

Priming Knowledge in Liver Cancer across Disciplines



MANAGEMENT OF HCC DURING COVID-19: ILCA GUIDANCE



Learning Objectives

- 1. Review the global status of Covid-19 and impact on death rates
- 2. Understand the effects of Covid-19 on liver function
- 3. Understand the impact of Covid-19 on management of HCC



Agenda

Introduction

Tim Meyer, Royal Free and UCL, London, UK

COVID-19 and liver disease

Elizabeth Verna, Columbia University Irving Medical Center (CUMC), USA

- Surveillance and management of early and intermediate HCC during the pandemic Amit Singal, UT Southwestern Medical Center, USA
- Oncological considerations and systemic therapies in HCC during the pandemic Stephen Chan, The Chinese University of Hong Kong, Hong Kong
- Questions

Augusto Villanueva, Icahn School of Medicine at Mount Sinai, USA



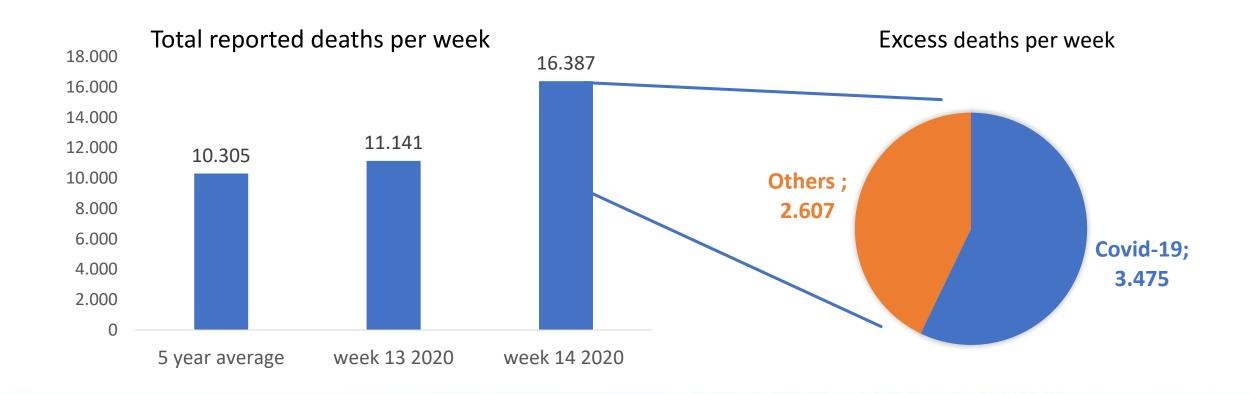
COVID-19 – global overview

- 31st Dec 2019 China reported a cluster of cases of pneumonia in Wuhan
- 11th March 2020 WHO declares COVID-19 a pandemic
- 17th April
 - Confirmed cases: 2,034,802
 - Confirmed deaths: 135,163
 - Countries affected: 213
 - PubMed references for Covid-19: 4766



Effect of COVID-19 on national death rate England and Wales data from ONS







Impact of COVID-19 on cancer patients

- Increased risk of infection due to hospital contact
- Increased risk of severe illness due to comorbidity and immunosuppression
- Lack of treatment provision due to redeployment of healthcare resource

Priming Knowledge in Liver Cancer across Disciplines



Surveillance and management of early and intermediate HCC during the pandemic

Amit G. Singal MD MS
David Bruton Jr. Professor of Clinical Cancer Care
Medical Director, Liver Tumor Program
Clinical Chief of Hepatology
UT Southwestern Medical Center



Outline

- Surveillance for HCC
- Early stage HCC treatment considerations
- Intermediate stage HCC treatment considerations
- Conclusions

General issues



- Risk of infection
- Shortage of beds, particularly ICU beds
- Shortage of anesthesiologists
- Shortage of personal protective equipment (PPE)
- The first consideration is universal, subject to contact tracing and vaccine availability
- The latter three are prone to substantial geographic and temporal variation



General considerations

- Telemedicine can be used in substitution of many in-person visits
 - Train clinic staff on symptom recognition and available COVID testing
 - Waiting rooms should facilitate 6 feet social distancing
- Careful selection of patients for highest benefit and lowest risk of complications
- Treatment decisions that deviate from standard of care should be discussed in multidisciplinary format
 - Recommend explicit discussion of risks and benefits of decisions with patients



HCC Surveillance

- Current standard: Semi-annual surveillance using ultrasound +/- AFP associated with improved survival in chronic HBV and cirrhosis
- Target population: Annual incidence is ~2% so >98% of patients unaffected if miss a single surveillance episode
- If prolonged delays, risk models may help identify high-risk subgroups of chronic HBV and cirrhosis pts
 - GAG-HCC, CU-HCC, REACH-B, PAGE-B among HBV patients on antiviral therapy
 - Models have been developed in cirrhosis patients (<u>www.hccrisk.com</u>) although have not been externally validated





ILCA INTERNATIONAL LIVER CANCER ASSOCIATION

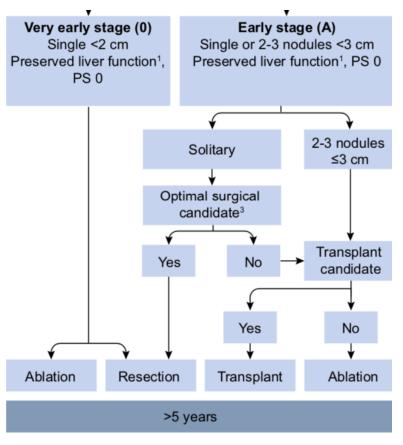
HCC Surveillance

- How often: Semi-annual surveillance increases early detection vs. annual surveillance but quarterly not superior to semi-annual
- No comparison of intervals of 4-8 months so could likely delay 1-2 months
- Test choice: Ultrasound and AFP are only validated surveillance tests
- Biomarker panels such as GALAD have promising phase II data (no phase III data) but could be considered if cannot obtain ultrasound-based surveillance
 - Sensitivity for early HCC detection 60-80% in case-control study with 6834 patients
- Follow-up: Risk of HCC low in lesions < 1 cm so CT/MRI not needed and can follow with repeat ultrasound



ILCA recommendations for Early HCC

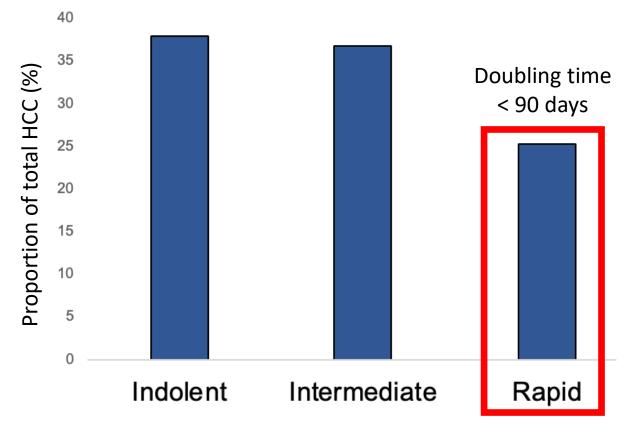




- Liver transplantation Unique considerations of COVID-donor derived infection and immunosuppression post transplant
- Consider cessation of LDLT (lower MELD) and delaying transplant in those with complete response
- Resection Can consider bridging locoregional therapy (TACE/TARE/SBRT), systemic therapy, or active monitoring
- Local ablation Reserve for those with best chance of response (size <3 cm) and can consider SBRT

Rapid growth observed in 1/3 of HCC



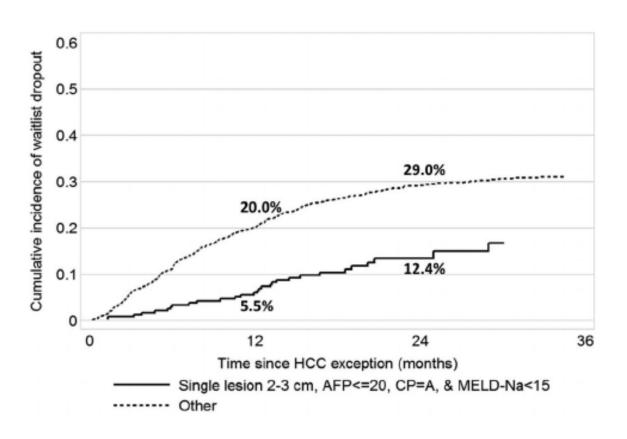


Rapid growth associated with smaller tumor size!





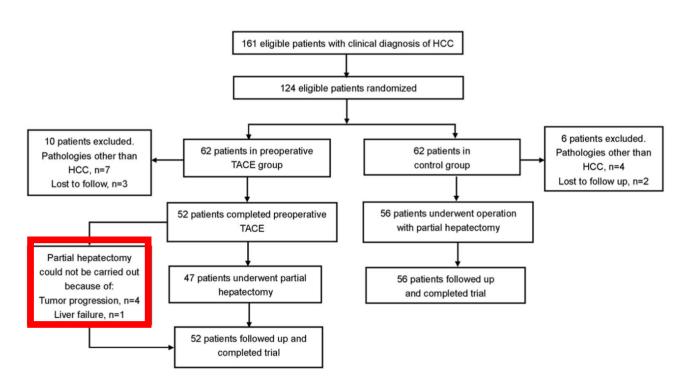
Liver transplantation waitlist drop-out



- Among 2052 listed patients (UNOS database), risk of dropout was 10.2% at 6 months
- Low-risk for drop-out defined by 4 factors: single lesion 2-3 cm, Child Pugh A, MELD < 15, and AFP< 20
 - These factors may help define a subset who can be delayed if needed
 - Majority of patients (>75%) received LRT while on list

Neoadjuvant TACE/TARE prior to resection





TACE associated with drop-out in ~10%

- Single arm study with TARE prior to resection (n=31)
- 25 major resection, 6 partial hepatectomy
- Median time from TARE to resection 2.9 months
- Disease control in 100% and 77% had 50% or greater tumor necrosis





Neoadjuvant systemic therapy prior to resection

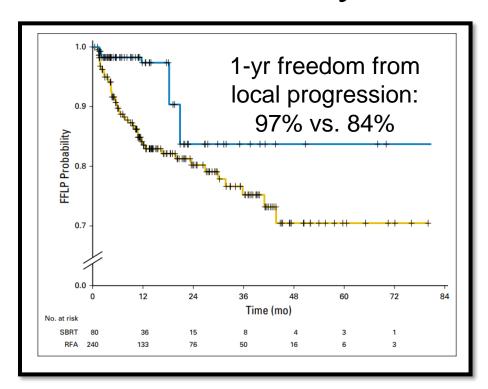
- Phase II study with neoadjuvant sorafenib * 4 weeks
- Of 28 patients, 3 had rarly dose-limit toxicity
- No reported data on disease control rate
- 88% R0 resection, no unexpected complications

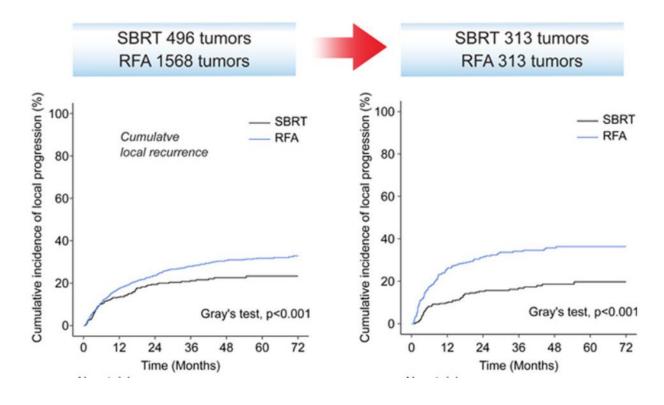
- Randomized phase II RCT of Nivo or Nivo/Ipi as neoadjuvant therapy
- Of 17 enrolled patients, 14 evaluable
- 2 aborted surgery (1 frozen abdomen, 1 tumor progression)
- pCR of 4/14 and 5/14 with grade III toxicity prior to surgery





SBRT may be considered in select cases





Potential benefit in this situation is SBRT does not require anesthesia





Monitoring after complete response

- Many centers will perform surveillance imaging q3 months for 1-2 years post resection or ablation, followed by q6 months
- Some data suggest can extend interval to q6 months post resection/ablation
 - Particularly in low-risk patients, e.g. unifocal lesion < 3 cm
- RETREAT score may help stratify recurrence risk post transplant and tailor surveillance strategies
 - Three-year risk of surveillance 1.6% in those with score of 0 compared to 29% with a score >4



ILCA recommendations for intermediate HCC



Intermediate stage (B) Multinodular, unresectable Preserved liver function¹, PS 0

- Consider TAE, DEB-TACE, or TARE to reduce risk of immunosuppression
- Consider HAP or up-to-7 criteria to select those most likely to benefit
- Systemic therapy as alternative

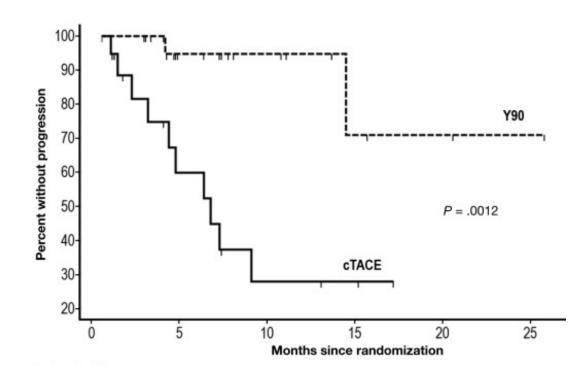
Chemoembolization

>2.5 years





- Data from PRECISION V showed small but statistically significant difference in LVEF between TACE and DEB-TACE
 - Suggests possible systemic effects from doxorubicin so may be safer to use DEB-TACE or TAE

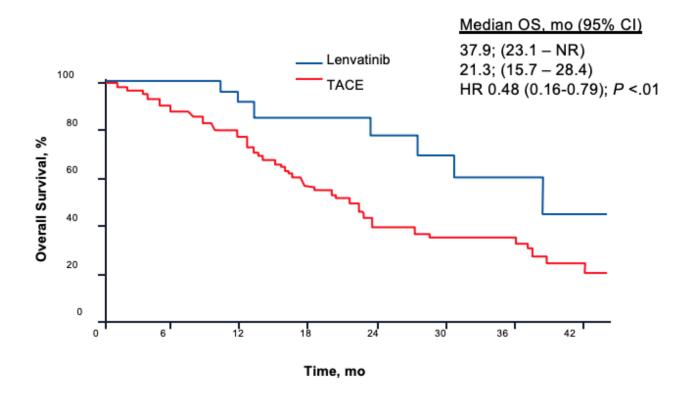


TTP: >26 vs.6.8 months (HR 0.12, 95%CI 0.03-0.56)



Systemic therapy for select BCLC B patients?

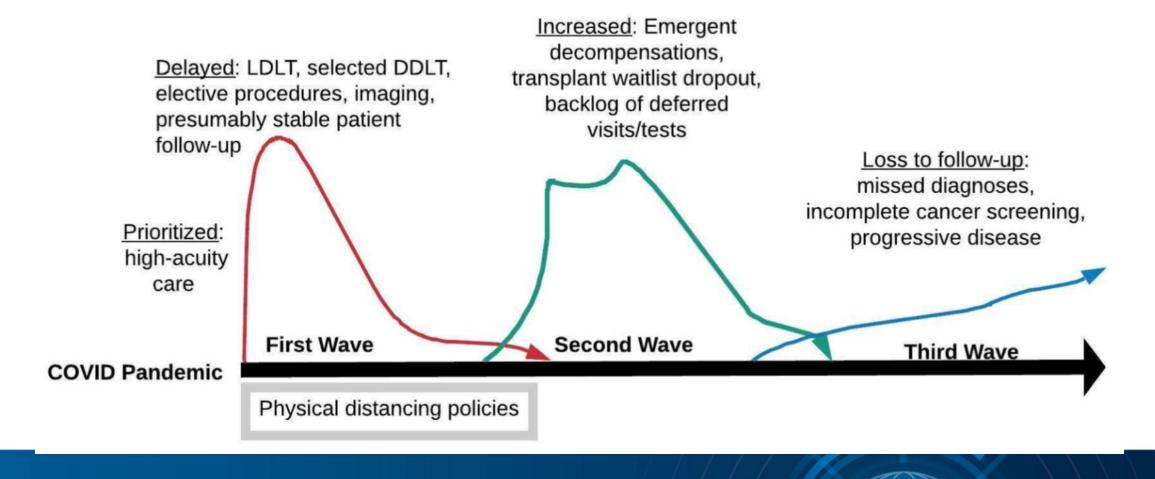




BCLC Stage B HCC beyond up-to-7 criteria

Impact of COVID extends beyond 1st wave





Summary



- Surveillance: Likely safe to delay surveillance exam for 1-2 months
- If prolonged impact, can consider risk models to select those in greatest need or use biomarkers as alternative (although unproven) strategy
- Early stage HCC: Can consider bridging therapies such as LRT or systemic therapy although there is risk of drop-out from otherwise curative therapy
- Intermediate stage HCC: Consider TAE, DEB-TACE or TARE instead of TACE and perhaps systemic therapy in some patients with large tumor burden
- Strategies should be tailored to local resources and evolving COVID status



Priming Knowledge in Liver Cancer across Disciplines



Oncological Considerations and systemic therapies in HCC during the pandemic

Stephen L. Chan

MD, FRCP

Associate Professor

Department of Clinical Oncology

The Chinese University of Hong Kong



Outline (15 minutes)

- Impact of the COVID-19 on cancer patients literature review
- Oncological considerations on treatment in HCC
- ILCA guidance on systemic therapy during the pandemic
- Conclusions



Outline

- Impact of the COVID-19 on cancer patients literature review
- Oncological consideration on treatment in HCC
- ILCA guidance on systemic therapy for HCC during the pandemic
- Conclusions

Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China



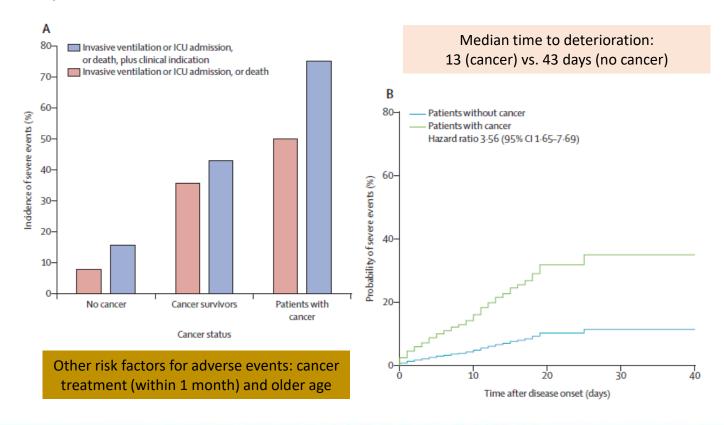
Liang W et al. Lancet Oncol 2020. 21; 335-337

Method

 Prospective cohort of a nationwide database in China (cut-off 31 Jan 2020)

Population

- Total 1590 COVID-19 cases; 18 (1%) had history of cancer
 - 5 Lung cancer; 4 colorectal cancer; 2 breast cancers; 2 bladder cancers
 - 75% cancer survivors; 25% underwent chemotherapy or surgery within the past month





Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention

Wu Z et al. JAMA. 2020 Feb 24 [Epub ahead of print]

Vital Surveillances



The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team

Method: Data summary from the Chinese Centre for Disease control and Prevention (as on 11 Feb 2020)

Population: 72314 Covid-19 patients

in China

Box. Key Findings From the Chinese Center for Disease Control and Prevention Report

72 314 Cases (as of February 11, 2020)

- Confirmed cases: 44 672 (62%)
- Suspected cases: 16 186 (22%)
- Diagnosed cases: 10 567 (15%)
- · Asymptomatic cases: 889 (1%)

Age distribution (N = 44 672)

- ≥80 years: 3% (1408 cases)
- 30-79 years: 87% (38 680 cases)
- 20-29 years: 8% (3619 cases)
- 10-19 years: 1% (549 cases)
- <10 years: 1% (416 cases)</p>

Spectrum of disease (N = 44 415)

- · Mild: 81% (36 160 cases)
- Severe: 14% (6168 cases)
- Critical: 5% (2087 cases)

Case-fatality rate

- 2.3% (1023 of 44 672 confirmed cases)
- 14.8% in patients aged ≥80 years (208 of 1408)
- 8.0% in patients aged 70-79 years (312 of 3918)
- 49.0% in critical cases (1023 of 2087)

Health care personnel infected

- · 3.8% (1716 of 44 672)
- 63% in Wuhan (1080 of 1716)
- 14.8% cases classified as severe or critical (247 of 1668)
- 5 deaths

Baseline characteristics	Confirmed cases, N (%)	Deaths, N (%)	Case fatality rate, %	Observed time, PD	Mortality, per 10 PD
Province					
Hubei	33,367 (74.7)	979 (95.7)	2.9	496,523	0.020
Other	11,305 (25.3)	44 (4.3)	0.4	165,086	0.003
Wuhan-related exposure*					
Yes	31,974 (85.8)	853 (92.8)	2.7	486,612	0.018
No	5,295 (14.2)	66 (7.2)	1.2	71,201	0.009
Missing	7,403	104	2.8	103,796	0.010
Comorbid condition [†]					
Hypertension	2,683 (12.8)	161 (39.7)	6.0	42,603	0.038
Diabetes	1,102 (5.3)	80 (19.7)	7.3	17,940	0.045
Cardiovascular disease	873 (4.2)	92 (22.7)	10.5	13,533	0.068
Chronic respiratory disease	511 (2.4)	32 (7.9)	6.3	8,083	0.040
Cancer (any)	107 (0.5)	6 (1.5)	5.6	1,690	0.036
None	15,536 (74.0)	133 (32.8)	0.9	242,948	0.005
Missing	23,690 (53.0)	617 (60.3)	2.6	331,843	0.019

hypertens on, and 5.6% for cancer. An ong the 44 672 cases, a to al of 1716 were health workers (3.8%), 1080 of whom were in wunan (65%). Overall, 14.8% of confirmed cases among health workers were classified as severe or critical and 5 deaths were observed.¹

COVID-19 rapidly spread from a single city to the entire country in just 30 days. The sheer speed of both the geographical expansion and the sudden in-





Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in

three hospitals within Wuhan, China

Zhang L. et al. Ann Oncol 2020 Mar 26 [Epub ahead of print]

Method

 Retrospective cohort of cancer patients with COVID-19 infection in 3 hospitals in Wuhan (13 Jan 20-26 Feb 20)

Population

- Total 28 patients identified.
- Lung cancer (25%); Esophageal cancer (14.3%);
 breast cancer (10.7%); 2 Liver cancer patients (7.1%)
- Recent cancer treatment (≤14 days) from Covid-19: Chemotherapy 10.7%; Targeted therapy 7.1%; immunotherapy 3.6%; radiotherapy 3.6%

Outcomes

- Mortality = 8/28 (28.6%)
- ICU admission rate= 6/28 (21.4%)
- Mechanical ventilation = 10/28 (35.7%)
- ARDS = 5 (62.5%)

Table 3. Multivariate analysis for the risk of severe events

Clinical Factors	HR	95% CI	P
Gender	0.574	0.162-2.038	0.390
Age	1.455	0.478-4.430	0.509
Anti-tumor <=14 days ^a	4.079	1.086-15.322	0.037
Patchy consolidation ^b	5.438	1.498-19.748	0.010

Abbreviations: A two-side P-value <0.05 was considered statistically significant. HR, hazard ratio; CI, confidence interval.



^a Time from last anti-tumor treatment to diagnosis of COVID-19

b CT scan on admission

Letters



RESEARCH LETTER

SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China

Yu J et al. JAMA Oncol. 2020; Mar 25 [Epub ahead of print)

Method

- Retrospective cohort of cancer patients in a tertiary hospital in Wuhan (30 Dec 19-17 Feb 20)
- Aimed to evaluate risk of COVID-19 infection in cancer patients

Findings

- Infection rate in cancer patients (0.79%; 12/1524)
 vs. incidence of COVID-19 in Wuhan (0.37%)
- Lung cancer (n=7); colorectal cancer (n=2); breast cancer(n=1); pancreatic cancer (n=1); urothelial cancer (n=1)

Risk of COVID-19 in cancer patients

Table 2. COVID-19 Pneumonia in Patients With NSCLC of Different Age Groups Treated at the Zhongnan Hospital of Wuhan University

	No. (%)	
Age, y	Total No. of patients with NSCLC (n = 228)	Patients with NSCLC with COVID-19 (n = 7)
≤60	111 (48.7)	2 of 111(1.8)
>60	117 (51.3)	5 of 117 (4.3)

Abbreviations: COVID-19, 2019 novel coronavirus disease, NSCLC, non-small cell lung cancer.

COVID-19 on cancer patients: summary of current literatures



- If infected with COVID-19, cancer patients generally have worse outcomes than noncancer patients.
 - Variable figures: Mortality 5->20%; ICU admission 20-50%
- Recent anti-tumor treatment and possibly advanced age is associated with adverse events during COVID-19 infection
 - Likely related to immunocompromised state
- Caveats
 - Liver cancer is under-represented in the current literatures.
 - Reported case number is still relatively small
 - ~approximately 100 cancer cases infected with COVID-19

More studies (larger sample size, Data from the West; and with higher representation of liver cancers) are required!





Outline

- Impact of the COVID-19 on cancer patients literature review
- Oncological consideration on treatment in HCC
- ILCA guidance on systemic therapy for HCC during the pandemic
- Conclusions



Oncological consideration on treatment in HCC (1)

- Most patients have comorbid chronic liver disease
 - Liver injuries related to COVID-19 infection or related treatment may damage liver function and worsen prognosis of HCC.
 - Experiences of SAR-COV in 2003: concomitant infection with HBV may lead to severe hepatitis¹

Importance of minimizing visits and travels of HCC patients to reduce risks of nosocomial and community infection

¹Huang Y et al. Chin J Clinic Hepatol. 2003: 342-343



Oncological consideration on treatment in HCC (2)

- Systemic treatment for HCC
 - No data on the precaution and toxicity of oral TKI or check-point inhibitors (ICIs) during COVID-19 pandemic
 - previous literatures on immunosuppressive treatment may not 100% apply
 - Adjust treatment according to risks/benefits and institutional situations
 - Consider surveillance in Child's B hepatic function
 - Switch to oral TKI in case iv formulations could not be given

Individualize treatment

ASCO Coronavirus Resources. 2020. https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19 COVID-19 rapid guideline: delivery of systemic anticancer treatments. https://www.nice.org.uk/guidance/ng161.



Oncological consideration on treatment in HCC (3)

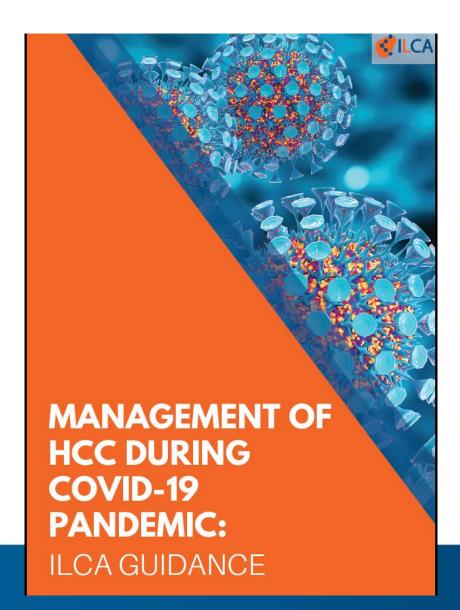
- Monitoring of treatment toxicity and response
 - Consider telemedicine or community service to monitor toxicity of systemic treatment
 - Avoid or delay follow-up scanning in patients with smaller disease burden

Modification of follow-up plan



Outline

- Impact of the COVID-19 on cancer patients literature review
- Oncological consideration on treatment in HCC
- ILCA guidance on systemic therapy for HCC during the pandemic
- Conclusions





Impact on clinical trials

Systemic therapy

Impact of COVID-19

- · Suspension of clinical trial recruitment
- Challenging to maintain compliance with protocol for patients on trial
- Outpatient capacity limited resulting in second line therapy deprioritised
- Increased risk of serious COVID 19 infection in patients receiving immunosuppressive therapy
- Limited data regarding infection risk or impact on course of COVID-19 for those receiving checkpoint inhibitors
- Reduced capacity for response imaging

Recognize the impact of immunosuppressive therapy and the unknowns





Telemedicine

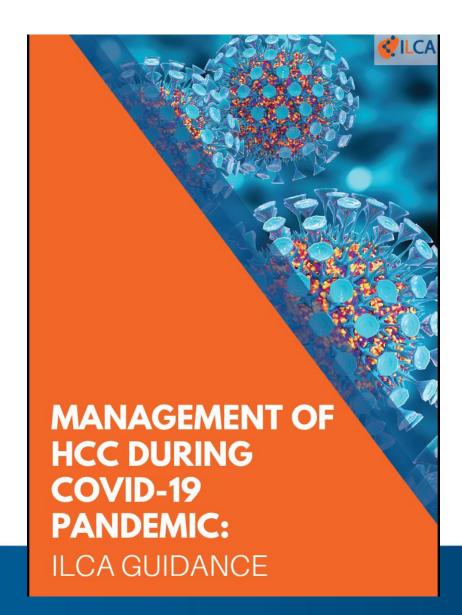
Adjust treatment

MANAGEMENT OF HCC DURING COVID-19 PANDEMIC:

ILCA GUIDANCE

Mitigation

- For patients on trial, discussion with sponsor required to accommodate variations in followup schedule, trial-related procedures and treatment location
- Select patients most likely to benefit according to performance status, Child-Pugh score and comorbidities
- First-line sorafenib or lenvatinib to replace trial recruitment and minimise hospital visits
- In regions where checkpoint inhibitors approved, the increased risk of attendance for infusion should be considered
- Patients to be managed by telemedicine to avoid hospital visits
 - Drugs to be dispensed by mail
 - Blood, urine dip and BP to be performed locally in community
 - Consider omitting radiology response assessment and continue to clinical progression according to tolerance





Alternative therapy

- Active monitoring (with imaging where appropriate)
- Supportive palliative care

Conclusions

- COVID-19 is impacting the outcomes and management of advanced HCC (resources, liver injury, immunomodulation) globally.
- Clinicians need to individualize management plan for each patient according to local situation.
- The ILCA guidance provides a framework for interim modification of clinical practices on drug treatment and monitoring of HCC.