CASE REPORT

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INDOCYANINE GREEN FLUORESCENCE FOR LIVER ASSESSMENT AND IMAGING-GUIDED RESECTION OF COLORECTAL METASTASES: A CASE REPORT

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Abstract. Introduction: *Liver resection is widely accepted as a treatment option for primary liver cancer and metastases. The goal of surgery is to resect all tumours with negative histological margins while preserving sufficient functional hepatic parenchyma and reducing postoperative complications. The use of Indocyanine green (ICG) for liver function assessment and fluorescence image-guided surgery could be used to achieve that goal.* ***Clinical Case Description:*** *We present the case of a 62-year-old female patient with diagnosed sigmoid colon cancer with four bilobar liver metastases who underwent a simultaneous sigmoid resection and ICG fluorescence image-guided liver resection 3 days after preoperative ICG liver function assessment. We decided to perform liver-sparing resection having in mind the liver metastases' number, size and location and the slightly impaired liver function (ICG retention rate 15 – ICGR15 was 14,02%). All liver tumours were removed without complications, and the resected margins were all microscopically free of tumour tissue (R0 resection). The postoperative period was uneventful, without any signs of postoperative liver failure.* ***Conclusions:*** *ICGR15 can be considered a safe and informative marker for liver function and indirectly for the degree of portal hypertension. ICG fluorescence provides an additional method to assist intra-operative tumour identification. The best timing of injection requires further study.*

Key words: *liver resection, ICG fluorescence image-guided surgery, liver metastasis, liver function, ICGR15*

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INTRODUCTION

Contemporary liver oncological surgery is based on three main principles: performing R0 liver resections, preserving healthy liver parenchyma, and reducing postoperative complications [1]. Postoperative liver failure (PHLF) is one of the most severe complications [2]. Its occurrence is closely related to the volume and functional capacity of the residual liver [2]. Conventional basic liver function tests (AST, ALT, bilirubin, albumin, GGT) can assess the absence or presence of liver damage but cannot provide a quantitative assessment of liver function [3]. Dynamic liver function tests are more sensitive and provide a qualitative and quantitative assessment of the functional liver capacity [3]. Worldwide, the Indocyanine green (ICG) 15-minute retention rate (ICGR15) is one of the most popular methods [3, 4].

In addition, ICG near-infrared fluorescence imaging can be used to improve the achievement of R0 liver resection and prevent missing tumour tissue. Ishizawa et al. reported in 2009 that intravenous injection of ICG caused “bull’s eyes” of fluorescence to be formed around primary or metastatic tumours in the liver [5, 6]. The preoperatively injected ICG is retained inside them due to biliary excretion disorders in the cancerous tissues [6]. The dose of ICG most frequently used to identify liver tumours is 0.5 mg/kg body weight, administered 1-14 days before surgery [6, 7].

We present the case of a patient with sigmoid colon cancer with liver metastases who underwent a simultaneous sigmoid resection and ICG fluorescence image-guided liver resection after preoperative ICG liver function assessment. As far as we know, this is the first case in Bulgaria reporting the combined usage of these methods. The case is a part of a study funded by GRANT – 2021 of the Medical University of Sofia (D-110/ 04.06.2021).

CLINICAL CASE DESCRIPTION

A 62-year-old female was referred to our hospital for sigmoid colon cancer with liver metastases diagnosed at another hospital. Her main complaints were mild pain and discomfort in the right hypochondrium. A colonoscopy revealed an ulceropolypic tumour at a distance of 35 cm from the anus. The CT images demonstrated an eccentrically thickened wall of the sigmoid colon, with high-grade lumen stenosis of about 4.8 cm in length. Prestenotic dilatation of 7.35 cm and locoregional lymphadenomegaly were also registered. The liver was enlarged and fatty, and hypodense lesions of various sizes were visualized in the parenchyma of both lobes. The tumour in segment VIII was 7 cm in size, and that in segment VI was about 2.4 cm. The patient had a history of previous appendectomy and laparoscopic cholecystectomy. Her concomitant diseases included obesity and ischemic heart disease. Laboratory tests were within the normal range, except for gamma-glutamyl transferase (GGT) – 62 U/l. Tumour markers were elevated – CA 19-9 – 195.8 U/mL; CEA – 43.9 ng/mL.

She received a preoperative ICG 15-minute retention test (ICG-R15 test) for liver function assessment at an ICG dose of 0.5 mg/ kg body weight. The result was 14,02%. She underwent a simultaneous sigmoid colon resection, omentectomy and liver-sparing hepatic resection 3 days after the ICG-R15 test. We used an ICG fluorescence imaging system and intraoperative ultrasound to identify liver tumours during surgery. Intraoperatively, we found a fatty liver with several metastatic lesions. The largest one, with a diameter of about 7.5 cm, was located in the VIII segment (Fig. 1). One was in the liver segment III about 3cm in diameter, and two of similar size were located in the VI and VII segments (Fig. 2). The primary tumour was in the middle third of the sigmoid colon. The lesion was about 4 cm in diameter, with hard cartilaginous density, almost entirely stenosing the intestibnal lumen. We decided to perform liver-sparing hepatic resection having in mind the liver metastases’ number, size and location and the slightly impaired liver function.

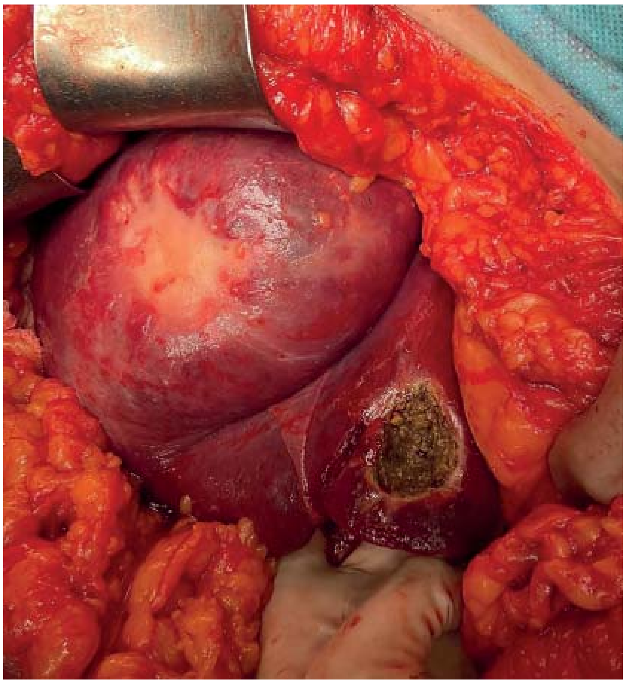

Fig. 1. Liver metastasis in VIII liver segment. The picture also shows the resection surface after the removal of the lesion in the III segment

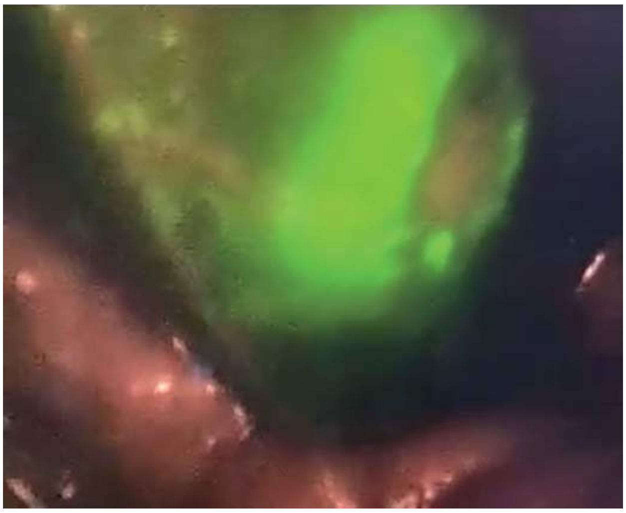

Fig. 2. ICG fluorescence imaging of the metastasis in VI liver segment

Before the liver transection, the entire liver pedicle was encircled with tape, and an intermittent period of inflow clamping using the Pringle manoeuvre was performed to prevent haemorrhage. During the surgical resection, ICG fluorescence imaging was also used to distinguish in real-time between tumour borders and normal liver parenchyma. Guided by the fluorescent signal, at least a 1-cm resection margin was marked, and hepatic transection was performed through a clamp-crushing method employing the Ligasure and bipolar forceps (Fig. 3). All the tumours were entirely removed without complications (Fig. 4).

Finally, the resected margins were all microscopically free of tumour cells (R0 resection). The postoperative period was uneventful, without any signs of PHLF. One month after the operation, adjuvant chemotherapy was initiated.

Fig. 3. ICG fluorescence imaging of the metastasis in VIII segment, distinguishing tumour borders and normal liver parenchyma

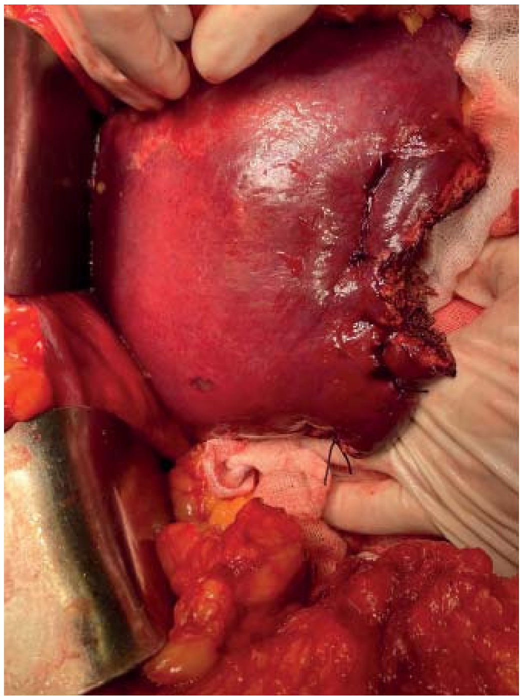

Fig. 4. The patient's liver after resection of the lesions in VI and VII liver segment

DISCUSSION

Liver resection is widely accepted as a treatment option for primary liver cancer and liver metastases (most commonly colorectal and from neuroendocrine tumours) [8]. Colorectal liver metastases (CLC) are the most common reason for liver resection in Western countries, and results in recent years have been encouraging – postoperative mortality in large series ranging from 0.2% to 3.5%, 1-year survival – 89%-97%, and the 5-year survival being between 15% and 50% [8].

The diagnostic and treatment approach in patients with liver tumours must be complex, multidisciplinary and individualized in order to achieve optimal results. The goal of surgery should be to resect all tumours with negative histological margins while preserving sufficient functional hepatic parenchyma [6, 9].

The appearance of PHLF is closely related to the volume and functional capacity of the residual liver tissue (RF) [2]. To prevent it, according to modern algorithms, a FLR > 20% is considered the minimum safe volume for patients with normal liver function, while a FLR above 30% is necessary for patients who have already received chemotherapy, and 40% is considered the minimum required for patients with cirrhosis [2].

Therefore, an accurate assessment of liver function is crucial. ICG has been widely used in clinical settings to estimate cardiac output and liver function since its approval by the US Food and Drug Administration in 1954 [10]. It is excreted unchanged and almost entirely (97%) in the bile [3]. Toxicity is extremely low, with allergic reactions and side effects reported in less than 1/40,000 cases [3, 4]. An easily performed method for evaluating liver function is the spectrophotometric determination of the ICG blood concentration 15 minutes after its application (ICG R15). Established reference values are 0-10% [3].

The indications for the ICG R15 test are: 1) evaluation of the functional liver reserve in patients before liver resection (the method is precise in patients with underlying liver disease – cirrhosis, steatosis) [3, 4]; 2) prediction of postoperative complications in liver surgery [3]; 3) evaluation of the liver function of the donor/cadaveric liver when planning a liver transplant [3]; 4) non-invasive assessment of portal hypertension and oesophagal varices [3, 11]; 5) early functional assessment of the graft after liver transplantation [3].

The benefits of this method are evident from the many publications on the subject. In 2014, ICGR15 was included in a modified liver damage grading system [Liver Damage Grading System (LDGS)] [12]. The Japanese Liver Cancer Study Group of Japan proposed and applied LDGS instead of Child-Pugh grading as a more accurate and appropriate tool for functional assessment of liver reserve [12, 13]. Many authors suggest different surgical approaches depending on the ICGR15 values. According to the accepted Makuuchi criteria, large-volume liver resections should be performed in cirrhotic patients with ICGR15 < 15%. Suitable candidates for right hemihepatectomies are patients with ICGR15 up to slightly > 10%, while left hepatectomies are also discussed in patients with slightly-high ICGR15 (range 10% to 19%) [14]. At 20-29%, ICGR15 segmentectomy could be performed, and at 30-39%, only partial, atypical, limited resection is feasible. The significance of using ICGR15 to assess the liver reserve and predict postoperative outcomes is also evident from the published experience of the Makuuchi group: zero mortality in 1056 hepatectomies performed between 1994 and 2002 [15]. Other authors reported that the lower ICG R15 limit for performing a safe large-volume hepatectomy is between 14% and 17%, the latter being accurate in young patients with milder liver disease [16]. In our case, we preferred the liver-sparing hepatectomies (limited resections) due to the number of liver metastases, their size and bilobar location, impaired liver function and the need for simultaneous bowel resection.

As mentioned before, precise detection of liver tumours and their resection in negative margins are crucial. Preoperative conventional imaging techniques as ultrasound, contrast-enhanced CT, and magnetic resonance imaging are currently used to diagnose cancer and are an aid in guiding the resection [6, 17]. However, liver metastases of colorectal cancer might be multi-focal, and small intrahepatic tumours are difficult to diagnose [6].

ICG is retained in tumorous tissues even after excretion from the background hepatic parenchyma, leading to unambiguous identification of liver tumours by intraoperative ICG fluorescence imaging [6]. In contrast to intraoperative ultrasound, it can identify superficial hepatic lesions with an excellent sensitivity of 96-100% [6, 18]. It can also detect small or occult tumours, which could be missed by conventional imaging techniques [10]. All lesions missed by intraoperative ultrasound usually are superficially located, whereas the lesions missed by ICG fluorescence imaging are profound because of the fluorescence tissue penetration. This suggests a potential role in combining intraoperative ultrasound and ICG fluorescence imaging to increase sensitivity and the chance of complete resection [6, 19]. Purich et al. demonstrated that when intraoperative ICG fluorescence imaging is used in conjunction with intraoperative ultrasound, ICG could detect additional superficial malignant lesions in 11.6% of patients [18]. Intraoperative histopathological analysis of frozen tumour margins is expensive, time-consuming, and may be inadequate in large lesions [6]. Defective biliary clearance in the transition area between tumour and normal liver tissue and liver tumours may result in ICG retention, which can be visualized using an ICG fluorescence imaging system [19]. The benefit of ICG fluorescence is easily seen during laparoscopic surgery since its fluorescent property compensates for the lack of tactile feedback during this procedure [6]. Regarding the timing of injection, it has been variously described [7]. Generally, ICG is administered 14 days before the operation day, and specifically within 3 days in most studies. An additional administration (0.02-0.5 mg/kg) is an option in case of a long interval between the administration and operation day [7]. In cirrhotic or fibrotic liver with impaired liver function, slower metabolic elimination of ICG leads to an increased false positive rate of tumour detection [20]. Studies, including a high rate of cirrhotic patients, tended to present intervals between ICG administration and surgery longer than 7 days [20].

CONCLUSIONS

ICGR15 can be considered a safe and sound marker for liver function and indirectly for the degree of portal hypertension. ICG fluorescence provides an additional method to assist intra-operative tumour identification. The best timing of injection requires further study.

Disclosure Summary: *The authors have nothing to disclose.*

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Ethics approval: *This study was approved by the hospital ethics committee and was carried out following the principles outlined in the Declaration of Helsinki. Consent from the patient was obtained. This report does not contain any information by which they could be identified.*

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