Sentinel lymph node mapping in gynecological oncology (Review)

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Abstract. The intraoperative mapping of sentinel lymph nodes (SLNs) is part of the treatment strategy for a number of types of tumor. To retrospectively compare results from the mapping of pelvic SLNs for gynecological oncology, using distinct dyes, the present review was conducted to determine the clinical significance of SLN mapping for gynecological oncology. In addition, the present study aimed at identifying an improved choice for SLN mapping tracers in clinical application. Each dye exhibits demerits when applied in the clinical environment. The combination of radioisotopes and blue dyes was identified to exhibit the most accurate detection rate of SLN drainage of gynecological oncology. However, contrast agents were unable to identify whether a SLN is positive or negative for metastasis prior to pathologic examination; additional studies are required.

Contents

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Abbreviations: SLN, sentinel lymph node; ICG, indocyanine green; ISB, isosulfan blue

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1. Introduction

The presence of lymphatic metastases of solid tumors is an important factor that affects the prognosis in all types of cancer (1-5). In gynecology, surgical treatment is typically combined with radical excision of the local tumor, with full lymphadenectomy in the drainage areas of the tumor. However, pelvic lymph node metastases were identified in between 21 and 26%, only, of patients with stages Ib and stage II (6-8), and ≤27% in early-stage cervical cancer (7-14). In early-stage endometrial cancer, the frequency of lymph node metastasis varies between 0 and 34% (15). Patients with pelvic lymphadenectomy may experience a number of complications (16), including lymphedema, nerve injury (17) and infection (18,19), particularly patients who are obese, elderly and with cardiovascular diseases (20,21). As an alternative, the sentinel lymph node (SLN) procedure was introduced in 1977 by Cabanas (22) to determine metastasis to the first lymph node by the original tumor (23). When lymphatic metastases occur, the SLNs will be primarily involved (24) and it is hypothesized that if the SLNs do not exhibit metastases, downstream lymph nodes may not exhibit tumor metastases (25). The concept of lymphatic mapping was introduced by Morton *et al* (26) at the end of the 20th Century, cutaneous lymphoscintigraphy with colloidal gold was used to identify the lymphatic drainage pattern of melanomas located at ambiguous sites. Since 1977, SLN mapping procedures have been included in the treatment for a number of types of tumor, including vulvar (27-29), breast (30), anal (31), colon (32), skin (33), gastric (34), penile (35), esophageal (36), bladder (37), prostatic neoplasm (38) and non-small cell lung cancer (4). A variety of types of lymphatic drainage tracers have been used, including radioisotopes (39), blue dyes (40), indocyanine green (ICG) (41,42) and a limited number of novel agents. The present review aimed at introducing a brief concept of a number of types of lymphatic tracers and to provide guidelines of SLNs mapping for gynecological cancers.

2. Literature search

A literature search in PubMed of articles published between January 1, 2000 and May 20, 2015 was conducted to identify

studies of SLN mapping using key words including 'dyes and sentinel nodes mapping in gynecological cancer', 'dyes and SLN drainage in gynecological oncology', 'blue dyes and sentinel node mapping in gynecological cancer', 'ICG and sentinel node mapping' and 'radioisotopes and SLN mapping'. Searches were restricted to human studies and studies published in the English language. In addition, other auxiliary examinations for SLN information, including transvaginal ultrasound of the pelvis, computed tomography, magnetic resonance imaging and positron emission tomography-computed tomography, and case studies of sentinel node mapping were excluded from the search. Citation lists of the selected studies were verified to ensure sensitivity of the search methods.

3. Lymphatic tracers

The principal lymphatic tracers for SLNs of gynecological oncology are radioisotopes, blue dyes, ICG and a limited number of novel agents. Studies were reviewed to introduce concepts of the clinical advantages and disadvantages of these tracers.

4. Radioisotopes and SLN mapping

Injection of radiolabeled colloids with intraoperative detection of the sentinel nodes, using gamma-ray detection probes, for breast cancer was introduced in 1993 by Krag *et al* (43). Surgeons localized the SLNs intraoperatively, on the basis of the signal coming from a hand-held gamma probe (44,45). Injection of the radioisotope may be performed 1 day before surgery or on the morning of surgery (46). ^{99m}Tc-labeled human serum albumin colloids and filtered ^{99m}Tc-sulfur colloids, two synthetic colloids, exhibit either low residence time in the SLNs or a low clearance rate from the injection site (47-50). Although other radiolabeled colloids may be used (including ^{123}I and ^{201}Tl), the short half-life of ^{99m}Tc enables shorter radioactive exposure for patients while allowing >24 h to determine positive nodes. In addition, smaller particles enable ^{99m}Tc to flow into secondary lymph nodes more rapidly, therefore enabling the determination of an increased number of positive nodes (51-53). Tissue depth, density and coloration may not affect ^{99m}Tc-based lymphotropic agents due to the highly penetrating gamma radiation.

In gynecology, the SLNs may be identified prior to surgery by lymphoscintigraphy, using an injection of radioisotopes. Pre- and intra-surgical lymphatic mapping, using ^{99m}Tc-labeled phytate was effective in identifying SLNs in patients undergoing radical hysterectomy and enabled patients to avoid a lymphadenectomy (54,55). Larger particles typically remain longer in lymph nodes; phytate may be more effective in SLN detection, compared with other agents in use. Ogawa *et al* (56) revealed that the sensitivity of ^{99m}Tc-labeled phytate was 100% and the false negative rate was 0%. In addition, Dzvincuk *et al* (57) identified that the rate of SLN detection was 79%. ^{99m}Tc-sulfur colloid has been identified to improve, compared with isosulfan blue dye, the detection of SLNs in inguinal dissections of patients with vulvar cancer (58), and Bogliolo *et al* (59) revealed a detection rate of 100% in patients with vulvar cancer. ^{99m}Tc-tilmanocept, which has been approved by the US Food and Drug Administration, demonstrated advantages in head and neck squamous cell carcinoma; however, the efficiency for gynecological oncology remains unknown (60).

The current gamma cameras are not able to provide adequate anatomical information, resulting in the radioactive signal depicted against a two-dimensional black background (61). Radiolabeled isotopes require enough time prior to surgery to enable transit time to SLNs, which may be 1 day before imaging. Additionally, the time between lymphoscintigraphy and surgery remains distinct and has been identified to be 1 day (51,62), between 3 and 6 h (63), or an interval <1 h (64). Although it has been demonstrated that small particles may be taken up by second- or third-tier lymph nodes, an increased volume of injected radiocolloid may be required to decrease distribution (65). Furthermore, the radio signals may be received by an audible gamma-probe when the signals are increased ≥10-fold, compared with background levels (66). Surgeons and patients may receive radio injury prior to and during the surgery; therefore, the organization of pre-surgical radiocolloid application and subsequent lymphoscintigraphy may be difficult and costly (67). If the SLNs are proximal to the original tumor, the 'hotspot' may be lost in the primary injection site, which may be problematic in cancer.

5. Blue dye and SLN mapping

The introduction of blue dye mapping was initially introduced by Morton *et al* (26) in 1992 and it was initially demonstrated in breast cancer in 1994 by Guiliano *et al* (68). Compared with the increased waiting time for radio isotope dyes to migrate to the lymph nodes, the injection of blue dyes may be administered to patients under anesthesia in surgery (46). Without a gamma-probe, blue dyes are readily taken up by the lymphatics and enable the surgeon to achieve intrasurgical lymphatic mapping of the regional basin. No preparation is required and blue dyes may be stored at room temperature.

Akrivos *et al* (69) revealed that the overall detection rate exhibited by blue dye was increased, compared with that exhibited by ^{99m}Tc in previous studies (58,70). The SLN positivity rate was identified to be 23% in endometrial cancer by Kuru *et al* (71). The overall sentinel node identification rate was 44% in a previous study of endometrial cancer (72). *Schwendinger et al* revealed that the detection rate for SLNs was 83% (73). The SLN detection rate was identified to be markedly increased in laparoscopy compared with that in laparotomy, following patent blue violet pericervical injection, in females with early-stage endometrial cancer (73). The SLN detection procedure using the blue dye technique is a feasible procedure in cervical cancer, as patent blue dye is a cheap, safe and effective tracer which may be used to determine sentinel nodes in carcinoma of the cervix (74). The sensitivity and negative predictive values were 90 and 97%, respectively, in early-stage cervical cancer (73). The detection rate of patent blue in cervical cancer has been identified to be 71% (67) and O'Boyle *et al* (75) revealed that the SLNs were identified in 60% of patients with cervical cancer.

Blue dyes are easily prepared and exhibit a limited number of risks to patients and surgeons; however, the efficiency of blue dyes in the identification of SLNs is limited. The low molecular mass of blue dyes enables rapid migration in the lymphatics and the retention of the dye in SLNs is poor. As a result, there is limited time for the surgeon to locate and remove the SLNs prior to the dye spreading to other nodes. Typically, dyes are useful only for visualizing superficial lymph nodes (for instance, in breast cancer and melanoma) blue dyes have difficulty reaching SLNs that reside in deep locations, particularly in overweight patients (76). Although uncommon, patients may exhibit an allergic reaction to patent blue dyes (77,78), as cases of anaphylactic shock have previously occurred during the sentinel node procedure in patients with melanoma and breast cancer (79-82).

6. ICG and SLN mapping

ICG was initially used as a visible dye marker in the detection of SLNs and it had success comparable with that of conventional dyes. ICG is easy to use, cost-effective, safe and has been used as a tracer for >40 years in clinical use (83,84). Fluorescence-guided imaging with ICG has a number of advantages, compared with conventional methods, including real-time lymphography, a low incidence of adverse reactions and an increased sensitivity, without requiring radiation.

The detection rate of fluorescence imaging with ICG has been identified to be increased, compared with that of colorimetric imaging with isosulfan blue (ISB), in females with endometrial cancer undergoing SLN mapping (76). ICG exhibited a markedly increased SLN detection rate, compared with that of blue dyes, in overall and bilateral detection (85). ICG alone exhibited an increased detection rate compared with that exhibited by a combination of blue dye and ICG (95 vs. 93%, respectively) for uterine and cervical malignancies (86). In addition, the SLN detection rate was 82 and 33% for cervical and hysteroscopic endometrial injection of ICG, respectively, in endometrial cancer (87).

The low molecular mass of ICG enables rapid migration in the lymphatics to the SLNs (between 1 and 10 min); however, the feasibility and accuracy of SLN mapping using ICG adsorbed to human serum albumin has been demonstrated, considering safety, cost and pharmacy preferences in vulvar cancer (88). These approaches have not demonstrated statistically significant improvements in the detection rate; however, the approaches have been identified to improve the strength of the fluorescent signal (41,89,90). Furthermore, leakage and adaptation of ICG fluorescence, causing halation of the image or an autofluorescent glow in the surgical field, has been identified. When the primary SLN was removed, ICG spreading throughout the surgical field makes the identification of other fluorescent nodes difficult. This problem was circumvented by ligating the primary lymphatic duct at a site proximal to the initial SLN to avoid lymphatic fluid retention; ligation of the afferent lymphatic vessel prevents ICG from accumulating in the surgical field (83,84).

7. Combination of dyes

The combined techniques appear to exhibit the most sensitivity and highest SLN detection rates (24), with the combination of ^{99m}Tc and blue dyes identified as the most successful, in comparison with other methods (1,21,24,51,67,91-113). Premixing ICG with Tc-nanocolloid provides real-time intrasurgical imaging of the SLNs and appears to be the optimal tracer combination, in terms of the intrasurgical detection rate of the SLNs (106,114). Radioisotope injection into the uterine cervix is useful and safe when combined with blue dye injection into the uterine body for early-stage endometrial cancer (112). However, Frumovitz *et al* (105) demonstrated that the combination of blue dye and the radiocolloid may not be a useful method in patients with endometrial cancer exhibiting increased risk factors.

8. Novel dyes for SLN mapping

Novel dyes including cadmium tellurium quantum dots (115), hybrid tracers (116), near-infrared-emitting polymer nanogels (117), fluorescent-labeled ^{99m}Tc-tilmanocept (118), poly (ethylene glycol)-conjugated bright near-infrared dye (119) and ^{99m}Tc- and ^{68}Ga-multimodal dextran-based probes (120) have been used for SLN drainage mapping, which exhibited novel advantages; although additional studies are required to be of use in the clinical environment.

A number of injection sites have been described in a previous study, including the cervix, myometrial (sub-serosal), peritumoral by hysteroscopy or by transvaginal ultrasonography, cervical and corporeal injections, which all exhibited improved overall detection rates (121). SLN biopsy, obtained through hysteroscopic injection of ^{99}Tc, was identified to be a feasible and safe method (122). Cervical injection, using either blue dye or a radiotracer, results in an increased detection rate and sensitivity (98). Furthermore, a meta-analysis by Kang *et al* (97) revealed that a cervical injection was the only anatomical site that markedly improved SLN detection. One criticism of cervical injection for endometrial cancer SLN detection is the difference in lymphatic drainage between the cervix and uterine fundus. However, in previous anatomical studies, deep injection into the cervix has demonstrated improved penetration to uterine vessels, parametria, lower uterine segment and cornual regions (46,107). An additional study indicates that cervical injection of dye is a reliable method of identifying the lymphatic drainage of the uterus. However, the technique and timing of application is important for the increased detection rate, particularly when using blue dye and ^{99m}Tc radiocolloid, as the size of the contrast agent affects the uptake into the lymphatic system, speed of transport through the system and retention inside drainage lymph nodes (123).

9. Conclusions

There are several types of lymphatic drainage tracers that may be used in the SLN mapping of gynecological oncology. All tracers mentioned exhibit a number of disadvantages in the mapping of lymph nodes and the tracers may only provide the location information of SLNs, without specifying the metastasis arising from the original tumor. Identifying the lymph node metastatic conditions is required in order for surgeons to determine whether the pelvic lymphadenectomy

may be performed. Additional studies are required to identify contrast agents which may reveal whether a SLN was positive or negative for metastasis, without removing it.

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