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Revisiting the effectiveness of a forgotten technique: the value of blue dye on sentinel lymph node biopsies of gynecological cancer

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Abstract

Sentinel lymph node biopsy with blue dye has been used extensively in the past for the evaluation of patients with gynecological cancer. While the technique has been negatively criticized as inaccurate in detecting an appropriate number of lymph nodes bilaterally, novel studies seem to suggest an acceptable detection rate that is directly attributed to the number of cases performed as well as the type of dye that is used. Taking into consideration the significant impact of comprehensive pelvic lymphadenectomy on the quality of life of these patients, it seems reasonable to suggest its use in the absence of appropriate economic resources, such as in low income countries. In the present study we summarize the available evidence concerning the diagnostic performance of the various techniques that are used in sentinel lymph node resection in gynecologic oncology, focusing on the potential benefits of blue dye in specific settings.

Key words: Blue dye, gynecologic oncology, indocyanine, sentinel lymph node, technetium 99

Introduction

Sentinel lymph node has been widely adopted in gynecologic oncology. Specifically, its application has been strongly recommended in surgical procedures for endometrial and cervical cancer.[1,2] Its application is used in combination with Ultrastaging pathology with the use of cytokeratin immunohistochemistry. This modern staging procedure permits an increase in the detection rate of lymph node metastases that reaches approximately 35% of cases.[3] Ideally, sentinel lymph nodes should be detected bilaterally, however, this is possible in approximately 70-80% of cases depending on the stage and type of cancer.[4,5] However, it has been noted that cases with bilateral detection have a significantly higher risk of lymph node metastases.[6]

Pelvic lymphadenectomy increases the morbidity of gynecological cancer surgery and common complications include perioperative bleeding and postoperative Lymphocyst formation as well as

lymphoedema of the lower extremities. The number of lymph nodes excised is directly correlated to the risk of lymphoedema formation[7] and the use of adjuvant therapy, namely radiotherapy, increases the risk even more.[8]

Sentinel lymph node biopsy has been proposed as an alternative to comprehensive pelvic lymphadenectomy in an effort to reduce the possibility of adverse effects. While the technique has been criticized during the early days of its use it produces comparable results in terms of diagnostic accuracy, especially among patients with risk factors for lymph node metastases.[9]

Several techniques have been adopted for sentinel lymph node biopsy in gynecological cancer including the use of radiotracer, indocyanine green and blue dye.[10] In the present short commentary with compare our experience with blue dye tracer[11] to that of previous studies in the field in order to help reach a conclusion concerning the actual value of blue dye tracer in facilities that cannot afford the cost of indocyanine or radiotracer.

Radiotracer

The introduction of radiotracers with the use of portable intra-operative gamma probes has been adopted by gynecologic oncologists taking into consideration their use in breast cancer surgery. Early studies combined radiotracers with blue dye and reported acceptable detection rates of at least one lymph node.[12] Several injection sites were proposed including the uterine fundus, the endometrium using hysteroscopy, and the cervix.[13] Of those cervical injection predominated the last years.

Technetium-99 when used alone was accompanied by a high detection rate of at least one lymph node (86%, 95% CI: 83-89%, 25 studies).[14] The use of novel radiotracers with nanocolloid properties seems to increase the diagnostic accuracy of the method; however, still evidence remains limited to draw robust conclusions.[15] The addition of SPECT/CT may also increase the detection rates of positive lymph nodes and it seems that patients with increased bone marrow uptake seem to have higher odds of detection failure.[16] The addition of blue dye also increases the accuracy of the method, although direct comparison with blue dye alone is reported scarcely in the literature and does not seem to be significantly inferior.[14,17] In a previous study researchers reported that the cost of Technetium 99 combined with blue dye reaches $21,089, whereas the cost of Technetium 99 alone costs more than the combined approach alone ($21,462).[18] The addition of methylthioninium chloride also increases the diagnostic accuracy of technetium 99, although this has been reported in only one study.[19]

Indocyanine green

Indocyanine green is the preferred method of sentinel lymph node mapping and biopsy as it is associated with superior diagnostic accuracy rates in both endometrial and cervical cancer patients.[14,20] It should be noted that the evidence is still limited, mostly to observational studies, whereas data from randomized trials suggest that the technique is not superior to that of a combination of technetium and blue dye.[21] Compared to blue dye alone, the technique, however, nearly doubles the detection rate according to the results of a randomized controlled trial (detection rate 97% vs 47%).[22] Most guidelines suggest its use over technetium and technetium and blue dye and it is considered the method of choice for gynecological cancer sentinel lymph node detection.[1,2]

Blue dye

Blue dye has been excluded from standard care of gynecological cancer patients as a tracer for sentinel lymph node detection. Several studies have suggested that as a technique it is inferior to indocyanine green and technetium 99.[23] Detection rates range from

inappropriate to average accuracy levels.[23,24] Newer reports suggest however, that with appropriate instillation overall mapping rates may reach 90% of cases and bilateral mapping can be achieved in 70% of cases.[25] In our previous study we reported that the sensitivity, specificity, false-negative rate, positive predictive value, and negative predictive value (NPV) were 55.6%, 95.1%, 4.9%, 55.6%, and 95.1%, respectively with a superior detection rate for cases with tumor size ≤2.2 cm, negative lymphovascular space involvement, and depth of stromal invasion ≤5 mm (sensitivity 100%, specificity 93.5%, NPV 100%).[11] It should be noted that different blue dyes may provide different detection rates as suggested by previous studies in the field[26] and a proportional detection rate to the number of cases performed is observed.

Implications for clinical practice

Taking this information into consideration, we believe that although blue dye should not be considered in the setting of high-income countries (HICs), it may be a useful alternative that may help substitute a significant number of cases treated in low income countries (LICs). Taking into consideration the quality-of-life issues that may arise following pelvic lymphadenectomy which are directly attributed to the occurrence of lower limb lymphoedema and lymphocyst formation it seems reasonable to suggest the introduction of sentinel lymph node with blue dye in the absence of appropriate resources to obtain a more comprehensive technique (technetium or indocyanine). Blue dye is relative inexpensive and can help surgeons in LICs to avoid a substantial number of comprehensive lymhadenectomies, therefore improving the quality of life of gynecological cancer patients. It is our belief that the introduction of this technique will also significantly reduce the accompanying costs of that are related to complete lymphadenectomies. Implementing blue dye in daily practice will also help evaluate the actual accuracy of the technique in large scale studies.

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References

1. N. Concin, X. Matias-Guiu, I. Vergote, et al., ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma, Int J Gynecol Cancer 31 (2021), pp. 12-39.
2. D. Cibula, R. Pötter, F. Planchamp, et al., The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer, Int J Gynecol Cancer 28 (2018), pp. 641-655.
3. L.C. Burg, E.M. Hengeveld, J. in 't Hout, J. Bulten, P. Bult, P.L.M. Zusterzeel, Ultrastaging methods of sentinel lymph nodes in endometrial cancer – a systematic review, International Journal of Gynecologic Cancer 31 (2021), pp. 744-753.
4. J. Du, Y. Li, Q. Wang, et al., Sentinel lymph node mapping in gynecological oncology, Oncology letters 14 (2017), pp. 7669-7675.
5. G. Favre, B. Guani, V. Balaya, L. Magaud, F. Lecuru and P. Mathevet, Sentinel Lymph-Node Biopsy in Early-Stage Cervical Cancer: The 4-Year Follow-Up Results of the Senticol 2 Trial, Frontiers in Oncology 10 (2021).
6. D. Cibula, N.R. Abu-Rustum, L. Dusek, et al., Bilateral ultrastaging of sentinel lymph node in cervical cancer: Lowering the false-negative rate and improving the detection of micrometastasis, Gynecol Oncol 127 (2012), pp. 462-466.
7. S. Togami, T. Kawamura, M. Fukuda, S. Yanazume, M. Kamio and H. Kobayashi, Risk factors for lym-

phatic complications following lymphadenectomy in patients with cervical cancer, Japanese Journal of Clinical Oncology 48 (2018), pp. 1036-1040.
8. H. Tada, S. Teramukai, M. Fukushima and H. Sasaki, Risk factors for lower limb lymphedema after lymph node dissection in patients with ovarian and uterine carcinoma, BMC cancer 9 (2009), pp. 47-47.
9. M.C. Cusimano, D. Vicus, K. Pulman, et al., Assessment of Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging, JAMA Surg 156 (2021), pp. 157-164.
10. A. Skanjeti, A. Dhomps, C. Paschetta, J. Tordo and F. Giammarile, Sentinel Node Mapping in Gynecologic Cancers: A Comprehensive Review, Seminars in Nuclear Medicine 49 (2019), pp. 521-533.
11. I. Koutroumpa, M. Diakosavvas, M. Sotiropoulou, et al., Identification and Biopsy of Sentinel Lymph Node in Early-Stage Cervical Carcinoma: Diagnostic Accuracy and Clinical Utility Cureus 14 (2022), p. e23838.
12. S. Kadkhodayan, Z. Shiravani, M. Hasanzadeh, et al., Lymphatic mapping and sentinel node biopsy in endometrial cancer--a feasibility study using cervical injection of radiotracer and blue dye, Nucl Med Rev Cent East Eur 17 (2014), pp. 55-58.
13. F. Khoury-Collado and N.R. Abu-Rustum, Lymphatic mapping in endometrial cancer: a literature review of current techniques and results, Int J Gynecol Cancer 18 (2008), pp. 1163-1168.
14. J.A. How, P. O'Farrell, Z. Amajoud, et al., Sentinel lymph node mapping in endometrial cancer: a systematic review and meta-analysis, Minerva Ginecol 70 (2018), pp. 194-214.
15. V. S, Anirudhan and L. Balasubramani, A Feasibility Study of Sentinel Lymph Node Biopsy in Endometrial Cancer Using Technetium 99m Nanocolloid, Indian J Surg Oncol 11 (2020), pp. 699-704.
16. S. Sahbai, F.A. Taran, A. Staebler, et al., Sentinel lymph node mapping using SPECT/CT and gamma probe in endometrial cancer: an analysis of parameters affecting detection rate, Eur J Nucl Med Mol Imaging 44 (2017), pp. 1511-1519.
17. A. Buda, C. Crivellaro, F. Elisei, et al., Impact of Indocyanine Green for Sentinel Lymph Node Mapping in Early Stage Endometrial and Cervical Cancer: Comparison with Conventional Radiotracer (99m)Tc and/or Blue Dye, Ann Surg Oncol 23 (2016), pp. 2183-2191.
18. H. Brar, L. Hogen and A. Covens, Cost-effectiveness of sentinel node biopsy and pathological ultrastaging in patients with early-stage cervical cancer, Cancer 123 (2017), pp. 1751-1759.
19. P. Li, S. Feng, G. Zhou, L. Zhang, X. Sheng and D. Li, Clinical Study of Sentinel Lymph Node Detection to Evaluate Pelvic Lymph Node Metastasis to Determine the Prognosis of Patients with Early Cervical Cancer, Appl Bionics Biomech 2022 (2022), p. 8394049.
20. G. Di Martino, C. Crivellaro, E. De Ponti, et al., Indocyanine Green versus Radiotracer with or without Blue Dye for Sentinel Lymph Node Mapping in Stage >IB1 Cervical Cancer (>2 cm), J Minim Invasive Gynecol 24 (2017), pp. 954-959.
21. H. Nagar, N. Wietek, R.J. Goodall, W. Hughes, M. Schmidt-Hansen and J. Morrison, Sentinel node biopsy for diagnosis of lymph node involvement in endometrial cancer, Cochrane Database Syst Rev 6 (2021), p. Cd013021.
22. M. Frumovitz, M. Plante, P.S. Lee, et al., Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial, Lancet Oncol 19 (2018), pp. 1394-1403.
23. J. How, W.H. Gotlieb, J.Z. Press, et al., Comparing indocyanine green, technetium, and blue dye for sentinel lymph node mapping in endometrial cancer, Gynecologic Oncology 137 (2015), pp. 436-442.

24. F. Vidal, P. Leguevaque, S. Motton, et al., Evaluation of the sentinel lymph node algorithm with blue dye labeling for early-stage endometrial cancer in a multicentric setting, Int J Gynecol Cancer 23 (2013), pp. 1237-1243.
25. T. Jose, R. Agarwal, G.D. Maiti, M. Saraswat and A. Singh, Blue dye single labelling for colorimetric sentinel lymph node mapping in early endometrial cancer: A feasibility study, Medical Journal Armed Forces India (2021).
26. R. Eitan, G. Sabah, H. Krissi, et al., Robotic blue-dye sentinel lymph node detection for endometrial cancer – Factors predicting successful mapping, European Journal of Surgical Oncology 41 (2015), pp. 1659-1663.

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