Review

Pelvic and aortic lymphadenectomy in cervical cancer: The standardization of surgical procedure and its clinical impact

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ABSTRACT

Cervical cancer ranks as the second most frequent cancer in women in the world, and nodal metastasis seems to be the first step of tumor spread in most cases. Since lymph node involvement is a major prognostic factor in cervical carcinoma, lymphatic spread of cervical cancer has been one of the most studied surgical topics in gynecologic oncology. Traditionally, lymph nodes stations have been accurately analyzed, improving surgical techniques of nodal dissection, which have been more and more intensive during years with the aim of improving survival. Oppositely, on the basis of recent acquisitions in cancer immunology and new anti-cancer immunotherapies and vaccines, the importance of lymph nodes has been recently reconsidered. Unfortunately, lymph node status is still difficult to be assessed pre-operatively with a high level of accuracy, and intra-operatively by sentinel node techniques, which remain inadequate for many aspects according to several gynecologic oncologists. The absence of definitive evidence of survival advantage given by extensive lymphadenectomy in all cervical cancer cases indicates that nodal dissection should be performed on the objective risk of node metastasis in each case. To date, the mainstay of detecting lymph node metastasis is still the histologic evaluation, therefore a proper resection of mostly involved lymph nodes remains a crucial surgical step when treating cervical cancer.

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Introduction

Cervical cancer ranks as the second most frequent cancer in women in the world, and it is mostly represented among women between 15 and 44 years of age [1]. Current estimates indicate that every year about 493,243 women are diagnosed with cervical cancer in the world and 273,505 die from the disease [12]. The main cause of disease is HPV infection and about 70% of invasive cervical cancer in the world is attributed to HPVs type 16 or 18 [1]. The introduction of largely applied screening programs has noticeably reduced the incidence of this cancer in developed countries, but unfortunately most patients worldwide are still diagnosed at advanced stage of disease. Recently introduced vaccines seem to give promising results even if longer follow up are warranted [1]. Spread of disease involves mainly parametria, upper vagina and uterus, and pelvic lymph nodes [2,3].

The incidence of lymph node metastases increases with clinical FIGO stage. According to literature, pelvic node metastases in stage Ib, stage Ila, and stage IIb cervical cancer are approximately 12%–22%, 10%–27%, and 34%–43%, respectively [4]. Nodal metastasis is strictly related to clinical stage, deep cervical stromal invasion, lymph-vascular space invasion, corpus and parametrial invasion [5]; para-aortic node metastasis is mostly secondary to pelvic nodes involvement, in fact the risk of aortic spread rises up to 25% if positive pelvic nodes are identified [3,6]. On the opposite, skip...
metastases to aortic nodes are also reported but very rare, accounting for less than 1% of cases [6,7].

Removal of para-aortic, superficial intercavoaortic, and para-caval lymph nodes represents an adequate procedure to evaluate aortic nodes status, particularly useful in advanced disease in order to plan the extension of radiation field [6,8]. Data from patients with locally advanced cervical cancer demonstrate that the pattern of lymphatic spread is similar to that observed in patients with early invasive disease, even if the high frequency of deep common iliac node metastasis suggests their systematic removal in order to avoid missing residual disease [5].

Lymph node involvement represents one of the most important prognostic factors in cervical cancer: while the reported survival rates for women with stage I cervical cancer are between 80% and 98%, the 5-year survival of these patients decreases dramatically as low as 50% if positive lymph nodes are encountered [9,10]. Several retrospective analyses have clearly shown the significant benefits associated to removing nodal metastases, with the extent of lymph node dissection positively correlated with an improved survival in such cases [2–4].

Traditionally, anatomical sites of lymph nodes have been studied and analyzed accurately, improving surgical techniques of nodal dissection, which have been more and more intensive during years by the aim of improving survival. Oppositely, on the basis of recent acquisitions in cancer immunology and new anti-cancer immunotherapies and vaccines, the importance of lymph nodes has been recently reconsidered [9,10].

Node metastasis represents the first step of tumor spread in most human cancers and in fact several studies have revealed that tumors can actively induce the formation of lymphatic vessels [11–17].

In consideration of lymph nodes clinical potential in anti-cancer immunity, new trends in oncology suggest now that negative nodes should be preserved. Unfortunately, their status is still difficult to be assessed pre-operatively with a high level of accuracy, and intraoperatively by sentinel node techniques, which remain inadequate for many aspects.

On the opposite, the status of pelvic primary nodal stations, properly defined as “sentinel lymph nodes stations”, can indicate a way for tailoring parametrectomy [18].

Modulation of radicality of hysterectomy is a relatively recent concept emerged by the need of reducing complications while preserving optimal survival outcomes [2,18]. In fact, an important concern is the clinical significance of parametrial involvement, that should be reconsidered on the basis of several reports indicating parametria as the primary site of lymphatic spread [2,3,18]. Accurate analyses of parametral giant sections have demonstrated a constant association between pelvic lymph nodes and parametrial disease, suggesting that pelvic lymph nodes status may represent a reliable predictor of parametrial status [2,18]. This cannot be ignored since most complications in surgical treatment of cervical cancer are strictly related to parametrectomy and lymphadenectomy, including lympho-vascular, neurologic and urinary tract injuries [18–20]. Extensive lymphadenectomy is an independent risk factor for the occurrence of intra- and post-operative complications and, even if the higher the number of lymph nodes removed the higher the risk of having postoperative complications, morbidity rates associated with lymph node resection varies widely in different series reported in literature.

In particular, the occurrence of postoperative pelvic lymphoedema, which can cause leg oedema, deep venous thrombosis, pulmonary embolism and abdominal pain, represents a relatively frequent and important complication following systematic pelvic lymphadenectomy, with a reported incidence varying from a high of 25% to a low of 1.5% in different series [19,20].

Modified (type II) or classical radical (type III) hysterectomy may be performed also in patients with locally advanced disease (FIGO stage IB2–IIIB) who show a clinical response to neoadjuvant chemotherapy [21], however for these patients the standard treatment remains concomitant chemo-radiation.

In Table 1 is briefly reported a summary of the evolution of surgical concepts and trends, during decades and by different authors, regarding the first increasing and then modulated radicality for approaching cervical cancer, taking into particular consideration both parametrical resection and lymph nodes dissection [3,16–18,22–31].

Concerning a preoperative setting, various serum cancer markers have been tested, and different imaging modalities have been used and compared each other during years by several authors in order to detect nodal metastases with an acceptable level of accuracy, but performed studies did not give unequivocal results [32–47], and the diagnostic sensitivity and specificity of current imaging modalities has been less than optimal in the evaluation of lymph node metastases from cervical cancer.

Unfortunately, also sentinel node procedure, in any technique in which it is performed, gave different results in terms of feasibility and accuracy in several series [30,31]. In cervical cancer the explanation of the frequently low reported detection rate could be that the real direct first site of lymphatic spread from the cervix is not the pelvic but the parametrical nodes, mostly randomly involved, moreover often not properly identified with gamma scan by the high concentration of technetium in the cervix itself [31]. Many authors reported a high rate of bilateral detection, and, in a portion of patients, more than one node per side may be detected [30,31]. Therefore many questions and discords still need to be answered and clarified before recommending routine use of sentinel node approach in cervical cancer.

Concerning the surgical technique employed to perform lymph node dissection, laparotomy transperitoneal or extraperitoneal and, more recently, the laparoscopic approach has also been introduced [48–50]. The laparotomic extraperitoneal and the laparoscopic approaches have demonstrated to be valid and minimally invasive surgical options [49,50]. Several authors have studied laparoscopic lymphadenectomy in gynecologic malignancies in the effort to evaluate surgical data and clinical outcomes of laparoscopy in.

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<th>Table 1</th>
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<td><strong>Lymph node</strong></td>
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comparison to laparotomic approaches [50–53]. Laparoscopic lymphadenectomy represents a feasible procedure with an acceptable morbidity, while it requires a longer learning curve and operative time when compared to laparotomic approaches [50]. Moreover, the number of recovered lymph nodes at laparoscopy is still often considered inadequate for a systematic lymphadenectomy [50], even if number of resected nodes may increase with surgeon experience [51]. For these reasons, laparotomy is still considered the standard approach in clinical practice for systematic pelvic lymphadenectomy in cervical cancer patients, whereas laparoscopic route is gaining more and more popularity among leading institutions. Several authors have advocated the use of extraperitoneal approach for lymphadenectomy and different techniques have been proposed [49,51]. Reported advantages of extraperitoneal approach include easy access on lateral pelvis and obturator fossa space, and short operative time [52]. In fact it has been reported that the median time required to perform lymphadenectomy using the laparoscopic procedures is significantly higher than for the extraperitoneal route (68 vs 48 min, \( P = 0.05 \)) [51]. In a recent randomized study comparing different surgical approaches to perform pelvic lymphadenectomy, operative time resulted shorter in extraperitoneal lymphadenectomy (EPL) group patients, postoperative stay and ileus were shorter in laparoscopic (LPL) group as well as in EPL group. Differences in intra- and postoperative complications resulted not statistically significant among groups' patients, while number of lymph nodes resected and, therefore, adequacy of lymphadenectomy were significantly worse in LPL group [53].

As it is evident, there are many areas of continuing debate regarding lymph node resection in cervical carcinoma, ranging from a proper and standardized nomenclature of nodal stations and the best surgical approach, to the most cost-effective pre- and intra-operative modalities of nodal status assessment, and to the clinical significance of systematic pelvic and aortic lymphadenectomy in different stages of disease.

**Surgical technique**

**Systematic pelvic lymphadenectomy**

Various pelvic lymph node stations have been identified to improve accuracy of surgical procedures and to standardize operative techniques [3,6,7,34].

The dissection is carried down towards the bifurcation of the aorta and continues at the level of the common iliac vessels. Presacral vessels are identified and the presacral space is prepared by mobilizing medially the sigma-rectum. At this stage, it is often possible to identify the presacral artery which sometimes originates from the posterior side of the aorta and its origin is therefore difficult to see. The para-colic and para-vesical spaces are created and retractors are placed to expose lateral pelvic vessels.

The dissection begins at the origin of the external iliac vessels and continues caudally preserving the aponeurotic fascia of the psoas muscle. To decrease the risk of neurologic postoperative complications, it is important to spare the branches of the genito-femoral nerve. The external iliac artery and vein are completely separated from each other and are held by vessel retractor. The lower limit of external iliac lymphadenectomy is represented by the deep inferior epigastric vessels. The lateral boundaries of the dissection are superficially delineated by the fascia covering the psoas muscle and deeply by the fascia covering the internal obturator and levator ani muscle. The lateralization of the external iliac vessels and the obturator nerve allows the identification of the medial margin of the lymphadenectomy, represented by an imaginary plane which is parallel to the umbilical artery and to the lateral aspect of the bladder and the rectum. The clearing of the obturator fossa begins with the mobilization of the superficial obturator nodes which are completely dissected after the identification of the upper face of the obturator nerve. These nodes are removed en block with the lymphatic fatty tissue which has been previously separated from the internal iliac vessels to the origin of the internal pudendal vessels.

For patients with locally advanced cervical cancer, pelvic lymphadenectomy continues with the dissection of the deep obturator nodes and gluteal nodes. The isolated and ligated obturator artery and vein are removed together with the lymphatic tissue of the inferior part of the obturator fossa. By moving the external and common iliac vessels medially and the psoas muscle laterally with a retractor, it is possible to remove node groups of this area (Fig. 1) and see the superior and inferior gluteal veins and the trunk of the sciatic nerve. This step ends pelvic lymphadenectomy.

Medial internal iliac lymph nodes are removed with caution towards the lymphatic channels entering the parametrium. The nodes are, in fact, connected with the lymph nodes of the base of lateral parametrium. These last lymph nodes can often be removed separately from the lateral parametrium when the lateral parametrium is prepared for the vessel by vessel technique of dissection. This last description of node dissection is mainly reserved for patients with positive “sentinel lymph nodes stations” or for locally advanced stages surgically treated (Stages ≥IB1).

In order to reduce the lymphatic loss, major lymphatic channels dissected may be ligated with hemoclips.

**Systematic aortic lymphadenectomy**

Exposing the retroperitoneal space includes 3 possible peritoneal incisions, as previously reported [54].

The first is made along the right paracolic gutter up to the hepatocolic ligament. The second is a diagonal cut on the peritoneum which goes along the route of the mesentery from the caecum to Treitz’s ligament. The third incision is made in the left side along the homolateral paracolic gutter almost up to the splenocolic ligament. By mobilizing and elevating the caecum and the ascending colon it is possible to identify the anterior leaf of the renal fascia which represents the surgical plane to follow. The entirely mobilized ascending colon and the small intestine are thus taken out of the peritoneal cavity, placed on the chest and wrapped in warm wet dressings or in appropriate plastic bags. A specifically provided retractor held in the left hand of the third assistant is used to keep the bowel off the surgical field. At this point, the main structures of the retroperitoneum including the right kidney, the renal vessels, the ureter, the homolateral ovarian pedicle, the vena cava, aorta and the inferior mesenteric artery and vein are identified. The right lateral margin of the para-aortic lymphadenectomy is delineated by the

![Fig. 1. Common iliac artery bifurcation with view of internal and external arteries after extraperitoneal systematic pelvic lymphadenectomy (left side).](image)
lymphatic dissemination of cancer and its clinical significance renewed interest in lymph nodes surgery, opinions regarding introduction of surgical staging into clinical practice has led to studied anatomical topics in gynecologic oncology. Even though the Discussion

Lymphatic spread of cervical cancer represents one of the most studied anatomical topics in gynecologic oncology. Even though the introduction of surgical staging into clinical practice has led to renewed interest in lymph nodes surgery, opinions regarding lymphatic dissemination of cancer and its clinical significance are likely biased for many aspects.

Data available in literature are often biased by marked differences in surgical techniques and a poor quality of pathologic reports that rarely state the number and site of nodes removed.

The possibility of multiple patterns of lymphatic diffusion and anatomic individual variabilities in nodal location and, lastly, the lack of a uniform, surgically-based classification and nomenclature for each group of lymph nodes recovered, contribute to make literature data still difficult to compare.

In fact, a better insight in different patterns of lymphatic spread by lymphoangiogenesis may significantly improve knowledge of natural history of gynecologic malignancies, since lymph vessels are likely the main pathway of cancer dissemination [13,17].

Tumor-induced lymphangiogenesis driven by tumors expressed lymphangiogenic growth factors such as VEGF family, fibroblast growth factor 2 (FGF-2), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), and platelet-derived growth factors (PDGFs) is associated with lymph node metastasis in experimental cancer models and in several types of malignancies [13]. The first specific lymphangiogenesis factors identified were vascular endothelial growth factor-C (VEGF-C) and VEGF-D, that mainly act via VEGF receptor-3 (VEGFR-3), expressed by lymphatic endothelial cells [14], and a significant correlation between cancer expression of VEGF-C or VEGF-D, and nodal metastasis has been reported by several authors [14–16]. It has also been demonstrated that activated VEGFR-3 may induce lymphatic endothelial cell proliferation and migration by multiple pathways, while blockade of VEGFR-3 pathway by specific antibodies efficiently inhibits experimental tumor lymphangiogenesis, and therefore it could represent a novel therapeutic avenue for anti-lymphangiogenic therapies [16,17].

In addition, chemokines are thought to play a role in attracting tumor cells and lymphatic vessels to each other, and lymphangiogenic growth factors secreted from a primary tumor may induce lymphangiogenesis in nearby lymph nodes, even before arrival of tumor cells, which may facilitate further metastasis [13,16,17].

However, to date, the quantitative contribution of these proteins to tumor lymphangiogenesis and lymphatic metastasis in different tumor types requires further clinical investigation.

Strong efforts have been made during last decade for developing accurate preoperative and intraoperative methods to identify nodal metastases, or at least the sentinel node, with a progressive trend in reducing nodes to be resected, aimed at limiting surgical morbidity, preserving patient immunity, and testing the efficacy of new immuno-based drugs and vaccines.

Fig. 2. Bulky lymph node at intercavo-aortic space at the level of common iliac artery and vein bifurcation.

Fig. 3. Intercavo-aortic and para-aortic space after aortic systematic lymphadenectomy with view of left renal vein.
Considering a preoperative setting, some authors tested combination assay of serum squamous cell carcinoma antigen (SCC) and CA125 levels, and they considered it useful in estimating lymph node status [32], while recently the cancer testis tumor-associated antigen MAGE-A expression resulted significantly associated to lymph node metastases in early stage cervical tumors [33]. However, it’s our opinion that all these results need to be further studied and confirmed in large trials before being recommended in clinical practice.

Concerning radiological detection of nodal metastasis, although imaging modalities are improving accuracy, there has been no large prospective trial demonstrating the comparability of any imaging modality compared to surgical evaluation of lymph nodes [34]. In a meta-analysis of studies evaluating computed tomography (CT) scan and magnetic resonance imaging (MRI) efficacy for assessing nodal status in cervical cancer patients, the authors concluded that these methods have only moderate sensitivity and specificity in detecting nodal metastases [35]. In particular, CT scan and MRI are relatively inaccurate in detecting small volume of disease in lymph nodes: suspicion is mainly raised when lymph node diameter is greater than 1 cm. Most metastatic lymph nodes, however, will not meet this size criterion and therefore will go undiagnosed [35].

Currently, even if 18F-fluorodeoxyglucose positron emission tomography (PET) scanning is recognised better at detecting microscopic node spread than other modalities, in a recent series it has demonstrated to be a poor predictor of nodal involvement with an overall sensitivity of 38% and a positive predictive value of 56% [36,37]. The results were clearly related to the size of involved nodes with detection slightly increasing when metastases were > 10 mm, making questionably the routine use of PET scan as sole decision-making tool in this setting of patients. A summary of most recent studies evaluating different imaging modalities efficacy in detecting nodal metastases is shown in Table 2 [38–47]. Moreover the Gynecologic Oncology Group (GOG)-0233/American College of Radiology Imaging Network (ACRIN)-6671 ongoing trial is going to assess the efficacy of preoperative FDG-PET/CT and Ferumoxtran-10 (an ultra small particle iron oxide – “USPIO” agent) MRI scanning to primary chemoradiation therapy to detect nodal metastasis in patients affected by locally advanced (IB2–IVA) carcinoma of the cervix.

Sentinel node detection by lymphoscintigraphy and laparoscopic approach could have an important role in the management of patients affected by IA2–IB1 cervical cancer. However, in a considerable percentage of cases bilateral and/or more than one sentinel lymph node can be detected.

Thus it’s our opinion that significant improvements in detection rate and its pathological analysis are needed prior to consider the sentinel node retrieval a routine procedure in cervical cancer patients. On this background, the concept of “sentinel lymph nodes stations” seems currently an acceptable compromise in order to limit lymphadenectomy and its morbidity, while maintaining staging accuracy [31].

Large trials in Europe and the United States are nearing completion and their results should help indicate the future direction for sentinel node techniques in cervical cancer; in particular, a prospective multi-institutional trial of lymphatic mapping and sentinel nodes in women affected by cervical carcinoma currently being undertaken by the Gynecologic Oncology Group (GOG 206) will possibly close and report its findings.

The removal of the lymph node groups primarily draining the cervix, namely the external iliac, interiliac, superficial obturator and superficial common iliac groups, makes it possible to identify nearly all of the positive-node patients. The concept of tailoring parametrial resection on the basis of these nodes status arises from the observation that in early stage cervical cancer nearly all women with pelvic nodal metastases show concomitant pathological evidence of parametrial involvement, therefore necessitating of a classical radical (type III) hysterectomy. On the opposite, patients showing negative pelvic primary nodes may benefit from a modified radical (type II) hysterectomy, without fear of jeopardizing cancer cure [2,18].

Neoadjuvant chemotherapy studies in locally advanced cervical cancers opened up new acquisitions on lymph nodal sensitivity to chemotherapy: their rate of involvement after chemotherapy, significantly lower than expected without it, makes no longer reasonable the concept of lymph nodes as “chemotherapeutic sanctuary” [55].

The benefit of lymphadenectomy has been largely demonstrated in several retrospective series reporting improved survival mostly for patients after debulking of grossly involved nodes [56–59], and similar survival for patients with completely resected lymph nodes has been reported whether microscopically or macroscopically involved [60].

There is now a strong evidence of the undeniable need to proceed resecting pelvic nodes up to the level of common iliac sites, and also aortic nodes in case of pelvic node disease detected intraoperatively, due to the high incidence of lymphatic upper spread in such patients [3,6]. When a systematic pelvic lymphadenectomy is rationally indicated, evidence suggests that it should be performed safely and in a standardized way by a gynecologic oncologist, with 25–35 nodes recovered in order to consider adequate the procedure, while 12–25 aortic nodes in case of para-aortic lymph nodes dissection [2,6,21,54]. The pattern of lymphatic spread should form the basis for establishing the criteria for a systematic lymphadenectomy with curative potential. When a therapeutic intent is pursued, the pattern of lymphatic metastasis suggests that a systematic dissection of all the lymphatic tissue located around the cervix and the pelvic vessels should be performed in patients with both early stage and locally advanced disease in order to remove the potential sites of metastasis entirely, while systematic aortic lymphadenectomy should be performed in cases of pelvic nodes involvement. In case of no diseased upper pelvic (common iliac) and aortic nodes, patients may be spared of the costs, side effects and complications of an unnecessary extension of external radiation field. Conversely, patients with microscopically positive lymph nodes may benefit from adjuvant chemotherapy or extended field radiation [61]. Finally, patients with macroscopically diseased lymph nodes mostly benefit from surgical complete debulking, also considering the reported limited effect of radiation in these cases [7].

Contraindication to remove grossly involved lymph nodes is represented by the evidence of gross extracapsular nodal spread, indicating a poor prognosis extra-lymphatic disseminated disease, with the possibility to administrate a chemotherapy, radiotherapy, or a concurrent chemoradiation [62]. With this purpose, a strict pre-operative and intra-operative collaboration between gynecologic oncologist and radiotherapist could represent an optimal chance for patients to benefit from the best treatment modality. The absence of definitive evidence of survival advantage given by extensive lymphadenectomy in all cervical cancer cases indicates a further insight in the clinical role of nodal resection, that should be properly tailored and performed on the objective risk of node metastasis: it’s our opinion

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<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>1999</td>
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<td>92%</td>
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<td>Williams et al.</td>
<td>2001</td>
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<td>48% vs 54% vs 25%</td>
<td>97% vs 91% vs 77%</td>
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<td>97%</td>
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<tr>
<td>Bipat et al.</td>
<td>2003</td>
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<td>60% vs 43%</td>
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<td>Lin et al.</td>
<td>2003</td>
<td>PET</td>
<td>86%</td>
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<td>97% vs 40%</td>
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<td>2006</td>
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<td>Vildirim et al.</td>
<td>2008</td>
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Table 2. Imaging modality efficacy in detecting nodal metastasis

Review of literature.
that the final goal in the future will be to remove only pre-operatively detected metastatic nodes, when present.

On the other hand we have to consider that the mainstay of detecting lymph node metastasis is still the histologic evaluation, therefore resection of lymph nodes remains a crucial surgical step when treating cervical cancer. In particular, concerning pathologic bulky nodes, the limited effect of radiation on these nodes gives lymphadenectomy the most important clinical impact for these patients.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References


