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Utility of Performing Sentinel Lymph Node Biopsy among Women with Early-Stage Cervical Cancer: Literature Review

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Abstract:

***Objective**: Evaluation of the pathological status of the pelvic lymph nodes (LNs) is the most important prognostic factor of recurrence and survival in early -stage cervical cancer. Radical hysterectomy and pelvic lymphadenectomy is the cornerstone treatment of cervical cancer, however the morbidity rate associated with pelvic LN dissection is significantly high. Applying the Sentinel LN (SLN) concept in cervical cancer has been proved to be superior to complete pelvic LN dissection (LND) as it associated with a lower rate of postoperative complications and a higher potential of identification LN metastatses.**Aim**: The purpose of this paper is to make a review of the literature data regarding the accuracy of using the SLN biopsy (SLNB) in the treatment plan of women with early-stage cervical cancer, and to assess the oncologic safety of omitting complete in all negative SLNB women.**Method:** We searched Pubmed, Medline, the Cochrane Register , and Embase for English language articles about the diagnostic accuracy ofSLN in detecting lymphatic metastases in cervical cancer using controlled vocabulary (e.g "cervical cancer") and key words (" sentinel", "lymphadenectomy"). Systematic reviews, retrospective studies and clinical non-randomized trials were selected, focusing on the influence of SLNB result on the surgical treatment of early-stage cervical cancer as well as its potential to provide ultra-staging in cervical cancer.**Conclusions:**The SLN technique for women with cervical cancer decreases the morbidity rate associated with pelvic lymphadenectomy, and has the potential to adequately evaluate the pelvic LN status of these patients. However, there is still concern that LN metastases may be missed if only the SLNs are removed. Despite a negative SLNB, in selected cases of early-stage cervical cancer, pelvic lymphadenectomy is still required.*

Keywords: *sentinel lymph node, cervical cancer, lymphadenectomy;*

Abbreviations:

SLN=sentinel lymph node;

LND=lymph node dissection;

OS=overall survival;

DFS=disease-free survival;

SPECT= single positron emission computed tomography.

1. INTRODUCTION

Worldwide almost 500,000 women per year are identified with cervical cancer, most of them being diagnosed in an early stage due to an increasing awareness of the importance of the screening program for cervical cancer. In order to prevent dissemination into the LNs,assessment of the LN status is essential to establish prognosis and determine the optimal treatment. Moreover, although the evaluation of the LNs is not included in the International Federation of Gynecology and Obstetrics (FIGO) staging system, detection of LN metastases is important for predicting recurrence and survival rates[1]. The mainstay treatment for early stage cervical cancer is radical hysterectomy and pelvic and/or para-aortic lymphadenectomy. In early stage cervical cancer, the incidence of LN metastases is between 0-16% when the tumor is <= 2 cm in size , and between 15 %-31% in stage IB[2], However, lymphadenectomy is still required as it is neither clinically nor with the help of the imaging techniquespossible to ascertain the lymphatic metastatic spread[3]. Another disadvantage of performing LND is the higher rate of postoperative complications, which may include lymphedema (10-15%),lymphocyst formation (20%), infection, vascular injury, blood loss, ureteral injury, thromboembolism[4].

In recent years, it has been progressively adopted the idea of determining pre-operatively the LN status in order to avoid unnecessary lymphadenectomy, and hence its associated complications. Furthermore, accurate assessment of LNs in the staging of cervical cancer helps choosing the optimal treatment and reduces morbidity[5]. One of the methods in determining the LN status is the SLN biopsy taking into consideration that the SLN is the first LN that drains the primary tumor, and should be removed because it functions as a filter for the malignant cells avoids dissemination into other regional LNs.If the SLN is negative, than all the other LNs in the lymphatic basin are not metastatic which means that the pelvic LND can be avoided[6].

The role of this paper is to evaluate the accuracy of using SLNB in the treatment plan of women with early stage cervical cancer.

2. SENTINEL LYMPH NODE MAPPING

The concept of the SLN was first described in 1951 by Gould who performed a total parotidectomy for parotid cancer and discovered a metastatic LN at the junction of the anterior and posterior facial veins. The first positive LN of the lymphatic basin was further discovered in other malignancies such as penile cancer and melanoma[7,8]. In breast cancer, SLNB is now recommendedfor routine use in selected groups, and long-term survival data for patients with negative SLNB patient's results have shown favorable outcomes. Recently, SLNB has proved to be useful in the treatment of vulvar carcinoma[9].

Applying the SLN concept in early-stage cervical cancer is reasonable as the cervix possesses a complex lymphatic drainage and the most frequent route of spread in cervical cancer is through the lymphatic vessels[10].

Summarizing, the principle is that a negative result from the SLNB is indicates that all the other LNs of the pelvic lymphatic basin are free of metastases, hence pelvic lymphadenectomy could be omitted. In this way, the rate of short-term and long-term postoperative complications associated with extensive pelvic dissection decreases. Moreover, ultrastaging(microsectioning and immune-histochemical staining of the nodes with the intention to detect metastases) permits an accurate detection of the metastatic LN (the rate of metastases detection increases with almost 25%), and allows the removal of SLN in aberrant locations or at the time of lymphadenectomy[11,12].

Two methods are currently used for the identification of the pelvic SLNs:injection of blue dyes (most frequently: isosulfan blue, patent blue violet, and methylene blue) around the tumor while carefully avoiding escape of the blue dye into the vagina or parametria; the other method consists of intracervical injection of radioactive substances, most commonly 99mTc-sulfur colloid, or 99mTc-nanocolloid human serum albumin. The dynamic signal is identified with the help of a gamma probe and/or lymphoscintigraphy or SPECT-CT[4,13].

The SLNs are defined as "hot" nodes in comparison to the background radioactivity,which consists of the average count rates of the surrounding non SNLNs. If the residual radioactivity is less than 20% of the counting rate in the hottest LN, then SLN removal is considered to be adequate[14].

The LNs draining the cervix are always located in the pelvis or lower aorta locations which can be easily identified by the surgeon at the time of radical hysterectomy without any pre-operative lymphoscintigraphy or SPECT-CT[3]

As regards the effectiveness of each method, radiocolloids remain in the SLNs much longer than blue dyes. Pre-operative lymphoscintigraphy helps the surgeon to precisely locate the exact SLN during the dissection and identify the presence of residual LNs. However, the risk of intra-operative bleeding is high, and it is a rather difficult approachable technique as it requires a nuclear medicine unit. On the other hand, if the SLN is in the parametrium, then injection of a blue dye is more useful as the gamma probe count depends on the proximity of thecervi[3,15].

Recent studies have demonstrated that the rate of SLN detection is considerably increased when both blue dye and radioisotopes are injected. Roy et al. used the combined method for lymphatic mapping in early-stage cervical cancer and found a detection rate of 99.1%, compared to the rate of 92.8% when blue dye alone was injected($p=0.009$)[11]. In the study of Rob et ala sensitivity count of 100% and a SLN detection rate of 96% with the combined technique have been reported[16].

Although magnetic resonance imaging and computed tomographyare available in comparison to lymphoscintigraphy, studies have shown that they do not bring more benefits than singlephoton

emission computed tomography (SPECT-CT). Compared to lymphoscintigraphy, the latter one has a detection rate of 95% – 100%, and the images correlate with the anatomic location of the SLNs in 95% – 100% of cases. In the study of Frumovitz et al[15], more than 70% of patients who were detected with only one SLN on lymphoscintigraphy had proved to have multiple LNs mapped intraoperatively[19]. Furthermore, due to a tridimensional anatomic view, SPECT-CT significantly improves the detection rate of LN metastases, and the intraoperative detection with gamma probe is easier. The intraoperative time for SLND is with almost 25 minutes shorter when using SPECT-CT in contrast to lymphoscintigraphy[18].

Other new techniques such as laparoscopic visualization of the SLNs after injection of blue dye and/or radiocolloid substances or robotic laparoscopic 3D vision significantly improve the accuracy of the SLN concept[19,20].

When referring to the location of the SLNs, their distribution has been described in many studies. Marnitz el al [21] found that 71% of SLNs were interiliac, 8% were along the internal iliac vessels, 5% were along the external iliac vessels, and 5% were along the common iliac vessels. In the SENTICOL trial, 85.3% of all SLNs were external, internal, or common iliac nodes[22]. Rare locations of the SLNs can be: the parametrium (between 7% and 11% of the SLNs), presacral, and para-aortic sites [21,22].

3. BENEFITS AND LIMITATIONS OF THE SLNB

Due to its high negative predictive values (between 88%-100%) and good sensitivity (between 94%-100%), the SLNB concept using both blue dye and radiocolloid material proved to be an advantageous a sensitive method for detecting lymph node metastasis for women with early-stage cervical cancer as well as allowingthe decision whether to perform or not pelvic LND. Additionally, it improves the detection rate of LN metastases by 2.8-fold[23-25].

Depending in the diameter of the tumor, metastases to SLNs can be:macrometastasis when the tumor is > 2 mm in size,micrometastasis when the tumor is between 0.3 mm – 2 mm in size or isolated tumor cells when the tumor is ≤ 2 mm in size.

Although any association between the tumor volume in the SLNs and overall prognostic has not been clearly established, some retrospective studies have sugesgested that women with micrometastases in the SLNs have a poor prognostic and that lymohadenectomy should not be omitted as their presence is associated with a high rate of recurrence. Micrometastases can be identified in 15–43% of negative nodes in immunohistochemical analysis or reverse transcriptase-polymerase chain reaction [26].

Altgassen et al [27] conducted a prospective multicentric study which concluded that SLNB in early-stage cervical cancer patients is accurate if there are isolated tumor cells in the SLNs (<=20 mm in size). However, LND should be still performed. In the same way, Darlin et al[19] emphasized that, in case of unilateral SLNs, lymph-adenectomy should be compulsory on the radio-negative side, and that all bulky LNs must be dissected.

SLN identification has been proved to be strongly related to tumor characteristics such as: stage, tumor size, histologic type, pre-operative conization or other pre-operative treatments.

With regard to the size of the metastases in the SLN, the detection rate and sensitivity for tumors< 2cm in size is 95%, and 100% respectively, in comparison to a detection rate of 80%, and a sensitivity of 89% for tumors > 2 cm in size[28]. Cervical cancer patients in stages IA2-IB1 benefit most from the SLNB which has a high sensitivity (almost 100%) and accuracy (almost 100%) when performed at this time point. Young women with cervical cancer in stages IA2-IB1 who desire fertility sparing are eligible for SLNB as, in this cases, the false negative predictive value is 0%. Other low-risk tumors such as tumors of grade 1 or 2 squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma benefit from SLNB without further pelvic lymphadenectomy [24].

By performinga SLN mapping with the aim of detecting all LN metastases, radical procedures such as parametrial resection in early stage cervical cancer are avoided, thus decreasing the morbidity and mortality rates associated with an extensive surgery. Detecting SLN bilaterally is essential for an accurate ultra-staging of the tumor status which in turn helps identification of recurrences in the remaining LNs [11, 29].

4. PERFORMING PELVIC LYMPHADENECTOMY OR NOT?

Although the majority of data have evidenced favorable results from SLND , further studies are required in order to decide whether SLN removal alone is sufficient in early-stage cervical cancer and can beimplemented in routine clinical practice. Cormier et al[30] have tried to elucidate this concern and have developed a SLN mapping algorithm in 122 women in order to identify all LN metastases and reduce the number of lymphadenectomies. The detection rate of the positive LNs was 100%. They concluded that:the mapped SLNs should be excised and ultra-staged, suspicious LNs should be removed, in case of unilateral mapping , a contralateral lymphadenectomy is required and parametrial resection en bloc with primary tumor resection is mandatory.

In the same way, Vicus and Covens [31] created a guide which permits decision of performing lymphadenectomy or not. Technetium is injected pre-operatively in all four quadrants of the cervix submucosally. If on pre-operative scintigram at least one SLN is not apparent on each side, then blue dye is injected intra-operatively, submucosally in all four quadrants of the cervix.

Lymphadenectomy is necessaryon the contralateral side if SLN are unilaterally detected or on the both sides, if bulky metastases are present as they may obstruct the lymphatic drainage patterns, hence increasing the risk of missing metastases.

Other authors have proposed a two-step strategy which refers to: firstly, an ultra-staging of all the SLNs is necessary. Secondly, if the SLNB is negative the therapeutically approach is to perform only radical hysterectomy without pelvic lymphadenectomy[32].

Summarizing, in the presence of grossly enlarged LNs or advanced disease with large cervical tumors and/or parametrial invasion, pelvic lymphadenectomy is mandatory.

5. CONCLUSIONS

The SLN concept has updated the treatment of patientswith early-stage cervical cancer by achieving a good evaluation of the pelvic LNs status without subjecting women to systematic lymphadenectomy and thus decreasing the rate of postoperative complications. It is a feasible and effective with higher detection rates and sensitivity. However, further investigations are necessary to confirm that complete pelvic lymphadenectomy could be eliminated in negative SLNs patients.

Many controversies such as: the most appropriate mapping technique, the pathologic evaluation of the SLN, the treatment of patients with micro-metastases, impact on life quality and introduction of the SLNB in the clinical practice have been not elucidated.

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