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Sentinel lymph node biopsy. A prospective medical advance to substitute the pelvic lymphadenectomy in early cervical cancer. A reappraisal.

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Introduction

Cervical cancer is the fourth most common malignancy in the female population and was the ninth cause of deaths in the female population in 2016¹. According to the American Cancer Society, 13240 new cases of cervical cancer will be diagnosed in the USA in the year 2018, while 4170 women will die from the disease². Unfortunately, 40% of them concern women younger than 45 years old in their reproductive age³.

Traditionally, the therapeutic strategy for early stage cervical cancer (IA1-IB1) includes radical hysterectomy and bilateral pelvic lymphadenectomy (Wertheim's procedure) with excellent oncologic outcomes⁴. Despite the excellent oncologic results of the procedure, sterilization, sexual-urological dysfunction and lymphedema are notable disadvantages of the surgical management⁵.

Cervical cancer staging, according to FIGO, unlike other gynecologic neoplasms is not a surgical process. Although not included in the FIGO clinical staging, the pelvic and para-aortic lymph node status is an important prognostic factor in cervical cancer staging because the survival rates of patients with metastases to the nodes are significantly lower than those of patients without metastases to the nodes^{6,7}. Therefore, an accurate staging and detection of lymph node (LN) metastases is essential in order to ensure appropriate treatment planning and prediction of prognosis for cervical cancer patients⁸.

A number of studies has evaluated the diagnostic performance of non-invasive modalities, such as CT, MRI and positron emission tomography (PET)-2-[18 F] fluoro-2-deoxy-D-glucose (FDG) in detecting LN metastasis in cervical cancer patients. MRI and CT

have been conventionally and widely used to detect LN metastases based on measurements like node size and morphologic information, with low sensitivity and specificity rates though. PET and PET/CT offer combined benefits of anatomic and functional imaging and have been used to localize areas of increased FDG uptake with improved anatomic specificity⁹. However, controversy still exists in relation to the application of PET/CT in clinical practice, mainly because of its high cost¹⁰. Furthermore, frozen section biopsy of LNs is an intraoperative module which is characterized by low accuracy rates in detection of metastases with high false negative rates for stages IA2 - IB1 (4.2%)¹¹.

Sentinel Lymph Node (SLN) phylosophy

Sentinel Lymph Node (SLN) is the first lymph node or group of nodes draining an anatomic area. In case of an established cancerous dissemination it is postulated that the sentinel node is the target organ primarily reached by metastasizing cancer cells from the tumor. Breast, penile, and skin cancer treatments have established the SLN procedure while negative SLN tests have helped avoid full lymph node dissection. Data from several studies of SLN biopsy in early cervical cancer are also satisfactory. In most studies the detection rates fluctuate between 95 and 100 per cent, false negative rates remain between 0 and 8 per cent and their negative predictive value is found between 97 and 100 per cent. Thus, in order to avoid complications associated with lymphadenectomy, SLN biopsy has been introduced in the surgical management of cervical cancer¹².

Anatomically, the most common drainage is the lymphatics that come out through the broad ligament. These lymphatics cross over the umbilical ligament as they end up in classic mapping areas such as the iliac or the obturator area and are most commonly found medially to the external iliac vessels

and ventrally to the hypogastric superior part of the obturator^{13,14}.

Clinical Utility

Lymph node metastasis rates in women with early cervical cancer are found between 15-20%¹⁵. Therefore, according to the traditional strategies, 80% of women will not benefit from pelvic lymphadenectomy and its associated complications (lymphatic cysts, lymphedema, urologic disorders and sexual dysfunction). Thus, using the SLN technique, these women with negative SLN could omit full pelvic lymphadenectomy⁵.

Frequently, patients demonstrate pelvic recurrency despite the fact that lymphadenectomy has been performed. This is due to lymph node involvement in atypical locations, in approximately 10% of women, (presacral, lower paraortic, common iliac, medial part of lateral parametrium) which was not excised during pelvic lymphadenectomy (Rob et al gyn oncol 2005). Rob et al. revealed that positive sentinel node rates in these atypical locations are about 15%¹⁶.

As already mentioned, the current management of women with early cervical cancer is radical hysterectomy (RH) with bilateral pelvic lymphadenectomy, while in cases that the histologic diagnosis reveals positive lymph nodes, patients will be referred for adjuvant radiotherapy (RT)¹⁷. When using the SLN procedure, if a woman has a positive SLN, the hysterectomy is abandoned and the patient is referred for primary RT¹⁸. If the SLN is negative then the patient can undergo RH or a more conservative fertility sparing treatment¹⁹.

The most attractive idea is to use the SLN procedure for triaging patients in order to prevent women with positive lymph nodes from radical operations²⁰. Furthermore, these women can be referred for another treatment modality (adjuvant radiotherapy), while omitting all the negative consequences²⁰. Attention should be paid to patients with false negative

SLN because an "overtreating" scenario with a radical surgery is possible²¹.

On the other hand the SLN procedure can be used to select patients who are candidates for less radical procedures when the SLNs are negative. In this case a false negative SLN can lead to "undertreatment" of patients because of the high false negative rates of the technique²¹.

Moreover, even if several studies have been conducted, the procedure is not yet established because of the severe false negative rates in patients with early stage cervical tumors. This fact leads in a demised trustworthiness of the SLN procedure and therefore in insufficient metastasis detection. Consequently, the challenge in protocol development is to detect micrometastases that can be missed¹⁸.

Low volume disease (LVD) is a new terminology that has been introduced in gynecological cancers. LVD concerns tumors smaller than 2mm²². Micrometastasis is a low volume metastasis measuring 0,2 - 2mm in the form of microscopic clusters and single cells while Isolated tumor cells (ITC) concern metastasis measuring lower than 0.2mm²².

Studies have shown that the survival rate in patients with micrometastasis seems to be equal to patients carrying macrometastasis²³. Furthermore, isolated tumor cells do not seem to affect survival rates²³. Therefore, the "ultrastaging protocol" has come to ameliorate the intraoperative histology procedures as it focuses in the detection of the metastases that could be potentially missed²².

When an SLN is sent for frozen section, a micrometastasis can be potentially included on the half node that will not be cut for examination. Consequently, the improvement of pathologic intraoperative processing is the activation of the Ultrastaging protocol. Ultrastaging in negative SLNs is a promising technique that can detect low volume metastasis. This protocol is activated by pathologists in cases of negative SLNs. With this process, further sectioning

of the lymph node will be able to capture a 2mm metastasis that may have been missed on the first cut^{22,24}. This technique consists of multiple serial sectioning of the negative SLNs and examination of them using immunohistochemistry methods giving the possibility to detect LVD which could be missed in the ordinary frozen section procedure. This way, even the 10% of negative SLN with micrometastasis can be diagnosed and moreover, the treatment strategy for these women who would not be referred to adjuvant RT will change²³.

Results from several studies have shown that the detection rate of SLN in cervical cancer is close to 99% and that the bilateral detection rate is 85%, especially with the use of Indocyanine green technique²⁵. Sensitivity in bilateral detection of SLN reaches up to 97% and false negative rates to 1,3%²³. However, Zarganis et al. revealed higher false negative rates in larger tumors, especially in stages IB2 and IIA²⁶. Tax C et al. showed that the residual risk on occult metastasis in early cervical cancer patients with negative SLNs after ultrastaging is 0.08%²¹.

Conclusion

In conclusion, the question at hand is whether the medical society is ready to replace systematic pelvic lymphadenectomy in early cervical cancer for the SLN biopsy only. This matter is under investigation in the Senticol III and the Sentix randomized prospective trials and their results are expected in order to establish detailed guidelines for the SLN biopsy in cervical cancer.

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