**Prognostic significance of** **the number of pelvic lymph nodes removed in early cervical cancer patients**

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**Abstract**

**Objective** The aim of the research was to study the prognostic significance of the number of pelvic lymph nodes removed in early cervical cancer patients.

**Methods** We searched the PubMed database with the terms ‘cervical cancer’ and ‘lymph nodes’ or ‘lymphadenectomy’. Studies about the association between the number of lymph nodes and prognosis or survival were identified. In summary, we studied retrospectively the related researches.

**Results** Ten retrospective studies were included. Two researches indicated that the number of lymph nodes had no association with the prognosis while three studies proved that they were related positively. Five studies indicated that some factors could influence the relationship between them.

**Conclusion** The number of lymph nodes removed may influence cervical cancer patients’ prognosis positively, maybe some factors may influence the relationship between the extent of lymph nodes removed and the prognosis. It needs more multicenter, large-samples, prospective studies to verify.

**Keywords:** cervical cancer, prognosis, the number of lymph nodes, pelvic lymphadenectomy.

**History and background**

Although the pelvic lymphadenectomy has been traditionally used for more than a century in the surgical treatment for early cervical cancer, the standard scope of lymphadenectomy, the optimal number of lymph nodes ought to be removed haven’t reached uniform conclusions. Standardizing lymphadenectomy is essential for further improvement of surgical quality and cervical cancer patients’ survival. In this review, we reviewed the existing studies on the prognostic value of the number of lymph nodes retrieved.

Tracing the development history of cervical cancer surgical treatment, Ernst Wertheim standardized the radical abdominal hysterectomy in 1912, which made this cancer curable and formed the basis of the current treatment for early-stage cervical cancer. And then Dr. Fred J. Taussig realized the importance of the careful removal of the pelvic nodes during his operative procedure. As he thought even if the tumor had been made to disappear from the lymph nodes, a recurrence might take place in them still, he dissected the nodes and their channels en bloc in the surgery[1]. After that, Joe Vincent Meigs combined his radical abdominal hysterectomy with Taussig's en bloc pelvic lymph node dissection, establishing a milestone in the treatment of cervical cancer. From large experiences, he believed that positive lymph nodes couldn’t be determined by inspection, palpation, or visualization, the only proof that lymph nodes were positive was the examination in the pathology laboratory after their removal[1]. Therefore, Lymph node dissection was performed on the basis of radical hysterectomy, achieving an 89.7% 5-year survival rate for Stage I disease, and a 63.0% 5-year survival rate for Stage II disease, far surpassing Wertheim's 18.4% overall five-year survival[1]。Meigs demonstrated that lymphatic invasion was much more common than previously believed and the en bloc resection of lymphatic tissue afforded greater survival benefit. Therefore, pelvic lymphadenectomy has been proceeding for years and of great necessity.

Nowadays, cervical cancer remains the fourth most prevalent female malignancy and the fourth leading cause of cancer death in women worldwide[2]. With the gradual popularization of cervical cancer screening, the early diagnosis rate of cervical cancer has been improved, and the proportion of early cancer in cervical cancer has increased. For early cervical cancer, the present standard method for surgical treatment is radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling, and systematic pelvic lymph node dissection is an integral part of surgical procedures recommended to treat early-stage cervical cancer. But what extent of pelvic lymphadenectomy we should conduct has not been reached a consensus.

There are no unified conclusions about the scope of cervical cancer pelvic lymphadenectomy. Benedetti-Panici etc. found that the lymph node metastasis rate was 7% the deep common iliac, 28% the superficial common iliac, 7% the deep obturator, 86% the superficial obturator, 29% the external iliac, 8% the internal iliac, 7% the presacral and 29% the parametrial lymph nodes in patients with cervical cancer[3]. Therefore, for the purpose of treatment, the researchers suggested that a systematic dissection of all the lymphatic tissue located around the cervix and the pelvic vessels should be performed in patients to remove the potential sites of metastasis entirely, including the above 8 groups of lymph nodes[3]. But In Soyi Lim’s and Q.D. Pieterse’s studies, the pelvic lymphadenectomy included bilateral common iliac, external iliac, internal iliac and obturator, a total of four groups of lymph nodes[4, 5]. However, in Antonino Ditto’s article, in addition to the above four groups, it also included presacral lymph nodes[6]. Nevertheless, Thales Paulo Batista pointed out that a systemic lymphadenectomy also included parametrial lymph nodes in addition to the above four groups of lymph nodes[7]. Whereas, Ting Hu thought that the systematic pelvic lymphadenectomy also included the inguinal lymph nodes in addition to the above four groups[8]. The scope of lymphadenectomy can influence the number of pelvic lymph node dissected (NPLD) directly. Besides, NPLD may vary greatly on account of the anatomy of the patient, the status of lymphoid tissue peripheral inflammation adhesion, the standard of surgical operator, the extent of surgery, and its examination by the pathologist. In the previous studies, the mean or median number of pelvic nodes removed ranged from 13–65[9, 10]. In Verleye L’s study, removal of more than 11 pelvic nodes was suggested as one of the quality indicators for pelvic lymphadenectomy[11]. Up to now, we still don't know how many lymph nodes should be removed to get the best treatment effect, and there are some findings studying the relationship between the prognosis of patients with the pelvic lymphadenectomy and the number of lymph nodes removed to help to standardize pelvic lymphadenectomy in early cervical cancer.

**The related studies**

While some studies have proved that the number of lymph nodes removed and prognosis of patients was positively correlated, some articles proved that they had no obvious correlations. Prapaporn Supraset studied 826 patients with radical hysterectomy and pelvic lymphadenectomy by retrospective analysis, stratifying them into four groups according to NPLD: 11–20 ,21–30 ,31–40 , and≥41. He found that there was no statistical significance between the four groups about 5-year disease-free survival（DFS）and NPLD was independent of the 5-year DFS in the further multivariate analysis, then he thought that NPLD was not an independent prognostic factor in early cervical cancer patients[12]. However, this study chose only 5-year DFS as a prognostic indicator, not including the overall survival (OS) and cancer-specific survival. Besides, the study didn’t include the patients removed less than 11 lymph nodes. Therefore, we cannot conclude that the two absolutely unrelated. And then in 2013, Antonino Ditto studied on 526 cervical cancer patients treated with radical surgery and found that the total number of lymph nodes removed did not affect the survival of patients by multivariable analysis[6]. But the author didn’t divide patients into groups according to the total number of lymph nodes, which might have an impact on the result. Hence the relationship between them needs more studies.

In the contrary, Monjri Shah et al studied 5522 Women with stage IA2-IIA cervical cancer who underwent radical hysterectomy with lymphadenectomy in the Surveillance, Epidemiology, and End Results (SEER) database. In the study，the total number of lymph node dissected was divided into four groups :< 10 、10-20、21-30 、> 30. The researchers found that, compared with the patients with less than 10 nodes removed, patients with 21-30 nodes removed were 24% less likely to die, while those with >30 nodes removed were 37% less likely to die from their tumors, they then concluded that a more extensive lymphadenectomy was related to improved survival[13]. Similarily, Soyi Lim studied patients with FIGO stage IB -IIA cervical cancer, splitting patients into two groups by 40 lymph nodes removed, found that the patients with lymph nodes removed > 40 had a better prognosis and proved the total number of the lymph nodes removed had significant effect on DFS and OS[4]. Likewise, Juan Zhou studied 11830 women with stage IA2-IIA cervical cancer who underwent radical hysterectomy with lymphadenectomy in the SEER database, allocating them into four groups: 1-10 、10-20、21-30 、> 30, and found the number of lymph nodes removed was an independent prognostic factor, which meant that the more lymph node removed ,the better survival outcome would be obtained[14]. From the above studies, we can conclude that the total number of lymph nodes dissected may be related to the prognosis of patients positively.

In addition, there are also some studies indicating that some factors - histopathological type, tumor size, neoadjuvant chemotherapy and lymph node status – can influence the relationship between the prognosis of patients and the total number of lymph nodes removed.

Juan Zhou et al. reviewed 7920 patients with cervical squamous carcinoma and 3910 patients with cervical adenocarcinoma, all cancers were in FIGO stage IA2-IIB. Zhou found that the number of lymph nodes removed was an independent positive prognostic factor in squamous carcinoma while it had nothing to do with the prognosis of patients in adenocarcinoma[14].

Soyi Lim reviewed 180 FIGO stage IB–IIA cervical cancer patients after radical surgery, separating them into bulky (tumor size > 4 cm) group and the non-bulky (tumor size ≤ 4 cm) group, found that the total number of lymph nodes removed was an independent prognostic factor when the tumor > 4 cm in diameter, which meant that the more extensive lymphadenectomy increased the survival of bulky cervical cancer patients. However, when the tumor was <4 cm, there was no significant correlation between the total number of lymph nodes dissection and OS or DFS[4].

When taking surgery as the principal treatment of early cervical cancer, there are two ways: surgery after neoadjuvant chemotherapy and directly surgical treatment. Hee Seung Kim divided the patients into two groups by 20 lymph nodes removed and found that more lymph nodes removed could improve DFS in patients without neoadjuvant chemotherapy. However, for the patients experiencing radical surgery after neoadjuvant chemotherapy, there was no obvious relationship between the total number of lymph node removed and the prognosis[15].

Monjri Shah’s study indicated that when the lymph nodes were positive, a more extensive lymphadenectomy had no effect on survival. While for women with negative lymph nodes, a more extensive lymphadenectomy was associated with improved survival[13]。By contrast, Juan Zhou et al found that the total number of lymph nodes removed in patients with lymph node metastasis was an independent prognostic factor for cause-specific survival and OS. In other words, the bigger number of lymph node excision, the better survival outcome. However, there was no correlation between the total number of lymph nodes removed and prognosis of patients without lymph node metastasis[14]. These two studies were all SEER studies, but the later one had a larger sample size (11830 versus 5222), and a larger proportion of patients were diagnosed after 2000 (76.4% versus 48％), so the second study’s conclusion may be more reliable. And in the same way, Si yue Mao studied 359 cases of patients with FIGO stage IA-IIB cervical cancer without lymph node metastasis, dividing them into five groups : < 10, 11-15,16-20, 21-25 ,> 25, according to the number of lymph nodes removed, found that when there was no lymph node metastasis, total number of lymph node resected had nothing to do with the prognosis[16]. Similarily, San - Gang Wu divided the early cervical cancer patients without lymph node metastasis into two groups by the number of lymph nodes removed10. By the univariate analysis, he found that the total number of lymph nodes examined was a prognostic variable of OS while it was irrelevant to cause-specific survival, but the multivariate analysis indicated that the total number of lymph node resected didn’t relate to the prognosis of patients without lymph nodes metastasis[17]. Then we may conclude that the number of lymph node removed is related to prognosis positively when there is lymph node metastasis, while not associated with prognosis when there is no lymph nodes metastasis. This conclusion needs more sophisticated studies to testify.

**Conclusions**

From the current studies, we can summarize that there may be a positive correlation between the prognosis of patients and the number of lymph nodes removed in general. At the presence of lymph node metastasis, lymph nodes should be removed as much as possible to get better prognosis, trying to reduce the intraoperative and postoperative complications at the same time. When there is no lymph node metastasis, the prognosis of cervical cancer patients and the number of lymph nodes removed may be not related, but only by radical pelvic lymphadenectomy can we completely and precisely make sure whether lymph nodes metastatic and remove them completely. The pelvic lymphadenectomy is irreplaceable at present. It deserves more researches to study and standardize it. So far, the research on whether new adjuvant chemotherapy, tumor size, histological-pathological type, lymph nodes status can influence the relationship between the extent of lymphadenectomy and the prognosis is limited. It needs more multicenter, large-samples, prospective studies to verify.

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**Conflict of interest**

The authors indicated no potential conflicts of interest.

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