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Progress and Challenges in the Study of Breast Micropapillary Carcinoma: From Pathological Features to Clinical Management

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Abstract

Breast micropapillary carcinoma (MPC) is a distinct subtype of breast cancer defined by unique histological morphology and aggressive biological behavior. It is characterized by tumor cell clusters forming micropapillary or grape-like structures without a fibrous vascular core, accompanied by frequent lymphovascular invasion, high rates of lymph node metastasis, and relatively poor prognosis. This narrative review summarizes the pathological diagnostic criteria, molecular biological characteristics, imaging features, clinical prognostic factors, and current treatment strategies and controversies of MPC. With the development of precision medicine, further elucidation of its molecular mechanisms is crucial to formulate individualized treatment regimens and improve patient survival.

Keywords

Breast Micropapillary Carcinoma, Pathology, Lymphovascular Invasion, Prognosis, Treatment, Research Progress

1. Introduction

Micropapillary carcinoma (MPC) of the breast, first clearly described in 1993, has been recognized as an important breast cancer subtype requiring intensive clinical attention. According to the latest WHO classification, pure MPC accounts for less than 2% of all invasive breast cancers, while mixed forms coexisting with other histologic types are more common. The hallmark of MPC is its characteristic growth pattern with reversed cellular polarity, which is closely related to its aggressive biological behavior, especially a strong propensity for lymphovascular in-

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vasion and early extensive lymph node metastasis. Even in small tumors, this aggressiveness leads to a significantly higher risk of recurrence and mortality [1].

The clinical and pathological importance of MPC has raised important questions regarding its definition as an independent entity, optimal adjuvant systemic therapy strategies, and potential targeted therapies based on its molecular features. These issues remain at the forefront of clinical and basic research as knowledge of MPC continues to evolve. This review focuses on the pathological diagnosis and classification, molecular biology, imaging features, clinical prognostic factors, and current treatment strategies of MPC, aiming to provide a comprehensive overview of this special subtype.

The pathological diagnosis of MPC has been continuously refined. Traditional morphological features and immunohistochemical profiles are crucial for differentiating MPC from other breast cancer subtypes. Classic histological features include micropapillary structures and reversed cellular polarity, which form the basis for accurate diagnosis. Immunohistochemical markers such as E-cadherin and MUC1 further help distinguish MPC from other invasive breast carcinomas. In addition, clarifying the clinical significance of pure and mixed MPC is essential for individualized treatment and prognosis evaluation. The difficulty in differential diagnosis, especially distinguishing MPC from lesions with micropapillary-like structures, highlights the need for continuous optimization of diagnostic criteria and clinical guidelines [2].

With in-depth study of the molecular biology of MPC, genomic and transcriptomic studies have provided important insights into its pathogenesis. High-frequency mutations such as PIK3CA and heterogeneous ER/PR/HER2 status have been reported, which help explain the aggressive behavior and therapeutic sensitivity of MPC. Loss of cellular polarity and epithelial-mesenchymal transition (EMT) are also key events in the development of MPC, suggesting potential therapeutic targets. Furthermore, the tumor microenvironment and lymphangiogenesis play important roles in the metastatic potential of MPC, reflecting the complexity of its biological behavior [3].

In terms of imaging features, mammography and ultrasound manifestations of MPC often overlap with other aggressive breast cancers, increasing the difficulty of preoperative evaluation. Advanced imaging modalities such as MRI have shown value in identifying specific features of MPC, including its tendency for lymphatic invasion [4]. Understanding the imaging features of MPC and their correlation with pathological invasiveness is important for improving preoperative evaluation and surgical planning.

Clinical prognostic factors of MPC are diverse. Lymph node metastasis and lymphovascular invasion are key factors affecting prognosis. Tumor size, histological grade, and the proportion of MPC component in mixed tumors also significantly affect prognosis [5]. Molecular subtyping including Luminal, HER2-enriched, and triple-negative subtypes further refines prognostic evaluation and treatment decision-making. In recent years, attempts to construct multi-parame-

ter prognostic models have aimed to improve predictive accuracy and guide individualized treatment.

Current treatment strategies for MPC remain controversial. Surgical methods including breast-conserving surgery and axillary lymph node management require careful selection due to the high aggressiveness of MPC. The necessity and intensity of adjuvant systemic therapy including chemotherapy, endocrine therapy, and anti-HER2 therapy are still under investigation, and emerging evidence supports the potential value of neoadjuvant therapy. The exploration of new targeted therapies and immunotherapies based on the molecular characteristics of MPC represents a promising direction.

In conclusion, although the understanding of MPC has improved greatly, challenges still exist in clinical management and research. Further efforts to clarify its biological characteristics, optimize diagnostic criteria, and standardize treatment strategies will be crucial to improve the prognosis of patients with this aggressive breast cancer subtype.

2. Micropapillary Carcinoma (MPC) Overview

2.1. Pathological Diagnosis and Classification Evolution

MPC has been recognized since its detailed description in 1993. According to the latest WHO classification, pure MPC accounts for less than 2% of invasive breast cancers, while mixed MPC is more common. The unique pathological feature of MPC—reversed polarity of tumor cell clusters—is closely related to its high frequency of lymphovascular invasion and early lymph node metastasis. With the deepening of research, the diagnostic criteria and classification system of MPC have been gradually improved, distinguishing pure and mixed types, which reflects its clinical complexity and guiding significance for treatment [1].

2.2. Diagnostic Criteria for MPC: A Structured Checklist

MPC diagnosis can be standardized using a practical diagnostic framework:

- **Required histologic features:**
  - Tight tumor cell clusters forming micropapillary or grape-like structures
  - **Reversed cellular polarity**
  - No fibrovascular cores within micropapillary clusters
  - Frequent lymphovascular invasion
- **Recommended immunohistochemical panel:**
  - MUC1/EMA: circumferential or luminal surface staining (reverse pattern)
  - E-cadherin: commonly retained or focally reduced
- **Mandatory pathological reporting elements:**
  - Presence and extent of lymphovascular invasion
  - Lymph node status (number of positive nodes, extranodal extension)
  - Percentage of MPC component in mixed histology tumors

These features enable reliable differential diagnosis from other invasive carcinomas [2] [4].

2.3. Clinical Pathological Significance of Pure and Mixed Types

Pure MPC is associated with higher rates of lymph node metastasis and poorer prognosis compared with most other breast cancer subtypes. Mixed MPC, coexisting with invasive carcinoma of no special type, presents heterogeneity in biological behavior and treatment response. Accurate distinction between pure and mixed forms is essential for risk stratification and individualized treatment decisions [4].

2.4. Differential Diagnosis

Differentiating MPC from lesions with micropapillary-like structures is critical to avoid misdiagnosis. Key points include architectural pattern, cellular polarity, stromal response, and specific immunohistochemical staining profiles. Correct differential diagnosis directly affects prognosis evaluation and clinical management [2].

3. Molecular Biological Characteristics and Pathogenesis

3.1. Genomic and Transcriptomic Features

Genomic studies have identified characteristic molecular alterations in MPC:

- **PIK3CA mutations**: frequent, reported in approximately 40% - 60% of cases
- **ER/PR/HER2 distribution**: Luminal subtype predominates, but HER2 positivity is higher than in conventional invasive ductal carcinoma (IDC)
- Compared with IDC, MPC shows distinct molecular alterations related to cell polarity, adhesion, and invasion

These molecular profiles help explain the highly aggressive clinical course of MPC [3].

3.2. Loss of Cell Polarity and Epithelial-Mesenchymal Transition

Loss of cellular polarity is a defining biological event in MPC. It is closely associated with EMT, which promotes tumor invasion and metastasis. The molecular mechanisms underlying polarity loss and EMT represent potential therapeutic targets for inhibiting progression and metastasis [3].

3.3. Tumor Microenvironment and Lymphangiogenesis

The tumor microenvironment of MPC promotes lymphangiogenesis and facilitates lymphatic metastasis. Interactions between tumor cells and stromal components enhance lymphatic vessel formation and cancer cell dissemination. Targeting the microenvironment and lymphangiogenesis may help reduce metastatic potential [3] [4].

3.4. Driver Genes and Signaling Pathways

Abnormalities in multiple signaling pathways including Notch and Wnt are involved in the pathogenesis of MPC, regulating cell proliferation, differentiation,

and survival. These dysregulated pathways contribute to the aggressive phenotype and may serve as therapeutic targets [4].

4. Imaging Features and Preoperative Assessment

4.1. Mammography and Ultrasound Findings

Mammography and ultrasound typically show irregular masses with non-circumscribed margins, often accompanied by regional lymphadenopathy. These features overlap with other aggressive breast cancers, making preoperative diagnosis challenging [4].

4.2. Value of Breast MRI

MRI provides detailed information on tumor extent, multifocality, and relationship to adjacent structures. It improves preoperative evaluation and surgical planning, especially in patients with suspected extensive disease or lymphatic spread [4] [6].

4.4. Correlation between Imaging and Pathological Invasiveness

Imaging features such as irregular shape, spiculated margins, and abnormal lymph nodes are significantly associated with lymphovascular invasion and lymph node metastasis. Combining imaging and pathological findings improves risk stratification [4].

5. Clinical Prognostic Factors and Predictive Models

5.1. Lymph Node Metastasis and Lymphovascular Invasion

Lymph node metastasis and lymphovascular invasion are the strongest independent prognostic factors in MPC. Their presence is consistently associated with higher recurrence rates and shorter survival in multiple clinical cohorts [4].

5.2. Tumor Size, Histological Grade, and MPC Component Ratio

Tumor size and histological grade are reliable prognostic indicators. In mixed MPC, the percentage of the MPC component is also associated with metastatic risk and prognosis, supporting its routine inclusion in pathology reports [2] [5].

5.3. Prognostic Significance of Molecular Subtypes

Molecular subtyping stratifies MPC prognosis:

- Luminal subtypes: relatively favorable
- HER2-enriched and triple-negative subtypes: more aggressive, poorer outcomes

This stratification supports subtype-adapted treatment [4].

5.4. Multi-Parameter Prognostic Models

Emerging prognostic models integrate clinical, pathological, and molecular fac-

tors to improve risk prediction. Such models help identify high-risk patients who may benefit from more intensive therapy [4].

6. Current Status and Controversies in Treatment Strategies

6.1. Surgical Treatment and Axillary Staging

Surgical treatment includes breast-conserving surgery and mastectomy. Given the high incidence of lymph node metastasis, axillary staging is strongly recommended in almost all MPC patients, regardless of tumor size. Surgical strategy should be individualized based on tumor extent and molecular subtype [4].

6.2. Adjuvant Systemic Therapy

Adjuvant therapy decisions should be based on:

- Lymph node status
- Tumor size and grade
- MPC component percentage
- ER/PR/HER2 status

Evidence from cohort studies and meta-analyses supports more active adjuvant strategies in MPC than in low-risk IDC due to its inherent aggressiveness.

6.3. Neoadjuvant Therapy

Neoadjuvant therapy can reduce tumor stage, increase breast-conserving rates, and provide prognostic information. Patients with high-risk features (large tumor, clinically positive nodes, high MPC component) may particularly benefit [2].

6.4. Radiotherapy Indications

Postoperative radiotherapy is recommended based on:

- Tumor size
- Lymph node involvement
- Surgical margin status

Local regional radiotherapy improves local control, consistent with MPC's high invasive and metastatic potential [4].

6.5. Emerging Targeted Therapy and Immunotherapy

Targeted therapy and immunotherapy are under active investigation. Agents targeting PIK3CA, HER2, polarity regulators, and EMT pathways are promising. Future studies should focus on MPC-specific cohorts to generate high-level evidence [3].

7. Limitations and Future Directions

Current research on MPC has several limitations:

- Low incidence leading to small sample sizes
- Most studies are retrospective and prone to selection bias
- Mixed histology may confound biological and prognostic analyses

- Lack of standardized endpoints and therapeutic guidelines

Future research should focus on:

- Prospective multi-center studies dedicated to MPC
- Multi-omics studies to identify specific diagnostic and therapeutic targets
- Standardized pathological reporting including MPC percentage
- Clinical trials to resolve controversies in adjuvant and neoadjuvant therapy
- Development of MPC-specific prognostic and predictive models

These efforts will promote precise diagnosis and individualized treatment of MPC.

8. Conclusions

As a special subtype of breast cancer, MPC has attracted extensive attention due to its unique pathological features and aggressive clinical behavior. Current studies consistently confirm that lymphovascular invasion and high lymph node metastasis rate are important markers of poor prognosis. Although MPC overlaps with conventional IDC in molecular classification, its distinct aggressiveness suggests unique biological mechanisms that require further exploration.

From a clinical perspective, it is necessary to integrate existing research evidence rationally. Due to the lack of large-scale prospective clinical trials for MPC, current treatment strategies mainly rely on retrospective data and experience based on its high recurrence risk. Future research should use multi-omics strategies to clarify the molecular mechanism of MPC and explore specific therapeutic targets. At the same time, prospective clinical studies are needed to clarify optimal neoadjuvant and adjuvant regimens. The integration of clinical, pathological, and molecular information into prognostic models will help refine risk stratification and realize precise individualized management.

In the future, collaborative research among pathologists, radiologists, surgeons, medical oncologists, and basic scientists will further improve the diagnosis and treatment level of MPC and ultimately improve the long-term survival of patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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