

The sentinel node in pelvic gynaecological tumors: an updated view

Summary

The sentinel lymph node (SLN) refers to the first lymph node susceptible to being affected, due to the lymphatic drainage of a primary tumor. The lymph node involvement in cancer patients is one of the main prognostic factors. Without affecting the prognosis at any time, the SLN seeks to reduce the morbidity associated with lymphadenectomy, reducing surgical time, reducing intraoperative and postoperative complications, such as lymphedema or neuralgia and costs associated with conventional surgery. Although its use has extensive experience in tumors such as breast, the SG in gynecological tumors is still in the early stages. With this review we intend to make a close and current view of the use of this technique in malignant tumors of the female genital tract.

Keywords: sentinel lymph node, gynecological tumors, indocyanine green, technetium-99m, blue dye, fluorescent real-time mapping

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Duro Gómez Jorge,¹ Zuheros Montes José David,¹ Rodríguez Marín Ana Belén,² Nieto Espinar Yolanda,³ Castelo-Branco Camil⁴

¹Department of Gynecology and Obstetrics, Reina Sofía University Hospital, Spain

²Department of Gynecology and Obstetrics, Hospital San Juan de Dios, Spain

³Department of Gynecology and Obstetrics, Hospital Universitario San Agustín, Spain

⁴Clinic Institute of Gynecology, Obstetrics and Neonatology-Hospital Clinic, Faculty of Medicine-University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Spain

Correspondence: Camil Castelo-Branco, Institut Clinic of Gynecology, Obstetrics and Neonatology, Hospital Clinic, Villarroel 170, 08036-Barcelona, Spain, Tel + 34 93 227 54 36, Fax + 39 93 227 93 25, Email castelobranco@ub.edu

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Introduction

The sentinel lymph node (SLN) refers to the first lymph node susceptible to being affected, due to the lymphatic drainage of a primary tumor.¹ Initially, it was implanted for penile cancer² followed by melanoma and breast cancer.³ The lymph node involvement in cancer patients is one of the main prognostic factors.

Regarding pelvic gynecological tumors, the first cancer in which it began to be implemented was for the vulva and has spread to cervical or endometrial cancer. Knowing the affectation or no ganglion besides not only will mark the prognosis⁴ determines, but also the adjuvant treatment in these patients. In addition, selective SLN biopsy is considered the strongest predictor of distant metastasis, particularly when its affectation is evaluated by immunohistochemistry with antibodies against the factor VIII or CD31-related antigen.⁵ Thanks to this, we will be in the habit of carrying out an adequate therapeutic strategy.

The implementation of SLN biopsy has among its objectives the reduction of morbidity associated with lymphadenectomy,⁶ the reduction of surgical time, the reduction of intraoperative⁷ and postoperative complications, such as lymphedema or neuralgia,⁸ as well as reducing the costs associated with conventional surgery. All this must be done without entailing a worsening of the prognosis of the target disease.

Although this technique has been accepted as an alternative to pelvic and para-aortic lymphadenectomy,^{9,10} it can be difficult to expose and understand by our patients, especially in cases in which it is associated with an increased risk of recurrence.¹¹ Perhaps these

patients are not willing to assume a higher risk at the expense of reducing the radicality of surgery, something that physicians are. It is a challenge on the part of the different specialists, to try to improve the results so that SLN does not reduce the treatment of oncological patients. For this, it will be essential to make an adequate selection of patients. Thus, we will increase our detection capacity in patients with early staging and lower tumor sizes.⁵ Before completely replacing the lymphadenectomy, ongoing controlled trials should explore and confirm the additional value of SLN biopsy in both perioperative morbidity and survival.¹² In this review, we intend to perform an update on the status of the sentinel node within the current gynecology.

Indications

In order to a certain tumor to be susceptible to SLN biopsy, it must follow a consecutive lymphatic drainage through a certain lymph node chain. In addition, there must be absence of disease at a distance and lymph node involvement both at the clinical level and in the imaging tests.¹³ Also, as a rule the disease should not be locally advanced.

In this way, SLN biopsy, whether by laparoscopy, laparotomy or robotic surgery, has proven to be feasible, efficient, safe and imitable.¹³ This technique SLN biopsy has been shown to be safe and feasible in several gynecological cancers such as vulvar cancer, cervical cancer and endometrial cancer.

Detection methods

There are different tracers used for the detection of SLN. Among them is technetium 99 (Tc99) or methylene blue (MB), with a detection of 66% to 86%. The most recent appearance is the use of

fluorescent matrices such as indocyanine green (ICG), whose use is increasing within the different protocols.¹⁴ ICG together with the near infrared fluorescence has gained a great utility with the advantage of providing real-time images during surgery. It is experimental, the use of carbon nanoparticles for labeling remains.¹⁵

The superiority of MB has been shown together with the tracer versus MB only.^{16,17} However, ICG has shown greater detection capacity than MB and Tc99m.¹⁸ In this prospective study by Holloway et al.,¹⁹ the ICG detected more SLN and more metastases than the MB and without safety problems.¹⁹ ICG has an excellent toxicity profile, with higher overall and bilateral detection rates compared to MB and higher bilateral detection rates compared to a combination of Tc-99m and blue dye.^{20,21} There are available studies that even underestimate the use of MB in favor of Tc99 or ICG.²² Given this, whenever possible, the use of ICG should be favored over the other tracers for SLN biopsy.²³

One of the variables to consider, is the time elapsed from the injection of the tracer until its detection. This period is related to the possible failure of intraoperative detection. Kushner et al. reported that the best time to detect sentinel lymph nodes with the MB was 30 minutes after the dye injection. 50 minutes after the injection the ICG could not be identified.²⁴ On the other hand, the ICG presents a good detection, from 5 to 60 minutes after its injection.²⁵ Taking into consideration the time in which the ICG should be detected, its real-time detection achieves better results with a higher bilateral detection rate.²⁶ In addition to the time elapsed, it is important to perform the injection of the tracer properly. There are different modalities depending on the type of tumor.^{27,28}

In addition to those mentioned, there are other factors that may affect the detection rate of the SLN and should be considered within the next protocols and studies. Among them and to highlight, the detrimental effect of body mass index (BMI) on ICG detection rates as a marker in obese patients.²⁹

Vulva

An adequate diagnostic and therapeutic strategy in the approach to vulvar cancer is essential due to survival is better when the treatment is rapidly established after diagnosis. The involvement of the inguinal or femoral nodes is the main prognostic factor.³⁰ In this article, we review the published data supporting the SLN biopsy as part of the standard treatment for women with early-stage vulvar cancer and discuss future considerations for the treatment of this disease.³¹

Adequate selection of patients with squamous cell carcinoma of the vulva is essential.³² The SLN biopsy in vulvar cancer should be limited to stages IB and II of the FIGO which they are unifocal tumors, less than 4cm and with clinical and radiological absence of lymph node involvement. This way, without affecting the prognosis, we achieved a reduction in operative mortality.³³ In 2008, the first Groningen international study on sentinel lymph nodes in vulvar cancer (GROINSS-V) demonstrated that the omission of inguino-femoral lymphadenectomy is safe in patients with early-stage vulvar cancer and negative SLN, simultaneously decreasing morbidity related to the treatment. There are sufficient studies that corroborate the viability, safety and reproducibility of SLN biopsy in these tumors.³⁴ Some of them, such as Slomovitz, show how SLN biopsy is associated with a better quality of life than complete lymphadenectomy, is more cost-effective than complete lymphadenectomy and achieves a better pathological evaluation.³²

Something to highlight in the SLN biopsy in vulvar tumors is the ultrastaging, since the introduction of this procedure in a standardized way, more and lower inguofemoral ganglion metastases have been diagnosed. The true clinical impact of micrometastases is unknown. What seems clear is that the larger size of the SLN metastases, make greater the chances of metastasis in non-sentinel lymph nodes and the lower survival rates. In this way, the size of metastases to the lymph nodes is included in the last staging system for vulvar cancer. However, micrometastases have not been included in the staging of this type of tumors. Further studies are needed to determine the clinical consequences of the size of the SLN metastases.³⁵

From a practical point of view, we have extensive experience in the use of technetium as a tracer. However, there are already studies that have shown that indocyanine green has a similar sensitivity, so it should be evaluated in new protocols in order to can incorporate it into our usual practice.³⁶

In short, we can see how it has been shown that complete inguofemoral lymphadenectomy is no longer necessary in most patients with this disease and there are no excuses for not incorporating SLN biopsy in the approach to vulvar cancer.

Cervix

Cervical cancer is one of the most frequent gynecological tumors in young patients, being one of the main causes of death by this reason in developed countries. Frequently, at diagnosis the tumor is limited to the cervix, around 47% according to OonK.³⁵ The usual approach of these patients goes through radical hysterectomy or trachelectomy with bilateral pelvic lymphadenectomy.^{1,37} This has achieved a high survival at 5 years when it comes to early stages.^{38,39} The SLN biopsy is an appropriate option in this type of patients.⁴⁰

The success of SLN biopsy in cervical cancer will be based on an adequate selection of patients in which the tumor is small and is treated with low staging. In general, it should be limited to stages IA2 and IBI. The best detection rate is found in tumors below 2cm.⁴¹ However, it should be considered that currently, it is an experimental technique with a low implantation rate.⁴²

To perform SLN biopsy in cervical cancer, MB can be used with or without Tc99. It must be injected into the cervix immediately after the anesthesia had been established.⁴¹ This can be established in each quadrant of the cervix, either at 3 and 9 o'clock in the cervix. Intraoperatively, MB can be located at a glance.

There are studies that compare these markers with indocyanine green. In patients with early-stage cervical cancer, a higher bilateral detection was confirmed using the IG instead of standard techniques.⁴³ It was also shown in this study by Buda et al. where the conization did not have a significant impact on the detection rate of the lymph nodes either with MB+Tc99 or with ICG. In the case of advanced cervical cancer (stage IB1>2cm), the detection rate was higher with ICG than with MB+Tc99.

So that we can see that ICG is a promising tool for SLN in cervical cancer, since it seems less affected by the stage of the disease, with a higher detection rate compared to traditional methods.⁴² In addition, currently the detection of the sentinel node with GI by means of robotics with the da Vinci Xi supposes an added advantage.⁴⁴

We want to highlight an additional advantage of SLN biopsy in cervical cancer. This is the possibility of detecting areas outside of

what includes the usual lymphadenectomy, thus being able to have additional histological information. On the contrary, there are some scenarios that make more studies necessary, such as its application in conservative fertility surgery and in patients with neoadjuvant chemotherapy.⁴⁵ In any case, the superiority of SLN biopsy over PET in the detection of lymph node disease has been demonstrated.^{46,47}

Although it is a new technique that will require more studies, according to the National Comprehensive Cancer Network guidelines, the BSGC is a viable option for the management of this type of tumors, including it within its therapeutic guidelines.^{23,30} In conclusion, according to the available evidence, the BSGC is a safe procedure with high detection rate and low false negative rate.⁴⁴

Endometrium

Endometrial cancer is the most frequent cancer of the female genital tract in the US with 6,180 cases in 2017.³⁶ So, if there is a gynecological cancer where the implementation of SLN biopsy is most interesting, it is in this tumor. In patients in initial stages, it is very important to perform a systematic screening of patients without metastasis to lymph nodes to reduce the range of surgical resection, and to reduce the incidence of the corresponding complications and improve the quality of life of the patients.¹⁴ SLN biopsy allows the reduction of unnecessary lymphadenectomies and reduces the risk of underdiagnosis in patients with metastatic lymph nodes.⁴⁸ However, this technique has the difficulty of the double lymphatic drainage pathway of these tumors.⁴⁹ In addition, the different existing types must be considered.^{50,51} According to the FIRES study, the SLN biopsy has a sensitivity of 97.2% and a negative predictive value of 99.6%.⁵¹

As in previous cases, several protocols can be used to the SLN biopsy in endometrial cancer. Among them, the Tc 99, the MB or the ICG. ICG has an excellent toxicity profile, with higher overall and bilateral detection rates compared to blue dyes, as well as higher bilateral detection rates compared to a combination of Tc-99m and MB.^{26,50,51} The ICG in addition to an excellent detection rate shows a low rate of false negatives. This superiority has been revealed even when we speak of advanced stages (IIIC)⁵¹ or high risk types, achieving a sensitivity, rate of FN and VPN acceptable. In this way, the SLN biopsy with ICG has managed to reduce the total number of complete lymphadenectomies, reducing the duration and the additional costs of surgical treatment.⁵²⁻⁵⁵

The study published by Niikura shows how the tracer injection in the cervix is very sensitive in the detection of SLN metastases in early stage endometrial cancer (stages I and II of FIGO). This is a particularly useful and safe modality when combined with injection of blue dye into the uterine body.⁵⁶ Controversy exists on the place of injection of the tracer. In this regard, the study published by Rossi shows how cervical ICG injection achieves a higher rate of SLN detection and an anatomical lymph node distribution similar to hysteroscopic endometrial injection in patients with endometrial cancer.⁵⁷

In summary, BSGC with GI is a feasible technique with high diagnostic precision that could eventually displace conventional lymphadenectomy in the coming years, thus reducing the associated morbidity and mortality.⁵¹

Ovary

There are few studies about SLN biopsy in ovarian cancer. Anatomy, various histological types and their drainage, or tracer

injection, are some of the difficulties that contribute to the limited scientific evidence available. An example of this is the study of the Buddha where ICG is used for aortic staging in 10 patients with ovarian cancer. In 9 cases the SLN was detected in the aortic region after the injection of the tracer. In 3 cases, SLN were also identified in the common iliac region.⁵⁸

Costs

There are few studies that evaluate the costs associated with the use of the sentinel lymph node. A sample of this is the study of Buddha, who showed that with SLN biopsy in endometrial cancer there is a reduction of more than 1000 dollars compared to conventional lymphadenectomy. Assuming a total of 66 million dollars less for the total cases of ca. Endometrium in the USA. On the other hand, when we refer to vulvar cancer, SLN biopsy seems the least expensive alternative, mainly due to the great impact of lymphedema associated with conventional surgery on quality of life.⁵⁹ According to the study of van der Vorst, with the SLN biopsy in vulvar cancer a reduction of 22416 dollars on an annual basis with respect to conventional surgery.⁶⁰

When comparing the use of the different tracers, the option that the ICG uses seems to be the most profitable strategy.^{61,62}

Conclusion

The BSGC in gynecological tumors is a current technique that manages to reduce the morbidity and mortality associated with traditional surgery, in addition to achieving a reduction in costs associated with it. This is also achieved, without interfering in the prognosis of these patients. New standardized studies are needed to reinforce and homogenize this technique so that we can incorporate it into our usual protocols.

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Conflicts of interest

The authors report no declarations of interest.

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