
12 evidence, a reliable clinical identification of a quantitative relevant subgroup of  
13 pathological complete responder with consecutive omission of potentially harmful  
14 surgery appears most likely. On the other side a survival disadvantage of delayed  
15 surgery in case of local tumor relapse appears unlikely in a protocol of close  
16 surveillance of clinical complete response. To support the clinical trial, the preceding  
17 scoping review will systematically identify and explore published, unpublished and  
18 ongoing clinical studies and study protocols comparing surveillance with surgery as  
19 needed versus surgery on principle in patients after neoadjuvant treatment for  
20 esophageal cancer before conducting the randomised controlled trial. It will allow us  
21 to finally define and/or adapt the research question including the methodology of the  
22 randomised controlled trial taking into account the findings e.g., research gaps, safety  
23 issues and/or pitfalls in the currently available study pool addressing similar  
24 questions. The randomised trial will add specific high level evidence to answer the  
25 research question and will influence the medical practice. Parallel to the scoping  
26 review patient's values and perspectives towards choice of treatment will be  
27 analyzed prior to the start of the randomised trial and patient oriented information  
28 material for the trial will be developed and provided. The final goal will be the  
29 development and verification of a protocol to identify patients with pathological  
30 complete response who would not need to undergo high-risk surgery in the growing  
31 group of post-neoadjuvant complete responders. This is expected to reduce morbidity  
32 and mortality rates, and increase the quality of life in this group of patients. Regarding  
33 the socioeconomic impact, omission of esophagectomy reduces length of therapy,  
34 complication rates and time of hospital stay resulting in reduced treatment costs and  
35 a faster return to normal life for this patient population.  
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### **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.

For peer review only

## 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

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## 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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Keywords:	Oesophageal disease < GASTROENTEROLOGY, Radiation oncology < RADIOTHERAPY, Gastrointestinal tumours < ONCOLOGY, Thoracic surgery < SURGERY

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## 35 **ABSTRACT**

### 37 **Introduction**

38 In current medical practice of curative treatment for non-metastatic esophageal cancer,  
39 surgery on principle is carried out by esophagectomy after neoadjuvant treatment.  
40 However, esophagectomy is often associated with postoperative morbidity and  
41 mortality. Taking into account that modern neoadjuvant therapy is effective and many  
42 of patients show no vital tumor cells in the operative specimens, we aim to perform a  
43 scoping review as part of the development phase for a prospectively planned  
44 multicenter randomised controlled trial investigating “surgery as needed versus  
45 surgery on principle in patients with post-neoadjuvant complete response of  
46 esophageal cancer”. This scoping approach will allow us to finally define and/or adapt  
47 the research question including the design and methodology of the randomised  
48 controlled trial taking into account the findings e.g., research gaps and/or pitfalls in the  
49 currently available study pool addressing this or very similar questions.

### 50 **Methods and Analysis**

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

### 61 **Ethics and Dissemination**

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

### 68 **Strengths and limitations of this study**

- 69 • The scoping review is part of the development phase for a prospectively planned  
70 multicenter randomised trial, addressing “*Surgery as needed versus surgery on*  
71 *principle in patients with post-neoadjuvant complete response of esophageal*  
72 *cancer*” (DRKS 00022801) .
- 73 • The scoping review will allow us to finally define and/or adapt the research  
74 question, the design and methodology of the following randomised trial.
- 75 • The scoping review protocol is guided by validated methodological frameworks  
76 and the scoping review will be reported according to the preferred reporting  
77 items for systematic review and meta-analysis statement for scoping reviews  
78 and, therefore, will be conducted in line with ‘the state-of-the-art’ criteria.
- 79 • We will conduct comprehensive literature searches and map the current  
80 ongoing and published studies by extracting and cluster key data such as  
81 neoadjuvant treatment protocols, diagnostic methods of response evaluation  
82 and surveillance, and therapeutic outcomes.
- 83 • The final scoping review will be limited to English and German language studies.

## 85 INTRODUCTION

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

## 101 OBJECTIVES

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2  
3 102 We aim to perform a scoping review as part of the development phase for a  
4 103 prospectively planned multicenter randomised controlled trial, addressing “*Surgery as*  
5 104 *needed versus surgery on principle in patients with post-neoadjuvant complete*  
6 105 *response of esophageal cancer*” (Prospective registration identifier of the clinical trial  
7 106 will be DRKS 00022801. Registration is currently in process and will be completed after  
8 107 we have incorporated the results of the scoping review). The scoping review will allow  
9 108 us to finally define and adapt the research question and methodology of the following  
10 109 randomised trial taking into account the findings (such as research gaps and/or  
11 110 methodological pitfalls) in the currently available pool of primary studies addressing  
12 111 this or very similar questions.  
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22 113 The objectives of the scoping review are as follows:

- 23 114 1. What specific neoadjuvant protocols of nCRT and nCTX have been studied for  
24 115 surveillance and surgery as needed
- 25 116 2. In what populations or settings have these protocols been studied?
- 26 117 3. Which diagnostic methods have been used for post-neoadjuvant tumor staging  
27 118 and surveillance of tumor response?
- 28 119 4. Which outcomes have been addressed in the clinical studies on surveillance  
29 120 and surgery as needed in esophageal cancer?  
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## 38 122 **METHODS and ANALYSIS**

39 123 This protocol is written with reference to the preferred reporting items for systematic  
40 124 review and meta-analysis protocols statement [8] and ‘a priori’ defines the  
41 125 methodology on which the scoping review will be based on:  
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### 48 127 **Eligibility criteria**

#### 49 128 *Participants/Population*

50 129 We will focus on studies including adults with non-metastatic esophageal cancer (after  
51 130 receiving neoadjuvant treatment). Studies including patients with distant metastases  
52 131 of esophageal cancer, presence of gastric cancer; and/or participants younger than 18  
53 132 years of age will be excluded.  
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3 134 *Intervention and Comparator treatment*

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5 135 We will consider surveillance after neoadjuvant therapy as eligible intervention.

6  
7 136 Surgery on principle after neoadjuvant therapy will be the comparator treatment.

8  
9 137

10 138 *Context*

11  
12 139 We will consider all neoadjuvant chemotherapeutic and neoadjuvant  
13  
14 140 chemoradiotherapeutic interventions implemented and evaluated in the context of non-  
15  
16 141 metastatic esophageal cancer.

17 142

18  
19 143 *Relevant Outcomes*

20  
21 144 We will capture any outcomes reported in the eligible study pool. Highly important  
22  
23 145 outcomes are displayed in Table 1. This table is non-exhaustive and will be completed  
24  
25 146 depending on the outcomes reported in the identified study pool.

26 147

27 148 **Table 1.** Outcome variables.

Outcomes (list will be completed depending on outcomes reported in the available study pool)
<ul style="list-style-type: none"> <li>• Overall survival;</li> <li>• Progression-free survival;</li> <li>• Proportion of radical resection margin;</li> <li>• Postoperative complications. (frequency and severity);</li> <li>• Rate and timing of distant dissemination;</li> <li>• Disease recurrence rate.</li> </ul>

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39 151 *Study Types*

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41 152 Randomised controlled trials; non-randomised controlled studies (using strategies of  
42  
43 153 non-random allocation for assigning interventions) and observational studies (with  
44  
45 154 control group) will be eligible for the scoping review. We will not consider single arm  
46  
47 155 studies. Due to a missing control group this study design. The reason for this exclusion  
48  
49 156 is that studies without a control group provide no reliable data to estimate comparative  
50  
51 157 effectiveness and will, therefore, not be useful for the planned randomised trial.  
52  
53 158 Furthermore, review articles, clinical guidelines and work that has not been peer-  
54  
55 159 reviewed (e.g., thesis, editorials, letters, comments) will be excluded.

56 160

57 161 We will not apply any exclusion criteria regarding study duration and/or the study  
58  
59 162 setting.

60 163

## 164 **Information sources**

165 The searches for this scoping review will be performed and conducted by following the  
166 recommendation of PRESS (Peer Review of Electronic Search Strategies) [9]; i.e., a  
167 medical sciences librarian will develop the search strategies; in addition, search  
168 strategies will be validated by checking whether they identified studies already known.  
169 We will not use any date restrictions in the electronic searches. For each database,  
170 the date of the search, the search strategy and the number of search results will be  
171 documented.

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

- 174 • Medline, Medline Daily Update, Medline In Process & Other Non-Indexed  
175 Citations, Medline Epub Ahead of Print (via Ovid) (a preliminary search  
176 strategy is displayed in Table 2);
- 177 • Web of Science Core Collection: Science Citation Index-EXPANDED (SCI-  
178 EXPANDED) (via Clarivate Analytics);
- 179 • Cochrane Library (via Wiley);
- 180 • Science Direct (via Elsevier).

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

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

190



191 **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

192

193 **Identification of Relevant Studies**

194 Titles and abstracts of the records identified by the searches will be screened and full  
 195 texts of all potentially relevant articles will be obtained. Full texts will be checked for  
 196 eligibility, by two reviewers and reasons for exclusions will be documented (full-text  
 197 screening). The complete screening process will be conducted in Covidence  
 198 (<https://www.covidence.org>).

199

## 200 **Extraction of Study Data / Data items**

201 The following study data will be extracted and relevant information tabulated:

- 202 • Study characteristics, i.e., author, year of publication, study type (randomised  
203 trial, non-randomised study) and design (superiority, non-inferiority trial), study  
204 status (e.g. planned, ongoing, completed, prematurely discontinued), start and  
205 end of study;
- 206 • Details regarding sample size calculation;
- 207 • Details on sample size (number of participants screened and  
208 randomized/finally included; reasons for screening failures and number and  
209 reasons for drop-offs and compliance);
- 210 • Aim of the study;
- 211 • Setting, i.e., geographical and organizational setting;
- 212 • Characteristics and definition of participants (age, gender, tumor histology and  
213 tumor stage);
- 214 • Details on neoadjuvant therapy (drug names, dose);
- 215 • Details on the diagnostic methods used for post-neoadjuvant tumor staging  
216 and surveillance of tumor response;
- 217 • Definition of complete responders;
- 218 • Characteristics of intervention/surveillance group (definition of surveillance);
- 219 • Characteristics of comparator/surgery group (type of surgery and time  
220 between neoadjuvant therapy and surgery)
- 221 • Pathohistological complete response rate after neoadjuvant therapy (surgery-  
222 group)
- 223 • On-demand surgery rate (surveillance group)
- 224 • All reported outcomes and their exact definitions, i.e. how and when the  
225 outcome measures were assessed;
- 226 • Recruitment and follow-up time (planned and actual time);

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

230

## 231 Risk of Bias

232 Risk of bias assessment is not part of a scoping review and will not be assessed  
233 accordingly [10, 11].

234 The methodology of the scoping review may be adapted minimally during the review  
235 process itself in terms of eligibility criteria, data extraction and outcome variables [12,  
236 13].

237

## 238 Data Analyses / Summary

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

242

## 243 Perspective / Discussion

244 Currently in Western Europe the majority of patients with non-metastatic resectable  
245 esophageal cancer are treated with nCTX or nCRT plus consecutive surgery. Despite  
246 post-neoadjuvant pathological complete response rates between 16 and 49%, surgery  
247 is carried out in all patients and independent of the results of post-neoadjuvant  
248 response evaluation [5-7]. The “Nationale Dekade gegen Krebs” program of the  
249 german national government ([https://www.dekade-gegen-  
250 krebs.de/de/praxisveraendernde-studien-fuer-eine-bessere-patientenversorgung-  
251 2018.html](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  
252 study group) challenging this “sometimes potentially harmful” algorithm by comparing  
253 post-neoadjuvant surgery on principle versus surveillance (with surgery only if needed  
254 in the event of a persisting or recurring local tumor). Using a randomised study design,  
255 we aim to optimize therapeutic outcomes by personalization of the therapeutic  
256 sequence. According to the current evidence and also supported by our clinical  
257 experience, it is likely that a subgroup of pathological complete responders (with  
258 consecutive omission of potentially harmful surgery) will be identified [14]. A survival  
259 disadvantage of delayed surgery in case of local tumor relapse is likely to be excluded  
260 in a protocol of close surveillance in complete responder [15].

261 Although the scoping review may not provide effect estimates including an evaluation  
262 of the certainty of evidence, it will be of great value to crystallize research questions,  
263 and the extent of available evidence by highlighting areas where evidence is lacking.  
264 The scoping review will support us to map the existing primary research for potential

1  
2  
3 265 duplications. Furthermore, it will provide an overview of the (i) characteristics and  
4 266 definitions of patient populations (included in available studies) and settings, (ii) details  
5 267 on the interventions (including type of neoadjuvant therapy, time between neoadjuvant  
6 268 therapy and surgery, definition of surveillance), (iii) details on the diagnostic methods  
7 269 used for post-neoadjuvant tumor staging, (iv) definition of complete responders, (v)  
8 270 outcome measures and (vi) follow-up times. Hence the scoping process will allow us  
9 271 to systematically develop the concept of the randomised trial based on current  
10 272 knowledge (including pitfalls) in this newly emerging treatment area.

11 273 By searching the searching the literature in different databases (i.e., behind Medline)  
12 274 and also study registers (e.g., clinicaltrials.gov), all relevant completed but also  
13 275 ongoing studies comparing surveillance with surgery on demand in esophageal  
14 276 cancer will be identified. Finally the results of the scoping review will reveal (i) whether  
15 277 the diagnostic methods used and the definition for complete responders were  
16 278 appropriate and homogenous, (ii) whether the included sample sizes were sufficient to  
17 279 draw conclusions on benefits and harms, (iii) what interventions were considered (e.g.,  
18 280 neoadjuvant chemoradiation and/or chemotherapeutic protocols), (iv) what outcomes  
19 281 of interest were covered, (v) whether follow-up times were sufficient and (vi) whether  
20 282 clinical results across studies are homogenous. We believe that the planned  
21 283 randomised trial will benefit from this state-of-the art research approach and, therefore,  
22 284 will provide patients, clinicians and other stakeholders with high evidence considering  
23 285 various patient-relevant outcomes when comparing these two treatment approaches.  
24 286 Furthermore, parallel to the scoping review patient`s values and perspectives towards  
25 287 choice of treatment will be analyzed (DRKS00022050) prior to the start of the  
26 288 randomised trial and patient oriented information material for the trial will be developed  
27 289 and provided.

28 290 Overall, the final goal will be the development and verification of a protocol to identify  
29 291 patients with pathological complete response (based on reliable diagnostic methods  
30 292 and definitions for complete responders) who would not need to undergo high-risk  
31 293 surgery in the increasing subgroup of post-neoadjuvant complete responders. This  
32 294 treatment procedure is expected to reduce morbidity and mortality rates, and increase  
33 295 quality of life. Regarding the socioeconomic impact, omission of esophagectomy  
34 296 reduces treatment duration, complication rates and time of hospital stay. This results  
35 297 in reduced treatment costs and a faster return to normal life for this patient population.

36 298

## 299 **ETHICS and DISSEMINATION**

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

303

304

### 305 **Contributors**

306 ChS, BN and JM designed the scoping review protocol.

307 ChS and BN designed the preliminary search strategy.

308 JH and JuH contributed as experts for surgical and multimodal treatment of esophageal  
309 cancer and provided scientific knowledge. ChS and JH wrote the scoping review  
310 protocol. JH and CS are guarantors of the manuscript.

311

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313 This work was supported by a research grant (grand number 01KD1908) “Nationale  
314 Dekade gegen Krebs” provided to JH by the federal ministry of education and research  
315 (BMBF). The funder was not involved in the development of the protocol. The article  
316 processing charge was funded by the Baden-Wuerttemberg Ministry of Science,  
317 Research and Art and the University of Freiburg in the funding programme Open  
318 Access Publishing.

319

### 320 **Competing interests**

321 None declared.

322

### 323 **Patient and public involvement**

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

330

### 331 **Patient consent for publication**

332 Not required.

333

**Provenance and peer review**

335 Not commissioned; externally peer reviewed.

336

**Open access**

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339 Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute,  
340 remix, adapt, build upon this work non-commercially, and license their derivative works  
341 on different terms, provided the original work is properly cited, appropriate credit is  
342 given, any changes made indicated, and the use is non-commercial. See: [http://  
343 creativecommons.org/licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/).

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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	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	x	<input type="checkbox"/>	3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	x	Not applicable
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input type="checkbox"/>	x	
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x	<input type="checkbox"/>	6-34
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x	<input type="checkbox"/>	315-320
<b>Amendments</b>	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	<input type="checkbox"/>	x	Not applicable
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	x	<input type="checkbox"/>	322-325
Sponsor	5b	Provide name for the review funder and/or sponsor	x	<input type="checkbox"/>	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	x	<input type="checkbox"/>	
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	x	<input type="checkbox"/>	87-101
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	x	<input type="checkbox"/>	104-122
<b>METHODS</b>					
<b>Eligibility criteria</b>	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	<input type="checkbox"/>	129-164



Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Information sources</b>	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	<input type="checkbox"/>	166-191
<b>Search strategy</b>	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	<input type="checkbox"/>	193
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x	<input type="checkbox"/>	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	<input type="checkbox"/>	
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	<input type="checkbox"/>	202-231
<b>Data items</b>	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	<input type="checkbox"/>	
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	x	<input type="checkbox"/>	
<b>Risk of bias in individual studies</b>	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	<input type="checkbox"/>	233-235
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input type="checkbox"/>	<input type="checkbox"/>	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>	<input type="checkbox"/>	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x	<input type="checkbox"/>	237-241
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	<input type="checkbox"/>	Not applicable, scoping review
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input type="checkbox"/>	Not applicable, scoping review