Critical Reviews in Oncology/Hematology 70 (2009) 195–205

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Nerve-sparing radical hysterectomy for cervical carcinoma

Polat Dursun*, Ali Ayhan, Esra Kuscu

Baskent University School of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey

Accepted 3 September 2008

Contents

Abstract

With the concept of the improvement of quality of life in the field of surgical oncology, recent studies have questioned the place of radical hysterectomy (RH) in the treatment of cervical carcinoma due to a high rate of long-term postoperative complications involving the pelvic autonomic nerve system. It has been demonstrated that RH frequently causes bladder dysfunction, anorectal mobility disorders, and sexual dissatisfaction in cervical cancer survivors due to surgical trauma involving the sympathetic and parasympathetic branches of the autonomous innervation of the pelvic organs. Nerve-sparing RH was first pioneered by Takashi Kobayashi in Japan and then other Japanese gynecologic surgeons introduced and improved this concept to Western countries. However, nerve-sparing RH has only become popular among gynecologic surgeons during the last two decades. Recently, European gynecologic surgeons modified this concept. Herein, a review of the evolution of nerve-sparing RH, a quick overview of long-term pelvic organ dysfunctions associated with RH, and the technical details of different authors and their oncological outcomes are presented. Today, the lack of randomized studies comparing the effectiveness and complications of RH with nerve-sparing RH is an important barrier to the widespread use of this concept. Nonetheless, while nerve-sparing RH still awaits prospective randomized trials in order to prove that its effectiveness is equal to or greater than that of conventional treatment modalities, and that is has fewer long-term complications, this surgical approach remains attractive for the patients and gynecologic oncologists based on the published results.

Keywords: Cervical carcinoma; Radical hysterectomy; Bladder dysfunction; Sexual dysfunction; Anorectal dysfunction; Morbidity; Quality of life; Nerve-sparing hysterectomy; Nerve-preserving hysterectomy; Okabayashi radical hysterectomy

1. Introduction

Carcinoma of the cervix is the second most common cancer among women and is one of the leading causes of cancer-related deaths in females, both in developed and

* Corresponding author at: Baskent University School of Medicine, Department of Obstetrics and Gynecology, Kubilay Sk. No: 36 Maltepe, Ankara, Turkey. Tel.: +90 5323845158.
E-mail address: pdursun@yahoo.com (P. Dursun).

1040-8428/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.critrevonc.2008.09.003

developing countries. Approximately 493,000 cases, with a total of 274,000 deaths, occur annually. Almost 85% of the cases occur in undeveloped countries, accounting for 15% of all cancers in women. In well-developed countries, it accounts for 3.6% of new cancers, with an incidence of 14 cases per 100,000 women. It is estimated that 9710 new cases of invasive cervical cancer and approximately 3700 cervical cancer-related deaths will occur in the US in 2006 [1–5].

The classical surgical management of early-stage cervical carcinoma includes the extirpation of the uterus and cervix, along with radical resection of the parametrial tissues and upper vagina, together with complete bilateral pelvic lymphadenectomy. This surgical approach, known as radical hysterectomy (RH), was first described and systematically performed by Wertheim [6] more than 100 years ago, and was then modified by Okabayashi in 1921 [29] and re-popularized by Meigs [7] in the 1950's. This operation yields 5-year survival rates of 75–90%. The surgical principles of this operation have undergone only minor modification throughout the years and it remains the basis for the surgical approach utilized by gynecologic oncologists today [6–8]. On the other hand, it is well known that radiotherapy (RT) irreversibly destroys reproductive capacity and negatively affects the ability to have sexual intercourse in young women. Therefore, despite the comparable efficacy rate of RT and RH, RH is the preferred treatment option for the treatment of early-stage cervical carcinoma in young women because of the possibility of preserving the ovaries and vaginal integrity.

With the concept of the improvement of quality of life in the field of surgical oncology, recent studies have questioned the efficacy and safety of RH due to a high rate of long-term postoperative complications involving the pelvic autonomic nerve system. As is known, the female pelvic organs, including the bladder, urethra, rectum, and vagina, are closely related to quality of life. Normal functioning of these pelvic organs depends on autonomic nerves, which arise from the thoracal and sacral nerve plexus. These autonomic nerves have important functions for sexual arousal, orgasm, urinary functions, and anorectal mobility. Although these autonomic nerves of the pelvic organs and their origins are well described in anatomy textbooks, these structures are rarely visualized in operating rooms during surgery and, unfortunately, basic anatomic landmarks are not commonly used by surgical oncologists until the recent publications of Fujii et al. [29,34,49].

Although RH is an effective approach for the management of early-stage cervical carcinoma, some recent studies demonstrated that it frequently causes bladder dysfunction, anorectal mobility disorders, and sexual dissatisfaction in cervical cancer survivors. These complications are believed to be the result of surgical trauma involving the sympathetic and parasympathetic branches of the autonomous innervation of the pelvic organs [9–12]. Injuries to the autonomic pelvic nerves can be encountered during the different phases of RH, as described below:

- Superior hypogastric plexus during pre-sacral and periaortic lymph node dissection.
- Hypogastric nerves during the resection of the uterosacral ligaments.
- Pelvic splanchnic nerve during the division of the deep uterine vein in the cardinal ligament.
- Inferior hypogastric plexus during division of the uterosacral and rectovaginal ligaments.
- Bladder branch from the inferior hypogastric plexus during resection of the vesicovaginal ligaments and the paracolpium (Figs. 1 and 2).

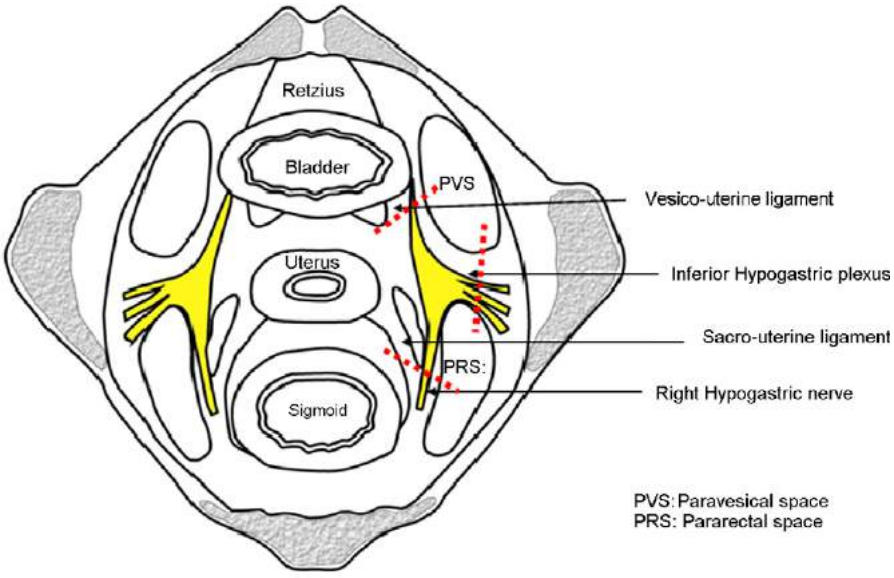

Fig. 1. Illustration of pelvic autonomic nerves of pelvic organs and potential sites of injury during RH. Modified from Ref. [33].

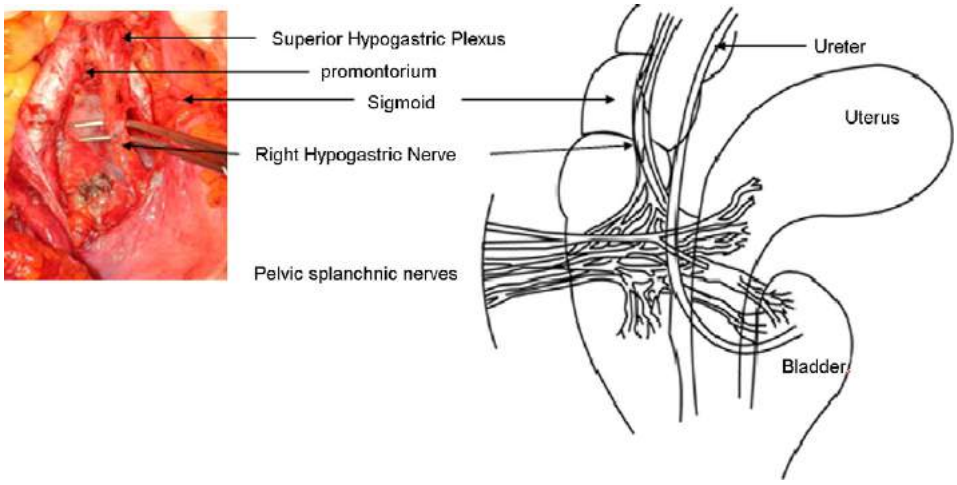

Fig. 2. Schematic illustration of hypogastric nerve and its relation with pelvic organs; left photo demonstrate intraoperative appearance of the hypogastric plexus and hypogastric nerve. Modified from Ref. [48].

Therefore, some investigators have focused on preserving the pelvic nerves to prevent surgery-related nerve damage in order to prevent pelvic organ dysfunction and to obtain a better quality of life in cervical cancer survivors. It has been suggested that there might be two main approaches for reducing postoperative surgery-related pelvic nerve damage in patients that undergo RH for cervical carcinoma:

1. Less radical surgery by reducing the extent of the resected parametrial tissues.
2. Preserving the nerves without reducing the radicality of surgery.

The benefits of less radical surgery for cervical carcinoma, in terms of postoperative long-term pelvic organ dysfunction, have been demonstrated by Landoni et al. in a randomized prospective study. They demonstrated the similar oncological outcomes with type II RH and type III RH, with a lower incidence of long-term pelvic organ dysfunction. The reason for the decrease in long-term pelvic complications with a less radical approach is related to the protection of the pelvic nerves [21]. On the other hand, some investigators have proposed that preserving the pelvic autonomic nerves with nerve-sparing surgical techniques may reduce the incidence of long-term complications following RH, without reducing the radicality of the operation. However, there is no randomized study on this subject to compare to those on less radical surgery [12,14].

Herein, some technical details and oncological outcomes of nerve-sparing RH are summarized together with a brief overview of pelvic organ dysfunction following RH and a historical perspective.

2. Search strategy and selection criteria

Data for this review were identified by searches of PubMed, and references from relevant articles using the search terms “nerve sparing hysterectomy” and “Okabayashi radical hysterectomy”, “cervical carcinoma”, “bladder dysfunction”, “anorectal dysfunction”, and “sexual dysfunction”. Abstracts and reports from meetings were included only when they related directly to previously published work.

3. Overview of pelvic organ dysfunctions after the radical hysterectomy

3.1. Bladder dysfunctions

The close proximity of the bladder to the uterus and cervix inevitably results in the disruption of its anatomic support, autonomic innervation, and blood supply during RH, and these surgical traumas may cause irreversible functional changes to the urinary tract [13]. A systematic review of the literature reported that even simple hysterectomy is related to increased risk of urinary tract dysfunction. The authors found that the risk of developing urinary incontinence after hysterectomy was about 40% higher than in the control group [15]. Furthermore, it was reported that significant changes in vesical sensitivity may occur after hysterectomy and these changes could persist for at least 6 months postoperatively [16]. As is known, the extent of hysterectomy and parametrial resection is closely associated with the increased risk of pelvic autonomic nerve injury; therefore, it can be expected that RH might be related to more serious effects on bladder dysfunction compared to simple hysterectomy. In a review of the literature regarding RH and urinary dysfunction, Zullo et al. reported that functional disorders of the lower urinary tract (sensory loss, storing and voiding dysfunctions, urinary incontinence, and detrusor instability) are the most common long-term complications following RH. The incidence of postoperative bladder dysfunction after RH has been reported to occur in 70–85% of reported studies [11,53–57].

Historically, two phases of postoperative bladder storage dysfunction have been described, an initial hypertonic phase characterized by a small, spastic bladder, followed by a hypotonic, overdistended bladder. The hypertonic bladder dysfunction phase is almost universal and usually transient, resolving in 8–12 weeks. The hypotonic bladder dysfunction phase occurs as a result of overdistension of the bladder and poor bladder management of bladder distension at the initial hypertonic phase. Therefore, it is generally accepted that careful management of the early phase with intermittent self-catheterization, etc. may reduce the rate of urinary dysfunction [13]. On the other hand, stress incontinence and detrusor overactivity are the most frequent urinary symptoms seen after RH. The real cause of these symptoms following RH is not clear, but injury to the anatomic support of the bladder and urethrovesical junction during resection of the upper vagina and parametrium, in addition to pudendal and pelvic nerve damage, and injury to the urethrovesical junction or the smooth muscle fibers of the detrusor might be underlying factors [13]. Others have reported that RH is also associated with significant urodynamic changes and that these alterations may persist for at least 1 year following surgery [17–19]. Scotti et al. reported that adjuvant RT after type III RH was significantly associated with more contracted and unstable bladders than surgery alone [17]. Although some authors have suggested the use of some medications, such as bethanechol, cisapride, beta2-agonists, etc., as a potential novel approach for reducing the risk of urinary disturbance after RH, this approach has yet to be proven [20,21].

3.2. Anorectal dysfunctions

Anorectal functions have an important impact on quality of life in women. However, research into the effects of RH on anorectal dysfunction has not been given the attention it deserves. Anorectal functions, including stool consistency and colorectal activity, and the relationship between the internal anal sphincter and external anal sphincter are coordinated by the parasympathetic and sympathetic nerves. Sympathic stimulation initiates defecation, while parasympathetic stimulation inhibits expulsion and stimulates the internal anal sphincter.

It has been suggested that simple hysterectomy may have a disturbing influence on bowel function in some patients; however, the actual effect of hysterectomy on bowel functions is not fully understood. During simple hysterectomy, only the ligaments with nerves innervating the uterus and cervix can be injured, whereas during RH the ligaments that contain the pelvic autonomic nerves are divided more laterally, which has been associated with increased risk of injury to the pelvic autonomic nerves and pelvic organ dysfunction. It was reported that following hysterectomy women were more likely to consider themselves as constipated and more often reported feeling bloated and feelings of incomplete evacuation [22].

On the other hand, van Dam et al. reported that 31 and 11% of women complained severe and moderate changes in bowel function after hysterectomy, respectively. The authors reported that changes in bowel function began within 1 month of hysterectomy and concluded that hysterectomy seems to play an important role in the pathogenesis of disturbed defecation [23]. In a retrospective study following hysterectomy for both benign and malignant disease, it was reported that 42% of patients complained of postoperative bowel dysfunction, predominantly severe straining [23]. Moreover, increased rectal sensitivity for up to 6 months following simple hysterectomy for benign conditions has been reported [16]. Dissection of the uterosacral ligaments or cardinal ligaments may cause partial denervation of the rectal autonomic nerves. In addition, the pudendal nerve supply to the external anal sphincter may be damaged during RH [13]. Constipation and related symptoms including excessive dyschezia, digitation, tenesmus, and the sensation of incomplete evacuation can be experienced after RH. The degree of constipation and related symptoms might be related to the degree of surgical radicality and injury to pelvic autonomic nerves. Sood et al. demonstrated significant changes in colorectal function after RH, suggesting a pattern that correlates to a partial denervation of the bowel [24]. Barnes et al. demonstrated rectal hyposensitivity and diminished ability of the internal anal sphincter to relax to baseline after RH, in addition to unchanged resting and squeeze pressure functions of both the internal and external anal sphincter [25]. Anorectal dysfunction after RH has not been investigated completely and the pathophysiological changes in anorectal function have not been fully understood; further research is needed to enhance our knowledge of this subject.

3.3. Sexual dysfunctions

The upper vagina, cervix, surrounding parametrial tissues, and sometimes the ovaries have to be resected during RH. It is well known that women undergoing RH may experience coital and orgasmic problems, dyspareunia, and sexual dissatisfaction due to a reduction in the size of the vaginal and damaged pelvic nerves [26]. Furthermore, RH seems to be associated with disturbed vaginal blood flow response during sexual arousal. As is known, loss of ovarian function may adversely affect sexual functioning. Women undergoing concomitant oophorectomy during RH may demonstrate negative psychosocial outcomes, such as reduced sexual interest, and diminished arousal and orgasm, as well as elevated depressive symptoms and impaired body image. Furthermore, the combined treatment of RH with RT may also cause reduced lubrication, reduced elasticity, and genital swelling during sexual stimulation [27]. Recently, it was reported that cervical cancer survivors treated with RT had a lower level of sexual functioning compared to women treated with RH alone [28]. In conclusion, the sexual health of women with a history of cervical cancer needs to receive more attention in order to improve the quality of life of cervical cancer survivors and

nerve-sparing RH might be an important development that could do so.

4. History of nerve-sparing radical hysterectomy

Historically, the pioneer of nerve-sparing pelvic surgery concept was the Japanese gynecologist, Okabayashi. In the 1921, he described the principles of his systemic RH technique (in English) in order to improve the outcomes of RH by Wertheim method while working at Kyoto Imperial University [50]. In 1944, he already proclaimed that preservation of the pelvic nerves would become an important part of the RH for the optimization of the RH outcomes (in Japanese) [51]. Subsequently, Kobayashi modified the Okabayashi's RH and identified the principles for the prevention of the bladder dysfunctions (in Japanese). Then, in 1983 Fujiwara emphasized the importance of the preservation of the bladder branch of the inferior hypogastric plexus and pelvic splanchnic nerves [40]. In 1992, Sakamoto introduced the Tokyo method for the preservation of the pelvic autonomic nerves during RH [10,30]. Subsequently, the principals of the nerve-sparing hysterectomy technique became familiar to Japanese gynecologic surgeons. Then other Japanese gynecologic surgeons like Yabuki et al. [35–37], Kato et al. [45], Sakuragi et al. [48] extensively investigated the anatomy of the pelvic autonomic nerves and modified the RH methods for the prevention of long-term pelvic autonomic dysfunctions [49]. During at that time, general surgeons and urologists adopted this nerve-sparing technique into their practice and developed nerve-sparing rectal surgery and nerve-sparing RH. Today, these two surgical specialities frequently use the nerve-sparing technique in their practices. Nerve-sparing radical prostatectomy and total mesorectal excision are widely performed by these surgical specialities. However, nerve sparing during RH only became popular among gynecologic surgeons during the last two decades [29].

In 1998 Höckel et al. (Leipzig, Germany) described the first non-Japanese method of nerve-sparing surgery during RH. In this technique they performed an extended RH with liposuction in order to preserve to the pelvic plexus in seven patients with cervical or vaginal carcinoma [31]. Subsequently, Professor Schnieder's Group (Jena, Germany) described their own method of identifying and preserving the pelvic splanchnic nerves in the cardinal ligament during laparoscopic-assisted type III RH in 2000 [32]. In 2001, Trimbos et al. (the Netherlands) described a modified nerve-sparing hysterectomy method for preserving the autonomic nerves during RH and concluded that nerve-sparing hysterectomy techniques were feasible for patients in Western countries [33]. Following the publication of these essential nerve-sparing RH techniques, new efforts, mostly from European countries and Japan, were also published and there remains on-going effort to improve the technique and outcome of nerve-sparing hysterectomy.

5. Technical details and oncological outcomes of nerve-sparing hysterectomy

In Japan, Hidekazu Okabayashi modified Wertheim method in 1921 [29,50]. Okabayashi's surgical technique was characterized by the extensive resection of the parametriums and the separation of the posterior leaf of the vesicouterine ligament. This essential step enabled the bladder to be separated from the ureter, completely away from the lateral side of the cervix and vagina [50,51]. His surgical technique was widely performed in Japan; however, it did not become a popular approach in the west. In 1961, Kobayashi at Tokyo University modified the Okabayashi's RH and identified the principles for the prevention of the bladder dysfunctions. Kobayashi preserved the pelvic splanchnic nerves by the separation of the vascular part and the neural part of the cardinal ligament during the resection of the parametrial tissues. Then, in 1983 Fujiwara emphasized the importance of the preservation of the bladder branch of the inferior hypogastric plexus and pelvic splanchnic nerves [40]. This concept was also used in the description of the Tokyo method. The Tokyo method modification of Okabayashi's RH technique, which was described by Sakamato who was a student of Kobayashi, could be accepted as minor modification of Kobayashi method. Sakamato noted that after pelvic lymphadenectomy, cardinal ligaments could be seen as two main parts: vascular and neural. Another crucial component of the Tokyo method is the cutting of the vascular part of the cardinal ligament, while preserving the autonomic nerves within the neural part of the cardinal ligament. However, in this technique the sympathetic branches of the pelvic nerves (hypogastric nerves) cannot been preserved, and postoperative residual urine 1 month after surgery occurred in 63% of patients in the nerve-sparing group and in 90% of the non-nerve-sparing group [10,30].

Subsequently, Yabuki et al. proposed a new terminology and another modification of nerve-sparing RH. In this method the terminology of parametrial dissection was changed and they suggested two connective tissue systems for the classification of the ligaments of the uterus, the suspensory system, and supporting system, instead of the classical ligament system. The suspensory system is a true musculofascial complex, which provides the connections of the bladder, uterus, and rectum dorsoventrally. The supporting system includes a ligamentous complex consisting the lamina ligamenti umbilicalis lateralis, and the cardinal and lateral ligaments. This nerve-sparing surgical procedure was planned according to the continuity of the uterine support system and performed by first excising the fascia and then dissecting the denuded areoral tissue with an ultrasonic surgical aspirator. They also preserved the vesical nerve branch after careful dissection of the deep layer of the vesicouterine ligament [35–37].

All these nerve-sparing techniques are based on Okabayashi RH in Japan. Recently, Fujii published the technical details of the Okabayashi RH, together with two excellent video presentations, which demonstrates the princi-

ples of Japanese nerve-sparing RH, and one historical video, which is of Okabayashi himself [29]. Furthermore, Fujii et al. described in detail how to identify the vesico-uterine ligament (VUL) during RH, which is essential for the preservation of the bladder's autonomic nerves. Briefly, after the complete separation of the uterine artery and veins from the ureters, genuine connective tissue of the anterior leaf of the VUL and the posterior leaf of the VUL under the ureter can be identified, and these steps might enable the preservation of the pelvic autonomic nerves [34]. Moreover, Fujii et al. first showed how to preserve pelvic autonomic nerves only dividing the uterine branch from the inferior hypogastric plexus, which is discussed below [49].

In the Western countries, Höckel et al. (Leipzig, Germany) described the first non-Japanese method of nerve-sparing RH. In this technique, they performed an extended RH with liposuction in order to preserve the pelvic plexus in seven patients with cervical or vaginal carcinoma. The topographic anatomy of the pelvis was evaluated with high-resolution magnetic resonance imaging before the operation. Then, they preserved the superior hypogastric plexus by identifying this nerve at the level of the sacral promontorium, following the nerves down along the mesorectum. After identification of the superior hypogastric plexus, they identified the pelvic splanchnic nerves and pelvic plexus within the cardinal ligament using liposuction. The pelvic plexus was mostly located below the uterine artery and vein at the level of the inferior vesical vessels [31]. Then, total mesometrial resection (TMMR) was suggested as a technique of high-resolution nerve-sparing RH, which is based on developmentally defined surgical anatomy. TMMR requires an experienced and talented oncological surgeon, and is performed in 21 steps, all of which are detailed in Hockel et al.'s publications. In brief, it is characterized as follows:

1. En bloc resection of the uterus, proximal vagina, and mesometrium.
2. Transection of the rectouterine dense subperitoneal connective tissue above the level of the exposed inferior hypogastric plexus.
3. Extended pelvic/periaortic lymph node dissection, preserving the superior hypogastric plexus [38].

Hockel et al. re-modified this surgical technique and published an updated series in 2005. In this article, they also provided the embryological basis of the TMMR concept [14]. Hockel et al. have also suggested that if treatment of cervical carcinoma is tailored according to the embryological concepts of TMMR, postoperative adjuvant RT is unnecessary, even in the presence of high-risk factors. They also described the distal Mullerian morphogenetic unit in female human embryos and cadavers, and then they performed TMMR and investigated its effectiveness in 106 patients with stage IB–IIB cervical carcinoma. Among them, 105 of the patients, 63 of whom were high risk, had tumor-free surgical margins. According to their results, macroscopic and microscopic local tumor spread was confined to the distal mullerian morphogenetic unit in patients with FIGO stage IB–IIB cervical cancer, and TMMR provided better surgical margins and a better disease-free survival rate, with less postoperative morbidity. The 3-years disease-free survival rate was 93%. They concluded, "radical en bloc resection of topographically defined anatomical territories from common precursor tissues leads to local tumor control, preservation of autonomic nerves, and a reduced need for adjuvant radiotherapy" [14].

The second non-Japanese nerve-sparing RH technique was published by Professor Schnieder's group (Jena, Germany). In their method, after the development of the pararectal, lumbo-sacral, and paravesical spaces, the cardinal ligament is completely freed of all lymphatic and fatty tissues. Then after bipolar coagulation, the vascular part of the cardinal ligament is divided at the pelvic sidewall and then pelvic splanchnic nerves are identified and preserved in the cardinal ligament during laparoscopic-assisted type III RH. They compared bladder morbidity in 28 patients that underwent the type III laparoscopy-assisted radical vaginal hysterectomy (LARVH) (non-nerve-sparing group) and 38 patients that were treated with the nerve-sparing type III LARVH procedure (nerve-sparing group). Suprapubic drainage was removed after a mean of 21 days in the non-nerve-sparing group and after a mean of 11.2 days in patients in the nerve-sparing group ($P < 0.0007$). With this method the middle rectal artery is used as a landmark in order to separate the neural part of the cardinal ligament; however, the hypogastric (sympathetic) nerve is not preserved and the authors noted that preserving the pelvic splanchnic nerves seems to be more important than preserving the hypogastric nerve for the preservation of bladder function. They also stated that the radicality of the operation, which was assessed by the mean length of removed parametrial tissue, did not changed after the nerve-sparing procedure [32].

In both German nerve-sparing techniques the focus is on the preservation of the nerves in the cardinal ligament. However, in an immunohistochemical investigation it was demonstrated that sacro-uterine ligaments contain a greater density of autonomic nerves compared to the cardinal ligament [39]. In 2001 Trimbos et al. (The Netherlands) described a modified nerve-sparing hysterectomy method for preserving the autonomic nerves during RH, which was originated from the Japanese surgical technique. Pelvic nerve preservation mainly consisted of three steps as described in their publication:

1. Preserving the hypogastric nerve and proximal part of the inferior hypogastric plexus.
2. Preserving the pelvic splanchnic nerves and the middle part of the inferior hypogastric plexus.
3. Preserving the distal part of the inferior hypogastric plexus.

In that study, Trimbos et al. reported that nerve-sparing hysterectomy techniques were feasible for patients from Western countries, with the exception of extreme obese indi-

viduals and those with bulky tumors. They emphasized that thin and non-obese body composition, and the non-deep structure of Japanese women make them better suited to nerve-sparing RH. Although initially some surgeons were skeptical about the oncological safety and effectiveness of nerve-sparing RH techniques, in a cadaveric study the same group also demonstrated that the nerve-sparing approach could more effectively preserve the pelvic autonomic nerves compared to classical RH [33,52].

Following the publication of these essential nerve-sparing RH techniques, new efforts were also published. Katahira et al. recently reported that intraoperative electrical stimulation (IES) of the pelvic splanchnic nerves while monitoring intravesical pressure during RH represents a technically simple and useful procedure for the prediction of postoperative bladder function. In this method, after pelvic lymphadenectomy, the vascular part of the cardinal ligament is clamped and divided. The hypogastric nerves are identified and separated under the ureter during pararectal space development. During the subsequent dissection of the rectovaginal ligament, care is taken not to damage the pelvic plexus. Then VUL is identified and taped on the lateral side of the uterus. IES of the pelvic autonomic nerves is performed using single bipolar electrode stimulation of the bilateral roots of S2-S4, PVL is marked with surgical tape, and the dorsal part of the vesicouterine ligaments bilaterally before resection of uterus and after the resection of the uterus. With this method preservation of pelvic splanchnic nerve function is accepted as an increase in intravesical pressure by at least 3 cm H_2O. They measured bladder function preoperatively and 3 months after surgery and increased intravesical pressure was observed with IES of the parasymphatic nerve (PSN) roots after uterine resection in 13 of 17 cases. They concluded, "IES, while monitoring intravesical pressure during RH, represents a technically simple and useful procedure for the prediction of postoperative bladder function" [41].

In 2005 Sakuragi et al. described the new modification of Japanese nerve-sparing hysterectomy. In the technique of Sakuragi et al., first step was to extensive pelvic and paraaortic lymphadenectomy and then to identify and lateralize the hypogastric nerves and the proximal part of the pelvic plexus during the dissection of the uterosacral ligament and rectovaginal ligament. The next step is to dissection of the cardinal ligament to skeletonize the deep uterine vein and the pelvic splanchnic nerves arising from the sacral surface are preserved. In this method posterior part of the vesicouterine ligament was also dissected and pelvic splanchnic nerves and all the pelvic plexus is put to the lateral side from the resection line. They successfully completed the nerve-sparing procedure in 81.5% of the 27 patients and 1 year after the operation, bladder symptoms were significantly improved in the nerve-sparing group compared to the non-nerve-sparing group. They also stated that "normal urinary function can be maintained by applying the operation with autonomic nerve preservation to the uninvaded side in patients with stage IIb cervical cancer, who have parametrial invasion only on one side." Furthermore, although their follow-up is limited (29 months), they concluded that patients' survival was not adversely affected by the nerve-sparing procedure [48].

Additionally, Raspagliesi et al. reported that a nerve-sparing RH technique using a cavitron ultrasonic surgical aspirator (CUSA) was feasible, showing promising results in terms of preventing early bladder dysfunction. In this technique, briefly, the authors first identified the hypogastric plexus and two hypogastric nerves, then the anterior and posterior parts of VUL were identified and divided. Next, nerve fibers arising from the hypogastric plexus, which run beside the lateral wall of the vagina to the bladder, were preserved, restricting the level of colpectomy to 2 cm below the cervix instead of the cranial upper third part of the vagina. Finally, the terminal part of the hypogastric nerve and the cranial part of the inferior hypogastric plexus were preserved during the dissection of the utero-sacral ligaments at the time of the development of the pre-rectal and pararectal spaces. In that study nerve-sparing type III RH was performed in 23 cases with cervical carcinoma, mean hospitalization was 10 days (range: 5–16 day), and 2 out of 23 patients (9%) were discharged with self-catheterization, but one of them began to void spontaneously before her first outpatient follow-up visit. The authors concluded that, "this nerve-sparing RH technique using the CUSA was feasible in terms of preventing early bladder dysfunction, but further prospective controlled studies are needed." [42].

Raspagliesi et al. also compared the postoperative morbidity of type II, nerve-sparing type III, and classical type III RH in terms of early bladder dysfunction and complications [43]. There were no intraoperative complications in either of the groups. The groups did not differ significantly in terms of severe morbidity. None of the groups differed in terms of urologic morbidity. Bladder recovery was significantly different in type II and type III nerve-sparing RH groups; also there was a significant difference between the groups regarding the number of patients discharged with self-catheterization. The authors concluded that, "type III nerve-sparing RH seems to be comparable to type II RH and superior to type III RH in terms of early bladder dysfunction."

Recently, Possover et al. described a laparoscopic neuro-navigation (LANN) system to help preserve the parasympathetic pelvic nerves and to reduce postoperative morbidity in laparoscopic-assisted radical pelvic surgery for cervical carcinoma or deep infiltrating endometriosis of the parametrium. In that study, the authors identified the S2, S3, and S4 sacral roots using a laparoscopic instrument and then they used a laparoscopic navigation system for the functional identification of and preservation of different sacral parasympathetic nerve routes. In this system, they used mono-bipolar laparoscopic forceps for electrostimulation, and a microtip rectal probe and an 8-F dual sensor microtip transurethral catheter with filling channel were used for intraoperative urodynamic testing. In their prospective cohort, 261 patients underwent this procedure and the rate of postoperative bladder dysfunction was less than 1% [44].

On the other hand, Kato et al. compared the outcome of bilateral nerve sparing (BNS, $n = 21$) and unilateral nerve sparing (UNS, $n = 11$) RH with respect to bladder morbidity in 32 patients with locally advanced cervical carcinoma. Post-surgery, greater bladder dysfunction was observed in the patients in the UNS group than in those in the BNS group. All the patients in both groups were discharged from the hospital without self-catheterization and with recovery of spontaneous voiding. Mean duration before the post-void residual volume became less than 50 ml was 11.5 days in the UNS group compared to 5.3 days in the BNS group ($P = 0.004$). However, none of the patients in either group developed neurogenic bladder requiring self-catheterization of the bladder [45]. Todo et al. provided the results of pre-surgery and at 12 months post-nerve-sparing RH using urodynamic evaluations. Abdominal pressure at maximum flow significantly increased in the non-nerve-sparing group ($n = 5$); however, there was no significant difference in compliance at the moment of strong desire to void, maximum flow rate, and residual urine volume before surgery and 12 months after surgery. Also, detrusor contraction pressure at maximum flow significantly decreased in the non-nerve-sparing group [46]. Pieterse et al. compared vaginal blood flow of classical RH, nerve-sparing RH, and control groups, and found that classical RH was associated with an overall disturbed vaginal blood flow response compared to the healthy controls. However, women with a history of nerve-sparing RH seemed to have had a better vaginal blood flow response during sexual arousal. Therefore, the authors stated that, "RH should be performed to prove without any doubt that nerve-sparing techniques lead to less sexual dysfunction" [47].

Recently, Kyoto university gynecology group leaded by Prof. Fujii extensively described the anatomical and technical details of nerve sparing hysterectomy and functional outcomes of Okayabashi RH in 24 patients using a surgical loop (×2.5).

In this technique, there are seven main steps:

- Isolation and separation of the deep uterine vein from the pelvic splanchnic nerve.
- Isolation and separation of the hypogastric nerve.
- Separation of the cut end of the deep uterine vein from the pelvic splanchnic nerve.
- Separation of blood vessels in the posterior leaf of the vesicouterine ligament.
- Isolation and division of the inferior vesical vein.
- Separation/division of the uterine branch from the inferior hypogastric plexus.
- Separation and division of the paracolpium.

After pelvic lymphadenectomy, the uterine artery is isolated, ligated and cut close to the internal iliac artery. Then, pararectal and paravesical spaces are developed. The superficial uterine vein and the inferior vesical artery are isolated and ligated. After these steps, adipose tissues and lymph nodes in the parametrial tissues are removed and the deep uterine vein secured and cut. Connective tissue on the side of the cervix is carefully separated. Then, a ureteral branch of the uterine artery is identified and ligated meticulous separation of the connective tissue between the ureter and the urinary bladder reveal that the superficial uterine vein has connection with the bladder and this vein also ligated and cut. After these essential steps genuine anterior leaf of the vesico-uterine ligament can be identified. In this method, instead of developing the ureteral tunnel, the connective tissue of the anterior leaf of vesico-uterine ligament is divided and ureter is completely freed of its attachment to the posterior leaf of the vesico-uterine ligament. Then, posterior leaf of the vesico-uterine ligament is divided. Then, the middle and inferior vesical vein are cut. Finally, the urinary bladder with ureters was completely separated from the lateral cervix and upper vagina. Briefly, these steps they identify a part of pelvic splanchnic nerves and on the rectal side of the pararectal space, the hypogastric nerve running parallel with the rectum is isolated. Also, during the division of the posterior leaf of the VUL, isolation of the inferior vesical vein could reveal the bladder branch from the inferior hypogastric plexus. Only the uterine branch from the inferior hypogastric plexus was isolated and divided. Then, the T-shaped nerve plane consisting of the hypogastric nerve, the pelvic splanchnic nerve and the bladder branch from the inferior hypogastric plexus were preserved. An evaluation of urinary functions (post-voiding residual urine, sensation of bladder fullness, satisfaction of micturition) after this method was excellent in all cases.

However, as emphasized by the authors the comparison of the bladder functions with the previously reported studies is difficult because the extent of RH and the evaluation of the urinary function of each study are various. Furthermore, operating time was obviously higher than the classical approach but better bladder outcomes justifies the longer operative time. Fujii et al. also stated that their technique of nerve sparing is very feasible in patients with stage Ib1 but not for IIb cases and also the effect of nerve sparing on the survival or time to progression is not yet known. Until now, many people described the concept of nerve-sparing RH, however, no body showed the exact anatomy of the cross-shaped inferior hypogastric plexus that is constructed by hypogastric nerve, pelvic splanchnic nerve, uterine branch from the inferior hypogastric plexus, and bradder branch from the inferior hypogastric plexus. The outcomes of the urinary function after the division of only uterine branch from the inferior hypogastric plexus were satisfactory [49]. Detailed description of the pelvic anatomy and surgical steps will provide the dissemination of the nerve-sparing hysterectomy [29,49].

In conclusion, nerve-sparing RH is promising and attractive approach because of improved urogenital, anorectal, and sexual functions in patients that undergo RH, however, there are several concerns about this surgical approach. The first and most important concern is oncological safety. It is accepted that complete resection of the tumor with

tumor-free margins is the main aim of the surgical oncologist and this must never be compromised with the aim of improving pelvic autonomic functions. Although oncological outcomes of nerve-sparing RH were not significantly different than with classical RH in the reported studies, it should be remembered that all of these studies included limited numbers of patients and these patients were probably carefully selected. Another important limitation, unfortunately, is that only experienced surgeons can perform these procedures. Furthermore, although more than 80% of cases with cervical carcinoma are diagnosed in undeveloped countries, till date there has not been any publication from an undeveloped or developing country in which the disease is more prevalent and the mortality rate is higher. Moreover, the necessity of having the sophisticated surgical devices (CUSA, laparoscopy, neuro-navigation system, etc.) necessary for these procedures poses a hindrance to the spread of this technique to those un- and underdeveloped countries that have the highest disease prevalence rates. Finally, the surgical steps of this concept should be clearly identified and disseminated to gynecologic oncologists to ensure reproducible results. The uniform reporting of precise surgical steps is required for reproducible results and to compare the data between the studies. Furthermore, lack of randomized studies comparing the effectiveness and complications of RH and nerve-sparing RH is another important barrier for the dissemination of this promising technique. Nonetheless, while nerve-sparing RH still awaits prospective randomized trials in order to prove its effectiveness is equal to or greater than that of the conventional treatment modalities, with less long-term complications, this surgical approach remains attractive to the patients and gynecologic oncologists based on the published preliminary results.

Reviewer

Prof. Shingo Fujii, Postgraduate School of Medicine, Department of Gynecology and Obstetrics, Kyoto University, Sakyoku, Kyoto, Japan.

Acknowledgements

I would like to thank the Turkish Scientific Research Council & Turkish-German Gynecology Association (TUBITAK-TAJD), European Society of Surgical Oncology (ESSO), European School of Oncology (ESO), and FIGO/IGCS Gynecologic Oncology Fellowship, which designated me (Polat Dursun) as a Clinical Gynecologic Oncology Fellow. I am also very appreciative of their financial and motivational support. Additionally, I would like to thank my hosts (Professor Dr. A. Schneider, Professor Dr. M. Höckel, and Dr. E. Leblanc) for their excellent mentorship and hospitality. I apologize to all others I could not mention.

References

[1] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
[2] Morice P, Castaigne D. Advances in the surgical management of invasive cervical cancer. Curr Opin Obstet Gynecol 2005;17(1 February):5–12.
[3] Dursun P, Leblanc E, Nogueira MC. Radical vaginal trachelectomy (Dargent's operation): a critical review of the literature. Eur J Surg Oncol 2007;33(8):933–41 [Epub Jan 5, 2007].
[4] Dursun P, Ayhan A, Kuscu E. New surgical approaches for the management of cervical carcinoma. Eur J Surg Oncol; in press.
[5] American Cancer Society. Cancer facts and figures 2006. Atlanta: American Cancer Society; 2006.
[6] Wertheim E. The extended abdominal operation for carcinoma uteri (based on 500 operative cases). Am J Obstet Dis Women Child 1912;66:169–232.
[7] Meigs VJ. Radical hysterectomy with bilateral pelvic lymph node dissections. A report of 100 patients operated on five or more years ago. Am J Obstet Gynecol 1951;62:854–70.
[8] Donato DM. Surgical management of stage IB-IIA cervical carcinoma. Semin Surg Oncol 1999;16:232–5.
[9] Ercoli A, Delmas V, Gadonneix P, et al. Classical and nerve-sparing radical hysterectomy: an evaluation of the risk of injury to the autonomous pelvic nerves. Surg Radiol Anat 2003;25(July–August (3–4)):200–6 [August 9, Epub].
[10] Maas CP, Trimbos JB, DeRuiter MC, van de Velde CJ, Kenter GG. Nerve sparing radical hysterectomy: latest developments and historical perspective. Crit Rev Oncol Hematol 2003;48(3 December):271–9.
[11] Zullo MA, Manci N, Angioli R, Muzii L, Panici PB. Vesical dysfunctions after radical hysterectomy for cervical cancer: a critical review. Crit Rev Oncol Hematol 2003;48:287–93.
[12] Landoni F, Maneo A, Cormio G, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. Gynecol Oncol 2001;80(1 January):3–12.
[13] Jackson KS, Naik R. Pelvic floor dysfunction and radical hysterectomy. Int J Gynecol Cancer 2006;16:354–63.
[14] Hockel M, Horn LC, Fritsch H. Association between the mesenchymal compartment of uterovaginal organogenesis and local tumour spread in stage IB–IIB cervical carcinoma: a prospective study. Lancet Oncol 2005;6(10 October):751–6.
[15] Brown JS, Sawaya G, Thom DH, Grady D. Hysterectomy and urinary incontinence: a systematic review. Lancet 2000;356:535–9.
[16] Prior A, Stanley K, Smith AR, Read NW. Effect of hysterectomy on anorectal and urethrovesical physiology. Gut 1992;33(2 February):264–7.
[17] Scotti RJ, Bergman A, Bhatia NN, Ostergard DR. Urodynamic changes in urethrovesical function after radical hysterectomy. Obstet Gynecol 1986;68(1 July):111–20.
[18] Chen GD, Lin LY, Wang PH, Lee HS. Urinary tract dysfunction after radical hysterectomy for cervical cancer. Gynecol Oncol 2002;85(2 May):292–7.
[19] Lin LY, Wu JH, Yang CW, Sheu BC, Lin HH. Impact of radical hysterectomy for cervical cancer on urodynamic findings. Int Urogynecol J Pelvic Floor Dysfunct 2004;15(6 November–December):418–21.
[20] Hamada K, Kihana T, Kataoka M, et al. Urinary disturbance after therapy for cervical cancer: urodynamic evaluation and beta2-agonist medication. Int Urogynecol J Pelvic Floor Dysfunct 1999;10(6):365–70.
[21] Madeiro AP, Rufino AC, Sartori MG, et al. The effects of bethanechol and cisapride on urodynamic parameters in patients undergoing radical hysterectomy for cervical cancer. A randomized, double-blind, placebo-controlled study. Int Urogynecol J Pelvic Floor Dysfunct 2006;17(3 May):248–52.
[22] Heaton KW, Parker D, Cripps H. Bowel function and irritable bowel symptoms after hysterectomy and cholecystectomy—a population based study. Gut 1993;34(8 August):1108–11.

[23] van Dam JH, Gosselink MJ, Drogendijk AC, Hop WC, Schouten WR. Changes in bowel function after hysterectomy. Dis Colon Rectum 1997;40(11 November):1342–7.
[24] Sood AK, Nygaard I, Shahin MS, et al. Anorectal dysfunction after surgical treatment for cervical cancer. J Am Coll Surg 2002;195:513–9.
[25] Barnes W, Wagonner S, Delgado G, et al. Manometric characterisation of rectal dysfunction following radical hysterectomy. Gynecol Oncol 1991;42:116–9.
[26] Jensen PT, Groenvold M, Klee MC, et al. Early-stage cervical carcinoma, radical hysterectomy, and sexual function. A longitudinal study. Cancer 2004;100(1):97–106.
[27] Bergmark K, Åvall-Lundqvist E, Dickman Pw, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. N Engl J Med 1999;340:1383–9.
[28] Frumovitz M, Sun CC, Schover LR, et al. Quality of life and sexual functioning in cervical cancer survivors. J Clin Oncol 2005;23(30 October 20):7428–36.
[29] Fujii S. Original film of the Okabayashi's radical hysterectomy by Okabayashi himself in 1932, and two films of the precise anatomy necessary for nerve-sparing Okabayashi's radical hysterectomy clarified by Shingo Fujii. Int J Gynecol Cancer 2008;18(2):383–5 [Epub Jun 22, 2007].
[30] Sakamoto S, Takazawa K. An improved radical hysterectomy with fewer urological complications and with no loss of therapeutic results for cervical cancer. Ballieres Clin Obstet Gynecol 1988;2:953–62.
[31] 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.
[32] Possover M, Stober S, Plaul K, Schneider A. Identification and preservation of the motoric innervation of the bladder in radical hysterectomy type III. Gynecol Oncol 2000;79:154–7.
[33] Trimbos JB, Maas CP, DeRuiter MC, Peters AAW, Kenter GG. A nerve sparing radical hysterectomy; guidelines and feasibility in Western patients. Int J Gynecol Cancer 2001;11(3):180–6.
[34] Fujii S, Takakura K, Noriomi M, et al. Tsukasa Baba precise anatomy of the vesico-uterine ligament for radical hysterectomy. Gynecol Oncol 2007;104:186–91.
[35] 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.
[36] Yabuki Y, Asamoto A, Hoshiba T, Nishimoto H, Satou N. A new proposal for radical hysterectomy. Gynecol Oncol 1996;62:370–8.
[37] Yabuki Y, Asamoto A, Hoshiba T, et al. Radical hysterectomy: an anatomic evaluation of parametrial dissection. Gynecol Oncol 2000;77:155–63.
[38] Hockel M, Horn LC, Hentschel B, Hockel S, Naumann G. Total mesometrial resection: high resolution nerve-sparing radical hysterectomy based on developmentally defined surgical anatomy. Int J Gynecol Cancer 2003;13(6 November–December):791–803.
[39] Butler-Manuel SA, Buttery LDK, A'Hern RP, Polak JM, Barton DPJ. Pelvic nerve plexus trauma at radical hysterectomy and simple hysterectomy: nerve content of the uterine supporting ligaments. Cancer 2000;89:834–41.
[40] Fujiwara T. Surgery for cervical cancer (in Japanese). Tokyo: Igakutoshyosyuppan; 1984.
[41] Katahira H, Niikuraa Y, Kaihob H, et al. Intraoperative electrical stimulation of the pelvic splanchnic nerves during nerve-sparing radical hysterectomy. Gynecol Oncol 2005;98:462–6.
[42] Raspagliesi F, Ditto A, Fontanelli R, et al. Nerve-sparing radical hysterectomy: a surgical technique for preserving the autonomic hypogastric nerve. Gynecol Oncol 2004;93:307–14.
[43] Raspagliesi F, Ditto A, Fontanelli R, et al. Type II versus Type III nerve-sparing radical hysterectomy: comparison of lower urinary tract dysfunctions. Gynecol Oncol 2006;102(2):256–62 [Epub Jan 30, 2006].
[44] Possover M, Quakernack J, Chiantera V. The LANN technique to reduce postoperative functional morbidity in laparoscopic radical pelvic surgery. J Am Coll Surg 2005;201:913–7.
[45] Kato K, Suzuka K, Osaki T, Tanaka N. Unilateral or bilateral nerve-sparing radical hysterectomy: a surgical technique to preserve the pelvic autonomic nerves while increasing radicality. Int J Gynecol Cancer 2007;17(5):1172–8 [Epub Jun 22, 2007].
[46] Todo Y, Kuwabara M, Watari H, et al. Urodynamic study on postsurgical bladder function in cervical cancer treated with systematic nerve-sparing radical hysterectomy. Int J Gynecol Cancer 2006;16:369–75.
[47] Pieterse QD, Ter Kuile MM, DeRuiter MC, et al. Vaginal blood flow after radical hysterectomy with and without nerve sparing. A preliminary report. Int J Gynecol Cancer 2008;18(3):576–83 [Epub Aug 10, 2007].
[48] Sakuragi N, Todo Y, Kudo M, Yamamoto R, Sato T. A systematic nerve-sparing radical hysterectomy technique in invasive cervical cancer for preserving postsurgical bladder function. Int J Gynecol Cancer 2005;15:389–97.
[49] Fujii S, Takakura K, Matsumura N, et al. Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. Gynecol Oncol 2007;1007:4–13.
[50] Okabayashi H. Radical abdominal hysterectomy for cancer of the cervix uteri, modification of the Takayama operation. Surg Gynecol Obstet 1921;33:335–41.
[51] Okabayashi H. Comments to the article entitled "Mibayashi's radical surgery for cervical cancer" (in Japanese). Jpn Med Wochenschr Tokyo 1944;1124:8–10.
[52] Maas CP, Kenter GG, Trimbos JB, Deruiter MC. Anatomical basis for nerve-sparing radical hysterectomy: immunohistochemical study of the pelvic autonomic nerves. Acta Obstet Gynecol Scand 2005;84(9 September):868–74.
[53] Scotti RJ, Bergman A, Bhatia NN, Ostergard DR. Urodynamic changes in urethrovesical function after radical hysterectomy. Obstet Gynecol 1986;68:111–20.
[54] Glahn BE. The neurogenic factor in vesical dysfunction following radical hysterectomy for carcinoma of the cervix. Scand J Urol Nephrol 1970;4(2):107–16.
[55] Seski JC, Diokno AC. Bladder dysfunction after radical abdominal hysterectomy. Am J Obstet Gynecol 1977;128:643–51.
[56] Kadar N, Saliba X, Nelson JH. The frequency, causes and prevention of severe urinary dysfunction after radical hysterectomy. Br J Obstet Gynecol 1983;90:858–63.
[57] Fishman IJ, Shabsigh R, Kaplan AL. Lower urinary tract dysfunction after radical hysterectomy for carcinoma of cervix. Urology 1986;28:462–8.

Biography

Polat Dursun is an Obstetrics and Gynecology specialist in the Department of Obstetrics and Gynecology at Baskent University School of Medicine in Ankara, Turkey. He received his M.D. in 2000 at the Cukurova University and then joined the Hacettepe University School of Medicine in Ankara to complete his training at the Department of Obstetrics and Gynecology. After completion of the his training in 2005, he visited the some pioneers of gynecologic oncologic surgery in Germany and France in order to learn the principles of the new surgical operations for the management of gynecologic cancers. During this 1-year period, he had learned the principles of laparoscopic oncologic operations, nerve-sparing hysterectomy, radical vaginal surgery, radical vaginal trachelectomy and vulvo-vaginal flap

techniques. During his visits, he was awarded by Turkish Scientific Research Council & Turkish-German Gynecology Association (TUBITAK-TAJD), European Society of Surgical Oncology (ESSO), European School of Oncology (ESO), and FIGO/IGCS Gynecologic Oncology Fellowship, and European Association of Cancer Research. His main focus is on surgical management of gynecologic malignancies. Now, he is working with Prof. Dr. Ali Ayhan the best-known gynecologist and oncologist of Turkey.