Editorial

Racial disparities in management of hepatocellular carcinoma

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"*Ho smesso di credere che gli ultimi saranno i primi*", Luigi Pintor.

Hepatocellular carcinoma (HCC) is a major global health problem and the second most common cause of death from cancer worldwide. Moreover, the incidence of HCC increases progressively with advancing age, reaching a peak at 70 years. Furthermore, there is a growing incidence of HCC worldwide (1).

The increased attention on the topic has led to diagnostic criteria, allowing the detection of HCC in early phase, and now worldwide based mostly on only radiological findings, making the need of histological confirmation generally avoidable, a part from those rare cases in which the radiological picture is not typical (2-4). Screening of HCC in cirrhosis is necessary to provide early HCC diagnosis (5).

A wide range of treatments are now possible for HCC, both curative and not (5,6). In fact, liver transplantation (LT) is the ideal treatment for HCC, curing both HCC and underlying cirrhosis. However, the role of LT is limited firstly by organ shortage and, then, only a minority of patients with HCC effectively can undergo LT (6). Moreover, many patients with HCC are treated with other curative therapies, both surgical or percutaneous, either as sole treatment or as a bridge to LT, with undeniable benefits in terms of survival (5).

Patients with intermediate HCC or those with early HCC who are otherwise unsuitable for curative treatment, can be treated with trans-arterial chemoembolization (TACE), a treatment unable to eradicate HCC but certainly able to reduce tumor progression and consequently to prolong survival (7). TACE is the recommended treatment for BCLC stage B multinodular asymptomatic tumors without vascular invasion or extrahepatic spread. Drug-eluting beads have similar efficacy to gelfoam-lipiodol with probably less adverse events. Both should be discouraged in decompensated liver disease and in case of macroscopic vascular invasion or extrahepatic spread (5). An alternative to TACE is radioembolization, a more expensive treatment, whose indication can however be extended also to cases with portal vein neoplastic thrombosis (8).

Anyway, the mainstay of palliative therapy for advanced HCC is sorafenib, which is indicated in advanced HCC or HCC progressing upon loco-regional therapies with well-preserved liver function and good performance status or in cases of extrahepatic metastasis. Registrative studies have shown a 3-months improvement of median overall survival of sorafenib compared to placebo. However, adverse events are frequent and can be severe (9,10). Furthermore, sorafenib has a limited but important role also in cases with HCC recurrence after LT (11). Finally, second line therapy with regorafenib has been shown to improve survival after sorafenib failure (12,13) and plenty other systemic therapies reported promising results.

Based on this premise, one would think that every patient at risk for HCC development, that is everyone with cirrhosis, could benefit from an early diagnosis and treatment of HCC. In fact, one question could be which is the gap between the theoretical possibility and the real picture of management of HCC in developed countries.

In a recent study, Xu and co-authors, using the surveillance, epidemiology, and end results (SEER) database

tried to retrospectively determine the factors associated with racial differences in survival among patients with HCC in the United States. First of all, the study does not lack originality. In fact, data focusing on ethnicity-based differences in clinical presentation, management and outcome, were previously reported for other cancers but HCC.

In the present study, a total of 58,186 patients with HCC were identified. Over two-thirds of patients were white, while 18% were Asian, 13% black and 1% native American. Authors reported that, in comparison to other racial groups, Asian patients with HCC tended to be older, were diagnosed with larger tumors and were also less likely to present with concomitant liver cirrhosis, while elevated levels of alpha-fetoprotein were more often noted among black patients. Compared to other racial groups, Asian patients were most likely to receive any form of treatment and in particular surgery. The median overall survival was 11 months with the worst prognosis noted among black patients. Moreover, Asian patients demonstrated the lowest risk for death while no differences were noted in the risk of death among other racial groups (14).

Overall, the main result, that is a better prognosis for Asian and a worst one for black ethnicity, remains unexplainable and surely needs future confirmation. In fact, which is the role of both genetic factors or of different etiologies, namely HBV, is not explained by the study, firstly because of its retrospective design. Another secondary but significant data is the evident high rate of LT reserved to white ethnicity. To speculate about the impact of social class as a potential co-factor affecting treatment and/or outcome of HCC is impossible because of both retrospective nature and limitations of the study. In fact, the study have some evident limitations. In particular, database is roughly incomplete, and data about non curative treatments, just like TACE or sorafenib, is missing. Moreover, the database could also be affected by the bias of reporting only cases with health insurance cover, so not reporting data of those without, probably the poorest and sickest population, so possibly altering the veracity of the results. However, despite these limitations, the rate of more than 70% of cases who did not receive any curative treatment appears impressive. These data sharply differ from those reported by an Italian multicenter database, including 5,192 patients with HCC, from different non-surgical centers, roughly half of which receiving a curative treatment (15). Probably, a significant difference in the access to screening programs could partly explain the difference between the insurance based US health system and the Italian one, due to the fact that the access to health system is universal in Italy. However, both the studies report too low rates of curative treatments, suggesting that the health system adopted could explain only in part the reasons of the issue (14,15).

Despite the limitation of the study, some conclusion can be attempted. Surely, there is a wide difference between the real life and the potential management of HCC. This difference could benefit some ethnicities but further prospective studies are needed to confirm in which direction and provide reasons of racial disparities in survival of patients with HCC. Furthermore, it seems that there is a lot to be done to improve screening programs and detect early HCC so increasing the rate of curative treatment in the US clinical real life. Probably, the theoretical improvement of HCC management has not had the consequence of an equivalent practical improvement of HCC management.

Luigi Pintor, fine intellectual, writer and founder of the Italian newspaper *il manifesto*, who spent his life struggling for the spread human rights, would not have many reasons to be optimistic looking at these data (16).

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