Original article

Study of the sentinel node in endometrial cancer at early stages: Preliminary results

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A B S T R A C T

Aim: To investigate the applicability of the sentinel lymph node biopsy technique in early stages of endometrial cancer.

Material and methods: A prospective study that included consecutive patients with a histological diagnosis of clinical state I endometrial carcinoma was performed. Two doses of 2 mCi (74 MBq) of 99mTc-albumin nanocolloid were injected in the uterine cervix, and planar and SPECT-CT images were obtained at 1 h, and at 24 h if no migration of the tracer was observed.

Methylene blue dye was also injected into the cervix immediately prior to the surgery. A gamma probe was used during the surgical procedure for sentinel lymph node identification.

In all cases, a hysterectomy, double adnexectomy and pelvic lymphadenectomy were performed, carrying out a histological analysis (hematoxylin–eosin) of the sentinel lymph nodes and the lymphadenectomy specimen.

Results: We included 19 patients, with a final diagnosis of endometrioid carcinoma (18 cases) and endometrial stromal sarcoma (1 case). At least one sentinel lymph node was identified in 17 of them (89.5% detection rate).

Twenty-nine sentinel lymph nodes were identified during surgery, all of them negative for neoplastic infiltration. No metastatic invasion was found in the pelvic lymphadenectomy specimens as well.

Conclusions: The sentinel lymph node biopsy technique seems to be a reliable tool in nodal staging of endometrial cancer at early stages, with an acceptable detection rate and high histological correlation. The low prevalence of lymphatic spread in this group of patients and the encouraging results obtained could make the sentinel lymph node an alternative to routine complete lymphadenectomy.

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Estudio del ganglio centinela en el cáncer de endometrio en estadios iniciales: resultados preliminares

R E S U M E N

Objetivo: Estudiar la aplicabilidad de la técnica del ganglio centinela en los estadios iniciales del carcinoma endometrial.

Material y métodos: Estudio prospectivo que incluyó pacientes consecutivos con diagnóstico histológico de carcinoma de endometrio, en estadio clínicamente I. Se inyectaron dos dosis de 2 mCi (74 MBq) de 99mTc-nanocoloide de albúmina en el cérvido uterino, obteniendo imágenes planares y SPECT-TC de la región pelviana una hora después, y a las 24 cuando no se observó migración del trazador.

Inmediatamente antes de la intervención, se inyectó azul de metileno vía cervical.

Los ganglios centinela se identificaron durante la intervención mediante sonda quirúrgica.

En todas se realizó histerectomía, doble anexectomía y linfadenectomía pélvica bilateral, con estudio histológico (hematoxilina–eosina) de los ganglios centinela y las piezas de linfadenectomía.

Resultados: Incluimos 19 pacientes, con diagnóstico final de carcinoma endometrioide (18 casos), tumor del estroma endometrial (1 caso). Se identificó al menos un ganglio centinela en 17 (tasa de detección del 89,5%).

Se identificaron 29 ganglios centinela en el acto quirúrgico, todos negativos para infiltración neoplásica. Tampoco se observó afectación metastásica ganglionar en las piezas de linfadenectomía.

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Endometrial cancer currently represents the most frequent gynecologic tumor in Spain, with an annual incidence of around 10–12 cases per 100,000 women. Nonetheless, globally, disease survival is good when diagnosis is achieved in the early stages of the disease and confined to the uterine body as occurs in approximately 75% of the cases. Survival is particularly good when the tumor is type 1 or endometrioid, expressing estrogenic receptors on the surface and constituting the most frequent histological type as the histological subtype. Metastasis is infrequent in cases of low risk, being of approximately 1% of these patients. Survival is particularly good when the disease and confined to the uterine body as occurs in approximately 75% of the cases. Metastasis is infrequent in cases of low risk, being of approximately 1% of these patients.3 However, in cases of infiltration of the pelvic lymph nodes, around half of these patients demonstrate invasion of the paraaortic chain. These characteristics condition the surgical approach in these patients and currently continue to be under debate.6 Thus, the possible beneficial effect on survival of hysterectomy and double annexectomy with pelvic lymphadenectomy in the subgroup of low risk is relevant, and there is a considerable risk of lymph node involvement in the initial stages and the possibility of complications such as hemorrhage and lymphedema secondary to lymphadenectomy.7–10 Although the current trend is to perform hysterectomy and double annexectomy without pelvic lymphadenectomy in patients with low risk, this approach remains without consensus. Indeed, the International Federation of Gynecology and Obstetrics (FIGO), as well as the European Society for Medical Oncology (ESMO), continue proposing the use of lymphadenectomy in these patients.11,12

For all of the above, in the last years the use of the sentinel lymph node technique has been the object of study since it has three important characteristics: the lymphatic system is the priority route of tumoral dissemination, the prevalence of lymph node involvement is low and the surgical complications of lymphadenectomy are frequent.

Here we present the results of the present study carried out in our center on the applicability of the technique in this type of gynecological tumor.

Materials and methods

Patients

Since 2009 all the patients consecutively diagnosed with endometrial carcinoma in our center have been included in this study. The study inclusion criteria were: diagnosis by hysteroscopy and endometrial biopsy of endometrial neoplasm, clinical stage I with no clinical suggestive signs of involvement of the cervix or parametrium according to the 2009 FIGO classification (Table 1).15

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Without invasion or with invasion of less than 50% of the endometrium</td>
</tr>
<tr>
<td>IB</td>
<td>Invasion greater than or equal to 50% of the endometrium</td>
</tr>
<tr>
<td>II</td>
<td>Invasion of the stroma of the cervix without extrauterine extension</td>
</tr>
<tr>
<td>III</td>
<td>Local or regional extension</td>
</tr>
<tr>
<td>IIIA</td>
<td>Invasion of the serosa of the uterine body and/or annexes</td>
</tr>
<tr>
<td>IIIB</td>
<td>Invasion of the vagina and/or parametrium</td>
</tr>
<tr>
<td>IIIC</td>
<td>Pelvic or paraaortic lymph node metastasis</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Pelvic lymph nodes</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Paraaortic lymph nodes (with or without pelvic lymph node invasion)</td>
</tr>
<tr>
<td>IV</td>
<td>Invasion of the bladder, intestinal mucosa or appearance of distant metastasis</td>
</tr>
<tr>
<td>IVA</td>
<td>Bladder or intestinal mucosa invasion</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastasis (including inguinal lymph nodes and intraabdominal metastasis)</td>
</tr>
</tbody>
</table>

Localization technique

To identify the sentinel lymph node we used two doses of 2 mCi (74 MBq) of 99mTc-albumin nanocolloid (Nanocoll®), diluted in 0.5 ml of physiological serum were injected into opposite points at 3 and 9 o’clock of the uterine cervix.

Approximately 1 h after injection of the radiotracer, planar images of the pelvis were obtained in anterior projection in a gamma camera model Symbia T, Siemens, with 5-min images in a matrix of 256 x 256. Immediately thereafter SPECT-CT acquisition was performed in the same equipment with 64 images in circular orbit, with a matrix of 64 x 64 and 20 s per projection.

Likewise, immediately prior to initiating the intervention, 2 cc of methylene blue were injected into the cervix at the two points at 3 and 9 o’clock.

For intraoperative detection of the sentinel lymph node we used a conventional Euroradio model surgical probe (EUROMEDICAL instruments) with a detector of 11 mm in diameter, identifying the sentinel lymph node(s) as that/those demonstrating detectable activity. When the identification with contrast differed from that of the scintigraphy, the latter prevailed. In the cases in which the intervention was performed by laparoscopy, the scintigraphic localization was undertaken on the material extracted ex vivo in the operating room, dissecting and adequately identifying the sentinel lymph nodes prior to being sent to the Department of Anatomic Pathology for study.

Histological study

Both the lymph nodes identified as sentinel lymph nodes as well as those found in the lymphadenectomy specimen were studied according to the conventional protocol with hematoxylin–eosin. Likewise, the grade of tumoral infiltration was established studying the remaining material obtained in the intervention.
The histological data allowed the staging of the patients following the last revision of the FIGO (2009) (Table 1).

### Results

Study of the sentinel lymph node was performed in a total of 19 patients ranging in age from 39 to 84 years. Fifteen underwent laparoscopy while laparotomy was performed in the remaining 4.

The final diagnosis was endometrial adenocarcinoma in 17 patients and tumor of the endometrial stroma in one. The remaining patient was finally diagnosed with endometrial hyperplasia with atypias in the surgical piece after study of the surgical specimen, although the presurgical biopsy had confirmed the presence of endometrial adenocarcinoma in the material obtained in hysteroscopy. The data referring to the tumoral study prior to and after surgery and the histological grade are shown in Table 2.

At least one sentinel lymph node was localized in the presurgical study (detection rate: 89.5%) in 17 of the 19 patients. Planar studies were performed in the 19 cases allowing detection of a total of 31 sentinel lymph nodes including one lymph node only visible in the study carried out at 24 h after injection of the tracer (Fig. 1). The SPECT-CT performed in 18 patients identified 33 sentinel lymph nodes and could not be done in only one case due to technical problems. The numbers and localizations of the lymph nodes coincided in the SPECT-CT and planar scintigraphies in 14 of the 18 patients in whom both acquisitions were carried out (Fig. 2). In 3 of the 4 remaining cases the SPECT-CT allowed identification of more lymph nodes which are probably secondary in more distal territories.

Bilateral pelvic drainage was found in the external left and right iliac chains in 3 of the 19 cases (15.8%). In the 2 cases in which the sentinel lymph node could not be identified by either lymphoscintigraphy or vital staining, no apparent cause was found to justify this.

At least one lymph node could be identified in the operating room in the 17 cases in whom one or more lymph nodes had previously been identified in the lymphoscintigraphy (total: 29 lymph nodes) while no lymph node was identified intraoperatively in the 2 patients in whom tracer drainage was not observed in either early or late scintigraphy (Table 3).

The results of the histological analysis of the lymph node(s) identified as sentinels were negative in all the cases as was the study of the lymph nodes included in the regional lymphadenectomy pieces.

### Discussion

Pelvic lymphadenectomy currently continues to be part of the most commonly applied treatment in women with endometrial cancer probably due to retrospective studies which have reported a certain improvement in the global survival of patients when the regional lymph nodes are resected in addition to the uterus and uterine annexes. However, an increasing number of prospective multicenter clinical trials such as ASTEC (A Study in the Treatment of Endometrial Cancer) are questioning the need to routinely perform both pelvic lymphadenectomy and external radiotherapy in patients with early stages of endometrial adenocarcinoma since these techniques do not increase the global survival or recurrence free survival but rather increase the incidence of early and late post-surgical complications.

An elevated number of pelvic lymphadenectomies are finally negative in the initial stages of the disease. Indeed, the lower the risk of the tumor based on the histological type and the grade of differentiation, the higher the number of negative results thereby questioning the real need to systematically perform pelvic lymphadenectomy in patients with low risk. Thus, Chi and collaborators did not find regional lymph node involvement in any of the patients studied with, stage I and histological grade I endometrial adenocarcinoma of the endometrial variety to constitute the subgroup of patients with lower risk of neoplastic dissemination, even independently of the grade of endometrial wall invasion. Altogether, only 30 of the 349 patients included in their study (9%) with a diagnosis of stage I endometrial adenocarcinoma showed regional lymph node involvement, with these 30 patients corresponding to grade 2 or 3.2

The relevance of the role the grade of lymphatic extension plays in the prognosis of these patients is currently under
Fig. 2. Coronal images CT, SPECT and fusion SPECT-CT of the pelvis obtained at 60 min after the injection in one of the cases with endometrial adenocarcinoma Ia and bilateral drainage. Thick arrows: sentinel lymph node in the right external iliac region. Thin arrows: sentinel lymph nodes in both common iliac regions.

debate. Although some authors have reported a certain prognostic implication in relation to the grade of regional lymph node involvement with respect to the prediction of survival and thus influencing the post-surgical therapeutic approach, at present only the histological grade, histological type and the grade of parietal invasion condition the risk of recurrence in stage I patients.16

In the present study including patients in early stages of the disease mainly corresponding to endometrial type adenocarcinomas (18 out of 19 patients), we did not find lymphatic involvement in either the sentinel lymph node study or in the lymphadenectomy piece independently of the histological grade, oncological stage and histological type similar to what has been reported in studies including larger series of patients with very scarce lymphatic involvement in the cases of lower risk.

Due to a lesser associated morbidity, selective biopsy of the sentinel lymph node may be performed as an intermediate alternative between pelvic lymphadenectomy and preservation of all the lymph nodes. In addition, study of a single lymph node or small number of lymph nodes would not only indicate the route the tumor has followed on having left the initial bed but would also allow more precise histological techniques to be undertaken (thin slicing, immunohistochemistry staining) which could detect smaller tumor cell deposits such as micrometastasis or isolated tumoral cells than conventional techniques. More precise knowledge of the grade of lymphatic extension could, according to some authors, influence the prognosis of the patients and condition the administration of adjuvant chemotherapy in endometrial carcinomas in early stages.18,19

The results obtained to date by the different series described are promising in regard to the rate of sentinel lymph node detection which is of about 89%20 (present study: 89.5%) and in the information provided of the grade of lymphatic extension of the disease. Thus, the recently published, prospective multicenter study SENTI-ENDO has reported that out of a total of 111 patients with early stage endometrial carcinoma and detectable sentinel lymph node 16 (14%) showed neoplastic involvement. However, another lymph node was also found to be involved on lymphadenectomy in only 2 cases (12%) thereby underlining the low risk of lymphatic involvement in these patients. Indeed, no patient with low or intermediate risk, based on histological type, histological grade and extension presented involvement beyond sentinel lymph node20 favoring the elevated negative predictive value of the technique. In our series almost wholly composed of patients diagnosed with endometrial adenocarcinoma (94.7%, 18 patients) in stage I (89.4%, 17 patients), mainly with histological grade I (63.1%, 12 patients) no lymphatic involvement in the sentinel lymph node or in the lymphadenectomy piece was detected in any case.

Nonetheless, the use of this technique is not without controversy and the methodology is not uniform in the different centers. Thus, some authors propose peritumoral or subserosal injection of tracer by hysteroscopy as the optimum route since migration of the tracer would, a priori, be the most similar to that of the tumor and would allow easier detection of lymph nodes in the paraaortic chain.13,21 However, isolated paraaortic involvement in patients in initial stages only occurs in 1% of the cases and some authors have warned of a possible risk of tumor dissemination

Table 3
Number and anatomical localization of the sentinel lymph nodes (SLNs) detected in the scintigraphic studies and during intraoperative localization.

<table>
<thead>
<tr>
<th>N°</th>
<th>Planar SLN</th>
<th>SPECT-CT SLN</th>
<th>Intraoperative SLNs</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>Common iliac and external right and interaortocaval</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>External right iliac</td>
</tr>
<tr>
<td>3</td>
<td>2 (24 h)</td>
<td>0 (2 h)</td>
<td>2</td>
<td>External iliac and right obturator foramen</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>External iliac and right obturator foramen</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Right and left external iliac</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>External iliac, inguinal and common iliac</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>Right external iliac and paraaortic</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>Right obturator foramen</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Left internal iliac</td>
</tr>
<tr>
<td>10</td>
<td>1 (24 h)</td>
<td>–</td>
<td>1</td>
<td>Left external iliac</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>Right external iliac</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>Left and right external iliac</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>Common left iliac</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>Left external iliac</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Left external and common iliac</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>Right obturator and common iliac</td>
</tr>
<tr>
<td>17</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>Right external iliac</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>33</td>
<td>29</td>
<td>–</td>
</tr>
</tbody>
</table>
through the Fallopian tubes secondary to uterine distension during hysteroscopy.  

Cervical injection is much easier, reproducible and less uncomfortable for the patients while also avoiding the eventual risk of neoplastic dissemination with hysteroscopy. On the other hand, the obtainment of paraaortic lymph nodes was lower. Thus, in the present study we opted for this route of tracer administration which, despite only showing one case of migration to the paraaortic chain, allowed easier and more comfortable injection for the patient with a good rate of posterior lymph node detection. In any case, in both peritumoral and subserosal as well as cervical injection the rate of sentinel lymph node detection improved with the use of double tracer with isotopic lymphoscintigraphy and injection of vital staining immediately prior to the surgery. Most of the studies performed report detection rates of around 80%, being lower than those observed in other tumors such as cancer of the cervix. This difference is attributed to the complexity of lymphatic drainage of the uterine body and possibly the delay between the injection of the radiotracer and the intervention, a procedure that is usually scheduled on two successive days. Some authors have described better results on increasing the volume of the injection. On the other hand, the obtainment of late images in our study allowed identification of lymph nodes not observed in the initial study in one case suggesting that this may be a valid alternative to attempt to identify lymph nodes not visible in the initial study. With respect to the SPECT-CT study, although the total number of lymph nodes detected did not significantly vary considering the sample as a whole (31 lymph nodes visible with planar technique, 33 with SPECT-CT) which may have been due, in part, to the scarce sample size, more precise presurgical knowledge of the location of the lymph nodes provided by the SPECT-CT techniques facilitated their localization during the intervention. Finally, in the last years studies have been performed to determine the possible influence the presence of small size lymph node metastasis or even micrometastasis may have on the prognosis and the adjuvant approach in these patients. This circumstance would contribute greater relevance to the use of the sentinel lymph node technique which allows a more detailed study of a very limited number of lymph nodes multiplying the probability of finding lymph node involvement with respect to conventional techniques. One of the limitations of the results of our study is precisely that detailed data of the histological study of the sentinel lymph node, which includes the performance of multiple thin slices and the use of immunohistochemistry techniques, have not yet been obtained.

**Conclusion**

The preliminary results reported here suggest that the sentinel lymph node technique may represent an alternative in the management of women with endometrial carcinoma in early stages. It could be especially indicated in women with an intermediate or high risk in whom pelvic lymphadenectomy must be systematically performed to avoid the associated morbidity and providing reliable knowledge of the grade of lymphatic extension of the disease. Nonetheless, although the experience reported in the literature is promising, it is, to date, scarce, and thus, in most centers this technique is not yet a part of the routine management of these tumors.

**Conflict of interests**

The authors declare no conflict of interests.

**References**


