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Review Article

Pitfalls in the Sentinel Lymph Node Concept in the Cervical Cancer

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Abstract

The article presents critical view of the authors on the concept of sentinel lymph node in cervical cancer. It raises the issue according to examination qualification possibilities and on making therapeutic decisions based on it: understanding the results coming from the employment of SLNC, tumor localization, tumor size, routes of metastasing, presence of enlarged or metastatic lymph nodes, "immunological cadavers" and skip metastases, number of SLNs that should be resected, technique and settings. The article is summarized with divagations on possible perspectives for the use of sentinel lymph node concept.

Keywords: Cervical cancer; Sentinel lymph node concept; Non-sentinel lymph nodes; Ultrastaging

Introduction

State of the art

Cervical cancer (CC) is the most common invasive cancer of the female genital tract worldwide [1]. Most patients are initially treated with surgery. Patients treated with sparing (less invasive) approaches are recently becoming more popular. This applies both to the methods of saving the cervix or at least the uterine corpus, as well as the lymph nodes, and to the lower number of complications associated [2]. The sentinel lymph node concept (SLNC) in oncology is the discovery of the most likely route(s) (station[s]) of the spread of cancer from the original tumor.

Sentinel node biopsy (SLNB) showed a clear advantage in reduction of unnecessary elective lymphadenectomies and reducing the risk of death in intermediate-thickness group skin melanoma patients [3]. In breast cancer patients, SLNB result allows stratification of patients for appropriate treatment (like breast conserving therapy without axillary lymphadenectomy) [4]. SLNs metastases may reach 42% of Merkel cell carcinoma patients, so it is recommended to perform SLNB to avoid unnecessary radicalization of lymph node treatment [5].Therefore, in all these cases SLNB gives an indispensable tool in cancer staging. Feasibility of SLNC has been shown in head and neck, endometrial, cervical and vulvar cancers but there are no randomized studies showing therapeutic advance of SLNC in comparison with elective lymphadenectomy, or the number of these studies is insufficient to draw relevant conclusions [6-9]. Similarly as in other cancers, SLNB is considered to be used in early CC [10]. According to the generally accepted definition, early cancer is an organ confined cancer without clinically apparent metastases to lymph nodes (stage I cancer). The International Federation of Gynecology and Obstetrics (FIGO) for some reasons did not approve the evaluation of the lymph nodes to the staging as the Union for International Cancer Control/American Joint Committee on Cancer (AJCC)-TNM system-does for great majority of cancers [11]. There is no obligation to perform imaging in order to evaluate the invasion of the lymph nodes, except for the evaluation of intermediate and advanced stages (IIB-IV) [11,12]. Man can draw a deceitful theory that some cases are undiagnosed, when we rely only on gynecological examination. From this point of view, all CC cases are early according to FIGO, so SLNB may be applicable in each case. European Society of Gynaecological Oncology assumes that the full lymph node dissection should not be performed in patients with FIGO stage IA1 without the lymph-vascular space invasion (LVSI) and in cases of IIB - IV cancers, where imaging is recommended in order to determine the type of primary treatment [12].

The prevalence of metastasis to the lymph nodes in stages of IA1 (by LVSI positive) - IB1 CC is at 0 - 17% but this applies to macroscopic ones, as regards the frequency of micrometastases- is estimated at 4-15% [13,14]. According to the definition of AJCC made for breast cancer, the cancer micrometastases are deposits in the lymph nodes of not less than 0.2 mm - up to 2 mm in diameter [15]. Their significance for the CC has not yet been determined, but it seems that is the same as the macrometastases (> 2 mm in diameter) [16]. If so, their detection means more complete staging – better planned treatment and in the perspective a better prognosis of the patient.

SLNC is based on the premise that a single (multiple) lymph node(s) indicate the state of the regional lymph nodes. We know, however, that there are several phenomena that may not permit using the SLNC in CC. All these phenomena can affect between 5 to as much as 30% of patients undergoing this procedure, taking into account all these aspects in one patient. The aim of this study was to summarize and underline these difficulties.

Pitfalls of the SLNC

Understanding the results coming from the employment of SLNC

There are concepts concerning avoidance of total lymphadenectomy in patients with low metastasis risk towards lymph nodes, which is in case of early breast cancer and melanoma. This concerns patients with no SLN changes and no anticipated non-SLNs metastases. It is generally accepted that in case of the risk of lymph nodes metastases less than 20% SLNC is to be considered. According to this concept, in such cases not only total lymphadenectomy but

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also chemo-radiotherapy could be avoided, what probably may be met in case of early CC. This concept is yet investigational and not widely used or recommended. The main benefit seems to improve the tumor staging and thus better adaptation of treatment to the patient and a more precise determination of prognosis as well. Bats et al. were among the firsts who attempted to practically use SLNC in the CC with respect to improving the staging [17]. They found that in approx. 35% of cases an additional information coming from SLN can be achieved that may affect the healing process. Moreover, no nSLNs metastases were found in a routine examination in cases of negative SLN. So far, Cibula et al. suggested a prognostic role of SLN micrometastases in CC to be equal to this of SLN macrometastases, but it was not the subject of this study to prove that the same is true for nSLNs [16]. However, the same prognostic effect can be expected in case of micrometastatic positivity of nSLNs. To the authors' knowledge, few publications do not give answers to the question about the actual value of ultrastaging of nSLN(s) in case of negative SLN(s) [18-25]. Only in three of them it was revealed that by negative SLN(s) we have to reckon with positive nSLN(s) in contrast to the results from the remaining studies [19,24,25]. In these studies the assumption of concordance between SLN(s) and nSLN(s) in terms of metastasis (including micrometastasis) is real. It is also not clear how many benefits may appear as a result of further detailed examination nSLN(s) after finding metastases in the SLN(s). Obtaining information about the entire nodal basin depending on the stage of cancer and possible factors modifying metastasing can only give a reliable answer about the potential of metastases in CC and the significance of "micrometastatic nodal disease". Currently, if you don't check the status of micrometastases in all lymph nodes on a ultrastaging basis, it cannot be stated in which patients with metastases to SLNs they are the only one metastatic site.

Tumor localization

Intracervical localization of tumor and its impact on the labeling of the SLNs has not been tested in accordance with our knowledge. It is possible; that localization of tumor is responsible for more specific drainage, i.e., tumor of anterior part of the cervix drives potential metastases to external iliac lymph nodes only (see "Routes of metastasing").

Tumor size

It has been shown, among others, the considerable sensitivity in the detection of metastatic lymph nodes by SLNC and for the first time indicated a higher degree of complexity of the technique when the tumor does not exceed 2 cm in diameter [26]. This was later confirmed in a multicenter study of the German Gynaecological Oncology Working Group (*Arbeitsgemeinschaft Gynäkologische Onkologie*, AGO), with the clinical suggestion that patients may benefit from SLN biopsy in CC FIGO stage IB1 ≤ 2 cm [27]. It should be emphasized that some authors suggest a limit of tumor size to 3 cm as a limit of usefulness of the SLN method. It is associated with a loss of drainage due to inaccurate injection of the cervix, and higher risk of occult metastases at a greater tumor. However, some authors deny the importance of tumor size by claiming it as an unreliable factor, and recommend employment of SLNC in patients with any stage of cervical cancer. Such an approach presents Cibula et al. based on a study of large number of patients [28]. In studies where SLNC was tested, a term of "low risk tumor" was implemented, which referred to the risk of lymph node metastasis, and associated with the tumor of specific morphological and histological features [29]. It can be recommended less individual adjusted or even routine SLN approach rather than assuming that the patient with tumor greater than 2-3 cm is not suitable for SLN biopsy because SLNC may bring only benefits in terms of staging improvement.

Routes of metastasing

It is difficult to reliably predict the pathways of spreading the metastases of CC. The nodes, regarded as sentinel and negative, may in fact be non-sentinel because of a number lymph routes and inability to detect them all. There are alternative routes of lymph flow, leading to the identification of nSLN or a lack of identification of any node. However, giving the dye/radiocolloid or other medium in 4 quadrants of the cervix is not always possible for technical reasons what is also a tumor-related issue. Such application would provide coverage of marking the lymph channels in 4 directions i.e. through lateral parametria to external iliac, interiliac and obturator lymph nodes (main routes), through the vesicouterine ligament to the external iliac lymph nodes (anterior route) and through the sacrouterine ligament to common iliac, sacral and para-aortal lymph nodes (posterior route) [30]. Detection of SLNs in infrequent locations is believed to improve the staging when compared to a situation of removal of the lymph nodes according to routine protocol [31].

The presence of enlarged or metastatic lymph nodes

Metastatic as well as enlarged nodes may be bypassed by the tumor cells migrating *via* collaterals lymph routes. Researchers dealing with the problem of abnormal lymph nodes (studies performed on smaller groups of patients) remain consistent that enlarged lymph nodes may hamper and falsify SLN identification- SLNs close to large tumors may not be stained, or not really sentinel ones will become stained [29]. For example, large lymph nodes cause penetrating of the mark into the parametrium which entails an identification of nodes localized there (nSLN) [32].

"Immunological cadavers" and skip metastases

We know from gynecological pathology that pelvic lymph nodes often represent changes in form of fatty degeneration as a result of a use or frequent stimulation of the immune-related inflammatory processes in the pelvis. This results in the presence of inactive nodes ("immunological cadavers"). Critics of the SLNC in CC underline a difficulty in predicting cervical metastasis routes, due to changed functionality of the lymph nodes. This route may have been changed during life of the individual. There is known a phenomenon of lymph node inactivation or skip metastasis, which increase the number of false negative results [33,34]. Low radiotracer uptake and more frequent detection of in-transit metastasis were observed more frequent in elderly than in young patients in studies on SLN in skin melanoma, therefore we may expect similar dependency in CC [35].

The number of SLNs that should be resected

However, in order to state the reliably of the status of SLN metastasis, it seems that a number of them should be examined. This number is not known, however for breast cancer it is suggested to remove of up to 5 SLNs, and the ones being doubtful in palpation [36,37]. The removal of the nodes on both sides of the pelvis is essential to maintain the SLNC sense, due to the fact that CC is a midline tumor [28].

Technique and Settings

Both SLNB technique itself and decision about treatment based on it, are a subjects of certain risk of making mistakes. Wrong or deficient diagnosis and disease evaluation may result from the technique imperfections, human errors resulting from insufficient experience in this method, and too far-reaching conclusions drawn from SLN evaluation performed during or after surgery only on nodal fragments detected by staining. Such situation may take place mainly in the context of surgery relevancy or adjuvant treatment (mainly irradiation). Percentage of possible micrometastasis detection during intraoperative examination may be as low as 33% [38], sensitivity- 20% (underestimation is caused by the presence of isolated tumor cells, ITC) [39]. However, some authors obtain much higher diagnostic results, close to 100% [3]. It is estimated that 4-15% are micrometastates within lymph nodes specified "negative" in routine examination [13,14]. Ultrastaging, besides precise SLN evaluation, may become inevitable and recommended procedure in routine clinical practice. The main and universal targets for the use of this method may be optimal staging, enabling to determine the range of nodal lymph surgery and the range of radiotherapy. Another benefit from using SLN (and nonSLN) procedure may relate to more advanced (than limited to cervix) stages of cancer [40].

Perspectives

The questions above may be answered by examining all the lymph nodes according to operational indications, by means of sentinel node biopsy and checkup of remaining nodes. All lymph nodes may be subjected to ultrastaging with immunohistochemical histopathological techniques. The subject has a practical background, due to increasing number of women opting for not necessarily radical treatment. This also applies to operations within lymph nodes, taking into account possible complications and social effects of physical and mental burden for the patient. Positron emission tomography or other functional imaging studies may replace histopathology in the future [41]. Maybe it can get out of the blind alley of lack of time for appropriate assessment and uncertainty in node status, which in part contains nonfunctional or unexamined lymph nodes.

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