

Evaluation narcotic analgesic use and survival time in terminal stage liver diseases compared with lung cancer: a retrospective chart review

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Hepatocellular carcinoma (HCC) and liver cirrhosis are fatal diseases. This study aimed to investigate survival time and palliative care in terminal HCC and/or liver cirrhosis compared with lung cancer. Between January 2004 and December 2010, we enrolled 116 patients with terminal cirrhosis and/or HCC or lung cancer admitted to a municipal hospital in Japan; 48 had liver cirrhosis, 35 HCC and 33 lung cancer. By retrospective chart review, we evaluated: (i) rate of usage of narcotic analgesics and (ii) survival time from onset of coma (Glasgow Coma Scale less than 8). Time between coma and death was significantly shorter in the liver disease patients (cirrhosis and/or HCC: 7.0 h) than in lung cancer (44.0 h, $p = 0.045$). Total bilirubin was higher in HCC compared with cirrhosis ($p < 0.01$). Rate of usage of narcotic analgesics was higher in lung cancer (20/33: 60.6%) than in liver disease (17/83: 20.5%, $p < 0.01$); analgesics were used more frequently in HCC than in liver cirrhosis ($p < 0.01$). These results suggest that liver cirrhosis and HCC patients do not always require palliative care and that survival time from onset of coma due to liver disease was not prolonged compared with lung cancer.

Key Words: hepatocellular carcinoma, liver cirrhosis, palliative care, coma, narcotic analgesics

Hepatocellular carcinoma (HCC) is the sixth most common malignant disease and has the third highest mortality worldwide.⁽¹⁾ In Japan, more than 50% of cases of HCC are due to hepatitis C virus, approximately 45,000 patients are diagnosed with HCC each year and approximately 34,000 patients per year die with HCC.⁽²⁾ Supportive care of HCC and/or liver cirrhosis, including nutritional support, has been improved recently, but it has not been clearly demonstrated whether the quality of life and prognosis of these patients have improved. Terminal care of HCC and/or liver cirrhosis is important; in Japan, terminal care is mainly provided in municipal hospitals rather than the hospital to which the patient was initially referred.

The questions most commonly asked by the patient and family during terminal care are “how long do I have?” and “how long does he/she have?”, indicating that estimated survival time is an important issue in terminal care. The survival time between onset of coma and death might be shorter in HCC than in other malignant diseases and the usage rate of narcotic analgesics might be less, but these factors have not been investigated in previous studies.

This retrospective study in a municipal hospital evaluated: (i) the rate of usage of narcotic analgesics and (ii) the survival time from onset of coma due to HCC and/or liver cirrhosis. These

factors were compared with lung cancer, which has a high mortality of approximately 70,000 per year in Japan.⁽³⁾

Materials and Methods

We enrolled patients with terminal cirrhosis, terminal HCC or terminal lung cancer with performance status (PS)⁽⁴⁾ greater than 3 who were admitted to Eguchi Hospital between January, 2004 and December, 2010 because the family could no longer care for them. PS was determined as follows: 0 – fully active, able to perform all pre-disease activities without restriction; 1 – restricted in physically strenuous activities but ambulatory and able to perform light or sedentary tasks (e.g. light housework, office work); 2 – ambulatory and capable of all self-care but unable to work, active for more than 50% of waking hours; 3 – capable of only limited self-care, confined to bed or chair for more than 50% of waking hours; 4 – completely disabled and unable to perform self-care, confined to bed or chair; or 5 – dead. All patients gave informed consent that their treatment would be limited to terminal care and that resuscitation would not be attempted in an emergency. Narcotic analgesics were applied as required. We retrospectively evaluated the patients’ main symptoms on admission, their consciousness level and the duration between onset of coma (Glasgow Coma Scale less than 8) and death.⁽⁵⁾

The data in Tables 1 and 2 were evaluated by the chi-square test for independence, the Mann-Whitney *U* test or the Kruskal-Wallis test. The data in Fig. 1 and 2 were evaluated by the chi-square test. Statistical analysis was performed using IBM SPSS Statistics ver. 19. Differences were considered significant if the probability of the difference occurring by chance was less than 5 in 100 ($p < 0.05$).

Results

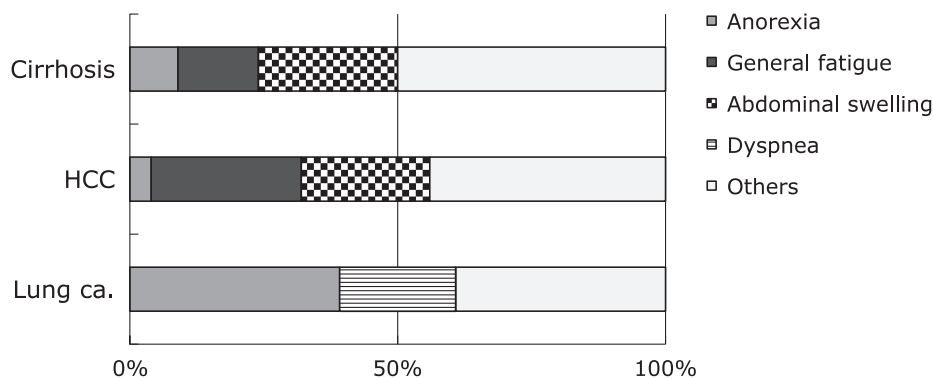
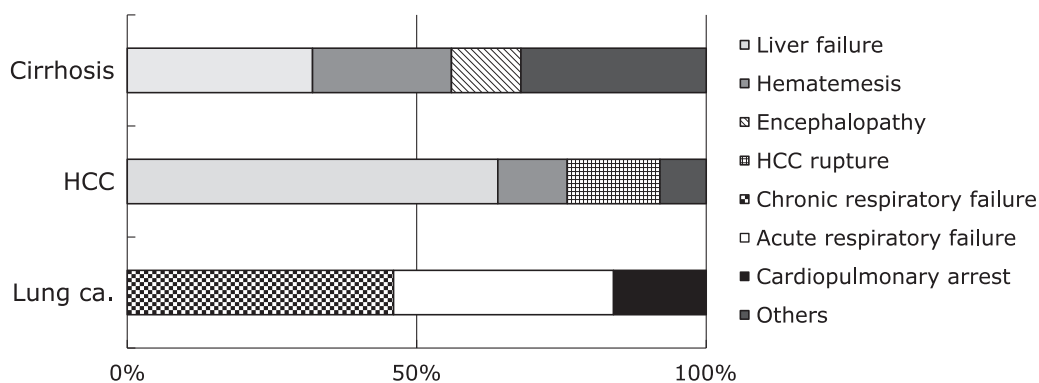
The background characteristics of the patients are shown in Table 1. There were 48 cases of terminal liver cirrhosis, 35 cases of terminal HCC and 33 cases of terminal lung cancer. Patients in the lung cancer group were older (82.0 ± 11.0 years) than those in the two liver disease groups (69.5 ± 11.9 years and 72.0 ± 10.2 years, respectively, both $p < 0.001$). Men predominated in both the lung cancer and the liver disease groups, but there was no significant difference in sex ratio among the groups. Duration of hospitalization did not differ among the three groups. Cause of

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Table 1. Background characteristics of the liver disease and lung cancer patients

	Cirrhosis (n = 48)	HCC (n = 35)	Lung cancer (n = 33)	p value
Age (years)	69.5 ± 11.9	72.0 ± 10.2	82.0 ± 11.0	<0.001
Sex (Men/Women)	28/20	26/9	21/12	ns
Period of hospitalization (days)	42.5 ± 89.6	28.0 ± 99.3	33.0 ± 62.9	ns
Cause of cirrhosis (HBV/HCV/alcohol/others)	6/28/9/5	4/27/1/3	—	ns
Child-Pugh (A/B/C)	1/12/31	4/7/23	—	ns

HBV, hepatitis B virus; HCV, hepatitis C virus; ns, not significant.

**Fig. 1.** Major complaint motivating hospitalization in liver cirrhosis, hepatocellular carcinoma (HCC) and lung cancer (Lung ca.).**Fig. 2.** Main cause of coma in liver cirrhosis, hepatocellular carcinoma (HCC) and lung cancer (Lung ca.).

liver cirrhosis and Child–Pugh class did not differ between the liver cirrhosis and HCC groups.

Fig. 1 shows the main complaints that led directly to hospitalization. In liver cirrhosis and HCC patients, these were general fatigue (15% and 28%, respectively) and abdominal swelling, mainly due to ascites (26% and 24%); the main complaints in the lung cancer patients were anorexia (38%) and dyspnea (21%).

Fig. 2 shows the direct cause of coma. In liver cirrhosis and HCC patients, the most common cause was liver failure (cirrhosis: 32%, HCC: 64%). Hematemesis and encephalopathy induced coma in the cirrhosis patients (24% and 12%, respectively) and hematemesis and rupture of HCC were risk factors in the HCC patients. Respiratory failure (chronic: 46%, acute: 38%) and cardiopulmonary arrest were the main causes of coma in the lung cancer patients.

Survival time from onset of coma and use of narcotic analgesics are shown in Table 2. Time between coma and death was significantly

shorter in the liver disease patients (cirrhosis and/or HCC: 7.0 h) compared with the lung cancer patients (44.0 h, $p = 0.045$), with no significant difference between cirrhosis and HCC. Total bilirubin was higher in HCC compared with cirrhosis, but there was no difference in the rate of ascites. Rate of usage of narcotic analgesics was significantly higher in the lung cancer patients (20/33: 60.6%) than in the liver disease patients (17/83: 20.5%, $p < 0.01$). Analgesics were used more frequently in HCC than in liver cirrhosis ($p < 0.01$).

Discussion

The results of the present study indicate that: (i) the rate of usage of narcotic analgesics in the terminal stage was significantly lower in patients with liver cirrhosis and/or HCC (17/83: 20.5%) compared with lung cancer patients (20/33: 60.6%, $p < 0.01$); and (ii) the time between onset of coma and death was significantly

Table 2. Time from onset of coma to death and rate of usage of narcotic analgesics in each group

	Cirrhosis (n = 48)	HCC (n = 35)	Lung cancer (n = 33)	p [†]	p ^{††}	p [§]	p [¶]
Duration from coma to death (hours)	10.5 (0.5–192)	5.0 (0.5–168)	44.0 (1.0–528)	0.045	0.06	0.09	0.31
Using rate of narcotic drugs (yes/no)	4/44	13/22	20/13	<0.01	0.053	<0.01	<0.01
Serum total bilirubin just before death (mg/dL)	4.15 (0.6–31.7)	11.1 (0.4–32.1)	—	—	—	—	<0.01
Ascites (yes/no)	41/6	29/6	—	—	—	—	ns

Data are the median (range). [†]Lung cancer compared with liver cirrhosis and HCC, ^{††}lung cancer compared with HCC, [§]lung cancer compared with liver cirrhosis, [¶]liver cirrhosis compared with HCC. HCC, hepatocellular carcinoma; ns, not significant.

shorter in liver disease patients (cirrhosis and/or HCC: 7.0 h) compared with lung cancer patients (44.0 h).

Metastasis from HCC might not be common compared with cancers originating in other organs.⁽⁶⁾ Recently, survival with HCC has been prolonged by advances in therapeutic approaches that have delayed metastasis to the late phase of the disease.^(7,8) A recent report from Japan observed metastasis from HCC to lung, bone, lymph nodes, adrenal gland, brain and peritoneum; the most common site was the lung.⁽⁹⁾ Lung metastases did not commonly lead to serious clinical symptoms; by contrast, metastasis to bone was not common (2–15%) but caused severe pain, walking difficulties and paralysis of the lower half of the body.⁽¹⁰⁾ The low incidence of serious complications from metastasis of HCC might be a major reason for the low frequency of use of narcotic analgesics compared with lung cancer, in which severe clinical symptoms in the early stage lead to early introduction of palliative care.⁽¹¹⁾

Highly impaired liver function might explain why the time between onset of coma and death was significantly shorter in the liver disease patients compared with the lung cancer patients. Surgical resection of up to two-thirds of the liver is possible even in cirrhosis patients if their total bilirubin is within the normal range,⁽¹²⁾ so coma does not occur in liver cirrhosis and/or HCC until the terminal stage of the disease. In contrast, lung cancer is complicated by dysfunctions of ventilation, pulmonary function and gas exchange,⁽¹³⁾ which lead to coma in the early stage of the disease.

Few studies have focused on the terminal stage of liver cirrhosis and/or HCC. The present study suggests that these patients do not always require palliative care and that the survival time from onset of coma is not prolonged. The limitations of this study, such as the small number of patients, the retrospective chart review and the comparison with lung cancer only, warrant further investigations.

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