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

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

**Abstract.**

**Objectives:** to evaluate pathologic and postoperative outcomes of open nerve-sparing para-aortic lymphadenectomy (NSPAL) as a part of radical hysterectomy (RH) С1 type, including the urinary tract dysfunction.

**Material and methods:** research was included 67 patients with cervical cancer stages IA-IIB. 43 patients of first group underwent NSPAL with RH С1 type. 24 patients of second group underwent PAL with RH C2 type.

**Results:** the frequency of hydronephrosis in the first group was 11.6% and in the second group - 37.5% (p<0.05). Rates of short-term bladder storage and voiding dysfunction, stress urinary incontinence were significantly lower in the nerve-sparing group than those in the second group: 4.7% vs 41.7%; none vs 20.8% respectively. The long-term bladder storage and voiding dysfunction 3 and 6 months after procedure were observed in 25.0% and 20.8% only in patients of second group (p<0.05). Para-aortic lymph nodes (PALN) metastases were found in 7.5%. Positive PALN were detected in 30.0% of adenocarcinoma and in 3.5% of squamous cell carcinoma (p=0.03). PALN metastases were found in 20.8% patients with low grade differentiated cervical cancer and no one patient with high or moderate grade differentiated cervical cancer (p=0.01).

**Conclusion:** the nerve-sparing surgical approach may perform in the treatment of cervical cancer stage IA-IIB to prevent the urinary tract dysfunction. NSPAL by the left renal vein is useful for treatment of 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**

To date the standard of surgical treatment of cervical cancer is radical hysterectomy (RH) C type and pelvic lymphadenectomy [1]. However, frequently the question of systematic рara-aortic lymphadenectomy (PAL) has been considered separately.Рelvic lymphadenectomy involves the removal of regional lymph nodes such as external, internal and common iliac lymph nodes, obturator and sacral lymph nodes. Рara-aortic lymphadenectomy is not included in the standard of surgical treatment for cervical cancer because para-aortic lymph nodes are a distant group of lymph nodes [2].

According to the new classification revision 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer distinguish two substages IIIC: IIIC1 - pelvic lymph nodes involvement and IIIC2 - para-aortic lymph nodes involvement [3].

Recently many researchers paid attentions to the systematic PAL how more radical surgical treatment of cervical cancer. Metastatic lesion of the para-aortic lymph nodes in locally advanced cervical cancer is noted in 6-13% cases [4,5,6,7].

Historically PAL has been the object of controversy during more than one hundred years. PAL was first described in 1910 by M.Chevassu in surgical treatment of testicular tumor [8]. Since the fifties of the twentieth century development of retroperitoneal lymphadenectomy connected with testicular cancer surgery [9]. A few decades later some authors reported results of systematic PAL in the treatment of gynecological cancer [10, 11].

Retroperitoneal lymphadenectomy allows to evaluate the histological status of para-aortic lymph nodes (PALN) for planning postoperative radiation therapy in the cases of microscopic metastases. On the other hand resection of bulky PALN is a clinically significant stage inasmuch as effectiveness of radiation therapy in treatment of these cases is limited [12].

M. Jewett et al. and J. Donohue et al. were introduced nerve-sparing approach and described the technique of nerve-sparing para-aortic lymphadenectomy (NSPAL) in 1988 and 1990 years respectively [13, 14].

The fundamental element of this operation is preservation of retroperitoneal sympathetic plexuses that allow saving the ejaculatory function in 100% cases. So far, NSPAL is commonly used in the surgical treatment of testicular cancer patients. The role of retroperitoneal autonomic nerves preservation in the surgical treatment of cervical cancer patients is not completely investigated. In single study Y.S. Lee et al evaluated short-term clinical outcomes of robot-assisted NSPAL as part of RH C1 type in the treatment of cervical cancer patients. The rates of urological complications were increased among 28 patients who underwent robot-assisted NSPAL [15].

This study was aimed to evaluate the PALN metastases mapping and long-term clinical outcomes using open systematic NSPAL with RH C1 type in the surgical treatment of cervical cancer patients.

**Material and methods**

67 patients with cervical cancer stages IA-IIB were treated at the Gynecology Department of Main Military Clinical Hospital named after N. N. Burdenko were included in research. The first group consisted of 43 patients who underwent systematic NSPAL 2-4 level (level 2 - n=1; level 3 - n=19; level 4 - n=23) with RH С1 type with nerve preservation. The second group included 24 patients who underwent systematic PAL 2-4 level (level 2 - n=10; level 3 - n=4; level 4 - n=10) with RH C2 type without nerve preservation. Pelvic lymphadenectomy were performed in all cases.

The systematic NSPAL 4 level was included the following steps. At the beginning right ovarian vessels were mobilized from surrounding fat tissues and the right ovarian vein was ligated from inferior vena cava (IVC), the right ovarian artery - from aorta. The upper and middle thirds of right ureter were isolated from ovarian vessels and fat retroperitoneal tissues. Then the right genito-femoral nerve and right sympathetic trunk were gradually separated and preserved before lymph node dissection around right common vessels and IVC. Further the superior hypogastric plexus (SHP) and upper thirds of hypogastric nerves were isolated and saved before bifurcation lymphadenectomy. The following step was separation and preservation of inferior mesenteric and intermesenteric plexuses as parts of abdominal aortic plexus before lymph node dissection in the interaortocaval space and anterior surface of aorta by the level of the left renal vein (LRV). After that the descending and sigmoid colon were mobilized, left ovarian vessels were separated from surrounding fat tissues, the upper and middle thirds of left ureter. The left ovarian vein was ligated from LRV and the left ovarian artery – from aorta. At the final stage the left genito-femoral nerve and left sympathetic trunk were isolated and preserved before left-side para-aortic lymphadenectomy by the level of LRV. The surgical procedure was continued in the pelvic region with typical preservation of pelvic autonomic nerves as described in reports Sakuragi N. et al. [16]. During the operation we did not perform the peritonization of para-aortic and pelvic regions and did not drain the para-aortic region. The bilateral pelvic retroperitoneal spaces were drained by two drainage tubes in all of cases. Drains were removed as soon as lymphorrhea less than 100-200 ml per day.

Аfter receiving the results of a planned morphological study the disease was restaged in 16 cases. So, the stage of cervical cancer was changed to IIIB (n = 10) as microscopic metastases in pelvic lymph nodes were confirmed. 6 patients were diagnosed the cervical cancer stage IV when microscopic metastases in PALN (n = 5) or ovarian cancer (n = 1) were determined.

We evaluated an operation time, blood loss, intraoperative vessels injury, lymphorrhea time and volume, quantity of resected PALN in compared groups. According to the type of lymphadenectomy we analyzed postoperative complications, as a para-aortic lymphocyst, postoperative hydronephrosis, urinary tract infection, ureteral fistula, short-term and long-term bladder storage and voiding dysfunction, stress urinary incontinence, pancreatitis, wound infection, venous thrombosis and pulmonary embolism.

The statistical software package STATGRAPHICS 3.0 (Statistical Graphics System), Manugistics Inc. (USA) was used for statistical analysis. Unpaired numerical data were compared with Student unpaired t test. Proportional data were compared using the χ² test or the Fisher exact test. P values less than 0.05 were considered statistically significant.

**Results**

Clinical and histological profiles of studied groups are presented in Table 1. There was no significant difference in distribution of each variable between the first and second groups.

Table 2 shows operative characteristics. There were significant differences in operative outcomes in compared groups: 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). The operative blood loss was 417.4±205.8 ml in the first group and 700.0±346.4 ml in the second group. This difference was also statistically significant (p=0.001). Despite the fact that the operative blood loss was 300 ml more in the second group than the first group, but the retroperitoneal vessels injury in the second group was not higher than in the first group (none 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 (p=0.048), but the time of lymphorrhea was no significant difference. The median quantity of PALN was 17.6±7.7 in the first group and 12.2±9.0 in the second group, it is statistically significant difference (p=0.02).

In table 3 we present rates of postoperative complications in 67 patients with cervical cancer who underwent PAL with or without nerve preservation as a part of RH C1 or C2 types. According to the study, there was significant difference in the frequency of hydronephrosis in the first group. So, dilatation of renal pelvis was detected only in 5 patients (11.6%) of first group and in 9 patients (37.5%) of second group (p=0.03). Moreover dilatation of renal pelvis more than 20 mm was occurred in 2 patients (4.7%) of first group and in 9 patients (37.5%) of second group (p=0.002). 4 (16.7%) patients of second group with hydronephrosis had external or internal draining of kidney and no one patients in first group with hydronephrosis. Rates of short-term/long bladder storage and voiding dysfunction, stress urinary incontinence were also significantly lower in the first group compared with second group as shown in the table 2. No one patient of first group have para-aortic lymphocysts, the frequency of noninfected lymphocysts in the second group was 8.3%. The difference is not statistically significant (p>0.05). The lymphedema was occurred in 1 (2.3%) patient of first group and in 1 (4.2%) patient of second group (p>0.05). The incidence of complications such as urinary tract infection, ureterovaginal or external ureteral fistula, postoperative pancreatitis, wound infection, venous thrombosis and pulmonary embolism had no significant difference in compared groups.

The results of histological examination are shown in Table 4. Lymph node metastases were observed in 15 (22.4%) patients of both groups. The rates of lymph nodes metastases were 20.0% (n = 9) in the cervical cancer stage IB and 42.9% (n = 6) in the cervical cancer stage IIA and IIB. The frequency of pelvic lymph nodes metastases was 19.4% (n = 13), 10.4% (n = 7) of them involved the obturator lymph nodes, 10.4% (n = 7) - the internal and external iliac nodes and 1.5% (n=1) - the lymph nodes of cardinal ligament. The rate of PALN metastases was not exceed 7.5% (n = 5). 2 patients (3.0%) had PALN metastases above the level of inferior mesenteric artery (IMA) on the anterior and left lateral surfaces of the aorta, 2 patients (3.0%) – below the level of IMA on the anterior and aortic bifurcation surfaces and 1 patient (1.5%) – above and below the level of 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%). The 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. The isolated PALN metastases were found in patients with cervical cancer stages IB1 and IIB, low grade differentiated tumor, diameter of the tumor did not exceed 1.5 cm but had endophytic growth.

In the present study, there was correlation between positive PALN and histological type and differentiation of tumor. Positive PALN were detected in 3 (30.0%) of 10 adenocarcinoma cases (all of them were above the level of IMA) and in 2 (3.5%) of 57 squamous cell carcinoma cases (all of them were below the level of IMA) (p=0.03). PALN metastases were found in 5 (20.8%) among 24 patients with low grade differentiated cervical cancer and no one among 43 patient with high or moderate grade differentiated cervical cancer (p=0.01). There was no correlation between positive lymph nodes metastasis and tumor size.

The relapse in the para-aortic region was not noted in the both groups after a median follow-up of 44.7 ± 19.3 months. However, 4 (9.3%) patients of first group had a local or regional recurrence and 2 (8.3%) patients of second group had a locoregional or local and distant recurrence (p=0.757).

**Discussion**

The detection of positive para-aortic lymph nodes is the most significant prognostic factor [17]. The RH C type and pelvic lymphadenectomy allows reaching the 5-year survival rate more than 90% for patients with node-negative disease [18]. However, the survival rate for patients with positive lymph-vascular space invasion or pelvic node-positive patients with squamous or adenosquamous carcinoma is decreased till 85.5% [19]. P. Morice et al. reported that isolated PALN metastases occur not more than 1% [20]. So, pathways of lymphatic tumor spread to PALN can be indirect - through pelvic lymph nodes, direct - through lymphatic vessels of sacro-uterine ligaments and through lymph nodes and vessels going near ovarian vessels [21]. Furthermore according P. Benedetti Panici et al. and our data the most of PALN metastases are observed on the anterior and left lateral surfaces of aorta, without involvement of lymph nodes on the right lateral side of IVC [22]. This fact confirms that surgeons need to carefully revise and remove the PALN on the left lateral side. However, the left-side PAL is more difficult than on the right-side especially at the nerves preservation because surgeon need to mobilize the left-side lymph nodes from left ureter and nerves encountering technical problems due to location of inferior mesenteric artery in this region.

Correlative dependence of PALN metastases from histological type and differentiation suggests that NSPAL by the LRV is useful for treatment of 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. According to recent retrospective trials, improvement survival of these patients relate with removing PALN and metastases [23]. Therefore the use of systematic PAL in the treatment of cervical cancer has significant benefits and allows performing the adequate surgical staging and the planning of adjuvant therapy [24].

On the other hand the procedure is associated with significant morbidity, especially on the part of urinary system. The reasons of urinary tract dysfunction are direct injury and displacement of autonomic nerves such as SHP during PAL at the bifurcation of aorta and IVC [15].

The role of damage the inferior mesenteric and intermesenteric plexuses as parts of the abdominal aortic plexus are not completely understood. So, S. Dobrowolski et al showed that patients who had aorto-aortic reconstruction surgery in the treatment the abdominal aortic aneurysm with injury of intermesenteric, inferior mesenteric and superior hypogastric plexuses does not significantly influence the anorectal functions, but dysfunction of urinary tract was not estimated in this research [25].

In present research rates of urological complications were 34.5% in the nerve-sparing group and 62.6% in the second group. Y.S. Lee et al reported that rates of urological complications after robot-assisted NSPAL were 28.6%. The rate of ureterovaginal or external ureteral fistula was high in both groups and was occurred in 4 (9.3%) and 1 (4.2%) patients respectively. All fistulas were in the lower third of the ureter. These patients underwent secondary surgery in 1 case or ureteral stenting in 4 cases. According this study PAL with or without nerve preservation had no influence on ureteral fistula in the upper or middle thirds of ureter. Similar results were described in another report wherein ureterovaginal fistulas were detected in 14.3% of patients undergoing extended NSPAL [15].

The dilatation of renal pelvis one month after operation was occurred only in 5 patients (11.6%) of first group and in 9 patients (37.5%) of second group (p=0.03). Moreover all of patients in the second group had the dilatation of renal pelvis more than 20 mm. 4 patients of second group with hydronephrosis underwent the draining of kidney by percutaneous nephrostomy or ureteral stent setting and no one patients with hydronephrosis of first group. In the another study hydronephrosis more than one month after operation was occurred in 4 (14.3%) patients after extended nerve-sparing lymphadenectomy [15]. Thus, the incidence of hydronephrosis one month after NSPAL with RH C1 type was lower compared with PAL and RH C2 type. This may be resulting of preservation the abdominal aortic plexus, fibers of which form the ureteral plexus and innervate the upper and the middle parts of the ureter [26].

The short-term bladder storage and voiding dysfunction was significantly lower in patients of nerve-spring group (4.7%) compared with second group (41.7%). Also we did not observe the bladder storage and voiding dysfunction in patients of first group 3 and 6 months after procedure compared with patients of second group where the bladder storage and voiding dysfunction was 25.0% and 20.8% respectively. In addition the other reason of hydronephrosis is vesicoureteral reflux associated with increasing intravesical pressure owing to postoperative bladder storage and voiding dysfunction in patients with injury the parasympathetic and sympathetic part of pelvic autonomic plexus and nerves. It is well known, that voiding difficulties are owing to damage the inferior hypogastric plexus. But the bladder storage dysfunction as a hypertonic bladder may result in injury the parasympathetic part of pelvic autonomic nerves - pelvic splanchnic nerves which arise from sacral nerve roots S2-S4. As a rule the hypotonic bladder is result of overdistension the bladder capacity [27]. The stress urinary incontinence was observed in 5 (20.8%) patients of second group. The one reason of stress urinary incontinence is damage of sympathetic part of pelvic autonomic nerves – the hypogastric nerves which arise from SHP and abdominal aortic plexus [15]. Therefore, preservation of autonomic nervous system integrity in the retroperitoneal area and small pelvic, namely: intermesenteric, inferior mesenteric, superior hypogastric and inferior hypogastric plexuses, hypogastric and pelvic splanchnic nerves made it possible to preserve the urinary tract function.

**Conclusion**

In conclusion, systematic NSPAL with RH C1 type does not increase the occurrence of intraoperative vessels injury, lymphedema, lymphocyst, venous thromboses, pulmonary embolism, urinary tract infection, ureterovaginal or external ureteral fistula, but significantly decrease the frequency of hydronephrosis, short-term /long-term urinary tract dysfunction and stress urinary incontinence compared with systematic PAL with RH C2 type. At the same time NSPAL by the LRV is useful for treatment of adenocarcinoma and low grade differentiated cervical cancer because NSPAL does not decrease 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 and RH C1-2 types**

|  |  |  |  |
| --- | --- | --- | --- |
| **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%)** |