Journal of Visceral Surgery (2014) 151, 117—124

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

REVIEW

Indocyanine green fluorescence imaging in the surgical management of liver cancers: Current facts and future implications

C. Lim[a,*], E. Vibert[b], D. Azoulay[a], C. Salloum[a], T. Ishizawa[c], R. Yoshioka[c], Y. Mise[c], Y. Sakamoto[c], T. Aoki[c], Y. Sugawara[c], K. Hasegawa[c], N. Kokudo[c]

[a] *Service de Chirurgie Digestive, Hépatobiliaire, Pancréatique et Transplantation Hépatique, Hôpital Henri-Mondor, Assistance Publique—Hôpitaux de Paris, 51, avenue du Maréchal-de-Lattre-de-Tassigny, 94010 Créteil, France*
[b] *Service de Chirurgie Hépatobiliaire, Pancréatique et Transplantation Hépatique, Hôpital Paul-Brousse, 12, avenue Paul-Vaillant-Couturier, 94804 Villejuif, France*
[c] *Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of medicine, University of Tokyo, Tokyo, Japan*

Available online 21 January 2014

KEYWORDS
Fluorescence;
Indocyanine green;
Hepatocellular carcinoma;
Liver metastases;
Camera

Summary Imaging detection of liver cancers and identification of the bile ducts during surgery, based on the fluorescence properties of indocyanine green, has recently been developed in liver surgery. The principle of this imaging technique relies on the intravenous administration of indocyanine green before surgery and the illumination of the surface of the liver by an infrared camera that simultaneously induces and collects the fluorescence. Detection by fluorescence is based on the contrast between the (fluorescent) tumoral or peri-tumoral tissues and the healthy (non-fluorescent) liver. Results suggest that indocyanine green fluorescence imaging is capable of identification of new liver cancers and enables the characterization of known hepatic lesions in real time during liver resection. The purpose of this paper is to present the fundamental principles of fluorescence imaging detection, to describe successively the practical and technical aspects of its use and the appearance of hepatic lesions in fluorescence, and to expose the diagnostic and therapeutic perspectives of this innovative imaging technique in liver surgery.

Introduction

During the last couple of years, medical imaging research has been rejuvenated by the development of lesion detection with fluorescence. Several medico-surgical specialties (dermatology [1], pulmonology [2], urology [3], neurosurgery [4], gastro-intestinal surgery [5], as well as plastic and reconstructive surgery [6]) now use fluorescence imaging techniques to diagnose cancer or premalignant lesions, and/or lymph nodes draining a tumor. The principle behind this imaging technique relies on the administration of

* Corresponding author.
E-mail address: chetana.lim@gmail.com (C. Lim).

1878-7886/$ — see front matter
http://dx.doi.org/10.1016/j.jviscsurg.2013.11.003

a fluorescent marker capable of specifically targeting ''fluorescent'' cancer cells; this has opened one of the most promising fields of tumor detection. Indocyanine green (IG) is a soluble dye, which emits a fluorescent light when illuminated by an infrared laser source. In hepatic surgery, IG clearance is used to evaluate hepatic function before surgical procedures [7—9], but the application of the fluorescent properties of IG is just beginning. The first application of this imaging technique in hepatic surgery was reported by Ishizawa et al. in 2009 [10].

The goal of this update was to report the experience of several Asiatic teams with this innovating intra-operative imaging technique in hepatic surgery, and, after presenting the concept and the technical bases of fluorescence imaging, to summarize the practical and technical aspects of its use, to describe the features of the images that can be obtained, to review the pathophysiologic mechanisms implicated, and finally to outline the limitations of its use in hepatic surgery.

Concept

Indocyanine green is a fluorescent dye that has been used in ophthalmology to visualize the retinal and choroid vascularization for more than 20 years [11]. Its metabolic characteristics (intravascular confinement enhanced by fixation to plasma proteins and rapid hepatic excretion into bile), the spectral proprieties of this molecule, and the development of new imaging systems has extended the fields of application of IG fluorescence to several other surgical specialties (cardiac surgery [12], neurosurgery [13], plastic and reconstructive surgery [6]). In oncologic surgery, IG fluorescence has been tested to detect kidney tumors [3], and has been used for detection of sentinel lymph nodes in breast cancer [14], malignant melanoma [15] and gastro-intestinal cancers [16—18].

In hepatic surgery, this dye has been used to evaluate hepatic function and outline hepatectomy strategies for oncologic resections [19,20], and for living donor hepatic transplantation [21]. More recently, teams from Asia have improved imaging techniques based on IG fluorescence, allowing the visualization of bile ducts [22—24], as well as hepatocellular carcinoma (HCC) and hepatic metastases during liver surgery [10,25]. Basically, IG is administered intravenously 12 to 48 hours before surgery and lights up the liver surface when illuminated with a near-infrared source. After injection, IG is rapidly taken up by tumoral and non-tumoral hepatocytes. In the presence of normal or subnormal hepatic function and in the absence of biliary obstruction, IG is excreted in the bile and disappears from healthy liver parenchyma within a few hours [26]. On the other hand, IG remains fixed in tumoral hepatocytes and in pathological areas of the liver, particularly around non-hepatocellular tumors. Thanks to particular features of the camera, the fluorescent light emitted by IG allows detection of hepatocellular (tumor fluorescence) and non-hepatocellular (peri-tumoral fluorescence) tumors.

Indocyanine green

Indocyanine green is a hydrosoluble molecule that fixes rapidly and intensely to plasma proteins after intravenous injection. Also, 98—99% of IG molecules link to proteins with a large proportion becoming fixed to high molecular weight proteins such as albumin. The mode of elimination is exclusively hepatobiliary. IG is selectively taken up by the hepatocytes and excreted in bile via an active transport system. IG is not metabolized and does not enter the enterohepatic circulation. Consequently, the disappearance rate of IG from plasma to bile reflects the excretory function of the liver [27].

Schematically, all molecules can take on different levels of electronic energy. In its basal state, molecular energy is minimal. Under the action of light, depending on wavelengths, absorbed light can raise the level of energy. As the molecule returns to its basal state, light is emitted with a wavelength superior to the light responsible for the excitation. The difference between excitation and emission wavelengths is exploited thanks to cameras equipped with interferential filters to obtain the images.

When the IG-protein complex is excited by a light source with a wavelength between 750 and 810 nm, fluorescent light with a wavelength of approximately 830 nm (wavelength situated in the infrared spectrum) [28] is emitted. The human eye cannot see these wavelengths.

Fluorescent light is largely attenuated by hemoglobin and water as it traverses biological tissues. Hemoglobin strongly attenuates all wavelengths less than 700 nm (which corresponds in fact to the entire visible spectrum excepting deep red). Water is transparent in visible and near-infrared light but attenuates wavelengths over 900 nm. There is therefore a ''window'' of wavelengths at the limit between deep red and near infrared (700—900 nm) where tissue transparency is maximal. This is one of the reasons why IG fluorescence can be detected in the near-infrared zone from as deep as 10 mm from the surface of tissues.

In France, the only fluorescent molecules approved for injection in man are fluorescein and IG and both can be administered intravenously. Indocyanine green has an advantage in that is absorbs light in the near infrared range (while the spectrum of fluorescein is in the range of visible light) and can be detected much deeper in tissues. Although IG seems to be better tolerated than fluorescein, several cases of allergy (hives, nausea and anaphylactic shock) have been reported in ophthalmology. Some of these cases have been attributed to the iodide contained in certain preparations of IG. In case of recognized allergy to iodine, it is necessary to use special preparations of IG that do not contain iodine [29].

Technique

Apparatus

The device used is not specifically designed for intra-operative use, but the camera can be equipped with a sterile cover that allows the operator to manipulate the apparatus under sterile conditions. A portable imaging system provides real time quantitative fluorescent imaging (Fig. 1). This imaging system includes an infrared camera and amplifier. The camera simultaneously provides the functions of fluorescence excitation with a laser (LED emitting an infrared radiance) diffused over the operative field and fluorescence image acquisition is ensured by a captor (CCD), which filters the light so that only near infrared wavelengths can be seen. In practice, the camera and cable do not need to be sterilized. The length of the cable allows the screen and amplifier to be placed sufficiently far away so that a non-sterile person can hold the infrared camera above the sterile operative field. New imaging systems have been developed recently,