The Prognostic Significance of Lymph Node Status and Local Tumor Factors in Stage IIIC Cervical Cancer: A Systematic Review

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Abstract：Cervical cancer (CC) remains a significant global health challenge, posing a significant threat to women's lives and well-being. Lymph node metastasis (LNM) is the primary pathway for the spread of cancer in CC and serves as a crucial prognostic factor, as well as a key consideration in treatment decisions. In 2018, the International Federation of Gynecology and Obstetrics (FIGO) updated its staging system to provide a more detailed classification of early-stage disease and to refine lymph node staging criteria. A notable change was the reclassification of all lymph node metastases into stage IIIC, which is further divided into stage IIIC1 (pelvic lymph node metastasis) and stage IIIC2 (para-aortic lymph node metastasis). However, the current staging system relies solely on the anatomical location of metastatic lymph nodes and does not consider other important factors such as the status of the lymph nodes or characteristics of the primary tumor. This limitation may reduce the staging system's prognostic accuracy and its ability to effectively guide treatment. This study aims to explore how various lymph node status parameters and primary tumor characteristics influence prognosis in stage IIIC cervical cancer. Specifically, the research will focus on factors such as primary tumor size, the number and size of metastatic lymph nodes, the lymph node ratio, and the log odds of positive lymph nodes to better understand their prognostic significance.

Keywords: FIGO Staging;Cervical Cancer Stage IIIC; Lymph Nodes; Prognosis

1. Overview and Controversies of FIGO 2018 Stage IIIC Cervical Cancer

1.1 Updates in FIGO 2018 Stage IIIC Cervical Cancer

According to the latest GLOBOCAN 2022 data, cervical cancer is the fourth most common malignancy in women worldwide in terms of both incidence and mortality [1]. Most cervical cancer cases are diagnosed at an advanced stage, with 5-year overall survival (OS) rates ranging from 83% in stage IB to 32% in stage IVA. Lymph node metastasis (LNM) is a significant adverse prognostic factor [2]. In 2018, the International Federation of Gynecology and Obstetrics (FIGO) revised the cervical cancer staging system, reclassifying all cases with LNM as stage IIIC, regardless of primary tumor size or extent. This stage is further subdivided into:IIIC1: pelvic lymph node metastasis (PLNM).IIIC2: para-aortic lymph node metastasis (PALNM) [3, 4].

The updated staging also integrates pathological and radiological findings with traditional clinical assessments, using "r" or "p" notations to indicate radiological or pathological confirmation of LNM.

1.2 Diagnosis and Treatment Strategies for FIGO 2018 Stage IIIC Cervical Cancer

The 2024 National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with radiologically confirmed IIIC1 disease undergo pelvic external beam radiotherapy + vaginal brachytherapy + concurrent platinum-based chemotherapy and immunotherapy ± para-aortic lymph node irradiation. Para-aortic lymphadenectomy (PAL) is also recommended for pathological staging to guide radiation fields, avoid over- or under-treatment, and improve prognosis through resection of bulky metastatic nodes [5].

However, indiscriminate surgical resection or extended irradiation may increase the risk of postoperative complications and radiotherapy toxicities (e.g., radiation enteritis, cystitis) [6]. Therefore, accurate pretreatment staging is essential to identify patients who will truly benefit from lymph node irradiation. Imaging modalities such as CT, MRI, and PET-CT are useful for evaluating lymph node involvement. Studies report sensitivities ranging from 65% to 80% for these techniques, with contrast-enhanced MRI being the preferred method for assessing locally advanced cervical cancer (LACC) and nodal status [7, 8].

1.3 Rationality and Prognostic Controversies of FIGO 2018 Stage IIIC

Although the FIGO 2018 staging system reduces discrepancies with the TNM system by incorporating nodal status, it creates a highly heterogeneous stage IIIC group. Numerous studies have demonstrated significant variability in OS and progression-free survival (PFS) among IIIC patients. For instance, survival rates in IIIC1 (PLNM only) and even IIIC2 (PALNM) patients are often comparable to or better than those in stages IIIA and IIIB [9–12]. This heterogeneity may stem from the system's reliance solely on nodal location rather than additional factors such as the number or size of metastatic nodes, as used in other solid tumors. This limitation may reduce the accuracy of prognostic prediction. Furthermore, although nodal status significantly influences prognosis, local tumor diameter and depth of invasion also play crucial roles [13, 14]. Therefore, comprehensive evaluation incorporating local tumor size and other nodal parameters remains an important direction for refining treatment strategies and prognostic assessment.

2. Lymph Node-Related Parameters and Prognostic Impact in Stage IIIC Cervical Cancer

2.1 Location of Positive Lymph Nodes

The 2018 FIGO update emphasizes the importance of nodal location. PALNM is associated with higher risks of recurrence and distant metastasis compared to PLNM. Long et al. reported significantly worse 5-year OS in IIIC2 than IIIC1 patients (54.1% vs. 23.1%, $P < 0.01$), with IIIC2 being an independent risk factor for mortality [15]. A meta-analysis of 25 studies by Han et al. confirmed worse 5-year OS and disease-free survival (DFS) in patients with PALNM compared to those with PLNM only [16]. The 2018 staging effectively distinguishes survival outcomes based on nodal location, underscoring the importance of anatomical site in prognostic stratification [17, 18]. Accurate assessment of nodal involvement is critical for selecting appropriate treatments and minimizing adverse effects.

2.2 Number of Examined Lymph Nodes (nELN)

The number of lymph nodes removed may also affect prognosis. The 2024 NCCN guidelines recommend removing at least 10–15 nodes for accurate staging, while other guidelines emphasize surgical thoroughness over a specific count [5]. Yong et al. identified nELN as an independent prognostic factor for 5-year OS in LACC, with ≥8 nodes required for improved long-term survival, though no additional benefit was observed beyond 17 nodes [19]. Jiang et al., in a retrospective analysis of 1101 patients who underwent radical hysterectomy and pelvic lymphadenectomy, found that extensive dissection ($nELN \geq 40$) reduced recurrence and improved survival in high-risk patients (e.g., parametrial invasion, large tumor size), while moderate dissection ($nELN \approx 27$) improved outcomes and reduced lymphedema in low-risk patients [20]. However, Wang et al. and Ditto et al. found no direct correlation between nELN and survival [21, 22]. Adequate nodal sampling improves staging accuracy and influences survival and recurrence risk, whereas excessive dissection may lead to complications such as lymphedema, lymphocyst formation, or lower limb dysfunction [23, 24]. The growing use of sentinel lymph node biopsy may reduce unnecessary systemic dissection in early-stage patients and provide more precise guidance for adjuvant therapy.

2.3 Number of Positive Lymph Nodes (nPLN)

The number of positive lymph nodes is another key prognostic factor. Guo et al. compared the prognostic performance of four parameters—2018 FIGO staging, nPLN, lymph node ratio (LNR), and log odds of positive

lymph nodes (LODDs)—and found that all significantly influenced PFS and OS, with nPLN demonstrating the best prognostic value and an optimal cutoff of 5 [25]. A single-center study of 3732 cervical squamous cell carcinoma patients classified nPLN into three groups: PLN0 (0), PLN1 (1–5), and PLN2 (>5). The 5-year OS rates were 94.1%, 85.1%, and 61.8%, and PFS rates were 90.6%, 71.7%, and 42.2%, respectively [26]. Other studies have proposed different cutoffs: the KROG-1504 study categorized metastatic pelvic lymph nodes (MPLN) into 0, 1–3, and >3, finding worse DFS in patients with >3 MPLN [27]. Another study of patients receiving definitive chemoradiation for advanced disease found that ≥3 metastatic nodes on MRI/PET-CT was associated with worse 3-year OS (37.8% vs. 69.8%, $P < 0.05$) [28]. Although increased nPLN generally indicates poorer prognosis, imaging-based assessment remains limited by false positives and negatives. Some studies suggest that extensive lymphadenectomy improves survival in node-negative early-stage patients but not in node-positive cases. Thus, the prognostic value and optimal cutoff of nPLN require further validation.

2.4 Lymph Node Ratio (LNR)

LNR, defined as the ratio of positive nodes to the total number examined, reflects both metastatic burden and extent of dissection. Theoretically, LNR reduces staging bias due to variability in nodal yield. Some studies suggest that LNR is a more objective prognostic indicator than nPLN alone in node-positive cervical cancer [29, 30]. A retrospective study of 3135 stage IIIC patients from a Chinese database identified an LNR cutoff of 0.11, with LNR > 0.11 associated with worse OS and DFS [31]. However, cutoffs vary across studies: KROG 15-04 used 0.17, with higher LNR predicting worse DFS and increased recurrence risk [27]. A meta-analysis of 3325 patients with pathologically confirmed LNM reported a median LNR of 0.0625 [32]. As a ratio, LNR mitigates confounding from variable nodal counts and offers an intuitive, easily calculable metric for risk stratification. However, with the widespread adoption of minimally invasive surgery (MIS), LNR may not accurately reflect true nodal burden. Kim et al. found that high LNR correlated with increased recurrence, particularly in the MIS group, possibly due to incomplete dissection [33]. Limited dissection may inflate LNR even with few positive nodes, while extensive dissection may lower LNR. Thus, reliable LNR assessment requires adequate nodal retrieval, and optimal nodal count remains debated, warranting further well-designed clinical studies.

2.5 Log Odds of Positive Lymph Nodes (LODDs)

LODDs is calculated as $\log[(nMLN + 0.5) / (nELN - nMLN + 0.5)]$, where nMLN is the number of metastatic lymph nodes. This parameter minimizes the impact of nodal count on prognosis. Kown et al. analyzed 50 node-positive patients receiving adjuvant chemoradiation after radical surgery and found LODDs to be the strongest predictor of DFS and the only significant prognostic factor for OS [34]. A SEER-based study confirmed LODDs as an independent prognostic factor and developed a predictive nomogram for stage IIIC patients, showing worse outcomes with higher LODDs and good accuracy in OS prediction [35]. Compared to nPLN and LNR, LODDs improves prognostic precision through nonlinear assessment, particularly in cases with limited dissection, extreme values, or need for nuanced risk stratification. It can differentiate patients with identical LNR, refining prognostic granularity and supporting personalized treatment planning.

3. Local Tumor Factors in Stage IIIC Cervical Cancer

Previous studies indicate that although LNM is a key prognostic factor, classifying all node-positive patients into the same stage introduces heterogeneity that may compromise prognostic accuracy. Prognosis in cervical cancer is also closely tied to primary tumor T-stage. Ye et al. analyzed 4086 stage IIIC patients from 47 Chinese hospitals (2004–2018) and found that 5-year OS and DFS decreased with higher T-stage (OS: T1–81.7%, T2a–75.8%, T2b–86.3%, T3–64.7%; DFS: T1–74.3%, T2a–64.9%, T2b–64.0%, T3–61.1%). Neoadjuvant chemotherapy plus surgery was inferior to radical hysterectomy in T1–T2b patients, while definitive chemoradiation outperformed surgery in T2b cases [36]. Similarly, Matsuo et al., using SEER data from 6888 IIIC1 patients, found significant survival variation by T-stage

(T1–74.8%, T2–58.7%, T3–39.3%), with a 35.5% absolute difference between T1 and T3 (P < 0.001)[9].Theselarge-scale studies highlight substantial heterogeneity within stage IIIC, emphasizing the prognostic importance of tumor burden. Beyond T-stage, tumor size is also critical. Liu et al. reported that patients with primary tumor diameter >4 cm had twice the risk of disease progression compared to those with smaller tumors [14]. Michihide et al. also linked larger tumors (>4 cm) to worse PFS [37]. These findings raise the question of whether IIIC1 should be subclassified into IIIC1a (PLNM with T2b or lower) and IIIC1b (beyond T2b) to better reflect the impact of primary tumor burden.

4. Conclusion

An optimal staging system should maximize homogeneity within stages, ensuring similar prognoses and guiding uniform treatment strategies. The current FIGO 2018 stage IIIC, based solely on nodal location, overlooks primary tumor characteristics and other nodal parameters, leading to prognostic inconsistencies and intra-stage heterogeneity. Both nodal status and primary tumor factors significantly influence outcomes, underscoring the need for accurate pretreatment evaluation to tailor individualized therapies and improve survival and quality of life. Prior to the 2018 revisions, many early-stage node-positive patients primarily underwent radical surgery, and much existing evidence derives from such cohorts. Post-revision, stage IIIC patients are more likely to receive concurrent chemoradiation (CCRT), and outcomes based on this approach require further validation. Future research should focus on refining staging strategies, identifying high-risk subgroups, and developing personalized treatments to enhance the precision and applicability of the staging system.

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