



Review Article

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Management of hepatocellular carcinoma in elderly and adolescent/young adult populations

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Hepatocellular carcinoma (HCC) presents unique challenges in both the elderly and adolescent/young adult (AYA) populations, requiring distinct management approaches. Recent epidemiological data show an increasing incidence of HCC in both age groups, with elderly cases rising significantly and AYA cases showing trends in specific regions. The clinical characteristics and treatment considerations vary substantially among these populations. Elderly patients with HCC typically present with hepatitis C virus infection, metabolic dysfunction-associated steatotic liver disease, well-differentiated tumors, and multiple comorbidities. In contrast, AYA patients with HCC often present with more aggressive tumor characteristics and predominantly with hepatitis B virus-related diseases. Treatment decisions for elderly patients with HCC require careful consideration of physiological reserves, comprehensive geriatric assessments, and potential complications. Recent studies have demonstrated that elderly patients can achieve outcomes comparable to younger patients across various treatment modalities when properly selected. While surgical outcomes are comparable to those of younger patients with proper selection, less-invasive options such as radiofrequency ablation or transarterial therapies may be more appropriate for some elderly patients. The treatment approach for AYA HCC emphasizes curative intent while considering long-term effects. AYA patients require specialized attention to their psychosocial needs, fertility preservation, and long-term health maintenance. Although data on AYA patients remain limited, they are known to have relatively favorable prognoses despite exhibiting more aggressive tumor characteristics. Management of HCC in both the elderly and AYA populations requires individualized approaches that consider age-specific factors. Both groups benefit from multidisciplinary team involvement and careful consideration of quality of life. (*J Liver Cancer* 2025;25:52-66)

Keywords: Carcinoma, hepatocellular; Aged; Adolescent and young adult; Personalized treatment; Clinical outcome

INTRODUCTION

Liver cancer is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide.¹ Hepatocellular carcinoma (HCC) accounts for approximately 90% of all primary liver cancers and constitutes a significant global health burden. Projections suggest that the incidence of HCC will continue to increase, with estimates surpassing 1 million cases by 2025.^{2,3} In the United States, HCC has been identified as the most rapidly rising cause of cancer-related deaths; however, some studies present conflicting findings regarding this trend.⁴⁻⁶ HCC

has been considered a disease that predominantly affects middle-aged individuals, with peak incidence occurring between the ages of 50 and 70 years.⁷ However, recent epidemiological data indicate a shift in the demographic profile of HCC, with an increasing number of cases being reported in age groups outside the middle-aged population.⁶

The management of HCC in these age groups presents unique challenges. Elderly patients with HCC frequently have comorbidities, altered pharmacokinetics, and reduced physiological reserves, which can complicate treatment decisions and outcomes.⁸ In adolescent and young adult (AYA) patients aged 15 to 39 years,

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HCC often presents with more aggressive characteristics and may involve distinct etiological factors, including genetic predisposition, congenital liver disease, or early-onset chronic viral hepatitis.⁹ However, there is a lack of evidence regarding the treatment of HCC in these age groups, and current guidelines do not provide specific recommendations based on age.^{10,11}

As the incidence of HCC continues to increase in young and elderly populations, there is an urgent need to understand better the epidemiology, risk factors, diagnostic approaches, and treatment strategies tailored to these age groups. This review aimed to comprehensively examine the current landscape of HCC management in elderly and AYA patients, focusing on differences in epidemiology, clinical presentation, treatment strategies, and clinical outcomes. Understanding these differences is essential for improving personalized care and optimizing patient outcomes across elderly and AYA age groups.

EPIDEMIOLOGY

Elderly HCC

The definition of elderly varies significantly across different societies and cultures, reflecting the complex nature of aging and the diverse ways in which different populations experience and conceptualize later life stages.¹² The definition of elderly in HCC research varies, with most studies using 65 years as the cutoff, though some now classify patients as elderly starting at 70 or 75 years. Some researchers have further stratified elderly patients with HCC into three subgroups: young-old (75–80 years), middle-old (80–85 years), and oldest-old (85 years and above).¹³ This detailed categorization allows for a more granular analysis of how age impacts HCC presentation, treatment efficacy, and outcomes. The evolving definition of elderly in HCC research has been influenced by several factors. The increasing life expectancy and shifts in HCC epidemiology, with certain etiological factors leading to later disease onset, have driven the redefinition of elderly in HCC research.⁶ Given this diversity in definitions, this review will consider various age thresholds and definitions of elderly as applied in different HCC studies.

Data from the Korean Primary Liver Cancer Registry (KPLCR), which includes a representative cohort of patients newly diagnosed with HCC in Korea from 2008 to 2017, showed that the proportion of elderly patients among the total cohort has steadily increased over time, rising from 33.5% in 2008 to 45.9% in 2017.⁸ A study analyzing data from the Korean National Health Insurance Service database on patients newly diagnosed with

HCC between 2008 and 2018 reported that both crude incidence rate and age-standardized rate (ASR) decreased across most age groups.⁶ However, the ASR in those aged ≥ 80 years showed a marked increase, rising from 70.0 to 160.2 per 100,000 person-years (average annual percent change [AAPC], +9.0%). By 2028, the number of patients with HCC aged ≥ 80 years is expected to increase fourfold, accounting for 21.3% of the total HCC population.

Reports from the Surveillance, Epidemiology, and End Results (SEER) database, which covers less than 30% of the United States population, indicate that the annual percent change (APC) in liver and intrahepatic bile duct cancer incidence for individuals aged 65–74 years was 3.0% from 2000 to 2012, 6.0% from 2012 to 2017, and 2.0% from 2017 to 2021.¹⁴ The AAPC was 4.2% from 2012 to 2021 and 2.0% from 2017 to 2021. In comparison, for individuals aged ≥ 75 years, the APC from 2000 to 2021 was 2.9%, with an AAPC of 2.9% during both 2012–2021 and 2017–2021, showing differences in incidence rate trends between those aged 65–74 years and those aged ≥ 75 years.

An analysis of all 50 states of United States from 2017 to 2021 showed that the age-specific incidence rate of liver and intrahepatic bile duct cancer increased from ages 65 to 69 years, reaching its highest at 80–84 years (43.2 per 100,000 people), followed by 75–79 years (42.8 per 100,000 people).¹⁵ An annual report on cancer occurrence and trends in the United States reported that HCC incidence rates increased by 8% in individuals aged 65–69 years and by 3% in those aged 70 years or older.¹⁶ The incidence rates of HCC in both men and women increased from age 55 to age ≥ 85 years. The epidemiological rise in elderly patients with HCC reflects significant changes in liver disease management and overall population health. Advances in the treatment of chronic liver disease over recent decades have extended life expectancy, thereby increasing the likelihood of developing HCC later in life.

Adolescent and young adult HCC

The National Comprehensive Cancer Network defines AYA patients with cancer as those between the ages of 15 and 39 years.¹⁷ The incidence of HCC in AYAs is significantly lower than that in older adults; however, this incidence has been rising in recent years, indicating a concerning trend. Data from the KPLCR (2008–2017) reported that AYA patients accounted for 2.7% of newly diagnosed HCC cases.⁸ A study that analyzed data from the Global Burden of Disease study between 2010 and 2019 on AYA primary liver cancer found a global estimate of 78,299 pri-

mary liver cancer cases, 60,602 deaths, and 2.90 million disability-adjusted life years in the young population.¹⁸ Globally, the APC of AYA primary liver cancer from 2010 to 2019 was only 0.2%. The Western Pacific region had the highest burden of primary liver cancer, showing the greatest increase in the incidence of AYA HCC compared to that in other regions from 2010 to 2019 (APC, 1.69%). This trend is likely due to the high prevalence of hepatitis B virus (HBV) in the region, as HBV infection is a major risk factor, accounting for over 80% of AYA HCC cases in some studies.¹⁹ Over half of the countries globally have experienced a rise in primary liver cancer incidence among AYAs. However, the APC from 2010 to 2019 was -0.35% in the European region and 0.21% in the American region.¹⁸ In the SEER database, the incidence rate of AYA HCC in the United States has shown only a modest rise, with an APC of 1.0% during 2000-2021 and an AAPC of 1.0% during both 2012-2021 and 2017-2021, respectively.¹⁴

Liver cancer-related deaths accounted for approximately 12.51% of deaths in this age group.¹⁸ While mortality from primary liver cancer due to most causes significantly declined from 2010 to 2019. An increase was observed in cases attributable to metabolic dysfunction-associated steatotic liver disease (MASLD) (APC, +0.87%) and alcohol consumption (APC, +0.21%). According to estimates from the International Agency for Research on Cancer under the World Health Organization, there were 36,302 new cases of liver cancer and 29,603 liver cancer-related deaths among individuals aged 15 to 39 globally in 2020, with an almost 1:1 ratio of new cases to deaths.²⁰ Liver cancer ranks as the fourth most common cancer in this age group. In China, where HBV infection is more prevalent, young individuals account for 48.1% of global liver cancer cases, making liver cancer the leading cause of death in the AYA population (21.59%). The epidemiological trends in AYA HCC are largely attributable to increased hepatitis virus transmission through drug use, alcohol abuse, and the prevalence of obesity.

CLINICAL CHARACTERISTICS

Elderly and AYA patients with HCC exhibit distinct clinical characteristics, leading to differences in prognosis and treatment outcomes (Table 1). Elderly patients with HCC are more likely to have hepatitis C virus (HCV) infection than younger patients, who are more commonly affected by HBV infection.^{21,22} The elderly group also have a higher proportion of non-viral etiologies, including MASLD. This difference is partly attributed to the natural history of liver diseases, as HCV- and MASLD-

related HCC take longer to develop than HBV-related HCC.²² The higher proportion of women among elderly patients with HCC compared to that in AYA patients with HCC may be attributed to women's longer life expectancy.⁸

Elderly patients tend to present with smaller HCCs than younger patients, with tumors in the elderly being more likely to be well-differentiated, encapsulated, and associated with less vascular invasion.²¹ In contrast, AYA HCC often exhibits larger tumor sizes, more aggressive characteristics, and higher alpha-fetoprotein (AFP) levels than elderly patients.²³ In AYA patients, a recent study showed that young men bear a higher burden of HCC and experience worse temporal progression than young women.¹⁸ This disparity can be attributed to several key factors. HCC in younger patients often exhibits higher cellular proliferation rates and faster growth, driven by increased metabolic activity and enhanced signaling pathways that promote tumor progression.²⁴ In addition, genetic factors also contribute, as younger patients tend to have a higher prevalence of genetic mutations and chromosomal instability, which are associated with more aggressive tumor characteristics.²⁵ While younger patients generally have more robust immune responses, which can paradoxically create selective pressure, favoring the survival and growth of more resistant and aggressive tumor cells.²⁶ AYA HCC is predominantly linked to HBV infection, which drives more aggressive tumor behavior. In contrast, HCC in elderly patients is more commonly associated with HCV or MASLD, which typically exhibit less aggressive tumor dynamics. Finally, younger patients are less likely to undergo routine health screening, resulting in delayed diagnosis at more advanced stages of the disease.

The aging liver undergoes significant structural, functional, and cellular changes that impair its ability to maintain homeostasis and respond to stress.²⁷ Structural shrinkage, reduced hepatic blood flow, and decreased bile acid secretion weaken digestive processes, while reduced cytochrome P450 activity limits drug metabolism.²⁸ Aging hepatocytes exhibit increased polyploidy and apoptosis, with metabolic shifts such as reduced gluconeogenesis and increased lipid accumulation, leading to hepatic steatosis.²⁹ Mitochondrial dysfunction, including fewer mitochondria, increased oxidative stress and diminished mitophagy, further compromises cellular health.³⁰ Immune function declines, characterized by impaired antigen presentation, reduced phagocytosis, and heightened production of pro-inflammatory cytokines, contributing to a pro-inflammatory state.³¹ Additionally, autophagy processes are disrupted, resulting in the accumulation of cellular waste.³² These age-related changes sig-

nificantly affect the liver's capacity to manage disease progression and influence treatment outcomes in elderly patients with HCC.

Elderly patients have a higher prevalence of comorbidities than AYA patients with HCC. A study of KPLCR data found that elderly patients had a significantly higher prevalence of diabetes and hypertension than non-elderly patients.⁸ Specifically, 34.8% of elderly patients had diabetes compared to 21.0% of non-elderly patients, while 52.4% of elderly patients had hypertension compared to 23.8% of non-elderly patients. AYA patients with HCC, on the other hand, tend to have fewer comorbidities at diagnosis than patients with HCC in other age groups.⁹ However, 40% of AYA cancer survivors develop multiple chronic conditions within 10 years of their diagnosis, compared to 20% of their peers without cancer.³³ Although specific data on the prevalence of comorbidities in AYA patients with HCC are not available, studies on AYA cancer survivors, encompassing various types of cancers, suggest general trends. AYA cancer survivors are two to three times more likely to experience cardiovascular complications such as cardiomyopathy and stroke than individuals without cancer.³³ Additionally, nearly half of AYA cancer survivors (47%) are overweight or obese at baseline, indicating a substantial risk of metabolic disorders such as diabetes and hyperlipidemia.⁸ Mental health issues are also prevalent, with 31% of AYA cancer survivors reporting mental health comorbidities.³⁴ Therefore, when determining treatment strategies for elderly patients with HCC, it is essential to consider their comorbidities to minimize complications associated with treatment. AYA patients with HCC face a higher risk of developing chronic conditions over time, highlighting the need for regular monitoring and follow-up care.

TREATMENT STRATEGIES

Elderly HCC

A study using KPLCR data showed that elderly patients with HCC received less aggressive treatment after diagnosis, with a higher proportion remaining untreated than non-elderly patients (25.2% vs. 16.7%) (Table 2).⁸ However, median overall survival (OS) was significantly longer in elderly patients who underwent treatment (38.6 months in the treated group vs. 22.3 months in the untreated group). Therefore, it is important to carefully select elderly patients who can benefit from treatment and adopt a more proactive approach to manage their disease. However, several factors must be carefully considered when determining the

treatment approach or whether to treat elderly patients with HCC.

Personalized treatment plans

Managing elderly patients with HCC presents the challenge of carefully evaluating the benefit-risk ratio and determining when the potential benefits of treatment outweigh the risks of toxicity in this population. This is particularly complex because of reduced life expectancy and diminished ability to adapt to physical and psychological stress. Such assessments are even more challenging in older adults and necessitate the use of specialized tools tailored to their needs.

In elderly patients with HCC, potential age-related decline in liver function plays a crucial role in determining treatment decisions. Models such as the Child-Pugh score, model for end-stage liver disease (MELD) score, and albumin-bilirubin score are useful for assessing liver function.^{35,36} In addition, the etiology of the underlying liver disease must also be considered, as it can influence treatment choices and outcomes. The tumor characteristics, including the number, size, and location of nodules and the presence of vascular invasion or metastasis, are critical for treatment planning. Additionally, the patient's immune status is a significant consideration, as it can impact the tolerability of specific therapies and overall prognosis. The Barcelona Clinic Liver Cancer (BCLC) staging system can help determine the most suitable treatment by integrating liver function, performance status, and tumor characteristics.³⁷

Comorbidities are another important factor in characterizing elderly patients, although there remains a debate regarding the best methods to define and stratify the risk of mortality based on the number and severity of these conditions.³⁸ The comprehensive geriatric assessment (CGA) is one of the most widely recognized methods for identifying frailty, a state of vulnerability to poor resolution of homeostasis following stress or an event.³⁹ CGA offers a multidimensional and interdisciplinary evaluation of an older adult's health status. This process encompasses the assessment of physical function, cognitive ability, comorbidities, medication use, nutritional status, psychological wellbeing, and social support. Key daily activities such as eating, bathing, managing finances, and using a telephone are also evaluated using tools such as activities of daily living (ADLs) and instrumental ADLs. Based on CGA findings, patients are categorized as fit, vulnerable, or frail. Fit patients are deemed suitable for standard treatment regimens, vulnerable patients may require tailored or modified approaches, and frail patients often benefit more from supportive care focused on symptom management and improved

quality of life. By combining insights from CGA with HCC-specific considerations, clinicians can formulate highly individualized treatment strategies. Personalized treatment plans for elderly patients with HCC enhance patient autonomy, minimize the risks of under- or overtreatment, reduce mortality, and improve overall outcomes.

Early-stage HCC

Treatment options for BCLC stage 0 or A HCC include liver resection, liver transplantation (LT), and local ablation.³⁷ The BCLC classification does not specify whether age influences treatment decisions, and the available scientific evidence on this matter remains inconclusive. KPLCR data showed that surgical treatments, including liver resection and transplantation, were performed at a lower rate in elderly patients than in non-elderly patients (23.9% vs. 39.5%) with very early and early-stage HCC.⁸ Conversely, elderly patients were more likely to receive transarterial therapy than non-elderly patients (45.0% vs. 36.3%). The use of local ablation therapy was similar between the two groups, performed in 19.2% of elderly patients and 19.0% of non-elderly patients. In patients with early-stage HCC, elderly patients had a significantly shorter median OS compared to non-elderly patients (41.6 vs. 111.6 months). However, among elderly patients, those who received treatment for HCC had a significantly longer median OS than those who did not (44.7 vs. 21.3 months).

Surgical resection

Surgical resection is the preferred treatment for localized HCC in patients without cirrhosis. For those with cirrhosis, it is recommended in cases of limited tumor burden, well-compensated liver function, absence of significant portal hypertension, and

sufficient future liver remnant volume.⁴⁰ For surgical resection in elderly patients with HCC, careful consideration of age-related liver changes is required, as factors like reduced hepatic blood flow, diminished bile acid secretion, and impaired immune function can impact surgical outcomes and recovery.⁴¹ Proper patient selection, considering tumor characteristics (size, number, location), liver function, hepatic reserve, and the presence or severity of portal hypertension, is crucial for achieving favorable surgical outcomes in elderly patients with HCC.⁴² In addition, the patient's overall performance status, comorbidities, and the estimated future liver remnant volume must be thoroughly evaluated to ensure suitability for surgical intervention.

According to KPLCR data, the proportion of elderly patients with HCC undergoing surgery was lower than that of non-elderly patients, with rates of 13.9% vs. 25.6% for BCLC stage 0 and 26.3% vs. 43.0% for BCLC stage 1.⁸ This discrepancy is likely due to concerns about higher operative risks and shorter expected survival in older patients. In early-stage patients with HCC who underwent surgical resection, the median OS was significantly shorter in elderly patients than in non-elderly patients, both before (86.3 vs. 133.9 months) and after the inverse probability of treatment weighting (IPTW) analysis (97.4 vs. 138.0 months). The 1-year and 5-year OS rates were 83.8% and 65.1% in elderly patients and 90.9% and 75.4%, respectively, in non-elderly patients with HCC.

However, a meta-analysis of 42 studies involving 7,778 elderly patients found similar OS outcomes between elderly and non-elderly patients, with 1-year and 5-year OS rates of 86.0% and 51.6% in elderly patients and 86.6% and 53.8% in non-elderly patients with HCC.⁴³ This difference may be attributed to variations in liver disease etiology among elderly patients with HCC

Table 1. Clinical characteristics of elderly and AYA patients with HCC

Characteristic	Elderly	Early-onset
Etiology	HBV is less common HCV or MASLD are more common	Predominantly HBV
Comorbidities	High prevalence of diabetes, hypertension	Fewer at diagnosis but higher risk of long-term chronic conditions
Tumor size	Smaller	Larger
Vascular invasion	Less frequent	More frequent
Tumor characteristic	Less aggressive	More aggressive
Alpha-fetoprotein	Lower levels	Higher levels
Family history	Less frequent	More frequent
Genetic predisposition	Less likely to have genetic risk factors	More frequent association with genetic mutations

AYA, adolescent and young adult; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 2. Key study findings on clinical outcomes in elderly and AYA patients with HCC

Study	Database	Comparator	Number of patients	Overall survival			Disease or recurrence-free survival				Adverse event (%)	
Surgical resection												
Lee et al. ⁸ (2023)	KPLCR	Elderly (≥65 years)	681	1-year (%)	3-year (%)	5-year (%)	1-year (%)	3-year (%)	5-year (%)	All	Major	Minor
		Non-elderly (<65 years)	1,708	83.8	71.9	65.1	-	-	-	-	-	-
Garcia et al. ⁴³ (2025)	Meta-analysis	Elderly (≥65 years)	6,636	90.9	83.6	75.4	-	-	-	-	-	-
		Non-elderly (<65 years)	19,659	86.6	64.7	51.6	74.2	44.6	30.2	34.0	14.5	21.9
Zeng et al. ⁸⁹ (2020)	Hospital	Non-elderly (<65 years)	699	86.0	64.7	53.7	67.3	43.8	31.5	24.2	12.2	13.7
Commander et al. ⁹⁰ (2022)	National Cancer Database	AYA (≤40 years)	3,805	81.2	61.0	45.3	54.7	39.7	28.2	-	-	-
		Older (>40 years)	3,805	86.4	65.3	47.7	63.8	41.1	28.0	-	-	-
		AYA (21-40 years)	1,102	70.0	54.0	48.0	-	-	-	-	-	-
		Pediatric (<21 years)	241	81.0	65.0	55.0	-	-	-	-	-	-
Radiofrequency ablation												
Lee et al. ⁸ (2023)	KPLCR	Elderly (≥65 years)	550	1-year (%)	3-year (%)	5-year (%)	1-year (%)	3-year (%)	5-year (%)	All	Major	Minor
		Non-elderly (<65 years)	838	80.8	65.3	50.8	-	-	-	-	-	-
Hung et al. ⁵² (2015)	Meta-analysis	Elderly (≥70-80 years)	932	Odds ratio (95% CI)			-	-	-	1.018	-	-
		Non-elderly (<70-80 years)	2,206	1.5	1.35	1.37	(0.78-2.88)	(0.94-1.94)	(1.07-1.76)	(0.52-1.98)	-	-
							Reference	-	-	-	-	-
Microwave ablation												
Wang et al. ⁵⁷ (2020)	Hospital	Elderly (≥65 years)	510	1-year (%)	3-year (%)	5-year (%)	1-year (%)	3-year (%)	5-year (%)	All	Major	Minor
		Non-elderly (<65 years)	1,053	95.0	64.0	34.1	67.0	33.7	17.5	-	-	-
Zhang et al. ⁵⁸ (2020)	Hospital	Elderly (≥75 years)	70	95.5	65.3	45.8	66.8	37.2	24.4	-	-	-
		Non-elderly (<75 years)	810	Median (months, 95% CI)			15.8 (5.2-30.1)			5.7	-	-
							42.4 (25.7-61.0)	18.9 (7.6-36.0)	3.0	-	-	
Transarterial therapy												
Lee et al. ⁸ (2023)	KPLCR	Elderly (≥65 years)	522	1-year (%)	3-year (%)	5-year (%)	1-year (%)	3-year (%)	5-year (%)	All	Major	Minor
		Non-elderly (<65 years)	644	70.7	48.6	31.6	-	-	-	-	-	-
Liu et al. ⁶⁷ (2014)	Hospital	Elderly (≥75 years)	812	72.3	56.8	43.4	-	-	-	-	-	-
		Non-elderly (<75 years)	2,270	57	42	39	-	-	-	-	-	-

Table 2. Continued

Study	Database	Comparator	Number of patients	Overall survival			Disease or recurrence-free survival			Adverse event (%)	
Chemotherapy											
Lee et al. ⁸ (2023)	KPLCR	Elderly (≥65 years)	150	1-year (%)	3-year (%)	5-year (%)	1-year (%)	3-year (%)	5-year (%)		
		Non-elderly (<65 years)	381	63.2	31.6	14.1	-	-	-		
Tada et al. ⁷⁵ (2022)	Hospital	Elderly (≥75 years)	143	3 months (%)	6 months (%)	9 months (%)	3 months (%)	6 months (%)	9 months (%)		
				95.8	90.0	83.9	76.6	50.3	-		
		Non-elderly (<75 years)	174	96.5	89.5	80.8	74.8	54.2	-		
				50 days (%)	100 days (%)	200 days (%)	50 days (%)	100 days (%)	200 days (%)		
Tada et al. ⁷⁸ (2020)	Hospital	Elderly (≥75 years)	50	93.3	93.3	79.3	91.3	64.3	47.1		
		Non-elderly (<75 years)	50	97.9	95.2	78.6	90.9	68.4	57.7		
Comparative study											
Ahmed et al. ⁴⁹ (2023)	National Cancer Database	Surgical resection	4,760	Median (months)	Hazard ratio (95% CI)		Median (months)	Hazard ratio (95% CI)		Odds ratio (95% CI)	
		Local ablation therapy	5,272	54.4	0.65 (0.57-0.73)*		-	-		-	-
Yoo et al. ⁵⁰ (2024)	Meta-analysis	Surgical resection	-	38.8	Reference		-	-		-	-
		RFA	-	60.0	1.44 (1.22-1.70)		31.0	1.40 (1.00-1.97)		Reference	Reference
Khan et al. ⁶⁰ (2023)	National Cancer Database	Surgical resection	4,674	60.0	Reference		26.3	Reference		0.22 (0.13-0.36)	0.33 (0.11-0.81)
		Liver transplantation	416	61.4	Reference		-	-		-	-
Luo et al. ⁵⁹ (2022)	Hospital	RFA	111	97.9	0.70 (0.59-0.82)*		-	-		-	-
		Cryoablation	112	1-year (%)	3-year (%)	5-year (%)	1-year (%)	3-year (%)	5-year (%)	All	Major
				90.0	68.0	63.0	59.0	28.0	20.0	-	5.0
				90.0	75.0	62.0	59.0	32.0	25.0	-	6.0

AYA, adolescent and young adult; HCC, hepatocellular carcinoma; KPLCR, Korean Primary Liver Cancer Registry; CI, confidence interval; RFA, radiofrequency ablation.

*For mortality.

included in the two studies. The meta-analysis included a population with 23.45% HBV and 38.6% HCV, whereas the KPLCR data showed 33.8% HBV and 17.7% HCV in elderly patients. Additionally, the KPLCR data included more recent cases from 2008 to 2017, whereas the meta-analysis included studies with older timeframes, which may further account for the observed differences.

In a meta-analysis, no significant differences were observed in recurrence-free survival, with 1-year rates of 67.3% vs. 74.2% and 5-year rates of 31.6% vs. 30.2% between the two groups.⁴³ However, elderly patients experienced a higher rate of minor complications (21.9% vs. 13.7%), while major complication rates remained comparable. These results may be attributed to recent advances in surgical techniques and perioperative management as well as the implementation of more careful selection criteria for elderly patients. In clinical practice, careful patient selection combined with a multidisciplinary approach is important to achieve acceptable mortality and morbidity outcomes and increasing the proportion of patients eligible for curative therapies. Perioperative assessment tools, such as the American Society of Anesthesiologists score, physiological and operative severity score for the enumeration of mortality and morbidity (POS-SUM/P-POSSUM), estimation of physiologic ability and surgical stress (E-PASS), and acute physiology and chronic health evaluation (APACHE II) scores, play a key role in assessing elderly patients.⁴⁴ Studies and meta-analyses of randomized controlled trials on enhanced recovery after liver surgery have further highlighted its benefits, including improved postoperative morbidity rates, shorter hospital stays, and faster functional recovery.

Over the past decade, laparoscopic and robotic techniques have been increasingly utilized in liver surgery to reduce surgical stress, improve outcomes, and demonstrate safety and effectiveness.^{45,46} Recent studies have highlighted the feasibility of these techniques in elderly patients. A Korean propensity score matching analysis reported shorter hospital stays in elderly patients, with no differences in OS, disease-free survival (DFS), or complication rates between laparoscopic and open hepatectomy.⁴⁷ Another propensity score matching study also observed fewer major complications and shorter hospital stays in elderly patients with HCC treated with laparoscopic liver resection.⁴⁸ These findings support laparoscopic and robotic surgery as viable and safe alternatives to open hepatectomy, emphasizing the need for clear selection criteria to maximize benefits for elderly patients.

Finally, elderly patients with HCC undergoing liver resection require specialized postoperative care to optimize outcomes and

minimize complications. This includes close monitoring in the intensive care unit, respiratory care with early ambulation and respiratory exercises, infection control, nutritional support, regular cognitive assessments, and management of comorbidities.

Local ablation therapy

Patients with solitary HCC who are not candidates for surgery or choose not to undergo surgery should be evaluated for curative ablative therapies.¹⁰ An ablation-first approach may be appropriate for patients with centrally located tumors requiring major hepatectomy or those with very early-stage HCC. A recent study using the National Cancer Database, which included 10,032 elderly patients (≥ 70 years) with HCC, showed that hepatic resection was associated with improved OS (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.57-0.73) compared to radiofrequency ablation (RFA).⁴⁹ Furthermore, the survival benefit of hepatic resection persisted even after 1:1 propensity score matching. A meta-analysis of 13 studies involving 4,903 elderly patients (≥ 65 years) with HCC showed that the surgery group demonstrated superior OS (HR, 1.44; 95% CI, 1.22-1.70) and DFS (HR, 1.40; 95% CI, 1.00-1.97) compared to the RFA group.⁵⁰ This advantage was also observed in patients with small HCC (tumors less than 3 cm), where the surgery group had better OS (HR, 1.42; 95% CI, 1.00-2.03) and DFS (HR, 1.32; 95% CI, 0.91-1.91). However, adverse events were significantly lower in the RFA group (odds ratio [OR], 0.22; 95% CI, 0.14-0.36), leading to shorter hospital stays (mean difference, 14.88 days; 95% CI, -22.44 to -7.32).

The significant benefit of surgical resection is its ability to remove potential venous tumor thrombi, achieve complete tumor resolution with clear margins, and provide valuable histopathological information. Although elderly patients with more comorbidities may be less suitable for surgery,¹⁰ Therefore, RFA offers several advantages, including minimal invasiveness, reduced blood loss, lower perioperative risk, and less impact on liver function.⁵¹ Therefore, local ablation therapy may be a more practical and appropriate option than surgical resection for certain elderly patients.

According to KPLCR data, after IPTW analysis, the median OS in elderly patients who underwent local ablation therapy was comparable to that of non-elderly patients (82.2 vs. 105.5 months).⁸ A meta-analysis including five studies of patients who underwent RFA found no significant differences in 1-year (OR, 1.5; 95% CI, 0.788-2.885) and 3-year OS (OR, 1.352; 95% CI, 0.940-1.944) between elderly and non-elderly patients undergoing RFA for HCC.⁵² However, at 5 years, younger patients showed

significantly better clinical outcomes (OR, 1.379; 95% CI, 1.079–1.763). Another study also reported higher 5-year mortality in elderly patients, and further analysis revealed that this difference was primarily due to liver-unrelated deaths in the elderly group.⁵³ Regarding safety, recent studies and meta-analyses have indicated no significant differences in hospitalization duration or serious adverse events between elderly and younger patients with HCC treated with RFA.^{52,54}

Microwave ablation (MWA) is more effective than RFA in achieving higher intra-tumoral temperatures, larger ablation volumes, and shorter procedure times, with an improved convection profile.⁵⁵ However, complications such as liver failure, bleeding, infection, abscess formation, bile duct stenosis, and organ injury occur in 2–3% of cases.⁵⁶ A retrospective study of elderly patients with HCC treated with MWA found no significant differences in OS between elderly (>65 years) and non-elderly (<65 years) patients with HCC.⁵⁷ However, elderly patients had higher rates of HCV infection, comorbidities, cirrhosis, larger tumors, poorer liver function, more ablation points, longer ablation times, and greater hospitalization costs. Another study demonstrated that elderly patients (>75 years), even those with significant comorbidities, benefited from MWA similarly to non-elderly patients, with no significant differences in complete ablation rates, major complications, OS, or progression-free survival (PFS) after matching over an 8-year follow-up.⁵⁸

Cryoablation is a type of local ablation therapy. In a prospective multicenter study including 223 patients aged ≥70 years with small HCC and no metastasis, the local tumor progression (LTP) rates at 1, 3, and 5 years were similar between the two groups (12%, 17%, and 20% for cryoablation and 17%, 18%, and 21% for RFA, respectively).⁵⁹ However, for tumors >3 cm in diameter, LTP rates at 1 and 3 years were significantly lower with cryoablation (13% and 22%) than with RFA (22% and 42%, respectively). The OS rates at 1, 3, and 5 years were comparable between the two groups (90%, 75%, and 62% for cryoablation and 90%, 68%, and 63% for RFA, respectively).

LT

LT is an ideal treatment option for patients with early-stage HCC who cannot undergo resection due to liver dysfunction or tumor multifocality, as it addresses both cancer and the underlying liver disease.¹⁰ Although LT offers better long-term survival than hepatic resection or local ablation, elderly patients are rarely considered for LT because of their lower priority in the context of limited organ availability. However, over the past 15 years, the age of liver transplant recipients has steadily increased in

both the United States and Europe.²⁷ In the United States, the proportion of liver transplant recipients aged 65 years or older increased from 9% in 2002 to 20% in 2017. Similarly, within the Eurotransplant region, the proportion of liver transplant recipients aged 65 or older increased by 16% between 2012 and 2016.

A study using the National Cancer Database analyzed elderly patients (≥70 years) diagnosed with HCC, including 4,674 who underwent resection and 416 who received LT.⁶⁰ In the study, patients receiving LT demonstrated significantly better OS and longer median survival (97.9 months for LT vs. 65.6 months for resection), suggesting that LT provides superior survival outcomes for well-selected elderly patients with HCC. However, in studies examining overall LT recipients, including those with HCC, while 1-year post-transplant outcomes were comparable between patients younger and older than 60 years, 5-year survival rates were consistently and significantly lower in recipients aged 60–70 years or older.^{61–63} The survival gap between elderly and non-elderly patients with HCC widens over time. In older transplant recipients, the decline in 5-year survival probability mirrors that observed in the general population of similar age groups. Early mortality is particularly high in elderly patients with high MELD scores (>25–28), although such scores do not appear to significantly affect late mortality risk in this population.^{64,65}

LT eligibility should not be determined by age alone; other factors, such as liver function, comorbidities, and perioperative risks, must be considered. However, the use of LT in elderly patients remains a topic of debate because of the shortage of liver donors, and the upper age limit for transplantation has yet to be clearly defined.⁶⁶

Intermediate-stage HCC

Intermediate-stage HCC is highly heterogeneous, with prognosis influenced by AFP levels and liver function impairment, even within Child-Pugh class A.³⁷ However, there are no strict cut-offs to guide treatment selection, and decisions regarding LT, transarterial chemoembolization (TACE), or systemic therapy must be individualized. According to KPLCR data, transarterial therapy was performed in 63.0% of elderly patients and 63.8% of non-elderly patients, while surgical resection was conducted in 11.0% of elderly and 15.7% of non-elderly patients with intermediate-stage HCC.⁸ In patients with intermediate-stage HCC, elderly patients had a significantly shorter median OS than non-elderly patients (34.5 vs. 49.7 months). The median OS was significantly longer in the elderly patients who received treatment for HCC than in those who remained untreated (36.5 vs. 28.4

months). In IPTW analyses, OS was comparable between elderly and non-elderly patients undergoing surgery, with a median OS of 66.0 vs. 90.3 months. Similarly, for patients receiving transarterial therapy, IPTW analysis showed no significant difference in OS between the two groups, with a median OS of 36.5 months in elderly patients and 37.2 months in non-elderly patients.

In a retrospective study of 875 patients who received TACE as their primary therapy (604 non-elderly and 271 elderly patients with HCC), long-term survival outcomes were comparable between the two groups.⁶⁷ The estimated 1-, 3-, and 5-year survival rates were 79% vs. 84%, 57% vs. 57%, and 42% vs. 39% for non-elderly and elderly patients, respectively.⁶⁷ A prospective study of 102 patients who underwent TACE as their first treatment also showed similar survival outcomes between elderly and younger patients, with age not associated with an increased rate of adverse events.⁶⁸ Although randomized controlled trials are limited, existing studies suggest that the cumulative risk of liver-related mortality and adverse events after TACE is comparable between elderly and younger patients. Therefore, TACE remains the preferred treatment option for elderly patients with intermediate-stage HCC. In addition, for patients who are eligible for resection but have a high perioperative risk, TACE can serve as an alternative due to its safety profile and the increased risk of surgical complications in this population.

Transarterial radioembolization (TARE) is often considered a safer alternative to TACE in patients with HCC because of its favorable safety profile and reduced treatment-related complications.⁶⁹ One key advantage of TARE is its lower incidence of post-embolization syndrome, which includes fever, abdominal pain, nausea, and vomiting, and can be particularly challenging for elderly patients with reduced physiological reserves. In contrast to TACE, TARE delivers targeted radiation without causing significant ischemic damage, thereby reducing the risk of liver dysfunction. TARE is better tolerated than TACE, with fewer complications and hospitalizations, making it a viable option for frail elderly patients. As an outpatient procedure, it also minimizes hospital stay and associated risks. Additionally, TARE offers comparable or superior tumor control and overall survival while avoiding the systemic toxicity of chemotherapy.⁷⁰ Although research on elderly patients with HCC remains limited, TARE may be a more suitable treatment option, particularly for those at higher risk of adverse events from TACE.

Advanced-stage HCC

Advanced-stage HCC includes patients with vascular invasion

or extrahepatic spread who remain relatively fit, as indicated by a performance status of <2 at staging, and those with preserved liver function.³⁷ Patients with BCLC-C should be considered for systemic therapy, with various effective first-, second-, and subsequent-line treatment options available for those meeting the criteria established in clinical trials leading to regulatory approval. However, KLPCR data showed that the most commonly received treatment for advanced-stage HCC was transarterial therapy, with 34.9% of elderly and 42.9% of non-elderly patients undergoing this treatment.⁸ Systemic therapy was administered to 16.5% of elderly patients and 21.2% of non-elderly patients. Since the data were collected between 2008 to 2017, the proportion of patients receiving systemic therapy is expected to have increased in recent years.

In KPLCR data, elderly patients had a significantly shorter median OS than non-elderly patients (24.3 vs. 31.4 months).⁸ However, elderly patients who received treatment had a significantly longer median OS than those who remained untreated (31.4 vs. 22.3 months). In IPTW analysis, OS was comparable between elderly and non-elderly groups treated with transarterial therapy (28.4 vs. 33.5 months). Similarly, IPTW analysis indicated that the median OS in elderly and non-elderly patients treated with chemotherapy was comparable (25.3 vs. 26.3 months).

The preferred first-line treatment is the combination of atezolizumab and bevacizumab (Atezo-Bev) or durvalumab and tremelimumab. The Atezo-Bev combination showed superior survival benefits compared to sorafenib, though it has not been directly compared with lenvatinib.⁷¹⁻⁷³ Patients eligible for Atezo-Bev must have preserved liver function (Child-Pugh A in cases of underlying cirrhosis) and no high-risk factors for bleeding on upper endoscopy, such as untreated esophageal varices or a history of variceal bleeding.⁷⁴ A multicenter retrospective study of 317 patients with HCC treated with Atezo-Bev found that elderly patients did not have worse OS or PFS, as shown by IPTW-adjusted univariate analysis (HR, 1.239; 95% CI, 0.640-2.399 for OS and HR, 1.256; 95% CI, 0.871-1.811 for PFS).⁷⁵ Additionally, treatment-related adverse events were similar between elderly and non-elderly patients. In addition, a subgroup analysis of elderly patients aged 75-79, 80-84, and ≥ 85 years revealed no significant differences in cumulative OS or PFS among these age groups, except proteinuria, which differed across groups.

Durvalumab and tremelimumab, another first-line treatment option for unresectable HCC, have demonstrated a significant OS benefit compared to sorafenib.⁷⁶ Although data on elderly patients are limited, the STRIDE study included 50.4% of patients classified as elderly. In a retrospective study including 120

patients with unresectable HCC, treatment-related adverse events by age group (<70 vs. ≥70 years) showed no significant differences between the two groups, suggesting comparable tolerability regardless of age.⁷⁷

If treatment with Atezo-Bev or durvalumab-tremelimumab is not feasible, lenvatinib can be used as a first-line chemotherapy option for HCC.¹⁰ A propensity score-matched study of 100 patients receiving lenvatinib included 50 elderly patients (≥75 years) and 50 non-elderly patients.⁷⁸ There were no significant differences in the frequency of adverse events between elderly and non-elderly patients. Similarly, OS and PFS did not differ significantly between the two groups (HR, 0.972; 95% CI, 0.374-2.529 and HR, 1.362; 95% CI, 0.687-2.700, respectively).

The efficacy and safety of Atezo-Bev and lenvatinib in elderly patients are comparable to those in non-elderly patients, indicating that advanced age alone is not a reason to limit chemotherapy. However, elderly patients with HCC require careful evaluation when considering systemic therapy due to their increased susceptibility to treatment-related adverse effects. A thorough assessment of underlying conditions and risk factors is essential to determine the most appropriate treatment while minimizing potential complications.

AYA HCC

The treatment of AYA patients with HCC should be individualized, considering both the aggressive nature of the disease in younger patients and the potential long-term impact of treatment. A multidisciplinary approach involving hepatologists, surgeons, and supportive care specialists is essential for optimal management. Given their younger age and generally better overall health, curative treatment should be prioritized whenever possible.

Treatment approaches

Compared with other age groups, AYA patients require specialized attention in treatment strategies, family counseling, psychological and behavioral support, and nursing care.⁷⁹ Certain AYA patients may tolerate more intensive therapies, compared to older adults, as they generally have fewer comorbidities that could limit treatment intensity.⁸⁰ Therefore, if intensive treatment is available for a specific disease and no contraindications exist, it may be a viable option for select AYA patients. Surgical resection, including hepatectomy, is often the preferred first-line treatment for localized diseases. LT is another viable option, particularly for AYA patients with cirrhosis or decompensated liver dis-

ease, provided that their tumor burden remains within internationally accepted criteria. However, AYA patients with HCC face unique challenges after LT, as they require lifelong immunosuppressive therapy and its associated complications for a much longer period than older patients. This prolonged risk increases their vulnerability to infections, metabolic disorders, and long-term complications, making continuous monitoring and management essential throughout their lifetime.⁸¹ For advanced-stage HCC, newer combination therapies, including immunotherapy, are also being evaluated and may offer promising results in AYA patients.

AYA patients should receive care from a multidisciplinary team specializing in AYA cancer treatment and addressing age-specific developmental concerns such as fertility, sexual health, education, career development, employment, family planning, pregnancy, sexually transmitted diseases, and substance use disorders.⁸² Upon cancer diagnosis, AYA patients should undergo a comprehensive assessment, which includes a psychosocial evaluation, discussion of cancer and treatment-related risks to fertility and sexual function, and education on fertility preservation methods and contraception. A thorough family history should be documented, and referrals for genetic counseling and familial risk assessment should be considered if needed.⁸³ They also face important decisions regarding their education, career, and employment. Throughout treatment, it is essential that AYA patients have the opportunity to remain as normal as possible, continue their studies or careers, and participate in key life events.⁸⁴ Physical and occupational therapy can play a vital role in helping them transition back to an age-appropriate lifestyle.⁸⁵ Pregnancy testing should be conducted before each treatment cycle per institutional protocol, with referrals to fertility preservation or reproductive health programs as needed.⁸⁶

AYA patients with cancer may engage in risky behaviors such as tobacco, alcohol, cannabis, or substance use, which can negatively impact their health. Due to both treatment- and lifestyle-related factors, AYA cancer survivors face a significantly higher risk (up to 5 to 15 times greater) of developing cardiovascular disease compared to the general population.⁹ As a result, lifestyle and dietary modifications are essential for improving long-term survival.⁸⁷ Encouraging healthy lifestyle behaviors, including regular physical activity during and after treatment, can provide both physical and psychological benefits.⁸⁸

Prognosis of AYA HCC

However, the effect of age at onset on the prognosis of liver cancer remains controversial. Some researchers have suggested that

younger patients with HCC have worse prognoses, with higher recurrence rates even after surgical treatment.^{89,90} In contrast, other studies report no significant difference in survival between younger and older patients and even indicate improved survival rates in younger individuals.⁹¹⁻⁹³ These conflicting findings may be due to institutional heterogeneity and the limited sample sizes of young patients in these studies.

A recent study using the SEER database, which included 1,005 AYA patients and 55,435 older adult patients with HCC, found that AYA patients generally had a more favorable prognosis than older patients across most subgroups.⁹ The 1-, 3-, and 5-year OS rates were significantly higher in AYA patients than in older patients before propensity score matching (PSM) (61.4%, 45.3%, 39.0%, 52.1%, 30.0%, and 21.8%, respectively) and after PSM (61.0%, 45.2%, 38.8%, 52.4%, 33.4%, and 25.4%, respectively). In the subgroup analysis, AYA patients had a better prognosis across most subgroups, with significantly improved outcomes observed in women, white individuals, AFP-negative patients, American Joint Committee on Cancer stage I-II cases, and those who did not receive chemotherapy. Among the risk factors, undifferentiated carcinoma was identified as the strongest negative prognostic factor for AYA patients (HR, 6.08), while partial hepatectomy was the most beneficial treatment option (HR, 0.29). This study highlights that AYA patients with HCC exhibit more aggressive tumor characteristics yet achieve better prognoses than patients with older age emphasizing the need for personalized surveillance and treatment strategies. However, further research, including prospective studies and investigations incorporating diverse racial and ethnic populations, is necessary to gain a more comprehensive understanding of treatment outcomes and prognostic factors in AYA patients with HCC.

CONCLUSION

The management of HCC in the elderly and AYA populations presents two distinct challenges in modern hepatology. While both groups showed increasing incidence trends, their clinical presentations, treatment considerations, and outcomes differed significantly. Future research should focus on developing age-specific treatment algorithms, understanding the biological differences that drive disease characteristics in these populations, and optimizing supportive care strategies.

Conflicts of Interest

The author has no conflicts of interest to disclose.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68: 394-424.
2. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021;7:6.
3. Yang JD, Roberts LR. Hepatocellular carcinoma: a global view. *Nat Rev Gastroenterol Hepatol* 2010;7:448-458.
4. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014;74:2913-2921.
5. Han J, Wang B, Liu W, Wang S, Chen R, Chen M, et al. Declining disease burden of HCC in the United States, 1992-2017: a population-based analysis. *Hepatology* 2022;76:576-588.
6. Chon YE, Park SY, Hong HP, Son D, Lee J, Yoon E, et al. Hepatocellular carcinoma incidence is decreasing in Korea but increasing in the very elderly. *Clin Mol Hepatol* 2023;29:120-134.
7. Sankar K, Gong J, Osipov A, Miles SA, Kosari K, Nissen NN, et al. Recent advances in the management of hepatocellular carcinoma. *Clin Mol Hepatol* 2024;30:1-15.
8. Lee HA, Lee S, Lee HL, Song JE, Lee DH, Han S, et al. The efficacy of treatment for hepatocellular carcinoma in elderly patients. *J Liver Cancer* 2023;23:362-376.
9. Guan Y, Gan Y, An J. Clinical characteristics and prognosis of early-onset hepatocellular carcinoma: a retrospective cohort study based on population data. *Dig Dis Sci* 2024;69:3563-3573.
10. Korean Liver Cancer Association (KLCA), National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. *J Liver Cancer* 2023;23:1-120.
11. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of hepatocellular carcinoma. *J Hepatol* 2025;82:315-374.
12. Löckenhoff CE, De Fruyt F, Terracciano A, McCrae RR, De Bolle M, Costa PT Jr, et al. Perceptions of aging across 26 cultures and their culture-level associates. *Psychol Aging* 2009;24:941-954.

13. Seo JH, Kim DH, Cho E, Jun CH, Park SY, Cho SB, et al. Characteristics and outcomes of extreme elderly patients with hepatocellular carcinoma in South Korea. *In Vivo* 2019;33:145-154.
14. National Cancer Institute. All cancer sites combined recent trends in SEER age-adjusted incidence rates, 2000-2021 [Internet]. Rockville (US): National Cancer Institute; [cited 2021 Apr 11]. Available from: <https://seer.cancer.gov/explorer/>
15. United States Cancer Statistics. Data visualizations tool technical notes: November, 2018 submission: diagnosis years 1999-2016. Atlanta (US): United States Cancer Statistics; [cited 2024 Dec 1]. Available from: <https://www.cdc.gov/united-states-cancer-statistics/technical-notes/pdf/uscs-data-visualizations-tool-technical-notes-2016-508.pdf>.
16. Ryerson AB, Ehemann CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual report to the nation on the status of cancer, 1975-2012, featuring the increasing incidence of liver cancer. *Cancer* 2016;122:1312-1337.
17. Coccia PF, Pappo AS, Beaupin L, Borges VF, Borinstein SC, Chugh R, et al. Adolescent and young adult oncology, version 2.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;16:66-97.
18. Danpanichkul P, Aboona MB, Sukphutanan B, Kongarin S, Duangsonk K, Ng CH, et al. Incidence of liver cancer in young adults according to the Global Burden of Disease database 2019. *Hepatology* 2024;80:828-843.
19. Wang J, Mao Y, Liu Y, Chen Z, Chen M, Lao X, et al. Hepatocellular carcinoma in children and adolescents: clinical characteristics and treatment. *J Gastrointest Surg* 2017;21:1128-1135.
20. Yu Z, Bai X, Zhou R, Ruan G, Guo M, Han W, et al. Differences in the incidence and mortality of digestive cancer between Global Cancer Observatory 2020 and Global Burden of Disease 2019. *Int J Cancer* 2024;154:615-625.
21. Kim YJ, Jang BK, Kim ES, Chung WJ, Park KS, Cho KB, et al. Hepatocellular carcinoma in the elderly: clinical characteristics, treatment, survival analysis in Korean patients older than 70 years. *J Korean Med Sci* 2012;27:1147-1154.
22. Cho E, Cho HA, Jun CH, Kim HJ, Cho SB, Choi SK. A review of hepatocellular carcinoma in elderly patients focused on management and outcomes. *In Vivo* 2019;33:1411-1420.
23. Yamazaki Y, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, et al. Hepatocellular carcinoma in young adults: the clinical characteristics, prognosis, and findings of a patient survival analysis. *Dig Dis Sci* 2007;52:1103-1107.
24. Li C, Chen K, Liu X, Liu HT, Liang XM, Liang GL, et al. Analysis of clinicopathological characteristics and prognosis of young patients with hepatocellular carcinoma after hepatectomy. *J Clin Transl Hepatol* 2020;8:285-291.
25. Shen J, Li C, Yan L, Li B, Xu M, Yang J, et al. Short- and long-term outcomes between young and older HCC patients exceeding the Milan criteria after hepatectomy. *Ann Hepatol* 2018;17:134-143.
26. Guo H, Wu T, Lu Q, Dong J, Ren YF, Nan KJ, et al. Hepatocellular carcinoma in elderly: clinical characteristics, treatments and outcomes compared with younger adults. *PLoS One* 2017;12:e0184160.
27. Durand F, Levitsky J, Cauchy F, Gilgenkrantz H, Soubrane O, Francoz C. Age and liver transplantation. *J Hepatol* 2019;70:745-758.
28. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther* 1997;61:331-339.
29. Slawik M, Vidal-Puig AJ. Lipotoxicity, overnutrition and energy metabolism in aging. *Ageing Res Rev* 2006;5:144-164.
30. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, et al. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* 2003;300:1140-1142.
31. Ikeda H, Togashi Y. Aging, cancer, and antitumor immunity. *Int J Clin Oncol* 2022;27:316-322.
32. Zhong HH, Hu SJ, Yu B, Jiang SS, Zhang J, Luo D, et al. Apoptosis in the aging liver. *Oncotarget* 2017;8:102640-102652.
33. Chao C, Bhatia S, Xu L, Cannavale KL, Wong FL, Huang PS, et al. Chronic comorbidities among survivors of adolescent and young adult cancer. *J Clin Oncol* 2020;38:3161-3174.
34. Lazow MA, Salloum R, Pressey JG. Comorbidity burden in a cohort of adolescent and young adult patients diagnosed with central nervous system tumors and sarcomas. *J Adolesc Young Adult Oncol* 2023;12:215-223.
35. Kamath PS, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). *Hepatology* 2007;45:797-805.
36. Toyoda H, Johnson PJ. The ALBI score: from liver function in patients with HCC to a general measure of liver function. *JHEP Rep* 2022;4:100557.
37. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol* 2022;76:681-693.
38. Brunot A, Le Sourd S, Pracht M, Edeline J. Hepatocellular carcinoma in elderly patients: challenges and solutions. *J Hepatocell Carcinoma* 2016;3:9-18.
39. Welsh TJ, Gordon AL, Gladman JR. Comprehensive geriatric assessment—a guide for the non-specialist. *Int J Clin Pract* 2014;68:290-293.
40. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology* 2023;78:1922-1965.
41. Nishikawa H, Kimura T, Kita R, Osaki Y. Treatment for hepatocellular carcinoma in elderly patients: a literature review. *J Cancer* 2013;4:635-643.
42. Federico P, Giunta EF, Pappalardo A, Tufo A, Marte G, Attademo L, et al. How to treat hepatocellular carcinoma in elderly patients. *Pharmaceuticals (Basel)* 2021;14:233.
43. Garcia EM, Nerurkar SN, Tan EX, Tan SY, Peck EW, Quek SX, et al. Characteristics and outcomes of elderly hepatocellular carcinoma patients following surgical resection: systematic review and meta-analysis. *Dig Dis* 2025;43:206-214.
44. Chu KKW, Chok KSH. Is the treatment outcome of hepatocellular carcinoma inferior in elderly patients? *World J Gastroenterol* 2019;25:3563-3571.
45. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg* 2015;261:619-629.
46. Hilal MA, Aldrighetti L, Dagher I, Edwin B, Troisi RI, Alikhanov R, et al. The Southampton Consensus guidelines for laparoscopic liver surgery: from indication to implementation. *Ann Surg* 2018;268:11-18.
47. Dumronggittigule W, Han HS, Ahn S, Yoon YS, Cho JY, Choi Y. Laparoscopic versus open hepatectomy for hepatocellular carcinoma in elderly patients: a single-institutional propensity score matching comparison. *Dig Surg* 2020;37:495-504.
48. Nomi T, Hirokawa F, Kaibori M, Ueno M, Tanaka S, Hokuto D, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in elderly patients: a multi-centre propensity score-based analysis. *Surg Endosc* 2020;34:658-666.
49. Ahmed FA, Khan SA, Hafeez MS, Jehan FS, Aziz H. Outcomes in elderly patients undergoing hepatic resection compared to ablative therapy for hepatocellular carcinoma. *J Surg Oncol* 2023;128:803-811.
50. Yoo JJ, Koo S, Choi GH, Lee MW, Ryoo S, Park J, et al. Radiofrequency ablation versus surgical resection in elderly hepatocellular carcinoma: a systematic review and meta-analysis. *Curr Oncol* 2024;31:324-334.
51. Conticchio M, Delvecchio A, Ratti F, Gelli M, Anelli FM, Laurent A, et al. Laparoscopic surgery versus radiofrequency ablation for the treatment of single hepatocellular carcinoma ≤3 cm in the elderly: a propensity score matching analysis. *HPB (Oxford)* 2022;24:79-86.
52. Hung AK, Guy J. Hepatocellular carcinoma in the elderly: meta-analysis and systematic literature review. *World J Gastroenterol* 2015;21:12197-12210.

53. Fujiwara N, Tateishi R, Kondo M, Minami T, Mikami S, Sato M, et al. Cause-specific mortality associated with aging in patients with hepatocellular carcinoma undergoing percutaneous radiofrequency ablation. *Eur J Gastroenterol Hepatol* 2014;26:1039-1046.
54. Cho SW, Steel J, Tsung A, Marsh JW, Geller DA, Gamblin TC. Safety of liver resection in the elderly: how important is age? *Ann Surg Oncol* 2011;18:1088-1095.
55. Cavagnaro M, Amabile C, Cassarino S, Tosoratti N, Pinto R, Lopresto V. Influence of the target tissue size on the shape of ex vivo microwave ablation zones. *Int J Hyperthermia* 2015;31:48-57.
56. Liang P, Yu J, Lu MD, Dong BW, Yu XL, Zhou XD, et al. Practice guidelines for ultrasound-guided percutaneous microwave ablation for hepatic malignancy. *World J Gastroenterol* 2013;19:5430-5438.
57. Wang Y, Cheng Z, Yu J, Li X, Hao G, Liu F, et al. US-guided percutaneous microwave ablation for early-stage hepatocellular carcinoma in elderly patients is as effective as in younger patients: a 10-year experience. *J Cancer Res Ther* 2020;16:292-300.
58. Zhang YX, Zhang XH, Yu XL, Han ZY, Yu J, Liu FY, et al. Prognosis of microwave ablation for hepatocellular carcinoma: does age make a difference? *Int J Hyperthermia* 2020;37:688-695.
59. Luo J, Dong Z, Xie H, Zhang W, An L, Yu Z, et al. Efficacy and safety of percutaneous cryoablation for elderly patients with small hepatocellular carcinoma: a prospective multicenter study. *Liver Int* 2022;42:918-929.
60. Khan SA, Ahmed FA, Hafeez MS, Feng LR, Seth A, Kwon YK, et al. Outcomes in elderly patients undergoing hepatic resection compared to liver transplant for hepatocellular carcinoma. *J Surg Oncol* 2023;128:1320-1328.
61. Cross TJ, Antoniadis CG, Muiesan P, Al-Chalabi T, Aluvihare V, Agarwal K, et al. Liver transplantation in patients over 60 and 65 years: an evaluation of long-term outcomes and survival. *Liver Transpl* 2007;13:1382-1388.
62. Schwartz JJ, Pappas L, Thieset HF, Vargas G, Sorensen JB, Kim RD, et al. Liver transplantation in septuagenarians receiving model for end-stage liver disease exception points for hepatocellular carcinoma: the national experience. *Liver Transpl* 2012;18:423-433.
63. Sonny A, Kelly D, Hammel JP, Albeldawi M, Zein N, Cywinski JB. Predictors of poor outcome among older liver transplant recipients. *Clin Transplant* 2015;29:197-203.
64. Sharpton SR, Feng S, Hameed B, Yao F, Lai JC. Combined effects of recipient age and model for end-stage liver disease score on liver transplantation outcomes. *Transplantation* 2014;98:557-562.
65. Garcia CE, Garcia RF, Mayer AD, Neuberger J. Liver transplantation in patients over sixty years of age. *Transplantation* 2001;72:679-684.
66. Gil E, Kim JM, Jeon K, Park H, Kang D, Cho J, et al. Recipient age and mortality after liver transplantation: a population-based cohort study. *Transplantation* 2018;102:2025-2032.
67. Liu PH, Hsu CY, Lee YH, Hsia CY, Huang YH, Su CW, et al. Uncompromised treatment efficacy in elderly patients with hepatocellular carcinoma: a propensity score analysis. *Medicine (Baltimore)* 2014;93:e264.
68. Cohen MJ, Bloom AI, Barak O, Klimov A, Nesher T, Shouval D, et al. Trans-arterial chemo-embolization is safe and effective for very elderly patients with hepatocellular carcinoma. *World J Gastroenterol* 2013;19:2521-2528.
69. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2016;151:1155-1163.e2.
70. Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: the LEGACY study. *Hepatology* 2021;74:2342-2352.
71. Finn RS, Qin S, Ikeda K, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382:1894-1905.
72. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-390.
73. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;391:1163-1173.
74. Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: an EASL position paper. *J Hepatol* 2021;75:960-974.
75. Tada T, Kumada T, Hiraoka A, Hirooka M, Kariyama K, Tani J, et al. Safety and efficacy of atezolizumab plus bevacizumab in elderly patients with hepatocellular carcinoma: a multicenter analysis. *Cancer Med* 2022;11:3796-3808.
76. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid* 2022;1:EVIDoa2100070.
77. Shimose S, Saeki I, Tomonari T, Ito T, Tani J, Takeuchi Y, et al. Initial clinical experience with durvalumab plus tremelimumab in patients with unresectable hepatocellular carcinoma in real-world practice. *Oncol Lett* 2024;28:397.
78. Tada T, Kumada T, Hiraoka A, Michitaka K, Atsukawa M, Hirooka M, et al. Safety and efficacy of lenvatinib in elderly patients with unresectable hepatocellular carcinoma: a multicenter analysis with propensity score matching. *Hepatol Res* 2020;50:75-83.
79. Zebrack B, Mathews-Bradshaw B, Siegel S; LIVESTRONG Young Adult Alliance. Quality cancer care for adolescents and young adults: a position statement. *J Clin Oncol* 2010;28:4862-4867.
80. Bleyer A. Young adult oncology: the patients and their survival challenges. *CA Cancer J Clin* 2007;57:242-255.
81. Vimalasvaran S, Souza LN, Deheragoda M, Samyn M, Day J, Verma A, et al. Outcomes of adults who received liver transplant as young children. *EClinicalMedicine* 2021;38:100987.
82. Bhatia S, Pappo AS, Acquazzino M, Allen-Rhoades WA, Barnett M, Borinstein SC, et al. Adolescent and young adult (AYA) oncology, version 2.2024. NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2023;21:851-880.
83. Ishibashi A, Okamura J, Ueda R, Sunami S, Kobayashi R, Ogawa J. Psychosocial strength enhancing resilience in adolescents and young adults with cancer. *J Pediatr Oncol Nurs* 2016;33:45-54.
84. Morgan S, Davies S, Palmer S, Plaster M. Sex, drugs, and rock 'n' roll: caring for adolescents and young adults with cancer. *J Clin Oncol* 2010;28:4825-4830.
85. Smith AW, Seibel NL, Lewis DR, Albritton KH, Blair DF, Blanke CD, et al. Next steps for adolescent and young adult oncology workshop: an update on progress and recommendations for the future. *Cancer* 2016;122:988-999.
86. Salama M, Isachenko V, Isachenko E, Rahimi G, Mallmann P. Advances in fertility preservation of female patients with hematological malignancies. *Expert Rev Hematol* 2017;10:951-960.
87. Quidde J, von Grundherr J, Koch B, Bokemeyer C, Escherich G, Valentini L, et al. Improved nutrition in adolescents and young adults after childhood cancer - INAYA study. *BMC Cancer* 2016;16:872.
88. Wurz A, Brunet J. Exploring the feasibility and acceptability of a mixed-methods pilot randomized controlled trial testing a 12-week physical activity intervention with adolescent and young adult cancer survivors. *Pilot Feasibility Stud* 2019;5:154.
89. Zeng J, Lin K, Liu H, Huang Y, Guo P, Zeng Y, et al. Prognosis factors of young patients undergoing curative resection for hepatitis B virus-related hepatocellular carcinoma: a multicenter study. *Cancer Manag Res* 2020;12:6597-6606.
90. Commander SJ, Cerullo M, Arjunji N, Leraas HJ, Thornton S, Ravindra K, et al. Improved survival and higher rates of surgical resection associated with hepatocellular carcinoma in children as compared to young adults. *Int J Cancer* 2022;151:2206-2214.
91. Shimada S, Kamiyama T, Yokoo H, Wakayama K, Tsuruga Y, Kakisaka T, et al. Clinicopathological characteristics and prognostic factors in young

- patients after hepatectomy for hepatocellular carcinoma. *World J Surg Oncol* 2013;11:52.
92. Chang PE, Ong WC, Lui HF, Tan CK. Is the prognosis of young patients with hepatocellular carcinoma poorer than the prognosis of older patients? A comparative analysis of clinical characteristics, prognostic features, and survival outcome. *J Gastroenterol* 2008;43:881-888.
93. Takeishi K, Shirabe K, Muto J, Toshima T, Taketomi A, Maehara Y. Clinicopathological features and outcomes of young patients with hepatocellular carcinoma after hepatectomy. *World J Surg* 2011;35:1063-1071.