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COMMENTARY

Predictive Pathologic Features of Nodal Metastasis and Tumor Recurrence in HPV-Associated Endocervical Adenocarcinoma

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Introduction

Endocervical Adenocarcinoma (EAC) is the second most prevalent malignancy of the uterine cervix, with a significant portion linked to high-risk HPV infection [1]. The incidence of EAC has risen notably, now accounting for up to 25% of new cervical cancer diagnoses at 1.44/100,000 women in the United States [2]. Overall survival is mainly related to the FIGO (International Federation of Gynecology and Obstetrics) stage with decreased survival in advanced staging.

The primary challenges in treating EAC are Nodal Metastasis (NM) and distant Tumor Recurrence (TR), which are the main causes of treatment failure and mortality [3]. Current prognostic methods and postoperative treatment decisions rely on surgical-pathologic findings and clinical staging [4]. However, due to substantial variability in the biological behavior of EACs within the same stage, predicting the metastatic or recurrent potential of localized tumors remains challenging. Approximately 10-15% of patients with localized tumors develop NM and/or TR, with a median 5-year overall survival rate of 51-78% [5,6]. Therefore, identifying a practical method to accurately distinguish between high-risk and inert localized tumors is crucial for clinical decision-making. Such a method would theoretically allow clinicians to identify those patients who would benefit the most from a more conservative approach to therapy or those requiring aggressive multimodal treatment from the beginning.

Current Limitations

Classification based on HPV status provide substantial prognostic information but is less useful within the HPV-associated subgroup [1,7]. Similarly, tumor grading in HPVA EAC is an unresolved and controversial issue with no validated and universally accepted grading system and with no consensus regarding its prognostic value [1,8,9].

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One practical advance that has garnered a significant recent interest is the invasive tumor growth pattern (hereafter referred to as the Silva pattern system). This system was developed by gynecologic pathologists with the intention of identifying tumor parameters that are easily recognized at the time of pathologic examination and which may provide information regarding the risk of NM, TR, and overall survival [10-12]. By evaluation of Silva patterns, HPV-Associated (HPVA) EACs are sorted into patterns A, B and C, depending on a variety of histologic features, most notably the extent and destructiveness of stromal invasion. Importantly, pattern a tumors reportedly do not metastasize to lymph nodes and do not recur, while pattern B tumors show about a 5% rate of nodal metastasis. Pattern C cases, however, may behave aggressively and display nodal metastasis in a significant proportion of patients [10-12].

The potential practical clinical application of this system is that carefully selected patients with pattern a tumors may be spared lymphadenectomy, while those with pattern B and C cancers are most likely to benefit from complete surgical staging with nodal dissection and radical hysterectomy, as well as adjuvant treatment when indicated. However, studies about the predictive value of the Silva patterns were primarily based on studies of full surgical resection specimens where regional lymph nodes had been dissected and the uterus, cervix, as well as the entire primary tumor had been removed. Silva pattern evaluation requires a substantial amount of tumor tissue and the presence of adjacent stroma to make a confident classification, and as such is suboptimally applicable to biopsies, predicting the true Silva pattern in only 37.5% of cases [12].

Recent Studies

Recent studies have underscored the prognostic significance of specific histologic features, namely Tumor Nuclear Grade (TNG) and the presence or absence of Necrotic Tumor Debris (NTD), in predicting Nodal Metastasis (NM) and Tumor Recurrence (TR) [13-16]. Although three of these studies [13-15] were based on relatively small datasets, the findings consistently support the potential of these features in clinical practice. The most notable study, a multi-institutional effort, involved 794 specimens from 397 patients treated at 19 institutions [16]. This study aimed to determine if these microscopically identifiable features from cervical biopsy specimens could reliably predict NM and patient outcomes in EAC cohorts.

The multi-institutional study by Wang Y, et al. [16] employed multivariate analysis along with extensive clinical follow-up data. The study aimed to identify EAC patients with minimal or negligible risk factors for NM and TR, which could support the consideration of conservative or fertility-preserving surgeries. The findings demonstrated that the presence of TNG1, the absence of NTD, or a combination of both, correlated with very low incidences of NM and TR, and these features were not associated with any fatalities from the disease. When comparing TNG1 cases to TNG2/3 cases, TNG1 cases had significantly reduced frequencies of lymphovascular space invasion, NM, and TR, and they were linked with lower FIGO stages and better survival outcomes in both univariate and multivariate analyses.

Similarly, tumors lacking NTD exhibited a lower likelihood of NM, TR, or death from the disease compared to tumors with NTD. When combining the absence of NTD with the presence of TNG1, the prognostic impact was notably significant. Among the 73 biopsies that exhibited this combination of features, none (0%) were associated with nodal metastases, and only one case (1.4%) experienced recurrence. The biopsy from the single recurrent case did not capture the most severe tumor characteristics, as the resection revealed Silva pattern C invasion along with high nuclear grade and NTD.

These findings highlight both the strengths and limitations of these histologic features when assigned in biopsies. A TNG1 and NTD-negative profile in a biopsy appears to predict a subset of HPV-associated EAC patients with negligible (0% in this cohort) risk for nodal metastases and a low risk (1.4%) of tumor recurrence. However, biopsies may not capture the most adverse histologic features in some cases. This underscores the importance of comprehensive histologic evaluation and suggests that while these features can significantly aid in risk stratification, they should be considered alongside other clinical and pathological factors.

Conclusion and Future Directions

The multi-institutional study using multivariate analysis and clinical follow-up data confirmed that the presence of TNG1, the absence of NTD, or both are associated with very low NM and TR rates and no deaths from the disease [16]. These findings suggest that a combination of TNG1 and the absence of NTD can identify a subset of HPV-associated EAC patients with negligible NM risk and low TR risk.

Such a predictive method could guide conservative treatment approaches, potentially preserving fertility and reducing the incidence of lymphedema in early-stage endocervical adenocarcinoma patients with negative lymph nodes [17]. Prospective clinical trials in well-prepared institutions, particularly comprehensive cancer centers, are essential to validate these histologic approaches before their clinical application. Accurate identification of NTD and TNG under a microscope is critical.

An accurate and practical predictive method applicable before primary surgery would allow for a more nuanced risk stratification and preoperative counseling, including fertility-sparing treatment options. Incorporating these prognostic factors into management guidelines could enhance the current FIGO staging system by adding these histopathological criteria, which would provide a more comprehensive assessment of tumor behavior and patient prognosis.

For instance, patients identified with TNG1 and absence of NTD could be classified in a distinct sub-stage within early-stage EAC, signaling a lower risk of metastasis and recurrence. This would help tailor treatment plans more precisely, allowing some patients to opt for less aggressive treatments while still maintaining excellent survival outcomes. Furthermore, these features could be integrated into post-operative decision-making processes to determine the necessity and extent of adjuvant therapies.

Ultimately, refining the staging system and treatment guidelines to incorporate these prognostic factors could lead to a paradigm shift in managing EAC, promoting more personalized and effective treatment strategies. By focusing on individual tumor characteristics, clinicians can better predict outcomes and optimize therapeutic approaches, improving overall patient care and survival rates.

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