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*REVIEW ARTICLE*

# Lymphadenectomy during radical hysterectomy for cervical cancer (stage IB 1-2, IIA): state of the art

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## Summary

*Pelvic lymphadenectomy during radical hysterectomy in surgical candidates with cervical cancer (stage IB1-2, IIA) has become a standard method of therapy starting from mid 20th century.*

*More knowledge about the natural history, predictive and prognostic factors of disease and effectiveness of surgical and adjuvant treatments of early stage cervical carcinoma has been accumulated over the past 5 decades.*

*During the latter part of the 20th century the accumulating information base led to more conservative approaches for cancer resection in an effort to decrease the morbidity of radical surgery and to preserve the fertility if possible.*

*Lymph node metastasis is a bad prognostic factor in the early stages of disease and automatically classifies a patient in a high-risk group necessitating adjuvant therapy.*

*Preoperative diagnostic procedures, such as echotomography, computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and lymphangiography are all helpful in determining lymph node status, although their accuracy rate is anywhere between 57-85%. Recent studies of sentinel lymph nodes and lymph node topography are still very controversial and neither give information on the extent of lymphadenectomy needed nor help in patient selection in planning additional adjuvant therapy.*

*Published results on laparoscopic lymphadenectomy demonstrate decreased postoperative morbidity, but still pose questions whether laparotomic lymphadenectomy should be replaced by this technique.*

*Thus the question remains: how many lymph nodes, of which groups and by which technique should be dissected during pelvic lymphadenectomy?*

**Key words:** cervix carcinoma, lymphadenectomy, pretreatment procedure, radical hysterectomy

## Introduction

Even though the era of lymphadenectomy in the surgical treatment of cervical cancer begins with Taussig, Meigs is known as the founder of the procedure known as radical hysterectomy and pelvic lymphadenectomy.

The concept of this surgical principle is based on the fact that lymph nodes serve as a mechanical barrier to the spread of malignancy, therefore explaining the necessity of removal of tumor cells together with their lymphatic supply. This concept changed somewhat over time testifying about prognostic significance of regional lymphadenectomy of tumor-involved lymph nodes [1-3]. The therapeutic benefit of removal of lymph nodes not affected by the tumor during radical hysterectomy still remains unknown.

In the last decade of the 20th century laparoscopic lymphadenectomy has been added to our surgical armamentarium, combined with different techniques of primary surgical removal of cervical cancer. It is clear

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that an ever increasing number of surgeons is now performing laparoscopic lymphadenectomy and even more complicated laparoscopic operations, but to this date there is no controlled clinical phase III trial to demonstrate that laparoscopic lymphadenectomy is better than the existing classical open lymphadenectomy.

In the beginning of the 21st century the focus becomes identifying the sentinel lymph node during pelvic lymphadenectomy for cervical cancer (IB1-2, IIA), with consecutive decrease in extensive radical surgery and its complications. At the same time, this selective principle helps correlate the stage of disease with the radicality of the procedure [4-6] and also helps preserve fertility as well as decrease urologic complications by using nerve-sparing techniques.

## Cervical cancer lymphatic spread and anatomy of its drainage

Lymph nodes are the main pathway of spread of cervical cancer. The first data on the lymphatic spread of cervical cancer date from the studies of Henriksen [7]. Later studies demonstrated the importance of the knowledge of the anatomy of the lymphatic drainage system and the mechanisms of spread of cervical cancer [8,9].

The cervix contains a lymphatic system underneath the epithelium and around endocervical glands forming a rich subserosal lymphatic system.

The lymph collection system is subdivided into:

1. Lateral, which drains to interiliac and hypogastric/obturator lymph nodes.
2. Anterior, which drains to the distal lymph nodes along external iliac artery.
3. Posterior, which drains to the upper rectal and subaortic lymph nodes.

The pelvic lymphatic system with its lymph nodes, efferent and afferent lymphatic vessels, is very rich and has many anatomic variations. The number of lymph nodes not only differs in different people, but also can vary during a person's lifetime. The mean number of pelvic lymph nodes is around 50 (range of 40-95). Anatomically speaking, the presence of parametrial and paracervical lymph nodes is questionable, but what is certain is that the lymphatic system around the cervix and in the broad ligament is the first barrier to the spread of cancer.

## TNM/FIGO classification of the lymph nodes

TNM 2002 classification divides lymph nodes into paracervical, parametrial, hypogastric (internal iliac/obturator), common and external iliac, presacral and lateral sacral lymph nodes [10]. Paraaortic and inguinal lymph nodes are classified into distant nodes.

FIGO classification does not include the lymph nodes status in the staging of disease, even though lymphadenopathy influences prognosis.

## Predictive factors for lymph node metastasis

Size and volume of tumor is the first factor predicting lymph node metastasis, which influenced dividing stage IB to 1 (< 4 cm) and 2 (>4 cm) [11-13].

The depth of stromal invasion (≥ 2/3) is also a predictive factor for nodal metastasis and is tightly correlated to tumor size [1,14,15].

Microinvasion of parametrial lymph nodes strongly correlates with metastasis to the pelvic lymph nodes [16,17].

The histopathologic tumor type is prognostic for neuroendocrine small cell cancer and certain histological subtypes of adenocarcinoma (serous, clear cell) [18,19].

Tumor grade, as predictive factor of nodal metastasis, needs to be looked at together with the previously mentioned factors.

The results of recent data point to the importance of invasion of lymphovascular space as the only independent predictive factor of metastasis to lymph nodes, questioning previous knowledge on the importance of tumor size as a prognostic factor, and the division of stage IB to 2 substages [20, 21].

## Preoperative diagnostic procedures

The preoperative evaluation of the lymph nodes status and retroperitoneal space (paraaortic lymph nodes) is based on ultrasonography (US), CT, MRI, lymphangiography and fluorodeoxyglucose positron emission tomography (FDG-PET). The accuracy of estimating the status of lymph nodes by the first 3 methods is increased with the stage of disease, with decreased accuracy in the early stages in the range of 57-85% [21]. The accuracy of these methods is understandable, since it is based on the size of a lymph node (≥ 15 mm), assuming that an enlarged lymph node is metastatic.

The use of lymphotrophic contrast (superparamagnetic nanoparticles) during MRI increases its sensitivity from 35.4 to 90.5% in detecting metastatic pelvic lymph nodes [22,23]. These promising results need further clinical confirmation.

Lymphangiography, even though it represents the oldest diagnostic procedure, is the only one that can show the lymph node structural change or presence of metastases. The accuracy of this method is 85% (range 38-85.6%) [24,25]. Knowing the limitations of lymphangiography, pre- and postoperative lymphangiography in the early stages of cervical cancer could be a baseline test determining the success of systemic lymphadenectomy (Figures 1 and 2).

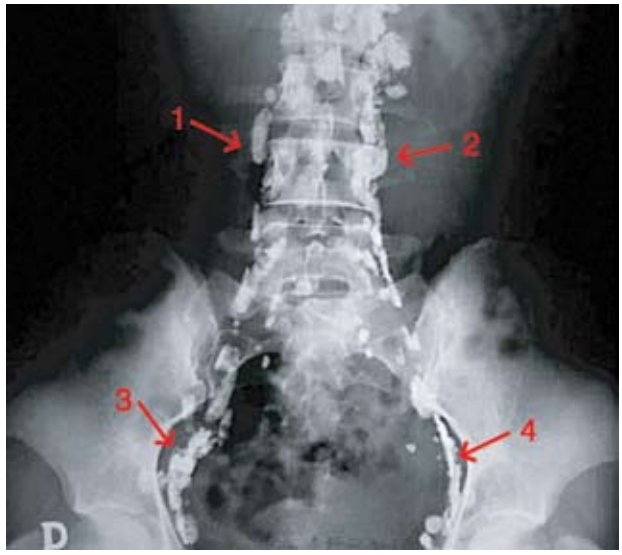


**Figure 1.** Preoperative lymphogram of cervical cancer stage IB. Arrows 1,2: paraaortic lymph node; arrows 3,4: pelvic lymph nodes (Courtesy dr. L. Ilić-Todorović).

**Figure 2.** Lymphogram post radical hysterectomy and pelvic lymphadenectomy (Courtesy dr. L. Ilić-Todorović).

Even though FDG-PET scan provides details not only about the size, but also of the lymph nodes structure (abnormal uptake FDG), the expected detection rate of nodal metastasis/micrometastasis is still lacking. The accuracy of the method is reported as 57% for the pelvic and 89% for paraaortic lymph nodes [26].

## Standard pelvic lymphadenectomy during radical hysterectomy (Wertheim-Meigs, Piver III) I/ILI modified radical hysterectomy (Wertheim, Piver II). Experience of the Obstetrics/Gynecologic Clinical Center "Narodni Front".

Pelvic lymphadenectomy is a required constitutive part of radical hysterectomy of the Wertheim-Meigs operation for cervical cancer stage IB1 to IIA. The practice of our center, where around 140 radical hysterectomies are performed annually, is to carry out a systematic and detailed lymphadenectomy for stages IB1-IIA. The decision about removing systemically or selectively the paraaortic lymph nodes depends on frozen sections of the common iliac lymph nodes or the preoperative evaluation of structural changes in the paraaortic lymph nodes. Paraaortic lymph node dissection is not performed for stage IB1 (< 2 cm) despite the described presence of metastasis in 3% of the cases in this stage.

The technique of lymphadenectomy consists of retroperitoneal dissection approaching the great pelvic vessels (Figure 3). The lymph nodes are dissected by sharp and blunt dissection along the external iliac artery, covering its lateral, medial and posterior side and then along its bifurcation to the femoral artery (Figure 4). Common

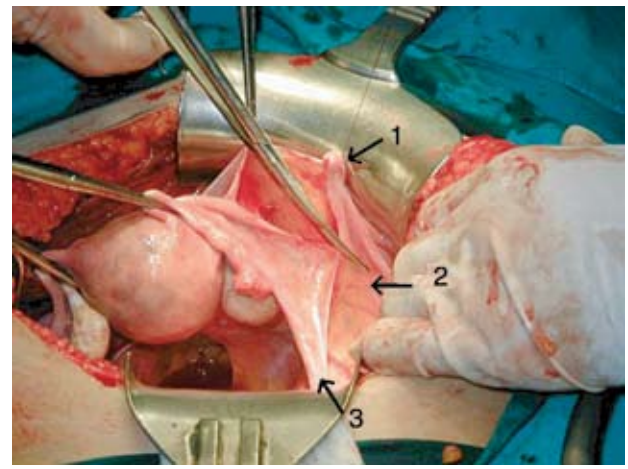


**Figure 3.** Dissection of ligamentum latum and approach of the great pelvic vessels. Arrow 1: lig. rotundum; arrow 2: lig. latum; arrow 3: lig. infundibulopelvicum (Courtesy dr. S. Runić).

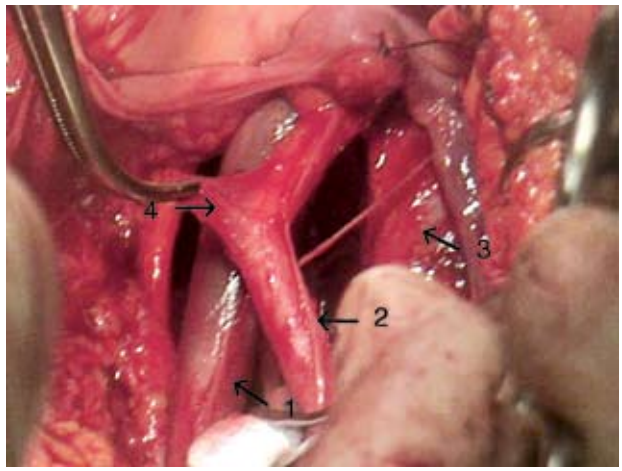


**Figure 4.** Extirpation of lymph nodes along the pelvic great vessels. Arrow 1: vena iliaca externa; arrow 2: arteria iliaca externa; arrow 3: m. psoas; arrow 4: extirpation of internal iliac lymph node (Courtesy dr. S. Runić).

iliac artery lymph node dissection is performed up to 2 cm above the aortic bifurcation. In the documented cases of preoperative metastasis to the paraaortic lymph nodes, mobilization of the ascending colon is performed and nodal dissection is continued up to the left renal vessels.

The constitutive part of pelvic lymphadenectomy is also dissection of hypogastric artery and vein lymph nodes, as well as nodes of the obturator and ischiorectal fossa and presacral and lateral sacral lymph nodes (Figure 5).

The operation is completed with retroperitoneal drainage of the obturator fossa by placing a JP-drain, without peritonealization.

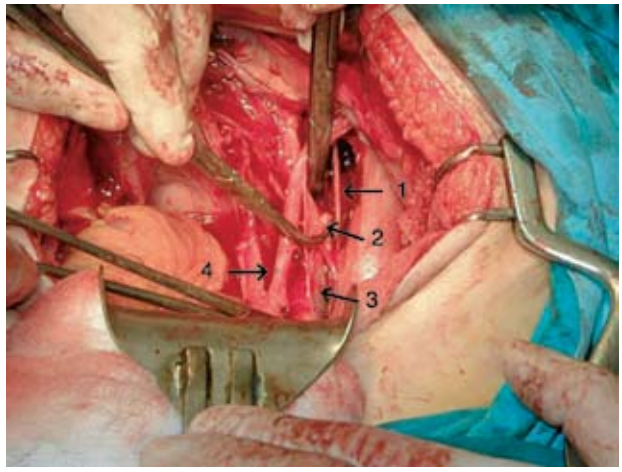


**Figure 5.** Lymph node dissection of obturator and ischiorectal fossa. Arrow 1: n. obturatorius; arrow 2: lymph nodes of the obturatory space; arrow 3: vena iliaca externa; arrow 4: arteria iliaca externa (Courtesy dr. S. Runić).

According to our results and experience, omitting peritonealization of the retroperitoneal space and establishing adequate drainage is the best way to avoid symptomatic and asymptomatic lymphocyst after such an extensive lymphadenectomy which is practised at our institution and confirmed by a recent randomized controlled study [27]. This technique has reduced the rate of lymphocyst formation at our institution from 8% with – to 1% without peritonealization, similar to the results of the previously cited study [27].

The most common complications after radical or modified radical hysterectomy with lymphadenectomy in the postoperative course at our institution are vesicovaginal fistula, venous thrombosis and lymphedema of the lower extremities. The rate of these complications is 1-5% and is directly correlated with the degree of radicality of the surgical procedure.

## Nerve-sparing radical hysterectomy with pelvic lymphadenectomy

Stage IB according to FIGO classification is divided into two substages depending on the size of the tumor ($\leq 4$ cm). Within one substage there is a wide range of tumor size (1-4 cm), so the question remains whether it is necessary to perform a radical hysterectomy with wide parametrial excision for all patients, therefore increasing their postoperative complication rate.

Nerve-sparing can be performed in two ways:

a. Reduced radicality

b. Nerve-sparing technique.

Modified radical hysterectomy with pelvic lymphadenectomy is the method of choice for low-risk groups, i.e. stage IB1 with tumor size < 2 cm, invasion up to 10 mm, without lymphovascular invasion and with negative pelvic lymph nodes [1,5,6].

Results of multiple studies demonstrate that nerve-sparing operations significantly decrease the dysfunction of the urinary bladder with quick recovery of its function in the postoperative course.

Nerve-sparing techniques are based on the good knowledge of the anatomy of the pelvic plexus (which is bilateral and formed by the hypogastric nerve with its sympathetic and parasympathetic branches originating from the sacral nerves 2, 3 and 4) and are characterized by operational radicality with sparing of the plexus. Sparing of these structures is important not only for the function of the bladder and rectum, but also for the sexual function postoperatively. Vaginal lubrication, changing the size of the vagina and contractions of small muscles during orgasm are all directly correlated with sparing of the pelvic plexus.

Identification of parasympathetic and sympathetic nerves, which innervate the bladder and pass through the caudal-lateral part of the cardinal, uterosacral and vesicovaginal ligament, is an important part of the nerve-sparing technique. Published results demonstrate fast recovery of the bladder function when compared with patients undergoing standard radical hysterectomy [28,29]. The precise criteria for patient selection for this technique are still not defined, even though it is used in low-risk groups of cervical cancer. Lymphadenectomy in the nerve-sparing technique is performed in the standard way.

## The dilemmas of lymphadenectomy

The definition of the prognostic factors for pelvic lymph nodes metastasis and its significance, practising of the endoscopic lymphadenectomy and decreasing the postoperative complications, all pose further questions:

a. The concept of sentinel lymph node lymphadenectomy.

b. Introduction of lymph node topography to the common clinical practice.

c. Which number of lymph nodes denotes adequate lymphadenectomy?

d. Minimal or maximal number of lymph nodes that should be histologically analyzed to determine the N0 status.

e. When is the paraaortic lymph dissection needed?

f. Which type of lymphadenectomy should be a procedure of choice: laparoscopic or by exploratory laparotomy?

## Sentinel lymph nodes during operative or laparoscopic lymphadenectomy

The predictive value of certain factors in the development of the nodal metastases is known.

The rationale for the identification of the first draining sentinel lymph node is:

a. The frequency of metastasis in the early stages of cervical cancer is 15% (range 10-25%), which means that in 75-90% of patients lymphadenectomy is performed without affecting the final disease outcome while it increases the complication rates associated with this procedure.

b. Cervix is located centrally in the pelvis and has a rich lymphatic supply, which requires extensive pelvic dissection to remove all the lymphatics.

c. Predictive factors are not helpful in determining the site of metastatically involved lymph nodes.

d. Preoperative diagnostic procedures are not accurate enough.

e. Exact determination of the status of lymph nodes simplifies subgrouping of the high-risk patients necessitating adjuvant therapy.

## Lymphatic mapping (topography) during lymphadenectomy

The procedure of identification of sentinel lymph node is inseparable from the topography of the pelvic lymphatics with the use of the blue dye and radiocolloid Technetium 99 (Tc 99).

Both of these methods could be used separately, although the combination of the two is more precise. Malur et al. [30] and Levenback et al. [31] reported accuracy of the combined methods at 90-100%, compared to only 50% using the blue dye [32,33] or 76% with the use of Tc 99 [34,35].

The aforementioned authors demonstrated that there are a small number of unilateral sentinel lymph nodes (up to 5%) as well as a large number (80%) of bilateral sentinel nodes in two lymph nodes (range 2-5). The most common localization (80%) of the sentinel lymph node is in the pelvis in the interiliac and obturator region.

Sentinel nodes of the paraaortic lymph nodes are discovered in 9% of cases with stage IB1 [31,32,34]. Identification of the sentinel lymph node of the paraaortic lymph nodes changes the concept of sequential, already accepted, model of metastasis of cervical cancer from before the era of lymph node topography [36-38]. The appearance of paraaortic lymph node metastasis demonstrates the importance of the posterior lymphatic drainage system which drains directly to the retroperitoneal lymph nodes.

The determination of a sentinel lymph node during laparoscopic lymphadenectomy is based on the combination of blue dye and lymphoscintigraphy with accuracy of 80% [33-35].

Regarding sentinel lymph node mapping, the published data are inconsistent. Some authors described this technique as highly accurate with a negative predictive value of 100% [31]. However, Marchiole at al. [39] reported a false-negative rate of 12.5% (negative predictive value of 87.5%) with 3 out of 24 patients who had micrometastasis in nonsentinel pelvic lymph nodes despite having negative findings on sentinel lymph node biopsy.

Multiple unanswered questions about sentinel node identification await the results of the ongoing GOG-0200 trial [40], as well as of the phase III sentinel node trials for melanoma and breast cancer [41].

## "Adequate" lymphadenectomy

The mean number of pelvic nodes is about 50, and this number changes during a woman's lifetime. The authors of this article believe that the concept of lymphadenectomy consists of complete extirpation of all the pelvic lymph nodes. The mean number of extirpated lymph nodes per patient for the authors of this paper is 21 (range 6-93). Surgical skills and experience, as well as oncological knowledge, increase the mean number of the dissected lymph nodes. The number of dissected nodes for the authors has increased from 6-10 to 21 per patient over 40 years of experience.

The results of Trimbos et al. [42] for the European oncology centers give a mean of 26 dissected lymph nodes per patient. Nijman et al. [43] states 11.46 as a mean of identified pelvic lymph nodes, confirming the importance of the surgical technique and surgeon's experience.

The prognostic significance of parametrial lymph nodes is already well known [17,44-46]. Since these nodes can be found in the distal parts of the parametria, the resection needs to be as close as possible to the pelvic sidewall, as described in the Meigs-Wertheim operation.

Because the sentinel lymph node lymphadenectomy in cervical carcinoma needs further justification through controlled randomized studies, the concept of extirpation of all the lymph nodes is still the standard approach used in clinical practice [47]. This concept is being used also in modified radical hysterectomy, since the word modified implies not the nodal dissection, but also a degree of parametrial, sacro-uterine ligament and vaginal resection.

## Minimal / maximal number of lymph nodes for N0

FIGO classification does not include nodal status in its staging of cervical cancer, differing from the TNM system which defines absence of metastasis if 10 or more lymph nodes are normal. It is unclear if that number refers to dissected and histologically examined nodes. If the number of lymph nodes is less than 10, the nodal status is still determined as N0 (TNM classification 2002, 6th edition) [10].

This statement is somewhat confusing, since the classification of the early stages of cervical cancer when the lymph node number is less than 10, can affect not only the plan of therapy, but also the prognosis of the disease. The retrospective immunohistochemical study of Lentz et al. [48] demonstrated increased number of micrometastases if the number of the dissected and analyzed lymph nodes was greater than 20. Metastases in 86% of the cases were found in the pelvis.

The significance of micrometastases and the therapeutic benefit of removal of the histologically negative lymph nodes still need further confirmation in clinical trials.

Even though N1(N+) changes the stage of disease in the TNM system and affects planning of therapy and prognosis, there is no clear definition of the number of positive nodes based on which a patient would be subgrouped, such as in other cancers (i.e. breast). Based on the GOG 92 protocol [49], all patients with N1 become high-risk group with poor prognosis.

A decrease in 5-year survival is associated with increased number of positive pelvic lymph nodes: N0 vs. N+1 vs. N+2-3 vs. N+4-5 vs. N+ >5; 5-year survival for the respective groups are 91, 75, 60, 55, and 14% for stage IB [50,51].

Results of multiple studies demonstrate that the number of tumor-involved lymph nodes is a more important prognostic factor than the presence of a positive node only. It is known that patients with one positive node have equal chance of good prognosis as those staged as N0 [50]. Retrospective studies show that the poor prognostic factor is not only the increased number of positive nodes, but also their location (e.g. obturator vs. common iliac nodes [44,51-54].

Based on retrospective [50,54] and prospective [49] studies, all patients with early-stage cervical cancer are divided in 3 prognostic groups: low, intermediate and high risk.

In our daily clinical practice we use the principle of extirpation and histological analysis of all the pelvic lymph nodes, since this is the best way of determining the degree of cancer spread, and plan postoperative therapy.

## Paraaortic lymph node dissection

Paraaortic lymph nodes are distant nodes in the progression of cervical cancer. The frequency of metastases to paraaortic nodes increases with stage IA2 to stage IIA from 0-10% [7-9,12].

Before the era of lymph node topography the concept of lymphatic drainage and metastasis was that of a stepwise nature in the following order: parametrial, obturator, hypogastric, external iliac, common iliac and, finally, paraaortic lymph nodes.

Lymphatic drainage mapping and the concept determining the sentinel node changes this concept and demonstrates direct drainage or metastasis to the

paraaortic lymph nodes in 8-15% of cases of stage IB-IIA [31,36-38].

In recently published studies, paraaortic lymph nodes were the first nodes metastatically involved in 9% of patients with stage IB1 cervical cancer [30,31, 52]. Results of other studies show high correlation between metastasis of common iliac and paraaortic lymph nodes [16,17,38].

Confirmation of positive common iliac nodes on frozen section necessitates extirpation of the paraaortic lymph nodes [44-46].

Our own, as well as the experience of other authors, demonstrates more frequent involvement of the left paraaortic lymph nodes [31,36,52].

While Benedetti-Panici et al. [44] propose extirpation of inframesenteric nodes, others suggest complete lymphadenectomy up to the left renal vein, which allows evaluation of the paraaortic lymph nodes [36,52]. Our way of approaching paraaortic lymph nodes has been already described [55].

The question of paraaortic lymphadenectomy for stage IB1 consisting of tumors 1-4 cm still remains, since the metastatic frequency is up to 3% for tumors < 2 cm and up to 9% for tumors >2-4 cm [36,56].

Suggested options are:

a. Complete paraaortic lymphadenectomy.

b. Selective lymphadenectomy of the lower paraaortic lymph nodes.

c. Avoidance of paraaortic lymphadenectomy and use of other adjuvant therapy such as radio- or radio/chemotherapy.

There is an improvement in survival in patients with tumor size of < 2 cm and positive lymph nodes if complete lymphadenectomy is performed [57,58], since radiotherapy with extended fields to the paraaortic lymph nodes is not sufficient [59,60].

The question of the therapeutic efficacy of extirpation of positive lymph nodes in the retroperitoneum remains open, awaiting further prospective clinical trials.

The authors' personal opinion is that with good surgical technique and minimal postoperative complications it is possible to completely dissect the paraaortic lymph nodes.

## Laparoscopic *versus* open lymphadenectomy

Laparoscopic methods are useful in identifying the degree of involvement and the status of the lymph nodes, therefore sparing patients not in need for such an extensive surgery or in deciding on a different mode of oncological therapy [33-35]. The technique requires large experience in the field of laparoscopy. It is possible to laparoscopically perform complete lymphadenectomy with or without hysterectomy with complication rates of up to 1%.

The most commonly cited advantages of laparoscopic methods are minimal complications, decreasing the postoperative recovery time and hospital stay. Until now there is still no recommendation to substitute the standard operative technique with the laparoscopic method with or without using the sentinel node biopsy [39,40].

## Conclusion

With the advances in the diagnostics of the nodal status in the early stages of cervical cancer (IA2, IB1-2, IIA), introduction of frozen section diagnosis and immunohistochemistry, lymph node topography, identification of sentinel lymph node during standard or laparoscopic lymphadenectomy, we conclude that patients with early-stage cervical cancer will mostly benefit from the standard operative lymphadenectomy with complete dissection of the pelvic and paraaortic lymph nodes.

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