COMMENTARY

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Pathway of care of hepatocellular carcinoma in 2017

Hepatic Oncology

Federica Invernizzi¹ & Massimo Colombo^{*,2}

“In the last two decades, treatment of hepatocellular carcinoma has evolved from an empirical approach to remove the visible tumor toward an evidence-based decision making algorithm based on evidence-based data.”

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In the last two decades, treatment of hepatocellular carcinoma (HCC) has evolved from an empirical approach to remove the visible tumor toward an evidence-based decision making algorithm based on evidence-based data [1–3]. In the end, all algorithms were constructed integrating breakthroughs in diagnostic imaging, both invasive and minimally invasive therapeutic procedures that have occurred in the last years, not to speak about the remarkable success in the prevention of liver disease complications driven by the pharmacological control of viral hepatitis, which turned out to improve both access to and outcome of anticancer therapies. The European Association for the Study of the Liver [1] played a strategic role in this endeavor, having promoted the first multidisciplinary meeting among experts in liver cancer, which in 2001 resulted in the release of the first recommendations for the management of HCC [4]. As expected for any healthcare process, at any time the therapeutic algorithm needs to be refined to be tuned with most impactful developments in the diagnosis and therapy arena while a number of challenges remain.

Linking diagnosis to care

Early diagnosis as it can be achieved through surveillance of patients at risk is the only hope for a cure of patients with an HCC [5]. Unfortunately, even in Europe screening and surveillance for HCC are undertaken owing to a number of geographical, economic and cultural barriers, one above all underestimation of the predisposing liver disease among the general population to the point that in a developed region like USA up to 40% of patients with alcoholic cirrhosis and 57% of those with metabolic cirrhosis missed any type of screening before being diagnosed as having an HCC [6]. The only hope to enhance early diagnosis of HCC rests on development of serological or urinary markers of liver disease and HCC that would allow easier targeting of

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¹Cattedra di Gastroenterologia Università degli Studi di Milano, Milan, Italy

²Humanitas Clinical & Research Center, Rozzano, Italy

*Author for correspondence: massimo.colombo@humanitas.it

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risk individuals in the general population while moving surveillance from the hospital settings to the community.

Toward optimized radiological diagnosis of HCC

One point of strength of the current algorithms for early diagnosis of HCC is the availability of sensitive and user-friendly noninvasive methods to make a confident diagnosis of HCC in screeners with a liver nodule detected at ultrasounds. The radiological diagnosis of HCC, as endorsed by EASL and other professional associations, is in fact based on the demonstration of a typical vascular pattern on multiphases CT and extracellular contrast MRI [1]. A pooled analysis of eight studies indicates that for tumors of 1–3 cm in size, MRI with extracellular contrast has greater sensitivity and specificity than CT scan and that this difference is retained for <1 cm nodules and is potentiated by the use of parenchymal contrast agents like gadoxetic acid [2]. While <1 cm undeterminate nodules require repeat imaging studies at three monthly intervals to achieve a radiological diagnosis, an echo-guided fine needle biopsy is advised for those nodules that fail enhanced radiological studies. As biopsy is associated with a 30% risk of false negative diagnoses mainly related to the frequent occurrence of dysplastic macronodules [7], immunostaining of cancer-specific proteins can be applied for differential diagnosis, yet with suboptimal (60%) sensitivity [8]. This explains why attempts have been made to improve the radiological diagnosis of small HCC with enhanced imaging methods like diffusion MRI, liver-specific contrast agents for MRI and PET-CT. All these methods look promising; however, none of them has been incorporated into recommendations due to the lack of validation studies. In addition, the diagnostic accuracy of liver cell-specific contrast MRI is challenged by some factors that may cause false negative results like genetic heterogeneity of liver expression of carrier proteins of gadoxetic acid and severe portal hypertension.

Expanding nontransplant options in the era of scarce donations

While surgical resection is the mainstay for an HCC arising in noncirrhotic livers, limited hepatic resection is indicated in solitary tumors restricted to the liver and arising in patients with compensated cirrhosis. In these latter patients, the best outcomes are in those with moderate

portal hypertension (hepatic vein pressure gradient [HVPG] <10 mmHg) and normal bilirubin, in whom a 5-year survival of 70% can be obtained; however, with a 70% risk of tumor recurrence [1]. While no restrictions in terms of tumor volume have been identified for candidates to resection with perfectly compensated cirrhosis; however, it is well established that the risk of recurrence increase in parallel with increased tumor volume. Over minimally invasive local ablation procedures, hepatic resection offer the advantage to identify patients with a <5 cm tumor with histologic markers predictive of tumor recurrence, like vascular invasion by tumor cells or satellites, these being prioritized to liver transplantation (LT) with excellent survival benefits [9]. At the same time, patients with a recurrence after resection are still good candidates to salvage LT with excellent survival outcomes not less than 60% at 5 years [10]. One major drawback of nontransplant procedures is the lack of adjuvant therapies to reduce long-term mortality caused by tumor recurrence, a fact that makes pretreatment patient selection on the basis of liver function the only pragmatic approach to optimize the outcome of hepatic resection. Clinically significant portal hypertension, in other words, HVPG >10 mmHG or presence of esophageal varices at endoscopy predict both risk of decompensation and long-term survival post-operatively [11], its predictive power though can significantly be potentiated in a pooled estimation of modified end stage liver disease (MELD) and planned extension of hepatectomy [12]. According to this algorithm, patients can in fact be stratified into low (5%), intermediate (30%) and high (60%) risk groups for decompensation after resection, having a hospital stay and risk of death that run in parallel. In practice, patients without significant portal hypertension with a MELD score <9 can safely afford major resection involving three segments of the liver, whereas patients with significant portal hypertension will have different outcomes according to the extension of resection and MELD score. Coupling these selection criteria with the use of laparoscopic limited hepatic resection, patients with an HCC can theoretically be offered a wide range of therapeutic choices than ever, with prevention of significant postoperative complications [13]. In the last decades, however, surgical treatment of small HCC has been obscured by the advent of safe, effective and cheaper locoregional ablative therapies, one above all radio frequency ablation

(RFA). In a recent meta-analysis, the 3-year survival was similar in patients with a <2 cm tumor and those with <3 each <3 cm tumors who received either limited hepatic resection or RFA, whereas surgery performed better in patients with a single tumor of 3 or 5 cm [14]. These differences in treatment outcomes reflect the ability of RFA to cause being tumor volume dependent: complete necrosis of cancer can be predicted in <2.5 cm tumors only [15] while thermal ablation is ineffective against microsatellites surrounding large tumors as distance of microsatellites increases in relation to the size of the original nodule [16]. In the near future, we expect micro-waves and cryoablation techniques to fully demonstrate their potential to destroy >3 cm tumors as robust efficacy data are currently not available.

Transplant benefit paradigm versus professional societies recommendations

The rigid application of Milan criteria for listing HCC patients to LT may prevent patients with expanded tumor burden to benefit from extended survival provided by transplant compared to survival provided by less effective, non-transplant interventions. Studies are deemed necessary to demonstrate whether a limited expansion of the criteria for organ allocation, that currently aim to maximizing clinical benefits by ruling out patients at excess risk of tumor recurrence, might still result in survival benefits following transplantation as it may be calculated by subtracting to the survival achieved with LT the survival obtained without LT. This means that properly selected HCC patients who do not fit the standard of care Milan criteria for LT, in other words, single <5 cm or three each <3 cm nodules and have poor chances of survival with non-LT therapies, could gain a net survival benefit with LT. This strategy, however, requires appropriate adjustment in each transplant center to avoid unfair organ allocation policies that would punish those patients at increased risk of dying on the waiting list whose prognosis cannot be improved by non transplant therapies. While several approaches have been suggested to expand from Milan criteria including a limited expansion of tumor burden, integration of TNM with biological markers of tumor aggressiveness like AFP, tumor grading and tissue ratio between lymphocytes and neutrophils, the most widely applied approach has been tumor downstaging with RFA or chemo-embolization (TACE), which infact is recommended by EASL

in T2 patients with a >6-month waiting list [1]. Transarterial chemoembolisation (TACE) has been mostly applied to downstage T3 tumors, however, literature does not define an ideal end point of bridge therapy, including burden reduction to within Milan criteria versus complete absence of tumor on radiographic findings and persistence of viable tumor cells at explant pathology. Further reason of uncertainty is the lack of specific form of ablation recommended, a fact that might also account for the wide range of cure reported (24–90%) nor which radiographic criteria best defines a successful HCC therapy. Last but not least, no standard waiting period following downstaging and subsequent optimal timing for LT has been established, though the post-LT survival of patients with a downstaged T3 tumor in centers with a short waiting list is worse than in centers with a longer waiting time due to excess recurrence rates [17]. This implies that radiological findings after downstaging of a T3 tumor coupled with baseline characteristic of the patient and wait list points might serve the purpose of creating a rank for prioritization in the perspective of transplant benefit [18].

How to improve treatment of intermediate & advanced HCC

TACE is the SOC option for patients with an intermediate HCC, the success rates climbing from an original 22 months of average survival to a recent report of survival rates of 40% at 5 years with the use of doxorubicin loaded beads [19]. Among the strategies to increase the benefits of TACE, a widely opted approach has been delivery of multimodality therapies, one above all combining TACE with RFA. In a recent meta-analysis of 25 studies, this approach was found to significantly increase the pooled median survival time from 13.5 to 22.7 months; however, in the face of an increased incidence of gastrointestinal complications (odds ratio = 12.80) and liver toxicities (odds ratio = 2.46) [20]. The clinical heterogeneity of Barcelona Clinic Liver Cancer (BCLC) B stage allows to select a minority of patients with an intermediate tumor who still fit the criteria for a safe resection. Surgical resection has infact been an option for carefully selected patients with a compensated liver disease leading to higher survival rates in a randomized controlled trial comparing resection to conventional TACE [21] and in a multinational study conducted in both the west and east [22]. While sorafenib is the SOC option for patients

with advanced HCC, tumor progression during therapy is expected, however, with different implications on survival depending on the pattern of disease progression. The worse prognosis, in fact, is in patients with portal invasion or onset of extra hepatic tumors (mean survival of 7.1 months), compared with the benefits of therapy in those patients with a limited growth (20%) of the tumor or appearance of new intrahepatic nodules where the survival was 14.9 months for BCLC C stage patients at the onset of sorafenib therapy versus 24.4 months for those who were in the better BCLC B stage at onset of treatment [23]. Integrating these on treatment predictors of response with the onset of grade 2 dermatologic adverse reactions within day 60 of therapy (30% of the cases), patients with advanced HCC can further be stratified for the likelihood of a response to sorafenib. Luckily enough, after years of failures on the row, a second-line therapy with the potent multikinase inhibitor regorafenib has become available to treat patients who failed but tolerated sorafenib [24], which apparently works in all the subclass of progressors under sorafenib [25]. Moving from multikinase regimens, the novelty is represented by a new class of antitumor agents represented by PD-1 inhibitors that affect their anticancer activity by shutting down innate immune tolerance of the liver. In a Phase I/II study with a monoclonal IgG4, half of the patients with advanced HCC including sorafenib-experienced patients, had a stable disease, while 14% had either a complete or a partial response to therapy with an overall survival time of 17 months, on average [26]. While these findings pave the way to the development of second-line therapies for patients who are intolerant to sorafenib, there are expectations that studies of molecular classification of HCC may contribute to a better understanding of cancer origin and help development of effective-targeted therapies for subpopulations of HCC patients.

Interferon-free therapy of hepatitis C virus & the risk of tumor recurrence

Owing to the undisputed survival benefits provided by hepatitis C virus (HCV) eradication in both patients with compensated and decompensated cirrhosis, antiviral therapy with direct antiviral agents (DAAs) is recommended for patients who have had a tumor eradicated and those with HCC awaiting LT [27].

Mitigating against the enthusiasm raised by the skyrocketing rates of virological responses

in these patients, however, have been reports of increased risk of early recurrence of HCC in patients who were successfully treated with DAA including those in the waiting list. While prospective studies are in progress to ascertain whether DAA therapy poses a safety risk in HCC patients, several hypotheses have been put forward to explain the potential interactions between DAAs and liver cancer likely to be caused by a swift eradication of HCV. These include impairment of natural killer cell-mediated tumor immune surveillance, TRAIL related de-escalation of apoptosis phenomena, impaired role of nonspecific inflammatory cells in tumor control while doubts remain that all these observations might have been biased by confounding factors and methodological issues typical of retrospective studies [28].

Conclusion

In the face of the important steps forward in the management of HCC that have been done in the last two decades, several unmet medical needs in HCC research remain. Owing to the tight epidemiological links between HCV and liver cancer, there is urgent need of clarifying safety of DAA therapy in the population with an HCV-related cancer that represent a majority of HCC patients in the west and Japan. Preclinical testing of novel drugs for naive and experienced patients, including adjuvant regimens need to be improved while second-line regimens for sorafenib intolerant patients are still missing. Development of biomarkers predictive of a response to medical therapy could help further optimize treatment of advanced cancer, whereas to enhance detection of potentially curable early tumors, liver cancer-specific biomarkers are needed to screen in the community that would allow transformation of clinically oriented screening into community-based programs, likely with favorable economic consequences. Last but not least, analysis of cost/benefits and quality of life should be incorporated in clinical trials.

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