

Nerve-sparing abdominal radical trachelectomy: a novel concept to preserve uterine branches of pelvic nerves



Satoru Kyo^{a,*}, Yasunari Mizumoto^b, Masahiro Takakura^b, Mitsuhiro Nakamura^b, Emi Sato^a, Hiroshi Katagiri^a, Masako Ishikawa^a, Kentaro Nakayama^a, Hiroshi Fujiwara^b

^a Department of Obstetrics and Gynecology, Shimane University Faculty of Medicine, 89-1 Enyacho, Izumo, Shimane 693-8501, Japan

^b Department of Obstetrics and Gynecology, Kanazawa University School of Medical Science, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan

ARTICLE INFO

Article history:

Received 4 February 2015

Received in revised form 24 June 2015

Accepted 30 June 2015

Keywords:

Trachelectomy
Cervical cancer
Nerve-sparing
Autonomic nerve
Uterine branch

ABSTRACT

Objectives: Nerve-sparing techniques to avoid bladder dysfunction in abdominal radical hysterectomy have been established during the past two decades, and they have been applied to radical trachelectomy. Although trachelectomy retains the uterine corpus, no report mentions the preservation of uterine branches of pelvic nerves. The aim of the present study was to introduce and discuss our unique concept for preserving them.

Study design and results: Four cases with FIGO stage Ia2–Ib1 cervical cancer, in which preservation of uterine branches of the pelvic nerves was attempted, are presented. Operative procedures basically followed the previously reported standard approaches for nerve-sparing radical hysterectomy or trachelectomy, except for some points. Before resection of the sacrouterine ligament, the hypogastric nerve was first identified and translocated laterally. Subsequently, the uterine branches of the pelvic nerve were identified as a continuation of the hypogastric nerve and could be scooped with forceps by detachment of the surrounding connective tissues. Further detachment toward the uterine corpus enabled them to be completely separated from the cervix. This separation was extended up to the level of the junction of the upper and lower branches of the uterine artery. Thereafter, standard resection of the parametrium and paracolpium was performed, followed by cervical resection when it was confirmed that the isolated uterine branches of the pelvic nerves were safely translocated and preserved. There were no recurrences of cancer in these patients.

Conclusions: Uterine branches of autonomic nerves can be safely preserved, and the procedure may be considered one of the nerve-sparing techniques for radical abdominal trachelectomy, which may hopefully improve the reproductive outcomes of this operation, although it needs to be evaluated with more patients.

© 2015 Elsevier Ireland Ltd. All rights reserved.

Introduction

Cervical cancer is the second most common malignancy in women. In recent years, the frequency of early-stage cervical cancer has increased in women during their child-bearing years [1]. As a fertility-sparing operation for such patients, conization can be widely used for carcinoma in situ (CIS) or microinvasive cervical cancer with FIGO stage 1a1. However, patients with more advanced disease have usually undergone abdominal or laparoscopic radical hysterectomy as curative operative modalities. Radical abdominal trachelectomy was first described by Smith

et al. in 1997 as conservative therapy for the uterine corpus [2]. Patients with FIGO stage Ia2–Ib1 with small tumor size (less than 2 cm in diameter) without retroperitoneal lymph node metastases have been likely to undergo this operation, and the oncologic outcomes have been reported to be satisfactory, comparable with radical hysterectomy [3–5]. However, the reproductive outcomes of this operation appear insufficient, and some reports indicated that radical vaginal trachelectomy, rather than abdominal trachelectomy, shows more favorable reproductive outcomes [3,6–9], while the oncologic outcomes of vaginal trachelectomy appeared to be inferior to those of the abdominal procedure, especially in patients with tumors larger than 2 cm [8,10–12]. The precise cause of the relatively poor reproductive outcomes of abdominal radical trachelectomy remains unclear, but it is possible that disruption of autonomic nerves that innervate the uterine

* Corresponding author. Tel.: +81 0853 20 2268; fax: +81 0853 20 2264.
E-mail address: satoruky@med.shimane-u.ac.jp (S. Kyo).

corpus may be involved. Nerve-sparing operations have been used not only for radical hysterectomy, but also for trachelectomy, and their techniques have been similar in both operations [13]. Therefore, the historical perspective of nerve-sparing procedures in radical hysterectomy needs to be considered first.

The uterus, vagina, urinary bladder, and rectum are innervated by sympathetic (hypogastric) and parasympathetic (pelvic splanchnic) nerves; the former come from T11-L2, which form the superior hypogastric plexus, and the latter come from sacral nerves (S2–S4) at the pelvic wall. These fibers merge and form the pelvic nerve plexus, the branches of which innervate the uterus and urinary bladder [14]. The concept of nerve-sparing radical hysterectomy was first proposed in the 1980s by Sakamoto et al. and named the “Tokyo method” [15]. They noted that the cardinal ligament only consists of blood vessels and nerve bundles, the soft upper vascular part and the firm lower neural parts, providing a fundamental way to preserve the lower nerve portions at the resection of the cardinal ligament. Thereafter, Yabuki et al. [16] and Kato et al. [17] proposed the novel concept that pelvic splanchnic nerves were distributed dorsolaterally to the cardinal ligament, and the pelvic nerve plexus was arranged almost sagittally in a small plate-like manner and was located near the bottom of the cardinal ligament, indicating that pelvic splanchnic nerves and the plexus were somewhat separated from the vessel portion of the cardinal ligament. Höckel et al. reported that clearing the uterine supporting structures from all fatty and lymphoid tissue using liposuction instruments in the cardinal ligament clearly identified the pelvic splanchnic nerves and the pelvic nerve plexus, contributing to sparing these nerves [18]. Trimbois et al. introduced operative procedures to preserve sympathetic nerves [19]. The sacrouterine dissection plane separates the medial ligamentous tissue and the lateral nerve fibers. The former can then be safely clamped, cut, and ligated without damaging the hypogastric nerves or the proximal part of the pelvic nerve plexus. The problem of sparing autonomic nerves to the bladder in the vesicouterine ligament has been addressed by Kuwabara et al. [20]. Intraoperative electrical stimulation of various parts of the vesicouterine ligament and the simultaneous measurement of intravesical pressure identified that the lateral layer of the posterior part of the vesicouterine ligament was the major pathway of the bladder branches of pelvic nerves. A surgical technique was developed in which a thin membranous layer containing the bladder branches from the lateral surface of the bladder was identified and spared.

Based on these historical studies, a recently established concept to spare autonomic nerves has been classified into 3 major steps in abdominal radical hysterectomy, with preservation of the hypogastric nerves at the presacral portion, of the splanchnic nerves and pelvic nerve plexus at the cardinal ligament, and of the bladder branches from the pelvic nerve plexus at the vesicouterine ligament. This concept has recently been carried over into abdominal radical trachelectomy, based on the results of a comparative study showing that nerve-sparing radical trachelectomy provided disease-free and overall survivals comparable to radical hysterectomy [21]. However, no attention has been paid to sparing uterine branches. Although the precise functions of uterine branches of pelvic autonomic nerves are largely unknown, it is possible that they are essential for good reproductive and obstetrical outcomes postoperatively. This background information prompted us to establish novel techniques for sparing the uterine branches of pelvic nerves in radical abdominal trachelectomy. Four successful cases who underwent this novel procedure are presented and discussed.

Methods and results

Abdominal radical trachelectomy was performed in 4 patients with stage Ia2–Ib1 cervical cancers between October, 2013 and

April, 2015, which basically followed the same approach that would be standard for radical abdominal hysterectomy. After opening the retroperitoneal cavity, bilateral pelvic node dissection was performed, including internal/external iliac, cardinal, obturator, and supra-inguinal nodes. The dissected lymph nodes were subjected to intraoperative pathological diagnosis to detect metastases. Bilateral uterine arteries were isolated from the origin to the bifurcation of the superior and inferior branches and preserved. Then, the superficial layer of the vesicouterine ligament was resected using LigaSure™ Small Jaw (Covidien, Dublin, Ireland). The autonomic nerves were preserved by the following procedures in a novel attempt to spare the uterine branches of the pelvic plexus.

Hypogastric nerve isolation

Okabayashi's pararectal space [22] was developed by sharp dissection of presacral visceral pelvic fascia just above the ureter, making a shallow dimple that could be developed bluntly [19]. With the use of forceps, a thin and loose lateral part directly underneath the ureter (named the mesoureter or ureteral leaf) containing the hypogastric nerve was laterally isolated, leaving a firm medial part consisting of the uterosacral fibers. Eventually, the hypogastric nerve was translocated laterally by this maneuver. Then, the medial part consisting of the sacrouterine fibers was resected, while the hypogastric nerve was far from the line of resection and safely preserved.

Isolation of uterine branches of the pelvic nerve plexus

Uterine branches of the autonomic nerves arise from the pelvic nerve plexus, which is formed from the hypogastric and pelvic splanchnic nerves from S2 to S4. After lateral translocation of the hypogastric nerve, an attempt was made to identify the uterine branches of the pelvic nerve. In general, the uterine branches are easily identified as a continuation of the hypogastric nerve, ascending up the uterine cervix toward the uterine corpus, and it can be scooped with forceps by detachment of the surrounding connective tissues. Further detachment of the connective tissue toward the uterine corpus facilitates complete separation of the uterine branches from the uterine cervix. This separation should be performed at least up to the level of the junction of the upper and lower branches of the uterine artery. The typical image of this separation is shown in Fig. 1 in another patient who underwent abdominal radical hysterectomy. In this case, the isolated tissue was resected at the time of hysterectomy and was histologically examined for the presence of nerve tissue. As shown in Fig. 1, the presence of peripheral nerves was confirmed, showing the technical accuracy of our procedures.

Separation of deep uterine veins from the pelvic nerve plexus

The cardinal ligament contains major vessels such as deep uterine veins, some vesical veins, and the middle rectal vein; all these veins converge into the internal iliac vein. These vessels are most clearly exposed by complete dissection of the cardinal lymph nodes with ultrasonic surgical aspirators [18]. The deep uterine vein alone was dissected, leaving more dorsal vessels to LigaSure™ Small Jaw or LigaSure™ Impact (Covidien, Dublin, Ireland). Since the area of the pelvic splanchnic nerves and plexus was anatomically separated from these vessels at the cardinal ligament [17], this dissection did not affect the function of the splanchnic nerves. Thereafter, the uterine side edge of the deep uterine vein was ventrally elevated by detaching the surrounding membranes over the upper border of the hypogastric nerve tract, resulting in complete separation of the deep uterine vein from the pelvic nerve plexus [23]. Since the bladder branch of the pelvic nerves arose

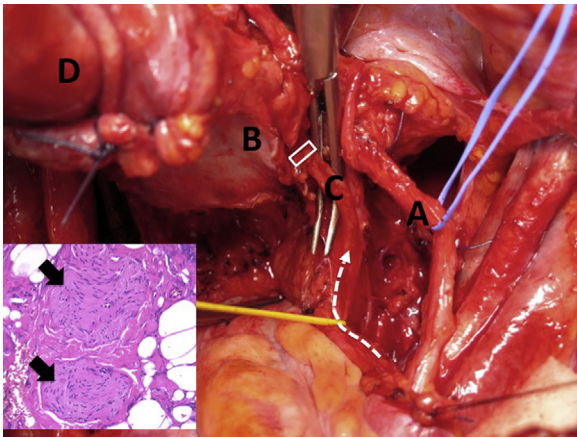


Fig. 1. Isolation of the uterine branch of the pelvic nerve, the lateral view in the right pelvic cavity in a patient who underwent abdominal radical hysterectomy. (A) Right ureter. (B) Uterine cervix. (C) Isolated ascending uterine branch of pelvic nerve. (D) Uterine corpus. Hypogastric nerves are shown by the dotted line. The isolated tissue (shown in the blank box) was histologically examined for the presence of nerve tissues. The HE staining clearly shows the presence of peripheral nerves (shown by the black arrowheads).

from the pelvic plexus at the same level with the hypogastric nerve tract, the subsequent resection of the rectovaginal ligament above this level guaranteed the preservation of the bladder branches of the pelvic nerves, while the deep uterine vein was fully resected. It is important to note that the isolated uterine branches of the pelvic nerve were located far from the resection line of the rectovaginal ligament and were therefore safely preserved (Fig. 2).

Isolation or recognition of the bladder branches of pelvic nerves

Then, the deep layer of the vesicouterine ligament was resected, and the vesical vein (called the superior vesical vein [24]) that drains into the deep uterine vein was isolated and clearly visualized, and it was then used as the lateral border of the vesicouterine ligament to be resected, because most of the bladder branches of

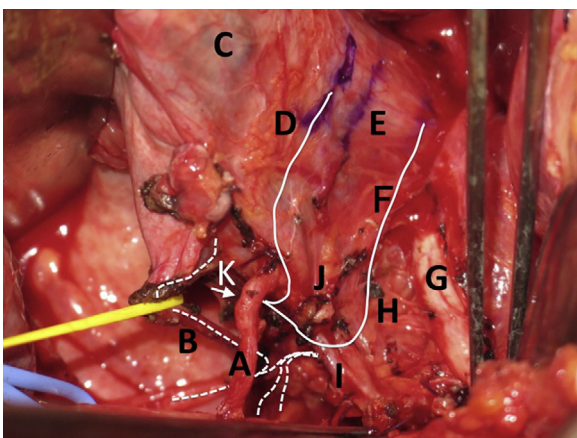


Fig. 2. The isolated uterine branch of the pelvic nerve is far from the rectovaginal ligament and cervix in the lateral view in the right pelvic cavity. (A) Uterine artery. (B) Isolated ascending uterine branch of the hypogastric nerve. (C) Uterine corpus. (D) Line of the upper edge of uterine cervix to be resected. (E) Level of the portio. (F) Line of the vaginal wall to be resected. (G) Left ureter. (H) Posterior layer of the vesicouterine ligament. (I) Supravascular vein. (J) Uterine side edge of the resected deep uterine vein. (K) Rectovaginal ligament. The autonomic nerve tracts are shown as dotted lines. Arrowheads indicate the line of resection of the rectovaginal ligament and uterine cervix. Note that the uterine branches of the autonomic nerves are fully isolated from the uterine cervix, thereby preserved after resection of the rectovaginal ligament and uterine cervix.

the autonomic nerves are located lateral to these vesical veins [23]. In some cases, surgical techniques could be used to separate the bladder branches of the pelvic nerves by isolating a thin membranous layer containing the nerves from the lateral surface of the posterior layer of the vesicouterine ligament [20]. Thereafter, the posterior layer of the vesicouterine ligament was dissected.

The parametria were then dissected, followed by complete resection of the vaginal canal with a cuff of 1.5–2.0 cm. Descending branches of uterine arteries were isolated and sealed with LigaSure™ Small Jaw. The upper edge of the resected cervix was finally resected (Fig. 3), leaving a cervical canal length of 1.0 cm. After cervical dissection, cerclage of the residual cervix was performed. Finally, the vaginal wall and residual cervix were sutured. Intraoperative pathological examination confirmed a negative surgical margin of the dissected cervix. No recurrence of uterine cancer has been found in these patients as of May, 2015. The reproductive outcomes have not been evaluated because none of the patients has yet attempted to conceive.

Comments

Preservation of the uterine branches of the pelvic nerves is a unique concept. Since their precise function and their anatomical location are largely unknown, no studies have reported their preservation, and this is probably the first report of the procedure. The mechanistic principle of the preservation is shown in Fig. 4. The technical key to success is how to achieve safe isolation from the cervix. The uterine branch of the pelvic nerve is composed of the hypogastric nerve and the pelvic splanchnic nerve, and the former is thought to be the main component of the uterine branch. Therefore, it can be identified as a continuation of the hypogastric nerve, which is easily visualized by the development of Okabayashi's pararectal space. Detachment of the surrounding connective tissues on the uterine cervix, scooping the continuation of the hypogastric nerve, further helps to isolate the uterine branches. Extended detachment of the surrounding connective tissues toward the uterine corpus enables complete separation from the cervix. This procedure sometimes requires considerable effort because the surrounding connective tissues are sticky, making isolation of the nerve from the cervix difficult. However, the use of an electric scalpel is helpful for isolation, although heat injury to the nerve should be avoided. The upper border of the isolation is the junction of the upper and lower branches of the uterine artery, because this line is usually near the upper border of the resected cervix. It took approximately 30–40 min to isolate the nerve on each side. Taping the isolated branches to mark them is essential to

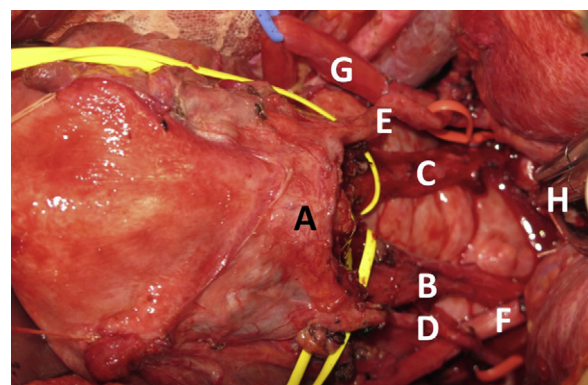


Fig. 3. Remaining uterine branches of autonomic nerves after cervical resection. (A) Stump of the remaining cervix. (B) Remaining right uterine branch of the pelvic nerve. (C) Remaining left uterine branch of the pelvic nerve. (D) Right uterine artery. (E) Left uterine artery. (F) Right ureter. (G) Left ureter. (H) Vaginal stump.

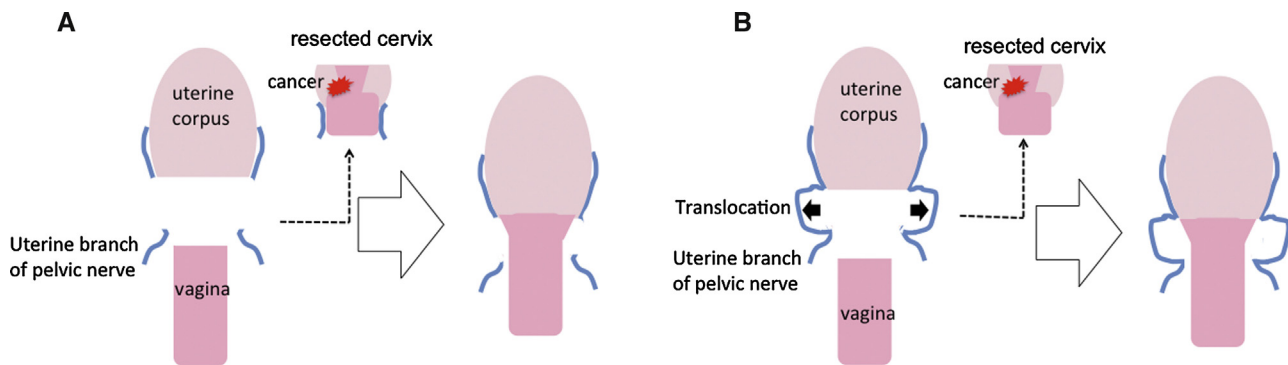


Fig. 4. Schematic representation of the standard procedure (A) and our procedure (B) for radical abdominal trachelectomy from the standpoint of the uterine branches of the pelvic nerves. (A) In the standard procedures of trachelectomy, the uterine branches of the pelvic nerve stick in the cervix and are simultaneously resected with the cervix.

avoid accidental amputation of the branches during operation, especially at the time of cervical resection.

The roles of the uterine branches of the pelvic nerves remain unclear. Recently, novel concepts have been developed that suggest that successful pregnancy is precisely regulated by multiple factors, including many components of the immune-neuro-endocrine network [25,26]. Mast cells (MCs), known to be a multifunctional readout of immune activities [27], are widely distributed in female reproductive tissues [28]. The number of uterine MCs and the level of histamine release are closely correlated with the intensity of immunity in the uterus in various pregnancy stages spanning to parturition [29,30]. Thus, uterine MCs may serve as an ideal index of local cellular immunity in utero. Yuan et al. examined the consequences of uterine neurectomy on embryo implantation events in rats [31]. Interestingly, the amputation of autonomic nerves innervating the uterus led to on-time implantation failure. Disconnection of autonomic nerve innervation significantly increased the number of uterine MCs, leading to enhanced histamine release from MCs in the uterus. Histamine, a mediator of inflammation, can modulate Th1/Th2 cell balance, and it enhances TGF- β 1-mediated suppression of the Th2 response [32]. Since a Th2-dominant immune response status in utero facilitates survival of the fetus during pregnancy, while a Th1-dominant immune response induces failure of gestation [33,34], it is possible that excessive levels of histamine before implantation may inhibit the Th2 response, enhancing the Th1 response, thereby leading to immune rejection and failure of implantation. The uterine nerves may thus play a critical role in successful implantation via regulating mast cell-secreted histamine levels that determine Th1/Th2 balance.

It is known that radical vaginal trachelectomy has better reproductive outcomes than abdominal trachelectomy [3,6–9]. The mechanistic reasons for this superiority remain unclear, but less invasive approaches preserving much more tissue and nerves around the cervix may contribute. Anatomically, the uterine branches of the pelvic nerves are supposed to be preserved in such a vaginal approach, which may be involved in better reproductive outcomes. In contrast, the decreased radicality of the vaginal approach may cause inferior oncologic outcomes [8,10–12]. Our novel operation is expected to resolve this contradiction, preserving the uterine branches of pelvic nerves while resecting the pericervical ligaments sufficiently.

In summary, a novel nerve-sparing radical abdominal trachelectomy for early-stage cervical cancer, in which both uterine and vesical branches of the pelvic nerves are safely preserved, was reported. Since the number of operated cases is too small at present, the efficacy of this surgical technique on reproductive

outcomes needs to be evaluated with more patients and compared with conventional abdominal trachelectomy and vaginal trachelectomy.

Acknowledgments

The authors are grateful to Drs. Chika Amano and Tohru Nabika, Department of Functional Pathology, Shimane University Faculty of Medicine, for the pathological review of the resected neural tissues.

References

- [1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
- [2] Smith JR, Boyle DC, Corless DJ, et al. Abdominal radical trachelectomy: a new surgical technique for the conservative management of cervical carcinoma. *Br J Obstet Gynaecol* 1997;104:1196–200.
- [3] Diaz JP, Sonoda Y, Leitao MM, et al. Oncologic outcome of fertility-sparing radical trachelectomy versus radical hysterectomy for stage IB1 cervical carcinoma. *Hum Reprod* 2008;111:255–60.
- [4] Beiner ME, Hauspy J, Rosen B, et al. Radical vaginal trachelectomy vs. radical hysterectomy for small early stage cervical cancer: a matched case-control study. *Gynecol Oncol* 2008;110:168–71.
- [5] Marchiole P, Benchaib M, Buenerd A, Lazlo E, Dargent D, Mathevet P. Oncological safety of laparoscopic-assisted vaginal radical trachelectomy (LARVT or Dargent's operation): a comparative study with laparoscopic-assisted vaginal radical hysterectomy (LARVH). *Gynecol Oncol* 2007;106:132–41.
- [6] Nishio H, Fujii T, Sugiyama J, et al. Reproductive and obstetric outcomes after radical abdominal trachelectomy for early-stage cervical cancer in a series of 31 pregnancies. *Hum Reprod* 2013;28:1793–8.
- [7] Speiser D, Mangler M, Köhler C, et al. Fertility outcome after radical vaginal trachelectomy: a prospective study of 212 patients. *Int J Gynecol Cancer* 2011;21:1635–9.
- [8] Cao DY, Yang JX, Wu XH, et al., China Gynecologic Oncology Group. Comparisons of vaginal and abdominal radical trachelectomy for early-stage cervical cancer: preliminary results of a multi-center research in China. *Br J Cancer* 2013;109:2778–82.
- [9] Pareja R, Rendón GJ, Sanz-Lomana CM, Monzón O, Ramirez PT. Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy – a systematic literature review. *Gynecol Oncol* 2013;131:77–82.
- [10] Rob L, Skapa P, Robova H. Fertility-sparing surgery in patients with cervical cancer. *Lancet Oncol* 2011;12:192–200.
- [11] Wethington SL, Sonoda Y, Park KJ, et al. Expanding the indications for radical trachelectomy: a report on 29 patients with stage IB1 tumors measuring 2–4 centimeters. *Int J Gynecol Cancer* 2013;23:1092–8.
- [12] Li J, Wu X, Li X, Ju X. Abdominal radical trachelectomy: is it safe for IB1 cervical cancer with tumors ≥ 2 cm. *Gynecol Oncol* 2013;131:87–92.
- [13] Cibula D, Slama J, Fischerova D. Update on abdominal radical trachelectomy. *Gynecol Oncol* 2008;111(2 Suppl.):S111–5.
- [14] Amussen M, Miller A. Clinical gynecological urology. London: Blackwell Scientific Publications; 1983.
- [15] Sakamoto S, Takizawa K. An improved radical hysterectomy with fewer urological complications and with no loss of therapeutic results for invasive cervical cancer. *Baillieres Clin Obstet Gynaecol* 1988;2:953–62.

- [16] Yabuki Y, Asamoto A, Hoshiba T, Nishimoto H, Kitamura S. Dissection of the cardinal ligament in radical hysterectomy for cervical cancer with emphasis on the lateral ligament. *Am J Obstet Gynecol* 1991;164:7–14.
- [17] Kato T, Murakami G, Yabuki Y. Does the cardinal ligament of the uterus contain a nerve that should be preserved in radical hysterectomy? *Anat Sci Int* 2002;77:161–8.
- [18] Höckel M, Konerding MA, Heussel CP. Liposuction-assisted nerve-sparing extended radical hysterectomy: oncologic rationale, surgical anatomy, and feasibility study. *Am J Obstet Gynecol* 1998;178:971–6.
- [19] Trimbos JB, Maas CP, Deruiter MC, Peters AA, Kenter GG. A nerve-sparing radical hysterectomy: guidelines and feasibility in Western patients. *Int J Gynecol Cancer* 2001;11:180–6.
- [20] Kuwabara Y, Suzuki M, Hashimoto M, Furugen Y, Yoshida K, Mitsuhashi N. New method to prevent bladder dysfunction after radical hysterectomy for uterine cervical cancer. *J Obstet Gynaecol Res* 2000;26:1–8.
- [21] van Gent MD, van den Haak LW, Gaarenstroom KN, et al. Nerve-sparing radical abdominal trachelectomy versus nerve-sparing radical hysterectomy in early-stage (FIGO IA2-IB) cervical cancer: a comparative study on feasibility and outcome. *Int J Gynecol Cancer* 2014;24:735–43.
- [22] Yabuki Y, Asamoto A, Hoshiba T, Nishimoto H, Nishikawa Y, Nakajima T. Radical hysterectomy: an anatomic evaluation of parametrial dissection. *Gynecol Oncol* 2000;77:155–63.
- [23] Fujii S, Takakura K, Matsumura N, et al. Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. *Gynecol Oncol* 2007;107:4–13.
- [24] Yabuki Y, Asamoto A, Hoshiba T, Nishimoto H, Satou N. A new proposal for radical hysterectomy. *Gynecol Oncol* 1996;62:370–8.
- [25] Haddad EK, Duclos AJ, Baines MG. Presence of activated macrophages in a murine model of early embryo loss. *Am J Reprod Immunol* 1995;33:354–66.
- [26] Piccinni MP, Scaletti C, Maggi E, Romagnani S. Role of hormone-controlled Th1- and Th2-type cytokines in successful pregnancy. *J Neuroimmunol* 2000;109:30–3.
- [27] Gordon JR, Galli SJ. Mast cells as a source of both preformed and immunologically inducible TNF-alpha/cachectin. *Nature* 1990;346:274–6.
- [28] Rudolph MI, Rojas IG, Penissi AB. Uterine mast cells: a new hypothesis to understand how we are born. *Biocell* 2004;28:1–11.
- [29] Shelesnyak MC. Inhibition of decidual cell formation in the pseudopregnant rat by histamine antagonists. *Am J Physiol* 1952;170:522–7.
- [30] Padilla L, Reinicke K, Montesino H, et al. Histamine content and mast cells distribution in mouse uterus: the effect of sexual hormones, gestation and labor. *Cell Mol Biol* 1990;36:93–100.
- [31] Yuan XJ, Huang LB, Qiao HL, Deng ZP, Fa JJ. Uterine autonomic nerve innervation plays a crucial role in regulating rat uterine mast cell functions during embryo implantation. *Prostaglandins Other Lipid Mediat* 2009;90:94–7.
- [32] Kunzmann S, Mantel PY, Wohlfahrt JG, Akdis M, Blaser K, Schmidt-Weber CB. Histamine enhances TGF-beta1-mediated suppression of Th2 responses. *FASEB J* 2003;17:1089–95.
- [33] Kelemen K, Paldi A, Tinneberg H, Torok A, Szekeres-Bartho J. Early recognition of pregnancy by the maternal immune system. *Am J Reprod Immunol* 1998;39:351–5.
- [34] Miyazaki S, Tsuda H, Sakai M, et al. Predominance of Th2-promoting dendritic cells in early human pregnancy decidua. *J Leukoc Biol* 2003;74:514–22.