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# Evidence mapping of histopathologic classification systems to characterize residual tumor in patients undergoing neoadjuvant treatment for breast cancer, including TNBC

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## ADMINISTRATIVE INFORMATION

**Support -** The study is funded by MSD China.

**Review Stage at time of this submission -** The review has not yet started.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202480026

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 August 2024 and was last updated on 06 August 2024.

## INTRODUCTION

**Review question / Objective** To provide a summary of the current evidence supporting Histopathological evaluation and classification systems to characterize residual tumour in patients undergoing neoadjuvant treatment in breast cancer.

**Condition being studied** Pathological evaluation of neoadjuvant therapy is crucial for assessing early efficacy and determining treatment options and clinical value. Currently, the effectiveness of neoadjuvant therapy is evaluated by assessing histopathologic response in patients, and pathologic complete response (pCR) is considered as a prognostic indicator in clinical trials of neoadjuvant therapy for breast cancer. To evaluate non-pCR, various assessment systems are used, such as the Miller-Payne system, residual cancer burden (RCB), American Joint Committee on Cancer ypTNM (AJCC ypTNM), and Sataloff system. These systems offer standardized frameworks for assessing treatment response and predicting outcomes but may have some heterogeneity, for example, in quantitatively evaluating the extent of residual tumor burden among non-pCR patients.

The relationship between response to neoadjuvant therapy and prognosis has been extensively studied and reviewed, mainly based on pCR. However, the utilization of non-pCR assessment systems to predict progression-free survival (PFS) and overall survival (OS) varies according to patient stratifications or clinical interests15,16. In China, the Miller-Payne (MP) system is widely employed in conjunction with pathologists, while the RCB system is more prevalent in breast cancer neoadjuvant trials. Owing to the importance of early pathological evaluation and the diverse assessment methods and results for non-pCR cases, an evidence-mapping review is necessary. This evidence-based mapping review summarizes the various histopathologic classification systems used to characterize residual tumors in patients undergoing neoadjuvant treatment for breast cancer, including TNBC, thus providing a comprehensive and clear understanding of the

current landscape. This systematic review aims to facilitate evidence-based clinical decision-making regarding the selection of appropriate evaluation systems and to bridge the knowledge gaps in pathological assessment that are observed by pathologists.

## METHODS

**Search strategy** PubMed
#1. "Breast Neoplasms"[Mesh] OR breast cancer*[tw] OR breast Carcinoma*[tw] OR breast gland cancer*[tw] OR breast malignan*[tw] OR malignant breast tumor*[tw] OR malignant breast tumour*[tw] OR malignant breast neoplasm*[tw] OR mammary cancer*[tw] OR mammary gland cancer*[tw] OR mammary malignan*[tw] OR mammary gland malignan*[tw] OR breast adenocarcinoma*[tw]
#2. Early[tw] OR "early phase"[tw] OR "early stage"[tw] OR "stage 0"[tw] OR "stage I"[tw] OR "stage II"[tw] OR "stage III"[tw] OR Ia[tw] OR Ib[tw] OR IIa[tw] OR IIb[tw] OR IIIa[tw] OR IIIb[tw] OR IIIc[tw]
#3. "Neoadjuvant Therapy"[Mesh] OR Neoadjuvan*[tw] OR "neo-adjuvan*"[tw] OR "pre-operati*"[tw] OR preoperati*[tw] OR postneoadjuvan*[tw]
#4. Patholog*[tw] OR Respons*[tw] OR residual[tw] OR Histolog*[tw] OR Cytopatholog*[tw] OR histopatholog*[tw] OR physiopatholog*[tw] OR clinicopatholog*[tw] OR "Miller-Payne"[tw] OR "MP grad*"[tw] OR "MP classific*"[tw] OR residual cancer burden[tw] OR RCB[tw] OR ypTNM[tw] OR TNM[tw] OR AJCC[tw] OR "CREATE-X"[tw] OR Sataloff[tw] OR Chevallier[tw] OR pathCR[tw] OR "non-Pcr"[tw] OR grad*[tw] OR classific*[tw] OR staging[tw]
#5. #1 AND #2 AND #3 AND #4
#6. ("controlled clinical trial"[pt] OR "Controlled Clinical Trials as Topic"[MeSH] OR "Random Allocation"[MeSH] OR "Double-Blind Method"[MeSH] OR "single-blind method"[MeSH] OR "Control Groups"[MeSH] OR "cross-over studies"[MeSH] OR random*[tiab] OR placebo[tiab] OR trial[tiab] OR groups[tiab] OR crossover[tiab] OR cross-over[tiab]) NOT ("Animals"[Mesh] NOT ("Humans"[Mesh] AND "Animals"[Mesh]))
#7. #4 AND #5
Cnki（期刊、学位、会议，中英文扩展：是，中文）
#1. (SU%=乳腺癌+乳腺肿瘤+乳腺恶性肿瘤+乳癌+TNBC OR TKA % 乳腺癌+乳腺肿瘤+乳腺恶性肿瘤+乳癌+TNBC) AND (SU%=新辅助+术前+手术前 OR TKA % 新辅助+术前+手术前) AND (SU%=病理+分级+ "Miller-Payne"+MP分级+MP系统+病理生理+病理学+响应+组织学+组织病理学+组织病理+细胞病理学+生理病理+临床病理+残余肿瘤负荷+残余负荷+ RDBN+ RCB + ypTNM+ AJCC+"CREATE-X"+ Sataloff+ Chevallier+分级+分期+Ⅰ期+Ⅱ期+Ⅲ期+Ia期+IIa期+IIIa期+Ib期+IIb期+IIIb期+IIIc期+AJCC+TNM TKA %病理+分级+ "Miller-Payne"+MP分级+MP系统+病理生理+病理学+响应+组织学+组织病理学+组织病理+细胞病理学+生理病理+临床病理+残余肿瘤负荷+残余负荷+ RDBN+ RCB + ypTNM+ AJCC+"CREATE-X"+ Sataloff+ Chevallier+分级+分期+Ⅰ期+Ⅱ期+Ⅲ期+Ia期+IIa期+IIIa期+Ib期+IIb期+IIIb期+IIIc期+AJCC+TNM)
#2. #1 AND (SU%=随机+盲法+双盲+单盲+三盲+交叉+RCT OR TKA=随机+盲法+双盲+单盲+三盲+交叉+RCT).

**Participant or population** Patients with early-stage breast cancer (including Triple-negative breast cancer, TNBC). Early-stage is defined as clinical stage I-III.

**Intervention** Neoadjuvant therapy, such as chemotherapy, chemotherapy plus immunotherapy, etc.

**Comparator** Not applicable.

**Study designs to be included** Randomized controlled trials (RCTs), only full manuscript will be considered.

**Eligibility criteria** The literature languages are English and Chinese.

**Information sources** The search databases included PubMed, MEDLINE, EMBASE, Cochrane Library, CNKI, and VIP from their inception, without limitations on date/time and document type. If any literature outside of Medline/EMBASE/CNKI/VIP will be reviewed as part of the ESA, it will not include Sponsor marketed product.

**Main outcome(s)** Overview of all histopathologic classification systems to characterize residual tumor, such as Residual Cancer Burden (RCB) , Miller-Payne (MP), etc.

**Additional outcome(s)** Different classification rate% in MP and RCB, etc. by different regimens in different Breast cancer type (If reported).
Efficacy data overview, such as Event-free survival (EFS), Recurrence-free survival (RFS), Progression-free survival (PFS), Overall survival (OS), etc.

**Data management** All data collected for the study should be recorded accurately, promptly, and legibly. For primary data collection, the investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. For data not obtained from a primary source (i.e., secondary data, such as claims and electronic health records), the investigator is responsible for reviewing data quality and relevance to the best of the investigator's knowledge. By signing this protocol either electron.

**Quality assessment / Risk of bias analysis** Two reviewers will independently assess the quality of the included studies using the risk of bias assessment tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions . Specific items that will be assessed included: randomization methods, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective outcome reporting, and other sources of bias. Each item was rated as low risk of bias, high risk of bias, or unclear risk of bias. Any disagreements were resolved through discussions or in consultation with a third reviewer if necessary.

**Strategy of data synthesis** There is no meta-analysis in this review.
To visually represent the landscape of histopathologic classification systems in breast cancer patients, including TNBC, after neoadjuvant therapy, a bubble chart can be utilized. This chart will illustrate the distribution of classification systems based on the specific types of neoadjuvant therapy and drugs used (horizontal axis) and the type of histopathologic classification systems (vertical axis). The color of the bubbles will represent the specific drugs used in neoadjuvant therapy, while the size of the bubbles will represent the sample size of the study. Additionally, the number inside the bubbles will indicate the number of original studies. By creating this bubble chart, a comprehensive overview of the different classification systems utilized in breast cancer research can be obtained.
To summarize the histopathologic classification systems based on efficacy outcome types, a table can be constructed. This table will list the classification systems as rows and the efficacy outcome types as columns. Each cell in the table will indicate the association between a specific classification system and efficacy outcome type, using figures to predict the number of included studies. By organizing the information in this manner, a concise summary highlighting the relationship between different classification systems and efficacy outcome types in breast cancer research can be presented.

**Subgroup analysis** Subgroup analysis will be performed based on different clinical characteristics and biological subtypes of breast cancer patients when data is available, specifically:
1) Luminal A: Hormone Receptor (HR) positive (Estrogen Receptor, ER positive, high Progesterone Receptor, PR, low Ki-67) and Human Epidermal Growth Factor Receptor 2 (HER2) negative.
2) Luminal B: HR positive (ER positive, low PR/high Ki-67) and HER2 negative.
3) HER2 like: HR negative, HER2 positive or HR positive and HER2 positive.
4) Basal-like/TNBC: HR negative (ER/PR megative), HER2 negative.

**Sensitivity analysis** Not applicable. This is an evidence mapping study, not a meta-analysis, hence sensitivity analysis is not applicable.None.

**Language restriction** The literature languages are English and Chinese.

**Country(ies) involved** China.

**Keywords** Early-stage breastcancer; Neoadjuvant therapy; Histopathologic classification systemsv.

**Dissemination plans** Early-stage breastcancer; Neoadjuvant therapy; Histopathologic classification systems.

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