Editorial

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Metabolic syndrome-associated hepatocellular carcinoma: Questions still unanswered

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Over the past 20 years, there has been a dramatic increase in the prevalence of obesity in most Western and some developing countries. In fact, the proportion of obese adults is now 34.9% in the US population [1] and 14.5% in the French population [2]. Several genes have been identified to be associated with the development of obesity in various animal models; in addition abnormal neural pathways have been proposed that may impact the regulation of energy balance, as well as innate and acquired immune activation in adipose tissue. These mechanisms do not account for the entirety of the obesity epidemic and clearly lifestyle choices including increased caloric intake, especially in fat, and low physical activity contribute to the increase in obesity. In turn, obesity has been noted to have adverse health implications such as a reduction in sleep duration, disruption of circadian rhythm, and an increased risk of diabetes [3]. Obesity-associated type 2 diabetes mellitus not only increases the risk of cardiovascular complications, but also the risk of cancer and cancer-related mortality, especially hepatobiliary cancer [4,5].

The so-called metabolic syndrome (MetS) involves a subgroup of obese patients and is defined by the association of: i) central obesity with increased waist circumference; ii) increased fasting glucose; iii) increased blood pressure; iv) reduced HDL cholesterol; and v) increased triglycerides [6]. This condition is associated with a high risk of non-alcoholic fatty liver disease (NAFLD), which is the hepatic consequence of insulin resistance, with accumulation of triglycerides into hepatocytes. Roughly, 25% of patients with NAFLD will end up developing non-alcoholic steatohepatitis (NASH) [7], which in turn may lead to cirrhosis and hepatocellular carcinoma (HCC). MetS-associated HCC can, however, develop without significant fibrosis in the underlying liver [8]. In particular, NAFLD, obesity, and type 2 diabetes are independent risk factors for HCC, and may mutually potentiate the risk of liver malignancy. The epidemiology of this new emergent source of HCC is not fully described yet. In most series of patients with HCC, the prevalence of NAFLD-related HCC ranges from 4% to 22% [9], however the incidence is expected to increase in the future considering the obesity epidemic worldwide.

In this issue of the *Journal*, a multi-institutional study from Italy sought to compare results of liver resection for HCC related to the MetS (MetS-HCC) and hepatitis C-related HCC (HCV-HCC) [10]. Specifically, the authors compared the postoperative course and long-term outcome of 96 MetS-HCC patients undergoing liver resection over 13 years to the outcome of 96 matched HCV patients undergoing liver resection during the same period. The reported characteristics of both tumor and background liver were in accordance with previous surgical series, i.e. isolated large sized well/moderately differentiated lesions occurring in the setting of a rarely severely fibrotic/cirrhotic underlying parenchyma [11]. In this setting, the authors observed that liver resection for MetS-HCC was associated with a similar postoperative course with identical rates of overall, major, liver specific and cardio-respiratory postoperative complications as matched HCV controls. In particular, the postoperative morbidity was comparable in both groups of patients. These data are in agreement with some previous publications from large academic medical centers that have examined cohorts of patients with steatosis and metabolic syndrome, which similarly noted the safety of modern day liver surgery among patients with obesity. However, other population data from the United States have suggested a higher incidence of complications among patients at the extreme of body mass index, even after adjusting for other clinical factors. Specifically, when examining large numbers of patients (i.e., n >2000), several authors have reported a near two-fold increase risk of complications among patients with obesity and MetS [12,13]. Data from the current study by Vigano, therefore, need to be interpreted cautiously. The overall number of patients included in the study was small (n = 96), patients were well-selected (only 6.1% of overall liver resections), and the surgical procedures were performed at 1 of 6 high volume HPB units. In light of these limitations, as well as the population based data that are at odds with the data from Vigano *et al.*, whether the risk of perioperative morbidity is truly comparable in MetS *vs.* non-MetS patients in the "general surgical community" remains undefined.

Regarding long-term results of liver resection for MetS-HCC, the data from Vigano *et al.*, are also somewhat difficult to interpret. The authors conclude that MetS-associated HCC correlates with excellent long-term results, better than HCV-HCC. The overall survival among patients with MetS HCC *vs.* non-MetS HCC was actually quite comparable (65.6% *vs.* 61.4%), with a marginal

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p value of 0.031. As such, a more conservative – and perhaps more appropriate – conclusion would be that long-term outcome was no different among patients with MetS HCC. In addition, of this particular note, the comparison of MetS HCC *vs.* HCV-HCC was made using a subgroup of HCV patients with a low prevalence of cirrhosis, which is uncommon. In other studies, overall and disease-free survivals were no different between MetS-HCC patients and those with HCC occurring on alcoholic or cryptogenic cirrhosis [14]. Long-term results of patients with MetS may be influenced by treatment of the different components of the metabolic syndrome aimed at reducing the cardiovascular complications, as well as mortality related to diabetes, etc. In the current study, Vigano and colleagues provide data to suggest that cancer specific recurrence-free survival was better among MetS patients – although again the difference was marginal ($p = 0.077$). Furthermore, interpreting recurrence data against a control population of HCV patients – who have traditionally been at a very high risk of recurrence – does not allow us to fully understand the risk of recurrence among MetS patients *vs.* other HCC patients (e.g. alcoholic HCC, HBV HCC, etc.). Moreover, it is difficult to analyze precisely the risk of HCC recurrence, which depends upon the tumor aggressiveness and presence of underlying cirrhosis (absent in most patients of Vigano's series) in HCV patients, and on underlying NAFLD and systemic inflammation due to obesity and insulin resistance in MetS patients. The suggestion of improved recurrence-free survival should not dissuade providers from maintaining a rigorous surveillance program for patients with MetS. MetS remains an important risk factor for both *de novo* and recurrent HCC, with an increased risk of HCC as high as 40–50% over baseline populations [15]. In turn, MRI should probably be the modality of choice, as the accuracy of this modality is better than CT imaging in the setting of a steatotic liver [16,17].

While Vigano and colleagues should be congratulated for helping to shed light on the important topic of MetS-associated HCC, further studies are necessary. The current study, although accumulated experience of 6 major centers, still suffers from small sample size characterized by data with wide 95% confidence intervals and lack of statistical power. For example, whether the lack of finding an association between steatohepatitis and outcome was "real" or due to a lack of power (only 24 patients had steatohepatitis among patients with MetS) remains to be seen – especially in light of other studies that have noted a negative effect of steatohepatitis [18–20]. Unfortunately, as the epidemic of obesity increases, MetS-HCC will be a much more common indication for surgical evaluation. Data from the current study confirm that resection will be central to the treatment of these patients.

Conflict of interest

The authors who have taken part in this editorial declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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