Utility of indocyanine green injection in patients with cervical cancer besides the identification of sentinel lymph node (Review)

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Abstract. Due to the wide introduction of screening tests, patients with neoplastic diseases of the uterine cervix trend to be diagnosed in early stages of the disease, and less invasive surgical procedures are needed in certain cases. In this respect, the technique of sentinel lymph node dissection has been widely implemented as part of the therapeutic strategy, indocyanine green (ICG) being one of the most reliable markers for sentinel lymph node detection. However, it seems that this agent is extremely useful in order to achieve better short-term and long-term results after cervical cancer surgery, due to its capacity to determine the uterine vascular perfusion in cases in which conservative treatment, such as trachelectomy, is performed, as well as to prevent and treat lower limb lymphedema. A literature review was conducted of the studies which focused on the role of ICG utility in cervical cancer patients besides sentinel lymph node detection, special focus was given to vascularization preservation and lower limb lymphedema prevention and treatment.

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Contents

1. Introduction

Cervical cancer still represents a serious health problem affecting women worldwide, even though screening tests have been widely implemented (1-4). Although the number of cases diagnosed in advanced stages of the disease reported a slight decrease in the last decade (5-7), the wide presence of human papilloma virus infection in population is still responsible for a significant number of newly diagnosed cases annually. Therefore, a significant number of cases are diagnosed in early stages of the disease when less invasive surgical procedures are feasible in order to achieve a good local control of the disease (1-3). In this respect attention was focused on elaborating new therapeutic strategies in order to provide an effective treatment which is able to preserve fertility and functionality of the genital function and, moreover, to assure a good oncological long-term outcome (8-12). The method of detection of the sentinel node, which is considered to be the first involved lymph node in a neoplastic disease and which, if identified, retrieved and analyzed might orientate the lymphatic extension of the disease, and might influence the choice of adjuvant therapy has gained significant popularity in the last decades in the field of gynecologic oncology, large studies have been published on this issue (3,4,11,12). In cervical cancer, the method has been included as part of the standard therapeutic strategy, being cited in worldwide recognized guidelines of treatment, such as National Comprehensive Cancer Network clinical practice guidelines in oncology (13) or European Society for Medical Oncology clinical practice guidelines (14). In order to maximize the effectiveness of the method (defined by the rates of true positive and false negative detection rates), the sentinel lymph node detection has been submitted to permanent changes, different traces being proposed so far. Among the most commonly cited tracers, technetium methylene blue and indocyanine green (ICG) play central roles; moreover ICG has been also cited in the above mentioned guidelines, demonstrating once again the wide acceptance and utility of the method (13,14). However, in recent years experimental studies have demonstrated that ICG might also bring other benefits when used in patients diagnosed and submitted to surgery for early stage cervical cancer (15,16). The aim of the current review is to present the principles of ICG utilization in cervical cancer and to focus on its utility besides sentinel lymph node detection; therefore, attention will be focused on the utility of ICG on investigation of uterine vascularization after conservative surgical procedures such as trachelectomy as well as in preventing and treating chronic lower limb lymphedema.

2. Principles of utilization of ICG in cervical cancer patients

Described for the first time in 1852 by George Gabriel Stokes, the phenomenon of fluorescence has been widely encountered in nature (17,18). One decade later the property of certain substances to emit fluorescent light has been widely implemented in medicine, the most commonly used fluorescent dye being represented by ICG (19). Composed of small particles having the property to exhibit fluorescence when exposed to near infrared light (defined by a wave length of 600-900 nm), ICG was initially used in angiography and later introduced in other domains such as cardiology, hepatology, oncogynecology or ophthalmology (19). Presenting an excitation peak at a wave length of 805 nm and a fluorescence peak at 835 nm, ICG detection in near infrared light has a tissue penetration depth ranging from 0.5 to 1.5 cm (20,21). When injected into the systemic blood flow, ICG binds to plasma proteins and is maintained for a period of time at the level of the intravascular space, allowing in this way to perform advanced studies regarding the vascularization of certain sites. Based on this property, intravenous ICG injection intraoperatively will provide extremely useful information regarding the patency of the vascularization of different structures; this information will further influence the intraoperative decisions of the surgeon regarding the extent of resection, and the type of anastomosis. Moreover, the absence of fluorescence in certain areas raise the suspicion of an interrupted vascularization at this level and demonstrate the necessity of resect this area in order to prevent the development of further ischemic complications. When injected into submucosal areas in the close proximity of a tumoral bed, it will bind to lipoproteins and it will be distributed in certain lymph nodes which will therefore be considered as sentinel lymph nodes and excised (19). Furthermore, applying the near infrared light on an area in which ICG has been injected will provide exact information regarding the lymphatic mapping and a lymphography can be obtained. Based on these findings, the surgeon will be able to identify the lymphatic routes which should be avoided in order to prevent the development of further complications such as lymphedema. In patients with cervical cancer the fluorescent agent is diluted in sterile water and 1.5 ml of this solution is injected at the level of the uterine cervix in four points. Few minutes after injection, the pelvic and retroperitoneal space will be inspected by a near infrared camera system and the lymphatic pattern as well as the sentinel nodes are visualized (22,23).

3. Utility of ICG in visualization of uterine vascularization and uterine artery branches

Although most surgical procedures regarding patients with cervical cancer consist of radical hysterectomy, and therefore the pattern of uterine vascularization presents no further significance, in a reduced number of cases diagnosed in incipient stages of the disease, less radical surgical procedures have been proposed with good long-term oncological results. Possibly the most commonly reported such procedure is represented by radical trachelectomy alone or in association with sentinel lymph node dissection, the extent of the procedure being dictated by the stage of the disease. In cases where radical trachelectomy has been considered as the option of choice ongoing debate regarding the fertility outcomes have been reported, especially in cases in which the uterine artery cannot be preserved; in this respect certain authors

demonstrated that uterine artery ligation or coagulation during radical trachelectomy will further induce chronic uterine vascularization issues and a negative impact on the future fertility of the patients (9,10,24).

This issue was initially investigated in animals, an experimental study using ICG injection in female cynomolgus macaques being conducted by Japanese authors (25). In this experiment, the authors ligated the left uterine artery and vein in a seven-year old cynomolgus macaque which was further made pregnant; the pregnancy had an uneventful course and, when the end of the gestational period was close, a Cesarean section was planned. During the surgical procedure the authors injected ICG before sectioning the uterus and observed that an appropriate collateral circulation developed from the right uterine vessels to the left part of the uterine body. Moreover, at the time of laparotomy for Cesarean section, the only visible modification was represented by the presence of a few adherences between the uterine body and greater omentum (25). These data raised the suspicion that uterine vascularization can be preserved even if one uterine artery is ligated and were further evaluated in humans.

In order to investigate the influence of uterine artery ligation during radical trachelectomy, Escobar *et al* (15) conducted a study including 20 patients with early stage cervical cancer in whom radical trachelectomy was the option of choice; in 10 cases the authors decided to preserve the uterine arteries during the procedure while in the other 10 cases the uterine arteries were ligated or coagulated; after the end of this surgical step an ICG arteriography was performed and the uterine fluorescence was measured; surprisingly, the authors reported similar fundal fluorescence intensities between the two groups; moreover, these results were demonstrated by the fertility outcomes, all patients reporting regaining the menstrual function in the 8th postoperative week as well as similar rates of pregnancies (40% in the artery sparing group and 30% in the non-sparing group) (15). These data were explained by the fact that the uterine vascularization is not entirely provided by the uterine vessels, a complex network being established between the ovarian, cervical and uterine arteries (25).

Utility of ICG angiography in patients with cervical cancer has been also demonstrated in order to diminish the risk of postoperative urinary tract complications; therefore, intravenous injection of ICG provides a facile identification of the uterine artery as well as of its ureteral branch. Once this branch is identified, it will be more easily preserved, providing a better blood supply for the ureters. In an experimental study conducted by Long *et al* (26) published in 2018 this method was successfully used in two cervical cancer patients, at a four month follow-up neither case had developed any kind of urinary tract complication such as ureteral stricture, fistula or hydronephrosis.

4. Utility of ICG in prevention and treatment of lower limb lymphedema

Limb lymphedema represents one of the most common and debilitating long-term complication which might develop after performing an extended lymph node dissection for breast, skin or genital cancer and therefore attention has been focused on determining the modalities for avoiding this complication (27-29). Initially this issue was investigated in animal models such as rabbit or canine specimens. Therefore, after removing the popliteal nodes in young and near adult rabbits studies demonstrated that lymphatic regeneration might occur; however this result was inconstant, not being demonstrated in adult rabbits or canine specimens (30-32). Lymphoscintigraphic studies were further performed in humans, utilization of the ICG technique offering significant improvement in diagnostic, prevention and even treatment of limb lymphedema (33,34). The method is now successfully applied in patients with breast cancer, ICG lymphoscintigraphy offering the possibility of mapping the arm lymph nodes and revealing which lymphatic groups should be preserved in order to avoid injury of the upper limb lymphatics; thereafter, the incidence of upper limb lymphedema in breast cancer patients reported a significant decrease (35,36).

Lower limb lymphedema induced by pelvic lymph node dissection for gynecological malignancies such as cervical cancer, ICG lymphography has been proposed to investigate the risk and pattern of development of lymphedema as well as the therapeutic options. Therefore, in the study conducted by Yamamoto *et al* (16) and published in 2013, the authors included 68 lower limb lymphedema secondarily to pelvic lymph node dissection, 37 cases being initially diagnosed with cervical cancer. In all cases ICG injection of 0.2 ml of substance was performed at the level of the lateral border of Achilles' tendon and lymphography was studied at 12-18 h after injection; the authors classified the obtained images according to three patterns of lymphedema: Splash, stardust and diffuse pattern. Splash pattern presented small aggregations of tortuous lines; the stardust pattern demonstrated the presence of spotted fluorescent lights, while the diffuse pattern revealed the presence of wide distribution of the tracer, with no identifiable aggregations or spots. The authors demonstrated that these models of ICG distribution as well as their extent at the level of the lower limb were significantly correlated with the gravity of lymphedema. Therefore, splash pattern at the level of the groin region was most frequently encountered in patients with clinically reduced lymphedema, while the diffuse pattern on the whole length of the lower extremity was encountered in patients with clinically significant lymphedema; moreover a similar correlation was observed between the three patterns of lymphedema and the severity of the genital lymphedema (16). Therefore, this study brought into light significant information regarding the correlation between the clinical extent of the lower limb lymphedema and the type of distortion of the lymphatic routes (revealed by lymphoscintigraphy).

This information plays a crucial role especially if surgery for lymphedema correction is taken into consideration. Therefore, evaluation of the location, extent and pattern of lymphedema will provide information regarding the sites in which the lymphatic flow has been interrupted as well as regarding the possibility of creating an anastomosis between a dilated, interrupted lymphatic channel and a venous structure (37-39).

Moreover, a recent therapeutic study conducted in Rome, by Visconti *et al* (40) revealed another extremely interesting utility of ICG in order to treat lower limb lymphedema. The authors reported a case series of 10 consecutive patients

diagnosed with cancer related to lower limb lymphedema in whom they performed a compartmental dual lymph node flap transfer harvested from the right supraclavicular area to the affected lower limb. In all cases a ICG lymphoscintigraphy was performed in order to assess the lymphatic mapping of the limbs. In all cases viable flaps were obtained and satisfactory decrease of lower limb lymphedema has been reported. Moreover, ICG injection provided a safe harvesting of the right supraclavicular flap, no neurological symptoms such as dysesthesia being reported.

5. Conclusions

Although initially proposed for sentinel node detection in cervical cancer patients, ICG proved its utility in other circumstances such as vascularization control after radical trachelectomy and prevention and treatment of lower limb lymphedema. According to the experimental studies published so far which injected ICG in the systemic circulation it seems that preservation of uterine arteries during radical trachelectomy is not mandatory in order to maintain uterine viability and functionality; studies conducted on the theme of lower limb lymphedema demonstrated that performing an intraoperative ICG based lymphography might prevent or treat lower limb lymphedema in patients submitted to lymph node dissection for cervical cancer. These data enable us to conclude that ICG utilization seems to play a crucial role besides the identification of sentinel node in cervical cancer patients.

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Authors' contributions

CD, EB, OB, DC and AN acquired, analyzed and interpreted the patient data regarding the principles of ICG utilization in oncology. CaS, CoS, IH, LI and AF analyzed and interpreted the patient data regarding the principles of ICG in vascularization studies. CB and MV studied the ICG utility in lymphoscintigraphy. NB, IBa and IBr made substantial contributions to the conception of the study and the interpretation of the data, drafted the manuscript and were major contributors in the writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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