



Significance of indocyanine green test in radiotherapy for hepatocellular carcinoma

Masashi Mizumoto¹, Yoshiko Oshiro^{1,2}, Hideyuki Sakurai¹

¹Department of Radiation Oncology, Proton Medical Research Center, University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan; ²Department of Radiation Oncology, Tsukuba Medical Center Hospital, Tsukuba, Ibaraki, Japan

Correspondence to: Masashi Mizumoto. Department of Radiation Oncology, Proton Medical Research Center, University of Tsukuba Hospital, Tsukuba, Ibaraki, Japan. Email: mizumoto1717@hotmail.com.

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Photon radiotherapy was originally not commonly used for hepatocellular carcinoma (HCC) because the large irradiation volume could lead to radiation-induced liver disease (RILD). According to a phase I study by Kim *et al.*, a dose of EQD2 ≥ 78 GyE₁₀ was necessary to achieve local control. Proton therapy (PT) was initially used only as radical radiotherapy for HCC, but many favorable results of PT for HCC at higher doses have been reported. In a phase II study of PT for HCC, Kawashima *et al.* found a 2-year local control rate of 96% in 30 patients who received 76 GyE in 20 fractions (1). In another phase II study, Bush *et al.* observed local failure in only 3 of 76 patients with HCC who received PT at 63 GyE in 15 fractions (2). In a large study performed at the Tsukuba Proton Medical Research Center (3), 266 patients with HCC received PT in three dose-fractionations of 66.0 GyE in 10 fractions, 72.6 GyE in 22 fractions, and 77 GyE in 35 fractions. The 1-, 3- and 5-year local control rates were 98%, 87%, and 81%, respectively, and there was no significant difference among the three protocols (3). A systematic review of PT for HCC by Dionisi *et al.* suggested that local control was approximately 80% at 3–5 years and the average overall survival rate at 5 years was 32%, with data comparable to surgery in the most favorable groups (4).

Recent progress with the photon radiation technique has made it possible to deliver a high dose to liver tumors with minimal doses to normal liver using photon beams. Recent studies of stereotactic body radiation therapy (SBRT) have shown a 65–100% local control rate with 24–54 Gy in

3–6 fractions (5–8). Huertas *et al.* also reported favorable results of SBRT for HCC at a dose of 45 Gy in 3 fractions for 77 patients with unresectable HCC, with 1- and 2-year local control rates of 99% (8).

In radiotherapy with photon or proton beam, liver function is an important predictor of prognosis and liver dysfunction after radiotherapy. Child-Pugh (CP) scores are commonly used for comprehensive assessment of liver function in clinical practice (9), and in radiotherapy for HCC, pretreatment CP scores are well correlated with prognosis after PT. Huertas *et al.* (8) found liver failure after SBRT in 2 patients with CP scores >8 , and one treatment-related death due to hematemesis in a patient with decompensated esophageal varices and a CP score of 10. Based on these outcomes, a CP score >8 was suggested as an independent prognostic factor for hepatic toxicity (8). In an evaluation of 259 patients who received PT for HCC (10), Mizumoto *et al.* found significant associations of increased CP scores at 12 and 24 months after treatment with pretreatment CP scores and with percentage volumes of normal liver receiving at least 0, 10, 20, and 30 GyE.

Indocyanine green (ICG) clearance reflects liver function and CP scores, and is a useful marker for predicting liver complications and an important indicator for the maximal extent of liver resection and assessment of surgical safety. ICG clearance reflects the extent of dye excretion, bile excretion, and liver blood flow, and is used as an index of the liver functional reserve in chronic liver disease, including cirrhosis. Thus, ICG-R15 is one of the most

frequently used kinetic parameters in clinical practice (11). Seyama *et al.* developed criteria for liver resection based on ICG-R15 <10%, 10–19%, 20–29%, 30–39%, and >40% as indications for trisegmentectomy, left lobectomy or right monosegmentectomy, subsegmentectomy, limited resection, and enucleation only, respectively (12). Patients with high ICG-R15 are not candidates for surgical resection, even for cases in CP class A.

In the first report on ICG clearance in radiotherapy for HCC, Cheng *et al.* suggested guidelines for dose determination using radiotherapeutic parameters to reduce liver complications (13). The radiation dose to the target volume ranged from 40 to 60 Gy in fractions of 1.8–2.0 Gy per day, dependent on the non-cancerous liver volume and functional reserve of the liver represented by ICG-R15. Yoon *et al.* found that ICG-R15 was the only significant factor affecting RILD in an analysis of 146 HCC patients treated with RT (14). In this study, a median total dose of 45 Gy (range, 45–65 Gy) in mean daily fractions of 1.8 Gy (range, 1.8–2.5 Gy) was used, and RILD was observed in 15 patients. The probability of RILD was suggested to increase gradually with an increase in pre-radiotherapy ICG-R15 (14). Kawashima *et al.* subsequently suggested that liver function was the only independent factor for prognosis, and that ICG was a significant factor, along with CP score and clinical stage (1). ICG-R15 and an irradiation volume of 30 GyE (V_{30}) may also be useful predictors for development of proton-induced hepatic insufficiency (1).

Stenmark *et al.* evaluated the relationship between ICG R15 and RILD in 60 patients who received hepatic irradiation with a median dose of 55 Gy (range, 28.8–82.0 with 1.5–3.3 Gy per fraction) (15). In this study, 3 patients developed RILD, and the ICG-R15 of these patients tended to worsen during radiotherapy, suggesting that this was as an early indicator of a lack of tolerance to hepatic irradiation. Another study suggested a significant relationship of ICG-R15 and CP score (16). In this study, 250 patients who received PT were analyzed retrospectively, and pretreatment ICG-R15 was evaluated for groups with CP classifications of A, B and C. In addition to identifying ICG-R15 and CP score as prognostic factors, the study suggested that ICG-R15 was an independent prognostic factor even in CP class A cases (16). Thus, some patients had a high ICG-R15 despite being in CP class A, and a poor prognosis was associated with high ICG-R15 in these patients. These results are compatible with the surgical criteria mentioned above. This indicates a need for care in determining an indication for radiotherapy for patients with

high ICG-R15 clearance, even in cases with CP class A liver function.

The recently published prospective study by Suresh *et al.* focused on the significance of ICG-R15 for prediction of liver function after SBRT (17). In this study, pre- and posttreatment ICG clearances were evaluated in 144 patients with HCC who received SBRT. Significant associations of changes of ICG-R15 with treatment toxicities (a 2-point increase in CP or a change in albumin-bilirubin) were suggested. All of the above results suggest that ICG-R15 is a useful predictor of prognosis and toxicity after radiotherapy for patients with HCC. However, information on the impact of ICG-R15 on radiotherapy is still limited, and more clinical evidence is awaited. However, changes in ICG-R15 may be important for prediction of treatment outcomes and for determining the indication for radiotherapy.

HCC has a multicentric nature, which results in frequent intrahepatic recurrence despite SBRT and PT achieving favorable local control, and appropriate treatment is needed for such recurrence. The indications for standard therapy for HCC, such as surgery, radiofrequency ablation (RFA) and transarterial embolization (TAE), are well established based on tumor location, size, and liver function. Oshiro *et al.* suggested that multiple courses of PT are safe (18), but an indication for repeated radiotherapy in combination with other treatment modalities for HCC is uncertain. Liver function including CP score and ICG-R15 may be useful as an indication for safe radiotherapy, and further studies are required.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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