Sentinel Lymph Nodes Mapping in Cervical Cancer a Comprehensive Review

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Objective: A comprehensive literature search for more recent studies pertaining to sentinel lymph node mapping in the surveillance of cervical cancer to assess if sentinel lymph node mapping has sensitivity and specificity for evaluation of the disease; assessment of posttreatment response and disease recurrence in cervical cancer.

Materials and Methods: The literature review has been constructed on a step wise study design that includes 5 major steps. This includes search for relevant publications in various available databases, application of inclusion and exclusion criteria for the selection of relevant publications, assessment of quality of the studies included, extraction of the relevant data and coherent synthesis of the data.

Results: The search yielded numerous studies pertaining to sentinel lymph node mapping, especially on the recent trends, comparison between various modalities and evaluation of the technique. Evaluation studies have appraised high sensitivity, high negative predictive values and low false-negative rate for metastasis detection using sentinel lymph node mapping. Comparative studies have established that of all the modalities for sentinel lymph node mapping, indocyanine green sentinel lymph node mapping has higher overall and bilateral detection rates. Corroboration of the deductions of these studies further establishes that the sentinel node detection rate and sensitivity are strongly correlated to the method or technique of mapping and the history of preoperative neoadjuvant chemotherapy.

Conclusions: The review takes us to the strong conclusion that sentinel lymph node mapping is an ideal technique for detection of sentinel lymph nodes in cervical cancer patients with excellent detection rates and high sensitivity. The review also takes us to the supposition that a routine clinical evaluation of sentinel lymph nodes is feasible and a real-time florescence mapping with indocyanine green dye gives better statistically significant overall and bilateral detection than methylene blue.

Key Words: Sentinel lymph node mapping, Cervical cancer, Sensitivity, Metastasis

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Sentinel lymph node (SLN) can be defined as the first lymph node or group of lymph nodes that cancer cells drain and invade into during metastasis. Sentinel lymph node is, hence, the primary chain node in the lymphatic basin that receives the lymphatic flow.[1]

Sentinel lymph node mapping (SLNM) is, thus, a diagnostic procedure that is useful to detect if cancer has metastasized beyond the primary cancer site, especially, into the lymphatic system. The basic procedure involves injecting a dye along with a radioactive tracer into the region surrounding a malignant site and allowing a time bound draining of the tracer and the dye into the sentinel or primary lymph node from the site for detection. Lymphatic draining of the radioactive tracer allows accurate location of the SLN by a radio-active counter and a surgical microincision allows the physical and pathological examination of the stained sentinel node (SN).

The diagnostic prominence of SLNM and technological innovations of the same in the management of cervical cancer in the recent years is perhaps due the recognition of the status of regional lymph nodes as being a pivotal prognostic factor for the detection and management of cervical cancer, especially in early stage cancer patients. The oncological view that if 1 or more SLNs are negative for malignancy, the remaining regional lymph nodes would be also negative and a complete node dissection could be avoided in case the SN shows no evidence of a metastatic involvement has further augmented its diagnostic denomination.

The present study is a comprehensive review of more recent literature on SLNM for the assessment of cervical cancer.

Search Strategy

The search strategy included cross-referencing of keywords and subsequent second stage use of the references of the articles identified in the first round to render the search effective. Subsequent to the identification of this core pool of studies, articulation of the inclusion and exclusion criteria was effected.

The search included studies pertaining to SLNM in the surveillance of cervical cancer to assess if SLNM has sensitivity and specificity for evaluation of the disease; assessment of posttreatment response; long-term surveillance and in assessing disease recurrence in cervical cancer. The search terms included SLNM, SLNM in the assessment of cervical cancer, SLNM techniques in cervical cancer, recent innovations in SLNM for assessment of cervical cancer, evaluation studies on SLNM and comparison of various SLNM techniques for cervical cancer assessment.

One hundred eighty-two studies were obtained in the initial search on recent trends and publications selected based on inclusion and exclusion criteria. Ninety-three studies were excluded as not pertaining to studies on cervical cancer. Forty-five studies were excluded as not pertaining to specific manifestation, more recent diagnostic and treatment procedures. Thirteen studies were excluded as being editorials instead of being research publications. Seven studies were excluded as letters to the editor. In the final selection, 24 studies were selected and coded as highly appropriate to the present review.

Methodology

The literature review has been constructed on a step wise study design that includes five major steps. This includes search for relevant publications in various available databases, application of inclusion and exclusion criteria for the selection of relevant publications, assessment of quality of the studies included, extraction of the relevant data, and coherent synthesis of the data. The results of the studies in this review have been summarized in a descriptive and narrative manner. Quality assessment has been done independently by 2 reviewers on quality of the methodology. The differences have been resolved by discussion with a third reviewer, wherever necessary in accordance with the guidelines of "The Cochrane Reviewers' Handbook."[2]

Review guidelines pertaining to health care review including clarity of the definition of the problem, well-framed objective specifying the type of population, interventions, and outcomes of interest and study designs have been incorporated. Because it is an established fact that nonrandomized studies construct estimates that signify more extreme benefits of the effects of health care than randomized trials, substantial efforts to identify and include studies other than randomized trials have been in place.[2]

The search period has been from the year 2010 till date to ensure more recent studies and technological trends. Search literature databases, websites and Internet search engines employed included *Biomed central, Cinahl, Cochrane Library, Embase, Picarta, PubMed, SCI,* www.doh.gov.uk, www.escriber.com, www.google.com *and* www.who.org.

Selection inclusion criteria comprised comparative research design, group protocol for assessment of posttreatment response and long-term surveillance in cervical cancer, prevention and control, specific research studies on SLNM in cervical cancer and SLNM awareness among scientific population.

Selection exclusion criteria included editorials, letters, descriptions nonspecific to SLNM and cervical cancer assessment in the target population.

RESULTS

On Recent Techniques in SLNM for Cervical Cancer

A new SLNM modality that employs indocyanine green (ICG) dye with near-infrared (NIR) fluorescence imaging (NIR-ICG) has gained extensive utility in lymphatic mapping for cervical cancer with the advantage of providing real-time imaging during surgery. Studies have revealed that a cervical injection of ICG provides good visualization of SLNs from 5 to about 60 minutes.[3]

Preliminary studies among 12 women for surgical nodal staging for early-stage gynaecologic malignancies including cervical cancer and subsequent assessment of the surgical and pathological outcomes, intraoperative image quality, handling and docking has shown that a *video telescope operating microscope system technology* which uses NIR technology with a fluorescent dye, such as ICG, is yet another easy to perform and reproducible tool in the management of patients with cervical malignancies.[4]

A NIR technology constructed on a *robotic Da Vinci Xi system* has also been shown to provide an enhanced real-time imaging. Preliminary case studies adopting the Memorial Sloan Kettering Cancer Center SLN algorithm for SLN mapping and subsequent ultrastaging in a cohort of 6 patients have shown a cent percent SLN detection with no perioperative complications.[5]

A technology that can image all lymph nodes in the body in real time and assess both the SN and all nodes simultaneously has been developed recently. The optical fluorescence technology capable of simultaneous mapping of pan lymph nodes and SLNs in the same patient is based on NIR fluorophores (fluorescence emission maxima either at 700 nm or at 800 nm) that can be injected intravenously for identification of all regional lymph nodes in a basin, and simultaneously locally injected for identification of the SLN.[6]

On Comparison Studies Between Different Dye Tracers and Techniques in SLNM

A recent study to compare the differences in overall detection rates, bilateral detection rates, and false-negative

(FN) rates among the conventional dye tracers have shown that ICG SLN mapping has higher overall (odds ratio, 0.27; 95% confidence interval [CI], 0.15–0.50; $P < 0.0001$) and bilateral detection rates (odds ratio, 0.27; 95% CI, 0.19–0.40; $P < 0.00001$) as compared with blue dyes (BD).[7]

Findings on the sensitivity of SLN mapping in terms of detection rate and bilateral mapping in women with cervical cancer by comparing technetium-99 (Tc99) radiocolloid and BD against fluorescence mapping with ICG have revealed that the fluorescence SLN mapping with ICG gives a significantly higher detection rate and bilateral mapping compared with standard radiocolloid and BD technique in women with early-stage cervical cancer. Nodal staging with an intracervical injection of ICG has also been established as accurate, safe, and reproducible in patients with cervical cancer.[8,9]

A previous study comparing Tc99 with patent BD and ICG with NIR fluorescence imaging in the laparoscopic treatment of cervical cancer in terms of sensitivity, specificity, and overall and bilateral detection rates have established that ICG SLN mapping in cervical cancer provides higher overall and bilateral detection rates.[10]

A retrospective study aimed to compare the SLNM results of methylene blue (MB) and ICG in women with early-stage cervical cancer has shown that real-time florescence mapping with ICG shows better statistically significant overall detection rate and bilateral mapping than MB.[11]

Earlier studies to compare preoperative SN mapping with planar lymphoscintigraphy (LSG) to single photon emission computed tomography with computed tomography (SPECT-CT) for differences in intraoperative SN retrieval time in surgically treated cervical cancer patients have shown that the bilateral intraoperative SN retrieval times for LSG and SPECT-CT as 75.4 ± 33.5 minutes and 50.1 ± 15.6 minutes, respectively, and SPECT-CT significantly reduces intraoperative SN retrieval with a clinically relevant time compared to LSG.[12]

A double-blind randomized study to determine if ICG adsorbed to human serum albumin (HSA) improves its performance and offers advantages over using ICG alone for SLN mapping in early-stage cervical cancer has shown that there is no observed advantage of ICG:HSA over ICG alone for the SLN procedure in early-stage cervical cancer.[13]

An earlier study to compare the relative value of colorimetric detection with isosulfan blue and radioisotopic detection with Tc99 of the SLNs and to evaluate the concept of the SLN mapping applied to cervical cancer in a cohort of 211 patients has established that SN mapping is feasible and the radioisotopic technique adds significantly to the rate of SLN detection. Further, the detection of micrometastases on ultrastaging that might be missed out on routine pathological evaluations and identification of the aberrant drainage sites have been illustrated as the major benefits of SLN mapping in cervical cancer.[14]

On Evaluation Studies of SLNM in Cervical Cancer Cases

An assessment study on the accuracy of SN mapping in the lymph nodal staging of cervical cancers has established SN mapping as an accurate method for the assessment of lymph nodal involvement in cervical cancers.

The study has further derived a pooled detection rate of 89.2% (95% CI, 86.3–91.6) and a pooled sensitivity rate of 90% (95% CI, 88–92) and corroborated that the SN detection rate and sensitivity are related to the method or technique of mapping and the history of preoperative neoadjuvant chemotherapy.[15]

A cross-sectional pilot study to evaluate SLN mapping in early stage cervical cancers based on a protocol involving 1 hour preoperative or intraoperative injection of 4 mL of 1% methylene BD in the tumor site with subsequent labelling of SLNs and staining with hematoxylin, eosin and antikeratin antibody has shown 87.5% detection rate of the metastatic disease. The FN rate for the technique has been established to be zero with a cent percent sensitivity and negative predictive value (NPV).[1]

Another study has validated the NIR-ICG modality and has substantiated NIR fluorescence imaging with ICG as an excellent and safe tracer modality for SLN mapping with a 96% (very high) overall and 88% bilateral detection rate.[16]

The sensitivity and NPV of SLN detection in cervical cancer using a combination technique, and validity of the SLN algorithm proposed by the Memorial Sloan Kettering Cancer Center has been evaluated as well in a cohort of 57 patients who underwent SLN mapping by technetium LSG and patent BD injection. The study has validated SLN as a safe and accurate technique that enhances metastatic nodal detection rates by 4.2% after immunohistochemistry.[17]

An earlier assessment study on the detection rate of SLNs using ICG and NIR fluorescence imaging for uterine and cervical malignancies in a cohort of two hundred and twenty-seven cases has established that NIR fluorescence imaging with intracervical ICG injection using a robotic platform has a high bilateral SLN detection rate and better than SLN mapping using BD alone.[18]

Sentinel lymph node mapping assessment for small volume cervical tumours (<2 cm) has also been shown to have high specific side detection rate, excellent negative-predictive value and high sensitivity.[19]

A retrospective multicenter cohort study to evaluate the sensitivity of SN ultrastaging and to define parameters that may reduce the overall FN rate in women with early-stage cervical cancer has shown that optimal bilateral SN detection substantially decreases the FN rate of SN ultrastaging and increases detection of micrometastasis.[20]

An evaluation study to test the hypothesis that the parametrial nodes are the true SLNs in women with cervical cancer and to ascertain if addition of India ink as a mapping agent would allow pathological identification of sentinel parametrial nodes using a "triple injection" technique (with BD, radiocolloid, and India ink) has shown that these cervical lesions drain directly to pelvic nodal basins bypassing small parametrial nodes and parametrial nodes, thus, need not always act as the SLNs in women with cervical cancer.[21]

A feasibility and dose-defining study to optimize the dose of ICG required to detect pelvic and paraaortic SLNs with robotically assisted endoscopic NIR imaging after cervical injection has established that a 1-mg cervical injection of ICG could identify a SLN in 88% of patients (95% CI, 64–99%) and robotically assisted fluorescence imaging is a

feasible, safe, time-efficient, and reliable method for lymphatic mapping in early-stage cervical carcinoma.[22]

A prospective, nonrandomized study to determine the SLN detection rates, accuracy in predicting the status of lymph node metastasis, and to access if pathologic ultrastaging improves the detection of micrometastases and isolated tumor cells at the time of primary surgery in a cohort of women with early-stage (Fédération Internationale de Gynécologie et d'Obstétrique stage IA1 with lymphovascular space involvement-IIA) cervical carcinoma has shown that SLN mapping in early-stage cervical carcinoma can yield high detection rates with a detection of a total 316 SLNs in 77 (95%) of 81 patients in the study.[23]

A prospective multicenter study (SENTICOL [Ganglion Sentinelle dans le Cancer du Col]) to assess the sensitivity and NPV of SLN mapping in a cohort of 139 patients with cervical carcinoma meeting the *International Federation of Gynecology and Obstetrics* criteria for stage IA1 with lymphovascular space invasion to stage IB1 by technetium 99 LSG and patent blue injection followed by laparoscopic lymph node mapping, SLN removal, and lymph node dissection has shown that combined labelling for node mapping is associated with high rates of SLN detection, high sensitivity and NPV for metastasis detection with at least one SLN detected in 136 patients (97.8%; 95% CI, 93.8–99.6%) in the study.[24]

Research studies aimed at establishing an algorithm that incorporates SLN mapping to the surgical treatment of early cervical cancer and accurate detection of lymph node (LN) metastases in a cohort of one hundred twenty-two patients has shown that employment of a surgical algorithm, where, SLNs are removed and submitted to ultrastaging; any suspicious LN removed regardless of mapping; a contralateral side-specific pelvic LND performed (including interiliac nodes) if only unilateral mapping is noted; and parametrectomy en bloc with primary tumor resection done in all cases allows for a comprehensive detection of all patients with nodal disease and spares complete LND in the majority of the cases.[25]

Feasibility studies have demonstrated a preliminary feasibility to successfully detect SLNs in cervical cancer patients using ICG:HSA using a safe cost-effective Mini-FLARE imaging system with an optimal ICG:HSA concentration of 500 μM for SLN mapping in cervical cancer patients.[26]

DISCUSSION

The proposition that if SLN, being the first node that receives drainage from the primary tumor is negative for malignancy, the remaining regional lymph nodes would also be negative and a complete node dissection could be avoided has prompted a recent surge in the interest toward innovation, optimization, and validation of SLNM in cervical cancer patients.

Evaluation studies have appraised high sensitivity, high NPV and low FN rate for metastasis detection using SLNM. Apart from reports on recent innovations and clinical protocols on SLNM, several comparative studies have established that of all the modalities for SLNM, ICG SN mapping has high detection rates, higher overall and bilateral detection rates. Corroboration of the conclusions of these studies further establishes that the SN detection rate and sensitivity are strongly correlated

to the method or technique of mapping and the history of preoperative neoadjuvant chemotherapy. The "triple injection" technique with BD, radiocolloid, and India ink has, especially, established that cervical lesions drain directly to pelvic nodal basins bypassing small parametrial nodes and parametrial nodes, thus, need not always act as the SLNs in women with cervical cancer.

Further, SLNM in cervical cancer has been shown to diminish the neurovascular injuries, loss of blood, cyst formation, bacterial infections, lymphedema, and other complications concomitant to pelvic lymphadenectomy.[27]

CONCLUSIONS

The review takes us to a strong conclusion that SLNM is an ideal technique for the detection of SLNs in cervical cancer patients with excellent detection rates and high sensitivity. The review also takes us to the supposition that a routine clinical evaluation of SLNs is feasible and a real-time florescence mapping with ICG dye can give a statistically significant overall and bilateral detection than with MB.

It is perhaps the right time to endorse an obligatory identification of the positive lymph nodes by SLNM and proclaim SLNM as the criterion standard of care for the management of cervical cancer.

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