Chapter 14

Sentinel Lymph Node Detection in Early Stage Cervical Cancer

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Additional information is available at the end of the chapter

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Abstract

Worldwide, cervical cancer is the fourth most common malignancy among women. Radical hysterectomy and pelvic lymphadenectomy is the standard treatment for early stage cervical cancer. If lymph node metastasis is present at the time of diagnosis, 5-year survival rate drops from 90% to 57%. The risk of lymph node metastases in women with early stage cervical cancer is approximately 15%, and determines the use of adjuvant treatment. Over 80% of patients do not benefit from pelvic lymphadenectomy, but may suffer from adverse complications or sequelae such as lymphedema, lymphocyst formation, and neurovascular and ureteral injury. The sentinel lymph node is the first node to which metastatic disease will spread from a primary tumor. The clinical benefits of biopsy of only the sentinel lymph node includes a significant reduction in the adverse effects of complete lymphadenectomy. The specific benefits of sentinel lymph node detection in early stage cervical cancer includes improved identification of metastatic lymph nodes through ultrastaging and identification of alternate lymph node drainage sites, as well as the possibility of intraoperative frozen section analysis, which may be used to guide surgical management. Sentinel lymph node detection in early stage cervical cancer could become the standard of care in the near future.

Keywords: Cervical cancer, sentinel lymph node, lymphadenectomy, ultrastaging, micrometastasis

1. Introduction

Worldwide, cervical cancer is the fourth most common cancer among women, after breast, colorectal, and lung cancers. Almost 70% of the global burden occurs in developing countries, where it accounts for almost 12% of all female malignancies, being a major public health problem in many developing countries [1]. It is well known that the most important cause of cervical cancer is the presence of a persistent papillomavirus infection [2]. The risk factors for developing cervical cancer are the same as those for acquiring the human papillomavirus (HPV) infection, such as early age intercourse, multiple sexual partners, and sexual contact with high-risk men. HPV type 16 and 18 are responsible for approximately 70–75% of all cervical tumors [3].

However, long-term (1992-2010) cancer incidence trends for all racial and ethnic groups show that cervical cancer has experienced the largest decrease in incidence among women [4]. This decrease in incidence is related mostly to cervical cancer screening programs with Papanicolaou smears and HPV DNA cervical detection. Moreover, cervical cancer screening programs are associated with a potentially significant reduction in the diagnosis of advanced cervical cancers and death. Cervical cancer screening is well established in developed countries, but it is still taken of in developing countries.

Most developed countries have introduced HPV vaccination in their vaccination calendar, expecting to lower the incidence of cervical cancer. However, cervical cancer still represents a health problem in developed countries with 54,517 new cases diagnosed and 24,874 deaths from this disease every year in Europe [5].

2. Diagnosis

Early stage cervical cancer is commonly asymptomatic, diagnosed by pathological Papanicolaou smears. Advanced cervical cancer can present with symptoms such as abnormal vaginal bleeding, intercourse bleeding, dyspareunia, or pelvic plain.

The diagnosis of cervical cancer requires histological confirmation in all cases. If the patient presents with a macroscopic cervical lesion, a direct biopsy ought to be performed. If changes are shown in the cytological study but there is no macroscopic lesion in the cervix a colposcopy should be carried out. If the colposcopy findings are suspicious of malignancy directed biopsies ought to be taken, on the other hand if the colposcopy doesn't present any alterations, an endocervical curettage is indicated. If microscopic cervical invasive lesions are present a conization is required for tumor staging.

There are three categories of epithelial tumor of the cervix recognized by the WHO: squamous, glandular (adenocarcinoma), and other epithelial tumors including neuroendocrine tumors and undifferentiated tumors. Squamous cell carcinoma accounts for approximately 70–80% of all cervical cancers, and adenocarcinoma for 10–15%. Neuroendocrine tumors of the cervix are highly aggressive, rare tumors with a prognosis worse than stage-comparable undifferentiated

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squamous cell carcinoma of the cervix, and have a different therapeutic management [6]. In this chapter we will be referring to squamous and adenocarcinomas of the cervix exclusively.

The histological report of the biopsy and/or conization of the cervix should include the following information: histological type, differentiation grade, tumor size, length of stromal invasion, and the presence or absence of lymph-vascular space invasion (LVSI). Pathological information is very important for the tumor risk assessment.

3. Tumor staging

Cervical cancer FIGO classification is based on clinical examination, considering the tumors size, vaginal and parametrial involvement, bladder/rectum extension and distant metastasis. If the clinical examination is difficult or uncertain considering vaginal and/or parametrial involvement, it should be performed under anesthesia.

To determine the tumor's extension, various imaging tests are helpful, such as computed tomography (CT) scan, magnetic resonance imaging (MRI), and positron emission tomography (PET-CT). CT scan, to detect pathological loco-regional lymph nodes. While MR imaging is suited for examining soft tissue alterations, helping to determine the size, degree of stromal invasion, possible parametrial involvement, possible vaginal infiltration, and pelvic extension of the tumor. PET-CT imaging is known to determine accurately the extent of the disease, mainly by detecting possible metastatic lymph nodes and distant metastatic disease.

Cervical cancer FIGO stages IA, IB, and IIA are considered early stage tumors (Table 1). Approximately 44% of all cervical cancers are diagnosed in the early stages. Stage IA tumors are defined as invasive carcinomas that present with a stromal invasion of less than 5mm, and a horizontal extension of less than 7mm. Stage IB tumors are defined as invasive carcinomas limited to the cervix that present with a stromal invasion and a horizontal extension greater than 5mm and 7mm, respectively. Stage IIA tumors are defined as invasive carcinomas that invade beyond the uterus but do not involve the parametrium or the lower third of the vagina.

The lymph node status is not included in the FIGO staging system (Table 1), although it is the most important independent prognostic factor in early stage cervical cancer. If lymph node metastases are present at the time of diagnosis, the 5-year survival rate drops substantially. In stages IB-IIA, the 5-year survival rate drops from 88%–95% without lymph node metastasis to 51–78% with lymph node metastasis [7].

To determine the lymph node status, several imaging tests have been used, including CT and MRI. The major problem of the CT scan and the MRI is that these imaging tests only detect changes in the size and form of the lymph nodes and are not able to distinguish between metastasis and inflammation of the lymph nodes, presenting both low sensitivity and specificity. More recently, PET-CT has been seen to accurately determine the extent of the disease, particularly determining the lymph node status, with a sensitivity of 53–73% and a specificity as high as 90–97% [8,9]. Although, PET-TC presents higher sensitivity and specificity than CT and MRI, it is known to detect only lymph node metastases larger than 6mm, possibly not

International Federation of Gynecology and Obstetrics Staging of Carcinoma of the Cervix	
Stage O	Carcinoma in situ, intraepithelial carcinoma; Cases of stage O should not be included in any therapeutic statistics for invasive carcinoma.
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded.)
Stage IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm. (The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular; from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.)
Stage IAl	Measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm.
Stage IA2	Measured invasion of stroma greater than 3 mm and rio greater than 5 mm in depth and no wider than 7 mm.
Stage IB	Clinical lesions confined tothe cervix or preclinical lesions greater than IA.
Stage IBl	Clinical lesions no greateithan 4 cm in size.
Stage IB2	Clinical lesions greater than 4 cm in size.
Stage II	The carcinoma extends beyond the cervix, but has not extended onto the pelvic wall; the carcinoma involves the vagina but not far as the lower third.
Stage IIA	No obvious parametrial involvement.
Stage IIB	Obvious parametrial involvement. The carcinoma has extended onto the pelvic wall; on rectal examination there is no cancer-free space between the tumor and the pelvic wall; the tumor involves the lower third of the vagina; all cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to another cause.
Stage III	No extension onto the pelvic wall, but involvement of the lower third of the vagina.
Stage IIIA	Extension onto the pelvic wall or h:ydronephrosis or nonfunctioning kidney.
Stage IIIB	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
StageIV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
Stage IVA	Spread of the growth to adjacent organs.
Stage IVB	Spread to distant organs.

Table 1. FIGO stage classification.

accurately detecting lymph node metastases in a high percentage of patients. Until the present moment, pelvic lymphadenectomy has been the standard surgical procedure for the assessment of the lymph node status in early stage cervical cancer, being an integral component of the definitive surgical management.

4. Treatment

There are several treatment options for cervical cancer, depending on the stage, the prognostic factors, and the wish to preserve fertility of the patient.

In early stage cervical cancer, surgery is considered the standard treatment, although radiotherapy is equally effective, only differing in terms of morbidity and complications. Surgery offers benefits over radiotherapy in early stage cervical cancer, such as ovarian function preservation, maintenance of a more functional vagina, and facilitation of the knowledge of

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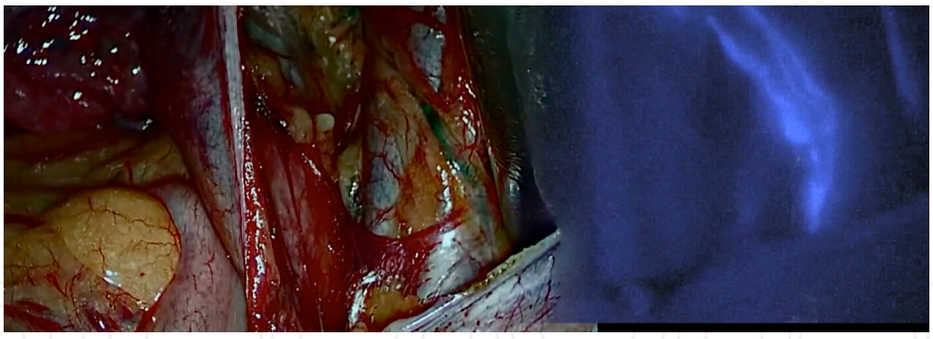

Figure 5. Lymphatic channels with fluorescein.

pathological prognostic factors. In locally advanced stages, a combination of radiotherapy and chemotherapy is the standard treatment.

Fertility-preserving surgery, consisting of radical or simple trachelectomy can be offered to young patients with early stage cervical cancer with a strong wish to preserve their fertility [10].

The goal of radical hysterectomy or radical trachelectomy is to remove the tumor with free margins by excising the uterus, cervix, and parametrium. Pelvic lymphadenectomy is performed to determine the presence or absence of lymph node metastasis, for both prognostic and therapeutic planning. Pelvic lymphadenectomy is a mere staging surgical procedure. In the absence of lymph node metastasis, pelvic lymphadenectomy has no therapeutic effect, with potential complications and associated sequelae.

There are different possible surgical approaches such as laparotomy, laparoscopy, or vaginal surgery. All surgical approaches are considered comparable in terms of oncological results when carried out by experienced surgeons. Minimally invasive surgery (laparoscopy) shows the same efficiency as conventional laparotomy, with lesser blood loss, shorter hospital stay, and lower perioperative morbidity [11].

The risk of lymph node metastasis in early stage cervical cancer is approximately 15%. Consequently, 85% of patients with early stage cervical cancer not only do not benefit from the pelvic lymphadenectomy, but can also suffer complications and morbidity. Pelvic lymphadenectomy is associated with a 4% risk of intraoperative complications such as vascular and neurological lesions, as well as long-term complications, especially lymphocyst formation and lymphedema [12]. Lymphocyst formation occurs in up to 30% of the patients subjected to a pelvic lymphadenectomy. Lymphedema of the lower abdomen, pubis, and lower extremities occurs in 25% of the patients, more frequently in those patients that receive adjuvant radiotherapy after surgery [13]. These complications are very hard to treat and can produce an important impact in the patient's quality of life [14].

Surgery is not recommended in patients with early stage cervical cancer who present with poor prognostic factors. There are pathological factors associated with high risk of relapse such as positive or close margins, metastatic lymph nodes, or microscopic parametrial involvement. If one or more of these poor prognostic factors are present at the time of diagnosis, chemo-

radiotherapy is indicated. Chemo-radiation therapy in high-risk patients is associated with better 4-year overall survival and progression-free survival [15].

Patients with metastatic pelvic lymph nodes are at risk of having para-aortic metastatic lymph nodes. In order to determine the fields of radiation, a para-aortic lymphadenectomy ought to be performed [16]. Radiotherapy administration after radical hysterectomy increases the risk of radiotherapy-related complications, especially intestinal complications by adhesion formation.

A correct pre-therapeutic evaluation is needed to select patients who will benefit from receiving radio-chemotherapy. Radical hysterectomy is not recommended in early stage cervical cancer that presents poor prognostic factors, such as lymph node metastasis, due to the fact that adjuvant radiotherapy and chemotherapy are required in an attempt to improve survival. The objective of avoiding surgery is to prevent the addition of morbidity caused by the association of radiotherapy and surgery.

5. Sentinel lymph node biopsy

Sentinel lymph node (SLN) is defined as the first node to which metastatic disease will spread from a primary tumor. Consequently, in the absence of metastasis in the sentinel lymph node, all other lymph nodes will also be free of disease. Therefore, if the sentinel lymph node has no trace of disease, lymphadenectomy can be avoided, reducing the morbidity associated with a complete lymphadenectomy.

Sentinel lymph node detection was first described by Cabanas in penile cancer [17]. Since then it has been described in multiples tumors, being the standard of care in melanoma, breast, and vulvar cancer, reducing significantly the morbidity associated with the performance of a complete lymphadenectomy in these patients.

Sentinel lymph nodes are identified by the injection of dye and/or a radioactive tracer around the tumor site. In cervical cancer, the sentinel lymph node is detected by injecting Technetium (Tc-99), blue dye, or both into the cervix. Protocols of detection vary in different studies, reporting that the highest detection rate is found when the combination of Tc-99 and blue dye is used [18]. The cervix point of injection varies in different studies. In some studies, the tracer is injected submucosally into the four quadrants of the cervix, and in others the tracer is injected submucosally into the 3 and 9 o'clock of the cervix; no significant differences have been found between these two techniques [9, 18].

After the radiotracer is injected, a lymphoscintigraphic localization imaging can be conducted. Lymphoscintigraphy is an imaging technique used to identify the lymph drainage basin, the sentinel lymph node, the location of the sentinel lymph node, the number of sentinel lymph nodes, and possible secondary drainage. Lymphoscintigraphy helps the surgeon to identify and localize the sentinel lymph node during the surgical procedure [19].

Different protocols of radiotracer injection and subsequent lymphoscintigraphic imaging have been described in the literature. Protocols differ in the time frame from which the radiotracer

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is injected till the surgery is performed, defining long and short protocols. In the long protocols the radiotracer is injected the day before surgery and lymphoscintigraphy is performed 1h after the injection [20]. In the short protocol the radiotracer is injected between 2 and 4 hours before surgery, and the lymphoscintigraphy is performed 20 minutes after the injection [9].

The blue dye is injected to the cervix in the surgery room after the anesthetic induction is performed, with the same technique as the radiotracer was injected.

The first step of the surgery is to look for the sentinel lymph node. The sentinel lymph nodes are identified by tracing the lymphatic chains with the gamma probe, identifying nodes with radioactive counts greater than five times the background count (Figure 1). The pelvic sidewalls, presacral, and para-aortic lymph chains should be scanned to identify "hot spots" by the gamma probe and/or by identifying blue-stained lymphatic channels and lymph nodes (Figures 2 and 3). Lymph nodes that appear "hot", blue, or both are identified as sentinel lymph nodes, and are removed (Figures 4 and 5). The sentinel lymph nodes are sent for intraoperative pathological review. Lymph nodes that appear to be grossly abnormal should be also removed, whether "hot", blue, or not, since the lymphatic channels may be obstructed by tumor, and the lymphatic drainage and tracer may be bypassing such nodes.

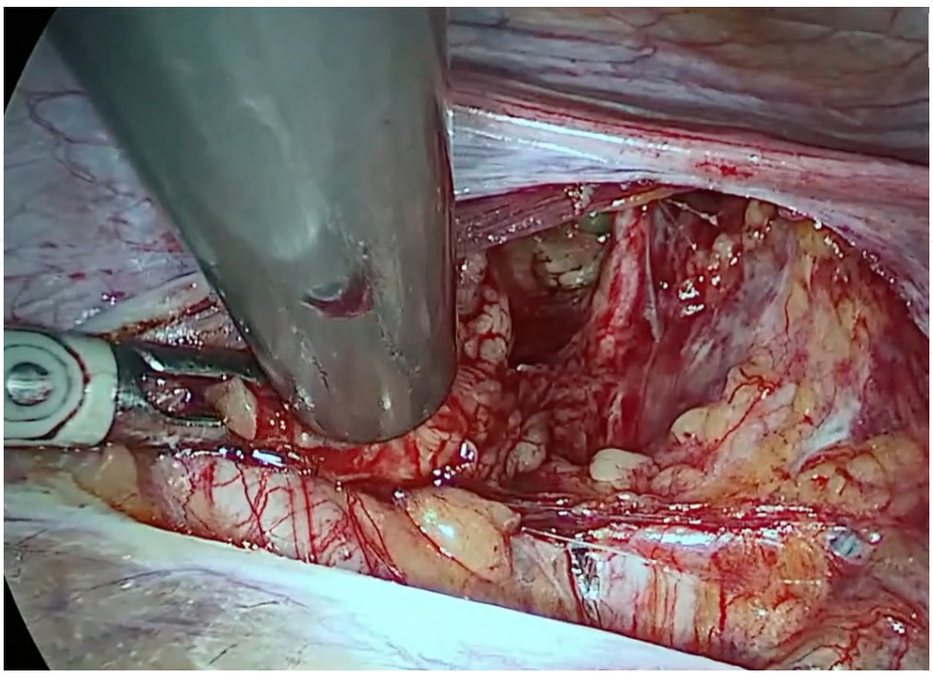

Figure 1. Detection of the sentinel lymph node with the gamma probe.

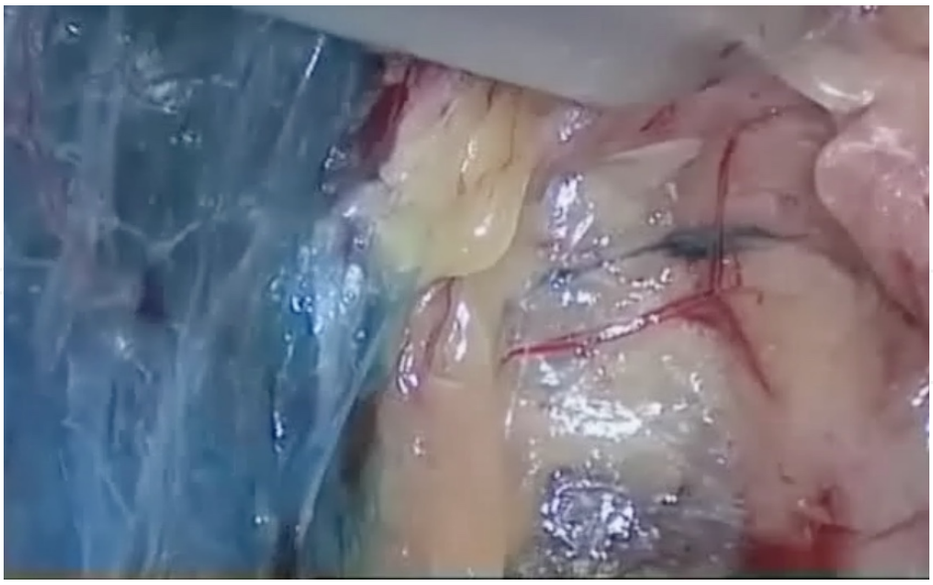

Figure 2. Blue chain of a sentinel lymph node.

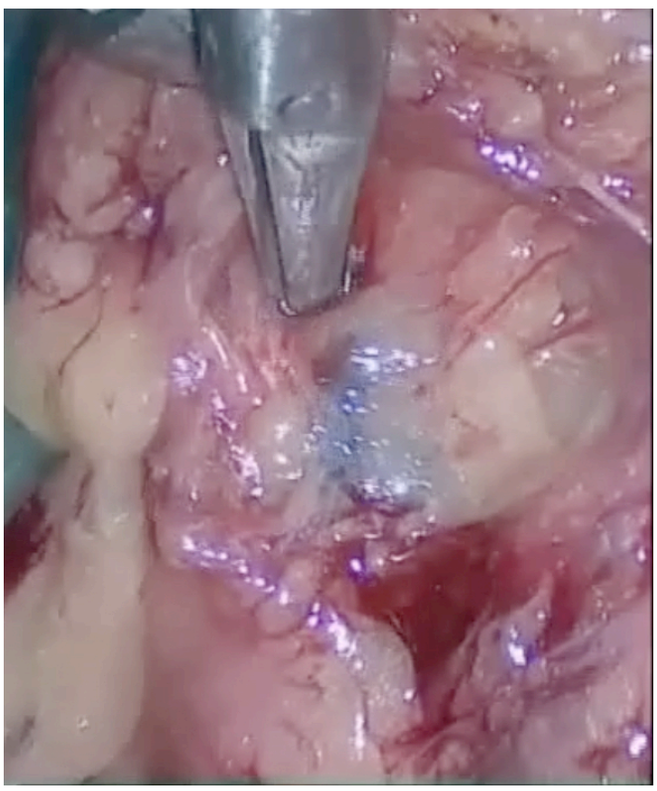

Figure 3. Blue sentinel lymph node.

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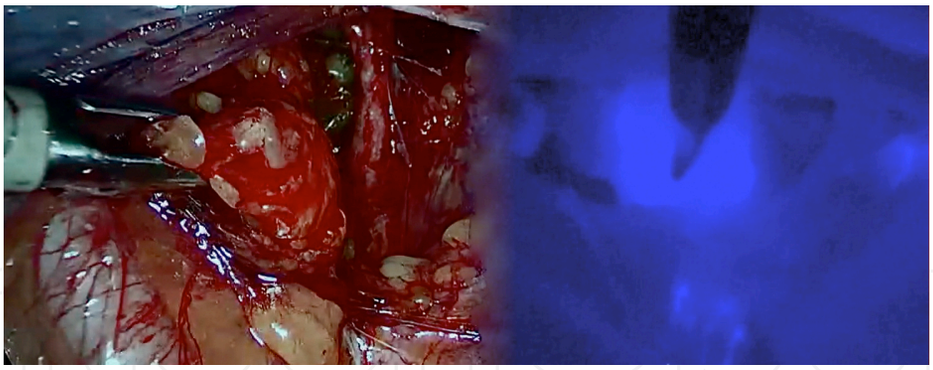

Figure 4. Resection of a blue and "hot" sentinel lymph node.

The cervix is a midline structure presenting a bilateral lymphatic drainage. The sentinel lymph node must be detected bilaterally in order to reduce the false negative rate. If no sentinel node is detected on one side, a complete lymphadenectomy must be performed on that side.

Sentinel lymph node detection in early stage cervical cancer presents several advantages over common pelvic lymphadenectomy [21]. First, it permits an intraoperative analysis of the node. Second, this technique can detect aberrant lymphatic drainage. And third, it permits ultra-staging of the sentinel lymph node and detection of micrometastasis and isolated tumor cells (ITCs).

As mentioned earlier, the association of radiotherapy and radical hysterectomy causes a higher risk of radiotherapy-related complications. To avoid the increase of morbidity caused by the association of treatments, a possibility is to perform the complete surgery in two phases instead of one. First, the pelvic lymphadenectomy can be carried out, waiting one or two weeks to obtain the definitive pathological report. If the lymph nodes are reported as negative a second surgery, a radical hysterectomy or trachelectomy, is performed. With the sentinel lymph node technique, information on the lymph node status is available in the operating room during the surgical procedure, permitting changes in the therapeutic management of the patient if necessary. If the sentinel lymph node is informed as metastatic, it is possible to complete the para-aortic lymphadenectomy as one procedure, not perform the hysterectomy, and avoid increased morbidity. Sentinel lymph node detection permits triaging patients toward surgery or chemo-radiation therapy, as well as selecting candidates for fertility-preserving surgery.

Aberrant lymphatic drainage or unusual locations of metastatic lymph nodes are due to those sentinel lymph nodes that are detected in lymphatic chains, which are not typically removed with the standard pelvic lymphadenectomy, as can be the presacral nodes or the common iliac nodes. Consequently, if a standard pelvic lymphadenectomy were to be performed without the sentinel lymph node detection technique, these metastatic nodes would not be detected. Bats et al. detected metastatic sentinel lymph nodes in an unexpected territory in up to 15% of the patients in which the sentinel lymph node technique was performed, and they concluded that the sentinel lymph node detection technique contributed to improved nodal staging [22].

Ultrastaging is the pathological process of studying the sentinel lymph nodes, consisting of a multiple serial sectioning with immunohistochemical assessment. Pathological ultrastaging

permits the detection of low volume disease, which includes micrometastasis and ITC, as defined for breast cancer by the American Joint Committee of Cancer (AJCC). Macrometastasis was defined as tumor deposit greater than 2mm in diameter, micrometastasis was defined as tumor deposit between 0.2 to 2mm in diameter, and isolated tumor cells were defined as tumor deposits no larger than 0.2mm [23]. The importance of the detection of low volume disease in cervical cancer is its relationship with poor prognosis. In a study published in 2012 by Cibula et al. [24] that included 645 patients, it was observed that the presence of micrometastasis was associated with a significant reduction in the overall survival similar to those patients that presented macrometastasis, while no increased risk was found in those patients that presented ITC. Micrometastases are being detected in the sentinel lymph node in 4–15% of the patients, depending on the study [25].

Ultrastaging is a time-consuming and costly technique, not feasible for the analysis of all the lymph nodes obtained after a pelvic lymphadenectomy, but it is possible if only two to four nodes are studied with this technique. Detection of SLN and subsequent ultrastaging may detect a group of patients that would be overlooked with the standard pathological study of the pelvic lymphadenectomy nodes, although they present prognosis similar to those patients with macrometastasis. These findings highlight the importance of the SLN detection in early stage cervical cancer.

The presence of non-diagnosed micrometastasis or aberrant metastatic lymph nodes could explain the 15% of patients with an early stage cervical cancer with apparently no poor prognosis factors at diagnosis, that recur in the follow-up.

The sentinel lymph node detection has the potential to increase sensitivity in the detection of lymph node metastasis by detecting aberrant lymphatic drainage and micrometastasis [26]. Data of more than 2000 patients have been subjected to the sentinel node technique In a review published by Eiriksson et al. [9], sentinel lymph node detection in tumors of less than 2 cm presents a sensitivity of 98.2% and a negative predictive value of 99.6%, with a false negative rate of less than 5% when each hemipelvis is interpreted independently.

6. Conclusion

Sentinel lymph node detection permits minimizing surgical morbidity while maximizing the pathologic information of nodal status in patients with cervical cancer. Sentinel lymph node detection could become the standard of care in early stage cervical cancer in a close the future.

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