INPLASY PROTOCOL

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Conflicts of interest:
We declare no conflicts of interest exist.

Tumor Budding and Epithelial to Mesenchymal Transition in Colorectal Cancer：A Systematic Review and Meta-Analysis

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Review question / Objective: **What's the clinical siginificance of tumor budding and epithelial to mesenchymal transition in colorectal neoplasms development? We will also try to identify the molecular alterations associated with epithelial to mesenchymal transition.**
Condition being studied: **The process of tumor budding appears to be the result of interactions between tumor cells and other components of the tumour microenvironment. Tumour buds might represent a subset of cells undergoing a partial or hybrid EMT, with features of so¬called 'migrating cancer stem cells. Since the clinical significance of TB and EMT has not yet been fully clarified in colorectal neoplasms, we aim to study its prognostic role with the first systematic review and meta-analysis on this topic.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 May 2020 and was last updated on 01 May 2020 (registration number INPLASY202050003).

INTRODUCTION

Review question / Objective: **What's the clinical siginificance of tumor budding and epithelial to mesenchymal transition in colorectal neoplasms development? We will also try to identify the molecular alterations associated with epithelial to mesenchymal transition.**

Rationale: **Several articles focus on tumor budding and epithelial to mesenchymal transition have been published,the conclusions are quite controversial,thus a meta-analysis and systemic review are urgently needed.**

Condition being studied: The process of tumor budding appears to be the result of interactions between tumor cells and other components of the tumour microenvironment. Tumour buds might represent a subset of cells undergoing a partial or hybrid EMT, with features of so¬called 'migrating cancer stem cells. Since the clinical significance of TB and EMT has not yet been fully clarified in colorectal neoplasms, we aim to study its prognostic role with the first systematic review and meta-analysis on this topic.

METHODS

Search strategy: ("colorectal*" OR "colon*" OR "rect*") AND("cancer*" OR "carcinoma*" OR "neoplasm*" OR "tumour*" OR "tumor*" OR "polyp*" OR "maglignan*" OR "adenoma*" OR "adenocarcinom*") AND("budding" OR "sprouting" OR "tumor-cell dissociat*" OR "tumour-cell dissociat") AND("EMT" OR "epithelial to mesenchymal transition").

Participant or population: Studies were eligible for inclusion upon meeting the following criteria: (1) a prospective cohort or retrospective study design; (2) contained a comparison of prognostic factors between high grade-TB vs. low grade-TB; (3) contained histological diagnosis of colorectal neoplasms with clear microscopic demonstration of TB; (4) contained data about mortality/recurrence of disease; (5) were published in a peer review journal or published abstract. We considered articles in any language. Exclusion criteria were: (1) no presence of colorectal neoplasms, (2) no clear microscopic demonstration of TB, (3) no data about prognostic parameters in the title/abstract, (4) no comparison between high grade-TB vs. low grade-TB patients, and (5) in vitro or animal studies.

Intervention: The number of tumor budding can be divided into high grade and low grade ,which can be regarded as intervention.

Comparator: High grade and low grade tumor budding are as control mutually and the same as the expression of epithelial to mesenchymal transition markers.

Study designs to be included: Cohort studies will be included.

Eligibility criteria: Studies were eligible for inclusion upon meeting the following criteria: (1) a prospective cohort or retrospective study design; (2) contained a comparison of prognostic factors between high grade-TB vs. low grade-TB; (3) contained histological diagnosis of Colorectal neoplasms with clear microscopic demonstration of TB; (4) contained data about mortality/recurrence of disease; (5) were published in a peer review journal or published abstract. We considered articles in English. Exclusion criteria were: (1) no presence of colorectal neoplasms, (2) no clear microscopic demonstration of TB, (3) no data about prognostic parameters in the title/abstract, (4) no comparison between high grade-TB vs. low grade-Tb patients, and (5) in vitro or animal studies.

Information sources: We will search Pubmed,Embase,Web of Science,Cochrane Library.

Main outcome(s): Maybe,high-grade TB has a potentially high clinical significance for the prognostic stratification of colorectal neopalsms.

Additional outcome(s): Maybe, TB shows a clear association with the process of EMT.

Data management: Two or three review authors will perform this independently, and a fourth review author resolved disagreements. We collected the following information about the included studies: study design and setting, study eligibility criteria, participant characteristics, intervention(s) given, outcomes assessed, funding sources, and declarations of interest of the primary researchers. We will use this information to populate the Characteristics of included studies tables.

Quality assessment / Risk of bias analysis: Two or Three review authors independently

will assess risk of bias of included studies using the Cochrane 'Risk of bias' tool ; NT resolved queries or disagreements. We will assess the following risk of bias domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Strategy of data synthesis: All analyses will be performed using Comprehensive Meta-Analysis 2. In our primary analyses, pooled risk ratios (RRs) and 95% confidence intervals (CIs) of risk of mortality and of recurrence between high grade-TB vs. low grade-TB will be calculated using DerSimonian-Laird random-effects models . In secondary analyses, pooled hazard ratios (HRs) with 95% CIs adjusted for the maximum number of covariates available in the articles, are also calculated for providing additional information if the relationship between TB status and outcomes was influenced by potential confounders. Heterogeneity across studies was assessed by the I2 metric and chi square statistics . In presence of significant heterogeneity ($p < 0.05$) after removing outlier studies, we will plan to conduct a series of meta-regression analyses according to TB status and each of prognostic parameters considered. Finally, we will investigate publication bias for our primary meta-analysis with a visual inspection of funnel plots coupled with Egger bias test.

Subgroup analysis: We will use prespecified tests for heterogeneity to compare tumor buddings between subgroups.

Sensibility analysis: We will perform the sensitivity analysis for primary outcomes to evaluate the robustness of meta-analysis results by excluding studies assessed as having 'High' risk of bias (DFS and PFS).

Language: English only.

Keywords: budding; epithelial to mesenchymal transition; EMT; colorectal cancer.

Contributions of each author:

Author 1 - Hui-jie Huang - protocol development, with contribution from all protocol co-authors; co-ordinating the review; study selection; data extraction; risk of bias assessment; correspondence with study authors and study contacts; data analysis; interpretation of data; writing the review.

Author 2 - Ying Zhu - study selection; data extraction; risk of bias assessment; revising the review.

Author 3 - Yong-qin Wen - contribution to protocol development; clinical advice.

Author 4 - Jian-fang He - contribution to protocol development; clinical advice.