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[18F]FDG PET metabolic parameters for the prediction of histological response to induction chemotherapy in osteosarcoma and Ewing's sarcoma: a systematic review and network meta-analysis

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ADMINISTRATIVE INFORMATION

Support - Nil.

Review Stage at time of this submission - Risk of bias assessment.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202440041

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 April 2024 and was last updated on 08 April 2024.

INTRODUCTION

Review question / Objective The aim of our study is to evaluate and compare the ability of [18F]FDG PET/CT metabolic parameters to predict the histological response to neoadjuvant chemotherapy (NAC) in patients with osteosarcoma and Ewing's sarcoma.
(i) population: children, adolescents and adults with osteosarcoma (OST) or Ewing's sarcoma (EWS) undergoing baseline and/or post-neoadjuvant chemotherapy (NAC) PET/CT with [18F]FDG
(ii) intervention (index test): [18F]FDG PET metabolic parameters: baseline/post-NAC maximum standardized uptake value (SUVmax), SUV ratio (SUV2 [post-NAC]/SUV1 [baseline]), baseline or post-NAC metabolic tumor volume (MTV1, MTV2) and ΔMTV, baseline or post-NAC total lesion glycolysis (TLG1, TLG2) and ΔTLG
(iii) comparator (reference test): histologic assessment using Picci's, Rosen's criteria, and Salzer-Kuntschik grading, including Grade and percentage of necrosis assessment.
(iv) outcomes: responders, non-responders, true positive results, true negative results, false positive results, false negative results, sensitivity, specificity, area under the receiver operating characteristic (AUROC), area under the summary receiver-operating characteristic (AUSROC)
(v) study design: prospective and retrospective cohort studies.

Rationale Osteosarcoma and Ewing's sarcoma present significant challenges in paediatric and adolescent oncology due to their diverse pathological features and clinical behaviours. The ability to predict the histological response to neoadjuvant chemotherapy is crucial for optimizing treatment strategies.

Condition being studied Osteosarcoma, Ewing's sarcoma.

METHODS

Search strategy A comprehensive systematic search was conducted, covering publications from Jan 1, 2008, to Jan 22, 2024. This search

encompassed databases such as PubMed, Medline, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) and was performed by two independent researchers. The search methodology utilized Medical Subject Headings (MeSH). Additionally, we employed forward and backwards snowballing methods for an exhaustive search (Litmaps service).

Participant or population Children, adolescents and adults with osteosarcoma (OST) or Ewing's sarcoma (EWS) undergoing baseline and/or post-neoadjuvant chemotherapy (NAC) PET/CT with [18F]FDG.

Intervention [18F]FDG PET metabolic parameters: baseline/post-NAC maximum standardized uptake value (SUVmax), SUV ratio (SUV2 [post-NAC]/ SUV1 [baseline]), baseline or post-NAC metabolic tumor volume (MTV1, MTV2) and ΔMTV, baseline or post-NAC total lesion glycolysis (TLG1, TLG2) and ΔTLG.

Comparator Histologic assessment using Picci's, Rosen's criteria, and Salzer-Kuntschik grading, including Grade and percentage of necrosis assessment.

Study designs to be included We will include prospective and retrospective cohort studies.

Eligibility criteria We focused on prospective and retrospective cohort studies that investigated the ability of [18F]FDG PET metabolic parameters (SUVmax, MTV, or TLG) to predict the histological response to induction chemotherapy in patients with OST and Ewing's sarcoma.The final inclusion criteria for this study were determined after a thorough full-text article analysis. Studies were excluded if they met one or more of the following criteria: 1) were review articles or clinical cases, 2) reported no relevant outcome data, 3) were animal studies, 4) used other radiopharmaceuticals, or 5) were duplicated publications.

Information sources PubMed, MEDLINE, Google Scholar, Cochrane Library, LitMaps service.

Main outcome(s) Responders, non-responders, true positive results, true negative results, false positive results, false negative results, sensitivity, specificity, area under the receiver operating characteristic (AUROC), area under the summary receiver-operating characteristic (AUSROC).

Quality assessment / Risk of bias analysis The internal validity and risk of bias will be assessed by two independent reviewers using the 'Quality Assessment of Diagnostic Accuracy Studies' (QUADAS-2) tool. Publication bias and small-study effects for NMA will be assessed using Bayesian NMA meta-regression.
The certainty of evidence will be assessed with the GRADE methodology integrated into the CINeMA approach.

Strategy of data synthesis Data extraction will be performed by two independent authors. These data will include: 1) basic study details such as the first author, publication year, country, journal, study design, period, number of centers involved, and sample size; (2) [18F]FDG PET scan data such as PET scanners used, fasting duration, preinjection blood glucose tests, postinjection interval, [18F]FDG dose, and PET/CT timing; (3) patient and tumor specifics, including cancer type, disease stage, tumor location, patient age and sex, histologic assessment method and histologic responder criteria; (4) [18F]FDG PET parameters such as MTV and TLG segmentation methods, SUV type, cut-off determination method and values; and (5) study outcomes (number of responders and nonresponders, sensitivity and specificity).
The predictive ability of [F]FDG PET/CT metabolic parameters will be evaluated through pooled metrics, sensitivity and specificity, along with the summary receiver operating characteristic area under the curve (AUSROC), with the corresponding 95% confidence intervals (CIs) employing the 'midas' and 'metandi' modules in STATA 18.0 software (StataCorp, College Station, TX). Interstudy heterogeneity will be evaluated using the I-squared (I2) statistic and the Cochrane Q test, as recommended by the Cochrane Handbook. The results of the diagnostic test accuracy (DTA) meta-analysis will be presented as forest plots. The statistical significance will be set at 0.05 for hypothesis testing.
A frequentist, random-effects network meta-analysis (NMA) will be conducted using the CINeMA (confidence in network meta-analysis) approach and CINeMA software. Additionally, we will conduct Bayesian random-effects NMA utilizing the ROB-MEN and MetaInsight web applications. Articles will be included in the NMA if they report data on any two or more [18F]FDG PET metabolic parameters.

Subgroup analysis We will analyze the following groups of patients:
1. Children, adolescents and young adults (≥75% of patients are 21 y.o. and younger)
2. Patients with OST, EWS.

Sensitivity analysis Sensitivity analysis will be conducted by evaluating the results of only low/moderate risk of bias studies.

Language restriction No language limitation.

Country(ies) involved Russian Federation.

Keywords osteosarcoma; Ewing's sarcoma; [18F]FDG PET/CT; neoadjuvant chemotherapy; histological response; systematic review; network meta-analysis.

Contributions of each author

Author 1 - Mikhail Yadgarov - collected the data, contributed data and analysis tools, performed the analysis, assessed risk of bias, certainty of evidence rating, wrote the paper.
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