



## Cervix Cancer Management and Challenges in Coming Years. How to Deal After FIGO 2018 Staging Update, SENTICOL I-II and LACC Studies Results?

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As the 4<sup>th</sup> most common cancer and the 4<sup>th</sup> cause of cancer death in women in the world, Cervix cancer still occupy an important part of oncological centers activity and has benefited from several changes in its Management over the past 4 years.

Cervix cancer is classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system, which has been updated in 2018 [1]. It established, in addition to physical examination, information obtained from imaging modalities. The new FIGO cervix staging is more based on MRI as a method of accurately measuring tumor size and detecting parametrial involvement. Also, the inclusion of lymph node detection, thanks to special imaging in fluorodeoxyglucose PET/CT, has an increasing role in the detection of nodal disease. In addition, lymph node status in final histology can upstage the patient [2].

The main changes of the former 2009 FIGO concerns the stage IB, which became divided into three size range criteria (IB1 < 2 cm, IB2 ≥ 2-4 cm, and IB3 ≥ 4 cm) and the inclusion of nodal disease (pelvic (IIIC1) and para-aortic (IIIC2) nodal disease) as a new stage IIIC. In addition, stage IA tumors are now defined by depth only. The width is totally excluded [1]. This modification was very criticized after because of the possibility of mismatch between stage IA2 and IB stages.

The changes were implemented in order to better estimate patient survival and to better guide management. Augmentation in 5-year overall survival (OS) and disease-free survival (DFS) have been noticed in several validation trials [3,4]. In the De Gregorio et al. study [3], 146 from 265 totally patients (55%) patients were reclassified into a higher FIGO stage. The main changes were in stage IB and from any stage to stage IIIC1, show this improvement to be statistically significant [3]. In the Ding-Ding Yan et al. study, out of 662 patients, 361 (54%) was upgraded. Survival of stage IIA1 pa-

tients was higher than stage IB3 patients. DFS and OS in stage IIIC1 was not homogenous, depending on the number of positive pelvic lymph nodes (PLNs) [4].

Despite the many contributions of this new classification, particularly regarding early staging (better staging) and lymph node involvement, some controversial issues remain unresolved, such as the definition of the size of parametrial involvement, ovarian metastases, and lower uterine segment extension.

2018 was also marked by a mini- revolution in early-stage cervical cancer surgery: the publication of the LACC study (prospective study of 740 patients) by Ramirez et al. It concluded that minimally invasive radical hysterectomy was associated with lower rates of DFS and OS than open abdominal radical hysterectomy among women with early-stage cervical cancer [5]. This study led to changes in practice patterns and change in guidelines in many scientific societies, such as ESMO/ESGO and NCCN [6,7]. On the other side, it was also considered as a regrettable "return in past" by many Gynecologists surgeons. Thus, many studies tried to reconsider the results of the LACC [8-10].

In fact, if we carefully analyze at the large literature data available, wondering if minimally invasive surgery can still be considered remains appropriate. Spillage of tumor cells in the peritoneal cavity under CO<sub>2</sub> insufflation seems to be the main responsible for the noticed harmful effect for Mini-Invasive Radical Hysterectomy (MIRH) [9,10].

Many retrospective studies suggest that less contact between tumor and peritoneal cavity is highly recommended (conservation lymph nodes excision, no uterine manipulators use, vaginal closing of the vagina cuff) [10,11]. Tumor volume seems also to be a main predictive factor, associated to a higher risk of tumor dissemi-

nation, especially if the preventative procedures pre-cited are not done [8-10].

However, according to these studies, minimally invasive surgery remains the technique of choice for the Sentinel Lymph Node (SLN) mapping procedure in patients who will benefit from Fertility Sparing Surgery (FSS). Other possible indications of this technique are patients with a previous cervical conization requiring an additional radical hysterectomy (RH) and in those with a tumor of less than 2 cm when surgery is scheduled at a reference centers. All these data are still preliminary, as there are no prospective studies yet, and patients should be informed of it. The final decisions belongs, of course, to the patient.

Other big changes in the cervix cancer management was the introduction of SLN technique in the management of the early-stages.

Until the end of 2010 decade, SLN biopsy in early cervical carcinoma remained unclear. The results were equivocal because of differences in the protocols of lymph node mapping protocols (type and number of tracers used, use of lympho-scintigraphy), histopathological analyses (number of sections, use of immunohistochemistry [IHC]). In addition, these studies were not multicenter and the evaluation criteria differed from one center to another.

In 2011, The SENTICOL (Ganglion Sentinelle dans le Cancer du Col) was published. It was a multicentre prospective randomised controlled trial including adults with cervical carcinoma for stage IA1 with lymphovascular space invasion to stage IB1 FIGO 2009 stages (< 4 cm). Technetium-99 lymphoscintigraphy combined with patent blue injection, followed by a laparoscopic lymph node mapping, SLN removal, and lymph node dissection were performed in 139 patients. The main purpose of this study was to evaluate the diagnostic accuracy of a standardized LNS biopsy technique in patients with early cervical cancer. The principal elements analyzed were the sensitivity and Negative Predictive Value (NPV) of SLN biopsy by using histologic examination of a full lymphadenectomy specimen as the reference standard. Describing SLN locations, determination the rate of micrometastases and Isolated Tumor Cells (ITCs) in SLNs and the rate of adverse events related to SLN biopsy were the second line aims. The principle conclusion was that the combined technique for node mapping was associated with high rates of SLN detection and with high sensitivity and NPV for metastasis detection. The only condition for the acceptance of the results

is when SLNs are detected bilaterally [12].

Thus, SENTICOL I confirmed that SLN identification has important advantages including a low rate of false-negative rates. The other advantages are as follows: identification of possible ectopic metastatic SN due to aberrant lymphatic drainage, identification of a limited number of nodes sent for frozen section assessment during surgery and the ability to provide more precise information, such as detection of micrometastases or ITCs. These results helped to establish more adapted recommendations for adjuvant treatment [13,14] and therapeutic algorithms as the MSKCC SLN algorithm [15] (Figure 1).

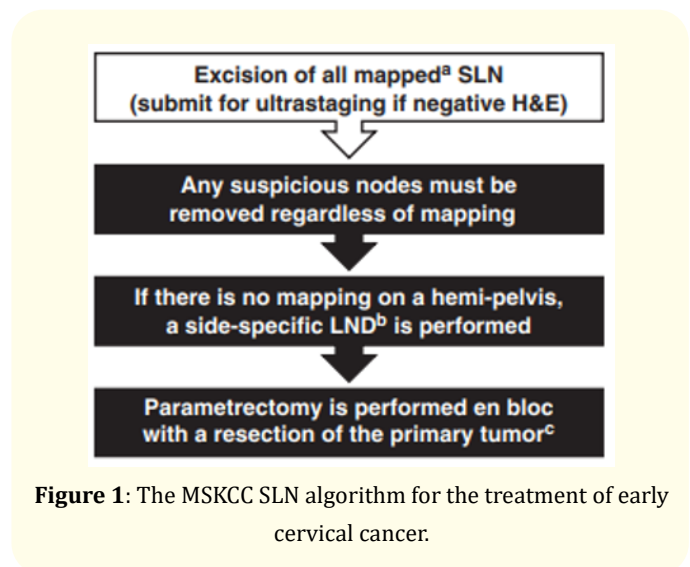


Figure 1: The MSKCC SLN algorithm for the treatment of early cervical cancer.

Pelvic Lymphadenectomy Dissection PLND is known to give several intraoperative (haemorrhage, ureteral and nerve lesions), and postoperative complications (lymphocyst or lymphedema). The number of nodes removed is likely to be the cause of these consequences [16]. Another important consideration for carriers of early cervical cancer (mostly young women) is quality of life. For all these problems, a prospective study evaluating early and late complications was mandatory.

The SENTICOL II study was designed as a multicentre prospective randomised controlled trial comparing SN resection alone to SN resection and PLND in early cervical cancer patients in aim to compare the morbidity, quality of life, and 3-year follow-up between women undergoing radical lymphadenectomy and women

who didn't (both groups having negative SLN) [17]. The protocol included a frozen-section evaluation of the SLN and, in the case of negative frozen-section assessment, a randomization between full pelvic lymph node dissection or SLN biopsy only. A total of 206 patients were randomized: 101 patients were allocated to the complete pelvic lymphadenectomy group (arm B) and 105 were assigned to the group "SLN alone" (arm A). No false negative case of the SLN biopsy was identified in arm B. The surgical morbidity related to the lymph node dissection was significantly reduced in arm A: 33 cases (31.4%) versus 52 cases (51.5%) in arm B ( $P = 0.0046$ ). Major morbidity related to the lymph node dissection was also reduced: 1 case in arm A versus 6 cases in arm B ( $P = 0.06$ ). The analysis of the quality of life (SF36) questionnaires demonstrates that there are significantly lower scores for the arm B group. The analysis of legs lymphedema shows that there is always a difference between the two groups in the values of root and mid-tight perimeters, the arm A group having lower circumferences. Also leg heaviness and leg fatigue are significantly worse in the arm B group. As a conclusion of this prospective study, SLN biopsy alone induced less surgical morbidity, less lymphedema, and better quality of life than full pelvic lymph node dissection. This study leads to the morbidity sparing approach in cervical cancer treatment while omitting the full pelvic lymph node dissection if the SLN are negative.

Recent international guidelines were based on the results of the SENTICOL II study published in 2019 and now recommend performing SLN biopsy in addition to PLND. The lack of prospective evidence on long-term oncologic safety remains the missing element for SLN biopsy to become the Gold standard. Other unresolved issues include the low accuracy of intraoperative assessment of SLN status by frozen section and the impact of micrometastases on prognosis. We hope that the SENTICOLIII prospective randomized clinical trial will answer these questions.

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