



Published: May 31, 2022

Citation Bravo E, Cartagena J, et al., 2022.

Intraoperative Detection of Lymph Nodes Metastasis in Early-Stage Cervical Cancer, Medical Research Archives, [online] 10(4).

<https://doi.org/10.18103/mra.v10i5.2796>

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DOI:

<https://doi.org/10.18103/mra.v10i5.2796>

ISSN: 2375-1924

RESEARCH ARTICLE

Intraoperative Detection of Lymph Nodes Metastasis in Early-Stage Cervical Cancer

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ABSTRACT

The treatment of early-stage Cervical Cancer consists of Radical Surgery or Radiochemotherapy, both with similar outcomes. Surgical treatment is preferred in young patients to preserve ovarian and sexual function. The combination of both therapies significantly increases risk of complications, so combined treatment should be avoided. Lymph node metastasis is a negative prognosis factor in these patients, forcing adjunctive therapy (radiochemotherapy), therefore, intraoperative metastatic node evaluation is crucial to avoid combined treatment. The present communication analyzes a cohort of patients undergoing radical surgery, with special emphasis on the detection of tumor nodes during lymphadenectomy prior to hysterectomy. Of a total of 170 patients undergoing surgery for early-stage Cervical Cancer, 26 patients (14.1%) had lymph node metastasis, 19 (73%) detected during the surgical act (lymphadenectomy) in contemporary biopsy and 7 (27%) in the postoperative period through final histology. In 12 patients, lymph node involvement is obtained through the sentinel lymph node, intraoperative 9 and 3 in final node biopsy reported as negative in contemporary biopsy. The remaining 10 intraoperative diagnoses were made in the contemporary biopsy due to macroscopic suspicion of tumor involvement. In this case series, the contemporary biopsy of the macroscopically suspicious nodes and sentinel lymph nodes, allowed intraoperative detection of 73% of patients with metastatic node, which spared this group of patients from receiving combined treatment with the consequent increase in risk of complications.

Keywords: Cervical cancer, metastatic lymph node involvement, contemporary biopsy, sentinel node, macroscopic suspicion.

Introduction

In early stages of cervical cancer (IA1 with lymphovascular space invasion, IA2, IB1 and IIA1), the standard treatment is Radical Hysterectomy or Radiochemotherapy, both with similar outcomes. Surgical management is preferred in young patients, since it allows the preservation of ovarian function, as well as sexual function. In surgical treatment, pelvic lymphadenectomy is considered as part of surgery, since the lymphatic system is the main route of spread, as well as the most important prognostic factor for the disease, with survival falling from 95% to 50% at 5 years when there is metastatic lymph node involvement¹, which forces to apply adjuvant therapy. The presence or absence of lymph nodes metastasis provides important information about the prognosis and allows decisions to be made regarding treatment.²

The combination of both therapies, imply a higher incidence of morbidity and the new ESGO / ESTRO / clinical guidelines/ESP indicate that the key objective is to avoid the combination of radical surgery followed by pelvic radiation therapy. Therefore, the images (MRI, CT scan, and ultrasound), as well as intraoperative evaluation of sentinel lymph nodes and nodes with macroscopic suspicion of metastatic compromise should be the first step in surgical management.^{3,4,5} Images have a limited role in the evaluation of lymph node metastases, especially micrometastasis (between 35% for CT, 55% MRI and 75% PET CT)⁶. If a positive node is detected for metastasis, the surgical procedure should be abandoned, previous lumboaortic nodal sampling in order to extend the radiation field if it's positive in final histology, and the patient should be referred for radiochemotherapy. The objective is to reduce the serious complications derived from the combined treatment.

The incidence of lymph node involvement increases with the FIGO stage. In early stages, it is estimated in around 15% of cases (up to 27%)⁷. In patients with pelvic lymph node involvement, around 40% have metastases to nodes in the lumboaortic territory with a greater compromise of their prognosis, which forces the radiation field to be extended.

The role of micrometastasis in cervical cancer as is not defined with certainty as it is in breast

cancer in that the prognosis of micrometastases does not have the same impact on survival.^{8,9} However, some studies indicate that the prognosis for metastatic involvement due to micrometastasis worsens the prognosis for both disease-free survival and global survival⁸.

The sentinel lymph node has emerged as an alternative to Systematic Lymphadenectomy in order to avoid complications of a surgical procedure of great magnitude and different techniques have been described with different results⁷ It is important to emphasize that there is no evidence that provides cancer safety to replace systematic lymphadenectomy with the study of the sentinel node. A greater number of prospective studies are required, since most of them are retrospective and combine sentinel node biopsy with systematic lymphadenectomy, and also, they use different ganglion processing protocols.^{10,11} A protocol that allows patients to be referred to radical hysterectomy or radiochemotherapy in one step is very limited, this due to the high number of false negatives in the intraoperative biopsy of the sentinel lymph node, about 50%, especially micrometastases and isolated tumor cells.¹⁰

The aim of this study is to describe the experience for detection of lymph node metastases in cervical cancer in early stages, both intra and postoperative, micro and macrometastasis, as well as survival for each group.

Descriptive statistical analysis and Kaplan Meyer, statistical significance test Xi2 re

Material and Method

Between April 2008 and November 2018 at Gustavo Fricke Hospital, patients with early-stage cervical cancer (IA1 with lymphovascular space invasion, IA2, IB1 and IIA1 according to the FIGO 2009 classification) and in which laparoscopic pelvic lymphadenectomy was required as part of their surgical management were recruited continuously and prospectively. This group includes Vaginal Radical Trachelectomies, Vaginal Simple Hysterectomies, and Vaginal Radical Hysterectomies, all surgeries assisted by Laparoscopy and without suspicion of metastatic lymph node involvement in preoperative imaging. All patients obtain informed consent at the time of surgery. In all of

them, Sentinel Node is performed with Patent Blue injection in the cervix, 4 cc, 1 cc per quadrant prior to surgery. Surgical intervention begins with the search for the sentinel lymph nodes and Laparoscopic Systematic Pelvic Lymphadenectomy. The nodes marked with patent blue, as well as those macroscopically suspicious nodes of metastatic compromise, were sent to frozen section assessment. When any pelvic node was reported positive for metastasis, pelvic surgery including lymphadenectomy was discontinued, and, the same laparoscopic route performed lumboaortic nodal sampling performed, in order to extend the field of radiotherapy if they show tumor involvement. When it was not possible to extend the surgery to this region for technical reasons, subsequently a PET-CT was performed to detect lumboaortic lymph node metastasis. The pathological study of the sentinel node or suspicious nodes in contemporary biopsy consists in: the nodes are sectioned into halves, taking imprints (cytology) from both section surfaces and allocating one of the halves to freezing and cutting by cryostat. While the tissue freezes, Pap smears are stained (fast method), examined by a cytotechnologist, and then referred to the pathologist for diagnosis. The pathologist then examines the freezing cut that has been stained with the Hematoxylin Eosin method (accelerated procedure) and makes a diagnosis. In case of agreement (negative cytology - negative biopsy for malignancy, or positive cytology - positive biopsy for malignancy, the pathologist informs the surgeon, leaving due record of it. In case of disagreement (positive or suspicious cytology - negative biopsy, and vice versa), the frozen section is repeated. If the disagreement persists, the surgeon is informed (for example, positive cytology - negative or inconclusive biopsy). The same applies to unmarked but macroscopically suspicious nodes. The procedure takes about 15 to 20 minutes on average.

Multiple nodes (3 or more) and macroscopically suspicious nodes are also section into halves, imprints are taken of all of them, and larger nodes are sectioned at 3 mm intervals.

Once the procedure is finished, the frozen piece is rescued, it is attached to its other half and they are processed for deferred histopathological study: fixation in 10% buffered formalin%, inclusion in paraffin and cuts in rotation

microtome, making cuts in 3 different levels separated by 50 microns from each other, reserving intermediate cuts for complementary techniques, if they become necessary (histochemical, immunohistochemical or other).

The diagnosis of deferred cuts are the "gold standard" required for freezing cuts (with very rare exceptions; example, sample exhaustion) and includes number of nodes studied versus involved, extranodal extension, size of metastases, considering those less than 2 mm as micrometastasis.

Pathological study of the sentinel nodes or suspicious nodes in contemporary biopsy is performed with three cuts, cytological imprint, and freezing. Deferred study is done based on cuts every 50 microns and eventually Immunohistochemistry. Clinical and pathological factors are analyzed from this group of patients, as well as global and disease-free survival.

Results

Of 170 patients undergoing surgery for early-stage Cervical Cancer in the study period, 12 Radical Trachelectomies, 11 Simple vaginal hysterectomies for low-risk small cervical cancer and the remaining 147 correspond to Laparoscopy-assisted Vaginal Radical Hysterectomies. All of them with Laparoscopic Systematic Pelvic Lymphadenectomy and a contemporary biopsy study of sentinel nodes or nodes with macroscopic suspicion of metastasis. 87% of patients achieve sentinel node labeling with Patent Blue injection in this series.

26 patients (14.1%) had a metastatic pelvic node, 19 (73%) investigated during the surgical act (lymphadenectomy) in contemporary biopsy, and 7 (27%) in the postoperative period through final histology. In all of them, the preoperative study with images (ultrasound, CT and MRI) were negative for metastatic suspicion.

Average age 43 years (22 - 61), 3 / 26 are previously conized. Average days of stay 2.4 days (1 - 6). In eight patients, annexes are preserved and the ovaries are suspended laparoscopically. Histological type, 21 (81%) Squamous carcinoma, 4 (15.4%) Adenocarcinomas and 1 (3.6%) Adenous squamous carcinoma.

In 12 patients, lymph node involvement is obtained through the sentinel node,

intraoperative in 9 and 3 in final histology reported as negative in contemporary biopsy. The remaining 10 intraoperatively diagnosed was made in contemporary biopsy due to macroscopic suspicion of tumor involvement. (Box 1)

In 17 of the 19 patients in whom surgery is discontinued, laparoscopic lumboaortic nodal sampling is performed. In the remaining two, PET-CT is performed to evaluate the lumboaortic nodes due to technical difficulty in performing lumboaortic lymphadenectomy during the surgery. The average lumboaortic nodes obtained is eight (2 - 16). In four (21% of the patients with lumboaortic nodal sampling), a lumboaortic lymph node involvement was found, so the radiotherapy field was extended to that region.

All patients undergo pelvic radiochemotherapy. Brachytherapy in those patients in whom surgery is abandoned and lumboaortic extension of the radiotherapy field in those patients with lumboaortic lymph node metastatic involvement.

In 12/26 patients (46.2%) the lymph node metastatic involvement is a micrometastasis, (Box 2), 6 intraoperative and 6 postoperative (deferred biopsy). Of the 7 patients in whom the diagnosis of lymph node involvement is made in

the postoperative period, one is macrometastasis. The remaining six are micrometastases. Three of them are found in the sentinel node where the contemporary biopsy had been reported as negative. No isolated tumor cells were found in this series.

Two patients with surgical complications, a laparoscopic repaired bladder injury and a pelvic lymphocele that was resolved by transabdominal puncture are presented.

Regarding complications of radiotherapy, 4 patients present it, a post-brachytherapy ureteral obstruction, a surgically resolved intestinal subocclusion, chronic edema of the left lower limb and a pelvic abscess that must be operated on.

Of the total number of patients 3 die, one of them with lumboaortic lymph node involvement and a recurrence in a patient who discontinued radiation therapy due to intolerance. The third recurrence after complete treatment.

Follow-up was performed every 3 months for the first 2 years, every 6 months for the next two years and then annually.

The overall survival of the 26 patients with a positive node is 88.5% at 5 years, with a median follow-up of 60 months.

Survival Functions

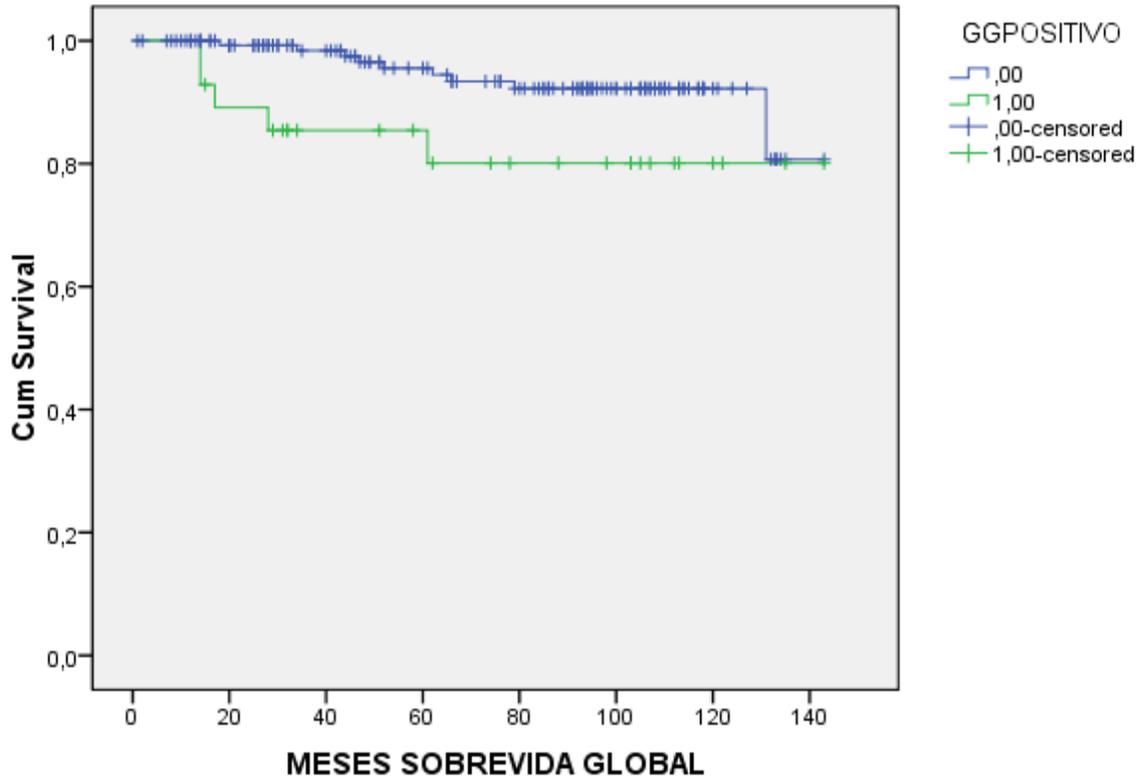


Image 1: N 170, global survival 95% vs. 88.5% at 60 months of follow-up, p 0.034, progression-free survival with similar difference, but with p greater than 0.05, Not significant and not graphical.

Overall survival is significantly less in patients with a positive node. However, in this series, for disease-free survival, it is not.

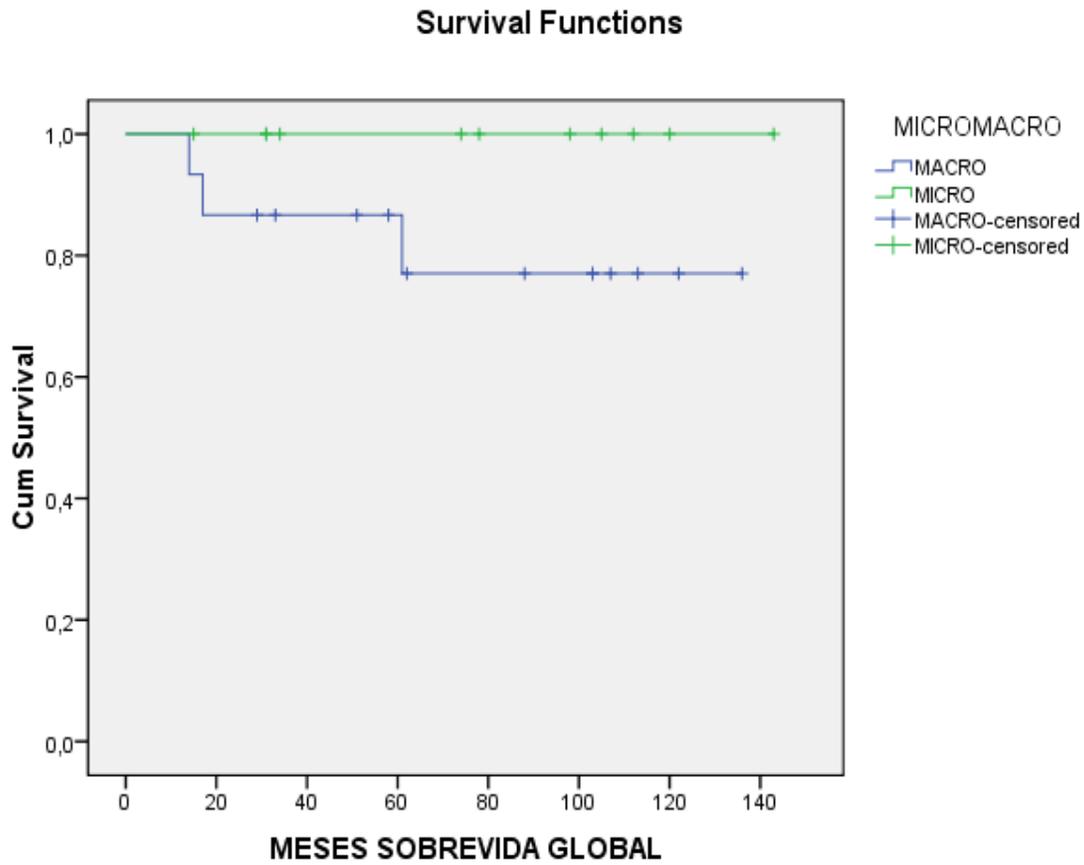


Image 2: N 26, overall survival 100% vs 75% at 60 months of follow-up, without events in microscopic compromise group, p greater than 0.05, similar difference for progression-free survival, p greater than 0.05 not plotted.

Overall and disease-free survival according to lymph node micro or macroscopic involvement is less for the latter, but without statistical significance at 5 years with a 60-month follow-up.

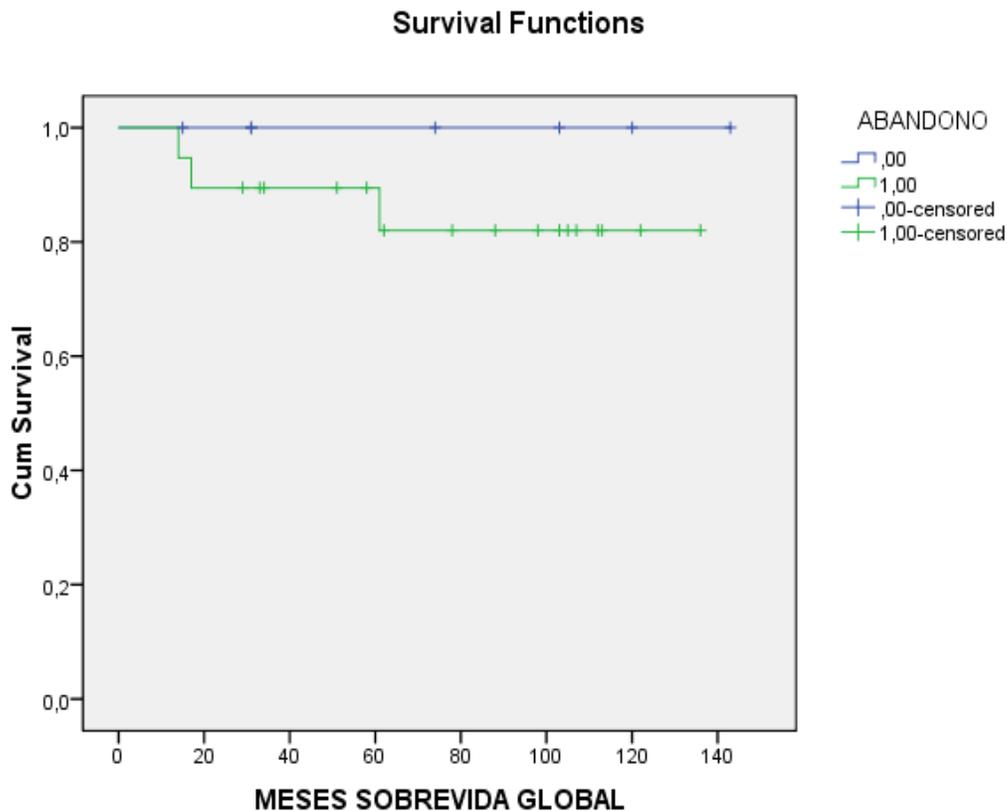


Image 3: N 26, overall survival 100% vs 80% at 60 months of follow-up, p greater than 0.05. Similar difference for progression-free survival, p greater than 0.05 not plotted.

Both overall and disease-free survival is greater for the group with detection of intraoperative lymph node involvement and suspension of surgery, but without statistical significance.

Discussion

Lymph node involvement is the most important prognostic factor for cervical cancer and requires rigorous management, since recurrence and mortality is very high and failure to detect nodal involvement can be fatal for the patient.¹⁰ In the present casuistry, overall survival is significantly less for patients with metastatic nodal (overall survival 95% vs. 83% at 60 months of follow-up, p 0.034). Patients, who have lymph node involvement, require postoperative adjuvant radiation therapy, and treatment of the primary tumor with any modality (surgical or radiant) provides similar outcomes at this stage of the disease. Lymph node assessment is of great importance to determine the most appropriate treatment for patients with early-

stage cervical cancer, since a positive pelvic node requires chemoradiotherapy rather than radical surgery.¹² However, combined treatment involves a greater number of complications, fistulas or stenoses, which should be avoided. These types of complications are due to adjuvant radioterapy after distal ureters, bladder and rectum have been surgically dissected. Therefore, intraoperative detection of lymph node metastases in patients with early-stage cervical cancer is highly desirable and convenient, avoiding undergoing unnecessary radical hysterectomy and combined treatment that will increase complications. Intraoperative lymph node evaluation is an opportunity to identify patients with lymph node involvement before further radical surgery.^{3,4,5,13}

Pre-treatment lymph node status is primarily assessed by computed tomography (CT), magnetic resonance (MRI), and/or positron emission computed tomography (PET/CT). Detection of lymph node metastases by imaging has low sensitivity, due to the limitations for detecting small lesions. CT 31 to 57%, MRI 37 to 55% and PET/CT 72 to 75% for clinically visible tumors.^{6,13,14}

The present study aims to communicate lymph node management in patients with early-stage cervical cancer, in whom systematic pelvic lymphadenectomy was performed laparoscopically, complementing the sentinel node technique, with the macroscopic suspicion of lymph node metastasis. The combination of both, allowed us to detect 73% of these cases in the same surgical act, avoiding combined treatment in these 19 patients (radical surgery + radiochemotherapy). The publications show figures that generally do not exceed 50%, since most of them are based only on the detection of sentinel nodes, which usually leaves much of micrometastasis undiagnosed.¹⁰ In fact, 12 of 26 patients have micrometastases, 6 of 19 detected intraoperatively through the sentinel node. On the other hand, it is worth noting the high detection of lymph nodes metastases due to macroscopic suspicion, since of the seven cases in which the investigation was carried out in the postoperative period, only one case had a macrometastasis. The remaining 6 were micrometastases, 3 of them in the sentinel node not detected during lymphadenectomy.

Another aspect to highlight in this casuistry is the detection of metastatic nodes by macroscopic suspicion, which allowed its identification in 13 patients intraoperatively, being searched in the postoperative period only one case.

The presence of micrometastasis in lymph nodes is an indication of adjuvant radiation therapy, according to the available evidence, which in retrospective studies shows a poor prognosis. The risk associated with isolated tumor cells is unknown due to their low prevalence and the unreliable detection even in ultrastaging.¹⁰ In our casuistry, 12/19 patients present lymph node micrometastasis, with 6 being detected in sentinel node during the surgical procedure. The remaining 6 are detected in final histology, 3 of them in sentinel node reported as negative in contemporary biopsy. The other 3 were found in

non-sentinel nodes in the postoperative biopsy, with the sentinel nodes of these patients being reported as negative for metastasis. In our casuistry, global and disease-free survival is greater for microscopic involvement over the macroscopic (100% versus 75% at 60 months of follow-up), but without statistical significance. There were no isolated tumor cells in this series.

Several publications have shown that intraoperative sentinel node analysis is not very sensitive in identifying lymph node involvement. Prospective French SENTICOL was unable to identify intraoperative metastases in 15 of 20 patients, 12 micrometastasis, and 3 macrometastases.¹⁵ In a Canadian study of 211 patients, 10/13 cases with positive nodes were false negatives in contemporary biopsy, 9 micrometastasis and 1 macrometastasis.¹⁶ Slama in its publication of 225 patients, correctly detects nodal involvement intraoperatively in 56% of cases (41/73) and a significant proportion of macrometastasis (16.7%, 8/48) were not detected intraoperatively, but in the final ultrastaging.¹⁷

In a study of 102 patients with early-stage cervical cancer, 12 of 20 (60%) of the cases with micrometastasis or ITC were not detected in the intraoperative evaluation.¹⁵

Therefore, triage for radical hysterectomy or radiochemotherapy in one-step is limited due to the high rate of false negatives in the intraoperative evaluation of the sentinel lymph node, mainly related to micrometastasis and ITC detection. This intraoperative evaluation allows detecting around 50% of the positive nodes for metastasis, the majority being macrometastasis; it has a poor diagnostic value.¹⁵

Some pathologists make more cuts (these may increase the accuracy of intraoperative sentinel node examination) or adjust the number of cuts to the lymph node size. However, there are no standard protocols for node processing in frozen biopsy, and information on this is very limited.^{12,17} The sentinel node processing technique in the frozen biopsy used in our patients incorporates a greater number of cuts, which allows the investigation of a greater number of small micrometastases and macrometastases.

Sentinel node biopsy has been described with the aim of avoiding systematic lymphadenectomy like in breast cancer and

vulvar cancer, but in cervical cancer, the procedure is not safe and reliable enough as shown by different studies,^{18,19,20,21} even less during the intraoperative period. In our study, 3 patients show false negative. However, its application and usefulness in order to investigate lymph node metastases intraoperatively, avoiding duplication of treatment and thus reducing the complications derived from it, it becomes important if it is complemented by the study by frozen biopsy of the macroscopically suspected nodes of metastatic compromise.

Because frozen biopsy does not detect about 50% of nodes metastases, the primary goal of sentinel node mapping (avoiding unnecessary lymphadenectomies when the sentinel node is negative in intraoperative biopsy) is not achievable in all cervical cancer patients in early stage, as noted above, unless the sentinel node processing technique improves. Unfortunately, ultrastaging in rapid biopsy is not currently feasible. As processing techniques improve metastasis detection and better results are obtained, this goal can be achieved.¹⁶ Sentinel node biopsy alone is not yet recommended without systematic pelvic lymphadenectomy for lymph node staging for early-stage cervical cancer except in the context of prospective clinical trials.⁶

There are three ongoing prospective clinical trials to assess the oncological outcomes of sentinel lymph node biopsy in early-stage cervical cancer: the SENTIX trial, the PHENIX trial and the SENTICOL III trial.

The SENTIX trial (NCT02494063) is a prospective multicentric observational trial, which aims to evaluate whether a less radical surgical approach with sentinel lymph node biopsy is non-inferior to treatment with systematic pelvic lymphadenectomy. Primary outcome measure is recurrence rate at 2 years of follow up.²²

The PHENIX trial (NCT02642471) is a randomized controlled trial to determine

whether pelvic lymphadenectomy can be replaced by sentinel lymph node biopsy in surgical treatment for patients with early-stage cervical cancer. This study comprises two parts: PHENIX-I: To compare the outcomes of managements with and without pelvic lymphadenectomy for patients with negative sentinel lymph node (2-year disease free survival); PHENIX-II: To compare the outcomes of managements with and without pelvic lymphadenectomy for patients with positive sentinel lymph node (3-year disease free survival).²³

The SENTICOL III trial is a prospective multicenter international randomized study designed to validate the Sentinel Lymph Node mapping technique in early cervical cancer. This study will compare 3-year disease free survival of patients with negative sentinel lymph node alone vs patients with negative sentinel lymph node with pelvic lymph node dissection.²⁴

Conclusion

In our patients, the combined use of sentinel lymph node with patent blue and performing a greater number of nodes sections in the frozen biopsy, added to the contemporary biopsy study of macroscopically suspected nodes, allowed intraoperative detection of 73% of patients with metastatic lymph nodes, which spared this group of patients from receiving combined treatment with the consequent increase in risk of complications. To this, we add the possibility of evaluate laparoscopically the lumbaortic retroperitoneum, investigating metastatic nodes in this region, with which it is possible to extend the field of radiotherapy exclusively to those patients who require it.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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BOX 1

TOTAL POPULATION: 170 Patients with Pelvic Lymphadenectomy and Sentinel Lymph Node
Of these: 147 Assisted Radical Hysterectomies (Op Schauta)

12 Vaginal Radical Trachelectomies

11 Assisted Simple Hysterectomies

Lymph node metastasis: 26 (14.1%)
19 (73%) intraoperative 4 lumboaortic +
7 (27%) postoperative

Average age 43 years (22 - 61 years)

Histological type: Squamous carcinoma 21 (81%)
Adenocarcinoma 4 (15.4%)
Adenous squamous carcinoma 1 (3.6%)

BOX 2

Sentinel Node Metastatic: 12
9 intraoperative
3 postoperative

Macroscopically suspected nodes metastatic 10 (intraoperative)
Metastatic non sentinel postoperative 4

Intraoperative TOTAL 19 (73%)
Postoperative 7 (23%)

Micrometastasis

Metastatic nodes 26 : Micrometastasis 6 Intraoperative
6 Postoperative

Macrometastasis 13 Intraoperative
1 Postoperative

Micrometastasis 12
Sentinel Lymph Node 9
No SentinelLymphNode 3