



Hepatocellular carcinoma in non-alcoholic fatty liver disease— a review of an emerging challenge facing clinicians

Daniel Geh^{1,2}, Derek M. Manas^{2,3}, Helen L. Reeves^{1,3}

¹Northern Institute for Cancer Research, ²Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; ³Hepatopancreatobiliary Multidisciplinary Team, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

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Correspondence to: Helen L Reeves. Professor of Liver Cancer, Northern Institute for Cancer Research, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK. Email: H.L.Reeves@newcastle.ac.uk.

Importance: Non-alcoholic fatty liver disease (NAFLD) is a rapidly growing cause of chronic liver disease and is becoming a leading cause of hepatocellular carcinoma (HCC) in many developed countries. This presents major challenges for the surveillance, diagnosis and treatment of HCC.

Objective: To discuss the clinical challenges faced by clinicians in managing the rising number of NAFLD-HCC cases.

Evidence Review: MEDLINE, PubMed and Embase databases were searched using the keywords; NAFLD, HCC, surveillance, hepatectomy, liver transplantation, percutaneous ablation, transarterial chemoembolization (TACE), selective internal radiotherapy treatment (SIRT) and sorafenib. Relevant clinical studies were included.

Findings: Current HCC surveillance programmes are inadequate because they only screen for HCC in patients with cirrhosis, whereas in NAFLD a significant proportion of HCC develops in the absence of cirrhosis. Consequently NAFLD patients often present with a more advanced stage of HCC, with a poorer prognosis. NAFLD-HCC patients also tend to be older and to have more co-morbidities compared to HCC of other etiologies. This limits the use of curative treatments such as liver resection and orthotopic liver transplantation (OLT). Evidence suggests that although NAFLD-HCC patients who undergo liver resection or OLT have worse perioperative and short-term outcomes, overall long-term survival is comparable to HCC of other etiologies. This highlights the importance of careful patient selection, pre-habilitation and perioperative planning for NAFLD-HCC patients being considered for surgical treatment. Careful consideration is also important for non-surgical treatments, although the evidence supporting treatment selection is frequently lacking, as these patients tend to be poorly represented in clinical trials. Locoregional therapies such as percutaneous ablation and TACE may be less well tolerated and less effective in NAFLD patients with obesity or diabetes. The tyrosine kinase inhibitor sorafenib may also be less effective.

Conclusions and Relevance: This review highlights how international guidelines, for which NAFLD traditionally has made up a small part of the evidence base, may not be appropriate for all NAFLD-HCC patients. Future guidelines need to reflect the changing landscape of HCC, by making specific recommendations for the management of NAFLD-HCC.

Keywords: Non- alcoholic fatty liver disease (NAFLD); hepatocellular carcinoma (HCC); liver transplantation; hepatectomy; catheter ablation; sorafenib; population surveillance

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and usually occurs in the context of liver cirrhosis. Worldwide liver cancer is the fifth most common cancer and is ranked third in cancer related mortality (1). Whereas overall cancer mortality is generally decreasing, liver cancer is the most rapidly increasing cause of cancer mortality (2-5). In the United States between 2000 to 2016, mortality from liver cancer has increased by 43% (10.5 to 15.0 per 100,000) in men and by 40% (4.5 to 6.3 per 100,000) in women (6). Despite some improvement in surveillance and treatments, the overall 5-year survival rate is around 15% (7). This growing burden of disease incidence and mortality has made HCC a significant public health concern.

The majority of HCC occurs in the context of liver cirrhosis. Globally chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) related liver cirrhosis are the leading causes of HCC (8). In western countries, where viral hepatitis is less prevalent, alcohol-related liver disease (ARLD) and non-alcoholic fatty liver disease (NAFLD) are the leading causes of liver cirrhosis and HCC (9).

In the last few decades there has been an epidemic in obesity, dyslipidemia, hypertension and type 2 diabetes mellitus (T2DM). These entities, collectively known as the metabolic syndrome, increase the risk of atherosclerotic cardiovascular disease and NAFLD (10,11). NAFLD has now become the most common cause of chronic liver disease with an estimated global prevalence of 25% (12). The rise of the metabolic syndrome, combined with the decline of viral hepatitis due to HBV vaccination and highly effective direct acting anti-virals to treat HCV, has contributed to NAFLD becoming one of the leading causes of HCC in western countries (13-15). This brings major challenges with surveillance, diagnosis and management of HCC. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/hbsn.2019.08.08>).

The increasing burden of HCC in NAFLD

NAFLD is a spectrum of disease made up of hepatic steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and end stage liver disease. Around 25% of the adult population in the United States have evidence of NAFLD, with the majority having hepatic steatosis without evidence of inflammation or scarring. Of those with hepatic steatosis, reported studies suggest that around 25% will

progress to NASH (6% of the general population), of which a significant number will develop cirrhosis (16). NASH is characterized by steatosis, ballooning degeneration of hepatocytes, and inflammation. Progression to fibrosis occurs in 26–37% of those with biopsy proven NASH, of which around 9% reportedly develop cirrhosis over 5.6 years (17). NAFLD cirrhosis is currently estimated to have a prevalence of 1–2% in the United States and is emerging as the most common cause of cirrhosis worldwide (16). Of additional concern, the prevalence of NAFLD in the paediatric population is also increasing and is believed to be between 7.6% to 34.2% (18).

Not surprisingly, along with rise in NAFLD the prevalence of NAFLD associated HCC has also increased. The annual incidence of HCC is estimated to be 2.6% in patients with NAFLD cirrhosis (19). In total, NAFLD cirrhosis makes up around 10–14% of HCC cases in western countries and the incidence has increased by 9% between 2004 to 2009 in the United States (20,21). The proportion of patients with NAFLD-HCC on liver transplant waiting lists increased from 2.1% to 16.2% in the United States between 2000 and 2016 (15). NAFLD-HCC can also develop in the absence of cirrhosis, with the number of non-cirrhotic individuals with HCC increasing in prevalence and accounting for 25–45% of total NAFLD-HCC cases (13,22). Although HCC can develop in other etiologies of chronic liver disease in the absence of cirrhosis, NAFLD has a higher risk of non-cirrhotic HCC when compared to HCV and ALD (23). Due to the very large number of patients with NAFLD though, the absolute risk of developing NAFLD-HCC without cirrhosis is still small (24). The pathogenesis of NAFLD-HCC in this context is poorly understood, but chronic inflammation, hyperinsulinemia, adaptive immune responses, hepatic progenitor cell populations and genetic susceptibility may all play a role (25).

Clinical features of NAFLD-HCC

NAFLD-HCC tends to be diagnosed at a more advanced stage compared to HCC related to other etiologies (22,26). A large Italian cohort demonstrated that NAFLD-HCC Barcelona Clinic Liver Cancer (BCLC) C tumours were significantly more common at the presentation of NAFLD-HCC compared to HCV-HCC (21% *vs.* 4%, $P < 0.0001$) (22). Both suboptimal HCC surveillance practice and NAFLD-HCC arising in the absence of cirrhosis and hence no surveillance practice, are likely contributory factors (22,26).

Overall, patients with NAFLD-HCC have a worse prognosis compared to those with other etiologies, which most likely relates to the more advanced stage of disease at diagnosis, as well co-morbidities in patients with the metabolic syndrome, which limits the use of curative treatments. The Italian cohort study reported an average survival of 25.5 months in NAFLD-HCC compared to 33.7 months in HCV-HCC ($P=0.017$), but when adjusting for stage and curative treatments, this survival difference disappeared (22). Of note, as NAFLD-HCC patients often don't have cirrhosis, their liver function can be preserved compared to other etiologies, so both curative and palliative therapies may still be appropriate for some (13,22,27,28). However, NAFLD-HCC patients are typically older, with a higher prevalence of T2DM, obesity, cardiovascular disease and cerebrovascular disease, which also need to be considered (13,27-29). Studies suggest that only a relatively small proportion of NAFLD-HCC patients are offered liver resection or orthotopic liver transplantation (OLT) (17.8% and 4.4% respectively) and are more likely to be offered supportive care than those with other underlying etiologies (22,27,28). Of note, although obesity and a raised BMI are associated with progression to cirrhosis in patients with NAFLD and generally poorer outcomes in those with the metabolic syndrome, body mass index (BMI) is positively associated with improved survival in HCC regardless of underlying etiology (28). This is very much in keeping with the marked negative impact that weight loss, constitutional symptoms and declining performance status are known to have on prognosis in patients with HCC (30).

Biology of NAFLD-HCC

The underlying pathophysiology of NAFLD-HCC is complex and the current understanding has been recently reviewed elsewhere (31,32). Chronic hepatitis, necro-inflammation and systemic metabolic dysfunction are all relevant, with proposed mechanisms including oxidative stress and DNA damage, dysfunctional DNA damage responses, dysfunctional autophagy, altered microbiome and innate and adaptive immune responses (31). In brief, fatty acid accumulation induces *de novo* lipogenesis and steatosis, as well as fatty acid oxidation associated with the production of reactive oxygen species (ROS) and DNA damage (33). DNA damage results in hepatocyte death, driving an inflammatory response with macrophages and neutrophils potentially releasing more ROS, causing further DNA damage (31,34). Aberrant DNA damage repair

responses may contribute to a permissive environment in which acquired genetic mutations promote HCC development (35,36). Cellular proteins can also be damaged and autophagy is the process by which cytoplasmic proteins are tagged, transported to and degraded by lysosomes in response to metabolic stress—recycling in addition to removing them, supporting the energy requirement of the cell (37). In the context of NAFLD, excess triglycerides and free fatty acids have been shown to inhibit autophagy, again leading to increased cellular stress and DNA damage (38). Microbiome dysbiosis is another factor considered important in NAFLD progression, with some species (Firmicutes, Prevotellaceae and Enterobacteriaceae bacteria) more prevalent in patients with NASH (39) and roles in hepatocarcinogenesis suspected. Animal models support a contribution from the gut, with increased intestinal permeability and leakiness potentially promoting the translocation of lipopolysaccharide (LPS) to the liver, exacerbating inflammation and driving disease progression and NAFLD-HCC (40). Finally, underpinning the range in disease severity, patient genetic factors, with variations in liver regulatory genes such as PNPLA3, TM6SF2 and MBOAT7, are believed to play a key role not just in NAFLD progression, but also in determining an individual's risk of developing NAFLD-HCC (41-44).

HCC surveillance in NAFLD

Current international guidelines recommend screening for HCC in all patients with cirrhosis or advanced fibrosis with 6 monthly abdominal ultrasound (US) with or without alpha fetoprotein measurements (45-48). Surveillance in patients with NAFLD is often suboptimal, with up to 52% of NAFLD-HCC cases not diagnosed by surveillance, presenting with liver-related complications instead (22). The failure of surveillance in this population more so than others can be attributed to a number of factors. In patients with known NAFLD cirrhosis, abdominal US is not as sensitive as an early detection tool compared to other etiologies, as the presence of fatty liver disease and obesity hamper performance (49). Furthermore, in many patients with NAFLD cirrhosis and HCC, the presence of cirrhosis is only apparent at the time of HCC diagnosis and the opportunity for surveillance and early stage detection missed. Finally, the proportion of NAFLD-HCC which arises in the absence of cirrhosis is in part to blame, as surveillance in non-cirrhotic NAFLD is not recommended (45). This is because it is simply not cost effective and surveillance can

cause harm (50). With the aim of reducing disease related mortality, cost effectiveness is influenced by the incidence of the disease in the target population, the availability of an acceptable and efficient diagnostic test at a reasonable cost, as well as the availability of effective treatments. Focused primarily on incidence, modelling studies have suggested that an HCC incidence of 1.5% per year or greater warrants surveillance in cirrhotic patients fit for resection (51). HCC incidence in NAFLD cirrhosis has been estimated to be in the region of 2.6% per year (19) and thus HCC surveillance justifiable. In the absence of cirrhosis with any etiology, the incidence is smaller, but patients may be able to withstand more radical therapies. Consequently an incidence in the region of 0.2% per year has been proposed as cost effective and on this basis, surveillance in non-cirrhotic patients with advanced or 'Metavir 3' fibrosis regardless of etiology has been advised, as has surveillance in non-cirrhotic HBV, with scores based on age, gender, platelet count and family history proposed to stratify risk (45). The challenge with NAFLD in the absence of significant fibrosis, is that the incidence is prohibitively small, estimated to be at most 0.01% per year in patients with simple steatosis (52), or 0.8/1,000 person years in individuals with type 2 diabetes (53). The numbers of patients presenting with non-cirrhotic NAFLD-HCC reflects the enormous population exposed to this very small risk. Thus, there is a need for much cheaper and effective surveillance tests, as well as NAFLD patient specific data that will help to stratify the larger population and inform surveillance decisions. Risk calculations using age, gender and genotypes, such as PNPLA3 and TM6SF2 genotypes, are being researched but are not at present clinically useful (50,54). Serum tests are cheaper than imaging and the GALAD serum score, comprised of α -fetoprotein, L3 α -fetoprotein and des- γ -carboxyprothrombin has been shown to be superior to abdominal US for HCC detection in a retrospective cohort in the United States (55). Further prospective and surveillance studies are still awaited. Other novel candidate biomarkers include circulating tumor DNA (ctDNA), extra-cellular vesicles, serum Dickkopf 1 and serum osteopontin (31,56-58). Improving HCC surveillance in NAFLD would be the first step in improving outcomes, as it would increase the number of early stage and potentially curable tumours.

HCC diagnosis in NAFLD

HCCs commonly have a relatively arterIALIZED blood supply relative to background liver, with arterial to venous

shunting within the tumours. When these features are present on contrast enhanced imaging—detecting arterial hypervascularity and rapid venous washout, a radiological diagnosis of HCC is sensitive and specific in patients with cirrhosis (45). Due to the numbers of NAFLD patients developing HCC in the absence of cirrhosis, special consideration is needed with regards to diagnostic imaging. The radiological appearance of HCC in cirrhotic and non-cirrhotic livers is generally similar, although the non-cirrhotic HCC are more often solitary without satellite lesions, larger and can have a central scar (59). Computer tomography (CT) imaging using properly administered contrast is essential for accurate assessment and can make the diagnosis of cancer with a high degree of confidence. Arterial enhancement and portal phase 'wash-out' is similar to cirrhotic livers, with features such as encapsulation, intralesional fat and foci of haemorrhage being more common (60). Despite these appearances, the probability of a 'typical lesion' being an HCC—rather than another type of cancer—is not as high as in the presence of cirrhosis. Thus, the nature of the malignancy cannot be assumed in the absence of cirrhosis. Any patient with a suspected malignancy in a non-cirrhotic liver, that is fit for therapy, should have a biopsy of the lesion to confirm the histological diagnosis. Distinguishing suspected cancers from benign lesions can also be challenging. 50% of non-cirrhotic HCC have a central scar—a feature often noted in the benign lesion focal nodal hyperplasia. Central scars are best characterised on MRI imaging using gadolinium. MRI is also better at detecting intracellular fat accumulation that may favour malignancy and is present in 10–17% of non-cirrhotic HCC and 36% of well differentiated tumours. Primovist MRI may help to increase the level of confidence that a lesion is benign, but generally the lack of central scar enhancement and the presence of satellite lesions on MRI, regardless of contrast agent, reportedly has a 98% specificity for malignancy (61). In summary, biopsy diagnosis is more common in patients with NAFLD-HCC. If there is any doubt that a lesion is benign, a biopsy should be considered. If a lesion in a non-cirrhotic liver is thought to be an HCC, biopsy confirmation should be performed regardless of the imaging.

NAFLD-HCC—implications for management

Staging of HCC in patients with NAFLD-HCC

The management of HCC is complex and a multidisciplinary approach is vital. The main factors that

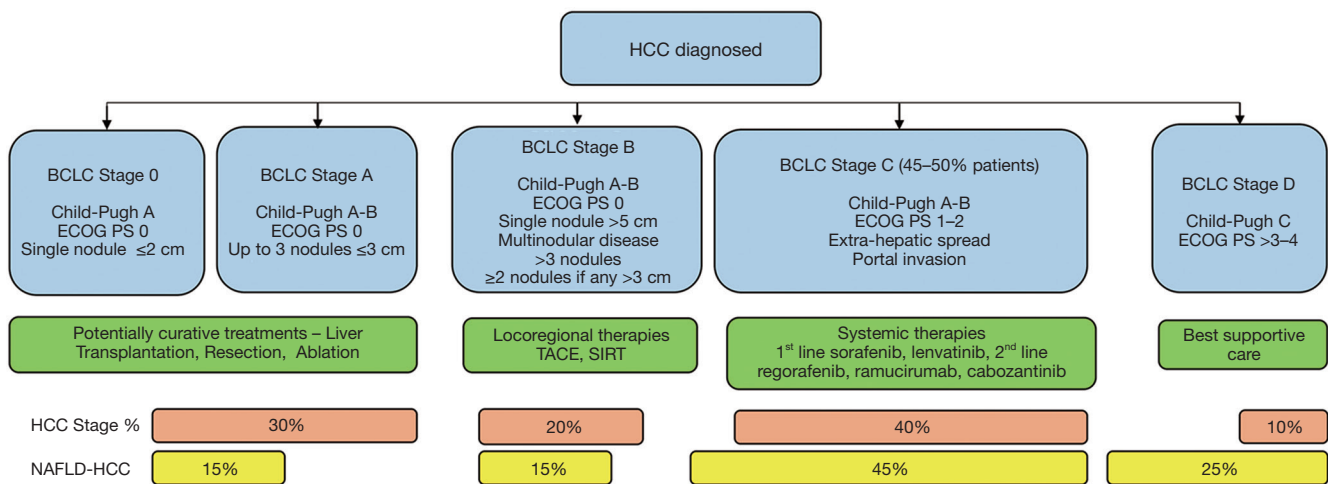


Figure 1 Hepatocellular carcinoma staging and treatment. The EASL guidelines recommend the BCLC algorithm for the management of patients with HCC (45). Patients are classified based on tumour stage, liver function and performance status into four categories (A-D) (blue boxes), with treatments ranging from resection, transplantation and ablation in fitter patients with early disease (BCLC-A), to supportive care in those with advanced HCC in association with poor liver function and/or performance status (BCLC-D) (green boxes). In the populations where HCV cirrhosis is highly prevalent (orange boxes), up to half the patients are suitable for curative or locoregional therapies, with 40% suitable for 1st line medical therapy. In regions where NAFLD is the commonest cause of HCC, the majority of treatable patients are classed BCLC-C (13) and may have age or metabolic syndrome co-morbidities less suitable for medical therapies (yellow boxes). The recent updated EASL guideline supports ECOG-PS stage being attributed to cancer associated symptoms only, potentially enabling an allocation of a patient with physical restrictions impacting performance to BCLC-A or BCLC-B categories, if they have preserved liver function and an earlier stage cancer. In reality, there is little evidence supporting the use of locoregional therapies in these patients. Neither are there evidence based guidelines directing therapies in the absence of cirrhosis. Medical therapies should be considered, but neither elderly patients nor NAFLD patients have been well represented in the clinical trials of medical therapies. HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic for Liver Cancer; EASL, European Association for the Study of the Liver; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; TACE, transarterial chemoembolization; SIRT, selective internal radiotherapy treatment; NAFLD, non-alcoholic fatty liver disease.

determine management are stage of disease, tumor burden, liver function and performance status. The staging system widely used is the BCLC system, which comprises of 5 stages; very early disease (0), early stage (A), intermediate stage (B), advanced stage (C) and terminal stage (D). Tumor burden is categorized by the number and size of cancers, as well as presence of tumour macro vascular invasion and extra hepatic spread. Liver function is categorized using the Child-Turcotte-Pugh score, which is a three-tier scale from A to C, with C indicating poor liver function. Performance status is categorized using the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (45). HCC staging and management is summarized in *Figure 1*.

Curative approaches for early stage disease with preserved liver function include liver resection and ablation, while liver transplantation can be used for early stage disease with poor liver function or portal hypertension. The commonest

first line therapy is transarterial chemo-embolization, offered to those with intermediate stage disease and preserved liver function. For those with advanced cancers and with preserved liver function, systemic therapies with multikinase inhibitors sorafenib and lenvatinib are now available first line, while regorafenib, cabozantinib and ramucirumab are approved for selected individuals in the second line setting. For those with poor liver function and performance status, the majority are managed with best supportive care (45,46), as liver transplantation is restricted to those fit enough with early stage cancers.

The relevance for the BCLC in guiding the management of NAFLD-HCC has been recently reviewed, highlighting both its strengths and weaknesses (31). Regardless of tumour stage, NAFLD-HCC patients more often don't have cirrhosis, but they do tend to be older, diagnosed at a more advanced age and with comorbidities such as obesity,

T2DM, cardiovascular disease and cerebral vascular disease (13,28). These are very relevant factors to consider when offering treatments, although their impact is not defined clearly within the BCLC algorithm, which was developed primarily as a tool to guide management for patients with viral hepatitis. The prognostic value of the BCLC across all etiologies is not in doubt, but the majority of NAFLD-HCC patients fall into the heterogenous BCLC-C category, which directs patients to medical therapy, or the BCLC-D category directing to supportive care. Classifying the majority of NAFLD-HCC patients fit for treatment as 'BCLC-C' may be appropriate in prognostic terms, but the evidence base to guide treatment is limited. Elderly NAFLD-HCC patients have not been well represented in trials of medical therapy and if medical therapies are offered, efforts should be made to monitor 'real life practice' (62). In reality, some BCLC-C patients with preserved liver function and a small tumour burden may benefit more from selected loco-regional therapies, but these too lack an evidence base and further data is needed. In a large tertiary referral centre in Newcastle-upon-Tyne, where the majority of patients with HCC referred have either underlying NAFLD, or another etiology in combination with the metabolic syndrome, we have devised a modified management algorithm, which is described in *Figure 2*.

As NAFLD-HCC often presents in the absence of cirrhosis, liver function in these patients may be well preserved, even in advanced disease (13,22). While some will have significant co-morbidities making them unsuitable for surgical or logoregional therapies, others may be fitter. Potentially therefore, the BCLC algorithm may well be too conservative. Increasingly there have been moves to 'downstage' patients with HCC, which is a term which typically refers to reducing the size of a tumour with transarterial therapy in order to consider liver transplantation. While transplantation is reserved for patients with cirrhosis, this downstaging principal can be applied in non-cirrhotic patients, who may subsequently have a lesser size or number of tumours, with residual disease suitable for treatment with ablation or resection. Thus, a patient treated initially with transarterial chemoembolization (TACE) may have ablation with curative intent to residual disease. Similarly, a non-cirrhotic patients with a large HCC may have selective internal radiotherapy treatment (SIRT) to reduce the size of their cancer in order to subsequently resect it (63). There is no randomised control trial evidence base for these practices and it is essential that management decisions

are made within the forum of a multidisciplinary meeting (MDM), with the opinions of expert physicians, surgeons, radiologists and oncologists considered (*Figure 2*).

The major focus on management hereafter, is centred on those patients being considered for potentially curative therapies, with brief reference to evidence, or lack of it, for treating patients with more advanced NAFLD-HCC.

Liver resection

The criteria for resecting hepatocellular cancer in patients with cirrhosis is well defined and includes those patients with non-clinically significant portal hypertension (hepatic vein pressure gradient of <10 mmHg), early stage disease (BCLC stage 0 to A), good performance status and preserved liver function. In the absence of cirrhosis, the criteria are less well defined. Since staging systems like the BCLC are associated with underlying cirrhosis, they are not relevant in these patients and tumour features are used for staging and prognosis. NAFLD-HCC patients more often than not, present with a more advanced stage of disease, with larger tumors which are technically more difficult to resect due to anatomical constraints or extra-hepatic disease making them un-resectable. This growing category of patients with non-cirrhotic NAFLD-HCC will also have metabolic syndrome co-morbidities—such as obesity, T2DM and cardiovascular disease—potentially increasing the risk of perioperative complications. These include bleeding, wound infection, delayed wound healing, venous thrombotic disease and pulmonary complications (64). In some experienced centres, up to 20% of NAFLD-HCC patients may undergo liver resection (22), although literature available on outcome from liver resection in patients with the metabolic syndrome is not, as yet comprehensive enough to inform evidence based guidelines.

A number of studies have reported comparable short-term mortality in patients with either NAFLD or obesity following liver resection, as compared to those with other etiologies (29,65-71). In a multi-centre, retrospective study of HCC patients undergoing liver resection, 90 day mortality and morbidity of metabolic syndrome related HCC (MS-HCC) was comparable to that of HCV-HCC despite the significantly higher prevalence of obesity and T2DM (69). In fact, MS-HCC resection patients had better overall survival compared to HCV-HCC patients at 65.6% *vs.* 61.4% at 5-year respectively (P=0.031). Recurrence in MS-HCC patients was also lower compared to HCV-HCC patients (44.6% *vs.* 65.2% respectively,

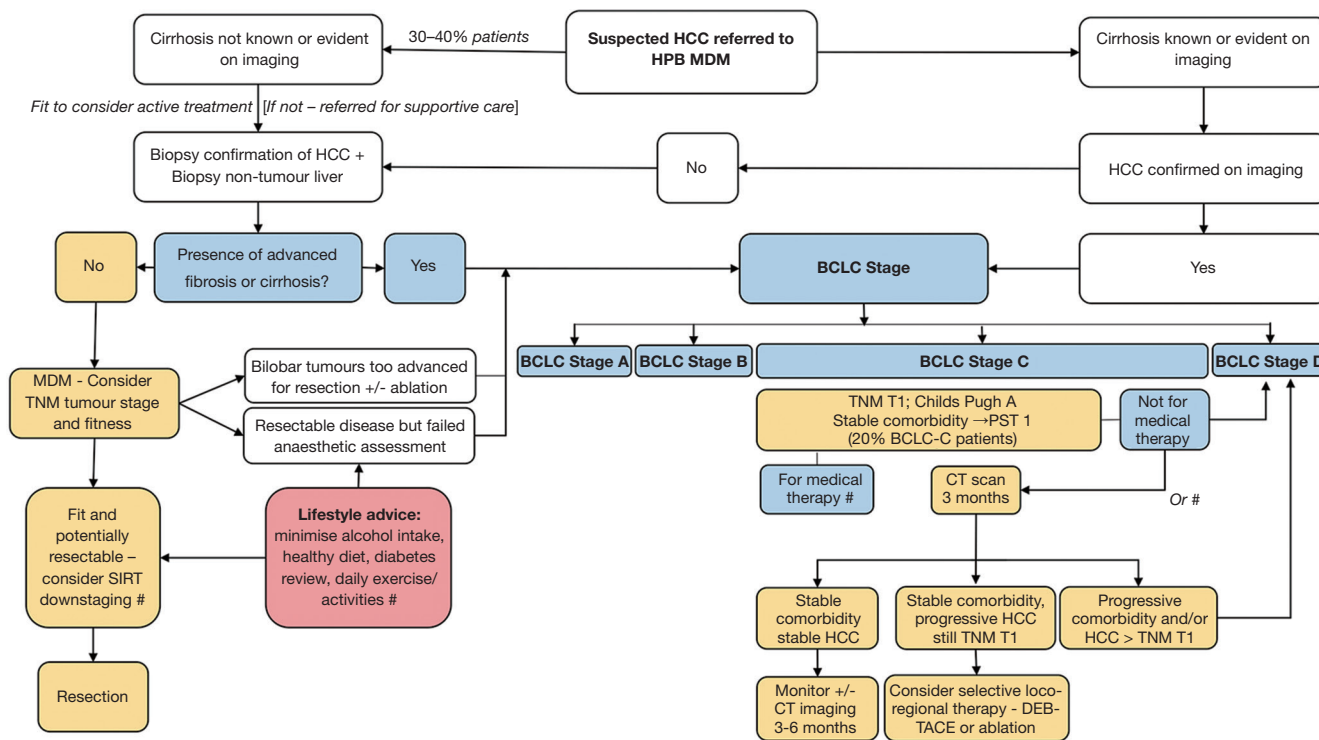


Figure 2 HCC MDT care in a centre with high prevalence of metabolic syndrome and NAFLD. In Newcastle upon Tyne, UK, NAFLD is the commonest cause of HCC and over two thirds of patients have the metabolic syndrome irrespective of their underlying liver disease etiology. NAFLD patients are more likely to present in the absence of cirrhosis and require biopsy confirmation of their HCC and liver disease stage. The BCLC algorithm guides treatment strategies in cirrhotic patients and in non-cirrhotic patients, liver function may be better preserved and more radical surgical approaches may be appropriate in those that are fit enough. In NAFLD patients classed as BCLC-C, medical therapies may not be ideal (e.g., restricted mobility, renal or cardiac impairment). Selective TACE may be better tolerated and preferable to supportive care in some instances. This figure summaries the modified BCLC pathway (yellow boxes) directed by the Newcastle upon Tyne Hepatopancreatobiliary multidisciplinary team (HPB MDT), with # noting those areas where the evidence base is lacking and research or service improvement audits are necessary to inform future modifications to clinical practice. HPB, hepatobiliary; MDM, multidisciplinary meeting; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic for Liver Cancer; TNM, tumor node metastasis; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HCC, hepatocellular carcinoma; MDT, multidisciplinary team; SIRT, selective internal radiation therapy; DEB-TACE, drug-eluting bead transarterial chemoembolization; NAFLD, non-alcoholic fatty liver disease.

P=0.005). Although the HCV-HCC group possibly had more poorly differentiated tumors, and the study predated the HCV DAA era potentially delivering viral eradication pre or post resection, it was notable that having the metabolic syndrome per se did not appear to negatively impact prognosis. From multivariate analysis, MS-HCC was reported as a protective factor from early recurrence and HCV-HCC a negative prognostic factor for overall survival and relapse free survival (69). An independent study comparing outcomes post resection of patients with and without steatosis similarly reported encouraging results,

with no significant differences in postoperative complication and mortality (70). The study was again a retrospective one, in which the steatosis group did have a slightly smaller tumor size, with a lower vascular invasion rate, which may have contributed to the better 5-year survival (70). Similar retrospective studies also report comparable perioperative and long-term outcomes in NAFLD-HCC compared to other etiologies following liver resection (29,71). As alluded to previously, there have been studies reporting greater intraoperative blood losses in obese compared to non-obese individuals (67), as well as increased wound

infections (66), but even some of these studies found no differences in survival. The presence of type 2 diabetes has also been reported to increase the risk of sepsis and even liver failure after liver resection (72-74), although again, increases in these perioperative complications does not necessarily have an impact on long term outcome (75).

Reports from centres in the Far East have also advocated resection as the primary curative treatment, Japanese patients with a high BMI ($>25 \text{ kg/m}^2$) have a better long term prognosis compared to those with a lower BMI ($<25 \text{ kg/m}^2$), with no increased risk of postoperative complications (76,77). In series such as these it is unclear whether lower BMI is a surrogate marker for more advanced HCC, with HCC related cachexia and poor functional reserve. A large Chinese study found patients with a BMI $<18.5 \text{ kg/m}^2$ (underweight) or BMI $>25 \text{ kg/m}^2$ (overweight) had a worse prognosis to patients with a BMI of 18.5–25 kg/m^2 (normal weight) (78). These data are notable, but the number of patients with a BMI $>30 \text{ kg/m}^2$ was low in these studies, while it is relatively common in some western populations—where surgery on individuals with BMI $<18.5 \text{ kg/m}^2$ is rare. These studies may not be relevant to westernised populations.

In addition to these encouraging, if somewhat limited, results referred to in the studies above, there have been studies that have reported poorer short-term outcomes for patients with metabolic syndrome (79-84). One of these was of a large cohort of 3,973 patients undergoing liver resection, in which patients with metabolic syndrome had an increased incidence of blood transfusion, reintubation, myocardial infarction, surgical site infection as well as postoperative death (79). Smaller studies have also reported significantly higher 30-day mortality and morbidity in NAFLD-HCC patients compared to HCV and HBV-HCC patients (82). Notably, several studies report increased morbidity and mortality in NAFLD patients with underlying NASH or cirrhosis compared to those with normal liver parenchyma (80-82). However, long-term outcomes in these studies were comparable. In NAFLD, careful surgical planning is needed in order to prevent post resection liver failure. Increased age, diabetes, steatosis and NASH are common in NAFLD-HCC patients and also increase the risk of post resection liver failure (85), possibly because these factors affect hepatic regeneration. The risk of post resection liver failure can be reduced with good preoperative planning utilizing qualitative and quantitative measures of liver function as well as the use of future remnant liver volume augmentation techniques such as

portal vein embolization (85).

Thus, there is variation in the reported studies, which is not uncommon in retrospective case series and cohort studies which are affected by factors such as selection bias. It does appear though, that in experienced centres NAFLD-HCC patients can do well post resection, particularly in the longer term. Thus, we should continue to explore and improve surgical options as well as tailor perioperative care to this complex group of patients. Laparoscopic approaches, which are better tolerated, with reduced intra-operative blood loss and reduced length of postoperative hospital stay, have been advocated by some centres (68).

While the focus here has largely been on factors most relevant to patients with the metabolic syndrome, generally speaking sarcopenia may be an alternative predictor of prognosis in HCC patients undergoing liver resection. A recent meta-analysis of 8 retrospective studies, including 1,161 patients of various etiologies undergoing either liver resection or radiofrequency ablation, reported that patients with sarcopenia had significantly increased rates of complications and tumour recurrence, as well as reduced 1- and 3-year survival (86). Whether or not it is possible to improve sarcopenia and positively impact outcomes is not yet known as very few studies have investigated the impact of interventions treating sarcopenia or improving nutritional status. One study investigating perioperative nutrition support in the form of enteral feeding reported a reduction in the length of hospital admission, but no difference in objective measures of morbidity or complications was demonstrated (87).

Liver transplantation

OLT is offered to patients who are deemed fit enough, with early stage cancers complicating cirrhosis, but in whom significant portal hypertension or impaired liver function is a barrier to safe resection. The tumour stage restriction most commonly applied is up to 3 nodules $\leq 3 \text{ cm}$ or a single nodule $\leq 5 \text{ cm}$ (88). OLT has the added benefit of curing the underlying liver disease. NAFLD cirrhosis is currently the second most common indication for OLT in the United States and is likely to become the leading indication in other western countries (89). Data from the European Transplant Registry shows an increase in the proportion of NAFLD transplants from 1.2% in 2002 to 8.4% in 2016 and shows that HCC is more common in patients transplanted for NAFLD compared to other etiologies (90). From 1988 to 1996, 54% of patients receiving OLT in the United States

were either overweight, obese, severely obese or morbidly obese (91). These figures are likely to be much higher now. As with liver resection, the generally older age of NAFLD-HCC patients, along with presence of co-morbidities, does affect fitness for transplantation and as a result NAFLD patients are less likely to be receive OLT compared to other etiologies (92). In the Italian cohort of 145 NAFLD-HCC patients described earlier, only 1 received OLT (22).

For those that are transplanted, short term outcomes and postoperative complications are reportedly worse in NAFLD patients undergoing OLT, whether for end stage liver disease or for HCC. NAFLD patients tend to have longer operative time, increased blood loss and longer length of stay postoperatively (93-95). Historically, the presence of NASH has been shown to be an independent factor that influences early OLT mortality (96). In studies reporting higher early mortality in NAFLD patients, sepsis and cardiovascular disease are the most common causes of increased death (97-100). Interestingly NASH has been shown to be a risk factor for the development of cardiovascular complications following OLT independent to other comorbidities and metabolic factors (99,101). A possible mechanism is that metabolic syndrome may stimulate erythrocyte hyperaggregability and hyperfibrinogenemia leading to a prothrombotic state which predisposes to thrombo-embolic and athero-thrombotic events (102). This emphasizes the importance of a tailored preoperative work up, including cardio-vascular testing. For OLT in the context of HCC, overweight and obese patients have a significantly increased incidence of perioperative life threatening complications, however 90 day mortality is reportedly unaffected (95).

Overall survival at 5-years following OLT for NAFLD-cirrhosis is comparable to other etiologies. Longer term post OLT survival is slightly lower for NAFLD-HCC compared to NAFLD-cirrhosis, with 5-year survival being 66.7% versus 72.5% respectively (103). NAFLD-HCC patients who undergo OLT do have a similar disease-free and overall survival compared to other etiologies of HCC (98,104,105). A large retrospective cohort study using United Network for Organ Sharing data from 2002 to 2012 demonstrated that 5-year survival post OLT for NAFLD, HCV and ARLD associated HCC was 65.5%, 65.7% and 63.9% respectively (105). In a retrospective study of 159 patients undergoing OLT for HCC patients who were overweight or obese had a significantly increased rate of disease recurrence and reduced time to recurrence

compared to patients of a normal weight (95). Diabetes also has a negative impact on outcomes with diabetes being associated with reduced 1- and 5-year overall survival as well as reduced graft survival (93). Furthermore, when diabetes co-exists with obesity, this further reduces 5-year survival rates and this is particularly apparent in patients with HCC (93).

A recent analysis of 68,950 liver transplants recipients between 2002 and 2016 using data from the European Liver Transplant Registry database has also reported reassuring results (90). Overall there was comparable patient and graft survival post OLT between NAFLD and non-NAFLD patients, with and without HCC. Recurrent HCC, infection and extrahepatic solid organ malignancy were the most common causes of death in NAFLD-HCC patients whereas infection and cardiovascular complications were the most common in NAFLD non-HCC patients. In NAFLD non-HCC patients, older age, Model for End-Stage Liver Disease (MELD) score >23 and BMI ≤ 18.5 or $>40 \text{ kg/m}^2$ were independent factors associated with death. Interestingly this association was not seen in NAFLD-HCC patients. Unfortunately, data on metabolic risk factors such as the presence of T2DM, hypertension, hyperlipidemia and cardiovascular disease were missing from the dataset (90).

These studies suggest that although NAFLD patients may be at increased risk of short-term complications post OLT compared to other etiologies, patients with NAFLD-HCC have comparable longer-term outcomes to those of other etiologies underlying their HCC. With the aim of reducing short term complications, the focus in many centres is on prehabilitation, optimising fitness, weight and glycaemic control in the work up to OLT (Figure 2). Unfortunately, despite good outcomes recurrence of NAFLD following OLT is common and may affect up to 39% of grafts (106). Preventing this by managing metabolic risk factors post-transplant is another important management step.

Another important consideration is the effect of the growing prevalence of NAFLD on the quality of donor grafts. With NAFLD affecting around 25% of the world's population (16) and the demand for organs increasing, the number of steatotic allografts has increased (107). These steatotic organs are being used more frequently as extended criteria donors. Steatotic grafts are associated with poorer graft function and reduced graft survival (108). Other than liver biopsy, which is liable to sampling error and increasing cold ischaemia time while reporting is awaited, there are

no validated tools to quantify steatosis. Better methods of detecting steatosis are needed in order to improve graft selection in a population with a high prevalence of NAFLD.

Percutaneous ablation

Percutaneous ablation is offered to patients with early stage disease but who are not suitable for surgery. Ablation is usually US guided and in patients with small single tumors has comparable efficacy to resection with far fewer complications (109). Ablative options include radiofrequency ablation, microwave ablation, irreversible electroporation and ethanol ablation. In theory NAFLD-HCC patients may have worse outcomes with ablation because of the difficulties of US in overweight and obese patients. US beams can become attenuated by intrahepatic and subcutaneous fat potentially increasing the risk of complications and reducing efficacy.

Comparable outcomes for percutaneous ablation were reported in 2007, in a prospective study comparing overweight (BMI >25 kg/m²) HCC patients to those of normal weight (BMI ≤25 kg/m²) (110). The 219 overweight patients needed significantly more radiofrequency ablation sessions, as compared to 524 normal weight patients, but there were no differences in complication rates, recurrence rates, tumour progression and survival at 1, 3 and 5 years (110). This study suggested that while percutaneous ablation may be more technically challenging in overweight patients, this did not affect outcome. The impact of advances in ablation technology, with techniques delivering more effective ablation and the wider use of CT rather than US guided ablation, have not formally been reported for obese, NAFLD patients per se, but these advances are ones likely to be of benefit for all.

Although much of the literature on the topic is rather dated, patients with diabetes undergoing percutaneous radiofrequency ablation have been reported to have a worse overall survival compared to patients without diabetes (111,112). Diabetic patients taking metformin reportedly have a significantly better survival post ablation compared to diabetic patients not taking metformin, although this benefit is likely attributed to 'non-diabetic' benefits of metformin, rather than being directly attributable ablation or glycaemic control at the time of ablation (111,112).

TACE

Patients with intermediate stage HCC (BCLC B) and good

performance status can be offered TACE. TACE involves intra-arterial infusion of a cytotoxic agent followed by embolization of the tumour blood vessels. HCC unlike normal hepatic tissue gets its blood supply from branches of the hepatic artery, therefore TACE generally spares normal hepatic tissue and preserves liver function (113). As described previously, within a tertiary centre HCC MDT, selected patients with BCLC-C HCC may also be offered therapies such as selective TACE with drug-eluting beads, but further studies are needed to define the roles of locoregional therapies in these patients. In general, the effectiveness of TACE in NAFLD-HCC has not been well studied. A small but relatively recent retrospective study of 57 patients undergoing TACE looked at radiological outcomes in overweight patients (BMI >25 kg/m²) compared to normal weight patients (BMI ≤25 kg/m²) (114), suggesting that an elevated BMI was associated with both a higher rate of residual disease post treatment and a shorter time to radiological progression (114). While there may be differences in the biology of HCC associated with liver diseases associated with obesity versus viral hepatitis related cirrhosis, data is insufficient to impact clinical decision making.

Systemic therapies and the relevance of concurrent anti diabetic treatments

Patients with advanced HCC (BCLC C), or those with earlier stage disease but with recurrence or progression following other therapies, with normal or only mildly impaired functional status (ECOG-PS 1–2), may be offered systemic therapies. Currently the tyrosine kinases inhibitors sorafenib and lenvatinib are the first line therapies approved by the Food and Drug Administration (FDA) (115–117). The FDA has approved regorafenib as a second line therapy (118). Cabozantinib another tyrosine kinase inhibitor has also shown efficacy along with the VEGF receptor 2 monoclonal antibody ramucirumab (119). For patients fit enough according to international guidelines, the recommendations for systemic therapy are the same, regardless of the underlying etiology of HCC. It should be noted, however, that patients with NAFLD-HCC have not been well represented in these studies. Furthermore, combined analyses of the Sharp and Asia-pacific studies reported that benefit for sorafenib was much greater for those with HCV related HCC rather than for other etiologies (120). Going forward, it would be helpful to have more NAFLD-HCC specific data, to inform clinical

decisions.

The impact of the metabolic syndrome and the relevance for patients with NAFLD-HCC given these systemic therapies is not clear. Metformin is commonly used to control T2DM in NAFLD-HCC patients and while it has been reported to improve outcomes in patients treated with radiofrequency ablation and offer protection against HCC recurrence, metformin may be associated with poorer outcomes in patients taking sorafenib (111,121-123). Two studies have demonstrated that HCC patients taking long term metformin for diabetes have significantly worse progression free survival (PFS) and overall survival (OS) compared to patients not taking metformin (121,122). In the larger of the studies, PFS and OS were 1.9 and 6.6 months respectively in patients taking metformin, compared to 3.7 and 10.8 months in patients not taking metformin ($P < 0.0001$). Of note, diabetic patients not on metformin but taking insulin had better outcomes (8.4 months PFS and 16.6 months OS) (121).

Metformin is believed to have anti-tumor activity in chronic liver disease and HCC (112), with a poorer outcome for sorafenib in metformin treated patients perhaps surprising. Potential mechanisms have been considered and recently reviewed (124). Metformin and Sorafenib both potentially contribute to inhibition of mammalian target of rapamycin (mTOR). Metformin does so by the activation of AMP-activated protein kinase (AMPK), which positively regulates sirtuin-3 (SIRT-3) (125). SIRT-3 is a nicotinamide adenine dinucleotide (NAD)⁺ dependent deacetylase and is a key effector in the AMPK/HIF-1 α /mTOR pathway, which regulates mitochondrial function, responses to oxidative stress and cell survival (125). Metformin rather than insulin treated patients reportedly have higher SIRT-3 and mTOR levels (121) and it has been suggested that patients who develop HCC whilst taking metformin, may have acquired intrinsic resistance to the anti-tumour activity of metformin, and consequently to sorafenib, owing to their converging pathway of action (121,124,126). This potential mechanism is not well understood (124) and as yet, there has been no published metformin based subgroup analysis from phase III studies showing sorafenib associated survival benefit (115-117). While further understanding may well be beneficial in the future, when considering the choice of medical therapy, there is no basis to discontinue the use of metformin in the pre-cancer or peri-cancer setting. Metformin may protect NAFLD patients from developing HCC and also has significant metabolic and cardiovascular benefits (112,127-129).

Novel therapies in clinical trials

There are several novel therapies under investigation for the treatment of HCC, with much interest in immunotherapy approaches. Initial trials with immune checkpoint inhibitors demonstrated good safety and tolerance with some evidence of efficacy (130,131). Although responses have been reported in all etiologies of HCC, which is potentially encouraging for patients with NAFLD-HCC, early indications from Phase III studies suggest failure as single agent therapies in 'all comer' trials and stratification biomarkers as well as combination approaches are likely to be needed. Combination approaches may include other standard therapies, such as locoregional therapies or medical therapies (sorafenib, lenvatinib), or possibly other immune therapies. Other immune approaches in pre-clinical trials include tumour vaccines, adoptive cell transfer with chimeric antigen T cells, natural killer cells, tumor infiltrating lymphocytes and cytokine induced killer cells (132). Thus, the landscape is changing, with hope that medical therapies more effective or better tolerated for patients with NAFLD-HCC will be available within the next 5-10 years.

Conclusions

NAFLD has become the leading cause of chronic liver disease worldwide and is becoming a leading cause of HCC. Patients with NAFLD-HCC tend to be older and have more co-morbidities than HCC of other etiologies. Due to the fact that HCC can arise in the absence of cirrhosis and that HCC surveillance programmes in NAFLD are suboptimal NAFLD-HCC tends to present at a late stage contributing to an overall poor prognosis. The late stage of presentation combined with patient age and co-morbidities reduce the use of curative therapies such as liver resection, OLT and ablation. Although NAFLD patients who undergo these therapies are at greater risk of perioperative complications, and therefore need careful preoperative assessment and optimisation, long term survival after treatment is comparable to other etiologies. The use of TACE and systemic therapies in NAFLD-HCC is not well studied but obesity may reduce the effectiveness of TACE and long-term metformin use may be associated with tumour resistance to sorafenib. More studies are needed to further evaluate this effect and to investigate if this association extends to other systemic therapies.

Currently clinical guidelines have a common algorithm for all etiologies of HCC, of which NAFLD has

traditionally only made up a small part of the evidence base. As the prevalence of NAFLD-HCC continues to increase globally the need to update clinical guidelines for this specific group will become apparent. Prevention of NAFLD-HCC is a priority. This will involve public health measures to reduce metabolic risk factors, improve tools to screen for NAFLD and screen for HCC in those with established NAFLD including those without cirrhosis.

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Footnote

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