Hepatocellular carcinoma in older adults: A comprehensive review by Young International Society of Geriatric Oncology

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Abstract

Given the prevalence and the rising incidence of hepatocellular carcinoma (HCC) in older adults worldwide, there is an urgent need to improve our understanding of the implications of treatment modalities in this population. The care of older patients with HCC is challenging due to the lack of evidence-based recommendations in this population. The current treatment approach for older patients relies on extrapolation of data from clinical trials conducted mostly in younger patients or fit older adults. Further, in the last few years, the arsenal of systemic treatments has increased with

currently seven FDA-approved therapies available for patients with advanced HCC. Therefore, understanding how to apply current data to this unique and diverse patient population is necessary. This review will aim to shed light on the approach to older adults with HCC through an assessment of available data in the literature.

1.   Epidemiology

Hepatocellular carcinoma (HCC) is rapidly becoming one of the most prevalent cancers worldwide and the third leading cause of cancer-related deaths.[1–3] As of 2012, there were over 14 million cases of HCC worldwide, and the number is expected to rise to 22 million over the next two decades.[4] Currently, the median age of patients with HCC is 63 years (median age of diagnosis ranges between 56–74).[5] Incidence rates have also increased by 8% in persons 65–69 years old and by 3% in persons 70 years or older.[6–8] HCC is increasingly relevant to older adults, especially in Europe and US, where later onset HCC may be related to risk factors acquired with aging, such as acquired hepatitis, fatty liver disease, and comorbidities.[5]

HCC accounts for over 90% of primary liver malignancies and predominantly occurs in patients with hepatitis and/or cirrhosis.[2] In the United States, Hepatitis C virus (HCV) infection is the most common cause of HCC, whereas in developing countries and Asia, Hepatitis B virus (HBV) infection is most common.[2,9,10] Despite effective treatments for HBV and HCV, the HCC risk is not completely eliminated, and HCC continues to prevail due to underlying cirrhosis and other risk factors, some of which are not clear.[7,11,12] These include rise in non-alcoholic fatty liver disease (NAFLD), resulting from the increasing incidence of obesity, insulin resistance, hyperlipidemia, and metabolic syndrome.[13–18]

Given the prevalence and rising incidence of HCC in older adults, we need to understand the unique issues that arise when treating this cancer in older adults and the implications of treatment modalities in this population. Many prior clinical trials have excluded older or unfit patients, but several retrospective reviews and meta-analyses suggest that selected older patients derive similar benefit to their younger counterparts from active treatment of HCC. [19–24] Standard management for older patients with HCC is yet to be defined, especially in vulnerable and frail older adults.

2.0   Geriatric assessment in older adults with HCC

Physiological and functional status are poorly correlated to chronological age alone in older patients with cancer.[25,26,27] Therefore, a systematic evaluation of the functional age of older adults with cancer is necessary prior to making treatment decision. Performance status scores (Eastern Cooperative Oncology Group (ECOG) and Karnofsky) are inadequate tools to evaluate the functional status in patients who are   65 years.[26,28,29] The comprehensive geriatric assessment (CGA) of older patients should include evaluation of several domains:

physical function, cognition, comorbidities, polypharmacy, nutrition, psychological status, social support, and geriatric syndromes.[25–27] This complex evaluation identifies deficits and abnormalities not detected by routine medical interview and physical examination. It may also aid in estimating survival, assist decision-making, and predict treatment related complications and toxicities.[26,28–38]

Several efforts have been made in order to find simple and feasible tools that fit the daily practice in oncology, resulting in evidence-based recommendations.[39–41] Based on the result of CGA, patients are categorized as fit, vulnerable or frail. Appropriate patient stratification, CGA-based interventions, and adapted treatments to functional status avoids under- or overtreatment, preserves quality of life and contributes to physical and mental well-being in older patients with cancer.[33–38] Thus, future studies in HCC should focus on older adults and incorporate CGA to determine the factors that affect treatment in this population.

3.0 Overview of HCC management.

The Barcelona Clinic Liver Cancer (BCLC) staging and treatment algorithm guides management of HCC.[42,43] Given the multi-modality treatment options for HCC, a multidisciplinary team-approach is vital in therapeutic decision-making.[2,42] In early stage HCC (Stage 0 or A), patients may be offered liver resection, liver transplant or local ablative therapies.[42,43] Those with intermediate stage HCC (Stage B) may be offered trans-arterial chemoembolization (TACE), and those with more advanced stage HCC (Stage C) may be offered systemic therapy.[42,43] For patients with end stage liver disease (Stage D), best supportive care is recommended.[2,42,43] Along with the CGA, we should account for older patients with varying liver dysfunction and disease burden. In this regard, scores, such as Cancer of the Liver Italian Program (CLIP),[44] allow us to understand prognosis and help us weigh the risks and benefits from cancer-directed treatments in older adults. The CLIP score is based on the Child-Pugh stage, tumor burden, α-fetoprotein level (AFP), and portal vein thrombosis, resulting in a score from 0–6 that correlates with a median survival from 1 month to 42.5 months (Table 1).[44] Although this helps with prognostication of survival based on tumor characteristics and liver function, neither functional age nor other comorbidities are built into any treatment algorithm for HCC. These guidelines lack guidance on how to treat patients who are vulnerable and/or have comorbidities.

Localized HCC

4.1 Liver Resection

The only curative treatments for HCC are surgical resection and liver transplant. Liver resection may achieve a 5-year survival of 60–80% and is the best option for those with early stage disease and preserved liver function.[42] The Italian Liver Cancer group performed a 20-year, multicenter, retrospective cohort and nested case-control study, which included 614 older patients (70+ years) and 1104 younger patients (<70 years), found that older patients were less often treated with liver resection or TACE and more often treated with ablative therapies when compared to younger patients.[19] However, when older patients were treated with liver resection, median OS was 52 months in older adults versus 47 months in younger adults (p=0.070).[19] Two meta-analyses have shown similar findings in patients who

underwent liver resections for HCC. Mizuguchi et al included five studies with 470 older patients and 1094 younger patients who underwent liver resection.[20] There was no difference in post-surgical morbidity and 3-year and 5-year survival when comparing older and younger adults (p=0.471, test for heterogeneity p=0.007) or mortality (p=0.888, test for heterogeneity p=0.219).[20] Hung et al assessed 6341 surgically resected patients in a meta-analysis.[45] The older group (70+ years) had higher 1-year survival but similar 3-year and 5-year survival after liver resection compared with the younger group; post-operative complication rates were similar.[45]

Another retrospective study of 262 patients with HCC compared surgical resection in older (70+) versus younger adults.[46] Older patients had a higher frailty score (modified Frailty Index, mean, 1.14 vs 0.51, p<0.001), more comorbidities (comorbidities 4: 28% vs 14%, p=0.005), and had more non-viral-induced HCC (65% vs 19%; p<0.001).[46] The overall complication rate and duration of stay were similar (p > 0.05).[46] Higher mortality rates were observed in the older adults (8% vs 2%, p=0.011).[46] Multiple logistic regression revealed that MELD 11 (Odds ratio [OR] 2.415; p=0.480) and positive surgical margin (Odds ratio 2.549; p=0.024) were independent predictors for major complications. The 5-year OS rate was 62% in older versus 68.5% younger adults (p=0.712), and the 5-year DFS rate 30.4% vs 38.8%, respectively (p=0.323).[46] Multiple Cox regression found that albumin < 4 gram/dL (Hazard ratio (HR) 2.533; p=0.002) and the presence of vascular invasion (HR 2.417; p=0.004) were independent predictors of poor survival.[46]

A Japanese study prospectively investigated whether a CGA may predict post-operative complications in older patients with HCC.[47] Seventy-one patients with a median age of 77 years (range: 70–89) underwent R0 hepatic resection.[47] CGA was done pre-operatively and then postoperatively at one, three, and six months.[47] Postoperative complications developed in 25% of patients, with median length of hospitalization due to complications of thirteen days (range: 6–189).[47] Patients with complications had significantly lower median G8 and mini-nutritional assessments (MNA) scores, higher incidence of cirrhosis, longer median duration of operation and more blood loss during surgery.[47] In multivariate logistic regression analysis, only the G8 score <14 was an independent predictor for complications (OR 24.4, 95% CI 1.66–157.08; p=0.0198).[47]

Overall, this data suggests the process of selecting older adults who benefit from surgical resection is complex. Fit older adults with low volume disease may benefit with long-term improvements in survival. However, older patients who are vulnerable or frail may be at higher risk for worse short-term outcomes. Therefore, geriatric assessments would help us better select patients for liver resection. Simple geriatric screening tools, such as G8, completed by the patient or caregivers within 5–10 minutes, can predict adverse events in older patients with HCC. Further risk factors, such as serum albumin, lower G8 and lower MNA scores, may help us identify patients who are frail or vulnerable who may benefit from pre-rehabilitation or supportive care.

4.2   Liver Transplant

Liver transplant is recommended for patients with HCC that meet the Milan criteria (one lesion <5cm or up to three lesions each <3cm) or the University of California San Francisco

criteria (1 tumor 6.5cm or maximum of 3 lesions with the largest 4.5cm and total tumor diameter 8cm).[43,45,48,49] Transplant is an ideal treatment for HCC as it offers potential to cure both the underlying liver disease and the HCC, with the 5-year survival being 65–80% in a highly selected patient population.[42]

Data for survival benefit of transplant in older versus younger adults are mixed. Some early registry data from the United Network for Organ Sharing (UNOS) during 1990 found lower survival in adults >65 (60% vs 72% 1-year survival), and other single institutional series during the 1990s suggested inferior long-term survival rates after transplant in older adults. [50–54] However, subsets of older adults with preserved synthetic function or lower pre-transplant bilirubin had similar survival to younger patients, suggesting that carefully selected older adults may benefit from transplant.[53]

Other analyses have demonstrated similar five-year mortality and graft loss in selected older adults 70 years compared with younger adults.[23,24,55] A large meta-analysis of patients receiving liver transplant for all causes from 2000–2018 found that 23,660 older (65+) patients and 218,827 younger (<65) patients had similar long-term survival and graft loss rates.[22] Internationally, transplantation guidelines do not exclude patients from liver transplant based on chronological age, but assessment should be based on functional age,[48] comorbidities and performance status,[42] with an expected survivorship of >50% at 5 years after a transplant.[49] Despite these recommendations, only a small proportion of older patients are offered a liver transplant (3.1% of transplants in 2014 in the United States and 1.3% of transplants in 2015 in Europe were assigned to patients 70+ years).[22]

Studies of frailty in patients awaiting liver transplant show older patients have higher rates of frailty than younger patients; and frailty is associated with about 2-fold increased risk of waitlist mortality.[56,57] The benefit of transplant should be weighed at the individual level regardless of chronological age for fit older adults with HCC with minimal comorbidities, excellent functional status, and an increased predicted life expectancy. Measures of frailty may guide selection of patients as well as interventions in patients awaiting liver transplantation.

4.3 Local Ablative Therapies

Several local ablation techniques are used in the treatment of early stage HCC (Table 2). Radiofrequency ablation (RFA) uses thermal energy to induce necrosis and has the most supporting evidence of efficacy.[42] In single tumors <3 cm, RFA may achieve 3-year survival rates of 76%[58] with a low procedure-related mortality rate of 0.15%.[59] A Cochrane meta-analysis compared surgery (average age 51–56 years) with RFA (average age 49–72 years) in early stage HCC and found that there was no difference in all-cause mortality between the two treatment approaches.[60] The cancer-related mortality was lower in the surgery group (17.4% versus 37.4%); however, serious adverse events were higher (23.3% versus 1.7%) with resection (odds ratio 17.96, 95% CI 2.28–141.60).[60] Microwave ablation (MWA), an alternative treatment that has larger ablation volumes and less affected by vessel proximity, has similar efficacy to RFA.[61]

The Italian Liver Cancer group retrospective series as well as a meta-analysis by Hung, et al, showed similar survival among older patients who underwent RFA when compared to younger adults.[19,21] There was no difference in the complication rates between the two groups.[21] Most recently, the SURF trial randomized patients with HCC (<3 tumors, <3cm) to surgery versus RFA, which showed 3-year RFS was 49.8% with surgery versus 47.7% with RFA (HR 0.96; 95% CI: 0.72–1.28; p=0.793).[62] In this study, all patient were < 80 years old with median age of 68 and 69, respectively.[62] Length of hospital stay with surgery was higher than RFA (p<0.01), and no mortality due to the procedures was observed.[62] When considering these treatments for older adults with BCLC Stage A HCC, local ablations should be considered due to their safety and efficacy compared to more aggressive surgical approaches.

4.4 Trans-arterial Chemoembolization

Trans-arterial chemoembolization (TACE) is a method of delivering chemotherapy directly to the tumor followed by embolization of the arterial supply to the tumor in order to induce necrosis.[63] Trans-arterial embolization (TAE) or "bland embolization" is done without chemotherapy and may be better tolerated in older adults with borderline liver function.[64] TACE demonstrated an improved survival over bland embolization[63] and over best supportive care[65] in two randomized controlled trials (RCTs). Therefore, it is recommended in the BCLC algorithm for intermediate stage (B) HCC with preserved liver function and patent portal vein.[42] The median OS in older studies was about 20 months, but with careful selection and optimal delivery, survival is currently up to 30–40 months.[2]

A retrospective multicenter analysis of 548 patients (27% >75 years) revealed that older patients undergoing TACE did not have increased risk of complications and had similar survival to younger patients.[66] A meta-analysis found that the cohort of older patients had an increased 1-year and 3-year survival after TACE compared with the younger cohort, with a similar 5-year survival and complication rate.[21] The Italian liver group study also noted similar survival after TACE in older and younger patient groups with a median OS of 26 months in the older group and 5-year survival of 6.4%.[19] Based on these data, TACE offers a relatively effective and safe treatment option for older adults with intermediate stage (B) HCC and may be considered in older adults with adequate renal and liver function.

4.5 Selective Internal Radiation Therapy

Selective internal radiation therapy (SIRT) is the injection of radiolabelled Yttrium-90 microspheres into the hepatic artery to induce tumor necrosis.[67] Cohort studies have suggested varying tumor response rates from 35 – 90% with SIRT.[2,42] The SARAH study, a RCT of intermediate to advanced HCC, compared SIRT with sorafenib, which is a tyrosine kinase inhibitor (TKI) and the first systemic treatment approved for HCC.[67] Although survival benefit of SIRT (8.0 months) over sorafenib (9.9 months) was not demonstrated, quality of life was significantly better in the SIRT group.[67] A retrospective analysis conducted across eight European centers included 128 older (mean age 74 years) and 197 younger patients who received SIRT between 2003 and 2009.[68] SIRT induced similar toxicities in both groups, without any differences detected in survival between the two groups.[68] SIRT may be an option for older adults who would otherwise require several

TACE procedures because of the size of their lesions or who are ineligible for TACE due to portal vein thrombosis. SIRT decreases the burden of travel on patients and caregivers, does not require a hospital stay, and thus avoids hospital-related complications, such as hospital delirium.

4.6 Stereotactic Body Radiotherapy

Single center studies have suggested that stereotactic body radiotherapy (SBRT) can achieve tumor control rates of >90% in tumors < 5 cm after 12 months.[43] In older adults, SBRT appears to have similar outcomes when compared to younger adults based on a single center study analyzing 54 patients ≥ 75 years and 63 patients <75 years.[69] This study found no difference in median OS or adverse events, and the 3-year disease control rate in both groups was 98%, although progression-free survival (PFS) was shorter in the older group.[69] SBRT may still be a suitable option when RFA is not possible, such as larger tumors or a challenging location of the tumors.[43] Furthermore, given SBRT is non-invasive and does not require anesthesia, SBRT is a feasible option for older adults with comorbidities and decreased functional status.

5.0 Systemic Therapy

The last two years have produced an unprecedented growth in systemic therapy options for HCC (Table 3). In published clinical trials leading to the approval of six first- and second-line targeted agents and immunotherapies, the median age ranged from 62 to 68 years.[70–74] Although many of these studies included older adults, few prospective randomized clinical trials have reported subgroup analyses in older adults or investigated therapeutic options for HCC in this specific population.[75]

5.1 TKIs

5.1.1 First-line TKIs

Sorafenib.: Sorafenib is a multi-kinase inhibitor with activity across vascular endothelial growth factor-2 (VEGF-2) and BRAF.[43] The SHARP trial established sorafenib as the standard of care in advanced HCC in a multicenter, phase 3, double-blind, placebo-controlled trial.[76] A total of 602 patients with advanced HCC and Child-Pugh A cirrhosis were randomized to sorafenib 400 mg twice daily versus placebo.[76] The median age in the sorafenib arm was 64.9 years (+/−11.1) and 66.3 years (+/− 10.1) in the placebo arm.[76] The median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group (HR 0.69; 95% CI: 0.55–0.87; p<0.001).[76] Higher toxicity, such as diarrhea, weight loss, hand-foot skin reaction, anorexia, and voice changes, was observed with sorafenib compared to placebo (p<0.001).[76]

The SHARP study did not publish a subgroup analysis on patients 65 years or older; however, several retrospective studies have been reported (Table 4).[77–82] These retrospective studies demonstrated that the efficacy of sorafenib is preserved in older adults with HCC with OS, TTP, and PFS either not statistically different from younger adults or with historical controls.[77,78,80,82]

Lenvatinib.: Ten years after the approval of sorafenib, lenvatinib, an oral multi-kinase inhibitor that has additional targets including VEGF1–3, fibroblast growth factor (FGFR) 1–4, platelet-derived growth factor (PDGF) receptor alpha, RET and KIT, was approved for first-line treatment of HCC.[70] The REFLECT trial, an open-label, phase 3, multicenter, non-inferiority trial recruited patients with unresectable HCC, with a median age of 62 years (20–88), with 30% of patients 65 to < 75 and 13% were 75+ years of age.[70] Patients received oral lenvatinib (12 mg/day for bodyweight 60 kg or 8 mg/day for bodyweight <60 kg) or sorafenib 400 mg twice daily.[70] The primary endpoint of this study was OS, which showed non-inferiority of lenvatinib when compared to sorafenib.[70] The subgroup analysis showed similar benefit from lenvatinib in patients <65 years versus 65+ years.[70] Although not powered for response rate, lenvatinib (24.1%) showed a higher response rate than sorafenib (9.2%) that was statistically significant (p<0.0001).[70]

The REFLECT study reported a higher rate of hand-foot syndrome among patients treated with sorafenib, while higher rates of hypertension was observed with lenvatinib.[76] Although subgroup analyses in regards to age and adverse events are not reported in HCC, studies of lenvatinib in older adults with thyroid cancer showed that younger lenvatinib-treated patients experienced significantly longer time to first dose reduction (3.7 versus 1.5 months) and lower proportion of grade 3 treatment-related adverse events (67% v 89%; p<0.001) compared with older patients.[83]

In summary, at this time, there are no predictive biomarkers to enable a more personalized choice between the two drugs. Clinicians must consider toxicity profiles when selecting appropriate treatment for older adults with HCC, along with careful evaluation of a patient's comorbidities (i.e., uncontrolled HTN, coronary artery disease, cerebrovascular disease, etc.) that may increase risk of toxicities. Therefore, in older adults with HCC, consider starting at a reduced dose of sorafenib (400 mg daily) or lenvatinib (8 mg daily) with up-titration to full dose as tolerated and close monitoring (i.e., every 1–2 weeks) due to increased toxicity, especially in vulnerable or frail older adults.

5.1.2 Second-line TKIs

Regorafenib.: Regorafenib is an oral pan-kinase inhibitor that blocks both angiogenic (VEGF-1, VEGF-2) and oncogenic (KIT, RET and BRAF) kinases.[84] Regorafenib is now a therapeutic option in HCC patients with Child-Pugh A cirrhosis that have progressed on first-line therapy with sorafenib.[43,71] Efficacy of regorafenib was demonstrated in the phase III RESORCE trial in which patients with advanced HCC and with Child-Pugh A cirrhosis were randomized to regorafenib or placebo as second-line treatment.[71] Regorafenib had a statistically significant median OS of 10.6 months versus 7.8 months with placebo (HR 0.63; 95% CI: 0.50–0.79; p<0.0001).[71] The median age was 64 years (54–71) in the regorafenib arm versus 62 years (55–68) in the placebo arm.[71] For patients 65+ years, the HR for median OS was 0.74 (95% CI: 0.49–0.87), suggesting that older fit patients derived benefit from regorafenib.[71]

All patients on the study had tolerated sorafenib prior to enrolling on this study.[71] Sixty-eight percent of regorafenib-treated patients and 54% of placebo treated patients required dose reductions due to drug toxicity and discontinuation of the treatment was seen in 10%

and 4% respectively.[71] The most common grade 3/4 treatment-related adverse events were hypertension (15%), palmar-plantar erythema (13%), fatigue (9%) and diarrhea (3%).[71] Toxicity profile in older adults with HCC has not been published. The ReDOS study demonstrated improved tolerability with a dose-escalation strategy in metastatic colorectal cancer,[85] which should be further investigated in HCC. Until more data is available, regorafenib may be offered to older patients who tolerated first-line sorafenib, with a consideration to start regorafenib at 80 mg and titrating upward as tolerated.

Cabozantinib.: Cabozantinib is an inhibitor of the MET, AXL and VEGF receptors 1, 2 and 3.[86] It is a second- or third-line systemic therapeutic option for patients with Child-Pugh A cirrhosis with advanced HCC.[72] The double-blind, placebo-controlled phase III CELESTIAL trial led to its FDA approval in January 2019.[72] Median OS was 10.2 versus 8 months (HR 0.76; 95% CI: 0.63–0.92; p=0.005) and median PFS 5.2 months versus 1.9 months (HR 0.44; 95% CI: 0.36–0.52; p<0.001), favoring cabozantinib.[72] Median age in the cabozantinib arm was 64 years (22–86) versus 64 years (24–86) in the placebo arm.[72]

An exploratory sub-group analysis showed that in patients 65+ years, there was benefit in terms of PFS (HR 0.74; 95% CI: 0.56–0.97) and OS (HR 0.46; 95% CI: 0.35–0.59), both favoring cabozantinib over placebo.[72] While 62% of patients required a dose reduction, while 16% discontinued cabozantinib due to toxicity.[72] Grade 3/4 toxicity occurred in 68% with the main adverse events being palmar-plantar erythema (17%), hypertension (16%) and diarrhea (10%).[72] Toxicity data specifically in older adults has not yet been reported. However, it is reasonable to start at 40 mg daily and then titrate up to full dose of 60 mg as tolerated, with close monitoring for toxicity.

5.2 Immunotherapy

Nivolumab.—Nivolumab is a fully human IgG4 monoclonal antibody directed against programmed cell death protein 1 (PD-1), blocking the PD-1 interaction with PD-ligand 1 (PD-L1) and PD-ligand (PD-L2), which results in immune activation.[87] Safety and efficacy of nivolumab as a monotherapy in advanced HCC was investigated in the CheckMate 040, a phase I/II non-randomized trial in patients who were sorafenib naïve, sorafenib refractory or intolerant.[73] Globally, 262 patients were enrolled, with a median age of 64 years in the dose-expansion phase (the primary endpoint was ORR).[73] Forty-seven percent of patients in the expansion phases were older than 65 years.[73] However, there were no age-specific data on toxicity or efficacy published for this trial.

Treatment with nivolumab resulted in ORR of 20% in dose expansion phase (nivolumab at 3 mg/kg every 2 weeks), irrespective of the line of therapy and etiology.[73] The 6-month OS rate was 83% in the dose-expansion phase.[73] Additional analyses showed a median duration of response of 17 months in a sorafenib-naïve group (n=80) and 19 months in patients previously treated with sorafenib (n=182).[73] Nivolumab showed a manageable safety profile, similar to prior reports in other diseases.[73] This led to the FDA granting accelerated approval for the use of nivolumab in patients with advanced HCC previously treated with sorafenib. Building on the favorable results of CheckMate 040, a randomized phase III trial

(CheckMate 459) is underway to investigate nivolumab versus sorafenib as first-line treatment in patients with advanced HCC (NCT02576509).

Pembrolizumab.—More recently, pembrolizumab, another fully human monoclonal IgG4 antibody targeting PD-1 has been investigated in HCC. The single-arm, multi-center phase II trial KEYNOTE-224 assessed safety and efficacy of pembrolizumab in 104 patients with advanced HCC, who received first-line sorafenib.[74] Based on KEYNOTE-224, the FDA granted accelerated approval to pembrolizumab for patients with advanced HCC who have been previously treated with sorafenib. To confirm these findings, a large randomized phase 3 trial (KEYNOTE-240) aimed to assess pembrolizumab versus placebo as a second-line therapy in advanced HCC, with a median age of 67 year (18–91) and 68 years (23–89), respectively.[88] The primary endpoints were median OS and median PFS (with a pre-specified statistical significance met if p=0.0174 and 0.0020, respectively).[88] Median OS was 13.9 months with pembrolizumab versus 10.6 months with placebo (HR 0.781; CI 95%: 0.611–0.998; p=0.0238); and median PFS was 3.0 versus 2.8 months, respectively (HR 0.718; CI 95%: 0.570–0.904; p=0.0022).[88] ORR was 18.3 % with pembrolizumab versus 4.4 % with placebo (p=0.00007).[88] Toxicities were similar to most immune checkpoint inhibitors: elevated liver enzymes, fatigue, nausea, diarrhea and decreased appetite.[88] Although the study did not meet the pre-specified statistical plan for significance, the magnitude of the hazard ratio for survival demonstrates benefit.[88] Therefore, as studies with pembrolizumab continue to mature, this continues to be another option for patients with HCC.

As we await final results of larger studies, efficacy results of immune checkpoint inhibitors are encouraging. Biomarkers, such as PDL-1, are currently not utilized to determine which patients may benefit from immune checkpoint inhibitors.[89] Until this is further validated, immune checkpoint inhibitors may be a good option for older patients intolerant to TKIs or for older adults in whom additional oral medications may be challenging (polypharmacy, noncompliance, cognitive deficits, etc.). Current data from pivotal studies across different tumor types do not show a significant difference in efficacy or toxicity rates in older patients when compared to younger adults, but toxicity management may need to be more tailored in older adults.[90‟93] Future studies with immune checkpoint inhibitors should incorporate subgroup analyses of older adults in regards to efficacy, safety, and quality of life.

5.3   Ramucirumab

Ramucirumab, a human IgG1 monoclonal antibody that inhibits ligand activation of VEGFR2, is approved for second-line treatment in HCC. The REACH-2 is the first positive phase III trial done in a biomarker-selected patient population (AFP of   400 ng/mL) previously received sorafenib.[94] Median age in this study was 63 years (55–71).[94] Median OS was better with ramucirumab versus placebo (8.5 months versus 7.3 months (HR 0.710; 95% CI: 0.531–0.949; p=0.0199).[94] Ramucirumab was well-tolerated, as most common adverse events were fatigue (27%), peripheral edema (25%), hypertension (25%), and decreased appetite (23%).[94] Although age-specific survival and toxicity are not available at this time, this may be a good option for older adults with HCC who develop or are at risk for

toxicities from TKIs, have difficulty with oral home medication regimens or have a contraindication to immunotherapy.

5.4 Clinical trials in HCC

The efficacy of PD-1/PD-L1 inhibitors may be enhanced if used in combination with other systemic therapies. At present, several clinical trials are ongoing with various combinations of PD-1 inhibitors and other immune checkpoint inhibitors, molecular targeted agents and local therapies. Given the increase in the rates of older patients with HCC, and the unique challenges their treatment poses, it is essential for studies to incorporate CGA and focus on subgroup analyses of older adults in regards to efficacy, adverse events, and patient reported outcomes that are specific to the older patient population.

6.0 Incorporation of CGA into the care of older adults with HCC

To the best of our knowledge, there are limited prospective trials investigating systemic therapies for HCC specifically in the older adult population. The development of effective therapeutic strategies in older adults with HCC represents an unmet need, particularly given the rising incidence of HCC in those aged 75 to 85.[95] As outlined in the large clinical trials evaluating systemic therapies, patient stratification was exclusively based on chronological age, without including any form of CGA. Thus, we need to advocate for older adults to be enrolled onto clinical trials, as well as work with pharmaceutical industries to design interventional studies that incorporate CGA.

We do see a trend over the last ten years that subgroup analyses deliberately assess efficacy in older adults; however, we cannot stop there. Clinical trials should also report and publish safety data and patient reported outcomes in older adults, so we can further understand implications of these treatments in this population. Furthermore, since larger studies mostly include very fit older adults without significant comorbidities and organ dysfunction, we need to design studies with CGA dedicated to all older patients, including vulnerable/frail. For example, the GO2 phase III trial was designed to find the optimal dosing of oxaliplatin/capecitabine in frail and older adults with advanced gastroesophageal cancer.[96] In addition to demonstrating similar survival with lower doses, this study evaluated toxicity and quality of life, showing that lower doses correlated with less toxicity and improved quality of life.[96] This study is one example of the feasibility and relevance of novel endpoints, such as toxicity and quality of life, in studies of vulnerable/frail older adults, which may be more meaningful in older adults with gastrointestinal cancers.

In older adults, the competing comorbid condition of cirrhosis makes HCC a challenging disease. Therefore, along with the geriatric assessment and patient preferences, we must also consider disease-related prognostic scores, such CLIP,[44] which will help us determine if the patient would benefit from cancer-directed treatments. Therefore, the multi-disciplinary team-based approach needs to be expanded beyond the oncologic clinicians we typically included in traditional multi-disciplinary tumor boards (Figure 1). Further, as cancer specialists may have time constraints or lack of specialized training in geriatrics, screening tools such as the G8, can help us identify patients who may be vulnerable or frail, and would benefit from a comprehensive assessment by a geriatrician or geriatric oncologist. These

screening tools also help to identify domains that need direct interventions in older adults with HCC. For example, cirrhosis is a complex competing comorbidity, often with sequelae of sarcopenia, hypoalbuminemia, ascites, gastrointestinal bleeding, and encephalopathy.[57] In addition to cancer treatments, these need to be co-managed by the entire treatment team as well. Therefore, incorporation of such assessments into the treatment algorithm for HCC is necessary for directed interventions (Figure 1).

7.0 Conclusions

Generally, older adults with HCC and good performance status seem to tolerate and benefit from standard treatments, including surgery, transplant, local ablative therapies, and systemic treatment, often with multi-modality treatment plans. Geriatric screening tools and CGA need to be prospectively studied as well as incorporated into clinical trials, so we can have a better understanding of how to predict outcomes and safety in older patients whether they be fit, vulnerable or frail. Such clinical interventions and research endeavors are essential to optimize and personalize care for our growing population of older adults with HCC.

Acknowledgements:

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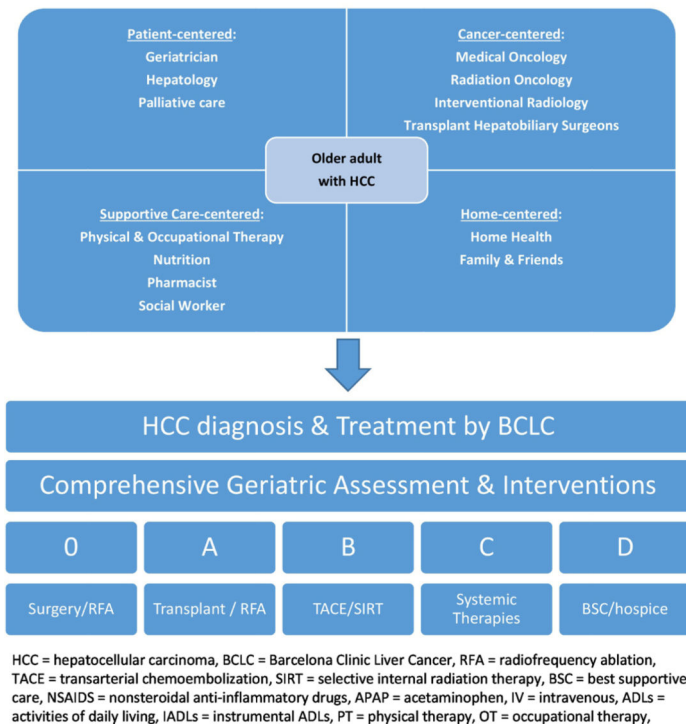
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Figure 1.
Revised treatment paradigm for older adults with HCC

Table 1.

Cancer of the Liver Italian Program (CLIP) scoring system for HCC.[44]

Score	0	1	2
Child-Pugh Score	A	B	C
Tumor morphology	Unilobular and extension 50%	Multinodular and extension 50%	Massive or extension >50%
AFP (ng/ml)	<400	400	----
Portal vein thrombosis	No	Yes	----
Based on total score, median survival: *0 = 42.5 months* *1 = 32.0 months* *2 = 16.5 months* *3 = 4.5 months* *4 = 2.5 months* *5–6 = 1 month*			

AFP = alfa-fetoprotein; ng/ml = nanogram/milliliter

Table 2.

Local ablative therapies in patients with localized HCC.

	Study	Survival	Survival in Older adults
Radiofrequency ablation (RFA)	Cucchetti et al[58]	3-year OS: 76%	n/a
	Mirici-Cappa et al[19]	mOS: 42 mo	n/a
	SURF trial[62]	3-year RFS: surgery 49.8% vs RFA 47.7% (p=0.793)	n/a
Transarterial chemoembolization (TACE)	Llovet et al[63]	2-year survival: 63% vs 27% control (p=0.009)	n/a
	Lo et al[65]	3-year survival: 26% vs 3% control (p=0.002)	n/a
	Zhou et al[97]	n/a	mOS: 21 mo *(70.4 +/− 4.6 years)*
	Mirici-Cappa et al[19]	n/a	mOS: 26 mo *(74.6 +/− 3.9 years)*
Selective internal radiation therapy (SIRT)	SARAH study[67]	mOS: 8.0 mo vs 9.9 mo sorafenib (p=0.18)	n/a
	Golfieri et al[68]	n/a	mOS: 14.5 mo older vs 12.8 mo younger (p=0.942) *(74.3 years ((70–87))*
Stereotactic body radiotherapy (SBRT)	Rajyaguru et al[98]	5-year OS: 29.8% RFA vs 19.3% SBRT (p<0.001)	n/a
	Teraoka et al[69]	n/a	mOS: 52 mo vs NR younger (p=0.27) *(79 years (75–93))*

OS = overall survival, mOS = median overall survival, mo = months, vs = versus, NR = not reached, n/a = not available

Table 3.

Clinical trials of FDA-approved treatments in patients with advanced HCC.

	Median Age (y) (range)	Overall Survival	Time to Progression	Objective Response Rate	Median Duration of Treatment	Survival in Older adults
First-line						
Sorafenib vs Placebo[76]	64.9 (n/a) vs 66.3 (n/a)	10.7 mo vs 7.9 mo (HR 0.69; 95% CI: 0.55–0.87; p<0.001)	5.5 mo vs 2.8 mo (p<0.001)	n/a	5.3 mo	n/a
Lenvatinib vs Sorafenib[70] *(non-inferiority)*	63 (20–88) vs 62 (22–88) *[65y- <75y: 30%; 75+: 13%]*	13.6 mo vs 12.3 mo (HR 0.92; 95% CI: 0.79–1.06; p n/a)	8.9 mo vs 3.7 mo (HR 0.63; 95% CI: 0.53 –0.73; p<0.0001)	24.1 % vs 9.2% (p<0.0001)	5.7 mo	mOS: 14.6 mo vs 13.4 mo (HR 0.84; 95% CI: 0.661.07)
Second-line						
Regorafenib vs placebo[71] *(tolerated prior sorafenib > 20 days at > 400 mg/day)*	64 (54–71) vs 62 (55–68)	10.6 mo vs 7.8 mo (HR 0.63; 95% CI: 0.500.79; p<0.0001)	3.1 mo vs 1.5 mo (HR 0.46; 95% CI: 0.37–0.56; p<0.0001	11% vs 4% (p=0.0047)	3.6 mo	mOS: HR was 0.74 (95% CI: 0.490.87)
Cabozantinib vs placebo[72] *(2nd and 3d line)*	64 (22–86) vs 64 (24–86)	10.2 vs 8 mo (HR 0.76; 95% CI: 0.63–0.92; p=0.005)	5.2 mo vs 1.9 mo (HR 0.44; 95% CI: 0.36–0.52; p<0.001)	4% vs <1% (p=0.009)	3.8 mo	mOS: HR 0.46 (95% CI: 0.350.59)
Ramucirumab vs placebo[94] *(AFP >400 ng/mL)*	64 (58–73) vs 64 (56–71)	8.5 mo vs 7.3 mo (HR 0.710; 95% CI: 0.531–0.949; p=0.0199)	2.8 mo vs 1.6 mo (HR 0.452; 95% CI: 0.339–0.603; p<.0001)	5% vs 1% (p=0.1697)	12 weeks	mOS: HR 0.641 (0.4290.957)
Nivolumab[73]	Expansion phase: 64 (56–70) *[65+: 47%]*	Not reached; 6-mo OS rate was 83%	4.1 mo (95% CI: 3.75.5)	20%	n/a	n/a
Pembrolizumab vs placebo[88]	(18–91) vs (23–89)	13.9 mo vs 10.6 mo (HR 0.781; CI 95%: 0.6110.998; p=0.0238)	3.0 mo vs 2.8 mo (HR 0.718; CI 95%: 0.5700.904; p=0.0022)	18.3% vs 4.4% (p=0.00007)	n/a	n/a

Mo = months, y = years, HR = hazard ratio, CI = Confidence interval, vs = versus, n/a = not available.

Table 4.

Retrospective studies of sorafenib in older adults with advanced HCC.

Author (n=older adults)	Median Age (years) (range)	Baseline Characteristics		Overall Survival	Time to Progression	Toxicity / Dosing
		Patient	Disease			
Wong 2011[82] (n=35)	73 (70–85)	ECOG 0: 25.7% ECOG 1: 60% DM: 31.4% CVD: 45.7%	CPA 62.9% CPB: 37.1% BCLC C: 91.4% Cirrhosisetiology: HCV 11.4% HBV 65.7%	5.32 mo	2.99 mo	Grade 3–4: 68.6% Dose interruption: 42.9%
Di Costanzo 2013[80] (n=60)	73 (70–85)	ECOG 0: 81.7% ECOG 1: 18.3% DM: 31.7% CVD: 46.7% Average Albumin: 3.7	CPA 90% CPB: 10% BCLC C: 76.7% CLIP <3: 60% Cirrhosisetiology: HCV 78.3% HBV 8.3% Non-viral 8.3%	16 mo	12 mo	Grade 3–4: 15.7%
Montella 2013[77] (n=60)	76 (70–90)	ECOG: n/a DM: 28% CVD: 45%	CPA 73% CPB: 22% BCLC C: 22% Cirrhosisetiology: HCV 68% HBV 5% EtOH 1%	10 mo	7 mo	No Grade 2–4 registered Reduced dose: 81.7% At 2 months: lADLs: 15% improved 15% reduced; ADLs: 9% improved 4% reduced
Edeline 2015[78] (n=51)	Median age (range)–n/a 70–74: 53% 75–79: 35% 80+: 12%	ECOG 1: 49% HTN: 54.9% CCI: 51%, 29.4%, 19.6%	CPB: 7.7% Cirrhosisetiology: HCV 5.9% HBV 5.9% EtOH 54.9% NASH 35.3%	12.6 mo	5.6 mo	Grade 3+: 51% Reduced dose: 58.8% Hospitalization: 13.7%
Willet 2017[81] (n=51)	78 (75–92)	ECOG 0: 49% ECOG 1: 49% HTN: 68.6% Average Albumin: 3.6 Median CCI: 14	CPA 84.3% CPB: 3.9% BCLC C: 74.5% Cirrhosisetiology: HCV 5.9% HBV 5.9% EtOH 54.9% NASH 35.3%	15 mo	n/a	Grade 3–4: 66.7% Reduced dose: 41.2% Discontinuation due to toxicity: 60.8%
Arora 2018[79] (n=31)	70 (65–93)	ECOG 0: 38.7% ECOG 1: 51.6% Hispanic: 74%	CPA 71% CPB: 29% BCLC C: 86.1% Cirrhosisetiology: HCV 61% EtOH 52%	13.5 mo	6.2 mo	Grade 3: Fatigue (9.7%) HFS (16.1%) Reduced dose: 70%

n = number, ECOG = Eastern Cooperative Oncology Group, DM = Diabetes mellitus, CVD = cardiovascular disease, CPA = Child-Pugh A cirrhosis, CPB = Child-Pugh B cirrhosis, BCLC = Barcelona Clinic Liver Cancer, CLIP = Cancer of the Liver Italian Program, HCV = hepatitis C virus, HBC = hepatitis B virus, mo = months, n/a = not available, EtOH = alcoholic, IADLs = instrumental activities of daily living, ADLs = activities of daily living, HTN = hypertension, CCI = Charlson Comorbidity Index, NASH = non-alcoholic steatohepatitis, HFS = hand-foot syndrome.