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Management of hepatocellular carcinoma in the time of COVID-19

To the Editor,

We have read the paper by Zhang et al.[1] reporting severe Coronavirus disease 2019 (COVID-19) in 28 cancer patients from China. Among these patients, there were two (7%) with hepatocellular carcinoma (HCC), who are at high risk of poor outcomes, if infected, according to age, comorbidities, and underlying cirrhosis. However, we should also consider the collateral damage it brings to the systems of care on which our patients depend, including interruption and delay in the schedule of HCC screening, treatments, and follow-up. Currently, Italy is facing the COVID-19 pandemic as are other Western countries, with clinical activities being reduced and postponed to minimize the risk of transmission and to have all health personnel involved in facing the emergency.

We agree that more intensive attention should be paid to patients with cancer during the COVID-19 crisis, both for reducing the risk of severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) infection and ensuring appropriate cancer patient management programs. In our center, all HCC cases are managed following European Association for the Study of the Liver (EASL) guidelines and the Barcelona Clinic Liver Cancer (BCLC) staging system based on discussion from multidisciplinary meetings.[2,3] To tackle the COVID-19 crisis by reducing as low as possible the risk of patients' exposure to SARS-CoV-2 and spreading of the infection within the hospital, we modified the management algorithm as follows:

- Telemedicine by video call has been preferred to face-to-face visits.
- The weekly multidisciplinary meetings are conducted by conference calls, sharing images online to reduce the risk for health-care operators without delaying decisions.
- Indications for liver transplantation (LT) have not changed, although management follows a recently published algorithm.[4] In summary, we have reserved LT for patients with high risk of drop-out due to progression of HCC. This decision has been made not only because of the shortage of intensive care unit beds availability, but also following the dramatic reduction in the donor pool.
- Moreover, to reduce the risk of disease progression during the waiting period, we encouraged locoregional treatment (LRT) as bridge treatment to LT, whenever possible.
- The SARS-CoV-2 test is carried out in all patients 1 day before admission; only negative patients are admitted to dedicated rooms in our ward (to protect them against nosocomial SARS-CoV-2 infection). To ensure safety for both our patients and providers, protocols have been implemented to prepare the staff and angiographic suite before the arrival of patients, by optimizing the ventilation systems and intraprocedural plus postprocedural workflow.[5]
- LRTs, such as microwave thermal ablation and radiofrequency thermal ablation (TA), are preferred to surgical resection to reduce both the needs of postoperative stays in the intensive care unit and hospitalization time, leaving surgery as a salvage option only in cases not achieving complete radiological response or not appropriate for LRTs.
- Palliative treatments, such as transarterial chemo(radio) embolization (TACE, TARE), are maintained, but postponed in the elderly (>80 years) and in patients with comorbidities, to minimize risk connected to hospitalization, weighing the oncological benefit versus the risk of exposure to SARS-CoV-2.
- The management of patients with advanced HCC treated with systemic drugs has been modified as well. Home blood sampling and drug delivery were implemented together with video calls to manage common adverse events. Intravenous anticancer therapies are dispensed in a dedicated section of our outpatient service.
- Imaging techniques carried out for diagnosis or staging are revised via the intranet, telemedicine, or after courier delivery. As far as patients who receive any treatment, radiological follow-up is scheduled as usual, but postponed up to 3 months in elderly patients and in those with comorbidities.

According to these modifications in our HCC management, we compared our performance between 24 February and 20 March 2020 with that in the same time frame in 2019 (Table 1). In summary, the HCC treatments for 42 patients were scheduled with a delay of ≥2 months in only 11 (26%) patients: two TA, four TACE, three TARE, and two systemic therapies. TAs were carried out instead of preplanned surgical resection in three patients.

Table 1. Management of HCC patients before and during COVID-19 emergency: a 4-week period in 2019 was compared with a 4-week period in 2020

Management	25 February to 22 March 2019	24 February to 20 March 2020
Outpatient visits, *n*	117	77[a]
Cases discussed in multidisciplinary meetings, *n*	46	42
Liver transplants for HCC, *n*	3	1
Surgical resections, *n*	3	2
MWTA and RFA, *n*	4	7
TACE, *n*	9	4
TARE, *n*	—	1
Total number of patients admitted to the ward	58	48

MWTA, microwave thermal ablation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.
[a] Week 1: 35 visits; week 2: 23 visits; week 3: 17 visits; and week 4: 2 visits.

As the pandemic evolves, our approach to HCC management will be reviewed and our procedures updated. However, we believe that many of these changes implemented today to face this crisis will remain useful in managing any future emergencies.

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Reply to the letter to the editor 'Neutropenia in metastatic colorectal cancer receiving trifluridine/tipiracil' by Colloca et al.

We thank Colloca et al. for their interest in our article on neutropenia and survival outcomes in the RECOURSE and J003 trials.[1,2] They expressed concerns that our data did not exclude the hypothesis that chemotherapy-induced neutropenia (CIN) is not only an indicator of trifluridine (FTD) pharmacokinetics but also an indicator of the systemic inflammatory response. RECOURSE is the first randomized phase III trial to investigate the pharmacokinetic data of FTD/tipiracil (TPI) exposure, pharmacodynamics, CIN, and outcomes. Patients with higher FTD had an increased risk of CIN and those with CIN also had improved overall survival (OS).[2] However, we did not analyse the association between baseline absolute neutrophil count (ANC) and outcomes, which was a limitation. We present additional *post hoc* analyses in this letter.

In the RECOURSE population, we analysed OS in the FTD/TPI and placebo groups by low and high baseline ANC (low ANC/high ANC), defined as <4.65 or $\geq 4.65 \times 10^9$/l median cut-off, respectively. Median OS was shorter in patients with high ANC than in patients with low ANC in both treatment groups {5.4 versus 9.1 months [hazard ratio (HR) = 1.67, 95% confidence interval (CI) 1.39–2.00] in FTD/TPI and 3.8 versus 6.7 months [HR = 1.97, 95% CI 1.53–2.55] in placebo}, indicating that baseline ANC affected prognosis in our study consistent with previous reports (Figure 1A).[3,4] Although the mechanism by which neutrophils affect prognosis remain unclear, neutrophils are associated with tumour inflammation and acceleration of disease progression. This might explain worse prognosis in patients with high ANC in the placebo group. We additionally analysed the association between baseline ANC and CIN in the FTD/TPI group. The CIN incidence in patients with low ANC and