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Minimum invasive sentinel lymph nodes dissection in cervical, endometrial and vulvar cancers

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ABSTRACT

Genital cancer in women is an ongoing challenge. A correct diagnosis together with a correct staging can lead to a favorable oncological or surgical conduct with an improvement of the prognosis. A literature review was performed to find relevant information regarding the sentinel node mapping in uterine and vulvar cancer. Different dyes are available, but the bioavailability and toxicity of green indocyanine are factors that seem to bring superiority to this tracer. Tracing the sentinel node with green indocyanine is a method that involves special equipment, but the benefits are visible.

Keywords: sentinel lymph node, indocyanine green, fluorescence, cervical, endometrial, vulvar cancer

INTRODUCTION

The most widely used method currently used to evaluate lymph nodes (LN) for staging purposes is to carry out a systematic lymphadenectomy. However the downside of this procedure this is its high degree of morbidity, especially if adjuvant therapy is simultaneously given [1]. Complications include lymphedema, lymphocyte formation, deep vein thrombosis, pressure-associated symptoms, and altered limb sensation. Therefore, minimally invasive surgical procedures are needed to reduce postoperative morbidities linked to systematic lymphadenectomy [2,3].

Sentinel node biopsy (sentinel node) involves the removal of a sentinel or guard node, which is the first one involved in the progressing chain of a tumor from primary cancer to lymph nodes. In case of a negative result, it is assumed that the other ganglion is not involved. Sentinel lymph node status may influence the overall oncology treatment plan including radiation, chemotherapy, or both. Amongst gynecologic cancers, the sentinel node could significantly impact women with endometrial cancer. Sentinel node biopsy is performed on many women with breast cancer and it will likely become the standard protocol for women suffering of vulvar cancer under NHS [4].

SENTINEL LYMPH NODE DETECTION IN CERVICAL CANCER

Bilateral pelvic lymphadenectomy is one of the standard surgical treatments of early-stage cervical cancer [5-7]. The pelvic lymph node involvement rates are only 0% to 4.8% for stage IA, 0% to 17% for IB, 12% to 27% for IIA, and 25% to 29% for IIB [5,8,9].

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Therefore, most patients receive pelvic lymph node dissection on a routine basis if there is no metastasis. This causes many complications, such as lymphedema [10], nerve injury, bleeding, ureteral injury, sensory loss, and lymph cyst formation [11]. Much research has been performed on sentinel lymph node (SLN) detection using safe and effective tracers, especially in clinical use [12]. This detection reduces the morbidity rate because it can show the position of local and regional lymph nodes in patients with cervical cancer [13].

The most common region in which the sentinel node was detected was around the external iliac vessels and in the space between the external and internal iliac vessels. [14-16]. About 10% of the sentinel node is located in less common regions. These regions include the pelvis of the presacral, parametric, or internal ganglia. More importantly, in 4-9% of patients, the sentinel node was located above the aortic bifurcation in the paraaortic region [15,16]. An important advantage of sentinel node biopsy is the identification of the sentinel node that are in less typical locations.

Recently, a new technique based on fluorescence imaging has been introduced in cervical cancer. Green indocyanine (ICG) is injected into the cervix as a tracer and detected by fluorescence imaging in the retroperitoneum. In 227 cases collected in three US institutions, there was an overall sentinel node detection rate of 95% and bilateral detection of 79% [17,18].

A 25-mg single container was utilized for each surgery. ICG was mixed with 20 ml of normal saline, ending up with a 1.25 mg/ml of ICG. Under general anaesthesia and before introducing the uterine manipulator, a total of 4 ml of ICG was injected directly to both sides of the uterine cervix, deep into the stroma and superficially as well. By assessing the retroperitoneum with a fluorescence camera, the SLN was identify, removed and sent to pathology [19].

SENTINEL LYMPH NODE DETECTION IN ENDOMETRIAL CANCERS

Lymphadenectomy in endometrial cancer will always be a hot topic causing a never ending discussion. Lymph node involvement is a keystone factor both for prognosis and treatment in endometrial cancer. The therapeutic value of lymphadenectomy is questionable. Value of sentinel lymph node (SLN) mapping technique resides in providing the necessary information while avoiding the morbidity related with a complete lymphadenectomy [20,21]. Multiple studies have tried cervical, subserosa and uterine hysteroscopic injections of blue or technetium-99 colloid, achieving an unsatisfactory detection rate of less than 80% [20-22]. Utilizing infrared fluorescence imaging, upon intracervical injection with indocyanine green (ICG) provides a higher detection rates in the range of 87-100% and appears superior to the use of blue dye or radioactive colloid [20,23-27].

SENTINEL NODE DETECTION IN VULVAR CANCER

The incidence of vulvar cancer is increasing over the last decades [28,29]. In 20% to 30% of patients, inguinal lymph node metastasis is present at diagnosis, which represents the most important prognostic factor of vulvar cancer [28,30,31]. The risk of inguinal metastasis correlates with the depth of infiltration and increases rapidly from an infiltration over 1 mm. With an infiltration below 1 mm (pT1a), inguinal metastases are uncommon [28,32]. Complete groin dissection lymphadenectomy is associated with considerable short- and long-term morbidity consisting of wound breakdown/infections in up to 30% of patients, particularly lymphoceles and lymph edema in up to 40% [28,33-34]. In the last years, inguinal sentinel lymph node dissection has been shown to be safe in unifocal vulvar cancer up to a tumor size of 4 cm with clinical unsuspicious lymph nodes and is now considered or even recommended in many guidelines [28,35-38]. The prognosis of an inguinal recurrence is poor and associated with a high mortality [28,38-39]. Therefore, high attention has to be directed to a correct application of both sentinel diagnostic and extirpation. The criterion standard of sentinel mapping in vulvar cancer is the use of radioactive technetium 99m (99mTc)Y labeled nanocolloid. In addition, mapping with patent blue may be performed, which is associated with significantly lower detection rates compared with 99mTc-labeled compounds [28,40]. Recently, successful sentinel lymph node detection and resection using near-infrared fluorescence by indocyanine green (ICG) have been reported for cervical cancer and endometrial cancer [28,41-43].

In the detection of sentinel lymph nodes in this type of cancer, an exoscope can be used. A total of 8 ml of green indocyanine solution is injected into the peritumoral area both superficially and at a depth of approximately 1 cm. Ten minutes after the follow-up injection, the first lymphatic drainage can be detected by transcutaneous fluorescence. At this stage of the procedure, an incision in the skin is placed parallel to the inguinal ligament. The lymphoid tissue is revealed. Integrity of the lymph vessels is importand, thus preventing unjustified leakage of the tracer. With the exoscope coupled to a infrared technology video the sentinel node can be identified and removed and sent to analysis [17].

DIFFERENT SENTINEL NODE DETECTION DYES

Historically, the first group of tracers used to map the sentinel node was that of radiolabeled colloids, usually the Technetium 99mTc isotope. Depending on the protocol applied for the next administration, 99mTc are injected between 20 and 24 hours ("long" protocol), 2-4 hours ("short" protocol) or intraoperatively ("ultrashort" protocol) [14,44]. The use of a colored non-radioactive dye, such as indocyanine green, is clearly preferred for several reasons. After injection of the radiopharmaceutical, performed preoperatively in a protected environment (nuclear medicine department), the tracer is transported with lymph to the sentinel nodes, where intraoperative detection is possible with the interpretation of an audiometric signal [45].

While potential adverse reactions have been identified with the use of blue dyes (such as methylene blue, patent blue and isosulfan blue), the risk profile of indocyanine green is excellent [46]. Blue dyes are easy to use because they do not require dedicated equipment and are based on a colorimetric signal that is easy to detect. However, blue dyes travel rapidly through the lymphatic system to the sentinel node, from where they migrate further to the echelon nodes. The sentinel node will usually turn blue within 5 to 10 minutes of injection and will remain stained for about 30 minutes or more. If the sentinel node cannot be promptly identified within this time, there is a risk that it may not be identified at all or that an echelon node, which has been stained in the meantime, may be taken as a sentinel node and biopsied instead [17].

Indocyanine green is a compound with extremely low toxicity. The dye can be injected intraoperatively and does not require additional preoperative imaging. Unlike 99mTc sentinel node mapping, which usually needs to be injected without anesthesia the day before surgery, followed by preoperative radiological imaging, most patients perceive the quality of care as higher when using green indocyanine dye. Similar to dyes blue, green indocyanine ICG travels rapidly through the lymphatic system to the sentinel node from where the agent migrates downstream to reach the echelon nodes. Unlike blue dyes, indocyanine green ICG accumulates in the sentinel node for a longer period of time, even after adjacent downstream nodes have been identified by fluorescence and therefore dependence. Time is not an issue for sentinel node mapping guided by enhanced fluorescence of indocyanine green. Another useful feature of the second method is that the fluorescent signal generated infrared illumination is usually very strong and easy to detect. The overall and bilateral sentinel node detection rate has been consistently reported to be higher when using green indocyanine fluorescence images instead of 99mTc and / or blue dyes [17].

CONCLUSIONS

Sentinel lymph node dissection has been widely implemented in the field on gynecologic surgery in order to avoid unnecessary lymph node dissection and to provide a proper staging of the oncologic disease. Although multiple methods have been proposed so far, it seems that indocyanine green represents the most efficient diagnostic tool.

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