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Sentinel lymph node in early stage ovarian cancer; a literature review

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Review

Sentinel lymph node in early stage ovarian cancer; a literature review

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Abstract

Although sentinel lymph node mapping has been widely implemented in gynecological malignancies in order to minimize the number of unnecessary lymph node dissections and to diminish postoperative morbidity rate, little is known about ovarian cancer sentinel lymph node mapping. This article presents a literature review regarding the effectiveness, safety and benefits of this method.

Sentinel lymph node detection in early stage ovarian cancer seems to be a safe and effective method, able to minimize the rate of patients submitted to unnecessary lymph node dissection. The second goal of the procedure, to minimize the risk of missing involved lymph nodes, seems also to have been achieved, most studies reporting a very small number of cases diagnosed with positive non-sentinel lymph nodes.

Considering all these data we can note that this procedure is not yet included as part of the standard therapeutic protocol, so that further studies would be necessary to include it as a common therapeutic approach in the case of patients with early stage ovarian cancer.

Keywords : sentinel lymph node, early stage ovarian cancer, mapping, standard therapeutic protocol

Highlights

- ✓ In early stage ovarian cancer, the sentinel lymph node detection seems to be a safe and effective method, able to limit unnecessary lymph node dissection.
- ✓ The risk of not identifying invaded lymph nodes is relatively low, most studies reporting a very small number of cases diagnosed with positive non-sentinel lymph nodes.

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Introduction

Ovarian cancer is one of the most common malignancies and the leading cause of death from gynecological cancers, especially due to the fact that most cases are diagnosed in advanced stages of disease when disseminated lesions are already present. However, up to one third of ovarian cancer patients are diagnosed in early stages of disease, with improved chances of long-term survival. Moreover, such cases present a low incidence of lymph node involvement; therefore, these women would not benefit should routine lymph node dissection be performed, while simultaneously being exposed to a higher risk of perioperative complications. In such patients, performing an extended lymph node dissection is usually associated with a longer operative time, a longer hospital stay, a larger amount of blood loss, and an increased risk of developing lymphoceles or chronic lower limb lymphedema without improving the survival rate (1-5).

Discussions

The pattern of ovarian lymphatic drainage

Studies regarding the pattern of lymphatic drainage of the ovaries demonstrated that in up to 84% of cases an isolated para-aortic drainage is expected, in 8% of cases isolated pelvic drainage is seen, while the remaining 8% of patients will experience both pelvic and para-aortic drainage (6). The development of para-aortic and para-caval metastases is explained by the dissemination through the lymph vessels accompanying the ovarian artery and vein, in the suspensory ligament while the appearance of pelvic metastases is explained by the tumor cell migration along the proper ovarian ligament to the para-uterine vessels, the broad ligaments, and further toward the iliac vessels (3, 4, 7).

Principles of sentinel lymph node detection after injecting the tracer in the ovarian area.

The principle of sentinel lymph node mapping has been initially studied in cases with normal ovaries or in patients submitted to surgery for ovarian cysts. The procedure consists of radiotracer injection in the mesovarian tissues; sentinel lymph nodes are detected at a mean interval of 4-6 hours after injection by performing a lymphoscintigraphy and are mainly detected in the para-aortic or pelvic and para-aortic areas. Interestingly, in post-menopausal women, isolated para-aortic drainage was seen more frequently when compared with pre-menopausal subjects (6, 8).

As for the chosen tracer, it must be a small particle size in order to provide rapid dissemination from the site of injection into the lymphatic system and therefore, a rapid accumulation in the sentinel lymph nodes (9, 10). Association between radioactive tracer and blue dye is also known under the generic name of dual mapping method and seems to decrease the rate of failure or false negative sentinel node detection (5, 11). However, the blue dye might disappear from the lymph nodes if a longer period of time passes between injection and exploration; moreover, certain authors have reported a higher risk of adverse reactions after blue dye injection, such as allergic reactions, including anaphylactic shock (12, 13).

Regarding the site of injection, subcortical or sub-peritoneal, intraligamentary injection has been proposed; while subcortical injection seems to be associated with a lower detection rates as well as with the risk of tumor puncture, the sub-peritoneal, intraligamentary route seems safer and more effective (5).

Due to the high risk of tumoral dissemination if ovarian cortex is injected, certain authors contraindicate this maneuver, routinely recommending intra-ligamentary, sub-peritoneal injections. The first study which evaluated the injection of the ovarian ligaments was conducted by Kleppe et al. in Maastricht University Medical Center, The Netherlands, and was published in 2014 (12). The authors included 21 patients in whom blue dye and radioactive isotope were injected on the ventral and dorsal side of the proper and suspensory ligaments of the ovary, underneath the peritoneal shield. Fifteen minutes after injection, the ovarian mass was resected and sent to frozen section, while the lymph node regions were examined by using an 11-mm straight gamma probe; any lesion presenting a radiation signal of at least 10-fold higher than background radiation was considered positive. In the meantime, the main lymphatic areas were classified as upper or lower para-aortic regions (separated by the origin of the inferior mesenteric artery), upper and lower paracaval regions, and right or left pelvic regions. After sending the adnexal masses for frozen section examination, seven cases proved to have a benign tumor, eight presented borderline tumors while the remaining six cases were diagnosed with epithelial ovarian cancer. After injecting the radioactive tracer, hot spots were present only in the para-aortic/para-caval region in 67% of cases, in the pelvic region only in 9% of cases, and in both para-aortic/para-caval and pelvic regions in 24%, all but two of the 3 identified sentinel lymph nodes being located on

the ipsilateral side. Moreover, patients presenting left ovarian tumors reported the presence of sentinel lymph nodes between the inferior mesenteric artery and the left renal vein while patients diagnosed with right ovarian masses were mainly located in the close proximity of the origin of the inferior mesenteric artery.

In all six cases in which para-aortic sentinel lymph nodes were discovered, a high capitation of the radiotracer was identified by using the gamma probe while two of these six patients also associated a blue staining of the sentinel lymph nodes. However, the reduced number of sentinel lymph nodes which were identified by using the blue staining technique was explained by the longer period of time between blue dye injection and retroperitoneal space exploration. A total of 18 sentinel lymph nodes were retrieved; in one case in which four sentinel lymph nodes were retrieved, three of the four presented metastases.

Therefore, the patient was submitted to a complete lymph node dissection, another positive, non-sentinel lymph node being discovered. In fact, this was the single case in which positive, metastatic sentinel lymph nodes were diagnosed; in all the other five cases none of the retrieved sentinel lymph nodes presented any tumoral involvement. When analyzing the radiation exposure to personnel, the mean exposure for the surgeon during three procedures was 0.06 mSv at the dominant hand and 0.17 mSv at the non-dominant hand. Therefore, the authors concluded that the method of intra-ligamentary injection of radiotracer or blue dye is a safe and effective method to correctly identify the sentinel lymph nodes in early stage ovarian cancer. Moreover, it seems that the exposure of personnel is minimal (12).

The role of postoperative lymphoscintigraphy after performing a sentinel lymph node excision procedure

Certain authors consider that performing a postoperative lymphoscintigraphy is the only method able to confirm the complete excision of all sentinel lymph nodes in patients with malignant lesions. Moreover, in patients with benign lesions, such imagistic studies can show the exact location of the sentinel lymph node and, therefore, can show the pattern of ovarian lymphatic drainage (5).

The role of sentinel lymph node biopsy in early stage ovarian cancer

Although the principles of sentinel lymph node mapping have been widely implemented in other gynecologic malignancies such as breast, cervical, endometrial, or vulvar cancer, data regarding ovarian cancer are rather scarce, only a few studies being conducted thus far. Given the estimated incidence of positive lymph node in early stage ovarian cancer ranging between 5-15%, sentinel node technique has been recently proposed for such cases in order to clearly identify which cases could benefit from an extended lymph node dissection and in which cases this procedure might be avoided in order to diminish the postoperative morbidity rate (14, 15).

In their study, Hassanzadeh et al. included 35 patients diagnosed with ovarian tumors (5). Sentinel lymph node mapping was provided by Tc-99m-phytate injection just after performing laparotomy; in the first 10 cases the tracer was injected in the normal cortex of the ovary while in the remaining 25 cases the injection was performed in the utero-ovarian and suspensory ligaments, in close proximity to the affected ovary. In the meantime, in four cases belonging to the second group, patent blue dye was also injected at the same points as the radiotracer. Ten minutes after injection the adnexal mass was resected and was sent for frozen sectioning. Once the diagnosis of malignancy was established, the sentinel nodes were identified using a hand-held gamma probe in the para-aortic and pelvic areas. All lymph nodes with three times more count than baseline were considered as sentinel, were resected, and sent for histopathological study while the surgeon completed the lymph node dissection.

In patients diagnosed with benign or borderline ovarian tumors, gamma probe was used to locate the hot areas. In the first day postoperatively, all patients were referred to the nuclear medicine service to submit to pelvic and abdominal lymphoscintigraphy. Among the 10 cases in which injection was performed in the ovarian cortex, three had malignant lesions while the remaining seven proved to be benign. As for the identification of sentinel lymph nodes, this method was successfully performed in four cases (two cases with benign lesions and the other two with malignant tumors). Among the other 25 patients who were submitted to intra-ligamentary, subperitoneal injections, the frozen sections revealed 11 malignant lesions, one borderline tumor, and 13 benign tumors; sentinel lymph node detection was possible in 21 cases (all cases with malignant tumors and in 10 cases with benign lesions).

An important factor that influenced the possibility of detection of sentinel lymph nodes was the association with ovarian torsion, in none of the four cases presenting adnexal torsion sentinel lymph node detection being impossible. This fact is mainly explained through the interruption of the lymphatic flow once the torsion has occurred. As for the areas in which the sentinel lymph nodes were found, in 12 cases they were reported only

in the para-aortic area (all patients presenting benign lesions), in the other nine cases they were identified in both pelvic and para-aortic areas, while in two cases (both with malignant pathology) sentinel lymph nodes were found in the pelvic area. In all cases in which blue dye injection was associated, all sentinel lymph nodes (detected by gamma probe usage) were colored in blue. Moreover, three patients with malignant lesions presented involved lymph nodes on pathology, all of them being previously diagnosed as sentinel lymph nodes; therefore, the sensitivity rate was 100%, no false negative result being encountered. The first patient who was diagnosed with a positive sentinel lymph node was a 60-year-old who was submitted to surgery for bilateral ovarian tumors, the frozen and histopathological studies demonstrating the presence of a papillary serous adenocarcinoma. After injecting the tracer, three hot sentinel nodes were identified (two among the para-aortic lymph nodes and one in the obturatory fossa), two of the three nodes being finally involved. Although complete pelvic and para-aortic lymph node dissection were associated, no other positive lymph node was found.

The second case was a 35-year-old patient diagnosed with bilateral ovarian tumors which proved to be a papillary serous adenocarcinoma; two hot and blue sentinel lymph nodes were seen in the para-aortic area, one of them being pathologically involved. Although surgery was completed by performing a total hysterectomy with bilateral adnexectomy, pelvic and para-aortic lymph node dissection, no other positive lymph nodes were found. The third case was a 35-year-old female woman diagnosed with bilateral papillary serous adenocarcinoma, two hot and blue sentinel lymph nodes being found in the para-aortic area. One of them proved to be histopathologically positive; in the meantime, after completing the procedure by performing a total hysterectomy with bilateral adnexectomy and pelvic and para-aortic lymph node dissection, another positive para-aortic non-sentinel lymph node was found. Moreover, in the second postoperative day, when performing the test lymphoscintigraphy, no remaining activity was seen either in pelvis or in the abdominal cavity in any of the three cases (5).

More recently, identifying the sentinel lymph nodes by using indocyanine green (ICG) injection has been proposed in patients with gynecological malignancies. Preliminary reports demonstrated the safety and effectiveness of the method in patients with endometrial cancer, further evaluation in other gynecological malignancies including ovarian cancer being expected (16). One of the first reports regarding the feasibility of ICG technique in early stage ovarian cancer was reported this year by Isid and colleagues from Nantes Hospital, France. The authors reported the case of a 47-year-old patient diagnosed with grade 3 endometroid ovarian cancer confined to the ovary after a laparoscopic right adnexectomy.

Twenty days later the patient was submitted to a comprehensive surgical staging, so that the ICG injection was performed. The sites of injection were the uterine cervix—in order to identify any pelvic sentinel lymph node—and the right infundibulopelvic ligament—in order to identify any para-aortic lymph node. When inspecting the pelvic and para-aortic lymphatic areas by using a near infrared high intensity light source, one sentinel lymph node was identified in each hemipelvis and one in the supramesenteric infra-renal area. Due to the experimental nature of the ICG technique in ovarian cancer, the authors decided to perform an extended lymph node dissection; however, none of the resected lymph nodes (sentinel or non-sentinel lymph nodes) were involved (17).

Conclusions

Sentinel lymph node detection in early stage ovarian cancer seems to be a safe and effective method to minimize the rate of patients submitted to unnecessary lymph node dissection. In the meantime, the second goal of the procedure, to minimize the risk of missing involved lymph nodes, seems also to have been achieved, most studies reporting a very small number of cases diagnosed with positive non-sentinel lymph nodes. However, further studies are necessary in order to standardize this method as part of the therapeutic protocol of these patients.

Conflict of interest disclosure

The authors declare that there are no conflicts of interest to be disclosed for this article.

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