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Treatment Strategies and Prognostic Factors of 2018 FIGO Stage IIIC Cervical Cancer: A Review

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Abstract

Cervical cancer is the fourth most common malignant tumor globally in terms of morbidity and mortality. The presence of lymph node metastasis (LNM) is an independent prognostic factor for progression-free survival (PFS) and overall survival (OS) in cervical cancer patients. The International Federation of Gynecology and Obstetrics (FIGO) staging system was revised in 2018. An important revision designates patients with regional LNM as stage IIIC, pelvic LNM only as stage IIIC1, and para-aortic LNM as stage IIIC2. However, the current staging system is only based on the anatomical location of metastatic lymph nodes (LNs). It does not consider other LN status parameters, which may limit its prognostic significance to a certain extent and needs further exploration and confirmation in the future. The purpose of this review is to summarize the choice of treatment for stage IIIC cervical cancer and the effect of different LN status parameters on prognosis.

Keywords

cervical cancer, lymph node, FIGO stage, concurrent chemoradiotherapy, surgery, prognosis

Abbreviations

CCRT, concurrent chemoradiotherapy; CT, computed tomography; DFS, disease-free survival; DWI, diffusion-weighted imaging; EBRT, external beam radiotherapy; EFRT, extended-field radiation; EF-IMRT, Extended-field intensity-modulated radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; IMRT, intensity-modulated radiation therapy; LNM, lymph node metastasis; LNs, lymph nodes; LNR, lymph node ratio; LODDS, log odds of positive lymph nodes; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NACT, neoadjuvant chemotherapy; OS, overall survival; PET-CT, positron emission tomography/computed tomography; PFS, progression-free survival; RLNs, removed lymph nodes; SEER, Surveillance, Epidemiology, and End Results Program

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Introduction

Cervical cancer, a malignancy of the cervix, is the fourth most common cause of cancer and the fourth most common cause of death from cancer in women worldwide. There are 265,700 deaths from cervical cancer each year, 90% of which occur in developing countries.[1] The standard treatment of cervical cancer mainly includes radical hysterectomy and concurrent chemoradiotherapy (CCRT) combined with adjuvant chemotherapy according to the specific treatment.[2] Generally, the treatment plan is formulated according to the International Federation of Gynecology and Obstetrics (FIGO) stage, and surgery is typically reserved for early stage disease, fertility preservation, and smaller lesions, such as stages IA, IB1, and selected IIA1 cases. At the same time, CCRT is generally the primary treatment choice for locally advanced cervical cancer (IB2-IVA stage). Systemic therapy is generally adopted for patients with stage IVB disease.[2] Despite the maximum treatment as mentioned above, the 5-year recurrence rate of patients with cervical

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cancer is 20% to 50%, and the pathological type, tumor size, FIGO stage, and lymph node metastasis (LNM) are the parameters that could lead to recurrence.[3–5] LNM is an independent prognostic factor for progression-free survival (PFS) and overall survival (OS) in early and locally advanced diseases and has been used to help guide postoperative adjuvant therapy.[6]

In the FIGO 2018 cervical cancer staging guidelines, patients with positive lymph nodes (LNs) are classified as stage IIIC, irrespective of the tumor size and extent.[7] Disease with pelvic LNM only is considered stage IIIC1, and that with para-aortic LNM is considered stage IIIC2. When LNM was diagnosed by pelvic magnetic resonance imaging (MRI), abdominal computed tomography (CT), or fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT), the stage was IIICr, while LNM was IIICp when confirmed by a pathological examination.[1] The 2019 National Comprehensive Cancer Network (NCCN) guidelines further emphasized modern cross-sectional and functional imaging, such as CT, MRI, and PET-CT, in the diagnosis and staging of cervical cancer and further affected the formulation of the treatment plan and the prognosis of cervical cancer.[2] Abdominopelvic CT and MRI are performed to evaluate retroperitoneal and pelvic lymphadenopathy (stage IIIC), and the diagnosis of lymphadenopathy by CT or MRI is generally based on morphology. There is variability in the literature on the acceptable size of the cut-off value, which ranges between 0.8 cm and 1.0 cm in short-axis measurements. When adding functional MRI sequences such as diffusion-weighted imaging (DWI), the lesion detection ability could be improved. For example, LNM is shown as markedly high signal intensities compared to the surrounding structure of normal vessels and bowel loops on DWI, and the corresponding ADC diagram shows low signal changes, making it easy to identify.[8] A LN is considered positive for metastasis when it is within the anatomic nodal drainage pathway for the primary tumor and demonstrates greater tracer uptake than normal LNs elsewhere on the PET-CT scan.[9] Generally, LNs with short diameter lines greater than 0.5 cm and a SUV_{max} >2.5 are designated as positive diagnostic criteria for LNM.[10] FDG PET-CT is more accurate for assessing LN status than CT or MRI in locally advanced cervical carcinoma.[11] In addition, because of its sensitivity in depicting LNM, PET and PET/CT can well predict disease-specific survival.[12]

Some studies have confirmed the positive effect of 2018 FIGO staging on the prognosis of cervical cancer.[5,13] However, the current staging system is only based on the location of LNM. It does not consider the No. of LNs, which might limit the accuracy of its prognostic significance to some extent. The LN staging of many other solid tumors usually depends on the location and the No. of nodules involved.[14–16] Although the presence of LNM greatly influences the prognosis of cervical cancer, survival is also strongly influenced by the extent of the local tumor.[17–19] For example, the survival rate of patients with pelvic LNM (stage IIIC1) was superior to that of women with stages IIIA and IIIB tumors and was closer to the survival rate of women with stage II cervical cancer. Even among women with para-aortic LNM (stage IIIC2), survival rates overlapped with those of women with stages IIIA to IIIB tumors.[20] Given previous studies, including all patients with LNM in the same stage would lead to heterogeneity.[20,21] Therefore, for patients with stage IIIC disease, the influence of LN-related factors on prognosis and the choice of individualized treatment is vital. This article mainly reviews the choice of treatment methods for 2018 FIGO IIIC stage cervical cancer and the influence of LN-related indices on prognosis.

Methods

Data for this review were identified by searches of the PubMed database, "similar articles" via PubMed, and hand searches of reference lists. English published articles were selected between 2000 and October 2021. The electronic search strategy incorporated the following keywords, including various synonyms: "Uterine Cervical Neoplasms", "International Federation of Gynecology and Obstetrics", "Lymph Nodes", "IIIC stage", "treatment", "radical hysterectomy", "radiotherapy", "chemoradiation therapy", "concurrent chemo-radiotherapy", "external beam radiation therapy", "overall survival", "progression-free survival", "survival", "recurrence", "adverse events", "Risk factors", "Prognostic Factors", "Magnetic Resonance Imaging", "computed tomography", "disease-free survival", "Diffusion Magnetic Resonance Imaging", "Positron Emission Tomography Computed Tomography", and "Prediction Model". See Supplementary Table 1 for the complete list of search terms. Only studies in English were included. The eligibility of the identified reports by electronic searches was assessed by titles and abstracts.

Results

Treatment Based on Radical Surgery

Adjuvant CCRT After Radical Hysterectomy and Lymphadenectomy. According to the NCCN guidelines, for early cervical cancer with LNM, adjuvant CCRT is the standard treatment that can improve OS.[2] Several single-arm studies have shown that postoperative adjuvant CCRT can significantly increase 5-year OS and improve the prognosis for early cervical cancer patients with high-risk factors (eg parametrial invasion, LNM, and surgical margins involvement).[22–24] Peter's and Rosa's studies have shown that postoperative CCRT can better improve the OS of patients with high-risk cervical cancer than pelvic radiation therapy alone as adjuvant therapy.[25,26] A recent population-based cohort study compared the recurrence-free survival, patient characteristics, and OS of postoperative radiotherapy (n = 253), postoperative chemotherapy (n = 319), and postoperative CCRT (n = 502), and its results showed that postoperative chemotherapy had similar survival results compared with postoperative CCRT for early cervical cancer with LNM, but when the tumor exhibits multiple factors, especially nonsquamous histology and parametrial involvement, it is reasonable to recommend CCRT as adjuvant therapy.[27]

Adjuvant CCRT After Radical Hysterectomy and Lymphadenectomy + Consolidation Chemotherapy. Patients with LNM are more likely to have distant metastasis after treatment, as short durations of chemotherapy in CCRT may not effectively eradicate potential undetected distant micrometastases. This highlights the need for consolidation chemotherapy that follows CCRT for distant disease control in certain very high-risk groups (eg multiple pelvic LNM, bilateral pelvic wall LNM, or parametrial invasion at the same time, etc.).[28] Zhong et al conducted a retrospective study of early cervical cancer; one group underwent adjuvant CCRT (n = 49), and the other group received three cycles of platinum-based consolidation chemotherapy following CCRT (n = 89). The results showed that for patients with LNM >3 or >2 + lymphovascular space invasion/≥1/3 stromal invasion, disease-free survival (DFS) and OS were superior in the consolidation chemotherapy group compared with the CCRT alone group. Still, consolidation chemotherapy was related to grade 3/4 myelosuppression.[29] Kwon et al also reported that pelvic LNM>3 increases the risk of distant metastasis and shortens tumor-free survival, which requires adjuvant CCRT plus chemotherapy.[30] Another study also proved that consolidation chemotherapy after radical hysterectomy + adjuvant CCRT could improve DFS in early stage cervical cancer patients with LNM.[31] A population-based cohort study using the Surveillance, Epidemiology, and End Results Program (SEER) showed that CCRT could not improve OS compared with radiotherapy alone for women with stage T1-2 cervical cancer with pelvic LNM. They suggested that the presence of LNM represents systemic disease with microscopic tumor spread. Current treatments may be inadequate in this setting because radiotherapy may not eliminate these tumors located outside of the radiation field, and the chemotherapy dose and regimen for radiosensitization may not be adequate to eliminate these tumors; thus, a treatment strategy with CCRT followed by systemic chemotherapy may need to be considered in this highest high-risk group.[32]

Radical Hysterectomy and Pelvic Lymphadenectomy + Adjuvant Chemotherapy. LNM is considered as a systemic disease with microscopic tumor spread. When LNM is diagnosed, systemic spread or micrometastases have occurred. In these cases, local treatment may not be enough. Therefore, some researchers recommended that systemic therapy is more effective for patients with pelvic LNM than local therapy. Adjuvant chemotherapy can effectively control distant metastasis and achieve the same OS and DFS as adjuvant RT or adjuvant CCRT but with a lower incidence of complications and is expected to become an alternative therapy for adjuvant CCRT in some patients with high-risk factors.[27,33–35] This can be particularly applicable to women who are not candidates for pelvic radiotherapy after surgery, for example, due to extensive pelvic adhesive disease or substantial intraoperative pelvic organ injury (eg urinary tract, intestinal, and vascular) and with fewer risk factors (eg nonsquamous histology, parametrial involvement, and high lymph node ratio [LNR]).[27] A multicenter phase II study evaluated the efficacy and safety of postoperative chemotherapy in patients with LNM, and the results suggested that postoperative chemotherapy could be a standard treatment in patients with 1 or 2 metastatic nodes.[36]

Neoadjuvant Chemotherapy + Surgery. Surgery for large tumors (≥4 cm) is complicated because large tumors usually lead to tumor invasion, and there is no clear boundary between the tumor and the surrounding tissues. Neoadjuvant chemotherapy (NACT) may improve the surgical resection rate for these patients and inhibit distant metastasis by eliminating micrometastases. NACT plus surgery, which could reduce LNM and even achieve longer 5-year DFS and OS, may represent a new therapeutic option for stage IIIC cervical cancer.[37,38] A systematic review and meta-analysis showed that in stages IB1 to IIB, preoperative NACT plus radical surgery resulted in a 23% probability of LNM, which was lower than those receiving radical surgery only. In stages IIA and IIB, the effect of NACT on reducing LNM was more obvious.[38] Another review reported the efficacy of NACT in the treatment of locally advanced cervical cancer, which showed that NACT reduced LNM and the tumor diameter in patients before surgery and the No. of high-risk patients who required postoperative radiation therapy.[39]

Based on CCRT

CCRT. CCRT was generally the primary treatment choice for stages IB2, IIA2, and IIB to IVA diseases. After revising the FIGO stage in 2018, CCRT was used for stages IB3 to IVA, including new stage IIIC diseases.[40] A previous study suggested that intensity-modulated radiation therapy (IMRT) and intracavitary brachytherapy with CCRT provided favorable treatment outcomes in cervical cancer patients with CT-based pelvic LNM.[41] Park et al found no differences in the oncologic outcomes between CCRT and radical hysterectomy followed by tailored adjuvant therapy in patients with early cervical cancer presenting with pelvic LNM; however, 88.7% of patients required adjuvant radiotherapy after surgery, these findings suggest that CCRT can avoid unplanned tri-modality therapy without compromising oncologic outcomes.[42] Standard radiation therapy fields for cervical cancer include the whole pelvis, external iliac, internal iliac, and presacral LNs.[43] Compared with standard radiation therapy, highly conformal therapy, such as IMRT, has the potential to reduce radiation-induced toxicity.[44] However, the quality of highly conformal therapy depends on the accurate delineation of regions at risk. A few positive common iliac nodes, external iliac and internal iliac LNs somewhat lateral to the standard radiation therapy fields, which could be at risk for undertreatment in several cases. PET-CT could identify these nodes and avoid this risk.[43] PET-CT can also identify uncommon regions: the presacral, perirectal, and medial inguinal regions.[43]

CCRT + Adjuvant Chemotherapy. Patients with LNM showed significantly higher rates of distant metastases than those with negative LNs, and adjuvant chemotherapy after standard CCRT is an option to eradicate residual tumors beyond the pelvis in these cases.[45] Abe et al found that adjuvant chemotherapy after CCRT exhibited no benefit to patients with pelvic LNM; however, it may be of therapeutic advantage in patients with para-aortic LNM over CCRT alone,[46] but the No. of cases involved in this study was relatively small. In another study, 159 patients with pelvic LNM cervical squamous cell carcinoma in stage IB-IVA were divided into an adjuvant chemotherapy group and a NACT group, and the results showed that adjuvant chemotherapy significantly improved 3-year distant metastasis-free survival and did not increase severe toxicities.[47] The results of a recent multi-institutional retrospective analysis also showed that adjuvant chemotherapy after CCRT has a potential role in further improving disease control for locally advanced cervical cancer patients with LNM.[48]

CCRT + External Beam Boost Irradiation. On the basis of CCRT, external beam radiotherapy (EBRT) boost is an effective strategy for patients with LNM. However, whole-pelvic radiation doses exceeding 45 to 50.4 Gy could increase the risk of enterotoxicity, so it is necessary to carefully select patients who can benefit from EBRT boost.[49] At present, the dose recommendation for patiens with positive LNs remains unknown and varies between 55 and 60 Gy.[50] Ariga et al retrospectively analyzed the treatment results of EBRT boost to LNM in patients with uterine cervical cancer and found that EBRT boost to LNM achieves favorable nodal control without increasing late complications; however, this study did not compare the radiotherapy dose between CCRT and EBRT boost.[51] Hata et al indicated that short diameter of LNM ≤24 mm can be controlled by irradiation dose of 50.4 Gy, whereas larger nodes may require higher doses, and most may be sufficiently controlled by irradiation at total doses of about 55.8 Gy, concurrent use of chemotherapy may enhance the efficacy of radiation therapy in controlling LNM.[52] Wujanto et al conducted a retrospective study that included 139 patients with cervical cancer, of which 67 patients had LNM (the average short diameter of pelvic LNs was 19 mm). The results showed that EBRT boost to pelvic LNM does not reduce recurrence or improve OS and DFS in locally advanced cervical cancer. The reason may be that the short diameters of LNM in this study were smaller.[53] The above results suggested that for nonbulky LNs, there may be no need to increase the dose of radiation.[52,53] To date, there is no unified definition of bulky LNs. Bacorro et al investigated nodal control probability according to dose/volume parameters, and the results showed that radiation dose and nodal volume are independent factors affecting nodal control probability. Combined with the dose/volume effect, nodal control probability can be better predicted, and larger LNs need a higher radiation dose.[54] A high level of preradiotherapy SCC-Ag and the involvement of multiple pelvic LNs have been proven to be significant risk factors for pelvic nodal failure. Patients with risk factors develop frequent nodal failures following whole-pelvic radiotherapy, and EBRT boost is necessary for these patients.[55]

Pretreatment Debulking Surgery of Bulky LNs + CCRT. CCRT was recommended as the standard approach for locally advanced cervical cancer.[7] For patients without nodal disease or with disease limited to the pelvis only through surgical staging, treatment consists of pelvic EBRT with concurrent platinum-containing chemotherapy and brachytherapy. The radiation therapy for these patients generally involves a radiation dose of approximately 45 to 50 Gy. However, this approach is insufficient in cases with enlarged LNs.[56] Wakatsuki et al described that the control rate of a 50 Gy radiation dose for cervical cancer patients with LN < 10 mm was 97%, while the control rate of LN > 10 mm was 76%.[57] The field failure rate of pelvic and para-aortic LNs > 10 mm was significantly higher than that of smaller LNs, which has also been confirmed by another retrospective study.[58] However, the efficacy of CCRT is reduced in cases of LNs swollen larger than 2 cm. Higher doses are not feasible because of the serious or fatal toxicity to adjacent organs, and thus, it is becoming increasingly common to remove these bulky nodes before CCRT treatment.[59] However, bulky lymphadenectomy requires strict screening of patients, otherwise it may lead to serious complications. Removal of the bulky LNs can be considered if the following 4 conditions are met: (1) absence of distant metastases, (2) primary cervical tumor can be controlled by CCRT or RH, (3) the bulky LNs are not involved in major blood vessels, and (4) the bulky LNs are not accompanied by bone infiltration..[59]

Treatment of Para-Aortic LNM. A trial showed that CCRT did not reduce para-aortic recurrence after long-term follow-up, and more than 50% of patients with para-aortic recurrence developed distant metastasis after CCRT.[60] This shows that basic CCRT is not enough to control the disease in patients with para-aortic LNM. For patients with para-aortic LNM, extended-field radiation (EFRT) of the pelvis and para-aortic region is recommended.[60] This shows that basic CCRT is not enough to control the disease in patients with para-aortic LNM. For patients with para-aortic LNM, EFRT of the pelvis and para-aortic region is recommended.[61] Previous studies have shown that EFRT with CCRT has achieved considerable efficacy in treating patients with para-aortic LNM.[62] However, treatment-related toxicity was serious when EFRT was delivered with conventional or conformal radiotherapy.[63] Extended-field intensity-modulated radiation therapy (EF-IMRT) combined with brachytherapy and CCRT is safe and effective for patients with para-aortic LNM.[64–68] IMRT possesses evident superiorities over 3D-CRT technology because the dose distribution is more reasonable and the incidence of treatment-related toxicity is lower.[69–72] There is no unified conclusion on the radiation dose of para-aortic LNs. Wu et al found that the dose delivered to positive para-aortic LNs was an independent factor for recurrence in patients with para-aortic LNM. Patients who received a para-aortic LN dose of ≥50.4 Gy had a better 3-year DFS than patients treated with a para-aortic LN dose of <45 Gy.[73] Liu et al concluded that a dose of >58 Gy to the positive para-aortic LNs may be reasonable.[66] A recent finding demonstrated that a dose of 62.5 Gy to positive pelvic or para-aortic LNs using IMRT with a simultaneous integrated boost method can achieve excellent clinical outcomes with acceptable toxicity.[74] The above showed that the standard radiation dose might need to be verified by large-scale prospective studies. In addition, a few authors suggested the use of adjuvant chemotherapy after EF-CCRT or NACT before EF-CCRT. However, this treatment plan is still in the clinical trial stage, and the No. of cases is small; thus, it needs to be verified by large-scale prospective trials.[46,75,76]

LN-Related Prognostic Factors

Location of LNM. According to the 2018 FIGO staging system, patients with pelvic LNM were classified as stage IIIC1, and patients with para-aortic LNM were classified as stage IIIC2. Para-aortic LNM is a definite adverse prognostic factor, so it is crucial to evaluate para-aortic LNM.[5,12,13,77–81] Guo et al evaluated patients who underwent radical surgery, and the results showed that the 5-year PFS and OS rates of stage IIIC2 patients were significantly lower than those of stage IIIC1 patients.[82] Yang et al established a nomogram to predict the prognosis of patients with locally advanced cervical squamous cell carcinoma, which showed that PFS and OS were poor in patients with para-aortic LNM.[83] For patients whose LNs are limited to the pelvic cavity, multiple sites of pelvic LNM have a poor prognosis. A retrospective study analyzed 155 patients with pelvic LNM confirmed by pathology and analyzed the influence of the factors associated with pelvic LNM on the survival, the 5-year PFS and OS of patients with more than 2 LNM sites were worse than those of patients with 1 or 2 LNM sites.[83] Another study on stage IA-IIB cervical cancer also showed that the survival of patients with multiple LNM sites was decreased.[84] In addition, the widespread pelvic LNs is often accompanied by para-aortic LNM, so some authors recommended that for patients with multiple sites of pelvic LNM, it is necessary to evaluate the status of para-aortic LNs.[85] In cervical cancer, the incidence of common iliac LNM is lower, but once common iliac LNM occurs, the OS is significantly reduced.[46,47,80,83,86,87] In a prospective cohort study of 560 patients at a single center, the risk of recurrent disease was shown to increase incrementally on the basis of the most distant level of LN involvement at PET, with a hazard ratio of 2.40 (95% confidence interval: 1.63, 3.52) for pelvic involvement, 5.88 (95% confidence interval: 3.80, 9.09) for para-aortic involvement, and 30.27 (95% confidence interval: 16.56, 55.34) for supraclavicular involvement.[12]

Number of LNMs. The KROG1303 study constructed a nomogram using the following variables: age, No. of pelvic LNM, parametrial invasion, lymphovascular invasion, and the use of CCRT to predict 5-year OS, and the results showed that the risk of death continued to increase with the increase in the No. of pelvic LNM.[88] Another study also showed that OS decreased with the increase in the No. of LNMs.[89] The cut-off values of the No. of LNMs were different in the case of different groups of patients. After radical hysterectomy and pelvic lymphadenectomy, the difference in survival was statistically significant in patients with one LNM and those with $\geq$2.[84,90–93] A previous study included 164 patients with cervical cancer who were treated with definitive CCRT or IMRT alone. A radiographic No. of LNM$\geq$3 is an independent prognostic factor for OS, cancer-specific survival, and distant metastasis-free survival.[94] A multicenter retrospective study included 249 IB to IIA patients and demonstrated that the No. of LNMs showed the best prognostic performance among parameters related to LN status, and the risk of recurrence in patients with LNM > 3 remained high even with postoperative chemoradiotherapy.[30] The cut-off value of the No. of LNMs in another study was also 3.[95] Guo et al compared the prognostic accuracy of 4 LN staging systems, the 2018 FIGO stage, No. of LNMs, LNR, and log odds of positive lymph nodes (LODDS) systems, in patients with node-positive cervical squamous cell carcinoma following radical surgery. The No. of LNM systems seemed to be the most accurate LN staging method, and the cut-off value of the No. of LNM was 5 in this study.[77] Another study investigated the prognostic value of 6 LN staging systems: TNM pN stage, 2018 FIGO stage, No. of LNM, No. of negative LN, LNR, and LODDS. The No. of LNM also appeared to be the most valuable and predictive LN staging system in cervical squamous cell carcinoma patients following radical surgery.[82]

Metastatic Lymph Node Ratio (LNR). The LNR has been described as the percentage of metastatic LNs to total LNs recovered and has been suggested as a newly emerging prognostic factor in cervical cancer during the last decade.[96–98] Theoretically, the LNR could avoid possible confounding effects related to the No. of LNs removed and regional LNs that vary in each individual. Some studies have shown that the LNR is more discriminative than the No. of LNMs in predicting the OS of node-positive cervical cancer patients.[96,98] The cut-off value of the LNR was adjusted according to the heterogeneity of the patients and the No. of LNs dissected by different institutions. Fleming et al performed a retrospective study of stage I or II cervical cancer patients with LNM who underwent radical hysterectomy and pelvic +/− para-aortic lymphadenectomy. They found that an LNR > 6.6% was associated with worse PFS, and an LNR > 7.6% was associated with worse OS.[19] Joo et al found that the DFS and OS rates were significantly different when the patients were grouped according to low (LNR<0.1), intermediate (0.1-0.4), and high (LNR>0.4) pelvic LNRs.[99] Another dual-institutional study included 185 cervical cancer patients with LNM who had undergone radical hysterectomy with systematic pelvic and para-aortic lymphadenectomy, and showed that an LNR $\geq$5% was associated with worse DFS and OS in women with stage IIIC cervical cancer.[97] The advantages of the LNR over other parameters are as follows: underestimation because of less aggressive dissection can be avoided, and it is an intuitive factor and easy to calculate. However, sometimes it did not reflect the real nodal tumor burden. For example, the LNR may appear relatively high in the case of a limited nodal count; in contrast, more extensive LN dissection may cause a low LNR. Therefore, it needs to be applied in accordance with the standard of LN dissection. However, to achieve an "adequate" standard of lymphadenectomy, the minimum No. of LNs that should be harvested remains controversial.[100]

Log Odds of Positive LNs (LODDs). LODDs are defined as follows: log [(No. of positive LNs + 0.5)/(No. of harvested LNs–No. of positive LNs + 0.5)]. The strength of LODDs lies in their ability to discriminate against patients with equal LNRs. In particular, Sun et al demonstrated that LODDs were still heterogeneous even though the LNR was equal to 0 or 1.[101] This finding suggested the potential of LODDs to distinguish different prognoses among patients with the same N stage. For example, if the No. of LNMs is zero, the LNR will be zero regardless of the degree of anatomy, but the LODD will vary according to the No. of negative LNs. Kwon et al retrospectively analyzed 50 high-risk patients who underwent radical hysterectomy and pelvic node dissection followed by adjuvant treatment, and LODDs were the only significant prognostic factor for both DFS and OS.[102] A recent study based on the SEER database showed that LODDS is an independent prognostic factor for patients with cervical cancer, and a nomogram based on LODDS has good accuracy in predicting OS.[103]

Removed Lymph Nodes. There is some controversy about the predictive value of the No. of removed lymph nodes (RLNs) on the survival of patients. Kim et al found that the increased No. of RLNs improved PFS in the primary surgical treatment group, especially in patients with LNM.[95] Another study also indicated that more RLNs led to better DFS for patients with LNM.[104] Taking 10% as the cut-off value, Chen et al proved that the increase in RLNs may be a more significant independent prognostic parameter for predicting poor prognosis in patients with stages IA2 to IIA cervical cancer with LNM.[89] Another study showed that within a specific RLN range, the 5-year survival rate of FIGO stages IA1 to IIA2 cervical cancer patients treated with radical hysterectomy and pelvic lymphadenectomy increased with an increasing NLN count, and the prognostic prediction of the RLN would thus be greatly improved if combined with the NLN count.[105] However, research on the SEER database showed that node-negative, early stage cervical cancer patients who underwent a more extensive lymphadenectomy had improved survival but had no effect on patients with LNM.[106] This may be because a more extensive lymphadenectomy can improve the detection rates of LNM and appears more likely to remove micrometastases not detectable by routine histological examination. In another two studies, the No. of RLNs did not affect DFS and OS of cervical cancer, which may indicate that the change in LN number is probably due to the variability or pathological process among individuals rather than the radicalization of surgery.[93,107] Excessive resection of negative LNs may increase the risk of postoperative complications.[108]

Size of LNM. Imaging is a helpful method to determine LNM in patients who do not have pathological results. Nevertheless, there is still controversy in defining LN positivity on MRI or CT by size. The universally accepted criterion is that the short-axis diameter is more than 10 mm as the size criterion for lymphadenopathy. When the short diameter of the pelvic LN is less than 10 mm, pelvic LN failure rarely occurs after treatment. However, when the short diameter of the pelvic LN is large, the prognosis decreases significantly. Similar to tumor size, LN size has also been studied by several authors, and several surgical series reported that metastatic LN diameter ≥20 mm was associated with poor prognosis.[109,110] Different cut-off values other than 20 mm were also tested, obtaining similar results. Patients with necrotic nodules or nodules with short diameters ≥14 mm have a greater risk of residual disease and a worse prognosis after definite treatment.[111]

Conclusion

The FIGO 2018 staging system better reflects patient prognosis, highlighting the need for new treatment strategies for stage IIIC cervical cancer. However, patients with cervical cancer in stage IIIC include patients with different T stages, which leads to some controversy in treatment choice. Before 2018, many early stage cervical cancer patients with LNM underwent surgery, and many results came from radical surgery-based studies. However, after the revised staging in 2018, patients with stage IIIC are more likely to receive CCRT-based treatment. There were a few studies on the survival prediction of stage IIIC cervical cancer treated by CCRT, which need to be confirmed over time. Therefore, it is necessary to accurately evaluate the primary tumor and LN status to distinguish tumor heterogeneity and plan individualized optimal treatment according to the prognostic needs of patients. In this way, the survival time and quality of life of patients can be improved.

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Supplemental Material

Supplemental material for this article is available online.

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