

What kind of surgery for cervical carcinoma?

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SUMMARY: What kind of surgery for cervical carcinoma?

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The incidence and mortality of cervical cancer have changed over the past 50 years in developed countries, but this kind of tumor still remains a significant clinical problem because it is the second most common cause of morbidity and mortality from cancer among women.

After histological confirmation of invasive cervical cancer, the extent of disease was determined using clinical criteria to assign a stage. This assessment is important because, while for the other gynecologic cancers clinical information obtained by surgery and histopathological examination is implemented and concurs to define the staging of the disease, the cervical cancer tumor stage is given after the primary diagnosis.

In this review we discuss how the surgical approach to cervical cancer has been evolved, in order to modulate the radicality of the intervention itself and thus to preserve the pelvic innervation. This step has been achieved by deepening knowledge of functional pelvic anatomy and modulating the radicality of hysterectomy according to well defined surgical landmarks.

RIASSUNTO: Quale chirurgia per il carcinoma della cervice?

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L'incidenza e la mortalità del tumore della cervice sono cambiate negli ultimi 50 anni nei paesi sviluppati, ma rimangono un problema clinico rilevante in quanto il carcinoma della cervice è la seconda causa più comune di morbilità e mortalità per cancro tra le donne.

Dopo la conferma istologica del carcinoma invasivo della cervice, l'estensione della malattia viene determinata utilizzando criteri clinici per assegnare uno stadio. Questo momento è clinicamente importante perché, mentre per gli altri tumori ginecologici vengono implementate le informazioni cliniche ottenute con intervento chirurgico ed esame isto-patologico, nel carcinoma del collo dell'utero viene assegnato lo stadio del tumore dopo la diagnosi primaria.

In questa review si discute di come sia stato modificato l'approccio chirurgico al tumore della cervice, al fine di modulare la radicalità dell'intervento stesso e dunque di preservare l'innervazione pelvica. Questo passaggio è stato ottenuto approfondendo la conoscenza dell'anatomia funzionale della pelvi e modulando il tipo di radicalità secondo reperi chirurgici ben definiti.

KEY WORDS: Cervix - Tumor - Staging - Radical hysterectomy - Anatomical landmarks.
Cervice uterina - Tumore - Stadiazione - Isterectomia radicale - Reperi anatomici.

Introduction

The total incidence and the rate of uterine cervical carcinoma mortality have been modified in the last 50 years in the developed countries, since its incidence and mortality were reduced of 75% (1, 2). In any case, the problem still remains clinically relevant, because the car-

cinoma of the cervix is the second more common cause of morbidity and mortality for cancer among women in developing countries. Indeed, in 2002, 493.243 new cases have been recorded and 273.606 related deaths, that correspond to a mortality rate of 55% (3). On the contrary, the introduction in developed countries of screening strategies directed against this cancer was able to reduce both the incidence and mortality. However, despite the screening done in 27 countries of the European Community, about 340.000 new cases have been observed, more than 16.000 causing women death (1). Moreover, the clinical problem of cancer of the cervix is further underlined by the fact that about 54% of affected women are less than 50 years old (2).

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Evaluation of the illness extent: the importance of the staging

After the histological confirmation of invasive cervical carcinoma, the extent of the disease must be determined, using clinical criteria to assign a stage. While criteria for staging of the other gynaecological tumors principally are the information obtained with surgery and the istopathological exam, in the carcinoma of the cervix the tumor stage is assigned upon the primary diagnosis, not necessarily of the invasive type (3-5). For these reasons, the careful stadiation of the cervical cancer is fundamental for subsequent therapeutic approach [primary surgery or chemo-radiotherapy in the early stages (stage I-II); primary chemo-radiotherapy of the locally advanced disease; systemic chemotherapy in case of the disease presenting with distant metastases]. The International Federation of Gynecology and Obstetrics (FIGO), in collaboration with the World Health Organization (WHO) and the International Union Against Cancer (IUCC), established the most commonly used staging system for cervical cancer (Table 1) (3), that is largely based upon physical examination. Therefore, a good pelvic examination is critically important and, for these reasons, should be performed by an experienced gynaecologist (4, 5). Since cervical cancer spreads locally by extension to the corpus, parametria, and vagina, the cervix and entire vagina should be both inspected and palpated to identify the spread of disease. Thus, colposcopy, hysteroscopy, cystoscopy, and proctoscopy can be used to assess adjacent organs and structures and suspicious lesions should be confirmed by biopsy (6, 7).

Surgical therapy

The tumor spread by continuity is considered a random process by which the migration of tumor cells occurs through pathways consisting of least resistance “loci”, such as the peri-neural or vascular spaces, then according to a model of tumoral peri-focal not oriented spreading. The translation of this on a clinical plan led to the adoption of two particularly aggressive approaches as surgical treatments for local control of neoplastic disease: *i*) the radical organ resection; *ii*) the extensive tumor excision (8).

In the first case, the strategy of the *radical organ resection* is based on the macroscopic removal of the affected organ, together with the adjacent tissue to a greater or lesser extent depending on the extent of the tumor. The *extensive tumor excision*, instead, consist the resection of the tumor surrounded by a set of tissues not involved, which is still within the limits of the affected organ and are more likely, from a probabilistic point of view, to be involved by the non-oriented peri-tumor spread. In any

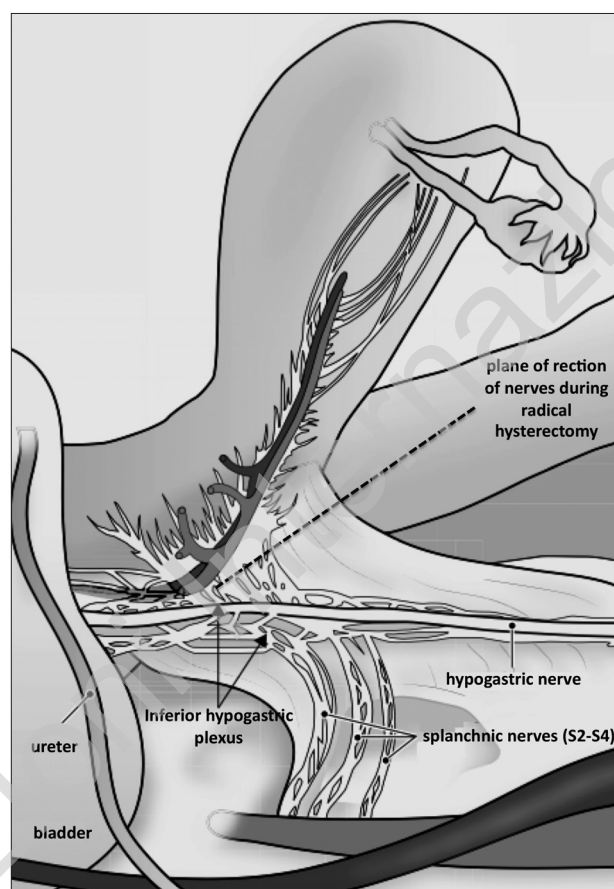


Fig. 1 - Knowledge of the main anatomical landmarks in order to identify and preserve the main nerve trunks and plexuses is essential in radical hysterectomy for the cervical cancer.

case, both types of intervention are combined with a more or less extensive lymph node dissection, depending on the histological type and stage of cancer, in order to obtain the best local tumor control (9). For carcinoma of the uterine cervix is assumed a local spread of the disease with an intra- and trans-cervical not oriented growth, so the standard surgical treatment even in early disease has long time been considered radical hysterectomy (10, 11). Despite the fact that surgery and radiotherapy for carcinoma of the cervix are two therapeutic approaches with similar results (for example, in stage IA1 with involvement of lympho-vascular spaces and in stages IA2, IB1, IB2 and IIA), radical surgery remains the first-line treatment especially in young women (12, 13). Almost certainly the surgery is preferred to radiotherapy for the damaging effects that radiation has on ovarian function and vaginal integrity, as well as the long-term sequelae. For early cancer of the cervix with negative lymph nodes 5-year survival of 88-97% has been reported with radical hysterectomy (11). These good results draw attention to the quality of life of survivors, as it is known that the standard radical hysterectomy with pelvic lymphadenectomy

may be accompanied by a significant early and late postoperative morbidity (14).

Surgical radicality and the preservation of pelvic innervation

An exhaustive knowledge of the anatomy of the pelvis is essential before embarking on a radical pelvic surgery (Fig. 1). The main morphological and topographical landmarks must be known, especially during the radical hysterectomy, for the perioperative preservation of the nerves, whose localization may occur in a wide range of anatomical variations. The current trend in the surgery of the cervical carcinoma is the identification of a treatment able to reduce early and late postoperative morbidity, largely due to the extensive lymph node dissection and resection of the paracervical tissue (parametrectomy).

The clinical experience, in addition to knowledge gained from anatomical studies on cadavers, showed that a high radical surgery is responsible for the damage of sympathetic and parasympathetic pelvic innervation (15-17). Indeed, the most serious injuries are related to the hypogastric nerves during resection of the dorsal part of paracervix (the utero-sacral ligaments) and the nerves located below the ureter originating from the inferior hypogastric plexus during the resection of the deep vesico-uterine ligaments (11). Thus, the extent of the surgical dissection should be tailored, taking into account many factors related both to the patient and the tumor extension.

For many years it was debated on the identification of women at low risk of paracervical involvement and pelvic lymph nodes. The development of imaging techniques, including MRI and ultrasonography (which can measure stromal invasion), along with biopsy may be useful in identifying those women who may benefit from a less radical surgery. Women who have a tumor <2 cm in greatest dimension or stromal invasion <10 mm have a significantly lower risk of the involvement of paracervix and pelvic lymph nodes. In contrast, tumors with stromal invasion greater than 2/3 or reaching the pericervical fascia or infiltrate the uterine body, have a high risk of involving paracervix and pelvic lymph nodes. In these cases radiotherapy instead of surgery must be considered as first choice (18-21).

The sentinel lymph node mapping allows the assessment of lymph nodes at greatest risk of tumoral cells invasion (22). In fact, according to the hypothesis of the sentinel lymph node, cancer cells that migrate from a primary tumor colonize one or a few lymph nodes before involving the lymph nodes of next groups. However, there are disputes as to the sensitivity of this test (21-23). Some studies have documented a relationship between nodal and parametrial involvement, as well as that isolated parametrial metastases, without involvement of pel-

TABLE 1 - STAGING CERVICAL CANCER ACCORDING TO INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS (FIGO).

Tumor (T)
<p>I - Cervical carcinoma confined to uterus (extension to corpus should be disregarded)</p> <p>IA - Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.</p> <p>IA1 - Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread</p> <p>IA2 - Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less</p> <p>IB - Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2</p> <p>IB1 - Clinically visible lesion 4.0 cm or less in greatest dimension</p> <p>IB2 - Clinically visible lesion more than 4.0 cm in greatest dimension</p>
<p>II - Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina</p> <p>IIA - Tumor without parametrial invasion</p> <p>IIA1 - Clinically visible lesion 4.0 cm or less in greatest dimension</p> <p>IIA2 - Clinically visible lesion more than 4.0 cm in greatest dimension</p> <p>IIB - Tumor with parametrial invasion</p>
<p>III - Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney</p> <p>IIIA - Tumor involves lower third of vagina, no extension to pelvic wall</p> <p>IIIB - Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney</p>
<p>IVA - Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis</p>
Regional lymph nodes (N)
<p>IIIB - Regional lymph node metastasis</p>
Distant metastases (M)
<p>IVB - Distant metastases (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)</p>

vic lymph nodes or sentinel nodes are absolutely rare. It must be realized that there is still a minimal risk of involvement of the parameters in the case of negative sentinel lymph nodes (24, 25). In any case, the sentinel lymph node mapping makes it possible to implement a less radical surgery of the parameters in sentinel node-negative women (modified radical hysterectomy, surgery with preservation of the nerves or simple removal of the cervix in order to preserve fertility) (24). However, if the patient shows a positive sentinel lymph node in the in-

tra-operative assessment, surgery would be completely replaced by primary chemo-radiation therapy to avoid the numerous side effects that may result from a multimodal treatment. Indeed, a literature review including 831 women who underwent lymphatic mapping and sentinel node detection as part of their cervical cancer therapy reported that a sentinel node was identified in 90% of cases with an overall sensitivity for metastatic disease of 92% (25). Another option to consider in these patients is the addition of extensive surgery (e.g. radical hysterectomy and lymphadenectomy) (26).

The neo-adjuvant chemotherapy is widely used in Europe for patients with stage \geq IB2 that hasn't a good prognosis. There are many reasons to support the use of neoadjuvant chemotherapy: *i*) to decrease the number of positive lymph nodes; *ii*) to avoid adjuvant radiotherapy; *iii*) to reduce the tumor volume before surgery or radiotherapy (25). Neoadjuvant chemotherapy approach, however, does not change the radicality of the surgical strategy, because it is not able either to modify the pre-operative clinical examination and, therefore, the tumoral staging, or may give us information on the histopathological extension of the lesion (microscopic infiltration of the disease). Thus, the use of neoadjuvant chemotherapy in the treatment of cervical cancer remains controversial, partly because it has not demonstrated to increase survival and, therefore cannot be recommended in the standard treatment (25).

The modulation of radicality in the total hysterectomy

Radical hysterectomy includes the removal of the uterus "en bloc" with parameters (round, broad, cardinal, and uterosacral ligaments) and the top one-third to half of the vagina, with the ovaries left intact (27). The radical hysterectomy was continually modified by many surgical groups in Europe, Asia and USA. Since 1970 the classification of Piver-Rutledge-Smith has been widely used (28), so that radical hysterectomy has been divided into five different classes of resection (Table 2). In 2007, new classification criteria were presented at the International Symposium on Radical Hysterectomy dedicated to Hidekazu Okabayashi (2007, Kyoto) to meet the new trends in surgery. The "Kyoto consensus" applies strict anatomical definition but at the same time considers new developments such as the saving of autonomic nerves, preservation of fertility, the lateral extension and new laparoscopic and robotic techniques (27). Despite this, all proposals for a new classification strictly join to traditional concepts and maintain utero-centric vision of the retroperitoneal anatomy of the female pelvis. This utero-centric view is misleading since it does not distinguish between tissues that are part of the utero-vaginal tract from tho-

se that are simply adhering to it, such as paracervical lymph nodes (that belong to the parietal pelvic compartment) and the mesovesical space with the vesical vessels and the vesical branches of the inferior hypogastric plexus (27).

With the aim to preserve fertility and, above all, sympathetic and parasympathetic innervation, a new classification of radical hysterectomy was published in 2008 by Querleu and Morrow (27), who have described four different types of surgery (Table 3). In the original classification of Piver-Rutledge-Smith in 1974 there was no mention of any anatomical landmark of international classification regarding the modified radical hysterectomy technique, especially in the procedures of type II, III and IV (Table 2), since these were suggested by Morrow Querleu and only in 2008 (27) (Table 3). Indeed, previously modified radical hysterectomy was a series of variations that differed among themselves in the extension of paracervical resection and lymphadenectomy (28). Instead, in the new approach the main difference lies in the reduction of deep vesico-uterine ligaments resection below the ureter and in the reduction of the lateral extension of paracervix dissection. Other differences concern the site of ligation of uterine artery and the pelvic lymphadenectomy (27). Only exceptionally a presacral dissection of the lymph nodes has been described, although subsequent studies showed the presence of positive sentinel lymph nodes in this region in the 3-5% of cases.

Nevertheless, the main aim of revisiting procedures related to radical hysterectomy is to minimize autonomic pelvic innervation injuries thus preserving nerves but without reducing radicality of surgery during "Type C radical hysterectomy" (type III in the previous terminology). A second alternative is to use surgery with less radical resections of paracervical tissue as in the case of "Type B radical hysterectomy" (type II in the previous terminology) (11, 27). Despite many initial reservations, today this classification is widely accepted. In addition, all types of radical hysterectomy are combined with lymph node dissection (Level 1: internal and external iliac lymph nodes; Level 2: level 1 plus common iliac and presacral lymph nodes; Level 3: Level 2 plus aortic inframesenteric lymph nodes; Level 4: level 3 plus aortic infrarenal lymph nodes level 3) (11).

Type A radical hysterectomy

The type A radical hysterectomy is an extra-fascial hysterectomy, because the paracervix is sectioned medially to the ureter and laterally to the paracervix. This is the standard procedure in the case of a tumor in stage IA1 without blood-borne spread (invasion <3 mm with a maximum horizontal diameter of 7 mm). An ultra-conservative approach has been described previously for the early carcinoma of the cervix, with pelvic and possibly paracervical lymphadenectomy. The extra-fascial approach is justified by the observation that *i*) in stages IA2 and

TABLE 2 - TYPES OF HYSTERECTOMY, ACCORDING TO PIVER-RUTLEDGE-SMITH, IN THE CASE OF CERVICAL CANCER (28).

Subtotal/supracervical
The uterus is removed. The superior portion of the cervix is amputated, the remainder of the cervix is conserved. Intrafascial hysterectomy is a subtype of subtotal hysterectomy in which the uterosacral ligaments are conserved
Class I
Extrafascial hysterectomy. The fascia of the cervix and lower uterine segment, which is rich in lymphatics, is removed with the uterus.
Class II
Modified radical hysterectomy. The uterine artery is ligated where it crosses over the ureter and the uterosacral and cardinal ligaments are divided midway towards their attachment to the sacrum and pelvic sidewall, respectively. The upper one-third of the vagina is resected.
Class III
Radical hysterectomy. The uterine artery is ligated at its origin from the superior vesical or internal iliac artery. Uterosacral and cardinal ligaments are resected at their attachments to the sacrum and pelvic sidewall. The upper one-half of the vagina is resected.
Class IV
Radical hysterectomy. The ureter is completely dissected from the vesicouterine ligament, the superior vesical artery is sacrificed, and three-fourths of the vagina is resected.
Class V
Radical hysterectomy. There is additional resection of a portion of the bladder or distal ureter with ureteral reimplantation into the bladder.

IB1 with tumor size <2 cm, tumor invasion <10 mm and negative pelvic lymph nodes the parametrial involvement is lower than 1%, and; ii) the risk of local recurrence remains low, as is the incidence of postoperative complications (especially lymphocele and lymphedema) (27).

Type B radical hysterectomy

The new classification of Querleu and Morrow (27) describes Type B radical hysterectomy as a partial resection of the uterosacral and vesico-uterine ligaments when the ureter is displaced laterally, allowing the section of the paracervical tissue at the level of the ureteral tunnel. The posterior paracervical neural component located caudally to the deep uterine vein is not removed, but a portion of the vagina is removed at least 10 mm from the cervix or cancer. Thus, Type B hysterectomy includes the subgroups B1 (corresponding to those described above) and B2 with the addition of lateral paracervical lymph nodes removal. The border between the parietal and paracervical (iliac and sopraobturator) lymph nodes is arbitrarily defined by the obturator nerve: paracervical lymph nodes are located medially and caudally to the obturator nerve. This definition moves towards the concept of radical hysterectomy type C1 (see below). This procedure corresponds to the simple removal of the cervix by the vaginal route (operation of Dargent) (29), which today is used in combination with laparo-

scopic lymphadenectomy (with or without paracervical lymphadenectomy) as a technique to preserve fertility. In this procedure, the reduction of the radicality involves also the preservation of the uterine artery (30).

Although the extent of radicalism in the paracervix varies among surgical groups, modified radical hysterectomy shows a decrease of early and late morbidity, although this technique can still lead to injuries of nerve fibers, especially in presacral region (31-33).

Type C1 radical hysterectomy

The steps leading type C1 radical hysterectomy are represented by the section of the uterosacral ligaments to the rectum, of the vesico-uterine ligament at the level of the bladder, followed by resection of about 15-20 mm of the vagina from cancer or cervix and resection of the corresponding paracolpium (the tissues alongside the vagina), only after the complete mobilization of the ureter (Table 3). This approach is justified by the need to preserve and respect the sympathetic and parasympathetic nerves of the pelvis and, it was felt as urgent in the modulation of radicality of hysterectomy for carcinoma of the cervix. The history of radical hysterectomy with preservation of nerves is closely related to Japanese Studies: Okabayashi (34), Fujii (35), Kobayashi (36), Yabuki (37), Sakuragi (38) are among the most important surgeons to have contributed in different ways

TABLE 3 - TYPES OF HYSTERECTOMY, ACCORDING TO QUERLEU E MORROW (27), DEPENDING ON THE NEW IDENTIFICATION OF SURGICAL LANDMARKS.

	Resection extent	Ureter	Notes
Class A: minimal resection of the paracervix	Paracervix is transected medial to ureter, but lateral to the cervix; uterosacral and vesicouterine ligaments are not transected at a distance from the uterus; vaginal resection—generally at a minimum, without removal of the paracolpos	Palpation or visualization without freeing from bed	
Class B: transection of paracervix at the level of the ureter	Paracervix is transected at the level of the ureteral tunnel; partial resection of uterosacral and vesicouterine ligaments; no resection of caudal (deep) neural component of the paracervix (caudal to the deep uterine vein); vaginal resection—at least 10 mm of the vagina from the cervix or tumor	Unroofing and rolled laterally	The border between paracervical and iliac (parietal) lymph-nodes is the obturator nerve (the combination of paracervical and parietal lymph-node dissections is a comprehensive pelvic-node dissection, and can be equivalent to that of a type C1 resection)
B1	As described above		
B2	As described above with removal of the lateral lymph nodes		
Class C: transection of paracervix at junction with internal iliac vascular system	Transection of the uterosacral ligaments at the rectum; transection of the vesicouterine ligaments at the bladder; resection 15–20 mm of the vagina from the tumor or cervix and corresponding paracolpos	Completely mobilised	
C1	With autonomic nerve sparing/preservation		
C2	Without autonomic nerve sparing/preservation		
Class D: laterally extended resection		Completely mobilised	
D1	Resection of the paracervix at the pelvic side, with vessels arising from internal iliac system, exposing the roots of the sciatic nerve		
D2	Resection of the paracervix at the pelvic side, with hypogastric vessels plus adjacent fascial or muscular structures (laterally extended endopelvic resection)		

and at different times to emphasize the importance of radical hysterectomy with preservation of the nerves for the improvement of postoperative bladder function, saving the splanchnic nerves [via separation of the vascular (containing the deep uterine vein) from the neural (containing splanchnic nerve) bundles during the division of the parametrial tissue] and the bladder branch of the inferior hypogastric nerves and the splanchnic nerve. Hockel (39), Trimbo (40), Possover (41) and Raspagliesi (42) have finally agreed a new contribution to

the development and diffusion of radical hysterectomy with preservation of nerves, studying and improving the different steps of the surgical technique.

Conclusions

The ideal surgical treatment for carcinoma of the cervix should reduce the early and late postoperative morbidity without compromising the radicality of surgery. The choice of the extent of radical surgery should be done

after taking into account several risk factors (eg, histopathological stromal infiltration, prognostic factors assessed by MRI). The intraoperative examination of sentinel lymph node is a new method that provides valuable information about the status of pelvic lymph nodes. Indeed, sentinel lymph node biopsy appears to perform better than imaging studies. This was illustrated in a meta-analysis of 72 studies including 5042 women with cervical cancer that evaluated several approaches, and found that the sensitivity and specificity for the detection of lymph node metastases for various approaches were: sentinel node biopsy (sensitivity 91% and specificity 100%); PET (75% and 98%); MRI (56% and 93%); and CT (58% and 92%) (43).

The concept of preservation of autonomic nerves during radical hysterectomy has become a standard concept

in many cancer Centers. But it must be stressed that, although the radical hysterectomy with preservation of nerve fibers shows an improvement in quality of life compared with standard resection, there are no prospective randomized trials that compared the two procedures. It is believed that this type of study is not very feasible. The modified Type B radical hysterectomy with or without removal of lateral paracervical lymph nodes is an alternative used in the treatment of early-stage cancers. Prospective randomized studies should be performed to compare the radical hysterectomy with preservation of nerves (Type C1) to Type B2 modified radical hysterectomy in the treatment of stage IB1 of cancer. The conservative surgery of type A is an experimental approach used in patients with stage IA1 and IB1, but with positive prognostic factors and negative sentinel node.

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