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Original research

Adverse impact of low skeletal muscle index on the prognosis of hepatocellular carcinoma after hepatic resection

Norimitsu Yabusaki [a, *], Tsutomu Fujii [a], Suguru Yamada [a], Kojiro Suzuki [b], Hiroyuki Sugimoto [a], Mitsuro Kanda [a], Goro Nakayama [a], Masahiko Koike [a], Michitaka Fujiwara [a], Yasuhiro Kodera [a]

[a] Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Japan
[b] Department of Radiology, Nagoya University Graduate School of Medicine, Japan

HIGHLIGHTS

- Skeletal muscle index (SMI) was measured in HCC patients by using preoperative CT.
- Low-SMI was an independent prognostic factor for RFS in patients with BMI $\geq$ 22.
- Body mass index and visceral fat area was not associated with prognosis.
- CT is a simple and useful tool for predicting prognosis.

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ABSTRACT

Background: Skeletal muscle depletion predicts poor prognosis of patients with certain cancers. However, the correlation between low skeletal muscle index (SMI) and the prognosis of hepatocellular carcinoma (HCC) is not well understood.

Methods: To determine their influence on prognosis, skeletal muscle index (SMI) and visceral fat area (VFA) were measured using computed tomography at the level of the third lumbar vertebra of 195 patients who underwent primary hepatectomy for hepatocellular carcinoma (HCC). We defined sarcopenia using cutoff values for SMI as 43.75 cm^2/m^2 and 41.10 cm^2/m^2 for males and females, respectively.

Results: Sarcopenia was present in 89 of 195 (45.6%) patients and correlated significantly ($P < 0.001$) with female sex, low body mass index (BMI), low subcutaneous fat area, low VFA, and low serum albumin levels. There was a trend indicating the association of sarcopenia with poor cumulative recurrence rate (CRR) ($P = 0.13$). In patients with BMI $\geq$22, CRR was significantly different between patients with or without sarcopenia (19.0 or 35.2 months, respectively, $P = 0.03$). In contrast, there was no significant difference in patients with BMI $\geq$22 as a function of VFA ($P = 0.47$). When the cohort was limited to patients with BMI $\geq$22, multivariate analysis showed that sarcopenia was a significant independent risk factor for recurrence (hazard ratio = 1.6; 95% confidence interval, 1.1–2.5; $P = 0.02$).

Conclusions: Low-SMI was an independent adverse prognostic factor for CRR in patients with BMI $\geq$22. Therefore, preventing muscle wasting may improve the CRR of patients with HCC.

1. Introduction

Hepatocellular carcinoma (HCC) causes approximately 740,000 deaths annually and is the second most frequent cause (after lung cancer) of cancer deaths worldwide [1]. Despite recent developments in diagnostic technologies and sophisticated surgical techniques [2], the recurrence rate of HCC after curative resection remains high, because 80–90% of HCCs develop from chronic hepatitis or cirrhosis caused by infection with hepatitis B or hepatitis C viruses. Therefore, simple, novel clinical prognostic indicators for HCC apart from genetic diagnosis [3–6] are required to

* Corresponding author. Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi, 466-8550, Japan.
E-mail address: n.yabusaki@med.nagoya-u.ac.jp (N. Yabusaki).

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predict and, if possible, prevent recurrence.

Prognostic factors based on assessment of body composition and inflammation attract the attention of clinicians, because these factors are significantly associated with the short- and long-term outcomes of certain cancers [7–11]. Among these factors, sarcopenia, generally defined as muscle mass ≤ two standard deviations below the mean muscle mass characteristic of healthy persons <40 years of age, indicates low functional capacity and is associated with a higher risk of falling and bone fractures of elderly people [12].

Moreover, sarcopenia is a predictor of poor prognosis of patients with cancers of digestive organs and those undergoing liver transplantation due to liver cirrhosis and hepatocellular carcinoma [13–17]. Similarly, in patients with HCC, evidence indicates that sarcopenia is an independent adverse prognostic factor [13,18,19]. In contrast, there is debate regarding whether high visceral fat area (VFA) predicts survival of patients with HCC [18,20]. In the area of liver disease, fatty patients might be more likely to have early recurrence of HCC from fatty liver. Conversely, we expected that the patients with low VFA are generally undernourished and may suffer from poor prognosis. However, most previous studies evaluating the impact of body composition on the prognosis of patients with HCC investigated only one parameter of many parameters of body composition [13,19–21].

To identify the features of body composition that may have a powerful impact on the prognosis of patients with HCC, we investigated the relationship between various body composition components, clinical factors, and outcomes of patients with HCC who underwent hepatic resection.

2. Methods

2.1. Patients

We enrolled 195 consecutive patients who underwent primary and curative hepatectomy for hepatocellular carcinoma (HCC) at the Department of Gastroenterological Surgery, Nagoya University Hospital, between July 2003 and October 2014. We confirmed the histological diagnosis of HCC for all patients. Written informed consent for inclusion in the study, as required by the Institutional Review Board of Nagoya University, was obtained from all patients.

2.2. Surgical procedure

Major and minor hepatectomies were defined as the resection of ≥4 or <4 Couinaud segments, respectively. Measurement of the rate of disappearance of indocyanine green from plasma and volumetric computed tomography (CT) were always performed to evaluate future functional liver reserves. Postoperative complications were graded according to the Clavien-Dindo classification [22], and postoperative complications were defined as Clavien-Dindo grade IIIa or higher. Tumor stage was categorized according to the guidelines of the Liver Cancer Study Group of Japan (The 5th Edition, Revised Version) [23].

2.3. Follow-up strategy

After discharge from the hospital, patients were examined once each month for 6 months and every 3 months thereafter. None of the patients received adjuvant chemotherapy. Blood tests, including serum α-fetoprotein and protein induced by vitamin K absence or antagonist- II, were performed each month. Abdominal ultrasonography was performed every 3 months, and dynamic contrast-enhanced CT scans were performed every 6 months. Cumulative recurrence rate (CRR) was calculated as the time between curative resection of HCC and confirmation of recurrence of disease.

2.4. Image analysis

Total skeletal muscle and fat tissue areas (cm^2) were evaluated from a single preoperative CT image acquired at the 3rd lumber vertebra (L3), using Hounsfield unit thresholds of −29 to +150 for skeletal muscle and −200 to −50 for visceral and subcutaneous fat tissues. All CT images were analyzed using SYNAPSE VINCENT software version 4.0 (Fuji Film, Tokyo, Japan). The cross-sectional skeletal muscle area (cm^2) was normalized using the square of the height (m^2) to obtain the L3 skeletal muscle index (SMI, cm^2/m^2). Cutoff values for skeletal muscle were defined as 43.75 cm^2/m^2 and 41.10 cm^2/m^2 for males and females, respectively [13,16]. Cutoff values for VFAs (cm^2) were 103 cm^2 and 69 cm^2 for males and females, respectively, which are recognized by physicians practicing in Japan [24]. We assigned patients to low-SMI or high-SMI groups and high-VFA or low-VFA groups according to these cutoff values.

2.5. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and range. Correlations between clinicopathological variables and skeletal muscle index (SMI) were analyzed using the χ^2 and Fisher's exact tests. Overall survival (OS) and CRR were calculated using the Kaplan–Meier method, and the differences in survival curves were analyzed using the log-rank test. The multivariate Cox proportional hazard model was used to determine independent risk factors associated with CRR. Data were analyzed using JMP v10 software (JMP, SAS Institute, Cary, NC, USA). The level of statistical significance was defined as $P < 0.05$.

3. Results

Patient demographics and clinical characteristics are listed in Table 1. The median follow-up period was 1121 days (range, 37–3622 days), and 67 (34.4%) patients died by the end of the follow-up period. Patients' mean age was 66 years, and the male to female ratio was 157:38. The mean BMI (kg/m^2) was 23.2 kg/m^2. The TNM stages of patients' cancers were as follows: stage I ($n = 20$), stage II ($n = 112$), stage III ($n = 42$), stage IVA ($n = 19$), and stage IVB ($n = 2$). Sixty-two (31.8%) patients underwent major hepatectomy, and 133 (68.2%) underwent minor hepatectomy or non-anatomical resection. Postoperative complications were present in 41 (21.0%) patients.

3.1. Correlation between body composition and clinicopathological factors

There was a significant positive correlation between BMI and SMI in males and females (Supplementary Fig. 1) ($P < 0.001$ for males, $P = 0.04$ for females). The mean SMI values were 45.3 cm^2/m^2 (range, 30.8–67.8) for males and 38.0 cm^2/m^2 (range, 29.2–66.6) for females. Similarly, there was a significant correlation between BMI and VFA in males and females (Supplementary Fig. 2) ($P < 0.001$, respectively). The mean VFAs were 136.2 cm^2/m^2 (range, 12.5–356) for males and 84.5 cm^2/m^2 (range, 11.4–298.5 cm^2) for females.

When the cutoff values for SMI were applied (43.75 cm^2/m^2 and 41.10 cm^2/m^2 for males and females, respectively), the cohort was divided into 89 (45.6%) and 106 (54.4%) patients with low and high-SMI. The comparisons of clinicopathological features of HCC patients with low or high-SMI are shown in Table 2. Females were more likely to have low-SMI compared with males ($P < 0.001$). The patients with low-SMI had significantly lower BMIs, VFAs, and