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Sentinel Lymph Node Evaluation in Women with Cervical Cancer

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Abstract

Lymph node status is the most important prognosticator of survival among women with early stage cervical cancer. This means that many cervical cancer patients will undergo pelvic lymphadenectomy as part of their treatment. Unfortunately, this procedure is associated with significant morbidity. Utilizing the sentinel lymph node technique for women with cervical cancer has the potential to decrease this morbidity. Multiple studies have suggested that sentinel lymph node mapping in these patients is feasible with excellent detection rates and sensitivity. This review examines the current body of literature regarding sentinel lymph node biopsy among women with cervical cancer.

Introduction

Of the more than 12,300 American women who will be diagnosed with cervical cancer in 2013, approximately 47% will have disease that is clinically localized to the cervix.[1, 2] The current standard of care for most of these women includes radical hysterectomy or trachelectomy and bilateral pelvic lymphadenectomy. For women with early-stage cervical cancer, lymph node status is the most important prognosticator of survival.[3] However, the majority of these patients will not have lymph node metastases.[4] Furthermore, pelvic lymphadenectomy is associated with multiple short- term and long-term complications that include neurovascular injury, increased blood loss, lymphocyst formation, infection, and lymphedema.[5] Utilizing the sentinel lymph node technique for women with cervical cancer has the potential to decrease this morbidity while maintaining the ability to adequately evaluate the pelvic lymph nodes of these patients.

For women with cervical cancer, ideally we would optimize the identification of positive lymph node spread in the minority of patients while limiting the morbidity of lymph node dissection for the majority of women who will ultimately have negative nodes. For that reason, there is significant interest in validating lymphatic mapping and sentinel node biopsy for women with this disease. The sentinel lymph node is the first node that receives drainage from the primary tumor. Therefore, if the sentinel lymph node is negative for metastasis, the

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remaining lymph nodes in the nodal basin should also be free of tumor. The use of lymphatic mapping and sentinel lymph node biopsy was first described by Cabanas in 1977 for patients with penile carcinoma.[6] Since that time, it has become the standard of care for the management of several malignancies, including melanoma and breast cancer.

The purpose of this review is to examine the current body of literature regarding lymphatic mapping and sentinel lymph node biopsy in women with cervical cancer.

Mapping Techniques

The use of blue dye alone was the first described technique for sentinel lymph node identification in cervical cancer patients.[7] For this procedure, isosulfan blue, methylene blue, or patent blue is injected into the cervix immediately after general anesthesia is obtained. Intraoperatively, the dye is visualized with the naked eye. Two injection techniques have been described: 1) Injection of dye into each quadrant of the cervix or 2) Superficial and deep injections at 3 and 9 o'clock.[8–11] Common adverse effects of use of the blue dye include transient discoloration of the skin and urine or a decrease in pulse oximetry readings due to colorimetric interference.[12, 13] Rarely, more severe reactions such as anaphylaxis may occur.[14]

Patent blue dyes are taken up by lymphatics and deposited in sentinel nodes fairly quickly (5–10 minutes or so). In addition, these mapping substances may also be deposited in second echelon, non-sentinel nodes soon after reaching the sentinel nodes. It is therefore important to identify the sentinel nodes at the beginning of the case as opposed to the end when the dye may have faded from sentinel nodes or moved on to non-sentinel nodes.

Intracervical radioisotope injection, such as technetium-99 or colloidal albumin, has also been used alone in the detection of sentinel lymph nodes for cervical cancer.[15–17] Though radiation doses are variable based upon which protocol is used, overall radiation exposure remains small. Intracervical injection techniques are similar to those described for blue dye. When utilizing radioisotopes, intraoperative detection of sentinel nodes relies on lymphoscintigraphy or SPECT-CT and/or a hand-held gamma probe.[18] To date, no significant adverse reactions to radiocolloids have been described.

Different protocols exist regarding the timing of radiocolloid injection (Table 1). Many published studies utilize a “long” protocol, whereby the tracer is injected intracervically the day prior to surgery.[15, 17, 19, 20] In these studies, preoperative imaging with lymphoscintigraphy or SPECT-CT is performed so that the surgeon will have this information ahead of proceeding to the operating room. If the isotope is injected less than 24 hours from surgery, reinjection is often unnecessary as the half-life of isotope is approximately 6 hours. Radiocolloids tend to remain in the sentinel node much longer than blue dyes, which will move on to non-sentinel nodes.

“Short” protocols are increasingly favored due to convenience for both physicians and patients.[21, 22] For this technique, tracer is injected in the morning only a few hours prior to surgery. Imaging is then performed just prior to presenting to the operating room for surgery.

More recently, “ultra-short” protocols have become popular among surgeons.[23] In this technique, radioisotope is injected after general anesthesia has been obtained. Preoperative imaging is omitted, and sentinel nodes are detected intraoperatively only with the use of a handheld gamma probe. Unlike a truncal melanoma where lymphatic drainage of the primary lesion is often ambiguous and therefore preoperative imaging is imperative to determine where incisions will be made, nodal basins draining the cervix are always in the pelvis or lower aorta (see location of sentinel nodes below). These nodes are easily accessible by the surgeon at the time of radical hysterectomy and can easily be identified without any added benefit of preoperative imaging.[24]

The earliest studies of lymphatic mapping in cervical cancer patients utilized blue dye alone. However, the detection rate varies from 70% – 100% when this method is used.[9–11] When radioisotope alone is used for sentinel lymph node mapping in these women, detection rates are comparable to that of blue dye at 88% – 94%.[15–17] However, when blue dye and radioisotope are combined to map lymph nodes in cervical cancer patients, the detection rates appear to be improved over either modality alone.[21, 23] In their study of more than 200 women, Roy and colleagues found that the combined method of lymphatic mapping has a detection rate of 99.1%, compared to the 92.8% rate of blue dye alone ($p=0.009$).[21]

Regardless of whether blue dye alone, radioisotope alone, or the combined method is used, the detection rate for sentinel nodes in patients with cervical cancer appears to be acceptable. Lukas and colleagues recently analyzed the published studies of lymphatic mapping in cervical cancer that included at least 50 patients. Studies that utilized blue dye only were excluded. In total, the review evaluated 15 published studies and 1,811 women. They found that the overall detection rate for sentinel lymph node mapping in cervical cancer patients to be 92.3%, with a sensitivity of 92.3%.[18]

As neither blue dyes nor radioactive colloids are detectable microscopically after pathologic processing, the use of other mapping substances has been explored. We utilized India ink along with patent blue dye and radiocolloid in a “triple injection” technique to determine if the addition of this substance would enhance sentinel node detection. Although the technique was feasible, India ink led to the identification of only one (0.3%) additional node not identified by blue dye and/or radiocolloid and its routine use is therefore not recommended.[25]

Sentinel Node Studies

Multiple single institution studies have reported their experience with sentinel lymph node biopsy in cervical cancer patients (Table 2). Though the type of tracer used in each of these studies is widely variable, almost all of them describe excellent negative predictive values, ranging from 88% – 100%.[8–11, 15–17] However, sensitivity appears to be more inconsistent. For example, Marchiolo and colleagues reported on their experience with 29 cervical cancer patients undergoing sentinel lymph node mapping and found a sensitivity of only 63%.[10] However, Darlin and colleagues published their study of 105 women and

found a sensitivity of 100%.[17] Other studies have subsequently demonstrated a sensitivity ranging from 94% – 100%.[11, 15, 16, 19, 26]

In an attempt to validate these smaller, single institution sentinel lymph node studies, the AGO Study Group designed a multicenter trial of 507 women with cervical cancer. Enrolled patients received intracervical injection with technetium, patent blue, or both. These women underwent lymphatic mapping and sentinel node biopsies followed by complete pelvic lymphadenectomy. The detection rate was significantly higher for the group who received the combination of technetium and blue dye than for the group who received only one of the injection agents (94% vs. 82%). However, the overall sensitivity was only 77.4%, and did not reach the predefined noninferiority margin. This led the authors to conclude that the sensitivity of sentinel lymph nodes in cervical cancer is too low.[27]

There have been several criticisms of the AGO study. Firstly, the study protocol did not include ultrastaging of the sentinel lymph nodes. Ultrastaging is the process of microsectioning and immunohistochemical staining of the nodes in an attempt to detect metastasis.[28] Metastases to sentinel lymph nodes are divided into one of three categories based upon the diameter of the tumor deposit: 1) macrometastasis where the tumor deposit measures > 2 mm, 2) micrometastasis where the tumor deposit measures 0.3 mm – 2 mm, or 3) isolated tumor cells where the metastasis is ≤ 2 mm. Though the prognostic implications of low volume metastases in cervical cancer are not wholly understood, retrospective data suggests decreased survival among patients who have micrometastasis.[29] Furthermore, the detection of additional metastasis, including micrometastasis, would increase the study sensitivity. A second critique of the AGO trial was that it did not allow or assess for the learning curve associated with sentinel lymph node evaluation and there was no requirement for surgeon experience with the techniques before enrolling patients. The breast cancer literature has established that sentinel node detection rates and success increase dramatically during a surgeon's first few cases.[30, 31] This finding likely translates to sentinel lymph node evaluation in cervical cancer. The most significant limitation of the AGO trial, however, was the inclusion of large tumors in the study. More than 20% of study participants had stage IIA – stage IV disease. In fact, when the authors limited the analysis to tumors ≤ 2 cm, they found a 94% detection rate and a sensitivity of 91%. This was significantly different from the 84% detection rate and 73% sensitivity of tumors > 2 cm. [27] Subsequent studies have confirmed the importance of tumor size in sentinel node detection.[17, 32] A recent analysis of published studies reported a detection rate of 95% and a sensitivity of 100% for tumors < 2 cm. In contrast, tumors > 2 cm demonstrated a detection rate and sensitivity of 80% and 89%, respectively.[18]

The SENTICOL study is the largest multi-institutional trial of sentinel lymph node biopsy limited to women with early stage cervical cancer. In this study, 139 women with stage IA1 or IB1 cervical cancer underwent intracervical injection with radiocolloid and blue dye followed by sentinel node dissection and pelvic lymphadenectomy. The authors reported a detection rate of 97.8% and a sensitivity of 92%. There were only two false-negatives discovered. However, in one of these patients the positive node was found in a hemipelvis that did not map. Of note, there were no false negatives among patients who had bilateral

sentinel nodes detected. The study concluded that sentinel node mapping is a sensitive method for detecting lymph node metastasis for women with early-stage cervical cancer.[33]

As evidenced by these studies, multiple groups have reported promising results with sentinel lymph node dissection in women with cervical cancer. These findings have led proponents of the sentinel lymph node technique to argue that too many pelvic lymphadenectomies are being performed in patients with early stage cervical cancer. However, opponents have voiced concern that some nodal metastases may be missed if only the sentinel lymph nodes are removed. This led Cormier and colleagues to develop a sentinel lymph node mapping algorithm with the aim of detecting all lymph node metastases while limiting the number of lymphadenectomies. Their algorithm dictates the following: 1) all mapped sentinel nodes are excised and ultrastaged, 2) all suspicious nodes are removed regardless of mapping, 3) if only unilateral mapping occurs, a contralateral lymphadenectomy is performed, and 4) all cases include parametrectomy en bloc with primary tumor resection. When this algorithm was evaluated in 122 women, 100% of positive lymph nodes were identified.[34] Though these findings are encouraging, additional studies are needed to validate the algorithm.

Location of SLNs

In cervical cancer, the sentinel lymph nodes are most commonly located along the internal or external iliac nodal basin. In their retrospective evaluation of 151 women undergoing sentinel lymph node evaluation for cervical cancer, Marnitz and colleagues found that 71% of sentinel nodes were interiliac, 8% were internal iliac, 5% were external iliac, and 5% were common iliac. [35] In the previously described SENTICOL trial, 85.3% of all sentinel nodes were external, internal, or common iliac nodes.[36] A similar sentinel node distribution has been described by multiple other studies. [7, 9, 11]

In addition to the iliac chain, cervical cancer sentinel nodes have been detected in more uncommon locations, such as the parametrium. In their evaluation of 20 women with 59 sentinel nodes, Frumovitz and colleagues noted that 8% of sentinel nodes were in the parametria.[25] This finding is similar to other studies that have typically reported 7% – 11% of sentinel nodes are in the parametria.[35–37] Though rare, the detection of presacral and paraaortic sentinel lymph nodes has also been described.

Preoperative Imaging of Sentinel Nodes

Lymphoscintigraphy is a nuclear medicine scan where the lymph node basin is imaged after injection of radiocolloid in an attempt to identify the sentinel lymph nodes preoperatively. This modality is most useful in malignancies such as melanoma, where the lymphatic drainage is unpredictable. However, when its utility has been evaluated for cervical cancer, lymphoscintigraphy has consistently been found to have little clinical value. In their study of 50 women with cervical cancer who underwent lymphoscintigraphy as part of a sentinel lymph node mapping protocol, Frumovitz and colleagues noted poor concordance between the location and number of sentinel nodes on preoperative lymphoscintigraphy and intraoperative lymphatic mapping. More than 70% of patients noted to have only one sentinel node on lymphoscintigraphy had multiple nodes mapped intraoperatively. The

authors concluded that lymphoscintigraphy is of little utility for lymphatic mapping in cervical cancer.[24] These findings have been confirmed by other studies.[38, 39]

Single photon emission computed tomography (SPECT) is another nuclear medicine imaging modality that utilizes gamma rays to provide three-dimensional imaging information. When overlaid with traditional computed tomography (CT) scan, SPECT allows surgeons to determine the anatomic location of sentinel nodes. The utility of SPECT/CT for lymphatic mapping in cervical cancer patients is promising. Initial studies of this modality found that preoperative SPECT/CT has a detection rate of 95% – 100%. Furthermore, the images correlate with the anatomic location of the sentinel node in 95% – 100% of cases.[40, 41] When compared with lymphoscintigraphy, SPECT/CT appears to offer a significant improvement in sentinel node detection and anatomic localization.[42–44] Additionally, there is some evidence that the advantages afforded by SPECT/CT may translate to decreased intraoperative time for sentinel node retrieval. A recent comparison of lymphoscintigraphy to SPECT/CT for robot-assisted laparoscopic cervical cancer surgery noted that the sentinel lymph node dissection took more than 25 minutes longer in the lymphoscintigraphy group.[45] Though these findings need to be validated, they provide further evidence for the utility of SPECT/CT in these patients.

Near-Infrared Fluorescence Imaging for the Identification of Sentinel Nodes

The majority of studies evaluating intraoperative mapping of sentinel nodes in cervical cancer have utilized blue dye, radiocolloid, or both to localize the nodes. However, there are limitations to the use of these tracers. For example, radiocolloid use exposes patients to radiation. Near-infrared fluorescence imaging with indocyanine green (ICG) is a technique that may help overcome these challenges. Similar to other tracers, the ICG is injected intracervically in the operating room. The surgeon can then detect the sentinel lymph nodes intraoperatively utilizing cameras that allow visualization of near-infrared fluorescence. Purported benefits of this technology include high tissue penetration, low autofluorescence, and lack of radiation exposure.[46] Significant adverse events with ICG use in sentinel lymph node mapping have not been reported. However, ICG has been utilized for many years for ophthalmic angiography and in the determination of cardiac output. Though rare, severe reactions such as anaphylaxis have been reported in these patients.[47, 48]

The feasibility of near-infrared fluorescence imaging has been assessed in women with cervical cancer undergoing sentinel lymph node dissection.[49–52] In one of the earliest studies, Furukawa and colleagues described their experience with ICG mapping of sentinel nodes in 12 patients with early-stage cervical cancer. They reported a detection rate of 83% and concluded that this technology may be useful for cervical cancer patients undergoing sentinel node biopsy.[51] Another study of 20 cervical cancer patients undergoing robotic-assisted surgery noted a detection rate of 88% with ICG use. The authors concluded that near-infrared imaging is both a feasible and reliable method of lymphatic mapping for these women.[52]

Though the detection rate of fluorescence imaging with ICG appears to be similar to that of blue dye or radiocolloid, there have been no comparisons of these modalities in cervical

cancer patients. However, in other malignancies, there is some suggestion that the use of ICG may improve detection rates. Holloway and colleagues recently reported their experience with ICG and isosulfan blue in 35 endometrial cancer patients undergoing lymphatic mapping. They found that fluorescence imaging with ICG had improved sentinel lymph node detection as compared with the blue dye. Furthermore, the detection rate of ICG combined with blue dye was better than either modality alone.[53] These findings should be further explored in women with cervical cancer.

Role of Frozen Section

The presence of lymph node metastases in women undergoing surgical management for cervical cancer is an indication to abort the procedure. In these cases, patients are typically treated with chemoradiation rather than radical surgery. For this reason, frozen section evaluation of sentinel lymph nodes has typically been used for these patients. Unfortunately, multiple studies have found that the accuracy of intraoperative frozen section is significantly limited by its inability to detect micrometastases and small macrometastases.[54–56] In their study of 225 patients, Slama and colleagues noted the overall sensitivity of frozen section to be 56% for detecting metastases. However, the sensitivity was merely 8% for the detection of micrometastases. [56] These findings have led many authors to agree that the use of intraoperative frozen section should be abandoned in cervical cancer patients undergoing sentinel lymph node evaluation.

Conclusions

Sentinel lymph node biopsy is currently the standard of care for certain malignancies, including melanoma and breast cancer. For women with early-stage cervical cancer, multiple studies confirm that the evaluation of sentinel lymph nodes is feasible with excellent detection rates and sensitivity. These findings have important implications as they suggest that less radical surgery is safe for selected patients. Ongoing studies seek to validate these findings and determine the impact of sentinel node biopsy on quality of life in these women.

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Table 1

Comparison of radioisotope protocols for detecting sentinel lymph nodes in cervical cancer

Protocol	Timing of Radiocolloid Injection	Timing of Lymphoscintigraphy	Radiocolloid Dose (mCi)
Long	20–24 hrs before surgery	1–3 hrs after injection	2 – 4
Short	2–4 hrs before surgery	20–30 min after injection	0.2 – 1
Ultra Short	Immediately prior to surgery	No	0.4 – 0.55

Table 2

Studies of sentinel lymph node mapping in cervical cancer

Study	Patients (n)	Technique	Detection Rate (%)	Sensitivity (%)	NPV (%)
Schwendinger et al [8]	47	Blue	83	90	97
O'Boyle et al [9]	20	Blue	70	100	100
Marchiole et al [10]	29	Blue	100	63	88
Dargent et al [11]	70	Blue	NR	100	NR
Du et al [15]	68	Technetium	94	100	100
Ogawa et al [16]	82	Technetium	88	100	100
Darlin et al [17]	105	Technetium	90	94	99
Kato et al [19]	50	Technetium	94	100	100
Silva et al [26]	56	Technetium	93	100	100
Altgassen et al [27]	590	Blue/Technetium	89	77	94
Lecum et al [33]	139	Blue/Technetium	98	92	98