

Nerve sparing radical hysterectomy in early stage cervical cancer. Latest developments and review of the literature

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Summary

Background: Cervical cancer is the second most common malignancy of the female genital tract worldwide. Radical hysterectomy with pelvic lymphadenectomy exemplifies the treatment of choice for early stage disease, whereas even if it is performed by gynaecologist-oncologist, still has the drawback of significant postoperative morbidity, especially for urinary bladder function. Nerve-sparing radical hysterectomy (NSRH) is a technique in which the neural part of the cardinal ligament which encloses the inferior hypogastric plexus, as well as the bladder branch (distal part of the plexus), remains intact. By this way, the bladder's innervation is safe and its functional recovery is more rapid. There is sufficient data to support the feasibility of the technique via laparotomy and laparoscopy, as well as the effectiveness related to the postoperative bladder dysfunction compared to conventional radical hysterectomy. On the other hand, the evidence related to survival outcomes is weak and derives from non-randomized trials. However, the low rate of local relapses after NSRH in early stage disease (IA2-IB1) with tumor diameter less than two cm makes the procedure suitable for this group of patients. **Conclusion:** According to the current evidence NSRH seems to be a suitable technique for gynaecologist-oncologist familiar with the method in early stage cervical cancer. It is a technique which improves significantly postoperative bladder recovery and the patients' quality of life (QoL), without compromising the oncological standard.

Key words: Radical hysterectomy; Nerve-sparing; Laparoscopy.

Introduction

Cervical cancer is the most common cancer of the female genital tract in the developing world and the second most common gynaecological malignancy after endometrial cancer in developed countries. Epidemiologic report from 27 European countries showed 40,000 new cases of cervical cancer every year [1, 2]. The overall five-year survival of patients with early stage cervical cancer is almost 90% [3, 4]. The appropriate therapy of patients with cervical cancer depends on the stage of the disease. Surgical approach or chemo-irradiation are both acceptable treatments especially for the early stages [5, 6]. Fertility-sparing procedures, such as deep cold-knife cone or radical trachelectomy with additional evaluation of pelvic nodes (via abdomen or laparoscopy), are also developed in case of young patients with early stage disease, who desire to preserve their fertility, although radical hysterectomy with additional pelvic lymphadenectomy is the standard surgical approach [7, 8]. However, radical hysterectomy and pelvic lymphadenectomy are surgical procedures with significant perioperative morbidity.

Nerve-sparing radical hysterectomy (NSRH), although it already known from old reports, in the last two decades became an attractive technique because of the low rate of postoperative pelvic organs' dysfunction (especially of the urinary bladder) and of improved patients' quality of life (QoL), compared to conventional radical hysterectomy.

In the present review there is a presentation of the different types of radical hysterectomy, a historical overview, and description of the technique of NSRH. Bladder postoperative function and survival outcomes after NSRH of patients with cervical cancer are also analyzed according to the evidence of the current literature.

Radical hysterectomy

The extension of the radical hysterectomy was not always unequivocal and of the same acceptance. In the early 1970s, Piver *et al.* introduced a classification of the different types of hysterectomy [9]. According to this classification, five different types (Piver I-V) of hysterectomy were presented based on the radicality of the surgical procedure. Although, Piver's classification was used widely in gynaecological oncology,

recently another comprehensive classification with four types of radical hysterectomies (type A-D) originated by Querleu and Morrow [10]. This new classification, does not include Piver I hysterectomy (simple hysterectomy), while lymphadenectomy is considered obligatory in any type of radical hysterectomy [10].

According to this classification: Type A, radical hysterectomy is an extrafacial hysterectomy in which direct vision or palpation is used to identify the ureters. The uterosacral and vesico-uterine ligaments are not dissected far away from the uterine body, while the paracervix (parametrium) is dissected medial to the ureters. Vaginal resection is less than ten mm from the fornix. By this technique the vascular supply of the ureters remains intact. The procedure is suitable in group of patients with micro-invasive (IA1) cervical cancer according to International Federation of Gynecology and Obstetrics (FIGO) staging, who do not desire to preserve their fertility.

Type B, is a proximal radical hysterectomy in which the resection of paracervix extends up to the level of the lateral part of the ureteral tunnel. The vesico-uterine and uterosacral ligament (anterior and posterior parametrium, respectively) are partially transected, while dissection of ten mm of the vaginal wall is acceptable. The operation is separated in two subtypes (B1 & B2), depending on the extension of paracervical lymphadenectomy. Using as a landmark the obturator nerve, subtype B1 and B2 are defined according to the paracervix nodal dissection, medial or lateral to the obturator nerve, respectively. It is indispensable to mention that the caudal (deep) part of the paracervix, including the neural component of paracervix, is not dissected in type B radical hysterectomy, preventing the damage of the autonomous pelvic plexus.

Type C is an extended radical hysterectomy. The resection of the uterosacral and vesico-uterine ligaments extends up to the bladder and rectal wall, respectively. The paracervix tissue is dissected laterally to the junction with the internal iliac vessels. The caudal part of the paracervix remains intact in subtype C1 hysterectomy, known also as modified radical hysterectomy or NSRH. Furthermore, in C1 hysterectomy the identification of the hypogastric nerve in the lateral wall of the uterosacral ligament must be done before the dissection of the uterosacral ligament up to the level of the rectum. Vaginal dissection 20 mm from the tumor or from the cervix margin is acceptable. Subtype C2 radical hysterectomy (suitable for advance cervical cancer, IB2-IIA), includes complete dissection of the paracervix, without preservation of caudal (neural) part of paracervix.

Type D is an extra-radical hysterectomy, in which the dissection of the paracervix is extended to the pelvic side walls, including the hypogastric vessels (subtype D1) or further fascial and muscular structure of pelvic wall (subtype D2). Dissection of uterosacral and vesico-uterine ligaments is done as previously described (type C).

Autonomic pelvic plexus

The hypogastric nerves originate from superior hypogastric plexus and contain sympathetic nerves. Presacral

area of the pelvis is the origin point of hypogastric nerves, while then lay in the lateral part of the uterosacral ligaments at the level of pararectal space. Additionally, sacral nerves (S2-S4) from plexus sacralis constitute the splanchnic nerves, which compose a plexus together with the hypogastric nerves. Both of them constitute the inferior hypogastric plexus. Actually, the inferior hypogastric plexus is an anastomotic autonomic pelvic plexus which is composed from sympathetic (hypogastric) and parasympathetic (splanchnic) nerves in the caudal-lateral part of cardinal ligament. From the inferior hypogastric plexus originates fibres directed to the rectum, uterus, and bladder reliable for the ano-rectal, sexual, and bladder function [11, 12].

Identification of autonomic pelvic plexus and introduction of NSRH

The surgical concept of the identification and preservation of the pelvic autonomic nerves was first introduced by Japanese gynaecologists. In the 1960s, Kobayashi working at the University of Tokyo published an extensive description of a modified Okabayashi operation, in which the autonomic nerves were identified and pushed aside before dissection of the cardinal ligament. This publication was in Japanese and the technique spread only throughout Japan [13-15]. Sakamoto, who had been an apprentice of Kobayashi, published the first paper in English in the 1980s. He meticulously described a nerve sparing surgical radical hysterectomy, which he named the "Tokyo method" [16]. He stressed the significance of preservation of the autonomic nerves of the pelvis during radical pelvic intervention to avoid postoperative sexual, bladder, and rectal dysfunction. The objective was to preserve the inferior hypogastric plexus without compromising the radicality of hysterectomy as it was introduced from Wertheim [17], the pioneer of the radical hysterectomy, and was later modified by Meigs [8]. Thereafter, modifications of the technique were made by other gynaecologists in Japan, emphasizing the preservation of the distal part of the inferior hypogastric plexus (bladder branch), to avoid urinary dysfunctions [16, 18-20]. In addition, thorough exploration of the anatomy of the sympathetic and parasympathetic nerves of the pelvis was performed in the same period, in an effort to meliorate the anatomic recognition of the autonomic pelvic plexus, improving thereby the outcomes related with pelvic organs dysfunction [12, 21-23].

The last two decades, European oncologic centers gave their descriptions of the nerve-sparing technique of radical hysterectomy. Höckel *et al.* in 1998 was the first who described the nerve-sparing technique with liposuction of cardinal ligament, in order to present a clear identification of the inferior hypogastric plexus. High-resolution magnetic resonance imaging has also been used preoperatively, for the better investigation of the pelvic anatomy. Total mesometrial resection (TMMR) was the base of the nerve-sparing technique, according to Höckel's report [24]. The technique however, has been revised by the same author later in an effort to optimize the mesometrial dissection,

based on embryological topographic anatomy, in order to omit the adjuvant treatment of patients with cervical cancer with free surgical margins, even if with high-risk prognostic factors for recurrence disease [25].

Trimbos *et al.* gave almost a similar description of NSRH with that has been reported by Japanese's school, emphasising the feasibility of the nerve-sparing technique in European female population [26]. According to Trimbos's technique, surgical points of unambiguous interest, performing NSRH, were the early identification of hypogastric nerve at the level of uterosacral ligaments, as well as the preservation of the proximal and distal part of inferior hypogastric plexus in the cardinal ligaments.

Recently, Raspagliesi *et al.* reported a study of 23 patients with cervical cancer who were treated with the nerve-sparing technique Piver III radical hysterectomy. In this study, an anatomical description of the autonomic pelvic plexus was given and the introduction of NSRH technique, using a cavitron ultrasonic surgical aspirator (CUSA), for the removal of the parametrial tissue, was presented [11].

According to the former descriptions from Japanese and European centres, critical points performing NSRH, are the protection of the origin of the hypogastric nerves in the lateral parts of uterosacral ligaments and the caudal-lateral part of paracervix (parametrium), which encloses the inferior hypogastric plexus. Moreover, the protection of the distal part of inferior hypogastric plexus is also of principal significance, since it encloses the bladder branch (motoric innervation of the bladder).

A brief description of NSRH is as following: Utero-sacral ligament is constituted by two layers: the medial and lateral. The lateral part contains the hypogastric nerve. The two layers of the uterosacral ligament are separated carefully by blunt dissection. By this means, the medial layer can be dissected during NSRH, leaving the lateral part intact without scarification of the enclosed hypogastric nerve. Caudal-lateral part of paracervix (parametrium) includes the main part of the inferior hypogastric plexus. Because of this, the cranio-medial part of paracervix can be dissected although some of the fibres will be scarified. The distal part of the inferior hypogastric plexus lies deeper in the lateral wall of the vagina and in the caudal-dorsal part of the vesico-uterine ligament. Identification of the ureter and of the inferior hypogastric plexus contributes to preserve as much as possible from the plexus. Restricting the colpectomy in the upper part of the vagina (no more than two cm), the majority of the fibres from the inferior hypogastric plexus which run along to the lateral wall of the vagina and of the bladder remain un-cut, preserving the innervation of the urinary bladder.

NSRH via laparoscopy

Laparoscopic exposition of the inferior hypogastric plexus and NSRH were also performed successfully in European centers the last decade. The advantage of the magnification of the laparoscope permits the clear identification and the

protection of the neural part of cardinal ligament, which includes the inferior hypogastric plexus. Possover *et al.* reported for the first time in Germany a description of nerve-sparing procedure during laparoscopic-assisted radical vaginal hysterectomy (LARVH) type III [27]. According to this description, the middle rectal artery was used as a landmark to separate the neural from the vascular part of the cardinal ligaments. With this landmark, after the clear exposition of cardinal ligament performing pelvic and paracervix lymph-node dissection, and with the merit of laparoscopic magnification, the medial part of the cardinal ligament can be safely dissected including only the vascular part of the paracervix. Vaginal-assisted laparoscopic nerve-sparing radical hysterectomy (LNSRH) has been also reported by other authors [28]. Recently, a description of the total LNSRH was presented [29, 30]. Thirty-two patients with cervical cancer underwent LNSRH with pelvic lymphadenectomy [30]. According to the technique, the superior hypogastric plexus was identified in pre-sacral space at the level of promontory. Hypogastric nerve was identified bilaterally along to the lateral sides of uterosacral ligament. The former procedure has been performed after pelvic lymphadenectomy and the identification of the ureter at the level of common iliac artery. Thereafter, the inferior hypogastric nerve was prepared towards the uterine artery (cardinal ligament) by blunt removal of the hypogastric nerve from the lateral sheet of the uterosacral ligament, as well as from the caudal-lateral part of the cardinal ligament. After the identification of inferior hypogastric plexus, radical resection of the cardinal ligament and uterosacral ligament was performed, without scarification of the inferior hypogastric plexus.

Bladder dysfunction after NSRH

Dysfunction of the pelvic organs is very common after radical hysterectomy [31, 32]. Postoperative bladder dysfunction has an incidence as high as 20% after radical hysterectomy [5, 33, 34], with further aggravation in the patients' QoL [35, 36]. Nowadays, there is a large effort to reduce the postoperative morbidity (ano-rectal, sexual, and bladder dysfunction) after radical hysterectomy without compromising the oncologic standard. NSRH has been widely introduced in the last two decades, since it comprises the ability to satisfy the previous criteria.

In a retrospective analysis by Raspagliesi *et al.*, 110 patients with cervical cancer (FIGO Stage IA2-III) were managed with type II, type III and nerve-sparing type III radical hysterectomy [37]. The objective was to evaluate the early bladder dysfunction (within three months after the operation) and the perioperative outcomes between the three groups of the study. The authors demonstrated that type II and NSRH are comparable, concerning the bladder dysfunction, and the perioperative complications, compared to type III radical hysterectomy. None of the patients treated with type II radical hysterectomy were discharged with self-catheterism, 7% after NSRH, and 55% after radical type III hysterectomy [37].

Kato *et al.*, in a series of 32 patients with FIGO Stage IB-IIB, of locally advanced cervical cancer (tumor more than 20 mm), performed radical hysterectomy and pelvic lymphadenectomy [23]. In case of unilateral spread of the tumor beyond the cervix, unilateral preservation of the autonomic pelvic plexus of the uninvolved parametrial side was performed [unilateral nerve-sparing (UNS) radical hysterectomy]. On the other hand, for the patients with medial position of cervical tumor (confined only to the cervix), bilateral nerve-sparing (BNS) radical hysterectomy was performed. Although the authors reported that all patients voided spontaneously without the need of postoperative self-catheterization, the mean duration of postvoid residual volume of less than 50 ml was significantly longer in the UNS (11.5 days), compared to BNS group of patients (5.3 days). The authors concluded that postoperative bladder dysfunction is more common after UNS radical hysterectomy [23]. Recently, Skret-Magierlo *et al.* confirmed the previous results [38]. Fujii *et al.*, in a similar analysis of postoperative duration of bladder recovery after NSRH, showed an average of 14 days for postvoid residual urine volume (< 50 ml), 11 days to obtain a sensation of bladder fullness, and 12 days to obtain satisfaction of micturition [12]. Moreover, the same authors demonstrated that all the patients had full bladder recovery 21 days after the operation [12].

Reports related to the “late” postoperative outcomes, such as bladder dysfunction (more than six months of follow-up period) are not so common in the bibliography. In one of them, 22 patients with cervical cancer were treated with systematic NSRH [22]. After one year follow-up period, none of them presented with urinary incontinence, while only two complained for diminished bladder sensation. These findings were significantly lower compared to that of the group of patients who underwent conventional radical hysterectomy (Sakuragi *et al.*, 2005). Similar results concerning the late morbidity following NSRH was shown by Cibula *et al.* [39].

Studies designed to investigate postoperative bladder dysfunction of patients managed laparoscopically, have shown comparable results with those published by laparotomic trials. Performing LAVRH type III with additional preservation of autonomic pelvic plexus, Possover *et al.* showed that the suprapubic drainage was removed significantly earlier (11 days) in case of preservation of autonomic pelvic plexus compared to the group of patients without nerve-sparing approach (21 days) [27]. Kavallaris *et al.*, performing total laparoscopic nerve-sparing radical hysterectomy, showed that all patients (n = 32) spontaneously voided in the third postoperative day. In the same day, ultrasound evaluation (two different measurements) of all patients showed that none of them had a postvoid residual urine volume > 50 ml [30].

Oncological outcomes after NSRH

Data related to the survival outcomes of patients treated with or without NSRH is sparse. Moreover, there is a lack of randomized controls trials to guarantee the safety of the nerve-sparing procedure concerning the patients’ prognosis.

Sakuragi *et al.* evaluated the disease-free survival in 27 patients with cervical cancer (FIGO Stage IB1-IIB). In this study, 22 patients were treated with systematic NSRH and compared with five patients, who underwent conventional radical hysterectomy [22]. The results showed a cumulative disease-free survival rate in 24 months 95.5% for the nerve-sparing group and 100% for the conventional group of treatment. Only one patient (IIB) of NSRH group presented with recurrence disease (pelvis), 13 months postoperatively and was successfully treated with radiotherapy. The non-randomized nature of the study, the short follow-up period, and the small sample size of the control group (n = 5), has limited the results of this series [22].

Querleu *et al.*, managed 95 patients with modified radical hysterectomy using combined laparoscopic and vaginal approach. Forty-seven patients were managed with laparoscopic nerve-sparing procedure (average follow-up 26 months), while 48 patients were not (average follow-up 41 months) [28]. The authors concluded that because of high recurrence rate of patients with FIGO Stage IB1, with tumor diameter > two cm, nerve sparing technique is not acceptable for this group of patients. However, for patients with IA2-IB1 cervical cancer (tumor diameter < two cm), the outcomes related to the recurrence disease was excellent with or without nerve-sparing technique [28].

Recently, Van den Tillaart *et al.* reported the safety of NSRH in cervical cancer with Stage IA-IIA [40]. In this cohort, 122 patients underwent NSRH and were compared with 124 patients treated conventionally. Both groups were well-balanced concerning FIGO staging. Local recurrence, within 24 months after the operation, was more common in NSRH group (8.3%) compared to the conventional group (4.9%), however did not reach significant difference [OR = 1.7 (95% CI; 0.6-4.9), $p = 0.27$]. Moreover, the estimated five-year overall survival did not significantly differ between the two groups of the study ($p = 0.4$) [40].

In conclusion, NSRH is a feasible technique in patients with cervical cancer. It can be performed via laparotomy or laparoscopy by an expert surgeon specialized in gynecological oncology and comprises an effective method concerning the postoperative bladder recovery and the patients’ wellness. Concerning the survival outcomes, nerve-sparing technique appears to be a suitable technique for the early-stage cervical cancer especially IA2-IB1 with tumor less than two cm. Further randomized trials are required to confirm the former results.

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