PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Post-neoadjuvant surveillance and surgery as needed compared with post-neoadjuvant surgery on principle in multimodal treatment for esophageal cancer: a scoping review protocol
AUTHORS	Schmucker, Christine; Nagavci, Blin; Hipp, Julian; Schmoor, Claudia; Meerpohl, Joerg; Hoeppner, Jens

VERSION 1 – REVIEW

REVIEWER	Ying-Shi Sun Peking University Cancer Hospital & Institute, China
REVIEW RETURNED	01-Dec-2020

GENERAL COMMENTS	General considerations: The purpose of this study was to perform a scoping review about comparing the surgery as need and surgery on principle in patients with post-neoadjuvent complete response of esophageal cancer. However, there are several problems with the study design which limited their value. Specifc comments: Esophageal cancer is an extremely devastating disease among the 10 most common malignancies leading to death. Whether the patients of esophageal cancer with pCR after treatment can benefit from the “wait and see” protocol was controversial. No studies supported that there were no significant difference of overall survival or disease recurrence rate between surgery as need and surgery on principle in esophageal cancer of pCR after treatment. The randomized controlled trail comparing prognosis between surgery as need and surgery on principle in pCR patients after treatment may increase the risk of recurrence rate. There are several problems as follows. Firstly, rectal cancer with pCR after treatment can benefit from “wait and see” protocol. However, esophageal cancer was more malignant than rectal cancer. Comparing rectal cancer, esophageal cancer has a relatively poor prognosis, and higher mortality rate. For esophageal cancer with poor prognosis, the patients may not benefit from the “wait and see” strategy. Secondly, the performance of diagnosing pCR after treatment is low using CT, EUS, and PET. It can hardly differentiate among viable tumor, inflammation, and scar tissue after neoadjuvant therapy in restaging. Recent studies showed that MRI may improve the performance of diagnosing pCR, but multiple-center study with large sample may be performed to verify the accuracy of diagnosing pCR in esophageal cancer. Thirdly, N staging is very important after treatment. There is no lymph node metastasis (N0) in pCR patients. Detection of pathologic lymph nodes depending on the size criteria, EUS, CT, PET or MRI may miss normal size lymph node that contain

	microscopic metastatic foci and led to an underestimation of node stage. Fourthly, the duration intervals of follow-up is not identified and which diagnostic methods, such as CT, PET, EUS, MRI or endoscopy with biopsy is used for surveillance of patients with pCR? Which strategy is best to diagnose the pCR and detect the recurrence as soon as possible. In addition, this protocol is to propose a scope review for a prospective clinical study. It aims to provide the basis for the development of the study on patient selection, index test, reference test and compliance timpoint. Therefore, the protocol should provide more detail for how to use the scope review results as well as how to analysis the literature. e.g. what would be concluded if there was small number of reference traced, as the study only included controlled studies, but "wait and see" strategy was an innovative strategy that is rarely used. It is also suggested that details be listed for extraction items for patient selection, index test, reference test and surveillance. And it is still necessary to take into account the quality and bias of study and heterogeneity among studies, e.g.the time from neoadjuvant treatment to surgery, the drop-off rate.

REVIEWER	Ilonen Ilkka Helsinki University Hospital, Finland
REVIEW RETURNED	01-Dec-2020

GENERAL COMMENTS	The issue I have is that there is little to none discussion on the histology of the tumour. I would focus either to squamous or adenocarcinoma, that present distinct disease. Also, the fact is that for adenocarcinoma, there is change from EOX to FLOT for adenocarcinoma in Europe. Secondly, North American centres gives chemorads to everybody. Thirdly, there is over presentation of squamous cases from China that do not receive neoadjuvant therapy, but also if these patients do receive chemorads -> are not postoperatively routed to adjuvant chemo. So knowing the global trends and protocols would benefit the proposed study design.

REVIEWER	Matthias Paireder Medical University of Vienna, Austria
REVIEW RETURNED	03-Dec-2020

GENERAL COMMENTS	Review of the Manuscript “Post-neoadjuvant surveillance and surgery as needed compared with post neoadjuvant surgery on principle in multimodal treatment for esophageal cancer: a scoping review protocol”. This manuscript presents a study protocol for a scoping review of the literature regarding the development process of a prospective multicenter randomized controlled trial (RCT) investigating neoadjuvant treatment followed by surgery versus a surveillance strategy. I commend the authors for designing a RCT regarding this current issue. Moreover the research group planned a meticulous strategy to develop the study protocol assessing the research question including design and methodology. The topic of a sophisticated surveillance protocol after neoadjuvant therapy is of high interest and will be a great significance of the reader of BMJ Open.

	I suggest to accept the manuscript after minor corrections. - Minor typo in the Introduction of the Abstract: wwe instead of we. - Strength and limitation section: the planned trial “Surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of esophageal cancer” (DRKS 00022801) is not available at the DRKS website at the time of this review process. Obviously the study is not fully registered and is currently in the status „in process“. Please add a comment that registration will be finished after the scoping review is completed. - Study Types: Excluding observational studies without control group may produce a significant selection bias. I suggest to include all observational studies, which report at least 4 out of 6 outcomes displayed in Table 1. I also suggest a funnel plot for good display of the potential publication bias in this meta-analysis. - I commend the authors for the comprehensive and transparent display of the search strategy, shown in Table 2. - Perspective/Discussion: this part is lacking citations. Especially when stated “According to the known evidence“. Please cite the most relevant literature.

VERSION 1 – AUTHOR RESPONSE

Point by point response to Ying-Shi Sun/Peking University (Reviewer 1)
Thank you very much for your time and the review of our manuscript. We found your comments and remarks very useful and addressed them in the manuscript and provide you with a short explanation below.

1. The protocol should provide more detail for how to use the scoping review results as well as how to analysis the literature. e.g. what would be concluded if there was small number of reference traced, as the study only included controlled studies, but "wait and see" strategy was an innovative strategy that is rarely used.

Authors: We fully agree with the reviewer that the current version of the scoping review protocol does not explain in enough detail how the results of the scoping review will be used. Therefore, we have “upgraded” the Perspective/Discussion section by providing more details how the results of the scoping review will support the following randomised trial. We are aware that although the scoping review may not provide clear answers about what works, it will be of great value to crystallize context, questions, and the extent of available evidence; i.e., scoping reviews highlight areas where evidence is lacking and can help researchers prioritize research questions (Page 9 and 10 / Perspective/Discussion).

2. It is also suggested that details be listed for extraction items for patient selection, index test, reference test and surveillance.

Authors: We provided more details regarding the items that will be extracted. Additionally we have added a table including the different items that will be extracted. Of note, we extracted diagnostic methods used for post-neoadjuvant tumor staging and surveilance of tumor response. However, we would like to point out that we are not planning to conduct a diagnostic test accuracy review. Such a diagnostic review would need a completely different approach and would not be in alignment of our research questions. Our aim is to explore studies investigating different treatment options. These studies are not reporting an index- or reference test, but usually provide us with information on the

diagnostic method used to for neoadjuvant tumor staging. Patient selection: In randomised trial patients are selected randomly, for non-randomised controlled studies we will extract the information provided in the clinical study. We will not consider one arm studies. The reason for this exclusion is that studies without a control group provide no reliable data to estimate comparative effectiveness and are, therefore, not useful for the planned randomised trial. We added this information to the revised version of the protocol (Page 5 / Study Types).

3. And it is still necessary to take into account the quality and bias of study and heterogeneity among studies, e.g. the time from neoadjuvant treatment to surgery, the drop-off rate.

Authors: We agree with the reviewer that the time from neoadjuvant treatment to surgery and the drop-off rate are important aspects that have to be considered when exploring the primary study pool. We have added these aspects and others to the extraction items of interest (Page 8 / Extraction of Study Data).
We also would like to point out again that a scoping review explores rather than summarizes the evidence. Consequently, scoping reviews do not include meta-analyses, assess risk of bias or the strength of evidence. Instead, they chart concepts and the amount and type of evidence available.
Point by point response to Ilonen Ilkka / Helsinki University (Reviewer 2)
Thank you very much for your time and the review of our manuscript. We found your comments and remarks very useful and addressed them in the manuscript and in the following point-by-point list.

1. The issue I have is that there is little to none discussion on the histology of the tumour. I would focus either to squamous or adenocarcinoma, that present distinct disease. Also, the fact is that for adenocarcinoma, there is change from EOX to FLOT for adenocarcinoma in Europe. Secondly, North American centres gives chemorads to everybody.

Authors: Both histologies show signinificant rates of complete response after neoadjuvant treatment following modern western neoadjuvant standard protocols (SCC 49% following neoadjuvant CROSS; AC 23% following neoadjuvant CROSS; AC 20-30% following FLOT; AC (Her2pos) 35 following FLOT plus per/tra). The planned clinical trial aims to adress the timepoint of surgery in sequence of multimodal treatment for both histologies without focussing on one or another. The neoadjuvant protocol won't be a part of the clinical trial itself, but completed neoadjuvant therapy (AC: e.g. FLOT/CROSS; SCC: e.g. CROSS) will be an inclusion criterium for the trial. As this is the protocol for a scoping review we have not discussed these issues in the current manuscript.

2. Thirdly, there is over presentation of squamous cases from China that do not receive neoadjuvant therapy, but also if these patients do receive chemorads -> are not postoperatively routed to adjuvant chemo. So knowing the global trends and protocols would benefit the proposed study design
Authors: In the western treatment standards neoadjuvant treatment is applied in >85% of all surgical patients. The trial aims to personalize and improve the treatment results of esophageal cancer for patients receiving multimodal therapy. Patients receiving upfront surgery are not addressed in the trial and will be excluded. Nevertheless the scoping review will include neoadjuvant studies from Asia. The results of the trial won't be transferable to patients receiving upfront surgery both in Asia and Western countries. Again, as this is the protocol for a scoping review we have not discussed these issues in the current manuscript.

Point by point response to Matthias Paireder / University of Vienna (Reviewer 3)
Thank you very much for your time and the review of our manuscript. We found your comments and remarks very useful and addressed them in the manuscript and in the following point-by-point list.

1. Minor typo in the Introduction of the Abstract: wwe instead of we.

Authors: The typing error is corrected in the revised manuscript.

2. Strength and limitation section: the planned trial “Surgery as needed versus surgery on principle in patients with post-neoadjuvant complete response of esophageal cancer” (DRKS 00022801) is not available at the DRKS website at the time of this review process. Obviously the study is not fully registered and is currently in the status „in process“. Please add a comment that registration will be finished after the scoping review is completed.

Authors: The comment is addressed in the revised version of the manuscript (Page 4 / Objectives): „Prospective registration identifier of the clinical trial will be DRKS 00022801. Registration is currently in process and will be finished after the scoping review is completed.”
Moreover the already active DRKS identifier (DRKS00022050) of the mentioned study on patient`s values and perspectives towards choice of treatment was amended (Page 11 / Patient and public involvement and Page 10 / Perspective/Discussion)

3. Study Types: Excluding observational studies without control group may produce a significant selection bias. I suggest to include all observational studies, which report at least 4 out of 6 outcomes displayed in Table 1. I also suggest a funnel plot for good display of the potential publication bias in this meta-analysis.

Authors: We understand the point of the reviewer being concerned about ignoring studies without control group (single arm studies). The goal of our scoping review is to receive a comprehensive overview of the primary studies evaluating comparative effectiveness comparing surveillance with surgery. The advantage of randomised trials is to ensure that the subjects receiving the treatment and control are equal with respect to all conditions except for the intervention and differences found by comparisons of the results of such studies can be attributed to the effect of the treatment when all other things are held constant. We are also aware that randomized trials are not always possible, therefore, we have already widened our inclusion criteria to non-randomised studies and observational studies with control group.
Considering studies without control group will neither be useful for the planned randomised trial taking into account that comparative effectiveness cannot be evaluated within such studies nor manageable taking into account the high number of single arms studies in this clinical area. We have added this information to the revised version of the protocol (see also 3rd Response to Reviewer 1 and Page 5 / Study Types).
Furthermore, a funnel plot (as suggested by the reviewer) would also exceed the goal of the scoping review. Although the scoping review may not provide clear answers about what works, it will help crystallize context, questions, and the extent of available evidence; i.e., scoping reviews highlight areas where evidence is lacking and can help researchers prioritize research questions. Therefore, a scoping review is not comparable with a meta-analyses. A systematic review with meta-analyses would be the next step (after completing the scoping review).

4. I commend the authors for the comprehensive and transparent display of the search strategy, shown in Table 2.

Authors: Thank you very much for your commendation.

5. Perspective/Discussion: this part is lacking citations. Especially when stated “According to the known evidence“. Please cite the most relevant literature.

Authors: The relevant references were added in the revised version of the manuscript (Page 9 and Page 13).

Response to editorial requirements / formatting amentments
1. Along with your revised manuscript, please include a copy of the PRISMA-P checklist indicating the page/line numbers of your manuscript where the relevant information can be found (http://www.bmj.com/content/349/bmj.g7647).

Authors: We have added a copy of the PRISMA-P checklist with all relevant information.