

# Utility of indocyanine green in the administration of cytotoxic drugs in breast cancer patients

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## ABSTRACT

Indocyanine green has been widely introduced in breast cancer protocol for sentinel node detection, for upper limb lymphedema prevention and for breast reconstruction. However, more recent studies came to demonstrate that these particles can be also used in order to provide an efficient intraoperative detection of metastatic deposits as well as for a more targeted delivery of cytotoxic drugs. The current paper aims to investigate the mechanisms of action, the principles and the benefits of indocyanine green as a therapeutic tool, part of the medical oncologic treatment of breast cancer patients.

**Keywords:** indocyanine green, breast cancer, metastatic deposits, chemotherapy

## INTRODUCTION

Indocyanine green represents a fluorescent dye with strong emission in infrared light and minimal interference of tissular auto-fluorescence which has been widely used in breast cancer patients with

multiple purposes: detection of sentinel node, identification of the upper limb lymphatics and identification of breast or flap vascularization before breast reconstruction, being effective in both angiographic and lymphographic mapping (1,2).

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## INDOCYANINE GREEN AS DIAGNOSTIC AND THERAPEUTIC TOOL FOR INFRACLINICAL TUMORAL LESIONS

Certain authors advanced and tried to find out if indocyanine green can be also used in order to detect infraclinical metastatic deposits; however, indocyanine itself has a short circulation half time and rapid clearance from the body (3-5). Therefore, silica nanoparticles, liposomes or micelles have been used in association with indocyanine green in order to increase the half time and to provide a higher tumoral overload with this agent (6-8). This dye also presents photosensitizing properties and therefore can generate oxygen species and can generate heat which will further destroy malignant cells (9,10).

Initially the method failed to prove its efficacy: a higher amount of indocyanine green molecules being found at the level of the surrounding tissues and not in the tumoral tissue itself (11); in the last decades this inconvenient has been eliminated by associating indocyanine green, certain nano-particles and cancer related antibodies which will further lead to the preferential accumulation of these complexes in the tumoral cells (12). According to the type of tumoral cells, different molecules have been proposed in order to maximize the accumulation of indocyanine green; therefore, super carbonate apatite indocyanine green nano-particles have been used for colorectal tumoral cells detection, indocyanine green loaded polymer lipid nanoparticles have been proposed for pancreatic cancer, silk fibroin nanoparticles have been proposed for glioblastoma while indocyanine conjugated micelles have been proposed for breast and lung cancer (4,13,14).

Once these benefits have been widely demonstrated, a better identification and, in certain cases, destruction of tumoral cells have been achieved especially due to the capacity of realizing free oxygen

radicals; in order to maximize these effects certain authors went further and proposed the association of these particles with doxorubicin molecules, a higher amount of this cytotoxic agent at the level of breast tumoral cells being achievable (15). Moreover, further studies regarding the possibility of association between indocyanine green, nanoparticles and immunotherapy has been proposed and is now under investigation (16). However, studies are still needed in order to investigate if such molecules have an increased specificity in order to concentrate exclusively at the level of the tumoral cells and not to affect the surrounding healthy tissues. Another interesting question and still unanswered is related to the capacity of these molecules to penetrate both the primary tumor and the metastatic lesions irrespectively to the tumor structure (17).

Certain authors proposed the usage of indocyanine green in association with ferritin nanoparticles in order to increase the uptake into breast cancer cells and to provide a more efficient intra-tumoral delivery (1).

## CONCLUSIONS

Besides the well-known utilities of indocyanine green such as sentinel node detection, upper limb lymphedema prevention and treatment and as part of the reconstructive surgery, indocyanine green also seems to be effective in order to detect infraclinical metastatic deposits and to provide a targeted oncological treatment. In order to increase the concentration of indocyanine green into the tumoral cells, different associations with specific nanoparticles have been proposed with promising results. Moreover, association between these particles with chemotherapy agents seem to increase the local accumulation and to maximize their cytotoxic activity.

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