

Clinical Controversies and Research Progress in Lymph Node Dissection for Cervical Cancer

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Abstract. Regional lymph node metastasis (LNM) is the main metastatic route of cervical cancer, whose rate of LNM increases in the cancer progression. LNM of cervical cancer is closely related to the cervical cancer staging, treatment method and prognosis. Lymph node dissection (LND) is an important part of standard cervical cancer staging surgeries. In recent years, Sentinel Lymph Node Biopsy (SLNB) has been used in treatments of some tumors, being considered as an alternative to Pelvic Lymph Node Dissection (PLND) in early-stage cervical cancer. However, validation regarding the feasibility of using SLNB alone as an alternative to PLND is still needed. Some scholars support PLND for patients with suspicious lymph nodes detected preoperatively due to reasons such as lower diagnostic sensitivity and specificity of preoperative imaging and potentially better prognosis for surgical staging of advanced stage of cervical cancer. However, recent basic research suggests that lymph nodes are important organs for providing tumor-specific immunity, the preservation of which facilitates immunotherapy. In this way, controversies about whether to use PLND still exist. This paper presents a brief review of the relevant research progress and discusses the new clinical definition and value of lymph nodes in the era of immunotherapy, with a view to providing new directions and ideas for the rational application of LND.

Keywords: cervical cancer; lymph node metastasis (LNM); sentinel lymph node biopsy (SLNB); lymph node dissection (LND); tumor-draining lymph node (TDLN).

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women[1]. Although HPV vaccines have achieved remarkable success in preventing cervical cancer in recent years, HPV vaccination rates are still low in developing countries, which leads to high incidence rates. LNM is highly prevalent in cervical cancer, which is an independent risk factor for cervical cancer prognosis. According to the 1st edition of the 2024 NCCN guidelines[2], pelvic lymphadenectomy has been required for stage IA cervical cancer with positive margins and no Lympho-Vascular Space Invasion (LVSI). LNM has traditionally been considered a central site for the development of systemic metastases. However, some current clinical analyses have disproved this view, proposing that LND does not lead to higher survival rates in early-stage lung cancers, melanomas, and breast cancers [3-5]. Controversies in medicine about whether to surgically remove lymph nodes or not exist. Some scholars believe that lymph nodes are still the hub of tumor cell metastasis for cervical cancers according to current research, which need to be removed as early as possible to prevent distant metastasis and worse prognosis. Through basic research on tumor immunity, opponents have found that lymph nodes, as important immune organs in the human body, play an indispensable role in anti-tumor immunity. Therefore, the clinical indications for the application of LND in cervical cancers are still controversial. This paper gives a review about alternatives to LND in cervical cancers and explores the role that tumor lymph nodes have played in anti-tumor immunity in recent years.

1. Characteristics, Distribution Probability and Influencing Factors of LNM of Cervical Cancers

As a common mode of metastasis and an important factor affecting patients' prognosis, LNM of cervical cancers has become a hotspot of research for many scholars. There are four main pathways



for LNM of cervical cancers: ①first to the lymph nodes of the pelvic side wall, such as the parametrial lymph nodes, the obturator lymph nodes, the internal iliac lymph nodes and the external iliac lymph nodes, ②from the lymph nodes of the pelvic side wall to the common iliac lymph nodes, ③then from the common iliac lymph nodes to the deep and superficial inguinal lymph nodes and the lymph nodes adjacent to the abdominal aorta, ④the lymph nodes adjacent to the abdominal aorta occasionally metastasize through the thoracic duct to the lymph nodes in the deltoid region of the left supraclavicular region. The majority of cervical cancer LNM are progressive as described above. However, a study by Ayhan et al. [6] showed that there is a 0.8% probability of solitary para-aortic LNM, also called skip metastasis. In the above study which included 522 women, the pelvic lymph nodes were the most common site of metastasis (190) in 36.4% of patients and para-aortic metastasis occurred in 48 patients (9.2%).

A study that included 975 patients with stage IA-IIA cervical cancers analyzed the distributional characteristics of LNM. Among the 395 metastatic lymph nodes, external iliac LNM was the most common (40.4%, 145/359). Obturator LNM was found in 39.3% of cases (141/395). Internal iliac had less, accounting for approximately 13.6% of cases (49/359). Common iliac LNM occurred the least (6.7%, 24/359). Multivariate analysis showed tumor lesion >4 cm (OR= 2.253, 95% CI: 1.486-3.416, P< 0.001), positive LVSI (OR = 5.353, 95% CI: 3.303 ~ 8.676, P<0.001), deep cervical stromal invasion (OR = 3.461, 95% CI: 2.106 ~ 5.688, P< 0.001); uterine corpus invasion (UCI \geq 50%) (OR=3.529, 95% CI: 1.321-9.427, P=0.012) are independent risk factors for LNM [7].

Another study initiated by Cai et al. [8] has provided statistics on the distribution of LNM in stage IB cervical cancers. Different from Cao's data, this study showed that cervical cancers have the most occurrences of obturator LNM, followed by external iliac, internal iliac, parametrial, and common iliac LNM. Patients presenting with parametrial LNM are more likely to develop metastases to other sites, while patients presenting with LVSI have a high risk of developing external iliac, obturator and parametrial LNM. In addition, the study also analyzed the independent risk factors for LNM, with the tumor size \geq 2 cm (P=0.001), deep mesenchymal infiltration (P=0.012), LVSI (P<0.001), and parametrial infiltration (P<0.001) all being the independent risk factors.

For advanced stage of cervical cancers, a study initiated by Li et al. [9] suggested that a risk factor for the metastasis of common iliac lymph node and para-aortic lymph node is the minimum axial diameter (MAD) of non-squamous cell carcinoma and pelvic lymph node \geq 1.0 cm plus numbers \geq 2, MAD of one pelvic lymph node \geq 1.0 cm and the MAD of common iliac lymph node and/or para-aortic lymph node within 0.5-1.0 cm.

2. SLNB Being Beneficial for Early-stage Cervical Cancer

Due to the high false-negative rate and low sensitivity of imaging in early-stage cervical cancer, some micro metastases are difficult to be detected. While micro metastases may be a risk factor for recurrence, sentinel lymph node biopsy has been promoted because of its advantages of less trauma, high sensitivity, fewer complications and better prognosis.

2.1. Lymph Node Tracer

Accurate sentinel lymph node biopsy needs localization. The most widely used tracers are blue dye, indocyanine green, and the radiotracer Technetium 99 (99mTc). Blue dye has a higher probability of allergic reactions. Studies have shown that the use of 99mTc in combination with blue dye is better than the use of 99mTc alone in terms of overall detection rate and sensitivity [10]. A study by Buda et al [11] showed that the detection rates of using 99mTc and blue dye, blue dye alone, and using ICG in SLN tracing of cervical cancer were 82%, 62%, and 100%, respectively. At the same time, ICG is non-radioactive to both patients and physicians, which makes it a safer choice. Some new tracers such as 18F-FDG can be used to differentiate involved lymph nodes from non-involved lymph nodes directly by immunofluorescence intraoperatively with its advantage of high uptake by tumor cells.

2.2. Advantages of SLND

2.2.1. Identification of Micro Metastasis

In systematic pelvic lymph node dissection (SPLND) where micro metastasis (MIC) and isolated tumor cells (ITCs) are more difficult to detect, and where MICs and ITCs may affect recurrence and prognosis, SLN Ultrastaging offers the possibility of detecting MICs and ITCs by making ultrathin sections of lymph nodes to detect smaller metastatic lesions. A study by Kim et al. [12] suggested ultrastaging requires lymph node spacing of 50 mm and two consecutive sections of approximately 5µm thick each. Separate HE and immunohistochemical staining are also needed. A summary of 57 studies by Dundr et al. [13] showed that the most common section thickness is 2 mm, and the most common section spacing is 150µm. Conventional SLNB without ultrastaging does not detect pelvic lymph node infiltration in approximately 6.4% of patients, leading to false negative results. Therefore, PLND is needed after SLNB to fully detect the lymph nodes, which may lead to recurrence of cervical cancer in the pelvic lymph nodes if positive lymph nodes are missed. This also makes SLNB without PLND an unsafe method [14]. However, PLND in turn causes postoperative complications such as early severe lower limb lymphedema. Ultrastaging is a heavy workload, complex and costly procedure, which makes its complete use in SLNB+PLND difficult to achieve. In this way, SLNB with ultrastaging is seen as a better and more appropriate alternative to SLNB+PLND.

2.2.2. Fewer Intraoperative and Postoperative Complications

The probability of cancerous infiltration of lymph nodes in early-stage cervical cancer is relatively low, ranging from 0%-8% in stage IA, 0%-17% in stage IB, 12%-27% in stage IIA, and 25%-29% in stage IIB61 [15]. This implies that at least 70% of patients experience non-essential LND, while PLND can cause severe complications such as lower limb lymphoedema. SLNB, as a minimally invasive LND, is viewed as an alternative surgical approach to PLND. A study by Lennox et al. [16] showed that bilateral para-abdominal aortic LND is associated with a higher intraoperative hemorrhage, operative duration, blood transfusion, hospital stay and postoperative incidence of infection compared to bilateral lymph node biopsy. After adjusting for the variables, there was no significant difference in recurrence rates between the two groups. Therefore, SLNB, which is less damaging and has a better prognosis, is recommended. The SENTICOL-II study also demonstrated a significant reduction in lymphatic morbidity (31.4%) after SLNB alone compared to lymphatic morbidity after SLNB+PLND (51.5%) (P=0.0046). Sensorimotor deficits were similarly significantly reduced (20.6%, 7.8% P=0.01). There was no significant difference in the three-year recurrence-free survival (RFS) between the two (94.4%, 92.0%) [17]. The results of this trial suggest that SLNB is a safe and effective lymph node detection method compared with SLNB+PLDN.

The new ESGO/ESTRO/ESP guidelines state that a key goal during the treatment of cervical cancer is to avoid the combination of pelvic radiotherapy after radical surgery, recommending that MRI can be a mandatory preoperative test and that intraoperative SLN assessment should be the first step of surgery [18]. Therefore, in cases where SLN positivity is found intraoperatively, radical surgery including further PLND and radical hysterectomy should be abandoned in favor of radiotherapy. This reduces serious complications due to the combination of radical surgery and pelvic radiotherapy.

2.3. Deficiencies of SLNB

2.3.1. Doctors Need to Have Rich Experience

During surgery, the surgeon's proficiency affects the success rate of SLNB and the detection rate of LNM. A study by Kim et al. [19] showed that a surgeon needs at least 27 operations to master SLN mapping of gynecological tumors. This implies that the surgeon has to be highly trained as well as have a sufficient number of operational practices if SLNB is to be used in place of SPLND.

2.3.2. Tumor Thrombi Obstructing Lymphatic Vessels

After metastatic tumor cells proliferate within the SLN and completely block the lymphatic vessels, the lymph nodes are blocked by the tumor cells. The lymphatic vessels lose their function of draining

lymphatic fluid, and the tracer is unable to enter the subsequent lymph nodes, which may result in a false-negative LN following blockage of the lymph nodes. Earlier studies have shown an overall SLN detection rate of 78% in 50 cases of cervical cancer, compared with an overall detection rate of 60% in 10 patients with positive pelvic lymph nodes. This discrepancy may be related to larger tumors leading to obstruction of lymphatic vessels by the tumor thrombus and poor drainage or redistribution of the tracer, which in turn leads to failure of positive SLN detection. Therefore, SLNB is recommended to be performed preferentially in patients with tumor diameters ≤ 2 cm [20].

2.3.3. Unclear Prognostic Impact of MIC and ITC: Ultrastaging in SLN May Not Be Necessary

There is no conclusive evidence on the effect of MIC and ITC on the recurrence and prognosis of cervical cancer. Some studies have shown that MIC is significantly associated with recurrence. However, the SENTICOL-II study showed that MICs and ITCs do not affect disease-free survival (DFS) and therefore do not influence the treatment method [17]. Under the influence of the above findings, the researchers raised a question as to whether they should continue to study the detection rate of MICs and ITCs in SLN. However, the trial had a small number of participants and may not be representative. Therefore, large sample size studies are also needed to investigate the impact of MICs and ITCs on prognosis, recurrence, and treatment methods.

The above retrospective studies have shown that SLNB is highly sensitive, specific, and reduces the incidence of postoperative complications as well as their severity. However, it should be noted that the oncological safety of SLN biopsy as an alternative to PLND has not been validated by adequate prospective trials. Most of the available data are from retrospective studies. Because of the need to calculate the detection rate of SLNB as well as the representativeness of SLNB for all LNs, patients were subjected to PLND by the investigators after SLNB. Therefore, the clinical feasibility of using SLNB alone instead of PLND needs to be further investigated. A related trial, the SENTICOL-III trial, will be completed in 2029.

3. Meanings of Lymph Node Excision (LNE)

For advanced stage of cervical cancer, the cancer embolus may block the lymphatic vessels, making SLNB impossible. At the same time, the chance of LNM in advanced stage of cervical cancer is much higher than that in early cervical cancer, and some non-sentinel lymph nodes are very likely to be involved. Secondly, surgical staging is more accurate compared with imaging staging, and the accurate LNM obtained from LND can be used to determine the precise scope of radiotherapy. It can avoid omission or over-treatment. Therefore, some scholars support that for patients with suspicious lymph nodes found before surgery, the metastasis can be determined by removing the pelvic lymph nodes, which is conducive to accurate treatment and improves the prognosis.

3.1. High Incidence of LNM

The rate of lymph node involvement in early-stage cervical cancer is low, and the metastasis of other lymph nodes can be judged and predicted by preoperative SLNB. However, as the stage of cervical cancer rises, the rate of lymph node involvement gradually increases and may even be accompanied by PALN metastasis. The negative rate of SLNB in patients in advanced stage is low. A study that included 1,182 patients with cervical cancer showed that LNM were present in 11.7% (85/724) of patients with FIGO stage I and 23.4% (107/458) of patients with FIGO stage II had positive lymph nodes. Lymph node positivity was more significant in FIGO stage II patients compared to FIGO stage I patients ($P < 0.001$) [21]. Approximately 10-25% of patients with locally advanced stage of cervical cancer have PALN metastases [22]. LNM is closely related to the progression and recurrence of cervical cancer, and resection prevents more distant and malignant spread of cancer cells through lymphatic vessels. Resection of larger lymph nodes also reduces the incidence of events such as difficulty in clearing LNM with standard doses of radiotherapy.

3.2. Low Sensitivity and Specificity of Diagnostic Imaging

Because patients with locally advanced and advanced stage of cervical cancer need to undergo pelvic radiotherapy routinely, the pelvic lymph node region is within the radiotherapy field. In order to determine the scope of radiotherapy and whether to carry out extended field radiotherapy, imaging is needed to assist in the assessment of LNM. PET-CT is currently the most accurate imaging staging tool, but has limitations in detecting microscopic lesions. In addition, 18F-FDG is not a specific radiopharmaceutical for tumor imaging. Inflammatory and lymph node proliferative lesions can also lead to increased concentrations of radioactivity when present, resulting in false-positive results. The sensitivity of PET-CT was 0.65 (0.60 ~ 0.69) [23] with a negative predictive value of 88.9% ~ 95.0% [24], and the sensitivity of MRI was 0.58 (0.54 ~ 0.63) [23]. The results of the above tests indicate that imaging is less sensitive and has a higher rate of missed diagnosis. Studies have shown that PET-CT misses about 25% of para-aortic LNM in stage IIIC [25].

In conclusion, in view of the fact that there are certain false-positive and false-negative rates in the imaging evaluation, para-abdominal aortic lymphadenectomy can be performed in patients with locally advanced and advanced stage of cervical cancer without contraindications to surgery. It can accurately find out whether there are metastases in the para-abdominal aortic lymph nodes and guide the use of extended field radiotherapy to avoid insufficient or excessive radiotherapy. However, skilled surgical techniques are needed to minimize the complications associated with surgery.

3.3. Surgical Staging May Have a Better Prognosis for Advanced Stage of Cervical Cancer

Patients after stage IIB have more extensive lesions, higher rates of recurrence metastasis, and shorter survival after implementation of NCCN-recommended therapies. There is a 10-15% probability of false-negative PET-CT in patients with PALN metastasis [26]. Therefore, surgical staging is currently used in clinical trials for locally advanced cervical cancer. Several studies have shown that compared to imaging, the treatment strategies developed after surgical staging are more accurate, with a more precise range of treatments, and can lead to a better prognosis for patients. A study by Smits et al. [27] showed that 7-58% of patients with locally advanced cervical cancer had improved treatment modalities after surgical staging. At the same time, patients' DFS and overall survival (OS) were improved. Although the trial by Gold et al. [28] showed that radiological evaluation resulted in lower staging and smaller reported tumors, surgical staging for stage III and stage IV patients had better 4-year progression-free survival (PFS) and OS. The largest current prospective international multicenter study (UTERUS-11) showed significantly higher DFS after surgical staging in patients with FIGO stage IIB (P=0.011). For patients with FIGO stage III, DFS after surgical staging versus clinical staging was not significant difference [29]. However, some studies have also shown that surgical staging is not associated with DFS or even decreases 5-year DFS [30]. The PAROLA trial will give results in 2027 as to whether surgical or pathologic staging improves DFS.

Therefore, for patients in relatively advanced stages, surgical exclusion of positive lymph nodes is instructive for subsequent radiotherapy. It also plays an important role in prognosis and reducing complications caused by overtreatment. Surgical staging has high accuracy and sensitivity compared with imaging staging in advanced cervical cancer, and it can also remove larger metastatic lymph nodes that are difficult to be removed by standard radiotherapy, which is worth promoting. However, the issues of surgical scope, surgical approach, extent of LND, and management of postoperative complications still need to be further discussed and resolved.

4. Significance of Lymph Node Retention

Studies have suggested the presence of extensive LNM of malignant tumors due to the presence of an immunosuppressive microenvironment in the lymph nodes induced by tumor cells [31]. Therefore, early resection of lymph nodes is recommended to prevent metastasis of cancer cells to systemic organs due to immunosuppression. Although most people currently believe that lymph nodes with metastatic cancer cells need to be removed as early as possible, some recent basic studies have shown

that preservation of lymph nodes facilitates a greater role for subsequent immunotherapy [32, 33]. Tumor-draining Lymph Nodes (TDLNs) generate tumor-specific memory T cells, which give rise to memory T lymphocytes targeting the tumor. The resulting tumor-specific T cells can still function when the tumor recurs. After the removal of lymph nodes, lymphocytes cannot be well developed, differentiated and mature, which is not conducive to the body to produce an immune response against the tumor. At the same time, it does not help for the PD-1 inhibitors to play a greater effect.

4.1. Lymph Nodes Provide Tumor-specific Immunity

Lymph nodes play an important role in tumor metastasis as the most common metastatic route for cervical cancer. It was previously believed that lymph nodes were the hub for most primary tumors to undergo distant metastasis. A study published in *Science* in 2018 showed that tumor cells can directly undergo distant metastasis through high endothelial microvessels [34], which implies that a single resection of the lymph nodes may not really achieve the previously believed goal of stopping tumor metastasis. In addition, recent studies have found that preservation of lymph nodes facilitates the activation of the immune system and the production of memory cells to fight against tumors. A study by Huang et al. [33] found that TDLN-TTSM from TDLN expresses memory T-cell-associated markers, which are not present in T-cells from tumor microenvironment. Tumor-infiltrating Lymphocytes (TILs) need to be preserved as an important extraction pathway for T cells in adoptive T-cell therapy (ACT). Anti-cancer immune responses can be detected in lymph nodes, blood and tumor microenvironment. Studies have shown that TDLNs are a rich source of polyclonal HPV16 E6- and E7-specific T cells. This type of T cells can be utilized for ACT treatment of cervical cancer patients after in vitro expansion. The study showed that the expansion of HPV-specific T cells from peripheral blood cells had only a 50% success rate. When TDLNs were used as a source of T cells, the success rate was 100% [35].

4.2. Lymph Nodes are the Source of T Cells that Respond to Immunotherapy

PD-1 inhibitors, as effective drugs for tumor immunotherapy, can block the local immunosuppressive microenvironment of cervical cancer, thereby blocking tumor metastasis [36]. A study by Dammeije et al. [37] found that TDLNs may be a key site for generating responses to PD-1/PD-L1 and storing tumor-immune T cells. A study by Rahim et al. [32] found higher abundance of progenitor or precursor T cell (Tpex) in uninvolved lymph node (uiLN) in patients with head and neck squamous cell carcinoma, while in tumor microenvironment (TME) exhausted T cells (Tex) were more abundant. The research team also pointed out that Tpex is produced in uiLN and differentiates into transitional intermediate exhausted T cells (Tex-int) in uiLN and then enters into tumor tissues by blood circulation to exert anti-tumor effects. Moreover, the research team found that although the level of Tpex in TDLN has decreased, it still has a certain anti-tumor effect. A study by Huang et al. [33] identified tumor-specific TCF-1+TOX-CD8+ T cells from TDLNs and named them TDLN-TTSM. The research team also pointed out that TDLN-TTSM is a subpopulation of T cells that truly responds to PD-1/PD-L1 and exhibits potent antitumor capacity after adoptive therapy. In the adoptive therapy, 100% of the tumor-bearing mice in the TDLN-TTSM group survived, indicating that TDLN-TTSM enabled the tumor-bearing mice to achieve complete remission. The response of TDLN-TTSM to PD-1/PD-L1 was also superior to the rest of the group.

A large body of evidence confirms the presence of an immunosuppressive microenvironment in the TDLN which is an important location for metastasis of cervical cancer cells, suggesting that doctors need to remove the lymph nodes when performing radical surgery. However, recent studies have shown that immunotherapy requires the presence of lymph nodes and that immunotherapy targets T cells in the lymph nodes rather than in the tumor microenvironment. Moreover, lymph nodes, as an important site for lymphocyte development, maturation and differentiation, are an important source of T cells that respond to immunotherapy and exert anti-tumor functions. A study by Huang et al. [33] also pointed out that resection of the TDLN during treatment disrupts the effects of PD-1/PD-L1 inhibitors. A 2014 study on the mechanism of LNM showed that tumor cells released a series of

growth factors that prompted the expansion of lymphatic vessels in the SLN to actively incorporate cancer cells, thus promoting the activation of the body's anti-tumor immunity [38]. All of the above studies have great clinical value, which can be considered for use in the anticancer treatment of cervical cancer patients with the presence of TDLN.

5. Conclusion and Prospect

LNM is an important factor affecting the treatment methods and prognosis of cervical cancer patients. Considering the important impact of LNM in the prognosis of cervical cancers, the new FIGO staging in 2018 identifies LNM detected by imaging or pathology as stage IIIC. The gold standard for accurately determining LNM is to remove the lymph nodes and then examine them pathologically. However, differences and controversies about whether to remove the lymph nodes or not are still around. Currently, ultrastaging of SLNB can examine the lymph nodes more accurately and precisely. Considering the high workload of ultrastaging, which is not applicable to the detection of all lymph nodes, SLNB can be combined with ultrastaging to achieve a higher detection rate of SLN microscopic lesions. In addition, SLNB is less invasive than LND with fewer problems of lymphedema due to extensive dissection, while it is more demanding on the surgeon, who needs to be experienced. False-negative lymph node testing may occur because of interferences. Scholars supporting resection believe that LNM has a higher incidence in cervical cancers and a greater prognostic impact if residual LNM is early. Compared with using SLNB first to determine the presence of metastasis followed by full LND, the trauma and impact of two surgeries are greater than direct systematic LND. Meanwhile, surgical staging is more accurate compared with imaging staging. Scholars disapproving resection have found that lymph nodes, as organs mature in the development and differentiation of lymphocyte production, can produce both memory cells and anti-tumor T cells in anti-tumor immunity in response to immunotherapy through some basic research. If resected, the important anti-tumor substances mentioned above cannot continue to be produced, having no positive significance in treatment. PD-1 inhibitors respond better to TDLN-T_{Tsm} than to non-TDLN.

In response to the clinical controversy of LND, there are also a series of clinical trials with pending results. Based on basic anti-tumor immune research, the current discovery of TDLN-T_{TSM} is prospected to be tried in clinical cervical cancer patients. PAROLA trial aims to explore whether the 3-year DFS of patients histologically proven PET/CT FIGO stage IIIC1 cervical cancer who had tailored chemo-radiotherapy and brachytherapy based on surgical staging and pathological examination is higher than patients using standard chemo-radiotherapy and brachytherapy based on PET-CT staging and EMBRACE II and ESGO/ESTRO recommendations. The current randomized controlled trial SENTICOL II trial has demonstrated that SLN has lower postoperative incidence and better quality of life compared with PLND. However, the feasibility and safety of using SLN alone instead of PLND need to be further verified. The trial, International Validation Study of Sentinel Node Biopsy in Early Cervical Cancer (SENTICOLIII), is required to be conducted under this situation. SENTICOL-III trial aims to compare the 3-year DFS and health-related quality of life (HRQoL) between using SLN alone and using SLN plus PLND. The study hypothesizes that DFS is non-inferior and HRQoL is superior after SLN compared to SLN plus PLN. The trial is expected to end in May 2029. Another trial, Sentinel Lymph Node Biopsy Versus Pelvic Lymphadenectomy in Early-stage Cervical Cancer (PHENIX/CSEM 010), divided patients into two groups according to the SLNB involvement status. PHENIX-I compared the 3-year DFS, OS, and quality of life (QoL) in SLNB-negative patients with versus without PLND. PHENIX-II compared the 2-year DFS, OS, and QoL in SLNB-positive patients with versus without PLND. The trial has been completed in December 2022, with follow-up data being given in 2026. All three of the large clinical trials examined the controversial issues of LND with the aim of determining the timing of SLNB, the feasibility of SLNB alone as an alternative to PLND, and how patients with FIGO stage IIIC1 cervical cancer should be staged.

Controversies and challenges in the diagnosis and treatment of LNM still exists. With the gradual development of precision medicine, how to select and implement precise individualized treatment for

different patients with cervical cancers and among many methods according to different conditions of metastatic lymph nodes without violating the principles is the direction of gynecologic oncologists' future efforts.

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