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# Review article Factors related to sentinel node identification in cervical cancer

# Phanida Jarruwale<sup>a</sup>, Kuan-Gen Huang<sup>b,\*</sup>, Doris R. Benavides<sup>c</sup>, Chyi-Long Lee<sup>b</sup>

<sup>a</sup> Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok, Thailand
<sup>b</sup> Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou and Chang Gung University College of Medicine, Kuei-Shan, Tao-Yuan, Taiwan
<sup>c</sup> Section of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of the Philippines College of Medicine and Philippine General Hospital, Philippines

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## ABSTRACT

Cervical cancer remains a common malignancy in women. Lymph node is one of the significant important prognostic factors. Until now, there is no reliable investigative study that can evaluate nodal status the same as the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system. Radical hysterectomy and pelvic lymphadenectomy is still one option in the standard treatment of patients with early-stage cervical cancer that can reveal metastatic lymph node but which can also produce treatment-related morbidities and complications. Sentinel lymph node identification has become a valuable technique for nodal status assessment. If lymph node metastasis was identified early, then unnecessary invasive surgical operations and complications may be avoided.

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# Introduction

The third most common female malignancy is cervical cancer; 530,000 new cases were diagnosed in 2008<sup>1</sup> and 250,000 deaths from it occurred in 2005, approximately 80% of deaths happened in developing countries.<sup>2</sup> Cervical cancer is still the fifth leading cause of cancer death (9.1 per 100,000) of women in Taiwan.<sup>3</sup> Nodal status is the most significant negative prognostic factor of cervical cancer and may also reveal the lymphatic spreading.<sup>4</sup> Likely as radical hysterectomy accompanied with pelvic lymphadenectomy still have the role in early stage cervical cancer treatment. If the risk factors of the lymphatic metastasis were identified, surgery may be skipped to another appropriate modality primarily.<sup>5</sup> Even though significant morbidity possibly occurred if extensive surgical procedures were performed. According to operative disadvantages, many studies were progressed for decreasing those adverse effects.

# Basis of sentinel lymph node detection

Sentinel lymph node (SLN) was defined as the first node in regional lymphatic basin that receives primary lymphatic drainage.<sup>6,7</sup> If SLN does not emerge, the remaining regional nodes

E-mail address: kghuang@ms57.hinet.net (K.-G. Huang).

should also be free of metastases. Thus SLN identification was an alternative resource for avoiding unnecessary lymphadenectomy and surgical interventions. The SLN concept is not only generated from many studies for nongynecologic tumors, such as penile cancer,<sup>8</sup> breast cancer,<sup>9</sup> and melanoma,<sup>10,11</sup> but it was also utilized for gynecologic malignancy treatment<sup>12,13</sup> thereafter. Nowadays, the practical lymphatic mapping methods use vital blue dye and lymphoscintigraphy techniques.<sup>6,7,14</sup> The modes for SLN identification are labeled as "hot" and/or "blue" as shown in Fig. 1. Types of materials and trial proceedings were selected dissimilarly.

# Materials used for detecting SLN

There are various reporting methods for SLN detection, e.g., vital blue dye and radioactive isotopes in single or a combined technique.<sup>6,15</sup> The three most commonly used vital dyes are isosulfan blue, patent blue violet, and methylene blue by injection intradermally 5–10 mm in depth around the primary cervical tumor, avoiding tumoral or intravascular infusion directly to avoidance of high background signal intensity that can decline SLN detection rate. The radioactive materials that are preferably used in different countries always contain Technetium-compounds. The efficiency of most trials was reported similarly in that the combined vital blue dye and isotope material technique had a detection rate of more than 80% to nearly 100% <sup>16–30</sup> and appears to be superior to lymphoscintigraphy <sup>16,21,28,31,32</sup> or vital dye technique alone.<sup>16,21,28,33,34</sup> However, there are many studies that display satisfactory results from noncombined methods.<sup>35–40</sup>



<sup>\*</sup> Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center and Chang Gung University College of Medicine, 5, Fu-Hsin Street, Kwei-Shan, Tao-Yuan 333, Taiwan.

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Fig. 1. The arrow indicates the positive blue stained node.

#### **Combined technique in SLN detection**

Many authors exhibit that combined technique had more than 90% and up to 100% of detection rate.<sup>17–22,24–29</sup> Malur S et al<sup>16</sup> reported 100% sensitivity rate with no false-negative result in combined Technetium 99 m (99mTc)-radiolabeled albumin (patent blue technique) group, while a 16.6% false negative result was found in the blue dye group. This is similar to Niikura et al<sup>23</sup> and Plante et al,<sup>19</sup> whose success consisted of a 93% detection rate, a 93% sensitivity, and a 0% false negative rate. Rhim et al<sup>18</sup> enrolled 26 patients with early stage cervical carcinoma into a study and reported a 94% SLN detection rate with a 4.76% false negative rate, while O'Boyle and associates<sup>33</sup> found 20% (4/20 patients) microscopic nodal metastasis using the blue dye technique. However, Lelievre et al<sup>41</sup> found only a 71.4% detection rate using the combined method. Their lymphoscintigraphy trial found that two patients had one hot spot in the presacral node. Meanwhile, the authors noted that these nodes may not be the first sentinel node and there was not enough radioactive value to uncover. The combined technique demonstrated significant high SLN detection.  $^{17,21}$  Altgassen C et al $^{42}$  study in all stages of 590 invasive cervical cancer patients, 77.4% overall sensitivity was reported. This series had variances in sample size between different disease severity; thus, the severity of disease allocation might affect the low sensitivity as well.

## Single technique in SLN detection

Van Dam et al<sup>31</sup> studied intraoperative 99mTc-labeled nanocolloid lymphatic mapping in 25 patients with cervical cancer and found an 84% SLN identification rate (21/25 patients). Angioli et al<sup>32</sup> reported a 89% detection rate by lymphoscintigraphy in 33/ 35 cervical cancer patients, and there are some reports that show a higher detection rate nearly or equal to 100%.<sup>35,36</sup> Malur et al<sup>16</sup> reported a detection rate of 76.2% in radiolabeled albumin but 55.5% in the blue dye group with 50% sensitivity. O'Boyle et al<sup>33</sup> studies isosulphan blue dye and identified SLN in 20 patients with early stage cervical carcinoma, reporting a 60% detection rate and 50% sensitivity. They suspected their technical method was insufficient and this might be the cause of the restricted dye uptake by tissue or lymphatic network cannot be exposed by operative procedure favorably. The same result was found by Seong et al,<sup>34</sup> they stated that SLN detection failure in patients more than 50 years old may be influenced by the aging process. With respect to anaphylactic reaction, a low dose of vital dye was used in their trial; thus, the SLN detection rate may have been affected. Nevertheless, these were good results in the different trials. Di Stefano et al<sup>38</sup> and Yuan et al<sup>40</sup> studied methylene blue in SLN identification for patients with cervical cancer using laparotomy approach for radical hysterectomy and pelvic lymphadenectomy, their results also had high SLN identification rate of 90% and 93.9%.

## Effect of process and materials in SLN detection

Each study has different manageable processes of investigating materials as well as dissimilar results. Levenback et al<sup>17</sup> studied 1.0-1.5 ml of filtered technetium-99 radiocolloid for preoperative lymphoscintigraphy. A total of 23 patients were injected into the cervix before the day of operation; 16 patients were operated on the day of the surgery. Isosulphan blue dye 3-4 ml was chosen and performed after induction of general anesthesia on the day of surgery for intraoperative lymphatic mapping. They found at least one sentinel node detected on lymphoscintigraphy in 33 patients (85%) and identified bilateral SLN in 21 patients, but there were no localized SLN on lymphoscintigraphy in six patients. They did, however, find intraoperative bilateral hot lymph nodes instead, and a gamma probe also detected hot SLN in all 39 patients. Lymph nodes were detected after applied isosulphan blue dye a median time of 7 minutes, and they remained blue for 21 minutes. At least one SLN was founded in each of the 39 patients also. Rhim et al<sup>18</sup> injected Technetium-99 m colloid albumin to the patients 3 hours before surgery and isosulphan blue dye injection after anesthesia. Identified SLN were located in external iliac, obturator, and internal iliac sites sequentially. Niikura et al<sup>23</sup> utilized 99mTc-labeled phytate radioisotope; because phytate has a larger particle size than sulfur colloid or colloid albumin, they suspected that it may extended in sentinel nodes and declined the missing SLN as well as Rob L et al<sup>26</sup> who used 99mTclabeled colloidal albumin with more than 80% particles of 100 to 600 nm in diameter. Several authors also considered that many factors may affect the study, the volume of different materials,<sup>17</sup> or different half life in each substance.<sup>17</sup> Some undetected SLN on preoperative lymphoscintigraphy become hot node detected by intraoperative radioactive counter. They explained that primary tumor site,<sup>17,18</sup> scanned timing before SLN can uptake radioactive matters,<sup>17</sup>different infusion areas,<sup>17</sup> or size of investigating mate-rials<sup>23,26</sup> may influence the results. Dargent et al<sup>37</sup> studied 35 patients with laparoscopic surgery. Varying doses of patent blue violet (PBV) were managed, then dye was injected at fornices in 16 cases and 53 into the cervix. They revealed not only the failure of SLN detection was 50%, 17%, and 8% after using PBV doses of 1.5 ml. 2.0 to 3.9 ml and 4.0 ml respectively but also happening for the site of injection (25% in fornices and 10% in cervix). The blue-stained lymph nodes could be found after dye injection between 20-150 minutes (25 minutes of median time) later. The resembling results in Yuan and companions' study<sup>40</sup> suggested that the SLN detection rate was higher in the group given 4 ml methylene blue and accomplished to detect the blue nodes at least 120 minutes after dye injection in all 26 cases. Kushner DM et al<sup>43</sup> evaluated SLN detection with a combined radiocolloid and dye method in cervical cancer patients. They visualized the blue node stable in 30 minutes and never seen after 50 minutes as well as Di Stefano et al never displayed the SLN before 20 minutes and after 70 minutes of blue dye injection.<sup>38</sup> The authors concluded that the blue dye dosage and site of injection, the time between dye injection and the operative procedure, may be factors that affected the detection of SLN. By contrast, Altgassen and partners<sup>39</sup>

compared 2 ml diluted isotonic solution to 10 ml and 4 ml of pure patent blue. A high overall SLN detection rate was reported. The dilutional blue dye pattern also demonstrated significant sentinel node detection in the parametrial region (37.0% vs. 10.3\%). In addition, Lelievre et al<sup>41</sup> remarked that the proper amount of dye material should be dictated because they experienced a troublesome tissue dissection when injecting nondiluted blue dye for sentinel node detection. Buist et al<sup>20</sup> suggested an observable point that there is sometimes difficult to find the true SLN because the blue dye had rapid absorbing time to lymphatic pathway, the proper dye quantity should be considered. Regarding radioisotope observation, maybe it is not clear-cut when separating groups of lymph nodes. All of the detected nodes should be inspected.<sup>20</sup> Nevertheless, this review article was focused on the traditional method of sentinel node detection in cervical cancer. There are limitations to the traditional method, including laparotomy and laparoscopy approaches, that were found in our review. Therefore, new research should be encouraged, including the near-infrared (NTR) mapping of sentinel lymph nodes, which has been previously suggested.

#### Laparotomy and laparoscopy surgical approaches

Concerning surgical techniques, laparoscopy manner appears to be a technique as feasible as laparotomy method in SLN identification procedures. A study of 50 cervical cancer cases of Malur et al<sup>16</sup> showed that SLN identification rate with laparoscopy method (76%) is similar in patients who received laparotomy operation (80%). Buist et  $al^{20}$  study used laparoscopic procedure for lymph node dissection and radical hysterectomy. They reported that the laparoscopic method was achievable in SLN node dissection but they had to face a laparoscopic complication of vascular injury and infected lymphocyst in three of the 24 patients (12.5%). Plante and associates<sup>19</sup> performed laparoscopically radical procedures for 70 patients with early stage cervical carcinoma. The many benefits, bloodless, promote the magnification of intended operative area were described and needless maneuver can be ceased when there is indicated. Similarly, Gil-Moreno et al<sup>25</sup> performed laparoscopic SLN identification and radical hysterectomy in 12 patients. There was good outcome and 100% detection rate, so the laparotomy procedure was not applied and no serious complications were found. The same results occurred during the study of Díaz-Feijoo et al.<sup>44</sup> They noted success in SLN identification when they used the laparoscopic approach method, including shorter hospitalization, and lower blood loss than a laparotomy procedure. The overall survival and disease free survival were also similar between the two groups. However, it should not be ignored that physician skills and appropriate equipment are important for good surgery and preventing potential complications from laparoscopic procedure.

# **Conization affecting SLN detection**

Several studies mentioned that the demographic data of patients does not seem to be related to factors of the SLN identification test, as well as the fact that preoperative conization was not affected by the possibility of SLN identification.<sup>17,37</sup> Perhaps Seong and companions<sup>34</sup> perceived that SLN was detected higher in preperative conization (73.3% vs. 49.1%), but all of these patients were older than 50 years. Thus, perhaps they presumed that the patients' ages may be tied to sentinel node detection. A similar result was suggested by Coutant et al,<sup>45</sup> who said that the false negative rates in previous conization compared with without preoperative conization were 33.5% and 8.3%, respectively. They explained that the blue dye injection might have passed through

the post conized cervical tissue and lymphatic drainage system might be altered in the post conized cervical tissue already.

# Cervical tumor size affects SLN detection

Rob et al<sup>26</sup> selected combined techniques for SLN detection in 183 early stage cervical malignant cases with different tumor sizes. They noticed that the SLN detection rate in patients with tumors <2.0 cm in diameter in both of the laparoscopy and laparotomy groups were 90.48% and 91.67%, respectively; furthermore, the detection rate of patients with tumor sizes >2.0 cm was 80% and, in patients with bulky tumors who received neoadiuvant chemotherapy, the researchers found that this group had the lowest detection rate (60%), adding that one patient had one positive presacral node when sentinel nodes were not detected. This finding was similar to the study of Fader and coworkers<sup>29</sup> who discovered there was a 100% SLN detection rate when tumor size was <2.0 cm. Even if one patient, who experienced of stage IB1 had a 3-cm cervical tumor mass, had been missed SLN detection on lymphoscintigraphy technique. The similar result was found in the O'Boyle et al<sup>33</sup> study, which elucidated that 73% (11/15 patients) of sentinel node detection in tumor size  $\leq$  4.0 cm and 20% (one of five patients) in tumors >4.0 cm in diameter. They noticed that the larger volumetric tumor may disturb lymphatic channel drainage, decreasing SLN identification rate<sup>29,33</sup> and skipping node metastasis<sup>29</sup> can be occurred. Other similar studies were reported the same. Barranger and colleagues<sup>46</sup> revealed the lower detection rate of SLN with a 20% false negative rate in locally advanced cervical cancer patients in the first laparoscopic SLN detection report, but they found no false negative rate in early cervical cancer stages. Silva LB et al<sup>35</sup> expressed that the SLN identification rate was less than 40% in advanced cervical cancer stages, which was the same as Altgassen and associates<sup>42</sup> who revealed a 94% sentinel node detection rate in tumor mass size 2.0 cm or less which has higher than tumor size more than 2.0 in diameter (83.6%) significantly. However, Daraï E et al<sup>30</sup> found that two staged IIB patients had metastasis negative in SLN and positive in non-SLN; furthermore, nine cases without parametrial involvement were found in two patients (22.2%). However, they accepted that the parametrial invasion were associated with lymphatic spreading factors, tumor size, or advanced disease. Thus, the authors in this study did not agree that SLN methods could support pelvic node status evaluation as well.

#### Conclusion

Nowadays, many gynecologic oncologists make efforts to find valuable strategies that can reduce morbidity and increase accuracy in cervical cancer treatment. Thus, lymphatic mapping with sentinel node detection by vital dye and radioisotope materials became an important role in management of cervical cancer. Many factors, including cervical tumor size, detection materials, surgical methods, and physician experience, are related to sentinel node identification in cervical cancer. More research should be encouraged to improve and standardize cervical cancer sentinel node detection in clinical applications.

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