

Comparison of nerve content in removed parametrial tissue after classic radical hysterectomy and nerve-sparing radical hysterectomy - histologic evaluation

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Summary

Purpose of investigation: The aim of this study was to find whether nerve-sparing radical hysterectomy resulted in a lower amount of nerves in the removed parametrial tissue. **Methods:** Histological specimens from nerve-sparing radical hysterectomy (28 cases) were compared with those obtained after classic radical hysterectomy (26 cases). Width of the parametria and vaginal cuff were measured. Using a point counting technique, nerve areal density was determined in cross sections of resected parametria at 0.5 cm (A), 1 cm (B), 1.5 cm (C) from the cervix. **Results:** The width of the resected parametria was smaller in the study group (right side $p < 0.013$; left side; $p < 0.011$). The nerve areal density in the lateral part of the right parametrium was lower in the study group ($p < 0.01$) (Student's t-test). **Conclusion:** Modified radical hysterectomy is less radical and is nerve-sparing.

Key words: Nerve-sparing radical hysterectomy; Parametrial nerve areal density.

Introduction

Nerve-sparing radical hysterectomy in the treatment of cervical cancer is still controversial, especially because of the strongly rooted opinion that only wide (total) resection of the lateral parametria ensures a complete removal of tumor tissue, which may not be the case with nerve-sparing techniques [1, 2]. However, total resection of the parametrium might represent over-treatment, at least in patients with Stage IB disease, especially if tumor diameter is less than 3 cm [3, 4]. Consequently, limiting the radicality of debilitating treatment options seems to be an unavoidable and logical trend, at least for low-stage tumors [5].

Many authors have described the techniques of nerve-sparing surgery [6-12]. However, only Butler-Manuel and co-workers analyzed nerve content in removed parametrial tissue by comparing *radical* and *simple* hysterectomy specimens. They found that in radical hysterectomy specimens, uterosacral ligaments contained a greater number of large trunks and free ganglia of sympathetic and parasympathetic nerve systems compared with cardinal ligaments, but free nerve content was higher in the cardinal ligaments [13, 14].

Regarding these findings, Trimbos and co-workers emphasized that the most important act in preserving the utmost of autonomic nerves was lateral dissection of the uterosacral ligament and lateralization of nerve fibers within it [15]. This kind of surgical preparation would not only preserve nerves during uterosacral ligament dissection but would also preserve nerves in the following acts of the modified dissection of the cardinal ligament.

We implemented the Trimbos technique of nerve-sparing radical hysterectomy in 2002. We were curious as to whether this technique in comparison with classic radical hysterectomy really contributes to a lower number of embedded nerves in the removed parametrial tissue. To find the answers to this question we designed a study in which we compared histologic specimens of two groups of patients – those who underwent nerve-sparing radical hysterectomy and control patients who underwent classic radical hysterectomy.

Materials and Methods

Patients

In the years 2005 and 2006, 60 patients were operated on for cervical cancer Stage IB1 to IB2. In 28 patients with IB1 cancer stage we applied the nerve-sparing technique; they represented the study group. A detailed description of the technique can be found elsewhere [15].

The analysis of surgical specimens involved the width of parametrial tissue removed and the length of vaginal cuffs. Nerve areal density of the parametria was determined, and the results were compared with those obtained in the control group patients ($n = 26$) in whom radical hysterectomy was performed for cervical cancer Stage IB1 as well, but before the year 2000 when only classic (non nerve-sparing) radical hysterectomy was performed at our institution [16].

Histologic preparation of the specimens and stereometry

The length of vaginal cuff and the length of parametria were measured before and after the cervix had been divided from the parametria. For histologic examination two consecutive 5 μm thick tissue sections were cut from each paraffin block. The first section was routinely stained with hematoxylin and eosin for tissue morphology assessment. The second section from each block was used for S100 immunohistochemical staining.

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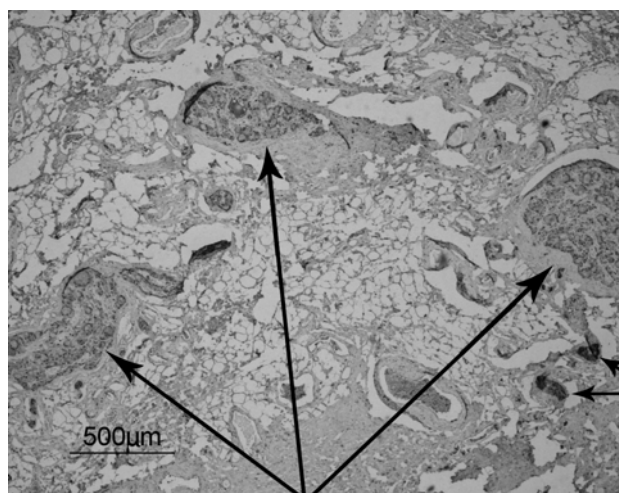


Figure 1. — Histologic specimen of the parametrial tissue subjected to immunohistochemical staining with S100 antibodies. Nerves are indicated by arrows.

Briefly, tissue sections were placed on a poly-L-lysine coated slide, deparaffinized and rehydrated. Antigen unmasking was performed by pressure cooking in citrate buffer (pH 6.0), and primary rabbit polyclonal anti S100 antibodies (DAKO, Glostrup, Denmark) diluted 1:100 were applied, followed by a standard ABC immunohistochemistry protocol using a biotinylated secondary antibody (DAKO, Glostrup, Denmark) and diaminobenzidine as chromogen (Sigma, Munich, Germany). The slides were counterstained with hematoxylin (Figure 1).

Nerve areal density was determined by stereometric analysis using a point counting technique by a pathologist who was blinded to the clinical history of the patients [17]. Depending on the availability, this was done at three planes of both the left and the right parametrium, A – representing the medial part of the parametria (originating just at the cervix and extending to almost 0.5 cm laterally from the cervix), B – representing the middle part of the parametria (from 0.5 cm to 1 cm from the cervix), and C – representing the lateral part of the parametria, spreading from 1 cm to a maximum 1.5 cm from the cervix.

Statistical analysis

The student's t-test was used for statistical analysis of differences between the groups. For comparison of adjuvant therapy and survival rates we used the chi-square test. Statistical significance was set at $p < 0.05$.

The study was approved by the national medical ethics committee.

Results

The five-year survival rate was 92.85% in the study group and 84.61% in the control group [18]. Of the 28 patients in the study group, 15 (53.57%) received adjuvant radiotherapy because of pelvic lymph node metastasis (5 patients; 17.85%), or spread of the tumor more than half the width of the cervix and evident lymphangio-invasion (10 patients; 35.71%). Four of the 15 patients (14.28%) with extensive lymph node infiltration received

Table 1. — Comparison of the parametrial width, vaginal cuff length and nerve areal density in resected parametria.

	Study group n	mean (SD)	Control group n	mean (SD)	p
Right parametrium (mm)	28	15.50 (7.579)	26	22.69 (12.59)	.013
Left parametrium (mm)	28	15.71 (8.700)	26	22.96 (11.49)	.011
Vaginal cuff anterior (mm)	25	13.36 (5.830)	24	12.54 (4.191)	.577
Vaginal cuff posterior (mm)	25	21.64 (7.947)	26	19.31 (5.620)	.231
Nerve Areal Density					
A – medial part, right (%)	28	8 (3.7)	27	7.0 (4.7)	.389
B – middle part, right (%)	26	7.4 (3.1)	25	8.5 (3.2)	.223
C – lateral part, right (%)	13	6.2 (2.6)	21	9.7 (4.1)	.011
A – medial part, left (%)	27	7.5 (3.7)	25	9.0 (3.3)	.124
B – middle part, left (%)	26	8.1 (4.0)	24	8.0 (3.9)	.940
C – lateral part, left (%)	10	6.3 (2.0)	19	7.8 (3.8)	.255

A, B, C – points of measurements of resected parametrial width.

chemotherapy. None of the study group patients had parametrial metastases. Of the two patients in the study group who died by the end of the observation period, one had positive sentinel lymph nodes and one had lymphangio invasion found on histologic examination. Both patients received postoperative adjuvant radiotherapy.

Of the 26 patients in the control group, 17 (65.38%) received adjuvant radiotherapy because of spread of the tumor more than half the width of the cervix and lymphangio-invasion (13 patients; 50%) or pelvic lymph node metastasis (4 patients; 15.38%), three (11.53%) of them combined with chemotherapy. Also in this group none of the patients had parametrial metastases. The four patients with positive lymph node metastases died.

Table 1 shows histological and stereometric data of the enrolled patients. The resection of the cardinal ligament was significantly wider with classic radical hysterectomy, both on the left and the right side. Mean parametrial widths were approximately 7 mm wider in the control group on both sides. The length of resected vaginal cuffs was almost the same in both groups.

Comparison of the stereometric analysis of the nerve areal density revealed no significant differences between the groups in the medial and middle part of the parametria. However, the nerve areal density in the lateral part of the right parametria (C) was significantly lower in the study group ($p < 0.011$) (Table 1).

Not all stereoscopic data were available for all the patients. This was due to tear of the specimens (medial and middle part: 2 patients in the study and 2 in the control group; lateral part in the control group – 7 patients) and shortness of the parametria (lateral part in the study group).

Discussion

Dysfunctions of the lower urinary tract and distal bowel after radical hysterectomy are well known and have been described by many authors [19-24]. These dysfunctions might be the consequence of disruption of neural struc-

tures such as the superior hypogastric plexus, hypogastric nerve, inferior hypogastric plexus, usually occurring during resection of the sacrouterine, cardinal and vesicovaginal ligaments, part of which the aforementioned structures are, or lay in close proximity [25].

Dutch gynecologic surgeons developed a technique which is feasible and effective in patients in terms of nerve-sparing and radicality [15]. As opposed to some other nerve-sparing techniques, this technique provides tangible parametrial tissue, bound to the uterus, which can be histologically assessed.

To analyze the nerve-sparing effect of the implemented surgical technique, we first compared the width of parametrial tissue removed between the group undergoing nerve-sparing (study group) and that undergoing classic radical hysterectomy (control group). We found that it was wider in the control group, indicating that classic radical hysterectomy was more radical, and also implying that for this reason a greater number of nerves had been dissected in the control group. The latter speculation is based on the anatomical knowledge about the nerve fibers running through the parametrium and the surgical landmarks such as the inferior vesical vein and the deep uterine vein [6-12, 25]. The inferior vesical vein is important in preparation of the vesicovaginal ligament and the deep uterine vein is important for the resection of the cardinal ligament. If nerves are to be preserved, parametrial dissection should not go beyond these points, otherwise the distal part of the hypogastric plexus (landmark – inferior vesical vein) or the main body of hypogastric plexus (landmark – deep uterine vein) could be embedded in the dissected parametrial tissue [15]. However, in the case with classic radical hysterectomy where the main goal was to dissect the parametrium as widely as possible, the aforementioned landmarks were not respected. Consequently, we believe that the amount of embedded nerves in the dissected parametrial tissue was larger compared with the nerve-sparing technique, although this had not been documented.

Nevertheless, the nerve-sparing effect is achieved not only through a less radical dissection of the parametria, but also through a meticulous preparation of the parametrial tissue as the main characteristic of this surgical technique is gentle lateralization of the hypogastric nerve from the uterosacral ligament and careful dissection of the cardinal ligament avoiding the inferior hypogastric plexus [5, 15]. This is the reason that we subjected the dissected parametrial tissue to stereometric analysis.

Stereometric analysis of the nerve areal density of the parametria involved 1.5 cm of tissue extending from the cervix on their way to the pelvic wall. This tissue represents the common parametrial trunk, where connective fibers of the uterosacral, cardinal and vesicouterine ligaments are still joined, before they disperse on their way to the pelvic wall.

Comparing the removed parametrial tissue of both groups with stereometry, we confirmed a lower nerve areal density only in part C of the right parametrium in the study group. This suggests that the nerve fibers running through the lateral part of the parametria to the lower

urinary tract (bladder) were at least partially spared. We presume that the nerve fibers spared were of the distal inferior hypogastric plexus, criss-crossing the parametrial trunk in its lateral side (below the landmark of deep uterine vein [15]), which were in the process of lateralization pushed even further laterally. On the other hand, medially positioned nerve fibers entering the uterus itself could not be spared in this process, and from there on non-significantly different nerve areal density in medial parts of the parametrium (regions A and B) was also expected.

Surprisingly, we confirmed lower nerve areal density only in the right lateral part of the parametria. We presume that with a higher number of specimens this would probably be observed in the left part of parametria as well, although we suspect that the preparation of the parametrial tissue on the left side was not as effective as that on the right side. The reason for this phenomenon is very likely in a less favorable position of the surgeon for the left-side preparation combined with dense interconnection between nerve fibers and supporting connective fibers, which does not permit more effective nerve preservation. However, this might also have been due to insufficient surgical skillfulness in the early period of implementing the new technique.

Considering the available data we should stress that nerve-sparing in the removed parametrial tissue is significant, although only slightly. This implies that lateralization of the sacrouterine ligament with gentle preparation of the hypogastric nerve, careful dissection of the cardinal ligament and not-too-deep dissection of the vesicovaginal ligament in subsequent steps are also important. However, we believe that if the operation should be effective as far as nerve-sparing is concerned, this is achieved by less radical parametrial dissection rather than by lateralization of the nerves themselves.

A histologic comparison of two different techniques of radical hysterectomy reveals that the nerve-sparing technique very likely contributes to smaller involvement of nerve fibers in the dissected parametrial trunk. However, this effect is only valid for nerve fibers criss-crossing the parametrial trunk (fibers of hypogastric nerve and inferior hypogastric plexus), whereas the effect on nerve fibers entering the uterus is insignificant.

We should emphasize that we are aware of the small number of patients investigated. This is a common characteristic of the studies concerning cervical cancer surgery, and is partly due to declining numbers of patients eligible for this type of treatment. We are also aware that the study was partly retrospective (control group) which might decrease the value of the reported results. However, in the case of early cervical cancer such as IB1, for which the best treatment option is in the opinion of many surgeons less radical parametrial dissection [3,4], randomization in two groups of which one (control) would be exposed to wide (classical) parametrial dissection, seems ethically controversial. Also, it would be improper to prospectively compare two parametrial tissue samples obtained after a different type of operation (nerve-sparing and classical radical hysterectomy), where the former

would be performed for cervical cancer IB1 and the latter for more advanced cervical cancer. For these reasons we believed that the only way to compare tissue samples after different surgical techniques was the comparison of the samples obtained for cervical cancer IB1, which were in our case obtained in two different time periods, as the surgical techniques for the same stage of disease were different as well. Because the main goal of this study was the analysis of nerve content in the dissected parametrial tissue, this seemed acceptable, and because of dealing with cancer treatment we additionally present the data of adjuvant treatment and survival rates. Regarding the survival rates so far, the nerve-sparing surgical technique seems to be an appropriate treatment for low-stage cervical cancer.

Despite all the limitations of the study, this modified radical hysterectomy preserves more tissue, and is consequently nerve-sparing. However, the complete preservation of autonomic nerves cannot be achieved with this type of operation.

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