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Prognostic significance of 18F-FDG PET/CT-based metabolic parameters in adults and children with bone sarcoma and Ewing's sarcoma: pairwise and network meta-analysis

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ADMINISTRATIVE INFORMATION

Support - Nil.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 July 2023 and was last updated on 21 July 2023.

INTRODUCTION

Review question / Objective The aim of our study is to investigate the impact of baseline and post-therapy 18F-FDG PET/CT-based metabolic parameters on overall and event-free survival in adults and children with bone sarcoma and Ewing's sarcoma.
(i) population: children, adolescents and adults with bone sarcomas (BS) and Ewing's sarcomas (EWS) undergoing baseline and / or post-neoadjuvant chemotherapy (NAC) 18F-FDG PET/CT
(ii) exposure: high baseline / post-NAC maximum standardized uptake value (SUVmax1 / SUVmax2), low SUV ratio (SUVmax2 / SUVmax1), high baseline or post-NAC metabolic tumor volume (MTV1 / MTV2), high baseline or post-NAC total lesion glycolysis (TLG1 / TLG2) values
(iii) comparator: low baseline / post-NAC SUVmax, high SUV ratio, low MTV1 or MTV2, low TLG1 or TLG2 values
(iv) outcomes: event-free survival (EFS), overall survival (OS)
(v) study design: prospective and retrospective cohort studies.

Rationale The conventional prognostic factors utilized by oncologists in patients with bone sarcoma (BS) and Ewing sarcoma (EWS), such as stage, presence of metastases, histological GRADE, tumor volume, and localization, exhibit limited prognostic efficacy.
The prognostic value of 18F-FDG PET/CT parameters in patients with BS and EWS has previously been studied in several meta-analyses, but patients with BS / EWS and soft-tissue sarcomas were considered together without subsequent subgroup analysis.
The results of some recent studies suggest less prognostic efficacy of PET/CT metabolic parameters in the pediatric population with osteosarcoma and EWS. At the same time, all previous meta-analyses did not consider this patient category separately.
Moreover, a comparative analysis of baseline and post-NAC SUVmax, MTV and TLG prognostic

efficacy has not been performed in previous studies.
Therefore, we decided to perform a systematic review, pairwise and network meta-analysis with additional age-subgroup analysis, thorough sensitivity analysis and GRADE certainty of evidence assessment.

Condition being studied Osteosarcoma, chondrosarcoma, Ewing's sarcoma.

METHODS

Search strategy Systematic literature search of studies published in the past 15 years (2008-2022) was carried out in Medline, PubMed, Google Scholar and Cochrane Library by two independent investigators. Additionally, the forward and backward snowballing methods were used. Medical Subject Headings (MeSH) terms were also applied.

Participant or population Children, adolescents and adults with BS or EWS undergoing baseline and / or post-NAC 18F-FDG PET/CT.

Intervention Exposure: patients with high baseline / post-NAC SUVmax, low SUV ratio, high MTV1 or MTV2, high TLG1 or TLG2 values.

Comparator Patients with low baseline / post-NAC SUVmax, high SUV ratio, low MTV1 or MTV2, low TLG1 or TLG2 values.

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

Eligibility criteria Inclusion criteria: cohort studies which included patients with BS or EWS and investigated the association between 18F-FDG PET-CT metabolic parameters (SUVmax, MTV, or TLG) and survival outcome (OS or EFS). Studies were excluded if they met one of the following criteria: 1) review articles, case reports; 2) other tumors (soft-tissue sarcomas, carcinosarcomas); 3) no relevant outcomes; 4) research on animals; 5) outcomes reported for mixed groups; 6) other radiopharmaceuticals used; 7) duplicated publications.

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

Main outcome(s) The main study outcomes included:
1) Event-free survival
2) Overall survival.

Quality assessment / Risk of bias analysis The internal validity and risk of bias will be assessed by two independent reviewers using the "Tool to assess risk of bias in cohort studies" contributed by the CLARITY Group at McMaster University. Publication bias and small-study effects will be assessed using Bayesian network meta-analysis (NMA) meta-regression, funnel plot and Egger's test analysis. The certainty of evidence will be assessed with GRADE methodology integrated in CINeMA (Confidence in Network Meta-Analysis) approach.

Strategy of data synthesis Data extraction was performed by two independent authors. These data included first author, year of publication, country, journal, design, PET scanners, study period, number of centers, follow-up period, sample size, cancer type, stage of disease, histological grade, tumor location, age and sex, PET/CT time points, segmentation methods for PET/CT parameters, cut-off determination method, and effect estimates for study outcomes.
For pairwise meta-analysis we will use STATA 17 (StataCorp LLC, Texas, US) and Cochrane tool Review Manager (RevMan version 5.3). Hazard ratio (HR) will be used to measure the association between 18F-FDG PET/CT metabolic parameters and survival. Univariate HR values will be extracted directly if available or calculated using Tierney et al. methodology for original studies. Meta-regression analysis using restricted-maximum likelihood (REML) random-effects model will be performed to assess whether the association between exposure and survival outcome varies by patient age, histological grade, tumor location, sex, cut-off value for metabolic parameters and study design.
Network meta-analysis will be performed using CINeMA (Confidence in Network Meta-Analysis) software, ROB-MEN web application and STATA 17.0 software.
Results of pairwise meta-analysis will be presented using forest-plots. NMA results will be presented using network plots, league tables and rankograms. Statistical significance was set at 0.05 for hypothesis testing.

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. Adults (≥75% of patients are over 21 y.o.).

Sensitivity analysis Sensitivity analysis will be conducted by using two models of analysis (fixed and random effects), by analyzing HR obtained in the Cox multivariable regression analysis in the

original studies and by evaluating the results of only low/moderate risk of bias studies.

Language restriction No language limitation.

Country(ies) involved Russian Federation.

Keywords PET/CT, 18F-FDG, osteosarcoma, chondrosarcoma, Ewing's sarcoma, SUVmax, MTV, TLG, survival, 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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