

Clinico-pathological aspects in hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma is one of the most common cancers and the age distribution of HCC patients has steadily increased because of the improved management of chronic liver diseases. The peak age of onset of hepatocellular carcinoma is continually increasing worldwide. This study aims to evaluate whether there exists any significant difference in the clinicopathological features between younger- and elderly-HCC patients. Consecutive 40 patients who had undergone surgical resection for the treatment of HCC from January 2005 to December 2009 were enrolled in our study. Among patients studied, 7 were elderly-HCC and 33 were younger-HCC. Hepatocellular carcinoma was predominantly associated with chronic HBV-infection. Abdominal pain was the most frequently symptom and hepatomegaly was the most frequently sign of HCC in our study. Most patients presented elevated serum AFP levels. In elderly group the most frequent Edmondson Steiner grading were poorly differentiated with 5 cases, while in young group were the same number, 15, of cases moderately and poorly differentiated.

Key words: hepatocellular carcinoma, clinico-pathological features, age

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers and the age distribution of HCC patients has steadily increased because of the improved management of chronic liver diseases (1-4).

Clinicopathological features and prognosis in elderly HCC patients compared to HCC patients in relatively younger group needs to be further explored for more appropriate approach for the management. Age is a known risk factor for HCC

(5-7). As the population ages, it is becoming increasingly important to recognize age-specific cancer epidemiologic trends and differences in cancer outcomes to aid in prevention strategies, diagnostic approaches, and treatment decisions.

MATERIAL AND METHODS

Consecutive 40 patients who had undergone surgical resection for the treatment of HCC at Fundeni Clinical Institute – Department of

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General Surgery and Liver Transplantation January 2005 to December 2009 were enrolled in our study. Patients below 70 years of age were defined as the younger group, while patients of 70 years of age or above were defined as the elderly group. Hence, in this study, we aimed to clarify the age specific clinical characteristics of HCC.

Patients' pre-operative clinicopathological characteristics including sex, age, presence of disease symptom(s) and sign, HBsAg carrier state, HCV infection, AFP level, hematological and biochemical work-up included complete blood picture, liver function tests, prothrombin time, albumin and total protein, pathological factors of the resected specimens (including tumor size, tumor number, capsule formation, venous invasion and liver cirrhosis) and histopathologic findings were compared between young and elderly patient groups.

Immediately after operation, the resected specimens were examined carefully by surgeon and pathologist. After curative resection for HCC, patients were observed every 3 months with serum AFP, abdominal ultrasonography or abdominal computerized tomography.

Data were processed and analyzed with SPSS for Windows Software, version 19.0. Quantitative data were expressed as mean±SD. Fisher test was used to examine the association between clinicopathological features and age in hepatocellular cases. A *p*-value of 0,05 or less was regarded as significant.

RESULTS

Forty patients with histologically, ultrasonographically and biochemically confirmed cases of hepatocellular carcinoma were seen during the study period. This study included 32 men and 8 women, the male to female ratio was 6:1 in the elderly and 3.7:1 in the younger group, showing that there was a higher proportion of women in the young group ($p_v = 0.68$).

The mean age of this study was 54,6 years with SD ± 11.7, range from 27 to 76 years.

The duration of symptoms before admission ranged from 1 month to 2 years. The clinical presentation of HCC in most cases was similar to the presentation of patients with cirrhosis.

Abdominal pain was present in 29 (72.5%) of the patients (Figure 1), 22 in the young group and 7 in the elderly group. It was localised to the right upper quadrant or epigastrium and was mostly described as a dull, continuous ache.

Abdominal distension (Figure 2), resulting from a right upper quadrant mass or from

ascites, was present in 50%, 15 in the young group and 5 in the elderly group.

Palpable hepatomegaly was present in 66.6% of the patients in the young group and was present in 100% of the patients in the elderly group. The liver was usually tender, nodular or hard.

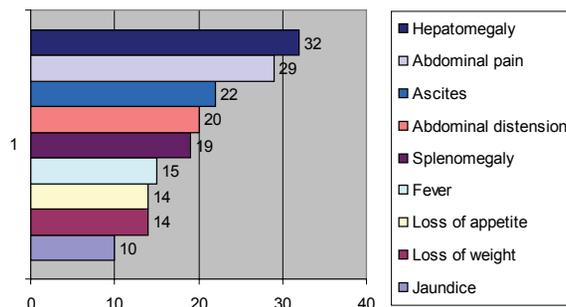


FIGURE 1. Symptoms and signs distribution in hepatocellular carcinoma patients



FIGURE 2. Abdominal distension in hepatocellular carcinoma with liver cirrhosis

Splenomegaly occurred in 47.5% (Figure 3) of the patients and was not always associated with ascites or cirrhosis on liver biopsy.

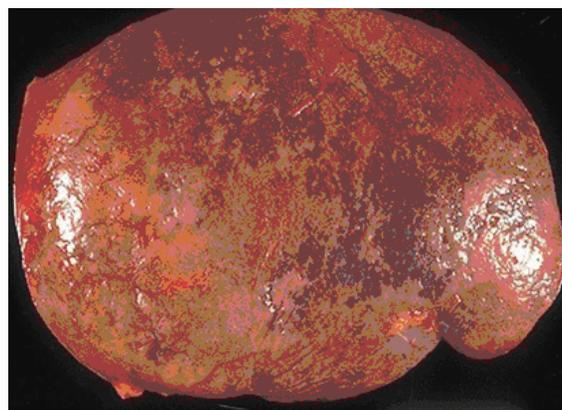


FIGURE 3. Splenomegaly in a hepatocellular carcinoma case

Ascites occurred in 55% of the patients. The protein content of the ascitic fluid had low values (mean 2,5 g/100 ml; mean serum albumin: 2 g/100 ml).

The other symptoms were loss of weight occurred in 35% of the patients, loss of appetite (35%), constipation, swollen feet, weakness, yellow eyes and dark urine (25%). Temperature was elevated in 37.5% of the patients. A bruit was heard in 25% of the patients.

Only 25% of patients were known to be cirrhotic at the time of presentation, but this increased to 47.5% after investigation. Younger patients were more frequently diagnosed as a result of HCC screening (57.3% versus 29.6%, $p_v < 0.0001$).

The presence of concomitant disease with a strong impact on the prognosis was recorded. Cardiovascular and cerebrovascular disease, chronic lung conditions, second primary malignancies, chronic renal disease, or cognitive disorders constituted the most common comorbid conditions. Concomitantly, among ≥ 70 -year-old patients, HCC was more common in non-cirrhotics, whereas among patients < 70 years old, HCC was more common in cirrhotics.

The proportion of patients with HCV infection was significantly higher in the elderly group (12.12% versus 57.1%, $p_v = 0.007$). The proportion of patients with HBV infection was significantly lower in the elderly group (42.8% versus 75.7%, $p_v = 0.09$).

The AFP level ranged from 18 to 4019 ng/ml with a mean level of 552.22 ng/ml SD \pm 679.12. Serum AFP was > 400 ng/ml in 60% of patients (Figure 4).

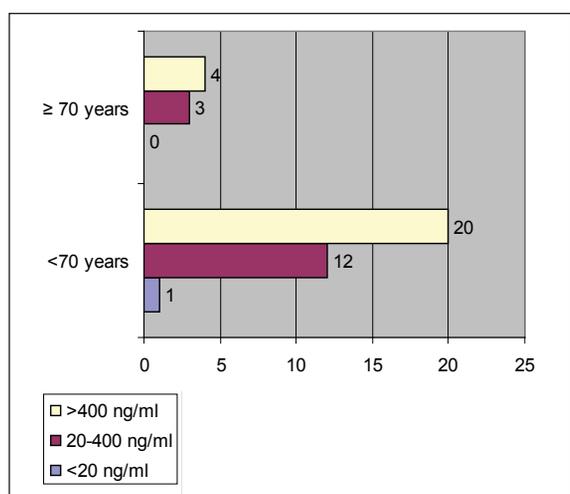


FIGURE 4. Distribution of alpha fetoprotein level in hepatocellular carcinoma patients

Patients ≥ 70 years old showed significantly lower levels of aspartate aminotransferase ($p_v = 0.03$) and alanine aminotransferase ($p_v = 0.02$). The prothrombin time and platelet count were

significantly higher in elderly group ($p_v < 0.001$ and $p_v < 0.02$, respectively).

In all cases, the final diagnosis of HCC was based on cytological and/or histological diagnosis.

Twenty cases were considered poorly differentiated, seventeen were moderately differentiated, and 3 were well differentiated. In elderly group the most frequent Edmondson Steiner (Figure 5) grading were poorly differentiated with 5 cases, while in young group were the same number, 15, of cases moderately and poorly differentiated.

The most common histological subtype in young and old patient was trabecular (72%), which usually consisted of parallel cords of hepatocytes with a predominantly well-differentiated pattern (Figure 6), polyhedral cells, and large hyperchromatic nuclei with prominent, occasionally multiple nucleoli.

The size of the tumors ranged from 1 to 15 cm in diameter (mean, 5.3 cm SD \pm 3.2). 45% of the lesions exceeded 5 cm in diameter.

Evidence of bile production was noted in 25% (10 of 40 patients). Presence of tumor capsules was detected in 18 (50.0%) of the 36 lesions with tumor-nontumor junctions available for assessment, and capsular invasion was seen in 17 (47.2%) of these encapsulated lesions. Slightly one half [$n = 20$ (50%)] of the tumors showed venous permeation.

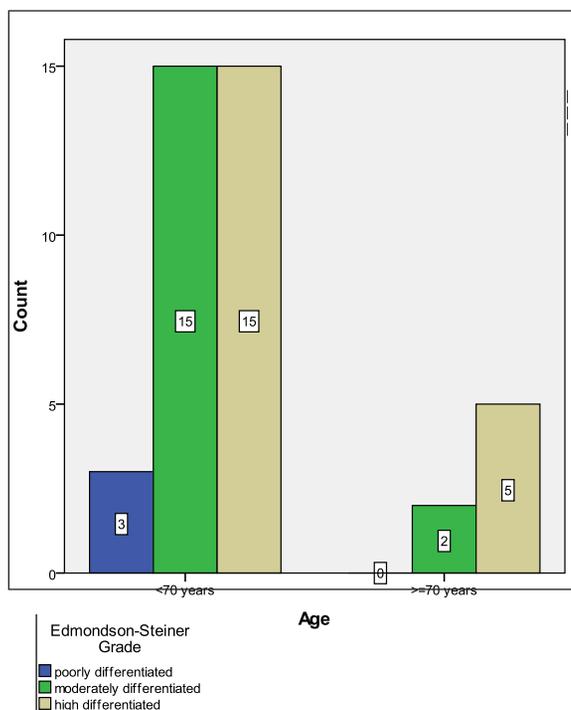


FIGURE 5. Distribution of Edmondson-Steiner grading in hepatocellular carcinoma patients

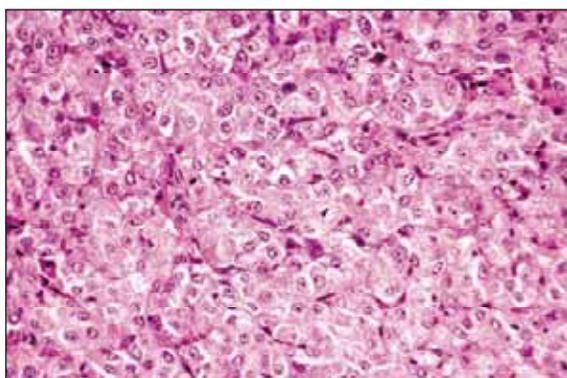


FIGURE 6. Hepatocellular carcinoma – trabecular pattern

DISCUSSION

The incidence rate of HCC among the elderly is progressively increasing (8). Age is a known risk factor for HCC (5-7). In recent studies, “the elderly” have usually been defined as to be at the ages of 60, 65, or 70 years and above (1,2). Clinical trials are a major source of information for clinical decision making. However, historically, elderly patients have been underrepresented in clinical trials (9).

The number of elderly adults with chronic liver disease, including hepatocellular carcinoma, has been increasing with the longer life expectancy of the population. In addition, it has been increasing in proportion to the increase in hepatitis C virus (HCV) – related HCC in many countries. Moreover, the decrease in global perinatal hepatitis B virus (HBV) infection and emerging antiviral drugs for HBV and HCV may increase the age of diagnosis of people with HCC, as supported by some studies that have shown that the age distribution at diagnosis of HCC has steadily increased (10-12).

The mean age of hepatocellular carcinoma patients in our group was 54,6 years with SD \pm 11.7, less than in other cohorts, although there were papers reporting a mean age of about 40 years (13).

This study shows that the difference in clinicobiological features really exists between the elderly and younger HCC patients. Different mechanisms of hepatocarcinogenesis may exist between younger and elderly HCC patient, which in turn makes the clinicopathological differences between the two groups. So, for the management of HCC patients older than 70 years, if there is no contraindication for surgery, resection still is the first choice of treatment.

A British study reported that people with HCC aged 65 and older received less or less-active treatment and had poorer survival than

younger people (14). In addition, an Italian study showed that older adults with HCC had a worse prognosis, probably because of undertreatment (15).

Several previous studies have shown differences in clinicopathological characteristics of elderly patients with HCC, including a lower rate of viral hepatitis positivity, lower M/F ratio, lower AFP values, smaller tumor diameter, and a higher proportion of stage I-II patients in elderly group. However, most of these studies were conducted in Asia, where HCC has a distinct epidemiologic pattern (16-18).

In our analysis no statistically significant difference was found in the sex ($p_v = 0.68$), between the older group and the younger HCC group. It is interesting that a higher proportion of women in elderly HCC patients were observed in a epidemiologic study that analyzed age-adjusted trends in HCC incidence using U.S. Surveillance, Epidemiology, and End Results (SEER) registry data (19). Although the reason for this difference has not been defined, it is possible that behavioral risk factors in younger males leading to earlier infection with HCV or HBV, and alcohol abuse might lead to a disproportionate increase in HCC incidence in younger males.

Compared with the younger group, the biological features of the elderly HCC patients showed the following characteristics: a low incidence of HBsAg positivity (42.8% versus 72.72%), a low incidence of anti-HCV positivity (12.12% versus 57.14%) ($p_v = 0.007$), a high proportion of AFP \geq 400 μ g/dl (85,7% vs 60%).

The elderly HCC patients had a low mean AFP value (384.5 SD \pm 157) than that of the younger HCC patients (587.78 SD \pm 741,7) ($p_v = 0.015$). This result is similar to the results published by other investigators (20). The exact mechanism is unclear. The possible reason is that the tumor growth is more active in the younger patients. Further, the biological heterogeneity of cancer cells at different ages may influence the serum AFP secretion.

No statistically significant difference was found in the sex ($p_v = 0.68$), Edmondson-Steiner grade ($p_v = 0.64$), histopathologic pattern ($p_v = 0.28$), presence of liver cirrhosis ($p_v = 0.79$) profile between the older group and the younger HCC group.

According to univariate analysis, the number of the liver segments involved with the tumor ($p_v = 0.192$), the presence of portal vein thrombosis ($p_v = 0.216$), and tumor margins ($p_v = 0.564$) did not show statistical significance.

The presence or absence of microscopic capsule formation ($p_v = 0.662$) and the presence

of nearly total necrosis ($p_v = 0.374$) did not show statistical significance.

Considering the poorer performance status, greater severity of comorbidity, and lower probability of receiving surgical resection in the older group, the cancer biology of older HCC adults may be more benign than in younger HCC people, although the older group showed a tendency toward a more-rapid decline in survival after 26 months; therefore, long-term survival may decrease significantly over time and requires further study (21).

The complexity of HCC diagnosis and management argues for development of a prospective multi-institutional HCC registration database. Prospective data collection is required to optimize evidence-based treatment choices ap-

propriate for elderly patients with HCC and ensure meaningful gains in survival and quality of life in the elderly population.

CONCLUSION

In conclusion, our study demonstrated that patients ≥ 70 years old with HCC had baseline clinical profiles that differed from those of patients < 70 years old. Hepatocellular carcinoma was predominantly associated with chronic HBV-infection. Abdominal pain was the most frequently symptom and hepatomegaly was the most frequently sign of HCC in our study. Most patients presented elevated serum AFP levels. The most common pattern in young and old patient was trabecular.

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