**Nerve-sparing systematic para-aortic lymphadenectomy in the surgical treatment of cervical cancer: prevention of lower urinary tract dysfunction**

**Authors**

Department of Gynecologic Oncology, N.A. Lopatkin Research Institute of Urology and Interventional Radiology – branch of the National Medical Research Center of Radiology, Ministry of Health of Russia; Moscow, Russia.

**Keywords:** Nerve-sparing surgery, para-aortic lymphadenectomy, urinary tract dysfunction, hypogastric nerves.

**Abstract.**

**Objectives:** To evaluate the pathologic and postoperative outcomes, including urinary tract dysfunction, of open nerve-sparing para-aortic lymphadenectomy (NSPAL) as a part of type C1 radical hysterectomy (RH).

**Material and Methods:** A total of 67 patients with cervical cancer (stages IA-IIB) were included in this study, of whom 43 patients underwent NSPAL with type C1 RH (group 1), and 24 underwent PAL with type C2 RH (group 2).

**Results:** The frequency of hydronephrosis was significantly lower in group 1 relative to group 2 (11.6% vs. 37.5%; P < 0.05). Relative to group 2 patients, those in group 1 also exhibited significantly lower rates of short-term bladder storage and voiding dysfunction (4.7% vs. 41.7%) and stress urinary incontinence (0% vs. 20.8%). Long-term bladder storage and voiding dysfunction at 3 and 6 months post-surgery were only observed among 25.0% and 20.8% of patients in group 2, respectively (P < 0.05). Para-aortic lymph node (PALN) metastases were observed in 7.5% of patients, including 30.0% of adenocarcinoma patients and 3.5% of squamous cell carcinoma patients (P = 0.03). PALN metastases were found in 20.8% of patients with low-grade differentiated cervical cancer and in no patients with high or moderate grade differentiated cervical cancer (P = 0.01).

**Conclusion:** The nerve-sparing surgical approach may represent an effective means of preventing urinary tract dysfunction when treating stage IA-IIB cervical cancer stage IA-IIB. NSPAL performed via the left renal vein is useful as a means of treating adenocarcinoma and low-grade differentiated cervical cancer. The level of NSPAL in the treatment of squamous cell carcinoma and high or moderate grade differentiated cervical cancer is inferior mesenteric artery.

1. **Introduction**

At present, the standard surgical treatment for cervical cancer is type C radical hysterectomy (RH) and pelvic lymphadenectomy [1]. However, the value of systematic рara-aortic lymphadenectomy (PAL) in these patients has been a topic of active discussion.Рelvic lymphadenectomy involves the removal of regional lymph nodes such as the external, internal, and common iliac lymph nodes, as well as the obturator and sacral lymph nodes. PAL is not currently a standard surgical treatment for cervical cancer, as the para-aortic lymph nodes (PALNs) are a distant group of lymph nodes [2].

The revised 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer differentiates between two stage IIIC disease subtypes: IIIC1 disease with pelvic lymph node involvement and IIIC2 disease with para-aortic lymph node involvement [3].

The value of systematic PAL as an aspect of radical surgical treatment for cervical cancer has been a topic of growing research interest in recent years, as metastatic lesions of the PALNs are observed in 6-13% of patients with locally advanced cervical cancer [4,5,6,7].

PAL has been a controversial topic for over a century. First described by M. Chevassu as a surgical treatment for testicular tumors in 1910 [8], the development of retroperitoneal lymphadenectomy approaches has largely been connected with testicular cancer surgery [9]. More recently, authors reported the use of systematic PAL in the treatment of gynecological cancer [10, 11].

Retroperitoneal lymphadenectomy enables the evaluation of the histological status of the PALNs, thereby guiding postoperative radiation therapy in the cases where microscopic metastases are evident. However, bulky PALN resection is a clinically significant operation, and the efficacy of radiotherapy treatment for these patients is relatively limited [12].

Jewett et al. and Donohue et al. introduced nerve-sparing PAL (NSPAL) approaches in 1988 and 1990, respectively [13, 14]. This procedure focuses on the preservation of the retroperitoneal sympathetic plexuses, enabling the preservation of ejaculatory function in 100% of cases. At present, NSPAL is commonly used in the surgical treatment of testicular cancer patients. The implications of retroperitoneal autonomic nerve preservation in the surgical treatment of cervical cancer patients are not completely understood at present. In one study, Lee et al. evaluated the short-term clinical outcomes of robot-assisted NSPAL as a part of type C1 RH in surgical cancer patients, and found that the rates of urological complications were increased among 28 patients who underwent robot-assisted NSPAL [15].

The present study sought to evaluate the PALN metastases mapping and long-term clinical outcomes associated with open systematic NSPAL with type C1 RH in the surgical treatment of cervical cancer patients.

**Material and Methods**

In total, 67 patients with stage IA-IIB cervical cancer were treated at the Gynecology Department of Main Military Clinical Hospital named after N. N. Burdenko were included in this study. These patients were separated into two groups, the first of which consisted of 43 patients who underwent systematic level 2-4 NSPAL (level 2 - n=1; level 3 - n=19; level 4 - n=23) with type C1 RH, and the second of which consisted of 24 patients who underwent systematic level 2-4 PAL (level 2 - n=10; level 3 - n=4; level 4 - n=10) with type C2 RH C2 without nerve preservation. Pelvic lymphadenectomy was performed in all cases.

Systematic level 4 NSPAL was performed through the following series of steps. First, the right ovarian vessels were mobilized from surrounding adipose tissue and the right ovarian vein was ligated to the inferior vena cava (IVC), while the right ovarian artery was ligated to the aorta. The upper and middle thirds of the right ureter were isolated from the ovarian vessels and retroperitoneal adipose tissues. Then the right genitofemoral nerve and right sympathetic trunk were gradually separated and preserved prior to lymph node dissection around the right common vessels and the IVC. The superior hypogastric plexus (SHP) and upper thirds of hypogastric nerves were further isolated and preserved prior to bifurcation lymphadenectomy. Separation and preservation of the inferior mesenteric and intermesenteric plexuses, as parts of the abdominal aortic plexus, was then performed before lymph node dissection in the interaortocaval space and the anterior surface of the aorta at the level of the left renal vein (LRV). Next, the descending and sigmoid colon were mobilized, and the left ovarian vessels were separated from the surrounding adipose tissues and the upper and middle thirds of the left ureter. The left ovarian vein was ligated from the LRV and the left ovarian artery from the aorta. In the final stage, the left genitofemoral nerve and the left sympathetic trunk were isolated and preserved prior to left-sided PAL at the level of the LRV. This surgical procedure was continued in the pelvic region with typical preservation of the pelvic autonomic nerves as described in reports by Sakuragi et al. [16]. During the operation, we did not perform the peritonization of the para-aortic and pelvic regions nor did we drain the para-aortic region. The bilateral pelvic retroperitoneal spaces were drained by two drainage tubes in all cases. Drains were removed as soon as lymphorrhea was less than 100-200 mL per day.

Аfter receiving the results of a planned morphological study, the disease was restaged in 16 cases, and the staging of cervical cancer was adjusted to IIIB for certain patients (n = 10) in whom microscopic metastases of the pelvic lymph nodes were confirmed. Six patients were diagnosed with stage IV cervical cancer when microscopic metastases in PALNs (n = 5) or ovarian cancer (n = 1) were detected.

We evaluated operative duration, blood loss, intraoperative vascular injury, lymphorrhea duration and volume, and the number of resected PALNs in the comparison groups. We compared postoperative complications among patients in our NSPAL and PAL cohorts, including para-aortic lymphocyst development, postoperative hydronephrosis, urinary tract infection, urethral fistula formation, short-term and long-term bladder storage and voiding dysfunction, stress urinary incontinence, pancreatitis, wound infection, venous thrombosis, and pulmonary embolism.

The STATGRAPHICS 3.0 (Statistical Graphics System) package (Manugistics Inc., USA) was used for statistical analysis. Unpaired numerical data were compared with unpaired Student’s t-tests. Proportional data were compared using the χ² test or Fisher’s exact test. P-values less than 0.05 were considered statistically significant.

**Results**

Clinical and histological profiles for the groups of patients included in the present study are shown in Table 1. There were no significant differences in the distributions of any of these variables when comparing these two patient groups.

Operative parameters for the patients in this study are summarized in Table 2. There were significant differences in operative outcomes when comparing these two groups. The operative time and time of systematic PAL were 358.1±62.6 ml vs 302.9±62.5 ml and 79.7±33.7 ml vs 43.7±27.0 ml respectively. These differences were statistically significant (P = 0.001). Intraoperative blood loss differed significantly between the NSPAL group (417.4 ± 205.8 mL) and the PAL group ( 700.0±346.4 mL)(P = 0.001). Despite the fact that the operative blood loss was 300 mL greater in the second group, there was no significantly higher incidence of retroperitoneal vascular injury in the second group relative to the first group (0% vs. 2.3%, P > 0.05). The volume of lymphorrhea was 3270.0±1936 mL in the first group and 2170.4±2006 mL in the second group, with no significant difference between these groups (P = 0.048). The median number of PALNs differed significantly between the first group (17.6±7.7) and the second group (12.2±9.0) (P = 0.02).

Postoperative complication rates for the 67 patients with cervical cancer who underwent PAL with or without nerve preservation as a part of type C1 or C2 RH are summarized in Table 3. There was a significant difference in the frequency of hydronephrosis between these groups. Dilatation of renal pelvis was detected in five patients (11.6%) in the first group and 9 patients (37.5%) in the second group (P = 0.03). Moreover, dilatation of the renal pelvis > 20 mm was evident in 2 patients (4.7%) in the first group and 9 patients (37.5%) in the second group (P = 0.002). Four (16.7%) patients in the second group with hydronephrosis underwent external or internal drainage of the kidneys, while no patients in the first group exhibited hydronephrosis. Rates of short-term/long bladder storage and voiding dysfunction, as well as stress urinary incontinence, were also significantly lower in the first group compared with the second group, as shown in Table 2. No patients in the first group exhibited para-aortic lymphocysts, while the frequency of noninfected lymphocysts in the second group was 8.3%, with no significant difference between these groups (P > 0.05). Lymphedema occurred in 1 (2.3%) patient in the first group and in 1 (4.2%) patient in the second group (P > 0.05). The incidence of complications including urinary tract infection, ureterovaginal or external ureteral fistula formation, postoperative pancreatitis, wound infection, venous thrombosis, and pulmonary embolism did not differ significantly between these patient groups.

Histological examination results are summarized in Table 4. Lymph node metastases were observed in 15 (22.4%) patients in the overall cohort. The rates of lymph nodes metastasis in stage IIA and IIB cervical cancer patients were 20.0% (n = 9) and 42.9% (n = 6), respectively. The overall frequency of pelvic lymph node metastases was 19.4% (n = 13), of which 10.4% (n = 7) involved the obturator lymph nodes, 10.4% (n = 7) involved the internal and external iliac nodes, and 1.5% (n=1) involved the lymph nodes of the cardinal ligament. The rate of PALN metastasis did not exceed 7.5% (n = 5). Two patients (3.0%) exhibited PALN metastases above the level of the inferior mesenteric artery (IMA) on the anterior and left lateral surfaces of the aorta, while 2 patients (3.0%) exhibited such metastases below the level of the IMA on the anterior and aortic bifurcation surfaces, and 1 patient (1.5%) harbored metastases above and below the level of the IMA on the interaortocaval, anterior, and left lateral surfaces of the aorta. We observed metastases in the pelvic and para-aortic regions in 3 cases (4.5%). Isolated PALN metastases were observed in 2 cases (3.0%) at the bifurcation of the aorta and at the anterior surface of the aorta below the level of the IMA. These isolated PALN metastases were found in patients with cervical cancer stages IB1 and IIB, low-grade tumor differentiation, and a tumor diameter not exceeding 1.5 cm but exhibiting endophytic growth.

In this study, a correlation was detected between PALN positivity, histological type, and tumor differentiation. Positive PALNs were detected in 3/10 (30.0%) of adenocarcinoma cases, all of which were above the level of the IMA. In contrast, they were detected in just 2/57 (3.5%) cases of squamous cell carcinoma, all of which were below the level of the IMA (P = 0.03). PALN metastases were detected in 5/24 (20.8%) patients with low-grade differentiated cervical cancer and in none of the 43 patients with high- or moderate-grade differentiated cervical cancer (P = 0.01). There was no correlation between positive lymph nodes metastasis and tumor size in this patient cohort.

Relapse in the para-aortic region was not observed in either group over a median 44.7 ± 19.3 month follow-up period. However, 4 (9.3%) patients in the NSPAL group exhibited local or regional recurrence, and 2 (8.3%) patients in the PAL group exhibited locoregional or local and distant recurrence (p=0.757).

**Discussion**

The detection of positive PALNs is the most significant prognostic factor [17]. Type C RH and PAL enable 5-year survival rates of over 90% for patients with node-negative disease [18]. However, survival rates for patients with positive lymph-vascular space invasion or pelvic node-positive patients with squamous or adenosquamous carcinoma are reduced to 85.5% [19]. Morice et al. reported that isolated PALN metastases occur in no more than 1% of patients [20]. Lymphatic tumor spread can occur indirectly via the pelvic lymph nodes, directly through the lymphatic vessels of the sacro-uterine ligaments, and through lymph nodes and vessels proximal to ovarian vessels [21]. Furthermore, according to Panici et al. and to our own data, the majority of PALN metastases are observed on the anterior and left lateral surfaces of the aorta without the involvement of lymph nodes on the right lateral side of the IVC [22]. This emphasized the need for surgeons to carefully revise and remove the PALN on the left lateral side. However, nerve-sparing left-sided PAL is more difficult to conduct as compared to this same operation on the right side of the body, as surgeons need to mobilize the left-sided lymph nodes from the left ureter and nerves, encountering technical problems due to the location of the inferior mesenteric artery in this region.

The correlative relationships between PALN metastases, tumor histologic type, and differentiation status suggest that performing NSPAL via the LRV is a useful treatment for adenocarcinoma and low-grade differentiated cervical cancer. The level of NSPAL in the treatment of squamous cell carcinoma and high or moderate grade differentiated cervical cancer is inferior mesenteric artery. Recent retrospective trials suggest that improved survival in these patients is associated with the removal of PALNs and metastases [23]. As such, systematic PAL offers significant benefits to the treatment of cervical cancer and allows for adequate surgical staging and the planning of adjuvant therapy [24].

This procedure is still associated with significant morbidity, most often affecting the urological system. Causes of urinary tract dysfunction include direct injury and the displacement of autonomic nerves such as the SHP during PAL at the bifurcation of the aorta and IVC [15].

The effects of damage to the inferior mesenteric and intermesenteric plexuses as components of the abdominal aortic plexus remain incompletely understood. Dobrowolski et a. found that patients that had undergone aorto-aortic reconstruction surgery to treat abdominal aortic aneurysms who suffered injuries to the intermesenteric, inferior mesenteric, and superior hypogastric plexuses did not exhibit significant changes in anorectal function, although this prior study did not discuss urinary tract dysfunction in these patients [25].

In the present study, 34.5% of patients in the nerve-sparing surgery group experienced urological complications as compared to 62.6% of patients in the second treatment group. Lee et al. reported that urological complications arose in 28.6% of patients that had undergone robot-assisted NSPAL. Rates of ureterovaginal or external ureteral fistulae were high in both groups, affecting 4 (9.3%) and 1 (4.2%) patients in these two groups, respectively, with all fistulae being present in the middle or upper third of the ureter. Similar findings have also been described in other studies in which ureterovaginal fistulae were observed in 14.3% of patients undergoing extended NSPAL [15].

Just five patients in the NSPAL group (11.6%) and nine patients in group 2 (37.5%) experienced dilatation of the renal pelvis at one-month post-operation (P = 0.03). All of these patients in the second group exhibited renal pelvis dilatation of > 20 mm. Four patients with hydronephrosis in group 2 underwent kidney drainage via percutaneous nephrostomy or ureteral stent placement, while no patients in the NSPAL group experienced hydronephrosis. In a separate analysis, hydronephrosis > 1-month post-operative was observed in 4 patients (14.3%) following extended nerve-sparing lymphadenectomy [15]. As such, these findings support a lower incidence of hydronephrosis one month after NSPAL with type C1 RH as compared to PAL with type C2 RH. This may be a result of the better preservation of the abdominal aortic plexus, fibers of which form the ureteral plexus and innervate the upper and middle portions of the ureter [26].

Rates of short-term bladder storage and voiding dysfunction were significantly lower among patients in the nerve-sparing group (4.7%) relative to those in group 2 (41.7%). At 3 and 6 months post-operation, no patients in the NSPAL group exhibited bladder storage and voiding dysfunction, whereas this outcome was observed among 25.0% and 20.8% of patients in the PAL group at these respective time points. Another prominent cause of hydronephrosis is vesicoureteral reflux associated with increasing intravesical pressure owing to postoperative bladder storage and voiding dysfunction in patients with injuries to the parasympathetic and sympathetic portions of the pelvic autonomic plexus and nerves. Voiding difficulties are primarily attributable to damage to the inferior hypogastric plexus. Bladder storage dysfunction may be linked to a hypertonic bladder as a result of injury to the parasympathetic portion of the pelvic autonomic nerves - pelvic splanchnic nerves which arise from sacral nerve roots S2-S4. As a rule, bladder hypotonia results from the overdistension of bladder capacity [27]. Stress urinary incontinence was observed in 5 (20.8%) patients in the PAL group. This urological condition can occur due to damage to the sympathetic portion of the pelvic autonomic nerves – the hypogastric nerves which arise from the SHP and abdominal aortic plexus [15]. As such, the preservation of autonomic nervous system integrity in the retroperitoneal area and small pelvis by avoiding damage to the intermesenteric, inferior mesenteric, superior hypogastric, and inferior hypogastric plexuses, as well as the hypogastric and pelvic splanchnic nerves, made it possible to preserve urinary tract function in patients that underwent NSPAL treatment.

**Conclusion**

In summary, systematic NSPAL with type C1 RH does not increase the occurrence of intraoperative vascular injury, lymphedema, lymphocyst formation, venous thrombosis, pulmonary embolism, urinary tract infection, or ureterovaginal or external ureteral fistula formation, whereas it does significantly decrease the frequency of hydronephrosis, short-term/long-term urinary tract dysfunction, and stress urinary incontinence relative to systematic PAL with type C2 RH. Performing NSPAL via the LRV represents a valuable approach to treating adenocarcinoma and low-grade differentiated cervical cancer, as NSPAL does not decrease the radicality of treatment. The level of NSPAL in the treatment of squamous cell carcinoma and high or moderate grade differentiated cervical cancer is inferior mesenteric artery.

**Disclosure Statement**

The authors declare no conflict of interest

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**Table 1**

**Clinical and histological profiles of 67 patients with cervical cancer who underwent PAL with or without nerve preservation and RH C1-2 types**

|  |  |  |
| --- | --- | --- |
| **Clinical and histological profiles** | **First group**  **n=43** | **Second group**  **n=24** |
| **Age (years)** | **44.1±10.4 (27-72)** | **49.2±9.6 (35-72)** |
| **Stage by FIGO:**  **IA**  **IB**  **IIA**  **IIB**  **IIIB**  **IV** | **n=6**  **n=23**  **n=2**  **n=2**  **n=6**  **n=4** | **n=2**  **n=12**  **n=3**  **n=1**  **n=4**  **n=2** |
| **Histological differentiation**  **G1-2**  **G3** | **n=30**  **n=13** | **n=13**  **n=11** |
| **Cell type**  **Adenocarcinoma**  **Squamous cell carcinoma** | **n=7**  **n=36** | **n=3**  **n=21** |
| **Neo-adjuvant therapy:**  **Chemotherapy**  **Radiotherapy** | **n=1**  **n=5** | **none**  **n=1** |

**Table 2**

**Operative characteristics of 67 patients with cervical cancer who underwent PAL with or without nerve preservation undergoing type C1 or C2 RH**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **First group**  **n=43** | **Second group**  **n=24** | **P** |
| **Median operative time (min)** | **358±62.6** | **302±62.5** | **p=0.001** |
| **Median time of PAL (min)** | **79.7±33.7** | **43.7±27.0** | **p=0.001** |
| **Median blood loss (ml)** | **417.4±205.8** | **700±346.4** | **p=0.001** |
| **Retroperitoneal vessels injury** | **2.3% (n=1)** | **none** | **p>0.05** |
| **Median time of lymphorrhea (day)** | **10.29±2.9** | **8.75±5.9** | **p>0.05** |
| **Median volume of lymphorrhea (ml)** | **3270.0±1936** | **2170.4±2006** | **p=0.048** |
| **Median quantity of para-aortic nodes** | **17.6±7.7** | **12.2±9.0** | **p=0.02** |

**Table 3**

**Rates of early and late postoperative complications in 67 patients with cervical cancer who underwent PAL with or without nerve preservation and RH C1-2 types**

|  |  |  |  |
| --- | --- | --- | --- |
| **Complication** | **First group**  **n=43 (%)** | **Second group**  **n=24 (%)** | **P** |
| **Para-aortic lymphocyst (asymptomatic) 1 month after procedure** | **none** | **n=2 (8.3%)** | **p>0.05** |
| **Lymphedema** | **n=1 (2.3%)** | **n=1(4.2%)** | **p>0.05** |
| **Postoperative pancreatitis** | **n=1 (2.3%)** | **none** | **p>0.05** |
| **Wound infection** | **n=1 (2.3%)** | **none** | **p>0.05** |
| **Venous thrombosis** | **n=5(11.6%)** | **n=1 (4.2%)** | **p>0.05** |
| **Pulmonary embolism** | **n=2 (4.6%)** | **n=1 (4.2%)** | **p>0.05** |
| **Urinary tract infection (postoperative secondary pyelonephritis)** | **n=6 (13.9%)** | **n=1 (4.2%)** | **p>0.05** |
| **Ureterovaginal or external ureteral fistula** | **n=4 (9.3%)** | **n=1 (4.2%)** | **p>0.05** |
| **Hydronephrosis 1 month after procedure** | **n=5 (11.6%)** | **n=9 (37.5%)** | **p=0.03** |
| **Short-term bladder storage and voiding dysfunction (1 month after operation)** | **n=2 (4.7%)** | **n=10 (41.7%)** | **p=0.0001** |
| **Long-term bladder storage and voiding dysfunction (3 months after the operation)** | **none** | **n=6 (25.0%)** | **p=0.003** |
| **Long-term bladder storage and voiding dysfunction (6 months after the operation)** | **none** | **n=5 (20.8%)** | **p=0.01** |
| **Stress urinary incontinence** | **none** | **n=5 (20.8%)** | **p=0.01** |

**Table 4**

**The rates of lymph nodes metastases in 67 patients with cervical cancer stage IA-IIB**

|  |  |  |  |
| --- | --- | --- | --- |
| **Lymph node metastasis** | **The rate of lymph nodes metastasis (n/%)** | | |
| **Negative lymph nodes metastasis** | **n=52 (77.6%)** | | |
| **Positive lymph nodes metastasis** | **n=15 (22.4%)** | | |
| **Pelvic lymph nodes metastasis** | **n=13 (19.4%)** | | |
| **Para-aortic lymph nodes metastasis +/- pelvic lymph nodes metastasis** | **n=5 (7.5%)** | | |
| **above the level of IMA** | **below the**  **level of IMA** | **above and below the level of IMA** |
| **n=2**  **(3.0%)** | **n=2**  **(3.0%)** | **n=1**  **(1.5%)** |