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

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Protocol

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Abstract

Background

Oesophageal cancer is increasing in incidence and has a poor prognosis. Patients with potentially curable disease have a staging positron emission tomography (PET) examination combined with a computed tomography (CT) to assess loco-regional and distant disease. Although a small proportion of patients are suitable for attempted surgical resection, the majority will receive neo-adjuvant therapy (chemotherapy with or without radiotherapy) before their operation. The current regimen prescribes all patients to complete the neo-adjuvant treatment prior to surgery, but some patients will not experience a beneficial response. A repeat PET/CT after one cycle of neo-adjuvant treatment may identify early response or non-response and could alter subsequent management. The purpose of this systematic review and meta-analysis is to estimate the early and completion response rate defined by fluorodeoxyglucose (FDG)-PET, 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, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Scopus, Web of Science, International Clinical Trials Registry Platform (ICTRP) Search Portal and ClinicalTrials.gov databases. Peer-reviewed studies published from 2005 onwards will be included. Data will be extracted from selected studies and a meta-analysis using a random effects model will be attempted. Pooled early and completion response rates, and diagnostic accuracy (sensitivity and specificity), will be calculated from available data. 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 and completion response rates to neo-adjuvant treatment and the corresponding diagnostic accuracy of PET/CT. This strategy has the potential to identify patients that will not respond to the treatment and to offer this group an alternative pre-operative treatment or proceed directly to operation, thereby avoiding a delay in surgical resection and optimising patient outcomes.

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 aiming to reduce the volume of disease prior to resection.

A number of neo-adjuvant 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 over surgery alone [8, 9]. However, more recently, perioperative chemotherapy with FLOT chemotherapy (5-fluorouracil (5-FU), Leucovorin, Oxaliplatin and Docetaxel) is established as the new standard-of-care for patients with operable oesophago-gastric cancer [10].

Positron-emission tomography combined with computed tomography (PET/CT) is now an established investigation in the routine staging pathway of oesophageal cancer [11]. 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. Focus has now been placed on the role of PET/CT to define treatment response, particularly at an early timepoint during neo-adjuvant treatment [13].

The decision to alter neo-adjuvant therapy based on an early assessment may differentiate metabolic responders from non-responders; the latter group could potentially be offered an alternative neo-adjuvant therapy or simply omit the remaining cycles and proceed straight to surgery, thereby reducing the exposure to potential side-effects of chemotherapy with or without radiotherapy and reducing the chance of progression during the interval before surgery.

Although the potential clinical benefits are apparent, studies often include heterogenous populations with mixed histological cell type and varying neo-adjuvant regimens. Furthermore, the optimal threshold at which to define a metabolic response has not been agreed upon. Here, we report the protocol for a systematic review and, if feasible, a meta-analysis of response rates 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 fluorodeoxyglucose (FDG)-PET after one cycle of neo-adjuvant therapy, in patients with oesophageal adenocarcinoma. The secondary objectives are to review the literature reporting diagnostic accuracy, response rate after completion of neo-adjuvant therapy (the current timepoint at which imaging is routinely performed) and to review survival rates between metabolic responders and non-responders. We will also aim to perform meta-analyses. Potential explanatory factors associated with different response rates will be explored. 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) [14]. Any important protocol amendments will be documented in PROSPERO.

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. Eligible studies will be grouped together to calculate response rates, rather than treating the studies separately.

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 chemo-radiotherapy prior to surgical resection and had an interim PET/CT examination (after one-cycle of neo-adjuvant therapy) and a PET/CT after completion of neo-adjuvant therapy. Recurrent oesophageal adenocarcinoma will not be included. Studies of patients with histology other than adenocarcinoma and those who did not have an interim or completion PET/CT examinations will be excluded. Studies with mixed patient cohorts will also be excluded.

PET/CT examinations

The radioisotope 18-Fluorine (^{18}F) FDG must have been used for the PET/CT examinations. Studies using other radioisotopes will be excluded but if the article contains FDG data, attempt will be made to extract these data alone. The maximum standardised uptake value (SUVmax) must have been measured by an appropriately trained and experienced professional. SUVmax is defined as the voxel with the highest SUV value in a defined region of interest [15].

Treatment response

The threshold for response classification, defined in terms of the percentage reduction in SUVmax, must be stated. The reference standard will be the pathological tumour regression grade (TRG), defined by validated pathological classification systems Mandard [16] or Becker [17]. 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
57	1. and 56

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. 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. Duplicate items will be identified and one of the copies deleted.

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). 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

- Patient characteristics; number of patients included, age, gender, tumour location, neo-adjuvant regimen, pathological response rate at surgery, length of survival.

- Study characteristics; primary author, publication year, study dates, country of study, study design, number of centres, length of time between interim PET and surgery, length of time between interim PET and surgery, conclusions of study.
- PET/CT characteristics; timing of interim 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, proportion of patients with response after completion of neo-adjuvant therapy.

Outcomes

The primary outcome of the systematic review will be the response rate based on SUVmax following early PET/CT after one cycle of neo-adjuvant therapy. The secondary outcomes will be the response rate following PET/CT after completion of neo-adjuvant therapy and the diagnostic accuracy of PET/CT both early and after completion of neo-adjuvant therapy. Diagnostic accuracy will be defined by calculating sensitivity and specificity, using the reference standard of pathological tumour regression grade. For diagnostic accuracy, responders will be classified at pathology as having a Mandard TRG 1–3 or Becker TRG 1–2 and non-responders as Mandard TRG 4–5 or Becker TRG 3.

Quality assessment and risk of bias

The methodological quality of eligible studies will be assessed using the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS–2) criteria [18], which comprises four domains, each assessing the risk of bias and clinical application. 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 3—QUADAS–2)

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 [19]) using the current version of R (R Foundation for statistical computing, Vienna, Austria) [20]. We will combine the percentage of patients with early and completion treatment response in each individual study to estimate a pooled prevalence with a 95% confidence interval (CI). Sensitivities and specificities of FDG PET in individual studies will also be calculated for early and completion PET/CT examinations, 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 [21]. We will also pool survival data for metabolic responders and non-responders obtaining a median survival time in each group with a 95% CI. We will assess heterogeneity between specific study

estimates using the inconsistency index (I^2 statistic [22]). If heterogeneity is considerable (I^2 > 75%) and the p value <0.1, quantitative data synthesis will not be performed [14]. We will investigate sources of heterogeneity between studies using subgroup analyses by stratifying original co-variates according to methodological quality (QUADAS–2 score), sample size, PET injection time, neo-adjuvant therapy regimen, number of cycles of neo-adjuvant therapy and histopathological response.

Discussion

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

Oesophageal adenocarcinoma is frequently FDG avid. Metabolic response following chemotherapy on serial FDG-PET has been described as a biomarker in this disease. Currently, the most validated metric for PET metabolic response is a reduction in FDG uptake (SUVmax) of 35% on day 15 following cisplatin–5FU based chemotherapy [23, 24]

However, there are several unanswered questions regarding the use of 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 develop on results from previous reviews [13, 25] and specifically focus on the response rate and diagnostic accuracy of early PET/CT in oesophageal adenocarcinoma. The findings of this review will inform planning of future clinical trials by demonstrating the proportion of patients that have a response rate after one cycle of neo-adjuvant therapy and clarify the optimum PET threshold used to define this 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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Velindre University NHS Trust. The funder nor the sponsor have not been involved in the study design or protocol development and will not contribute to data collection, analysis or publication.

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 the guarantor of the review. All authors read and approved the final manuscript.

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