

Response rate and diagnostic accuracy of early PET/CT during neo-adjuvant therapies in oesophageal adenocarcinoma: protocol for a systematic review

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Protocol

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Abstract

Background Patients with potentially curable oesophageal adenocarcinoma have a staging positron emission tomography (PET) examination combined with a computed tomography (CT) to assess loco-regional and distant disease. Although only 20-30% of patients are suitable for surgical resection, the majority receive neo-adjuvant therapy (chemotherapy with or without radiotherapy) before their operation. However, less than 25% experience any clinically meaningful benefit from the neo-adjuvant therapy. A repeat PET/CT after one cycle of treatment can assess for early metabolic response but remains exploratory. Patients without an early response could be offered alternative treatment strategies. The purpose of this systematic review and meta-analysis is to estimate the early response rate defined by PET/CT, its diagnostic accuracy and explore associated factors. **Methods** Primary studies reporting response rates and diagnostic accuracy of PET/CT will be identified from MEDLINE, Embase, Cochrane Library, Scopus, Web of Science, International Clinical Trials Registry Platform (ICTRP) Search Portal and ClinicalTrials.gov databases. Peer-reviewed randomised control trials, observational cohort, cross-sectional and case-control studies reporting original response rate data, published from 2005 onwards will be included. Studies recruiting mixed cohorts and with PET/CT repeated after more than one neo-adjuvant treatment cycle will be excluded. The reference standard will be pathological response, defined by either validated Becker or Mandard tumour regression grade (TRG) classifications. The primary outcome will be metabolic response rate after one neo-adjuvant treatment cycle, defined by a reduction in maximum standardised uptake value (SUVmax) of 35%. Secondary outcome will be the sensitivity and specificity of early metabolic response to predict pathological response at this SUVmax reduction threshold. Pooled early response rate, sensitivity and specificity will be calculated using a random effects model with data extracted from selected studies. Heterogeneity between studies, risk of bias and methodological quality will be assessed. **Discussion** This systematic review and meta-analysis will identify and synthesise evidence to determine early response rates to neo-adjuvant therapies and the corresponding diagnostic accuracy of PET/CT to guide future clinical trials. This strategy could identify patients that will not respond to neo-adjuvant therapy and to offer this group alternative treatment strategies. Systematic review registration: PROSPERO (registration number CRD42019147034)

Background

The incidence of oesophageal cancer is increasing worldwide, with more than 450,000 patients diagnosed each year [1]. The prognosis of oesophageal cancer is poor, especially in locally advanced and metastatic disease [2]. Despite only 20-30% of patients being suitable for surgical management [3], the majority of these receive neo-adjuvant therapy which aims to reduce the volume of disease prior to resection, and improve survival.

A number of neo-adjuvant therapy trials have shown an overall survival benefit over surgery alone [4]. The neo-adjuvant chemotherapy Medical Research Council OE02 and Adjuvant Gastric Infusional Chemotherapy (MAGIC) and peri-operative chemotherapy ACCORD-07 trials have shown significant benefit over surgery alone [2, 5–7]. Similarly, the Chemoradiotherapy for Esophageal Cancer followed by

Surgery Study (CROSS) trial showed improved survival benefit of neo-adjuvant chemoradiotherapy over surgery alone [8, 9]. More recently, perioperative chemotherapy with FLOT (5-fluorouracil (5-FU), Leucovorin, Oxaliplatin and Docetaxel) was established as the new standard-of-care for patients with operable oesophago-gastric cancer [10] in the UK, but neo-adjuvant chemoradiotherapy is still commonly used in Europe and the USA.

Positron-emission tomography combined with computed tomography (PET/CT) is now an established investigation in the routine staging pathway of oesophageal cancer [11]. 18F-fluorodeoxyglucose (FDG) is the radioactive isotope used for oesophageal cancer staging. The main advantage of PET/CT is its greater sensitivity for undetected metastases on CT, which changes management in a significant number of patients [12], thus preventing them from undergoing major surgical intervention for little potential benefit. Research focus has now been placed on the role of PET/CT to predict pathological response earlier in the treatment pathway [13]. Pathological response to neo-adjuvant treatment is a good surrogate marker for overall survival [8], therefore prediction of which patients will have a favourable pathological response is important.

Different classifications for pathological response exist, and each are prone to subjective user error [14]. The two main histopathological classifications are the Becker [15] and Mandard [16] tumour regression grade (TRG) classifications, which are used throughout the Western world. Becker TRG 1 (either 1a, no residual tumour, or 1b, <10% residual tumour) defines a good clinical response. Similarly, Mandard TRG 1 or 2 (no residual cancer, or rare residual cancer cells, respectively) represent a good response, and was significantly associated with overall survival in a multi-centre study of oesophageal adenocarcinoma patients [17].

Metabolic response, defined by PET/CT imaging, is thought to predict underlying pathological response. In PET/CT, a quantitative metric called the maximum standardised uptake value (SUVmax) represents the highest recorded uptake of FDG within the tumour [18]. Preliminary work demonstrated that a reduction in SUVmax of 35% from baseline PET/CT to a repeat PET/CT after one cycle of neo-adjuvant chemotherapy was predictive of pathological response, and was associated with overall survival [19]. This threshold was validated [20], and is commonly used in studies assessing early metabolic response.

Subsequent Phase II trials [21] have shown promising results using this early response threshold of 35%. However, phase III trials are required to test the application of early metabolic response assessment in larger populations of oesophageal adenocarcinoma patients before it is adopted into clinical practice. To adequately power these trials, an accurate estimation of early response rate in this patient population is required. This systematic review and meta-analysis will aim to synthesise the evidence to provide these data.

Early metabolic response assessment has the potential to change clinical management by differentiating patients with an early response from those who are resistant to treatment. The latter group could potentially be offered an alternative neo-adjuvant therapy or simply omit the remaining cycles and proceed directly to surgery, thereby reducing the exposure to potential harmful side-effects, and reducing

the chance of progression during the interval before surgery. Although the potential clinical benefits are apparent, studies often include heterogeneous populations with mixed histological cell type and varying neo-adjuvant regimens. Furthermore, consensus regarding the optimal threshold to define metabolic response has not been agreed. Here, we report the protocol for a systematic review and, if feasible, a meta-analysis of early response rate to neo-adjuvant therapies in patients with oesophageal adenocarcinoma.

Objectives

The primary objective of the study is to systematically review the available literature reporting early response rate, defined by PET/CT after one cycle of neo-adjuvant therapy, in patients with oesophageal adenocarcinoma. The secondary objective is to review the literature reporting diagnostic accuracy; specifically, the sensitivity and specificity of early PET-CT, using a threshold reduction in SUVmax of 35%, to predict pathological response. We will aim to perform meta-analyses. Potential explanatory factors associated with early response rates will be explored using meta-regression. The protocol is registered with PROSPERO (registration number CRD42019147034) and has been reported in accordance with the PRISMA-P guidelines (additional file 1 – PRISMA-P checklist) [22].

Methods

Eligibility criteria

Studies will be selected for review according to the eligibility criteria below.

Study design and participants

This review will include randomised control trials, observational cohort, cross-sectional and case-control studies reporting original response rate data in adult human participants. Participants will be patients with biopsy-proven oesophageal, or gastro-oesophageal junction adenocarcinoma (confirmed by histopathologist), who have been treated with neo-adjuvant chemotherapy or neo-adjuvant chemoradiotherapy prior to surgical resection and had an early PET/CT examination (after one-cycle of neo-adjuvant therapy). (Fig. 1) Recurrent oesophageal adenocarcinoma will not be included. Studies of patients with histology other than adenocarcinoma and those who did not have an early PET/CT examination will be excluded. Studies with mixed patient cohorts will also be excluded.

PET/CT examinations

The radioactive isotope FDG must have been used for the PET/CT examination. Studies using other radioactive isotopes will be excluded but if the article contains FDG data, attempt will be made to extract these data. The SUVmax must have been measured by an appropriately trained and experienced professional. SUVmax is defined as the voxel with the highest SUV value within the tumour [18].

Treatment response

The threshold for response classification, defined in terms of the percentage reduction in SUVmax, must be pre-specified at 35%. The reference standard will be the pathological TRG, defined by validated pathological classification systems Becker [15] or Mandard [16]. Occasionally, patients will progress during neo-adjuvant therapy and no longer be suitable for surgery. Attempt will be made to capture these data also.

Searches

Electronic Searches

A comprehensive search strategy using text words and controlled vocabulary has been designed using MEDLINE (OVID). (Table 1)

Table 1. Search terms and strategy

#	Searches
1	Esophageal Neoplasms/
2	((oesophag* or esophag*) adj (neoplas* or adenocarcinoma or tumo?r*)).tw.
3	1 or 2
4	exp Adenocarcinoma/
5	(oesophag* or esophag*).tw.
6	4 and 5
7	3 or 6
8	Positron Emission Tomography Computed Tomography/
9	(PET-CT or PET CT).tw.
10	((early or interim or ad interim or endpoint or timepoint) adj2 (PET or FDG-PET)).tw.
11	Positron-Emission Tomography/
12	(PET or FDG-PET or 18-FDG).tw.
13	Fluorodeoxyglucose F18/
14	or/8-13
15	7 and 14
16	exp Treatment Outcome/
17	exp "Predictive Value of Tests"/
18	exp "sensitivity and specificity"/
19	exp Disease-Free Survival/
20	exp Prognosis/
21	(sensitivity or specificity).tw.
22	((treatment or therapeutic) adj1 (response or outcome*)).tw.
23	(predict* or prognos*).tw.
24	((tumo?r or metabolic) adj2 response).tw.
25	tumo?r glucose.tw.
26	(glucose adj (standard uptake or SUV)).tw.
27	Glucose/
28	or/16-27
29	15 and 28
30	limit 29 to (english language and yr="2005 -Current")
31	randomized controlled trial.pt.
32	controlled clinical trial.pt.
33	randomized.ab.
34	placebo.ab.
35	drug therapy.fs.
36	randomly.ab.
37	trial.ab.
38	groups.ab.
39	or/31-38
40	exp animals/ not humans.sh.
41	39 not 40
42	epidemiologic studies/
43	exp case control studies/
44	exp cohort studies/
45	Case control.tw.
46	exp Longitudinal Studies/
47	exp Retrospective Studies/
48	exp Prospective Studies/
49	(cohort adj (study or analys* or studies)).tw.
50	exp Follow-Up Studies/
51	(Follow up adj (study or studies)).tw.
52	exp Cross-Sectional Studies/
53	(observational adj (study or studies)).tw.
54	(Longitudinal or Retrospective or Cross sectional).tw.
55	or/42-54
56	41 or 55

This strategy will be translated and run in the following electronic databases: MEDLINE [OVID], Embase [OVID], Cochrane Library [Wiley], Cumulative Index of Nursing and Allied Health Literature (CINAHL) [Ebsco], Scopus [Elsevier], Web of Science [Thomson Reuter], International Clinical Trials Registry Platform (ICTRP) Search Portal [World Health Organisation] and ClinicalTrials.gov.

The search will be limited to articles published in English from 2005 onwards, because 3D PET became integrated into most PET/CT scanners providing more standardisation in SUVmax from this timepoint onwards [13]. Study filters for randomised control trials and observational study types will be applied. Reference lists of all eligible studies will be checked and undergo citation tracking for additional eligible studies.

Selection process

Following the systematic search described above, all titles and abstracts will be screened by two independent authors against the defined eligibility criteria. Duplicate items will be identified and one of the copies deleted prior to screening. Full text articles will be obtained for all studies that meet the criteria. In cases of disagreement following screening of titles and abstracts, a third author will be asked to review and decide upon the suitability of the study. Reasons for exclusion will be recorded. A flowchart will be used to summarise the numbers of included and excluded studies at each stage of the selection process.

Data management and extraction process

The results of the screening process will be shared between the reviewers using an output file that can be imported into Mendeley Desktop 1.19.4. Authors will be instructed to create a new library to keep the screened studies separate. The full-text articles will be included in the output file.

Relevant data will be extracted from the final set of eligible articles. Data will be inputted into a Microsoft Excel 365 spreadsheet designed specifically for this review (additional file 2 - SystRev_DataItems_Extraction). Two independent authors will extract the relevant data from the articles. In cases of disagreement, a third author will be asked to review the article and decide upon the data to be recorded. Articles reporting findings from duplicate sets of patients will be combined and extracted as a single study.

Data items

- a. Patient characteristics; number of patients included, age, gender, tumour location, neo-adjuvant regimen, pathological response rate at surgery, length of survival.
- b. Study characteristics; primary author, publication year, study dates, country of study, study design, number of centres, length of time between early PET and surgery, length of time between early PET

and surgery, conclusions of study, risk of bias.

- c. PET/CT characteristics; timing of early PET/CT (days after treatment inception), type of scanner and acquisition (including PET reconstruction method), length of fasting before injection, time between FDG injection and PET, PET quantification method, interpreter(s), threshold criteria for defining response, proportion of patients with early response after one cycle of neo-adjuvant therapy.
- d. Diagnostic accuracy data; true positives, false positives, false negatives, true negatives, sensitivity, specificity, positive predictive value, negative predictive value.

Outcomes

The primary outcome of the systematic review will be the early response rate on PET/CT after one cycle of neo-adjuvant therapy. The secondary outcome will be diagnostic accuracy of early metabolic response, defined as the sensitivity and specificity of PET/CT to predict pathological response using the 35% SUVmax reduction threshold. The reference standard for pathological response will be the tumour regression grade (TRG). Pathological responders will be classified at pathology as having a Mandard TRG 1-2 or Becker TRG 1, and non-responders as Mandard TRG 3-5 or Becker TRG 2-3.

Quality assessment and risk of bias

The methodological quality of eligible studies will be assessed using two pre-specified quality assessment tools; the Newcastle Ottawa scale (modified for this review) [23] and the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS-2) criteria [24]. The Newcastle Ottawa scale will be used for the primary objective and QUADAS-2 for the secondary objective. The overall components of the quality assessment for each study will be reported using the star-rating system of the Newcastle Ottawa scale. Studies with no stars for any of the individual components of the NOS (selection, comparability and outcome assessment) will not be included in the quantitative synthesis. (additional file 3 - Modified NOS) For QUADAS-2, perceived quality will be graded low, high or unclear risk. The question "were uninterpretable and/or intermediate test results reported?" has been added to the QUADAS-2 checklist. (additional file 4 – QUADAS-2) The strength of the overall weight of evidence for both primary and secondary outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology [25].

Data synthesis

If the studies are sufficiently homogenous in their design, outcome assessment and follow-up, we will conduct a meta-analysis using a random effects model (DerSimonian and Laird [26]) using the current version of R (R Foundation for statistical computing, Vienna, Austria) [27]. We will combine the percentage of patients with early metabolic response in each individual study to estimate a pooled early response rate with a 95% confidence interval (CI).

The sensitivity and specificity of early PET/CT using the 35% threshold level to define metabolic response in individual studies will be calculated and subjected to meta-analysis, if feasible. The results of the individual studies will be displayed with a receiver operator curve (ROC) curve, and a weighted symmetric summary ROC (sROC) curve with a 95% CI will be computed [28].

We will assess heterogeneity between specific study estimates using the inconsistency index (I^2 statistic [29]). If heterogeneity is considerable ($I^2 > 75\%$) and the p value < 0.1 , quantitative data synthesis will not be performed [22]. Publication bias will be assessed by visually inspection or funnel plots [30].

We will also investigate sources of heterogeneity between studies using meta-regression subgroup analyses by stratifying original co-variables according to methodological quality (Newcastle Ottawa and QUADAS-2 score), sample size, PET injection time, neo-adjuvant therapy regimen, type of neo-adjuvant therapy and TRG classification used. The time interval between injection of FDG and scanning can affect the SUVmax of the tumour [31]. Differences in pathological response rates have been reported depending on the type of neo-adjuvant therapy used [8, 10]. Also, the effect of the TRG classification system will be explored.

Discussion

Despite significant improvements in overall survival with neo-adjuvant therapies, less than half of patients who are treated are cured of their cancer [2, 8]. Therefore, identification of patients who are unlikely to benefit from treatment either before or at an early timepoint during neo-adjuvant treatment is desirable.

PET/CT is commonly used in oesophageal cancer staging because the tumours frequently demonstrate metabolic activity. Metabolic response following chemotherapy on early PET/CT has been described as an imaging biomarker in this disease. Currently, the most validated metric for PET metabolic response is a reduction in SUVmax of 35% on day 15 after one cycle of cisplatin-5FU based chemotherapy [19–21].

However, there are several unanswered questions regarding the use of early PET as a biomarker, particularly with chemotherapy regimens having evolved over the past decade. Specifically, the early response rates to different neo-adjuvant therapies are unknown and the optimum threshold for defining metabolic response remains controversial.

Possible limitations of this review include the validation of early response. This distinction is largely based on imaging findings alone at present because a lack of gold standard histopathological reference standard exists, in contrast to the time following completion of neo-adjuvant therapy, when the most direct comparison can be made with surgical resection. Other possible limitations include a possible paucity of evidence from the primary literature and significant heterogeneity between studies which would hamper the ability to perform a meta-analysis.

This systematic review and meta-analysis will build on results from previous reviews [13, 32] and specifically focus on the response rate and diagnostic accuracy of early PET/CT in oesophageal adenocarcinoma. The findings of this review will inform design of future clinical trials by demonstrating the proportion of patients that have an early response after one cycle of neo-adjuvant therapy and determine the pooled diagnostic accuracy of early PET/CT to predict pathological response.

Abbreviations

PET	Positron emission tomography
CT	Computed tomography
PET/CT	PET combined with CT
FDG	Fluorodeoxyglucose
CINAHL	Cumulative Index of Nursing and Allied Health Literature
ICTRP	International Clinical Trials Registry Platform
MAGIC	Medical Research Council OE02 and Adjuvant Gastric Infusional Chemotherapy
CROSS	Chemoradiotherapy for Esophageal Cancer followed by Surgery Study
5-FU	5-fluorouracil
FLOT	5-FU, Leucovorin, Oxaliplatin and Docetaxel
¹⁸ F	18-Fluorine
SUVmax	Maximum standardised uptake value
TRG	tumour regression grade
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews
CI	Confidence interval
ROC	Receiver operator curve
sROC	Summary ROC

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study will be made available from the corresponding author on reasonable request.

Competing interests

The authors declare they have no competing interests.

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Authors' contributions

JJ participated in pilot data extraction and helped draft the manuscript. BC designed the search strategy. KB, ESmyth and ESpezi contributed to study design and manuscript preparation. AH provided statistical advice and contributed to data synthesis design. KF conceived the study idea, drafted the manuscript and is guarantor of the review. All authors read and approved the final manuscript.

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Figures

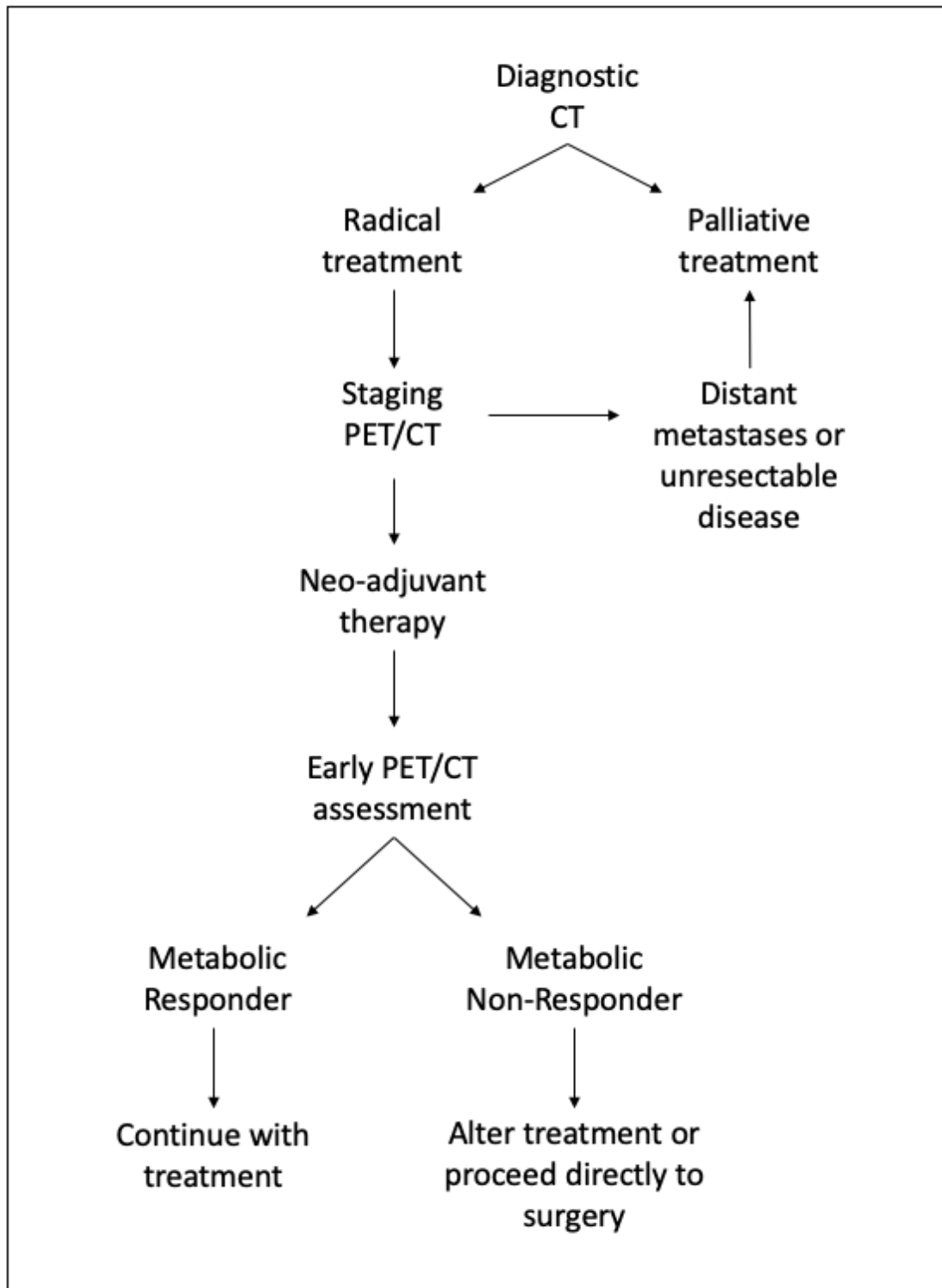


Figure 1

A schematic representation of the oesophageal cancer staging and treatment pathway, including early PET/CT, and the effect early PET/CT could have on clinical management.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1PRISMAPChecklist.docx](#)
- [Additionalfile2SystRevDataItemsExtraction.xlsx](#)
- [Additionalfile3ModifiedNOS.xlsx](#)
- [Additionalfile4QUADAS2.docx](#)