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Pelvic nerve injury during radical hysterectomy for cervical cancer: key anatomical zone

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Summary

Objectives: To precise key-points of surgical neuroanatomy of the female pelvis to improve nerve-sparing radical hysterectomy (RH). *Material and Methods:* Review of the literature, computer-assisted anatomical dissection, and classic dissection of a female cadaver. *Results:* The superior hypogastric plexus (SHP) divides into two hypogastric nerves (HN). HN run postero-medially to the ureter and in the lateral part of the uterosacral ligament until the superior angle of the inferior hypogastric plexus (IHP). Pelvic splanchnic nerves (PSN) emerge from ventral rami of S2-S4 and join the posterior edge of the IHP. IHP passes lateral to the cervix and the vaginal fornix. *Conclusions:* Preservation of SHP necessitates an approach on the right side of the aorta and a blunt dissection of the promontory before lomboaortic lymphadenectomy. To preserve HN, only the medial part of the uterosacral ligament should be resected. The middle rectal artery, the deep uterine vein, and the ureter should be identified to preserve PSN and IHP during resection of paracervix. .

Key words: Cervical cancer; Nerve-sparing; Radical hysterectomy; Pelvic female anatomy; Inferior hypogastric plexus.

Introduction

Cervical cancer is the second most common cancer among women and is one of the main causes of cancer-related deaths in females, both in developed and developing countries, with approximately 500,000 new cases and 274,000 deaths each year [1–3].

According to the National Comprehensive Cancer Network guidelines for treating FIGO Stage IB1 to IIA2 cervical cancer, Radical hysterectomy (RH) is recommended mainly in Stage IB1 or IIA1 disease with tumor size < 4 cm, whereas radiotherapy is preferred in Stage IB2 to IIA2 disease with bulky tumor (> 4 cm). The classical surgical management of early-stage cervical carcinoma consists in a RH which 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 defined as the Piver-Rutledge type III or the Querleu-Morrow type C2 [4, 5].

Considering that five-year survival rates of 88–97% have been reported, RH is an effective treatment for early-stage cervical cancer and surgeons have directed the attention on quality of life outcomes for survivors [1, 6, 7].

In spite of its therapeutic efficacy, RH is often associated with several significant complications such as urinary, anorectal, and sexual dysfunctions which noticeably affect the quality of life of the patients. These complications are perhaps underestimated because only 5% of patients seek medical care for that reason [8]. The incidence of early postoperative bladder dysfunction has been reported between 70% and 85% of cases; however clinical studies suggested that the vesical function is restored within 9–12 months, if postoperative bladder care is adequate [9, 10]. Long-term clinically significant bladder dysfunction is the most common long-term complication of RH and occur in about 8% to 80% of patients [7, 9–14]. Colorectal motility dysfunction also occurs in up to 20 % of cases after RH but it seems to be generally less problematic, particularly in chronic cases [9, 15, 16].

These complications result from surgical trauma involving the sympathetic and parasympathetic branches of the autonomous innervation of the pelvic organs which are disrupted [9, 10, 17]. Resection of the anterior, lateral, and posterior parametrium, and the vaginal cuff can lead to parasympathetic nerve disruption which causes a hypocon-

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tractile or acontractile bladder with decreased sensation or sympathetic nerve disruption which results in a bladder with decreased compliance and high storage pressures [10]. The distribution of sympathetic nerve fibers to the urethra and trigone is of particular importance to urethral sphincter function and a sympathetic denervation is responsible for a decrease in the urethral pressure according to a study using urodynamics and ultrasonography [18, 19]. Autonomic nerve disruption also results in altered vascular function during sexual arousal (lubrication and swelling of the vagina), and possibly disordered orgasm [9, 20].

Particular attention should be paid to the preservation of nerve structures and connective tissue that support uterus and vagina. Since the first classification of RH surgical techniques by Piver *et al.*, an increasing number of technical modifications of RH has been suggested in order to reduce postoperative morbidity and the side effects of the radical treatment of cervical cancer [5, 11, 15, 21, 22]. Thus, nerve-sparing radical hysterectomy (NSRH) has been developed in the last 30 years to decrease postoperative bladder, colorectal, and sexual dysfunction without compromising oncologic outcomes. NSRH may provide an improvement of the quality of life on which the attention of gynecological oncology surgeons has to be focused because benefits from oncological surgery must not be evaluated only in terms of disease control, but also by the functional end outcomes that may affect the quality of life.

Uterus, vagina, urinary bladder, and rectum are innervated by pelvic autonomic nerves including the superior hypogastric plexus (SHP), hypogastric nerves (HN), pelvic splanchnic nerves (PSN), sacral splanchnic nerves (SSN), inferior hypogastric plexus (IHP), and efferent branches of the IHP. In most textbooks of anatomy, a few differences between male and female pelvic innervation have been discussed and a common model for both males and females is generally used for clinical anatomy [19]. Despite the fact that several studies have described the neuroanatomy female pelvis in cadavers [17, 23–25], these structures are rarely visualized in RH during surgery and basic surgical anatomic landmarks lack and are not used by oncologic surgeon. There is no theoretical background for the prevention of nerve injuries and no consensus on which part of cardinal ligament (CL) and/or uterosacral ligament (USL) should be resected.

In this review of the anatomical and surgical literature, the authors aimed to precise the neuroanatomy of the female pelvis in order to provide key-points of surgical anatomy to improve NSRH for cervical cancer.

Materials and Methods

An extensive review of the current literature was done in Medline database via PubMed on female pelvic nerve anatomy, and NSRH for cervical cancer up to 2016. The following key-words were used: "cervical cancer", "nerve-sparing", "radical hysterectomy", and "pelvic female anatomy". Only publications in English or in French were included. The authors analysed bibliographies of original reports and reviews and added pertinent references.

In order to illustrate the key anatomical zones at risk of pelvic nerve injury during RH, the authors used a computer-assisted anatomical dissection (CAAD) model of three human female fetuses of 13, 15, and 24 WG. The fetal specimens were obtained from miscarried fetuses or fetuses aborted legally and were authorized for scientific use by the parents and approved by the French Biomedicine Agency. The entire pelvis, from the sacrum to the pubic arch, was removed en bloc, fixed in formalin, then cut into 5-mm blocks and embedded in paraffin. A series of 5-µm-thick sections was prepared every 100−150 µm in order to obtain 122 to 575 sections per fetus. An histological examination with Haematoxylin-Eosin-Safran was performed and an immunohistochemical staining of neural structures was done by using anti PS-100 antibodies that could reveal nerve fibers. All sections were digitized by direct scanning at 9600 dpi resolution. Pelvic anatomical structures and nerve fibers were manually outlined and reconstructed in 3D using WinSurf software [26]. The authors also performed a dissection of an 88-year-old fresh female cadaver at the Paris Institute of Anatomy.

Results

Study selection

A total of 79 out of 168 studies were identified that corresponded to the aim of this review. Of these, 50 studies gave useful data and were eligible. They consisted in 12 studies on anatomy or histology exclusively and 38 on female pelvis surgical anatomy and techniques, of which 34 with clinical analysis of functional complications after NSRH.

Anatomy of the pelvic nerves

Superior hypogastric plexus (SHP)

The SHP constitutes the main source of the sympathetic fibers to the pelvis and contains nerves that originate from abdominal aortic plexus and lumbar paravertebral sympathetic trunks (T11–L2), and is the downward continuation of the inferior mesenteric plexus which lies below the origin of the inferior mesenteric artery [23, 25, 27]. The SHP also receives fibers from the first and second lumbar splanchnic nerves which are anastomosed directly with the lateral roots of the SHP or from the 3rd and 4th lumbar splanchnic nerves [8]. This condensation of thoracolumbar sympathetic nerves is often made of two nerve filaments which run along the aorta directly in contact with his anterior aspect, and join together at the level of the aortic bifurcation in front of the sacral promontory to form the SHP as a triangular-shaped net of nerve medial to both ureters [20, 23, 28] (Figure 1). Raspagliesi *et al*. consider that the SHP is constituted of a superior part at the level of the aorta bifurcation and an inferior part at the level of the sacral promontory that they refer to as the middle hypogastric plexus [15]. The SHP is a retroperitoneal and median structure which is covered by peritoneal sheet and by the ante-

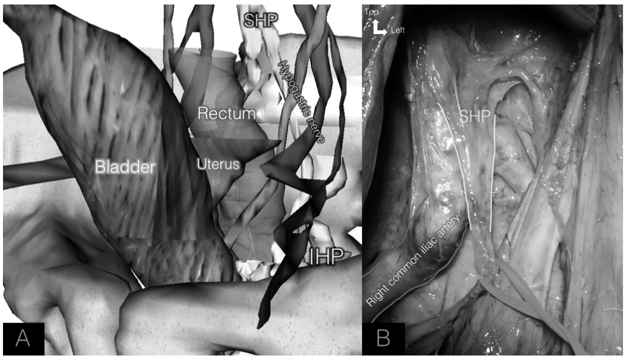

Figure 1. — Superior hypogastric plexus under the aortic bifurcation. A) 3D Reconstruction B) Dissection.

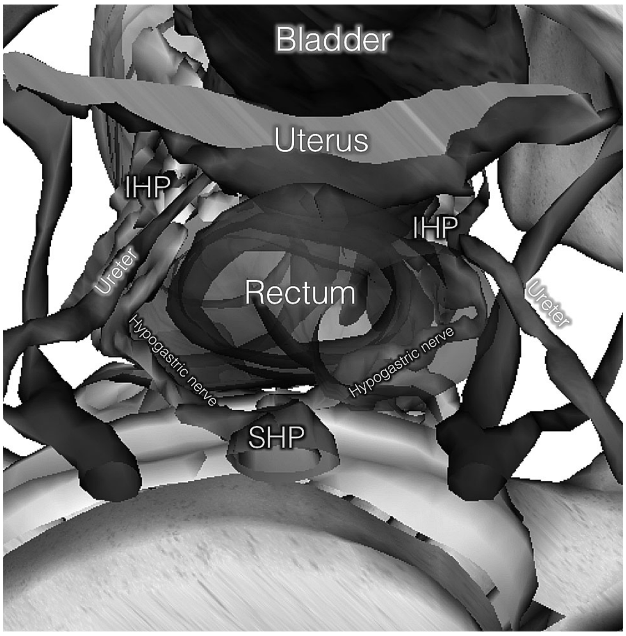

Figure 2. — Superior view of the 3D reconstruction – the superior hypogastric plexus divides into two hypogastric nerves.

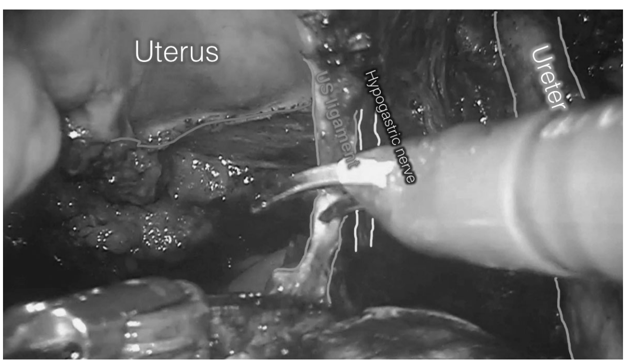

Figure 3. — Division of the uterosacral ligament (peroperative view).

rior layer of the visceral pelvic fascia.

Paraskevas *et al*. dissected 35 formalized cadavers and recorded the morphologic variations in the SHP. They distinguished four morphologic types: type I as a single thin rounded nerve (17.14%), type II as a wide plexiform formation (28.57%), type III as a broadened band-like nerve trunk consisting of nerve bundles connected with loose connective tissue, seen macroscopically as well as microscopically (22.85%), and type IV as two distinct nerves in close proximity with each other (31.44%). They found that the SHP extended beyond the sacral promontory up to a distance of 12.3 mm in 37.14% of cases and the main portion of fibers of the SHP are located mainly left to the midline of the abdomen [25]. Underneath the promontory, the SHP caudally and laterally divides into two filaments of variable width (4–7 mm), which are hypogastric nerves.

<u>Hypogastric nerves</u>

Hypogastric nerves (HN) originate from the division of the SHP and run laterally in front of the sacrum and lateral to the anterior sacral foramina. They take an oblique ventro-caudal direction with a concave course inside. The right and left inferior HN, descend for 8–10 cm along the lateral sides of mesorectum, into the bilayered visceral pelvic fascia, parallel to the common iliac vessels then inside of the internal iliac vessel. They follow the ureteral course in a dorsal and caudal direction [19, 28, 29]. HN run parallel to and approximately 1-3 cm medio-dorsally of the ureters into the small pelvis until nerve fibres fuse to the IHP where they are at 2 cm underneath the ureters [1, 15, 23] (Figure 2). Ercoli *et al.* showed that HN were composed by a single bundle of nerve fibers which ran about 10 (range 5–30) mm below the ureter in 22 of 30 (73%) hemipelves. In the other cases, HN were constituted of multiple thin nervous fibers always showing a subureteral course [17].

Yabuki *et al.* describe that the dorsal mesentery of the ureter contains the HN. The area between the ureter and the HN seems to contain some nerve fibers to the ureter and the trigone [19]. When the ureter is separated from its dorsal mesentery, the HN is located in the remaining lateral part of the sacrouterine ligament which probably corresponds to the continuation of the dorsal mesentery of the ureter [30].

The HN descend along the sigmoid just dorsally to the sigmoidal and superior rectal artery, then run along the rectal side of the pararectal space and lie in the upper part of the rectovaginal ligament [7, 11, 14]. The HN passes through connective tissue, which corresponds to the postero-lateral layer of the USL [1, 15, 31, 32] (Figure 3). Fujii *et al.* found that the highest density of nerve fibers were at a distance of 16.5 to 33 mm and at a depth of 3 to 15 mm of the point of fixation of USL to the cervix [33].

The HN join bilaterally the IHP from the superior dorsal side [1, 19] or the superior ventral side [34, 35]. Therefore, HN are themselves an anatomical landmark of NSRH be-

Figure 4. — Superior and right view during dissection. PSN originating from the sacral roots S2-24 on the postero-lateral face of the rectum.

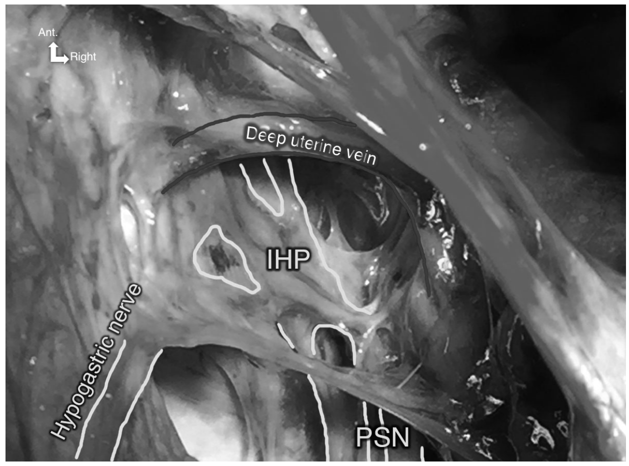

Figure 5. — Right view of IHP during dissection. IHP and PSN are located under the deep uterine vein.

cause they constitute the upper limit of the IHP and its vesical branches.

Pelvic splanchnic nerves (PSN)

PSN are parasympathetic nerves which generally originate from the ventral roots of sacral spinal nerves of S2-S4 [15, 36] near the sacral foramina, whereas the right vagus nerve innervates only the level of the proximal colon [11]. Numbers and origin of these fibers could be variable: never from S1, once from S2 (10%), once from S5 (20%), and from S3 and/or S4 in the remaining cases [17, 23]. The S3 and S4 roots are the main components of PSN, the S3 roots being the largest one [8] (Figure 4).

The first 3 cm of the parasympathetic fibres are covered by the pelvic parietal fascia. Three to five branches of PSN perforate the parietal endopelvic fascia sheet covering the ventral part of piriformis muscle at 1–2 cm lower and 3–4 cm from the pouch of Douglas [20] and penetrate into the pararectal space at the level of the ischiococcygeal muscle dorsally and caudally to the level of the vascular part of the cardinal ligament [11]. They are situated at the postero-lateral face of the rectum on the bottom of the pararectal space within the lateral rectal ligament, which contains the middle rectal artery when present. The lateral rectal ligament attaches to the rectum and continues with the parametrium. Concerning their relationship with middle rectal vessels, Ercoli et al. found that in 21 hemipelves (70%), the PSN cross the pararectal space along the lateral pelvic wall up to the posterior surface of the internal iliac vessels and then ran toward the IHP parallel to the middle rectal vessels. However, in nine (30%) hemipelves, the PSN were independent of the middle rectal vessels and rejoined the IHP 15–35 mm posterior to the internal iliac vessels [17]. Some authors used the middle rectal artery as a landmark separating the vascular from the neural part of the cardinal ligament [9, 11, 37, 38].

According to the ‘‘Tokyo’’ method of NSRH, the cardinal ligament is divided into two parts, the pars nervosa that contains the PSN and has to be preserved, and the pars vasculosa, which can be resected. The pars nervosa of the cardinal ligament crosses the pars vasculosa in an angle of 30°, constituting a small cavity, that Possover *et al*. called the “preneural space,” which contains lymph nodes and fat tissue [11, 15, 37]. According to Kato *et al.* the neural part of the cardinal ligament did not seem to contain PSN, but was formed from collagenous connective tissue similar to the transverse cervical ligament and PSN seems to be located in the medial wall of the pararectal space or over the floor of this space [37]. Raspagaliesi *et al.* indicate three different groups of fibers in the pararectal space: the first group runs along the lateral side of the pararectal space to the dorsomedial part of the CL, the second group crosses through the pararectal space over the pelvic floor, and the third group runs along the medial side of the pararectal space, parallel to the USL [15].

The deep uterine vein is another anatomosurgical landmark which is used to identify the plane dividing the parametrial ‘pars vasculosa’ (anterior and superior) from ‘pars nervosa’ (posterior and inferior) [20, 22, 37] (Figure 5). Crossing the pararectal space, PSN have a medial direction to reach the dorsal edge of IHP in the caudal part of the rectovaginal ligaments and were located lateral to the fibers of HN [8, 15, 29] (Figures 6 and 7).

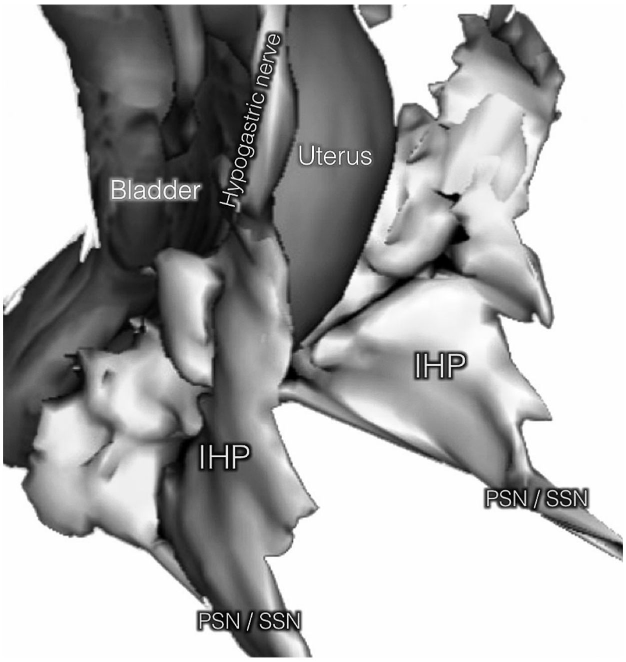

Figure 6. — Hypogastric, pelvic splanchnic, and sacral splanchnic nerves. Postero-lateral view of the 3D reconstruction.

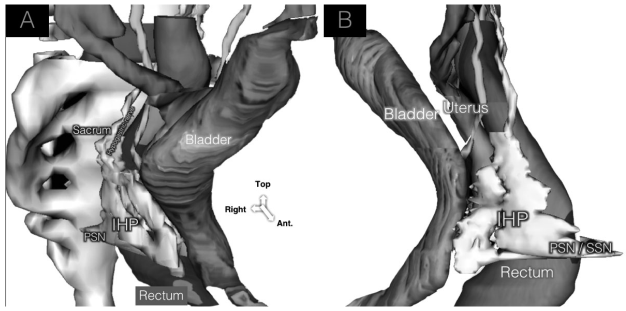

Figure 7. — Inferior hypogastric plexus and its afferences. A) Antero-lateral view of the 3D reconstruction. IHP has a triangular form. B) Left lateral view. PSN originates from the sacral roots S2-24 on the postero-lateral face of the rectum.

Sacral splanchnic nerves (SSN)

SSN are sympathetic nerves which originate from the four sacral ganglia of the pelvic sympathetic trunk. The main component originates from the sympathetic ganglia S2 and less frequently from the sympathetic ganglia S1 [38]. In 70% of cases there is a single afference and in 30% there are two branches [23]. They adopt the same course as PSN and reach the dorsal edge of the IHP. (Figures 6 and 7).

Inferior hypogastric plexus IHP)

IHP is a network of sympathetic fibers from HN and SSN and parasympathetic fibers from the PSN. The female IHP has a triangular form with a posterior base and an anterior inferior top and is located in a sagittal plane. It is irregularly fenestrated, especially in the postero-inferior part where it gives numerous efferent branches. It can be described as having two aspects (lateral and medial), three edges, and three angles [23] (Figure 7). The three edges include: a superior edge which runs parallel to the posterior edge of the internal iliac artery both inside and behind, at a distance of 10 mm, a posterior edge in relation with sacral roots S2– S4, and an inferior edge, extending dorsally from the fourth sacral root ventrally to the ureter's point of entry into the posterior layer of the broad ligament. The three angles include: a superior angle constituting the origin of the pelvic plexus and receiving the homolateral HN, an anterior inferior angle which is located exactly where the ureter penetrates the posterior layer of the broad ligament. This is the top of the triangle of the IHP at the base of the parametrium, and a postero-inferior angle in relation with the fourth sacral root.

The IHP extends from the anterolateral face of the rectum, passes lateral to the cervix and the vaginal fornix, and attempts to reach the lateral vaginal wall and the base of the bladder [9]. IHP is mainly found at the level of the USLs (57%) and less commonly at the level of the parametrium (30%), between the lateral vaginal wall and the bladder (11%), or at the rectal wall (2%) [38]. The IHP is about 15-20 mm long, 10-20 mm thick, and 30 mm wide [17, 35]. The width of the hypogastric plexus represents 30% of the area of the rectum, 93% of the area of the uterus, 71% of the area of the bladder, and 29% of the area of the intravertebral disc [26] (Figure 7).

IHP could be divided in three parts: a proximal part which lies along the infero-lateral portion of the USLs where the rectal branches merge, a middle part in the postero-lateral portion of the cardinal ligament where the utero-vaginal branches merge, and a distal part within the paracolpium and the vesico-vaginal ligament, where the bladder branches merge [15, 29]. The IHP is located between the ureter cranially and the pelvic floor caudally and is traversed by the middle rectal vessels [17]. Internal iliac vein and ureter can also be used as anatomical landmarks to identify the IHP. The superior angle of IHP is at 10 ± 5 mm from the internal iliac vein confluent and 36 mm from the commune iliac vein confluent [23]. The IHP is situated at 10–30 (range 5–30) mm below the ureter where it crosses under the uterine artery [2, 17]. Vaginal and bladder branches merge from IHP regarding the intersection of ureter with uterine artery.

Efferences of the IHP

Between the two layers of the broad ligament, the crossing point of the uterine artery and the ureter corresponds exactly to the rise of the vesical and vaginal efferences, at 15-20 mm of the fornix of the vagina, which run to the vesicovaginal septum and the rectovaginal septum [24] (Figure 8). No dissection should be performed under this

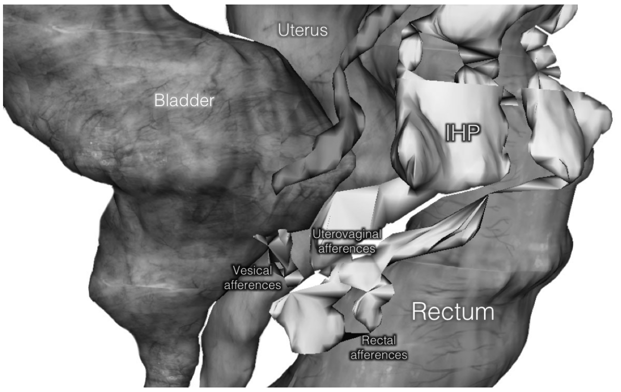

Figure 8. — Efferences of IHP: vesical uterovaginal and rectal branches (left lateral view of the 3D reconstruction.

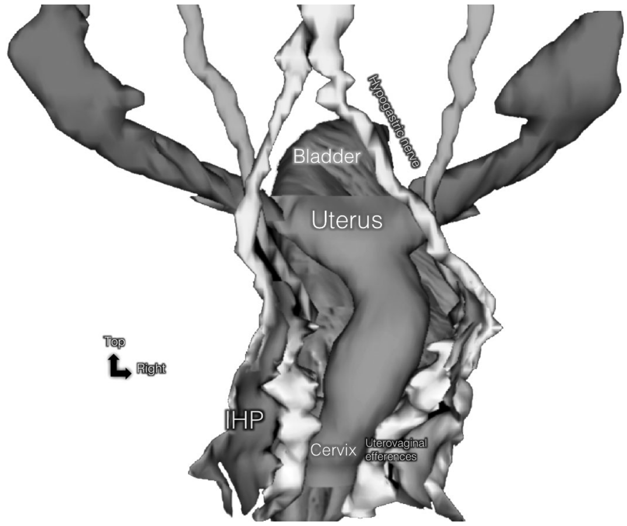

Figure 9. — Utero-vaginal efferences of IHP. Posterior view of the 3D reconstruction. Rectum is hidden. Uterine branches are distributed to isthmus and the supravaginal part of the cervix.

intersection considering the high risk of nerve injury. The efferent branches surround the dorsal, lateral, and ventral face of the uterus until the dorsal face of the bladder. The right and left side of IHP present fine efferent fibers between the bladder and the uterus which cross the median line and anastomose with the branches coming from the opposite side [26]. Efferences of the IHP are constituted by three main plexuses: anterior and lateral – a vesical plexus which gives the vesical nerve, anterior and medial – a vaginorectal plexus which gives the vaginal nerve and superior rectal nerve, and inferior – an inferior rectal plexus which gives the inferior rectal nerve.

Vesical efferences originate from the vesical plexus, which is located laterally to the crossing point of the ureter and the uterine artery. However, independent branches from the IHP could originate directly from the HN and lie along the ureter to the trigone [19]. The vesical plexus gives the vesical nerve which runs underneath and lateral the ureter to the posterior face of the bladder through the dorsal vesicouterine ligament as shown with intraoperative electrical stimulation while monitoring intravesical pressure [39] (Figure 7).

The vesico-uterine ligament is delimited by the deep uterine vein at the top, the ureter inside, the inferior vesical, and vaginal arteries outside and the levator ani at the bottom [17]. There is a functional distribution of this vesical nerve network between the ventral half which contains more motor nerve and the dorsal half which contains more sensory nerves [35].

On either side of the uretero-vesical junction, the vesical nerve divides into a medial vesical nerve to the trigone and a lateral vesical nerve to the neck, and the lateral face of the bladder along the dorsal vesico-uterine ligament. The lateral vesical nerve arises laterally and ventrally to the ureter and adopts sagittally an inferior and anterior course to the lateral edge of the bladder. Nerve fibers penetrate the muscularis and reach the neck of the bladder. The medial vesical nerve run to the lateral part of the trigone above the vesico-vaginal septum that separates it from the uterovaginal efferences [24].

Uterovaginal efferences originate from the vaginorectal plexus at the top of the IHP, medial to the intersection of the ureter with the uterine artery. The vaginal nerve lies under the uterine artery and run along it, through the paracervix to the uterus and the vagina. At the supero-lateral part of the vagina, the vaginal nerve divides into rami to the uterus, an anterior vaginal nerve, and a posterior vaginal nerve which run both through the paracolpium. Uterine branches follow the uterine artery until its end through parametrium and are distributed to isthmus and the supravaginal part of the cervix [17, 26] (Figures 8 and 9).

The anterior vaginal nerve lies over the anterior vaginal wall and its nervules never cross the vesico-vaginal septum. This nerve is thin and is responsible for the innervation of the anterior two-thirds of vagina. The posterior vaginal nerve is the largest, lies over the posterior vaginal wall, and gives further the superior rectal nerve [24].

Rectal innervation depends on the superior and the inferior rectal nerve. The posterior vaginal nerve sent nervule cross the rectovaginal septum and run further to the anterior surface of the rectum, making up the superior rectal nerve that innervates the superior part of the anterior surface of the rectum [24]. The inferior rectal plexus emerges from the inferior edge of the IHP. The inferior rectal nerve comes from the inferior rectal plexus and runs vertically through the mesorectum to the inferior and posterior part of the rectum [17] (Figures 8 and 10).

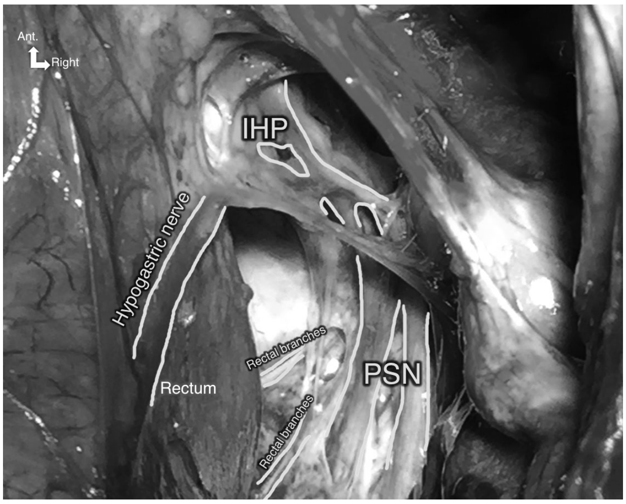

Figure 10. — Right view of the rectal efferent branches come from the inferior edge of IHP.

Discussion

This review provides useful information on the general morphology and precise topography of each pelvic nerve component that permits to determine the key-anatomical zone where nerve injuries occur during pelvic oncological surgery.

<u>The para-aortic lymphadenectomy</u>

The SHP could be injured during pre-sacral and periaortic lymph node dissection [3, 25, 28]. The SHP should be identified at the first step of the lomboaortic lymphadenectomy in the presacral space [40].

Considering that the main portion of fibers of the SHP are located mainly left to the midline of the abdomen, Paraskevas *et al.* suggested to incise the posterior peritoneal plane along the right side of the abdominal aorta and along the right common iliac artery in order to protect the SHP [25]. Between the rectum medially and the ureters laterally, the promontory should be accessed by a blunt dissection laterally until the lateral part of SHP is seen [28].

The SHP could be identified retrogradely by following the HN down along the mesorectum. Although the para-aortic lymphadenectomy is performed close to the aorta and the inferior cavous vein, SHP and HN are rarely injured at this step because they are fixed to the dorsal face of the posterior peritoneal sheet.

<u>Resection of the uterosacral ligaments (USL) and rectovaginal septum</u>

Considering that HN run along the USL and in the upper part of the rectovaginal ligament, injuries to HN can occur during the resection of USL at the posterior pelvic wall [3, 28] and of rectovaginal ligaments [7, 16, 22, 36].

USL constitutes a major pathway for HN to the uterus, vagina, and bladder and its wide resection, especially the medial and deep parts, result in pelvic organ dysfunctions [2, 31]. HN represent with SSN, sympathetics nerves. They inhibit the detrusor muscle of the bladder, stimulate the urethral sphincter, have acontractile effect on the uterus, vagina, rectum, and anal canal (internal anal sphincter) and inhibit parasympathetic activity. Urodynamical studies showed that their disruption involved in a decreased vesical compliance and high storage pressures with a decrease in maximum urethral closing pressure [9]. Damage of only the HN also implies a modification in the feeling of bladder filling, as a an impaired sensation for bladder fullness, whereas damage of the whole IHP leads to bladder dysfunction with urinary retention by loss of contraction of the smooth muscle of the bladder and loss of sensation of fullness of the bladder because of both sympathetic and parasympathetic injuries [11, 28]. Concerning sexual function, the HN also serves as the normal physiology of vaginal lubrication and orgasm and injuries of these nerve result in anorgasmia and disturbed fantasy-induced lubrification [9].

Regarding their course and their relationship, attention to HN has to be paid in three key zones: beneath the ureter, laterally to the USL, and laterally to the rectum in the pararectal space. As already shown, HN are located postero-medially to the ureter, at 1–3 cm inside the mesoureter. The mesoureter plays the role of guide of HN's identification. The tissue connecting the ureter and the posterior leaf of the broad ligament has to be dissected down until the top of pararectal space [41]. Together with the ureter, the mesoureter containing HN fibers is lateralized from the posterior layer of the broad ligament [42, 43]. The initial peritoneal cut, overlying the ureter, is enlarged to the pouch of Douglas, and pararectal space is developed [32, 44]. On the rectal side of the pararectal space, the HN run along the rectum and is identified as white nerve fibers within the connective tissue of the lateral rectal wall that is continued by the mesoureter [15, 22, 34, 36]. The Okabayashi's space corresponds to the area between the meso-ureter and the USL. The prerectal space is then developed. Between the prerectal space and the Okabayashi's space, USL and rectovaginal septum are individualised [42, 43]. At the level of the USL, sparing the HN consists in the division of the USL into a medial part that is fibrous and a smaller lateral part which contains the HN and the proximal part of IHP [1, 15, 41]. The medial part of USL is resected while the lateral part is saved (Figure 3).

<u>Resection of the dorsal paracervix</u>

PSN can be injured during the division of the deep uterine vein in the cardinal ligament for the resection of the dorsal paracervix and during the dissection of lymph nodes medial to the internal iliac vein and around the deep uterine vein. [1, 3, 28, 36]. PSN are also exposed to a high risk of injury during preparation of the pararectal space and resection of the lateral rectal ligaments considering that these nerves are close to these ligaments in 70% of cases [17].

The PSN correspond to parasympathetic fibers that stimulate the detrusor muscle of the bladder, relax the urethral sphincter, and stimulate intestinal peristalsis. Parasympathetic nerve disruption causes a hypocontractile or acontractile bladder with decreased sensation [9]. Landi *et al.* suggested that identification of PSN at their origin from the sacral roots permitted a safe laparoscopic dissection of rectal wings and lower mesorectal planes but this procedure lacks precision [20].

In order to preserve PSN, two main landmarks should be identified : deep uterine veins and middle rectal artery. The middle rectal artery is a well-known landmark for parasympathetic fibers however it is rarely observed in the cardinal ligament [11, 45]. PSN, merging from S3, run to the IHP behind the middle rectal artery and just above it, the cardinal ligament should be dissected as close as possible to the pelvic sidewall [34, 46]. The cardinal ligament should be freed of all lymphatic and fat tissue in order to distinguish laterally the pars vasculosa of the parametrium, including middle rectal artery, and antero-medially the pars nervosa of the parametrium including the PSN and the proximal part of the IHP. The pars vasculosa is resected after bipolar coagulation the most laterally to the pelvic sidewall including middle rectal artery and thereafter PSN are individualised and preserved [11].

Eastern surgeons prefer to use deep uterine veins as landmark to divide the pars vasculosa of parametrium and to spare branches of PSN [22, 36]. The preservation of the PSN necessitates the separation of the pars vasculosa that contains the deep uterine vein from the lower hard bundle that corresponds to pars nervosa and includes the splanchnic nerve during the division of the parametrial tissues. The cardinal ligament separates the paravesical anteriorly and the pararectal space posteriorly, and corresponds to the parametrial connective tissue that contains the uterine artery, the superficial uterine vein, and the deep uterine vein. The uterine artery and superficial uterine vein are respectively isolated, clamped, cut, and ligated near their origins. The subsequent removal of the connective, lymphatic, and fat tissues in the deeper portion of the parametrial connective tissue reveals the deep uterine vein. Below the uterine veins are the branches of the PSN, which run toward the IHP. The deep uterine vein of the uterine side runs parallel to the pelvic splanchnic nerve in the rectal lateral wall [22, 36, 42, 47, 48]. The PSN are in close proximity to the lower part of the vein at its insertion at the internal iliac vein [32] and anastomosing with the IHP or HN, appear as several thin branches emerging from the pelvic sidewall [45]. However, Kato *et al*. have shown, by dissection of fresh cadavers and using immunostaining studies, that the neural part of the cardinal ligament did not seem to contain the PSN, but was composed of a collagenous connective tissue similar to the transverse cervical ligament. Therefore, they suggested that during NSRH the PSN were located in the medial wall of the pararectal space or at the floor of this space and significant injuries to the PSN during lateral parametrial resection seemed unlikely [37].

<u>Dissection of lateral paracervix and selective transection of uterine branches of the IHP</u>

The proximal part of IHP could be injured during the resection of the uterosacral and rectovaginal ligaments [3, 28] and the middle part of the IHP during resection of the lateral part of the paracervix in beneath the uterine vein.

Fujii *et al.* described a pelvic nerve plane at the posterior-lateral wall of the uterus that corresponds to a connective tissue which contains the IHP, these afferent and efferent fibers [36]. The uterovaginal branches are identified just to the postero-lateral face of the vagina. These branches are selectively cut and the nerve plane is lateralized on the posterior side from the lateral wall of the lower cervix/the upper vagina and the rectum. This achieves the posterior part of the dissection of the paracervix [48].

Benedetti-Panici *et al.* showed a correlation between the height of the resected paracervix and the occurrence of vesical functional disorders and fixed the resection limit at 2.7 cm [12].

<u>Resection of vesicouterine ligaments</u>

The distal part of the IHP corresponds to vesical, uterine, vaginal, and rectal branches. Vesical branches run to the bladder through the posterior layer of vesicouterine ligaments. The posterior part of the vesicouterine ligament is located laterally and caudally to the distal ureter. Any dissection performed underneath the ureter in this part of the paracervix result in a highly risk of partial nerve injury [1]. After identifying and cutting the middle and inferior vesical veins, the anterior leaf of the vesicouterine ligament is separated from the posterior leaf of the vesicouterine ligament [47, 49]. The ureter is completely unroofed and the ureteral tunnel is developed medially and ventrally to the ureter in order to be freed from its attachment to the posterior leaf of the vesico-uterine ligament [20, 43]. If the cardinal ligament is resected laterally to the ureter, IHP and vesical branches are damaged, and the connection between the cardinal ligament and the deep layer of the vesicouterine ligament is cut [7]. The lateral nervous part, which is saved and lateralized more, and the medial vascular part of the posterior sheath of the vesicouterine ligament can be distinguished by finger palpation [9] and are dissected.

<u>The future: nerve visualization by near-infrared fluorescence</u>

Nerves are often hidden by surrounding tissue, especially adipose tissue, that make difficult their correct identification and nerve anatomy could vary grossly.

Some near-infrared fluorescence agents can target nerves

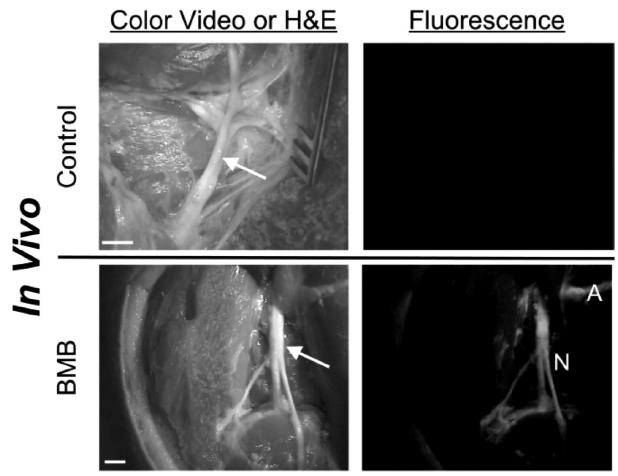

Figure 11. — Real-Time Image-Guided Nerve Surgery in Pig using BMB. The sciatic nerve (arrow) of a control pig in color video and fluorescence (top). The sciatic nerve (arrow) of a pig injected with 2.3 mg/kg BMB eight hours before imaging in color video and fluorescence (bottom), where adipose (A) and nerve (N) are highlighted by using the FLARE intraoperative imaging system. Scale bars = 1 cm. (52)

and could permit their intraoperative detection [50]. These agents are systematically administered and highlight nerve by contrast so that they can be used for nerve-sparing image-guided surgery.

Whitney *et al.* [51] used nerve binding peptides whose sequences were complementary to peripheral nerves protein (NTQTLAKAPEHT (NP41)) conjugated to fluorescein- 5(6)-carbonyl group (FAM) or to the deep red fluorophore Cy5 in mice. After systemic injection, all peripheral nerves were highlighted within two hours and useful contrast between adjacent tissue and nerve lasted until eight hours. Histological examination of human tissue sections showed that the fluorescence was similar to the binding pattern in murine nerves [51].

Gibbs-Strauss *et al.* [52] used 4,49-[(2-methoxy-1,4-phenylene)di-(1E)-2,1-ethenediyl] bis-benzenamine (BMB) and 4-[(1E)-2-[4-[(1E)-2-[4-aminophenyl] ethenyl] -3-methoxyphenyl]ethenyl]-benzonitrile (GE3082) in rats and pigs. With a systemic injection, these nerve-targeted fluorophores were localised in nerve tissue after crossing the blood-nerve barrier and blood-brain barrier, and highlighted myelinated nerves with wavelengths of 560 and 600 nm respectively. They realised simultaneously fluorescence imaging of nerves and blood vessels (with indocyanine green) during surgery using the fluorescence-assisted resection and exploration (FLARE) imaging system [52] (Figure 11). Although no in-human trials have been performed, this new technique would be benefic in nerve-sparing and image-guided surgery.

Conclusions

In most of cases, NSRH for cervical cancer can be performed. Anatomical landmarks as middle rectal artery, deep uterine vein, inferior vesical vein and ureter, and the respect of nervous part of uterine ligament and of parametrium provide the surgeon a safe preservation of pelvic innervation without compromising oncological outcomes.

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