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Review

Indocyanine green utility in sentinel node detection for cervical cancer patients

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Abstract

With wide implementation of screening tests for the Human Papilloma Virus, the number of diagnosed cases of premalignant or early stages of cervical cancer has increased considerably. As a consequence, surgeons' attention has focused on determining how best to limit the surgical procedure so the benefits of the procedure will not be surpassed by postoperative morbidity. In this respect, extended lymph node dissection, routinely associated so far with cervical cancer patients, has in the last decades been replaced with sentinel node detection and biopsy. Initially performed through radiocolloid injection, this method has undergone permanent changes in order to maximize its efficacy and safety. Although the laparoscopic approach had been widely used in the past, a new method has been proposed, i.e., the use of indocyanine green injection, which has yielded promising results for sentinel node detection in the early stages of cervical carcinoma. This paper reviews the literature of the most relevant studies conducted on this topic.

Keywords : cervical cancer, sentinel lymph node detection, indocyanine green

Highlights

- ✓ Sentinel lymph node detection by using indocyanine green injection seems to be a safe and effective method in cervical cancer patients.
- ✓ Attention should be paid to the method of dilution and injection of this product, in order to avoid the association of false positive results.

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Introduction

The benefits of detecting the sentinel node were demonstrated in cases of solid tumors almost a century ago. More recently, the method again proved safe and effective in treating other gynecologic malignancies such as breast cancer and vulvar cancer (1-4).

Regarding cervical cancer, the technique of sentinel node biopsy has been implemented since 1996 and consisted of blue dye and/or radiocolloid injection. Although the method had encouraging results, it nevertheless failed in detecting bilateral sentinel lymph nodes in almost half the patients. As a consequence, a significant number of patients were further subjected to extended lymph node dissection even though the malignant process had been diagnosed in an early stage of the disease (5, 6). However, the failure to detect the sentinel nodes argued in favor of searching for a more specific tracer. Specifically, the administration of radioisotopes such as Technetium proved to be painful to the patient, expensive, challenging for the team, and even dangerous due to possible radioactive contamination after the injection (7, 8). Other tracers such as blue dye, although less costly, were associated with rapid clearance from the sentinel nodes, meaning they could no longer be detected after a period of time. Specifically, due to the reduced dimensions of the molecules, these dyes seemed to be associated with a rapid migration from the level of the sentinel nodes. Therefore, by the time of surgery, the true sentinel nodes might be missed, while the blue dye accumulates at the level of the next lymph node stations. As a result, the rates of false positives increase and the effectiveness of the method decreases (9, 10). Moreover, the injection of such dyes is sometimes associated with allergic reactions, including anaphylactic shock (9-11). For these reasons, there was need to identify other types of tracers that could provide a higher rate of detection, with lower rates of adverse reactions and better identification of the sentinel nodes bilaterally (12).

Discussions

The utility of indocyanine green for sentinel lymph node detection in gynecologic malignancies.

This method uses an indocyanine green injection (approved by the FDA for many years) and the near infrared fluorescence imaging, due to the fluorescent properties of this substance in the 700-900 nm light spectrum (13). According to a study by Jewell and colleagues, the method consists in diluting a 25 mg vial in 20 cc of sterile water, thus obtaining a concentration of 1.25 mg/ml, and injecting one cc at 3 pm and 9 pm in the superficial and deep layer respectively at the level of the uterine cervix. The injection was done just after draping the patient, but before the insertion of the uterine manipulator and prior to laparoscopic surgery (12). Another site of injection is the endocervical or intrauterine cavity during hysteroscopy. The intracervical injection has been associated with the best results due to the presence of rich parametrial lymphatic drainage.

However, when the surgeon decides to inject the indocyanine green, several points should be considered: the product contains up to 5% iodine-based excipients, so it cannot be used in patients with known allergies to iodine; the substance should be diluted in sterile water and not in other substances such as sodium chloride (due to the fact that it is not readily soluble in saline solution), and the fact that the product is a negatively charged ion should be noted. Moreover, if the product is dissolved in saline solutions, the molecules trend to aggregate, influencing the optical properties (14, 15). In addition, once the product is dissolved, it should be kept in a dark room in order to preserve its fluorescent properties (16).

An interesting study on the topic of the influence of the concentration and volume of the injected indocyanine green was conducted by Xiong et al. (2014). In this study, cases in which the concentration was lower than 5 mg/ml and the volume was higher than 2 ml were associated with the best rates of detection of sentinel nodes in cervical cancer patients (17). Furthermore, according to the National Comprehensive Cancer Network (NCCN) Guidelines, Version 1.2018, the indocyanine green injection should be administered at the level of the uterine cervix, while the sentinel nodes are usually located medial to the external iliac vessels, ventral to the internal iliac vessels or at the level of the superior area of the obturator fossa (18).

However, debates regarding the protocol of indocyanine green injection in cervical cancer patients stem from the relatively low number of cases making use of this therapeutic protocol. Once the number of cases increases, a more standardized protocol can be expected. Moreover, similar to other malignancies, synchronous intracervical and intrauterine injection might also be considered. For colorectal cancer, some authors have proposed synchronous submucosal and subserosal injection with encouraging results (19). According to a meta-analysis by Emile, the submucosal and subserosal injection of indocyanine green in association with preoperative injection is correlated with a significantly higher rate of sentinel node detection (19).

Indocyanine green sentinel node detection as part of a dual method

To test the efficacy of the method, indocyanine green injection was initially used as part of a dual method of detection, in association with blue dye injection or with radiotracer administration. Jewel et al. (2014) analyzed the results of 227 patients with uterine malignancies submitted to surgery between 2011 and 2013 at the Memorial Sloan Kettering Cancer Center, in New York, the USA (12). Among these cases, the final histopathological studies confirmed the cervical origin of the malignancy in 18 cases. Among the entire cohort, the median time for detecting the sentinel node following injection was 30 minutes, while the median number of identified sentinel nodes was 3. Indocyanine green was used as a single method to detect the sentinel node in 87% of cases, while the remaining 13% of cases benefited from the dual method consisting of combined indocyanine green and blue dye injection. The authors reported no significant difference in terms of sentinel node detection after the indocyanine green injection alone or in association with blue dye injection. However, the rates of bilateral lymph node detection were an improvement over other techniques, thus demonstrating the efficacy of the method. Therefore, the overall detection rate was 95%, while the rate of bilateral detection was 79%. However, the authors underscore the fact that even if indocyanine green injection is used, the rates of detection are still poor among patients with a higher body mass index. The authors further observed that no additional lymph nodes were eventually found after blue dye injection when compared to indocyanine green injection, so they excluded the use of blue dye and injected only indocyanine green. As for the use of technetium, the higher rates of bilateral lymph node detection reported after indocyanine green injection as well as the various limitations of technetium injection (higher costs, exposure to radioactivity) led the authors to support the superiority of the fluorescent method (12).

One of the more relevant studies demonstrating the safety and efficacy of indocyanine green injection in uterine cancer malignancies was conducted by Anabela Rocha and colleagues, published in 2016 (16). The article reviewed papers published on this topic between January 2010 and May 2015, reviewing data from 10 studies involving 422 patients: 368 cases submitted to robotic surgery, 15 cases to laparoscopic surgery, and 10 cases to open surgery. Of these reports, six studies focused on cervical cancer patients. The authors emphasized the fact that the indocyanine green injection occurred at the level of the uterine cervix or directly into the uterine cavity through hysteroscopy. However, the intracervical injection was associated with a significantly higher rate of sentinel node detection. Among the reviewed studies, the mean number of retrieved lymph nodes was 4.7, no complication being related to the indocyanine green administration. Similar to the previous study, this paper also highlighted the importance of the indocyanine green injection in providing bilateral sentinel lymph node detection, the detection rates for bilateral mapping being of 97% for indocyanine green injection and 77% for blue dye injection. Moreover, studies which used indocyanine green alone or in association with isosulfan blue injection demonstrated that the detection rate was even higher when indocyanine green was administered alone. As for the method of injection, multiple techniques have been proposed. While most studies involved injecting indocyanine green at the level of the uterine cervix just before inducing the pneumoeperitoneum (in minimally invasive surgery) or just before performing the incision (in open surgery), other studies injected the dye directly in the uterine wall by hysteroscopy before beginning the surgical procedure. Moreover, other authors have injected the dye into the uterine cervix immediately after exposing the pelvic lymph nodes. As for the period of time between the injection and the intra-abdominal detection of the indocyanine green, various intervals (between 29 and 69 minutes) have been reported. However, 30 minutes might be considered an approximate time of migration (16).

In order to increase the rates of sentinel node detection after indocyanine green injection, some authors have proposed the combination of indocyanine green and human serum albumin. Currently, however, this combination has not demonstrated superiority, similar rates of sentinel node detection being reported for both two methods (20).

Conclusions

Sentinel lymph node detection by using indocyanine green injection seems to be a safe and effective method in cervical cancer patients. The method has been associated with increased rates of sentinel node detection and bilateral mapping while the rates of adverse reaction are almost null. Moreover, the method appears to improve results when used as a single agent or as part of a dual method. However, attention should be paid to the method of dilution and injection of this product in order to avoid the association of false positive results.

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Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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