Fluorescent-Guided Liver Surgery: Paul Brousse Experiences and Perspective

11

Mohamed Bekheit and Eric Vibert

Introduction

Dr Irwin Fox reported the clinical use of indocyanine green (ICG) for the first time in 1960 at Mayo Clinic [1]. Its high safety profile and sensitivity makes it appealing for many clinical applications. Since it is exclusively removed from the body via the biliary system, the study of liver function using the indocyanine green became widely adopted [2]. The indocyanine green 15 min retention test is commonly used for preoperative assessment of liver reserve [3]. Furthermore, its plasma clearance rate was a significant predictor of liver regeneration after portal vein embolization (PVE) [4].

Recently, with the development of easily installed near-infrared camera systems, the live intraoperative evaluation of liver fluorescence became available. In general, the evaluation of tissues uptake and excretion of ICG requires prior to surgery administration. The time window between injection and evaluation ranges from 24 to 72 h. On the other hand, evaluation of vascular structures and perfusion requires intraoperative administration of ICG. In most instances the required preoperative dose is between 0.25 and 0.5 mg/kg. Intraoperatively, we inject 1 cm of a diluted ICG solution once or twice for a total dose of 0.25 mg.

In Paul Brousse, we first used the infrared camera systems PDE developed by Hamamatsu Photonics (Hamamatsu, Japan) in 28 patients operated for colorectal liver metastases or hepatocellular carcinoma by laparotomy. All patients received intravenously ICG at a dose of 0.5 mg/kg between 12 and 24 h before the surgical procedure. Four (14.3 %) patients presented new lesions that were neither detected by preoperative imaging nor by intraoperative ultrasound. Three (75 %) of those four patients had lesions confirmed to be CRLM. This sensitivity was supposed to improve the surgical radicality in 11 % of our series [5].

Because of these encouraging results of PDE and our leading French experience in this field, since our group performs around 230 liver resections and 130 liver transplantations by year, we tested a new device (Fluobeam®) developed by a French company (Fluoptic, Grenoble) (Fig. 11.1).

M. Bekheit, M.B.Ch.B., M.Sc., M.R.C.S.
Hepatobiliary and Liver Transplant, Paul Brousse Hospital, 12 Avenue Paul Vaillant Couturier, Villejuif 94800, France
e-mail: dr_mohamedbekheit@hotmail.com

E. Vibert, M.D., Ph.D. (✉)
Hepatobiliary and Liver Transplant, Paul Brousse Hospital, 12 Avenue Paul Vaillant Couturier, Villejuif 94800, France

Centre Hépato-Biliaire, Hôpital Paul Brousse, 14 Avenue Paul Vaillant Couturier, 94800 Villejuif, France
e-mail: eric.vibert.pbr@gmail.com

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Fig. 11.1 Fluobeam® medical device; central processing unit and the camera head

Fluobeam® Medical Device

The Fluobeam® medical device allows visualizing, on a computer screen, the flow, the distribution and/or the accumulation of near-infrared fluorescent agents such as ICG, injected to patient before and/or during surgery for various indications such as:

Intraoperative visualization and detection of primary liver tumors and/or hepatic metastases located less than 0.5 cm from liver surface.

Intraoperative better visualization of tumor margin on the raw liver surface during parenchyma transaction.

Intraoperative identification of bile ducts.

Intraoperative assessment of liver vascularization.

Fluobeam® is composed of (Fig. 11.1):

1. *Optical head*, which is composed of the camera and the optical elements such as fibers, filters, lens, and diffusers. The optical head is also the place where light emission occurs: laser and LEDs (Light Emitting Diodes).
2. *Control box* including all the elements to control, monitor, and supply power to the optical head.
3. *Cable* including electrical wires and optical fibers. Cable is mechanically linked to the optical head, and can be plugged/unplugged to/from the electrical case through a dedicated connector.
4. *Power supply* and RJ 45 cable.
5. *Imaging software (Fluosoft™) (Fig. 11.2)*, which allows real-time visualization of the fluorescent images acquired by the optical head. It also contains the control commands of the Fluobeam® and allows the recording of images, sequence of images and videos.

Fluobeam® is a class IIa CE marked medical device. It allows the visualization of fluorescent moiety with a maximum emission between 760 and 850 nm for an excitation wavelength of 750 nm. Fluobeam® includes a class 1 laser source which is safe under all conditions of normal use. The laser light is conveyed from the control box to the optical head via an optical fiber. Two laser beams are emitted from the optical head shedding light on an elliptic area of 15 cm × 10 cm at a distance of 20 cm from the optical head.

Fig. 11.2 Fluosoft™ screen shot demonstrating the various functional commands

Fluobeam® includes an illumination ring based on white and near-infrared LEDs in order to provide a natural white illumination during the surgery. A zoom of 10× can be directly driven by the user via two push-buttons located on the front side of the optical head, which allow changing of the field of view from a maximum of 20 cm × 15 cm to a minimum of 2 cm × 1.5 cm. For distance ranging from 20 to 50 cm between the optical head and the examined area, the camera autofocus ensures a precise focusing and leads to sharp image. Depending on the intensity of the fluorescence signal, the exposure time of the camera can be adjusted from 1 ms to 1 s which allows the acquisition of videos with a frequency ranging from 25 images per second to 1 image per second.

One of the advantages of Fluobeam® is the software accompanying the devices that allow to optimize the exposure according to the intensity of fluorescence. These settings were automatic or manual and allowed to improve largely the quality of images that could be recorded on the software as images and movies. A subsequent analysis of the intensity of fluorescence in specific area of the image according to time could be made on the same software.

As for the other devices, the main drawback of Fluobeam® device was the relatively large size of the camera head that renders the exposure of the upper part of the liver surface difficult.

Our Experience with Hepatic Malignant Tumors

The small number of patients that we had analyzed to date with Fluobeam® is not sufficient to conclude concerning the accuracy of this device to detect underestimated superficial lesion. We presented in this chapter some images that we had obtained with Fluobeam® in some specific situation to demonstrate the quality of images obtainable by this device.

Currently, we aim at increasing the specificity of this technique especially in patients with abnormal liver function and/or cirrhosis where we observed more lesions were falsely interpreted as potentially malignant compared to patients without cirrhosis (Fig. 11.3).

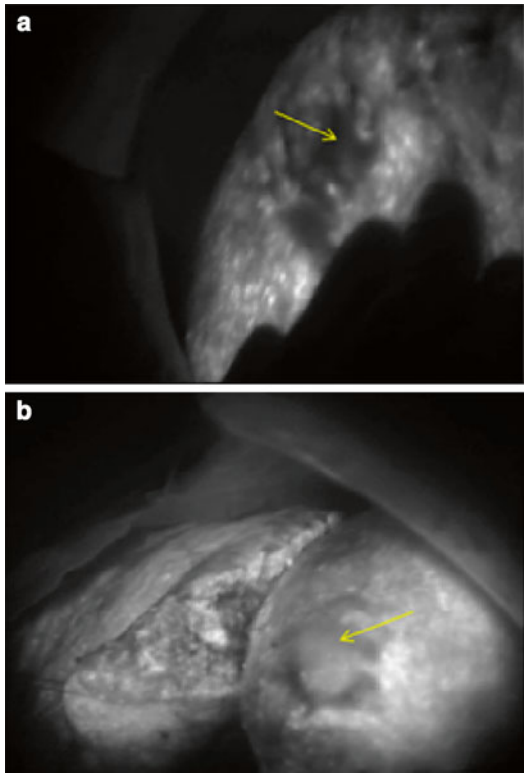

Fig. 11.3 (**a**) Undifferentiated HCC (*arrow*) on a cirrhotic liver background. (**b**) Moderately differentiated HCC (*arrow*) over cirrhotic liver

Hepatocellular Cancers

Fluorescence intensity correlated well with the differentiation of the HCC when analyzed by fluorescence microscopy [6]. In live fluorescence-guided surgery, we were able to notice the difference in the HCC differentiation based on the brightness. Although this was done in retrospect, after the histopathologic examination of the specimens, it demonstrates that real-time fluorescence could be useful in tumor grading. We are currently working on stratification and quantification of this relation. demonstrates different grades of HCC with different brightness (Fig. 11.3).

Due to its relatively uncommon incidence, there is no specific report on the use of indocyanine green during surgery for fibrolamellar carcinoma. In our experience, fibrolamellar carcinoma captures well the indocyanine green and subsequently emits strong fluorescent signal (Fig. 11.4).

Cholangiocarcinoma

The same concept is applicable for cholangiocarcinoma. The tumor retains the indocyanine green

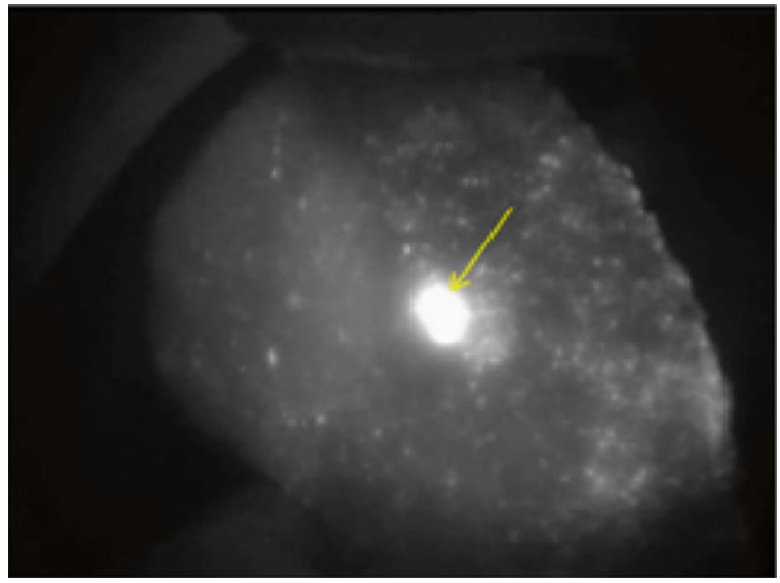

Fig. 11.4 Fibrolamellar HCC (*arrow*) on a non-cirrhotic background

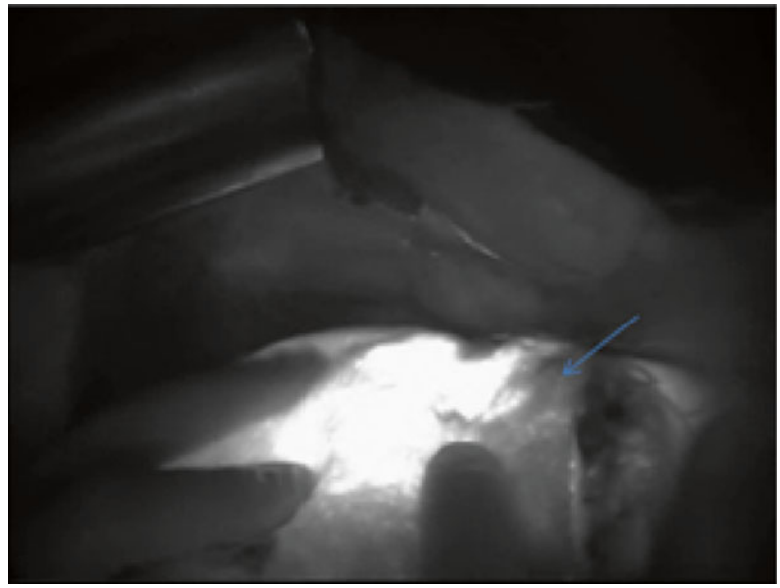

Fig. 11.5 Bright cholangiocarcinoma with surrounding safety margin (*arrow*) during anatomical resection

and emits strong bright fluorescence on exposure to the near infrared light. Real-time determination of the free resection margin is of paramount importance to minimize the recurrence. As shown in Fig. 11.5, fluorescence imaging was a useful tool in ascertaining the tumor safety margin.

Colorectal Liver Metastasis

Metastases to the liver from the colorectal cancers did not capture indocyanine green therefore they appear as dark masses or spots; contrary to the liver tissue that captures and emits fluorescence; giving them a bright image. Since metastasis are surrounded by a rim of compressed hepatic cells, these hepatic cells are responsible for the hyperfluorescent rim surrounding the dark tumor mass (Fig. 11.6) [7].

Achieving an R0 resection is an oncologic target during surgery for liver tumors. Theoretically, the smaller the lesion the less compression it exerts on the surrounding tissue and the lower difference between tumor and non-tumor brightness. Nonetheless, the use of fluorescence has been reported to improve the detection rate of tumors smaller than 3 mm compared to the combined use of CT and IOUS [8]. This would lead to improving the radicality of surgery. In Fig. 11.7, small contralateral tumor was detected during right hepatectomy for colorectal liver metastasis following PVE.

Visualization of Bile Duct

Real-time fluorescence could be useful in delineation of the bile duct anatomy. The direct visualization might allow to safely ligate and cut sacrifiable ducts (Fig. 11.8). Although we did not have the opportunity to test it, bile leak could be also detected as demonstrated in other studies.

Potential limitations of the current real-time fluorescence in surgery for hepatic tumors:

Beside the limitation in detecting tumors deeper than 0.5 cm, there is, nonetheless, some inaccuracies related to the real-time fluorescence assessment using the endocyanine green techniques. Not every illuminating lesion is cancer. For instance, biliary proliferative lesions and benign regenerative nodules could appear, as well, bright (Fig. 11.9) [7].

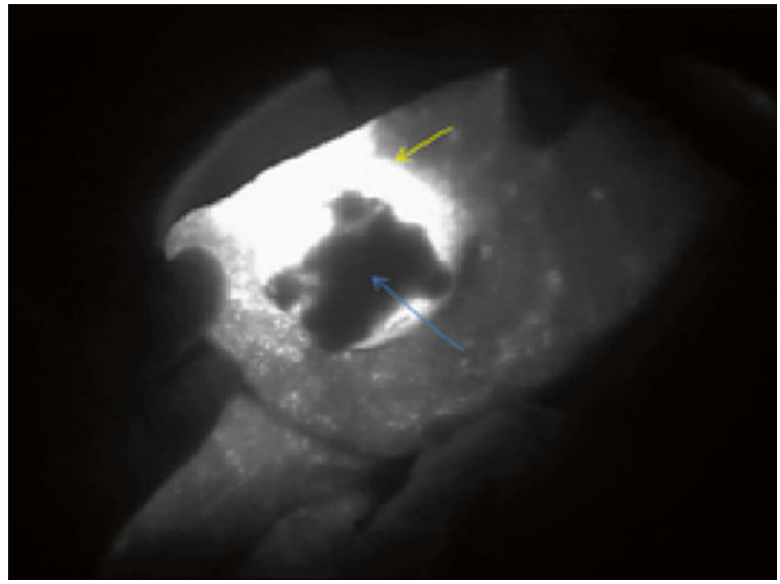

Fig. 11.6 Dim colorectal liver metastasis (*blue long arrow*) with surrounding bright rim of compressed liver tissue (*yellow shorter arrow*)

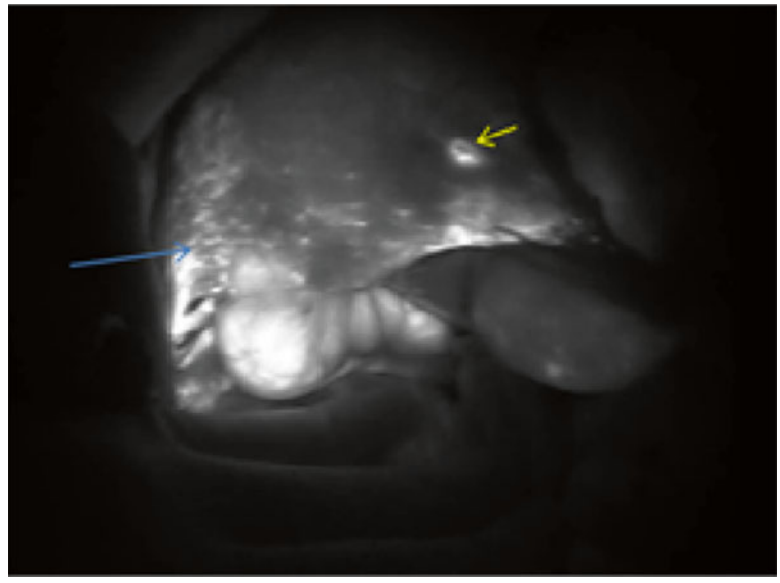

Fig. 11.7 Parenchymal liver appearance after portal vein embolization (*long blue arrow*) with ICG injection 24 h prior to surgery for right hepatectomy for colorectal liver metastasis and the appearance of small lesion in the left lobe (*short yellow arrow*)

Our Experience with Liver Transplantation

Anticipation of early graft function could facilitate preventive measures against graft loss. The integrity of hepatic microcirculation has been directly linked to the early post-implant graft function [9]. Reduction of sinusoidal blood flow, due to reduced portal venous flow, along with cellular death are the end results of the different implicated pathophysiologic pathways [10]. Disorders in sinusoidal perfusion could be reflected through fluorescence uptake and emission [11].

Our group previously reported the value of the ICG elimination rate as a predictor for post-liver transplant graft function and in the evaluation of

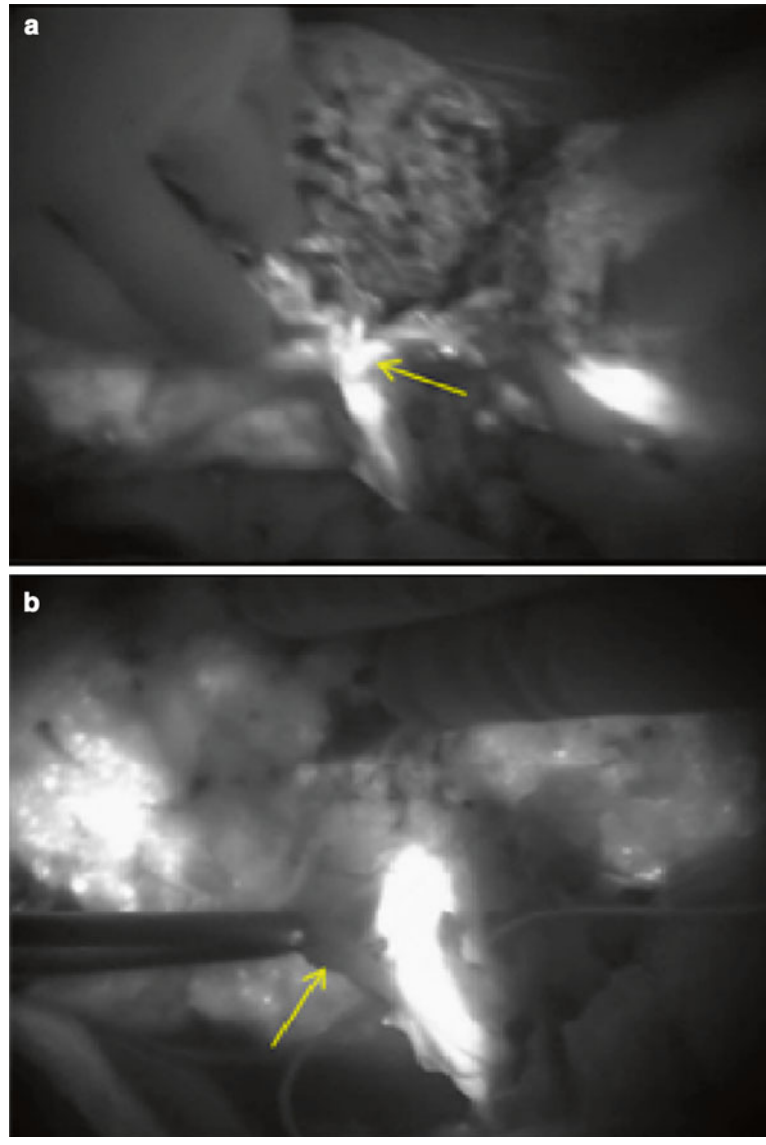

Fig. 11.8 (**a**) Visualization of the bile ducts during liver transection demonstrating preserved integrity of the main ducts. The *arrow* marks the biliary confluence. (**b**) forceps grasping the cystic duct (*arrow*) which does not show fluorescence emission. Contrary to the bright main biliary system

hepatic artery thrombosis [12, 13]. It was possible to quantify the ICG uptake and excretion and correlate these rates with the degree of ischemia–reperfusion injury. Recently, we started to use the Fluobeam technology for intraoperative evaluation of the liver perfusion at the microcirculation level.

In theory, the real-time assessment of the hepatic microcirculation should be feasible through analysis of the homogeneity of fluorescence emission. Homogeneous fluorescence could reflect the homogeneity in microcircular perfusion and cellular capturing of fluorescent material and vice versa. We currently aim at testing this hypothesis on micro- and macroscale levels in a pig model.

The initial crude data highlight the presence of two main patterns of perfusion disorders that could be described as systematic and unsystematic. The pattern is unsystematic when there is patchy or mottled surface fluorescence, and this pattern is highly probable in conditions related to disturbances in the hepatic microcirculation

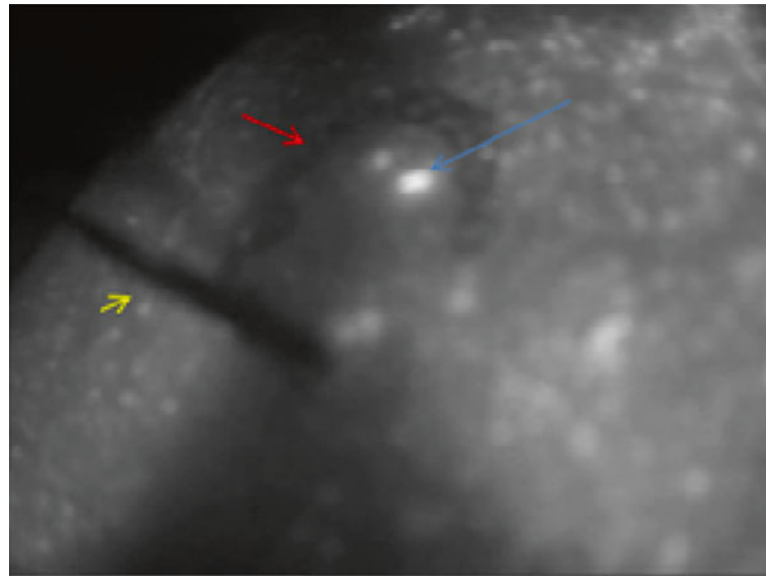

Fig. 11.9 Small false-positive lesions (*blue arrow*), surrounded by burned ring (*red arrow*) during electrocautery dissection (*yellow arrow*)

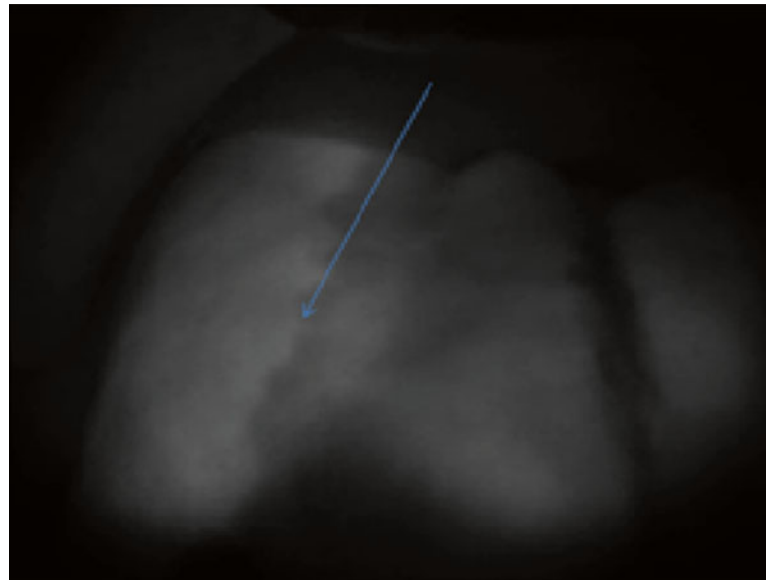

Fig. 11.10 Perfusion difference between the right and left hepatic hemilivers suggesting left inflow problem. The *arrow* marks the line of demarcation between the perfused right and less perfused left hemilivers

(i.e. ischemia/reperfusion injury). Unlike the patchy pattern, the systematic pattern is described when the fluorescence difference is related to a major anatomical region. In the last case the perfusion disturbance is related to a major vascular structure (i.e. arterial or portal branch(s)). Figure 11.10 demonstrates a case with left hepatic hypofluorescence that was consistent with the Doppler finding of left arterial spasm, which recovered 10 min later.

The presence of a systematic perfusion disorder warrants further examination of the extrahepatic inflow and outflow systems in real time with an extra-bolus of ICG. Vascular patency could be confirmed by the presence of indocyanine flow particularly in small vessels for which the sensation of a pulse is sometime difficult (Fig. 11.11).

Bile excretion is a good indicator of regain of function after liver transplantation [14]. The immediate secretion of bile after hepatic reperfusion

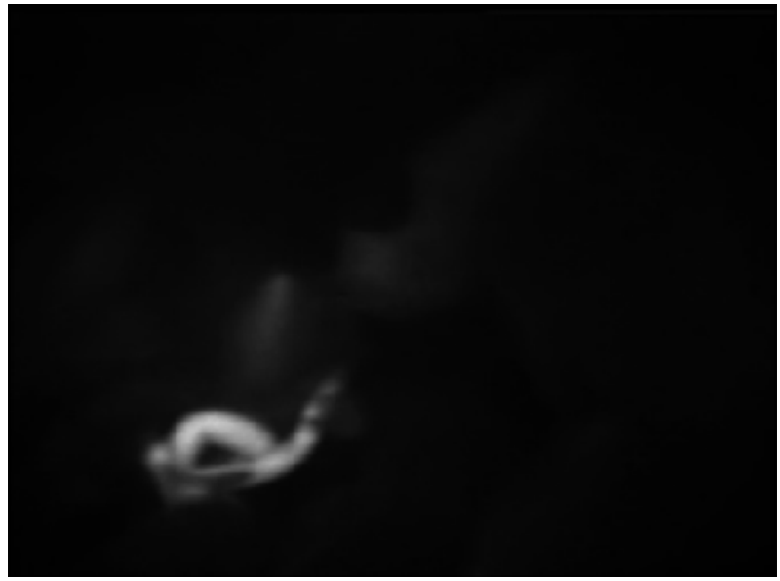

Fig. 11.11 Arterial illumination confirming the patency through the anastomosis

is a predictor of the early good graft function [15]. Besides, real time evaluation of the integrity of the biliary anastomosis could be possible.

Summary

Real-time fluorescence evaluation using Fluobeam® is an interesting tool of evaluation of the liver condition at reperfusion during transplantation and of the oncologic radicality during hepatic surgery for cancer that has many perspectives.

The authors declare no conflict of interest

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