Editorial

Sentinel node mapping for uterine cancer: are we at the turning point?

Gabriele Siesto, Domenico Vitobello

Department of Gynecology, IRCCS, Humanitas Research Hospital, Milan, Italy

Correspondence to: Gabriele Siesto, MD. Department of Gynecology, Humanitas Research Hospital, IRCCS, Via Manzoni 56, 20089 Rozzano, Milan, Italy. Email: gabriele.siesto@gmail.com.

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The assessment of the nodal status is a mainstay of the surgical staging of endometrial and cervical cancer. In fact, this data contributes to establish the risk factors for survival and therefore to properly address adjuvant therapies, if needed.

Among the last 20 years the concept of sentinel lymph node (SLN) mapping has progressively emerged in the gynecologic oncology community and, as the experiences have grown, it has become an always more popular option for the surgical staging of apparently early stage uterine cancers. Indeed, SLN mapping represents the right compromise to achieve an accurate retroperitoneal staging without burden on the lymphadenectomy-related morbidity.

Based on the results of several studies, including randomized trials (1,2) and prospective experiences (3,4), the latest versions of the National Comprehensive Cancer Network guidelines for endometrial and cervical cancer have included the sentinel node mapping protocol among the viable options for the surgical staging of early stage conditions (5,6). A strict adherence to an algorithm, as that designed by the Memorial Sloan Kettering Cancer Center (5-7), for instance, must be considered as a minimal requirement to perform this kind of surgery in safety: and it includes: (I) inspection of the abdomen; (II) identification of suspicious bulky nodes; (III) bilateral identification and removal of the first sentinel nodes; (IV) pathologic evaluation of the SLN through an ultrastaging process. All these steps together are crucial to guarantee that this image-guided precision surgery works in order to identify a low-volume disease.

We have learned that a neoplasia involving the uterus has a predictable lymphatic drainage: indeed, the vast majority of SLN are found in the pelvis. However, a bilateral migration of the tracer is needed to consider the procedure as satisfactory and historically this has been the main issue during the development of the SLN technique.

Studies have passed from colorimetric to radiometric tracers used alone or in combination, with always improving results, but it is when the indocyanine green (ICG) has been introduced in the SLN mapping that things have dramatically turned working (7,8).

This fluorescent dye, combined with a near-infrared imaging technology, easily allows not only to detect the lymph nodes, but also to design and follow the entire lymphatic drainage as to distinguish between the usual pattern of drainage into the interiliac region to the uncommon pattern which goes to the presacral and paraaortic region.

Soon after its introduction in the gynecologic oncology setting for the SLN mapping, the advantages of the ICG in terms of bilateral detection rates have been noticed: just a randomized controlled trial (RCT) was lacking in order to establish the supremacy of ICG over the other tracers currently available and to better define the standards for SLN mapping, until now, when finally, the results of the FILM trial have been released (9).

The "Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM)" study is a randomized, phase 3, multicentre, non-inferiority trial that aimed to compare the fluorimetric dye

(the ICG) with a conventional colorimetric (isosulfan blue dye) alone or in combination. The primary outcome of the study was to evaluate the efficacy of ICG versus blue dye in the identification of lymph nodes, defined as the number of lymph nodes identified by each dye (and confirmed by pathologist). The secondary outcomes were the rate of intraoperative detection of at least one sentinel node per patient and the rate of detection of bilateral SLN with ICG compared with isosulfan blue dye, and the safety of each tracer.

Despite the FILM trial has been designed to establish that ICG was not-inferior to the blue-dye for the SLN mapping, it definitely resulted into an almost 80% *vs.* 30% rate of bilateral mapping. These results cannot be ignored and, furthermore, they contributed to raise some other turning points: since the Food and Drug Administration (FDA) approval in 1959, ICG was initially used for several intravenous applications including the evaluation of the hepatic function and more recently during digestive and neurosurgical procedures, nevertheless the use for SLN is off-label, still. With these results, we hope that the FDA may approve the on-label use of ICG also per SLN mapping.

Second: SLN are always nodes? In the era of the SLN mapping surgeons will provide to pathologist a small amount only of lymphatic tissue, that should really represent the nodal status of the patients. In the FILM trial 39 out of 517 (8%) of the so-called SLN did not have lymphatic tissue inside: obviously for a small but not negligible proportion of patients undergoing SLN mapping, this translates into an under-staging. Despite the SLN algorithm includes only ultra-staging evaluation of the SLN removed, an intraoperative pathological assessment of the SLN might improve the overall procedure.

In conclusion, we must be aware that the FILM trial will represent a cornerstone for the improvement of our knowledge in SLN mapping in order to obtain a more accurate and easy reproducible procedure: some more refinement will probably contribute to make this technique complete.

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