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ORIGINAL ARTICLE

Sensitivity and validity of sentinel node biopsy in early-stage cervical cancer at an oncology institution

Sensibilidad y validación de la biopsia de ganglio centinela en el cáncer cervicouterino de etapa temprana en una institución de oncología

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Abstract

Objective: *To determine the validity of sentinel lymph node biopsy (SNB) in women with early-stage cervical cancer (CeCa).* **Methods:** *We carried out a study of 46 patients with CeCa of FIGO stages IA1c-IB2 treated with radical uterine surgery. The technique for the identification of BGC was performed with patent blue dye and technetium-99m. For its validation, a bilateral pelvic lymphadenectomy (BPL) was performed, and all sentinel lymph nodes underwent pathological ultra-staging. We determined the detection rates of SNB, bilaterality, sensitivity, specificity, and negative and positive predictive values.* **Results:** *The sensitivity of the SNB was 100%, specificity was 95%, positive predictive value was 75%, negative predictive value was 100%, diagnostic accuracy was 93%, and the false negative rate was 0%.* **Conclusions:** *The BGC technique in patients with CeCa in the early stages who undergo radical hysterectomy is a feasible and safe method at Instituto Nacional de Cancerología. The importance of this method is that BPL can be avoided when it migrates bilaterally, reducing the morbidity of the procedure.*

Keywords: *Sentinel lymph node. Cervix cancer. Lymphadenectomy.*

Resumen

Objetivo: *Determinar la validez de la biopsia de ganglio centinela (BGC) en mujeres con cáncer cervicouterino (CaCu) en etapa temprana.* **Métodos:** *Se realizó un estudio de 46 pacientes con CaCu en etapas FIGO IA1c-IB2 tratada con cirugía radical uterina. La técnica para la identificación de la BGC fue con colorante azul patente y tecnecio-99m. Para su validación se realizó linfadenectomía pélvica bilateral (LPB) y a todos los ganglios centinela se les realizó ultraestadificación patológica. Se determinaron las tasas de detección de BGC, la bilateralidad, la sensibilidad, la especificidad y los valores predictivos negativo y positivo.* **Resultados:** *La sensibilidad de la BGC fue del 100%, la especificidad del 95%, el valor predictivo positivo del 75% y el valor predictivo negativo del 100%, con una precisión diagnóstica del 93% y una tasa de falsos negativos del 0%.* **Conclusiones:** *La técnica de BGC en pacientes con CaCu en etapa temprana que son sometidas a histerectomía radical es un método factible y seguro en el Instituto Nacional de Cancerología. La importancia de este método es que puede obviarse la LPB cuando migra de forma bilateral, disminuyendo la morbilidad del procedimiento.*

Palabras clave: *Ganglio centinela. Cáncer de cérvix. Linfadenectomía.*

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Introduction

The most important prognostic factor for survival in early-stage cervical cancer (CC) (IA1-IB2) according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) classification is lymph node metastasis, which occurs in the pelvic lymph nodes in 15-20% of cases.[1-4] Radical hysterectomy and bilateral pelvic lymphadenectomy (BPL) are the standard treatment for these patients. However, BPL has been associated with a higher risk of intraoperative complications, such as greater blood loss and ureteral, nerve, or vascular injury, as well as late postoperative complications, such as lymphocysts and lower-limb lymphoedema (LLL); the latter is probably the most important and serious long-term complication, and its incidence varies. In the prospective GOG-244 study, Carlson et al. documented that up to 65.2% of patients with surgically treated cervical cancer developed symptoms related to lymphoedema, underscoring the impact of lymphadenectomy and the extent of treatment on its occurrence.[5] Cibula et al.[6] prospectively evaluated LLL in patients undergoing sentinel lymph node (SLN) biopsy and found a cumulative incidence of LLL at 24 months of 17.3% for mild LLL, 9.2% for moderate LLL, and 0.7% for severe LLL.

Sentinel lymph node biopsy (SLNB) has been shown to be a very safe procedure that evaluates the first SLN or SLNs through which tumour cells from the primary cancer drain.[7] These lymph nodes reflect the regional status of lymphatic involvement. This procedure has been extensively validated in other neoplasms and is the standard of care for breast cancer and melanoma.[1,2]

The first results of SLNB in CC were published in the 1990s, and the findings of numerous studies conducted at different oncology centres have subsequently been evaluated. Many studies have demonstrated the high sensitivity of SLNB for predicting lymph node metastases.[3-10]

Currently, the standard of care for early-stage CC classified as IA1 with lymphovascular space invasion, IA2, or IB1 according to the 2018 FIGO classification is radical hysterectomy with BPL, and SLNB is a feasible and safe option recommended in international clinical practice guidelines.[11]

This study presents the experience of a tertiary oncology institute in Mexico with the use of the SLNB technique in patients with early-stage CC, with the aim of determining the validity of SLNB.

Methods

We conducted a retrospective review in the Department of Gynaecologic Oncology of the *Instituto Nacional de Cancerología* between 2010 and 2020 in patients diagnosed with early-stage CC who underwent SLNB. The 2018 FIGO classification was adapted for the study, and patients with CC stages IA1 with lymphovascular space invasion and IA2-IB2 with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma who underwent radical hysterectomy, SLNB, and BPL were included. Patent blue dye and technetium-99m (Tc-99) were used as tracers. As part of the validation of the study, both procedures – SLNB followed by BPL – were performed to identify false-positive and false-negative SLNB results compared with assessment using the standard procedure. Surgery was performed by laparotomy. In the Department of Pathology, all SLNs were stained with haematoxylin and eosin, and those negative for macrometastases underwent ultrastaging.

Patients with lymph nodes showing macrometastases intraoperatively and those who did not undergo complementary BPL were excluded.

Preoperative procedure

With the patient under anaesthesia and placed in the gynaecological position with the lower limbs abducted, the Tc-99-labelled rhenium sulphide radiotracer and 1% patent blue dye were injected into the cervix at the 3 and 9 o'clock positions. The injection was performed superficially and deeply into the cervical stroma, at 1-2 mm and 10 mm, respectively.

Operative procedure

The peritoneum was opened to identify the pelvic retroperitoneal structures, both ureters, and the external and internal iliac vessels. After development of the lateral and medial pelvic spaces, the lymphatic channels and SLNs were identified by visualisation of the patent blue dye and use of a gamma probe (Gamma Probe®). Once the "blue or hot" lymph nodes had been identified, they were excised for definitive pathological analysis.

Pathological evaluation and ultrastaging

The SLNs were processed in the Department of Pathology. Each SLN was sectioned at 2-mm intervals

along the longest axis of the specimen and completely embedded in the required number of cassettes. One slide was obtained for haematoxylin-eosin staining, and if it was negative for metastasis, 2 additional sections were obtained 50 μm apart. One slide was stained with haematoxylin-eosin (Fig. 1), and the other was reserved for immunohistochemistry with CKAE1/AE3 cytokeratins (Fig. 2) if no neoplastic cells were identified on the haematoxylin-eosin section. Metastatic size was reported and classified as macrometastasis if > 2 mm, micrometastasis if < 2 mm and > 200 isolated cells, and isolated tumour cells when < 200 cells were present. When more than 1 SLN was identified, each lymph node was processed and reported separately.

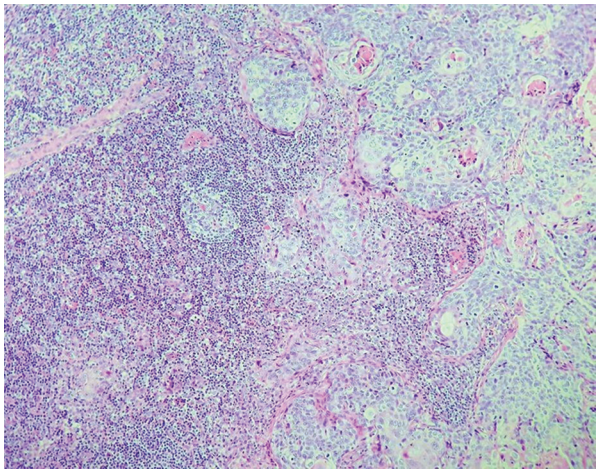


Figure 1. *Haematoxylin-eosin staining: macrometastasis.*

Statistical analysis

A descriptive analysis was performed. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were reported as median and interquartile range (IQR). Detection rate, bilaterality, sensitivity, specificity, and negative and positive predictive values were determined.

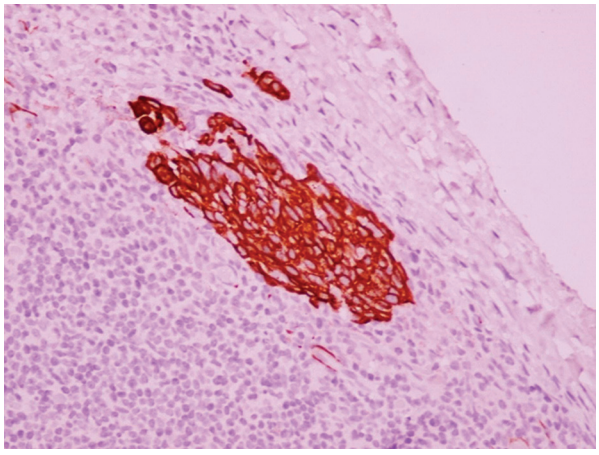


Figure 2. *CKAE1/AE3 immunohistochemistry: obturator lymph node with a 5-mm metastasis and 1-mm foci.*

Results

A total of 46 patients surgically treated between 2010 and 2020 were included. Median age was 47 years (IQR, 39-53 years). Squamous cell carcinoma was identified in 34 patients (73.9%), making it the most frequent histological type, followed by adenocarcinoma in 11 (23.9%). Regarding the type of radical hysterectomy, 40 patients (87.0%) underwent type B and 6 (13.0%) type C hysterectomy. The most frequent clinical stage was IB1, in 41 patients (89.1%) (Table 1).

Regarding tumour size, 29 tumours (63.0%) were categorised as ≤ 2 cm and 17 (37.0%) as > 2.1 cm. Between 1 and 3 SLNs were dissected in 41 patients (89.1%), and 3-6 SLNs in 5 (10.9%).

Regarding bilaterality, SLNs were bilateral in 27 patients (58.7%) and unilateral in 19 (41.3%).

Pathological evaluation of the SLNs using haematoxylin-eosin alone yielded negative results in 42 patients (91.3%) and positive results in 4 (8.7%). With immunohistochemical ultrastaging, 8 patients (17.4%) had positive findings: 6 (13.0%) with macrometastases, 2 (4.3%) with micrometastases, and none (0.0%) with isolated tumour cells (Table 2).

The assessment of the validity of SLNB compared with evaluation of lymph nodes obtained by BPL is shown in table 3. Metastases were identified in 8 SLNs from 6 patients. The SLNs were correctly localised with radiocolloid and patent blue dye. SLNB sensitivity was 100%, specificity was 95%, positive predictive value was 75%, and negative predictive value was 100%, with a diagnostic accuracy of 93% and a false-negative rate of 0%.

Discussion

The SLNB procedure has been widely used in patients with penile, breast, and vulvar cancer and melanoma, with good results in lymph node assessment.[7,8] Specific benefits in CC include fewer nerve injuries, less blood loss, shorter operative time, and

Table 1. Demographic data (n = 46)

Variables	n (%)
Age, median (IQR)	47 (39-53)
Histology	
Squamous cell carcinoma	34 (73.9)
Adenocarcinoma	11 (23.9)
Adenosquamous carcinoma	1 (2.2)
Clinical stage	
IA1	3 (6.5)
IB1	41 (89.1)
IIA1	2 (4.3)
Surgery	
Type B radical hysterectomy	40 (87.0)
Type C radical hysterectomy	6 (13.0)

IQR, interquartile range.

Table 2. Sentinel lymph node biopsy procedure data (n = 46)

Variables	n (%)
Tumour size	
> 2 cm	29 (63.0)
< 2 cm	17 (37.0)
Total number of sentinel lymph nodes	
1-3	41 (89.1)
4-6	5 (10.9)
Laterality	
Unilateral	19 (41.3)
Bilateral	27 (58.7)
Haematoxylin-eosin	
Negative	42 (91.3)
Positive	4 (8.7)
Immunohistochemistry	
Positive	8 (17.4)
Micrometastases	2 (4.3)
Macrometastases	6 (13.0)
Isolated tumour cells	0 (0.0)
Negative	38 (82.6)

improved identification of true metastatic lymph nodes through ultrastaging. According to the results of our study, ultrastaging doubled the identification of metastases; initial evaluation using haematoxylin-eosin identified metastases in 4 cases (8.7%). With the application of ultrastaging, the number of positive cases increased to 8 (17.4%), including 2 micrometastases (4.3%) and 6 macrometastases (13.0%). Consequently, ultrastaging increased the detection of metastatic disease by an additional 8.7%.

Radical hysterectomy with BPL is the standard of care for CC clinical stages IA1 with lymphovascular space invasion, IA2, and IB1.[11] An algorithm published in 2011 by Cormier et al.[12] suggests that, for improved staging using SLNB, the SLNs and any suspicious adenopathy should be excised and that, if an SLN is not identified in any lymphatic drainage region, lymphadenectomy should be performed to adequately assess bilateral lymph node status.

A prevalence of lymph node metastases of up to 15% has been reported in patients with early-stage CC, indicating that 85% of patients undergoing lymphadenectomy will derive no benefit from the procedure but will remain exposed to its associated complications and long-term morbidity.[13]

Potential complications of BPL include injury to vessels, pelvic nerves, and ureters, as well as less common complications such as infections, thromboembolic events, fistulas, and lymphoceles, which may affect patients' quality of life.[13,14] As part of the validation of SLNB, all our patients underwent BPL, but no immediate or late operative or postoperative complications were documented in their health records.

To reduce short- and long-term complications, SLNB has been proposed as a method for improving lymph node assessment and detecting micrometastases and isolated tumour cells.[12] This study reports the experience of the *Instituto Nacional de Cancerología* with SLNB in cervical cancer, with adequate diagnostic accuracy (93%), sensitivity (100%), and specificity (92.6%).

Numerous studies have been conducted at different oncology centres to evaluate the diagnostic accuracy of SLNB in CC.[9,10] Bats et al.[15] determined the diagnostic value of SLNB using radiocolloid and dye in patients with early-stage CC, obtaining a detection rate of 97.8%. There were 17 false negatives: 4 with macrometastases, 4 with micrometastases, and 9 with isolated tumour cells. Among the recommendations derived from the study, optimal SLN detection was found in tumours smaller than 2 cm, particularly when a combined dye and radiotracer technique was used, administered by injection into the cervical quadrants.[15]

The application technique consists of radiocolloid injection 1 day before or on the day of surgery at the 4 cardinal points of the cervix, followed by surgical assessment through detection of the dye and radiocolloid with a gamma camera.[12]

Frumovitz et al.[16] conducted a non-inferiority comparative study in patients with endometrial cancer or clinical stage I CC undergoing curative surgery who were randomized on a 1:1 ratio to lymphatic mapping

Table 3. Validation of sentinel lymph node biopsy

Ultrastaging	Haematoxylin-eosin			Predictive value
	Positive	Negative	Total	
Immunohistochemistry				
Positive	6	2	8	PPV: 75%
Negative	0	38	38	NPV: 100%
Total	6	40	46	
	Sensitivity: 100%	Specificity: 95%		

NPV, negative predictive value; PPV, positive predictive value.

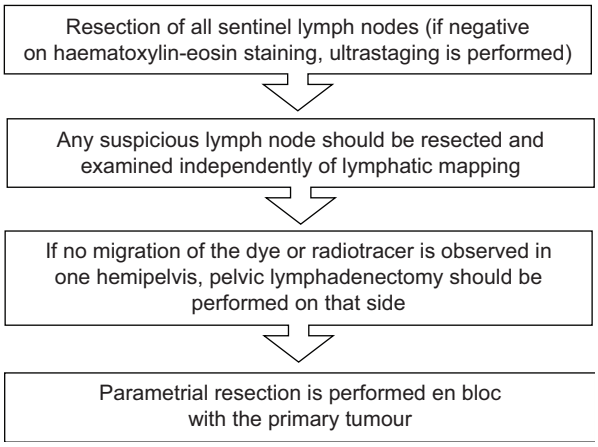


Figure 3. *Management algorithm using sentinel lymph node biopsy to improve staging, proposed by Memorial Sloan Kettering Cancer Center.*

with isosulfan blue dye (visualised under white light) followed by indocyanine green (visualised using near-infrared imaging), or indocyanine green followed by isosulfan blue dye. They concluded that indocyanine green dye with near-infrared fluorescence imaging identified more SLNs than isosulfan blue dye in women with CC and uterine cancer, with no differences in pathological confirmation of lymph node tissue between the 2 mapping agents.[16]

The SENTICOL 1 clinical trial was a prospective multicentre study that evaluated the sensitivity and negative predictive value of SLNB. Intraoperative mapping with radioisotope and blue dye detected at least 1 SLN in 136 patients (97.8%; 95% CI, 93.8-99.6), of whom 23 had true-positive results and 2 had false-negative results, with a sensitivity of 92.0% (23 of 25; 95% CI, 74.0-99.0) and a negative predictive value of 98.2% (111 of 113; 95% CI, 74.0-99.0) for the detection of lymph node metastases, with no false negatives. Bilateral SLNs were identified in 104 patients (76.5%). It was concluded that lymph node mapping was associated with high SLNB detection rates, high sensitivity, and a high negative predictive value for detecting metastases. However, SLNB was completely reliable only when SLNs were detected bilaterally.[17] The technique used in our study involved Tc-99 and patent blue dye and was performed in all patients, yielding a bilaterality rate of 58.7% and a sensitivity of 100%.

The SENTICOL 2 trial was a prospective randomised study in early-stage CC (FIGO 2009 stages IA2-IIA1). Patients were randomly assigned to SLN resection alone (SLN group) or SLN resection with pelvic lymph node dissection (SLN + BPL group).[18] Resection was followed by radical tumour surgery (radical hysterectomy or radical trachelectomy). The study concluded that SLN resection alone was associated with reduced early lymphatic morbidity compared with SLN plus BPL in early-stage CC.[18]

A *post hoc* analysis of the SENTICOL I and SENTICOL II cohorts was conducted to compare oncological outcomes in patients with early-stage CC and negative lymph nodes who underwent SLNB or BPL.[19] Median follow-up was 47 months (range, 4-127). During follow-up, 21 patients (8.1%) experienced recurrence, including 4 (1.9%) lymph node recurrences, and 9 patients (3.5%) died of CC. Disease-free survival and disease-specific survival were similar in the SLNB and BPL groups: 85.1% vs 80.4% (p = 0,24) and 90.8% vs 97.2% (p = 0,22), respectively. It was concluded that omission of complete pelvic lymphadenectomy in patients with negative bilateral SLNs did not appear to be associated with an increased risk of recurrence. Non-inferiority in terms of survival should be confirmed in prospective trials.[19]

Three prospective randomised trials are currently underway – SENTIX,[20] SENTICOL III,[21] and PHENIX/CSEM 010[22] – evaluating the oncological safety of SLNB vs BPL in patients with early-stage CC. Once the results become available in the coming years, they will probably lead to a change in practice, either

allowing SLNB alone to be performed safely or, if non-inferiority vs BPL is not demonstrated, leading us to discontinue a safe, low-morbidity procedure such as SLNB.

The strengths of this study include its conduct at an institution with a high volume of cancer cases, evaluation of all lymph nodes by a single pathologist with extensive experience in gynaecological tumours, and ultrastaging of the SLNs. However, its limitations include those inherent to its retrospective nature.

Conclusions

SLNB is recommended in patients with early-stage CC measuring up to 4 cm, with better detection and bilateral identification in tumours < 2 cm. The use of patent blue dye and Tc-99, administered in at least 2 lateral cervical quadrants at the 3 and 9 o'clock positions, is a safe and effective technique; according to the international literature, the use of indocyanine green tracer improves SLN detection.

Pathological ultrastaging should always be considered when analysing SLNs because it doubles the detection rate of lymph node metastases not identified by haematoxylin-eosin staining alone.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments involving humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data, medical records, or human biological samples and therefore does not require ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no type of generative artificial intelligence was used in the writing or creation of content for this manuscript.

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