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The Weight of Risk: Exploring the Link Between Obesity and Liver Cancer

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ABSTRACT

Obesity is a chronic, preventable condition, and has a significant public health concern. Its implications extend beyond metabolic syndrome, casting a shadow over the development and prognosis of various cancers, with a particularly strong tie to hepatocellular carcinoma (HCC) among all cancer types. Non-Alcoholic Fatty Liver Disease (NAFLD) is now a leading cause of liver cancer, along with the treatment of hepatitis B and C. Liver cancer is the fourth most common cause of cancer related deaths worldwide, with obesity, exacerbating the risk especially two times higher in Body Mass Index (BMI) above 30 and four times higher in BMI above 35. Visceral adiposity, measured by waist circumference, is considered more important risk factor than general adiposity. Several mechanisms have been proposed to explain the pathophysiology of how obesity can trigger HCC, but the precise mechanisms that control the progression from steatosis to steatohepatitis and tumor initiation remain unclear. Hepatocellular cancer may occur in patients with NAFLD without cirrhosis. The diagnosis of HCC in NAFLD can be challenging due to an increase in poor-quality ultrasound in obese individuals, which necessitates a more accurate and cost-effective surveillance strategy for early detection. The delay in diagnosis, older age, and the presence of relevant comorbidities limit the possibility of therapeutic intervention. Weight management through lifestyle changes and surgical interventions like bariatric surgery offers promise in mitigating both metabolic syndrome and the risk of HCC. Diagnosis hinges on advanced imaging techniques like multiphase Magnetic Resonance Imaging or Computed Tomography scan using specific criteria. Treatment modalities for HCC are multifaceted, depends upon tumor characteristics, metastasis, cirrhosis, and overall liver function. However, despite advancements, there remains a pressing need for more efficacious interventions to combat obesity and curb the trajectory of HCC, given its persistently high mortality rate. Surveillance protocols for HCC in cirrhotic patients entail regular abdominal ultrasounds with or without Alpha Fetoprotein testing at six-month intervals. However, there is a need for cost effective surveillance strategies for HCC in non-cirrhotic NAFLD.

Keywords: Obesity, Liver Cancer, Hepatocellular Carcinoma, Carcinoma, HCC, NAFLD, NASH, Lean NASH, Cirrhosis, HCC surveillance, Risk, Prognosis, Mortality.

Introduction

Obesity, defined as a body mass index (BMI) equal to or higher than 30 kg/m^2, represents a chronic condition the prevalence of which has increased substantially over recent decades. In the United States alone, the prevalence surged from 30.5% in 1999–2000 to 42.4% in 2017–2018, with severe obesity (BMI > 40) climbing from 4.7% to 9.2% during the same period, as reported by the National Center for Health Statistics (NCHS). This escalation poses a substantial strain on healthcare systems, evident from Figure 1. Obesity is a known risk factor for type 2 diabetes mellitus, hypertension, dyslipidemia, and coronary artery disease, and it is evident that obesity is also a risk factor for multiple cancers[1,2]. Cancer is not only a disorder of proliferation but also considered a metabolic disease due to cancer related metabolic changes in tissues[3,4]. With this background it is postulated that there is likely an overlap in the mechanisms that may connect obesity with metabolic syndrome and cancer[5]. Based on the literature so far there is convincing evidence that obesity is a risk factor for colorectal cancer, postmenopausal breast cancer, endometrial cancer, renal cell carcinoma, esophageal adenocarcinoma, pancreatic cancer, hepatocellular cancer (HCC), ovarian cancer, advanced stage prostate cancer, gallbladder cancer, and gastric cardia cancer[6-11]. Notably, pancreatic cancer and HCC exhibit the most pronounced elevation in risk among these malignancies[12].

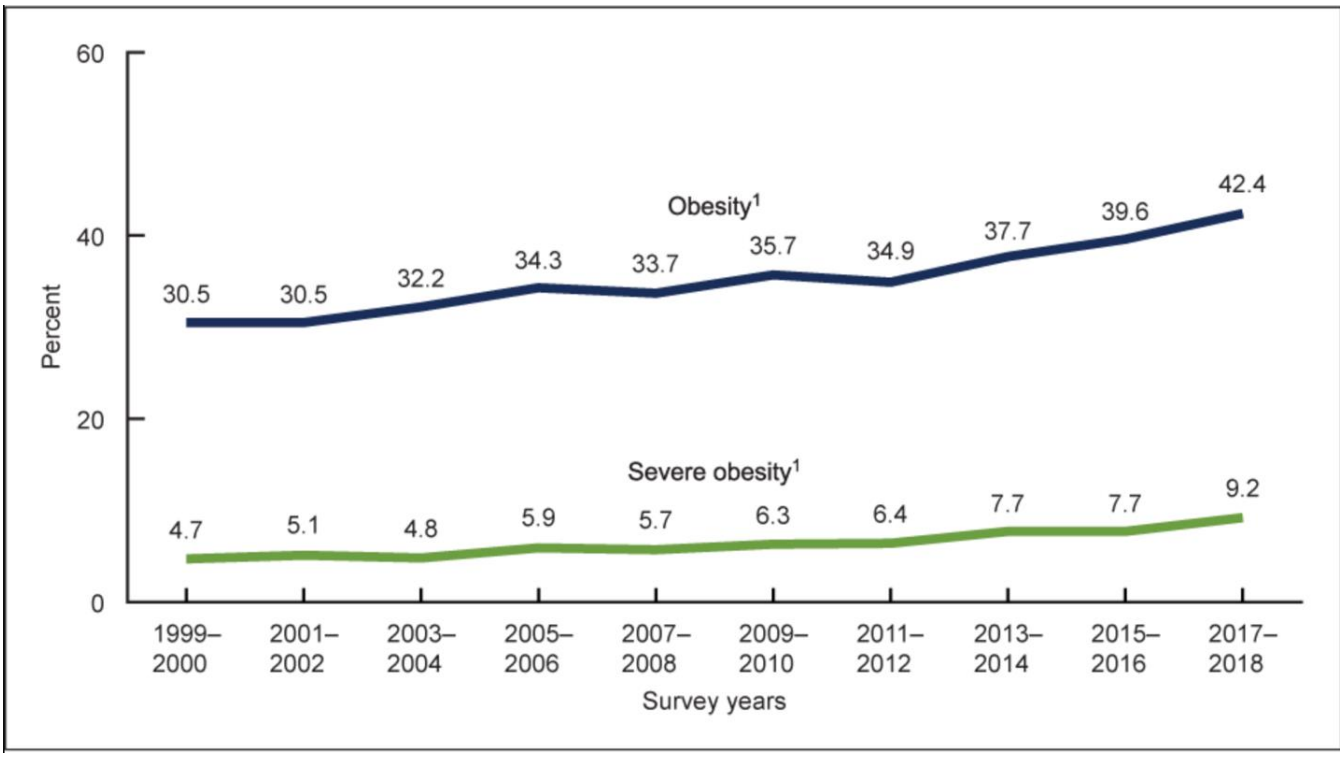

Figure 1: Trends in age-adjusted obesity and severe obesity prevalence among adults aged 20 and over: United States, 1999–2000 through 2017–2018 (National Center for Health and Statistics)

Liver cancer is the fourth most common cause of cancer related mortality worldwide and the fifth most common cancer in men worldwide[13]. Hepatocellular cancer is the predominant type of primary liver cancer and is projected to affect more than one million globally by 2025[14]. Multiple factors like viral hepatitis, nonalcoholic fatty liver disease (NAFLD), alcohol abuse, and exposure to dietary toxins (e.g., aflatoxins) contribute to the genesis and progression of HCC[15]. Non-Alcoholic Fatty Liver Disease-related HCC is the most rapidly growing indication for liver transplantation in many countries[16]. Obesity emerges as a significant risk factor, particularly prevalent among NAFLD patients, where nearly 90% of obese individuals exhibit NAFLD[15]. A subset of NAFLD cases progresses to Non-Alcoholic Steatohepatitis (NASH), characterized by liver necroinflammation and fibrosis, affecting about 20% of all NAFLD patients[16]. In severely obese patients having bariatric surgery, more than 90% had NAFLD[17]. This article delves into the intricate relation between obesity and the development of hepatocellular carcinoma.

Obesity and Hepatocellular carcinoma:

Obesity stands as a persistent, preventable health issue imposing a substantial burden on public health. The etiology of obesity is multifactorial, which includes genetic, environmental, endocrine, socioeconomic, physiologic, and behavioral or psychological influences as shown in Figure 2[18]. Numerous epidemiological studies have shown that obesity is an independent risk factor for various malignancies, including breast cancer, endometrial cancer, colon cancer, renal cell carcinoma, esophageal adenocarcinoma, pancreatic ductal adenocarcinoma, and HCC; and associated with poor prognosis of breast cancer and colon cancer[12]. Hepatocellular cancer ranks as the fourth leading cause of cancer-related deaths globally, constituting 80% of liver cancers, with cholangiocarcinoma (10-20%) and angiosarcoma (1-2%) being other types[19,20]. Major risk factors for HCC include Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), diabetes, obesity, alcoholic fatty liver disease (AFLD), and NAFLD. While chronic HBV and HCV infections have long been recognized as key HCC culprits, the past decade has seen fatty liver disease, both alcoholic and nonalcoholic, take center stage as a primary cause of chronic liver disease that may progress to HCC[19].

Figure 2: Risk factors leading to obesity.

Obesity has been implicated in the pathogenesis of metabolic syndrome, including insulin resistance, type 2 diabetes, and NAFLD, a spectrum of non-cancerous liver diseases which comprises Non-alcoholic fatty liver (NAFL), NASH, and cirrhosis[21]. Non-Alcoholic Fatty Liver is characterized by the accumulation of lipid in the liver (hepatic steatosis) which can cause inflammation and turn into NASH which can lead to advanced fibrosis, cirrhosis, and development of HCC as shown in Figure 3. In its early stages fatty liver is reversible, however without adequate lifestyle measures it may progress. Obesity is highly prevalent in patients with NAFLD, (estimated to be 51.3%) and NASH (estimated to be 81.8%)[22]. There is now convincing evidence that obesity increases the risk of liver cancer[7]. A meta-analysis assessing the association between overweight, obesity and risk of liver cancer published in British Journal of Cancer reveal that overweight and obese individuals face a 17% and 89% higher risk of HCC, respectively, compared to their normal-weight counterparts, with a more pronounced risk observed in men[23]. It appears that there is a sex differential regarding the risk of cancer with men having a higher risk compared to women with same BMI[24]. This difference might be due to hormonal changes in women or poor reflection of central obesity as measured by BMI[25]. In some of the studies which used waist circumference (WC) which is a simple direct measurement and strong predictor of central obesity compared to BMI, risk is equal in men and women[24,26,27]. In a systematic review and meta-analysis of prospective observational studies evaluating the risk of BMI and incidence of cancer showed that relative risk (RR) of HCC was 1.24 with increase in BMI >5kg/m^2 in men and 1.07 in women[28]. Another meta-analysis of prospective studies assessing the risk of BMI and HCC showed RR of 1.39 with increase in BMI of >5kg/m^2 with more pronounced risk if BMI >32[29]. The risk of HCC was 1.67 significantly higher in patients with known liver disease, with HBV and/or HCV infection, cirrhosis[29]. The RR of HCC related mortality was also higher 1.9 and 4.5 times in patients with BMI between 30 to 35 and in those with BMI >35[30]. A recent metanalysis showed an increase in BMI was associated with the occurrence of primary liver cancer (Hazard Ratio HR, 1.69; 95% confidence interval, 1.50–1.90, $I2$=56%). A BMI-dependent increase in the risk of occurrence of primary liver cancer was reported. HRs were 1.36 (95% CI, 1.02–1.81), 1.77 (95% CI, 1.56–2.01), and 3.08 (95% CI, 1.21–7.86) for BMI >25 kg/m2, >30 kg/m2, and >35 kg/m2, respectively. Furthermore, increased BMI resulted in enhanced liver cancer-related mortality (HR, 1.61; 95% CI, 1.14–2.27, $I2$=80%)[31].

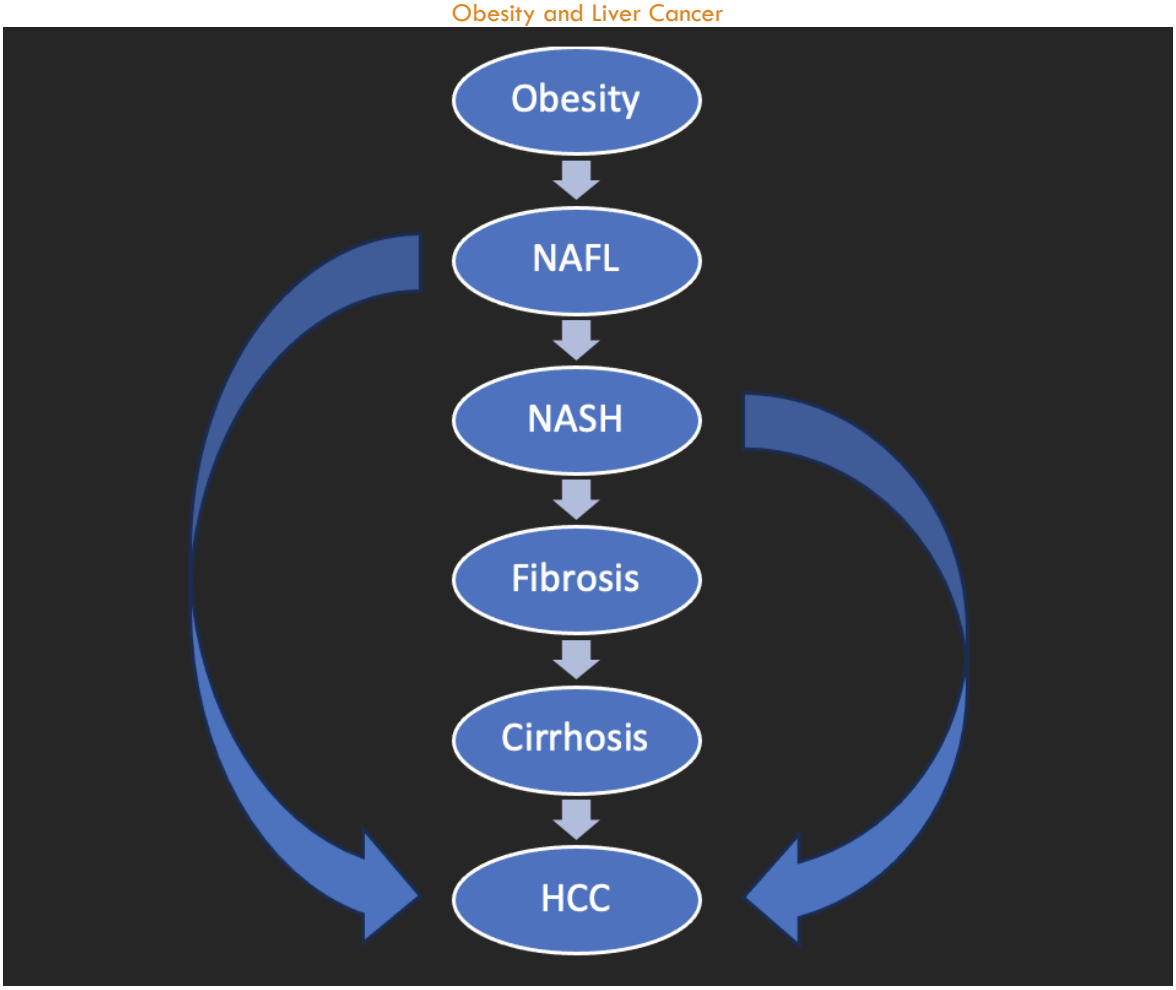

Figure 3: Progression of Non-Alcoholic Fatty Liver Disease leading to Hepatocellular Cancer.

Non-Alcoholic Fatty Liver Disease in Lean Individuals:

While NAFLD predominantly affects overweight/obese individuals; it can also be seen in the absence of obesity, a condition termed Lean NAFLD. The term Lean has been defined as BMI<25 Kg/m2, or <23 kg/m² in Asian populations[32], and even lower (<19 kg/m²) in those with type 2 diabetes[33]. The prevalence of NAFLD in lean individuals has been growing recently affecting 7-20% of Western population and 5-26% of Asian population[34,35]. There are variations among different studies regarding the prevalence and reporting due to several limitations which include variation in the definition, varying methods to diagnose and ascertainment bias. Risk factors for Lean NAFLD mirror those of obese NAFLD, along with other risk factors such as genetic predispositions (higher prevalence of Patatin-like phospholipase domain-containing protein 3 PNPLA3, rare congenital defects of metabolism such as lysosomal acid lipase deficiency (LAL-D) and familial hypobetalipoprotein B (FHLB)), dietary intake of high fructose and cholesterol, infections, drugs (Amiodarone, Tamoxifen, Diltiazem), and alterations in the gut microbiome[36]. Clinical features are like NAFLD in obese individuals but with lesser severity. Histology may show the similar features as obese NAFLD but overall, they can display the full spectrum of liver damage[35]. Since Lean NAFLD is associated with less obesity related comorbidities it is believed to take relatively benign course[35]. Several studies have shown increased insulin resistance, metabolic syndrome, cardiovascular disease, and cancer related mortality in lean NASH, but risk of HCC has not been elucidated[37].

Management strategies entail identifying and addressing underlying environmental factors, adopting a healthy lifestyle, and managing concurrent conditions such as diabetes, hypertension, and dyslipidemia. Researchers have found that NAFLD can be reversed in 67% of non-obese patients after lifestyle intervention, with most of the patients achieving NAFLD remission with weight loss of 3-10%[35].

Pathophysiology:

The precise mechanisms underlying the association between liver cancer and obesity is unclear. Several mechanisms have been proposed to explain the possible link, how obesity might increase the risk of HCC.

1) Obesity stems from a disruption in the delicate equilibrium between calorie consumption and energy expenditure, resulting in the excessive accumulation of fat and the formation of adipose tissue (AT). This AT can deposit centrally or viscerally as white adipose tissue and peripherally as brown adipose tissue. Visceral adipose tissue is metabolically more active, which not only acts as energy reservoir but also as an endocrine organ that secrets adipokines (Leptin and Adiponectin). In obese individuals, heightened levels of leptin can spur cell proliferation, while decreased levels of adiponectin, known for its anti-tumor properties, exacerbate the imbalance. This imbalance between leptin and adiponectin precipitates chronic low-grade inflammation, a key player in the process of hepatic carcinogenesis[38].
2) Obesity triggers insulin resistance and hyperinsulinemia, setting off a cascade of molecular

events. Insulin's activation of Insulin Receptor Substrate-1 (IRS-1), Insulin-like Growth Factor-1 (IGF-1), and IGF-binding proteins (IGF-BP) in the liver initiates the release of cytokines such as Tumor Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6). These cytokines, in turn, drive the proliferation and progression of hepatocellular carcinoma (HCC) by promoting anti-apoptotic mechanisms, stimulating angiogenesis, and enhancing cell proliferative activity[39].

3) Within the gastrointestinal tract, a diverse array of 500 to 1000 species coexists symbiotically with the host. However, in obese individuals, this delicate balance is disrupted, leading to dysbiosis. Dysbiosis fosters the proliferation of ammonia-producing bacteria, contributing to elevated levels of ammonia and myostatins in the bloodstream. These myostatins instigate muscle breakdown, known as sarcopenia, which, intriguingly, may promote hepatic carcinogenesis through mechanisms yet to be fully elucidated[40]. Changes in intestinal microbiota can lead to increase in deoxycholic acid, a secondary bile acid. Elevated deoxycholic acid levels prompt cellular senescence in hepatic stellate cells, resulting in the secretion of inflammatory cytokines, chemokines, and extracellular matrix-degrading enzymes, ultimately paving the way for carcinogenesis[41].

4) Both Non-Alcoholic Steatohepatitis (NASH) and cirrhosis elevate levels of reactive oxygen species (ROS) and induce oxidative stress. These oxidative insults directly target DNA, triggering chromosomal instability that ultimately fosters the development of hepatic carcinogenesis[38].

Management:

DIAGNOSIS OF NON-ALCOHOLIC FATTY LIVER DISEASE:

Diagnosis of NAFLD is based on the presence of steatosis either by imaging or by histological examination (Figure 4) excluding alcohol consumption and other liver diseases[42]. Although liver biopsy remains the gold standard, its employment is hindered by cost, invasiveness, and associated risks such as bleeding, infection, organ damage and rare mortality risk of <0.01%[43,44]. Additionally, sampling errors and variations in interpretation by pathologists pose challenges to diagnostic accuracy[42]. Liver biopsy is typically reserved for patients with advanced fibrosis undergoing clinical trials or if uncertainty in diagnosis in the presence of coexistent liver diseases[45,46]. Non-Alcoholic Steatohepatitis is diagnosed with liver biopsy showing hepatic steatosis of more than 5%, hepatocyte ballooning degeneration, and hepatic lobular inflammation[47]. Ultrasonography (US) stands as the most economical and commonly used noninvasive method for assessing hepatic steatosis. Other noninvasive imaging techniques encompass vibration-controlled transient elastography (Fibro Scan), shearwave elastography utilizing US, and magnetic resonance elastography (MRE). These modalities offer varying degrees of sensitivity. Fibro Scan has a sensitivity of 85% for detecting advanced fibrosis and 92% for detecting cirrhosis[48]. Magnetic Resonance Elastography has a sensitivity of 86% for identifying patients with advanced fibrosis[49]. Furthermore, noninvasive biomarkers such as the Fibrosis 4 (Fib4) index, AST to Platelet Ratio Index (APRI), and NAFLD fibrosis score have emerged for NAFLD screening[50].

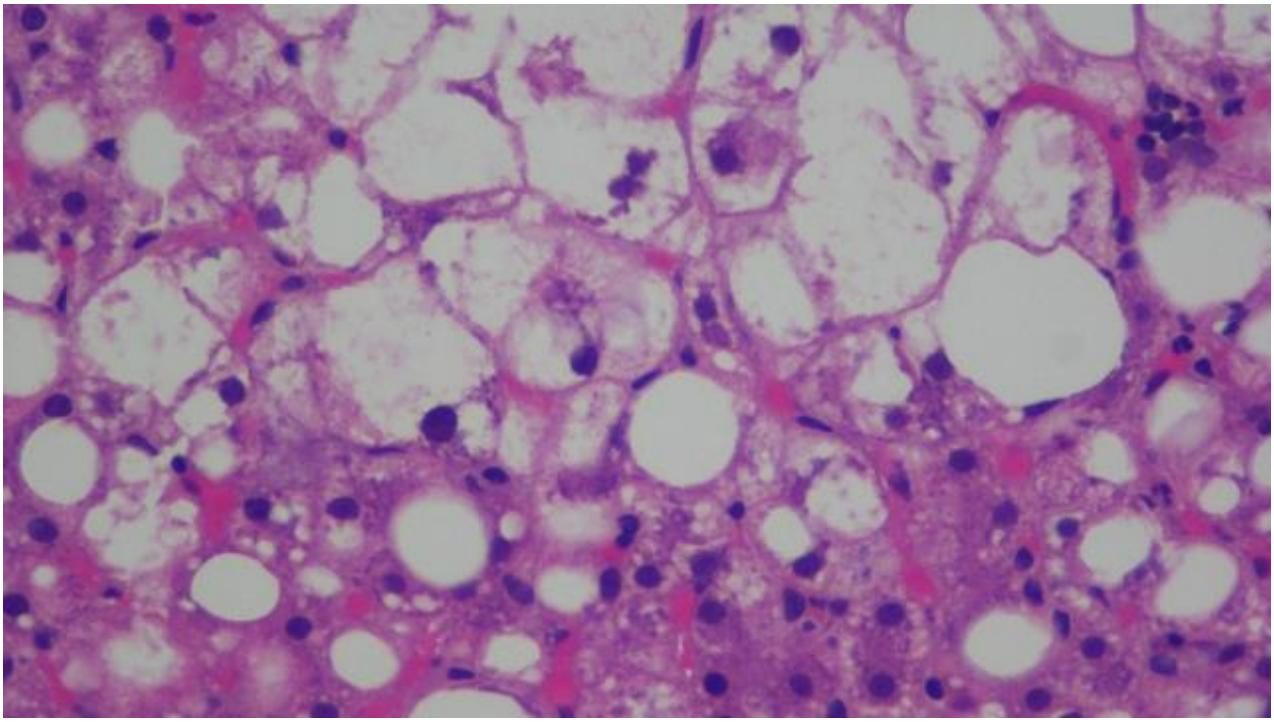

Figure 4: Histopathology showing features of Non-Alcoholic Steatohepatitis.

Treatment of Obesity and Non-Alcoholic Fatty Liver Disease:

Although there is no single curative approach, treatment aimed at weight loss significantly decreases obesity-related comorbidities and reduces its related costs. Weight loss of 5-10% has been linked to improvement in dyslipidemia, hyperglycemia, osteoarthritis, stress incontinence, Gastroesophageal reflux disease, and hypertension, while a 10% weight loss is required for improvement in NAFLD and sleep apnea[51]. Main strategies for weight loss includes diet, physical activity, and behavioral modification. Dietary options range from balanced low-calorie, low-fat, moderate-fat/low-

calorie, to low-carbohydrate diets, with the Mediterranean diet showing promise with a 50% reduction in HCC incidence[52]. Even though less potent than dietary restriction physical activity approximately 30 minutes or more for five to seven days can improve cardiovascular health[53]. In cases where diet and lifestyle modifications fall short, pharmacotherapy or surgery may be warranted. glucagon-like peptide-1(GLP1) agonists have been shown to help achieve 10 – 20 % weight loss and may improve NASH. Initially liraglutide was the only GLP1 receptor agonist approved for the treatment of obesity in patients without diabetes[54] until, Semaglutide was approved by Food and Drug Administration (FDA) in 2021[55]. Tirzepatide is another GLP1 agonist shown to achieve substantial weight loss of 20 % and is awaiting FDA approval[56]. Other FDA approved medications include orlistat and phentermine-topiramate combination. When considering pharmacological interventions, an individualized approach accounting for patient comorbidities, preferences, insurance coverage, and costs is paramount. Bariatric surgery (sleeve gastrectomy, adjustable gastric band, Roux-en-Y bypass, Biliopancreatic Diversion with Duodenal Switch) can be considered in patients with BMI >40 kg/m2 or BMI >35kg/m2 with at least one comorbidity who failed to achieve weight loss with diet, lifestyle, and pharmacotherapy[51]. Caiazzo et al showed significant improvement in NAFLD with Roux-en-Y bypass irrespective of weight loss[57].

Diagnosis of Hepatocellular Carcinoma:

Hepatocellular cancer is diagnosed using multiphase Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) using the Liver Imaging Reporting and Data system (LIRAD) scoring system[58]. The pattern of arterial enhancement, delayed washout in venous phase and tumor size is used for the scoring system. A LIRAD score of 5 denotes a definitive HCC while a LIRAD score of 4 is probable HCC and may necessitate a biopsy for diagnosis (Figure 5). Lesions categorized as LIRAD 3 are deemed possibly benign and necessitate repeat imaging within a specified time frame for further evaluation.

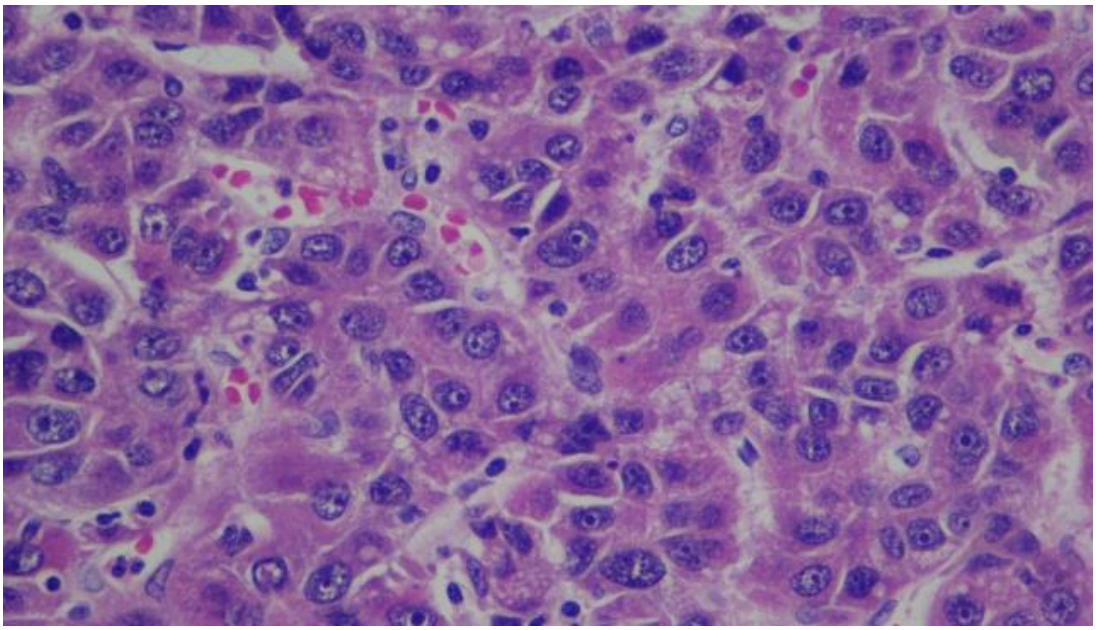

Figure 5: Histopathology showing features of Hepatocellular Cancer.

Treatment of Hepatocellular Carcinoma:

The treatment of liver cancer depends on size of the tumor, presence of metastasis, portal vein thrombosis, presence of cirrhosis, patient's preference, and overall health. Treatment modalities encompass tumor resection, liver-directed loco-regional therapies such as microwave ablation, radiofrequency ablation (RFA), and electroporation, as well as percutaneous ethanol injection. Other options include trans-arterial chemoembolization (TACE), trans-arterial radioembolization using Y90 (TARE), external beam radiation therapy, and systemic therapy. Hepatectomy is an option when tumor involves only a part of the liver that is resectable in patients with good hepatic function. Liver transplantation is an option in patients within Milan criteria (single tumor that is 5 cm or smaller or 2-3 fewer tumors, each of which is smaller than 3 cm and with no evidence of gross vascular invasion, nodal or distant metastases) or after downsizing to Milan criteria with liver directed therapy if total tumor size is below 8 cm. These patients are eligible for Model for End stage Liver Disease (MELD) exception points after 6 months if Alpha Fetoprotein (AFP) remains below 500. For several years sorafenib, a Tyrosine Kinase Inhibitor was the only available treatment for non resectable HCC[59]. Patients with unresectable HCC (presence of tumor thrombus in portal vein, metastases) and are Child A status can be treated with combination of atezolizumab and bevacizumab (combination of programmed death-ligand 1 inhibitor with Vascular Endothelial Growth Factor inhibitor) which showed increased overall survival and progression free survival than sorafenib[60]. Duravalumab has also been shown to be non-inferior to sorafenib in the Stride trial[61]. In patients that do not respond to combination immunotherapy treatment or ablative therapy treatment options include several tyrosine kinase inhibitors or nivolumab sequentially (American Association for the Study of Liver Diseases AASLD 2018 HCC guidelines). Barcelona Clinic Liver Cancer (BCLC) algorithm is advised by AASLD guidelines in deciding treatment for HCC and is outlined below (Figure 6)[62].

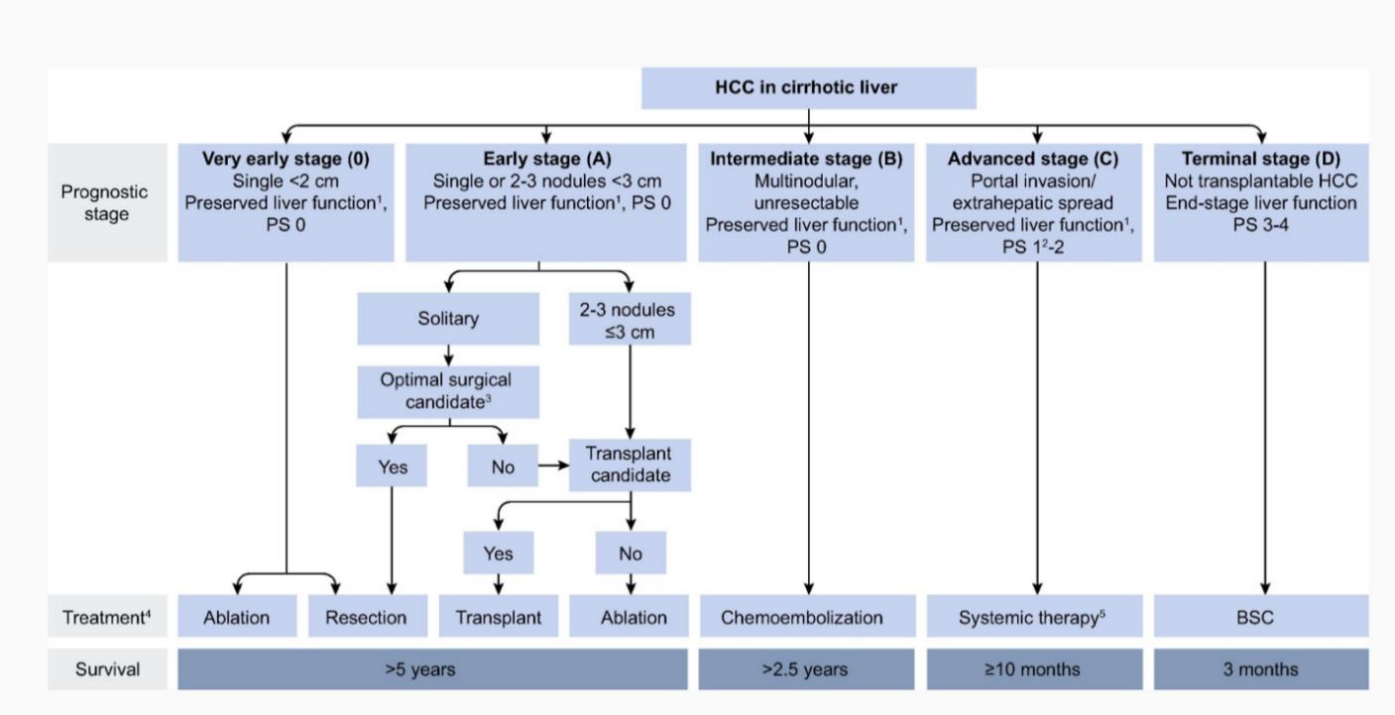

Figure 6: Barcelona Clinic Liver Cancer staging and treatment strategy. The figure was reproduced with the permission from the authors Diamantis I. Tsilimigras, Timothy M. Pawlik. (Tsilimigras DI, Pawlik TM. Hepatocellular carcinoma beyond Barcelona clinic liver cancer resection criteria: resecting the aggressive tumor. *Hepatoma Research*. 2021; 7:63. http://dx.doi.org/10.20517/2394-5079.2021.51)

Surveillance for Hepatocellular Carcinoma:

Screening for liver cancer is considered cost effective in patients with cirrhosis as HCC incidence exceeds 0.2 % per year[63]. Although patients without cirrhosis may develop HCC, screening is not cost effective but can be considered in patients with higher risk. Despite high prevalence of NAFLD in general population, only 50% of NASH associated HCC arises in the context of non-cirrhotic liver compared to 80% in cirrhotic liver, thus active surveillance is not cost effective to screen for HCC in non-cirrhotic NAFLD[64-66]. Current AASLD guidelines recommend patients with cirrhosis undergo ultrasound (US) abdomen every 6 months with or without Alpha Fetoprotein (AFP) while earlier European Association for the Study of the Liver (EASL) guidelines does not include AFP. The sensitivity of US ranges from 58 to 89%, with an excellent specificity (above 90%) making it most widely accepted imaging modality (67). Ultrasound screening in obese individuals may be poor quality with studies showing 3-8-fold higher risk of having an inadequate examination[16]. Surveillance with computed tomography or magnetic resonance imaging may need to be considered in patients with high BMI. Abbreviated MRI is a promising tool being evaluated for HCC screening[68].

Alpha Fetoprotein is a glycoprotein produced by fetal liver, yolk sac but AFP alone is not used as primary surveillance of HCC due to low sensitivity and specificity as increased levels are also seen in chronic liver disease and germ cell tumors[62]. An AFP level of 20 ng/mL is a threshold to trigger evaluation for HCC in usual practice[69]. Serum AFP levels >400 ng/mL in a high-risk patient are nearly diagnostic of HCC, with a specificity of >95 percent, however those levels are seen only in 20%[70,71]. Alpha Fetoprotein is not expressed at high levels in all HCC especially in potentially curable small tumors. A Lens culinaris agglutinin A-reactive fraction of alpha-fetoprotein (AFP-L3) fraction of AFP can be detected in the serum of approximately 35% of the patients with small HCC (<2 cm)[72]. When AFP levels are <200 ng/ml AFP-L3 can be a useful marker for surveillance but has not been validated yet. Lens culinaris agglutinin A-reactive fraction of alpha-fetoprotein (AFP-L3) results of 10% or above are associated with a 7-fold increased risk of developing hepatocellular carcinoma. Nonetheless, there remains an unmet need for effective surveillance strategies in individuals with non-cirrhotic NAFLD.

Conclusion:

The association between obesity and hepatocellular cancer is increasingly recognized as a public health concern. This exploration reveals that obesity is a complex metabolic disorder that increases the risk of developing HCC. Epidemiological data is showing a strong correlation between elevated body mass index and the incidence of HCC, underscoring the need for interventions targeting obesity prevention and management. Preventative measures such as diet and lifestyle modifications, and early screening for liver diseases in obese individuals are crucial. Additionally, more research is needed to better understand the mechanism linking obesity and HCC, which could unfold the way for novel and cost-effective surveillance strategies and therapeutic approaches.

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References:

1. Haslam DW, James WP. Obesity. *Lancet*. 2005;366(9492):1197-1209. doi:10.1016/S0140-6736(05)67483-
2. Nimptsch K, Pischon T. Body fatness, related biomarkers and cancer risk: an epidemiological perspective. *Horm Mol Biol Clin Investig*. 2015;22(2):39-51. doi:10.1515/hmbci-2014-0043
3. Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. *Carcinogenesis*. 2014;35(3):515-527. doi:10.1093/carcin/bgt480
4. Coller HA. Is cancer a metabolic disease?. *Am J Pathol*. 2014;184(1):4-17. doi:10.1016/j.ajpath.2013.07.035
5. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care*. 2010;33(7):1674-1685. doi:10.2337/dc10-0666
6. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. *Proc Nutr Soc*. 2008;67(3):253-256. doi:10.1017/S002966510800712X
7. World Cancer Research Fund International/American Institute for Cancer Research (2015) Continuous update project report: diet, nutrition, physical activity and liver cancer. https://www.wcrf.org/wp-content/uploads/2021/02/liver-cancer-report.pdf
8. World Cancer Research Fund International/American Institute for Cancer Research (2014) Continuous update project report: diet, nutrition, physical activity and ovarian cancer. https://www.wcrf.org/wp-content/uploads/2021/02/ovarian-cancer-report.pdf
9. World Cancer Research Fund International/American Institute for Cancer Research (2015) Continuous update project report: diet, nutrition, physical activity and gallbladder cancer. https://www.wcrf.org/wp-content/uploads/2021/02/gallbladder-cancer-report.pdf
10. World Cancer Research Fund International/American Institute for Cancer Research (2014) Continuous update project report: diet, nutrition, physical activity and prostate cancer. https://www.wcrf.org/wp-content/uploads/2021/02/prostate-cancer-report.pdf
11. World Cancer Research Fund International/American Institute for Cancer Research (2016) Continuous update project report: diet, nutrition, physical activity and stomach cancer. https://www.wcrf.org/wp-content/uploads/2021/02/stomach-cancer-report.pdf
12. Sun B, Karin M. Obesity, inflammation, and liver cancer. *J Hepatol*. 2012;56(3):704-713. doi:10.1016/j.jhep.2011.09.020
13. Villanueva A. Hepatocellular Carcinoma. *N Engl J Med*. 2019;380(15):1450-1462. doi:10.1056/NEJMra1713263
14. Zhang C, Liu S, Yang M. Hepatocellular Carcinoma and Obesity, Type 2 Diabetes Mellitus, Cardiovascular Disease: Causing Factors, Molecular Links, and Treatment Options. *Front Endocrinol (Lausanne)*. 2021;12:808526. Published 2021 Dec 23. doi:10.3389/fendo.2021.808526
15. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol*. 2019;16(10):589-604. doi:10.1038/s41575-019-0186-y
16. Saitta C, Pollicino T, Raimondo G. Obesity and liver cancer. *Ann Hepatol*. 2019;18(6):810-815. doi:10.1016/j.aohep.2019.07.004
17. Definition & facts of NAFLD & NASH. National Institute of Diabetes and Digestive and Kidney Diseases website. https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts
18. Jukaku SA, Williams SRP. The cause of obesity is multifactorial but GPs can do more. *BMJ*. 2021;373:n956. Published 2021 Apr 13. doi:10.1136/bmj.n956
19. Suresh D, Srinivas AN, Kumar DP. Etiology of Hepatocellular Carcinoma: Special Focus on Fatty Liver Disease. *Front Oncol*. 2020;10:601710. Published 2020 Nov 30. doi:10.3389/fonc.2020.601710
20. Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region. *Gut Liver*. 2016;10(3):332-339. doi:10.5009/gnl15257
21. Diehl AM. Hepatic complications of obesity. *Gastroenterol Clin North Am*. 2010;39(1):57-68. doi:10.1016/j.gtc.2009.12.001
22. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(1):73-84. doi:10.1002/hep.28431
23. Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. *Br J Cancer*. 2007;97(7):1005-1008. doi:10.1038/sj.bjc.6603932
24. Moore LL, Bradlee ML, Singer MR, et al. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *Int J Obes Relat Metab Disord*. 2004;28(4):559-567. doi:10.1038/sj.ijo.0802606
25. Donohoe CL, O'Farrell NJ, Doyle SL, Reynolds JV. The role of obesity in gastrointestinal cancer: evidence and opinion. *Therap Adv Gastroenterol*. 2014;7(1):38-50. doi:10.1177/1756283X13501786
26. Wang Y, Jacobs EJ, Patel AV, et al. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. *Cancer Causes Control*. 2008;19(7):783-792. doi:10.1007/s10552-008-9141-x
27. Steffen A, Schulze MB, Pischon T, et al. Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev*. 2009;18(7):2079-2089. doi:10.1158/1055-9965.EPI-09-0265
28. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective

observational studies. *Lancet*. 2008;371(9612):569-578. doi:10.1016/S0140-6736(08)60269-X
29. Wang Y, Wang B, Shen F, Fan J, Cao H. Body mass index and risk of primary liver cancer: a meta-analysis of prospective studies. *Oncologist*. 2012;17(11):1461-1468. doi:10.1634/theoncologist.2012-0066
30. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625-1638. doi:10.1056/NEJMoa021423
31. Sohn W, Lee HW, Lee S, et al. Obesity and the risk of primary liver cancer: A systematic review and meta-analysis. *Clin Mol Hepatol*. 2021;27(1):157-174. doi:10.3350/cmh.2020.0176
32. Younes R, Bugianesi E. NASH in Lean Individuals. *Semin Liver Dis*. 2019;39(1):86-95. doi:10.1055/s-0038-1677517
33. Singh SP, Kar SK. The Lean NASH Conundrum. J Diabetes Metab. 2016;7: 642. doi:10.4172/2155-6156.1000642
34. Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. *JHEP Rep*. 2019;1(4):329-341. Published 2019 Aug 30. doi:10.1016/j.jhepr.2019.08.002
35. Younes R, Bugianesi E. NASH in Lean Individuals. *Semin Liver Dis*. 2019;39(1):86-95. doi:10.1055/s-0038-1677517
36. Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. *JHEP Rep*. 2019;1(4):329-341. Published 2019 Aug 30. doi:10.1016/j.jhepr.2019.08.002
37. Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology*. 2015;62(6):1723-1730. doi:10.1002/hep.28123
38. Rajesh Y, Sarkar D. Association of Adipose Tissue and Adipokines with Development of Obesity-Induced Liver Cancer. *Int J Mol Sci*. 2021;22(4):2163. Published 2021 Feb 22. doi:10.3390/ijms22042163
39. Adamek A, Kasprzak A. Insulin-Like Growth Factor (IGF) System in Liver Diseases. *Int J Mol Sci*. 2018;19(5):1308. Published 2018 Apr 27. doi:10.3390/ijms19051308
40. Nishikawa H, Enomoto H, Ishii A, et al. Elevated serum myostatin level is associated with worse survival in patients with liver cirrhosis. *J Cachexia Sarcopenia Muscle*. 2017;8(6):915-925. doi:10.1002/jcsm.12212
41. Yoshimoto S, Loo TM, Atarashi K, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome [published correction appears in Nature. 2014 Feb 20;506(7488):396. Hattori, Masahisa [corrected to Hattori, Masahira]]. *Nature*. 2013;499(7456):97-101. doi:10.1038/nature12347
42. Hashimoto E, Taniai M, Tokushige K. Characteristics and diagnosis of NAFLD/NASH. *J Gastroenterol Hepatol*. 2013;28 Suppl 4:64-70. doi:10.1111/jgh.12271
43. Nalbantoglu IL, Brunt EM. Role of liver biopsy in nonalcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(27):9026-9037. doi:10.3748/wjg.v20.i27.9026
44. Nalbantoglu IL, Brunt EM. Role of liver biopsy in nonalcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(27):9026-9037. doi:10.3748/wjg.v20.i27.9026
45. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol*. 2010;53(2):372-384. doi:10.1016/j.jhep.2010.04.008
46. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55(6):2005-2023. doi:10.1002/hep.25762
47. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357. doi:10.1002/hep.29367
48. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology*. 2011;54(3):1082-1090. doi:10.1002/hep.24452
49. Idilman IS, Keskin O, Celik A, et al. A comparison of liver fat content as determined by magnetic resonance imaging-proton density fat fraction and MRS versus liver histology in non-alcoholic fatty liver disease. *Acta Radiol*. 2016;57(3):271-278. doi:10.1177/0284185115580488
50. Sheka AC, Adeyi O, Thompson J, Hameed B, Crawford PA, Ikramuddin S. Nonalcoholic Steatohepatitis: A Review [published correction appears in JAMA. 2020 Apr 28;323(16):1619. doi:10.1001/jama.2020.5249]. *JAMA*. 2020;323(12):1175-1183. doi:10.1001/jama.2020.2298
51. Cefalu WT, Bray GA, Home PD, et al. Advances in the Science, Treatment, and Prevention of the Disease of Obesity: Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care*. 2015;38(8):1567-1582. doi:10.2337/dc15-1081
52. Turati F, Trichopoulos D, Polesel J, et al. Mediterranean diet and hepatocellular carcinoma. *J Hepatol*. 2014;60(3):606-611. doi:10.1016/j.jhep.2013.10.034
53. Piercy KL, Troiano RP, Ballard RM, et al. The Physical Activity Guidelines for Americans. *JAMA*. 2018;320(19):2020-2028. doi:10.1001/jama.2018.14854
54. Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study [published correction appears in Int J Obes (Lond). 2013 Nov;37(11):1514] [published correction appears in Int J Obes (Lond). 2015 Jan;39(1):187. doi: 10.1038/ijo.2014.88]. *Int J Obes (Lond)*. 2013;37(11):1443-1451. doi:10.1038/ijo.2013.120

55. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
56. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038
57. Caiazzo R, Lassailly G, Leteurtre E, et al. Roux-en-Y gastric bypass versus adjustable gastric banding to reduce nonalcoholic fatty liver disease: a 5-year controlled longitudinal study. *Ann Surg*. 2014;260(5): 893-899. doi:10.1097/SLA.0000000000000945
58. Tang A, Bashir MR, Corwin MT, et al. Evidence Supporting LI-RADS Major Features for CT- and MR Imaging-based Diagnosis of Hepatocellular Carcinoma: A Systematic Review. *Radiology*. 2018; 286(1):29-48. doi:10.1148/radiol.2017170554
59. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390. doi:10.1056/NEJMoa0708857
60. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745
61. Kudo M. Durvalumab plus tremelimumab in unresectable hepatocellular carcinoma. *Hepatobiliary Surg Nutr*. 2022;11(4):592-596. doi:10.21037/ hbsn-22-143
62. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma [published correction appears in J Hepatol. 2019 Apr;70(4):817. doi: 10.1016/j.jhep.2019.01.020]. *J Hepatol*. 2018;69 (1):182-236. doi:10.1016/j.jhep.2018.03.019
63. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An update. *Hepatology*. 2011;53(3):1020-1022. doi:10.1002/hep.24199
64. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet*. 2018;391(10127):1301-1314. doi:10.1016/S0140-6736(18)30010-2
65. Piscaglia F, Svegliati-Baroni G, Barchetti A, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. *Hepatology*. 2016;63(3):827-838. doi:10.1002/hep.28368
66. Paradis V, Zalinski S, Chelbi E, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. *Hepatology*. 2009;49(3):851-859. doi:10.1002/hep.22734
67. Kim CK, Lim JH, Lee WJ. Detection of hepatocellular carcinomas and dysplastic nodules in cirrhotic liver: accuracy of ultrasonography in transplant patients. *J Ultrasound Med*. 2001;20(2):99-104. doi:10.7863/jum.2001.20.2.99
68. Gupta P, Soundararajan R, Patel A, Kumar-M P, Sharma V, Kalra N. Abbreviated MRI for hepatocellular carcinoma screening: A systematic review and meta-analysis. *J Hepatol*. 2021;75(1):108-119. doi:10.1016/j.jhep.2021.01.041
69. Kanwal F, Singal AG. Surveillance for Hepatocellular Carcinoma: Current Best Practice and Future Direction. *Gastroenterology*. 2019;157(1):54-64. doi:10.1053/j.gastro.2019.02.049
70. Chan SL, Mo F, Johnson PJ, et al. Performance of serum α-fetoprotein levels in the diagnosis of hepatocellular carcinoma in patients with a hepatic mass. *HPB (Oxford)*. 2014;16(4):366-372. doi:10.1111/hpb.12146
71. Farinati F, Marino D, De Giorgio M, et al. Diagnostic and prognostic role of alpha-fetoprotein in hepatocellular carcinoma: both or neither?. *Am J Gastroenterol*. 2006;101(3):524-532. doi:10.1111/j.1572-0241.2006.00443.x
72. Li D, Mallory T, Satomura S. AFP-L3: a new generation of tumor marker for hepatocellular carcinoma. *Clin Chim Acta*. 2001;313(1-2):15-19. doi:10.1016/ s0009-8981(01)00644-1

