

# Status of hepatocellular cancer in Europe

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**Abstract:** Hepatocellular cancer (HCC) accounts for 47,000 deaths per year in Europe and the incidence is expected to increase over the next 10-15 years. The highest incidence is found in Southern Europe, mainly attributable to chronic hepatitis C infection. The most widely used staging system used is the Barcelona-Clinic Liver Cancer (BCLC) classification according to which, 30-40% patients are suitable for potentially curative therapies including transplantation, resection or ablative therapy while the remainder are offered palliative therapy with transarterial therapy, systemic therapy or supportive care. Here we review the indications and outcomes of these interventions as applied to the European population.

**Keywords:** Hepatocellular cancer (HCC); liver resection; liver transplantation; ablative therapy; transarterial therapy; Europe



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## Etiology and epidemiology of hepatocellular carcinoma (HCC) in Europe

HCC is a leading cause of cancer death worldwide. It represents the fifth commonest cancer worldwide and over 500,000 new cases are diagnosed per year (1). There is marked variation in the geographical incidence of HCC reflecting the contribution of different viral, genetic, metabolic and environmental factors. In Europe, HCC accounts for around 47,000 deaths per year and the incidence is comparatively low with the exception of Southern Europe where the age-standardized incidence rate in men is 9.8 per 100,000 as compared with 3.8 in Northern Europe, 4.6 in central and Eastern Europe and 7.2 in Western Europe (1). However, in the UK, mortality rates from HCC are expected to rise by 14% between 2006 and 2025 (2) representing the largest increase in any male cancer. Cirrhosis of any cause is an important risk factor for the development of HCC with up to 90% of HCC developing within cirrhotic livers and HCC is also the leading cause of death in cirrhotic individuals. Chronic hepatitis B affects 0.5-0.7% of Europeans and the prevalence of chronic

Hepatitis C ranges between 0.13-3.26%. NAFLD is present in 2-44% of the general population and 43-70% of those with type 2 diabetes (3). Mortality from alcohol related liver disease also varies across Europe being highest in Hungary at 49 per 100,000 and lowest in Uzbekistan and Israel. Overall, in Europe, hepatitis C is the major risk factor accounting for 60-70% cases of cirrhosis while alcohol is the causative factor in 20% and hepatitis B in 10-15%.

## Surveillance for HCC

When HCC presents symptomatically with abdominal pain, ascites, weight loss or distant metastases, the prognosis is extremely bleak with a median survival time of only 6 weeks. Consequently most centers offer a surveillance strategy to detect early tumors in high-risk individuals including those with cirrhosis or hepatitis B infection. In Europe the recommended surveillance comprises six-monthly ultrasound (4,5) and some centers also monitor AFP although sensitivity and specificity of blood markers for early disease is low and the benefit unproven. Ultrasound surveillance has never been subjected to a randomized

clinical trial in Europe but it is clear that six-monthly surveillance leads to better outcomes whilst there appears to be no distinct advantage to shortening the surveillance interval to three months (5,6). Thus the standard of care in Europe is biannual ultrasound.

### Diagnosis and staging of HCC

Most HCC arising in a high-risk setting such as cirrhosis can be diagnosed noninvasively using dynamic contrast enhanced CT or MRI. The classical imaging features of HCC are a lesion that demonstrates increased enhancement compared to the background liver in the hepatic arterial phase of the scan. In addition to arterial hyper-vascularity a lesion must also show washout in the venous or delayed phase of the scan to be defined a HCC. The combination of arterial hypervascularity and washout in the context of a high risk setting (cirrhosis or hepatitis B) is highly specific for HCC and biopsy is not required for these lesions if greater than 1 cm in diameter (7). For lesions that do not display classical imaging criteria either a second dynamic imaging study can be applied or the lesion can be biopsied. Some small HCC however are hypovascular and therefore do not conform to the classical imaging criteria and can only be diagnosed on biopsy. Hypovascular HCC are usually well differentiated and therefore some authorities would recommend enhanced surveillance for this group of patients given that most of these lesions will acquire classical imaging characteristics as they grow. Conversely an aggressive approach to biopsy is advocated by some as these lesions have the best chance of cure if treated early (8). The differentiation of very early HCC from regenerative nodules can be difficult and it is recommended that pathological analysis of biopsies takes place in specialist centers.

Given that most HCC arise within the setting of pre-existing liver disease, an accurate assessment of prognosis is dependent on both the degree of liver dysfunction and the tumor characteristics. A number of staging systems have been proposed but, in Europe, the most widely used is the Barcelona-Clinic Liver Cancer (BCLC) classification. The BCLC system incorporates characteristics of the tumor, the background liver function and also the patient's performance status. It has been externally validated as a prognostic classification and can also be used to guide treatment decisions (9). However, in practice, European centers often deviate from these guidelines. AFP is increasingly used to inform decisions about transplantation and resection (10), tumors greater than 2 cm in diameter

are resected with good outcomes (11) and TAE may be used rather than transarterial chemoembolization (TACE) (12). The guideline also has no place for transarterial radioembolization (TARE) which is increasingly used in Europe (13). It is also recognized that the BCLC B stage is very heterogeneous and proposals have been made to sub-classify this group (14,15).

### Liver resection for HCC

In patients without cirrhosis, the treatment of choice for HCC is surgical resection. In Europe, individuals with HCC suitable for resection make up only 5% of the total number of HCC patients (16). Surgical resection may also be offered to patients with well-compensated cirrhosis but these individuals must be selected carefully to avoid the risk of postoperative decompensation (17). In Europe, the decision to offer surgery for HCC in cirrhosis relies on the measurement of a normal serum bilirubin and the absence of clinically significant portal hypertension as measured by a hepatic venous pressure gradient measurement of <10 mmHg (18,19). If these guidelines are followed then the risk of decompensation of the liver disease following resection is extremely low. Functional tests of liver reserve such as indocyanine green clearance studies also have a role in determining both suitability for resection and the extent of resection (20). Outcomes for surgical resection vary but most centers report 5-year survival rates of between 50% and 70%; Recurrence rates however are high even after resection of small tumors. A recent multi-center French study has reported equivalent outcomes in patients undergoing laparoscopic resection and this may be favored in selected patients (21). According to the BCLC classification, tumors traditionally thought suitable for treatment with resection are limited to those of early stage (i.e., Single tumors of 2 cm or less with normal portal pressure and serum bilirubin). Outcomes in these patients following resection are usually excellent with 5-year survival exceeding 90%. However the occurrence of these early stage tumors is rare with only 75 cases reported from a large volume center over a 20-year period. Whilst 5-year survival in these cases was generally excellent, recurrence rates were high at 68% reflecting the more aggressive nature of small tumors in European patients (22). Recently the restriction of resection to patients with very early or early stage disease has been challenged. In response to the publication of single center reports of resection in patients with intermediate stage (large or multiple) or advanced (portal vein invasion) stage tumors, the HCC East-West study group performed a

multi-centric study of resection outcomes for HCC across all BCLC categories (11). A total of 2,046 patients were studied from ten centers across three continents. The majority of the patients had BCLC stage very early or early disease but 36% and 14% were from BCLC intermediate or advanced stage. The results of the study confirm that, for early stage disease, outcomes are generally good with 5-year overall survival of 61% and disease free survival of 21%. For patients with intermediate or advanced stage tumors the disease free survival was poor at 5 years (12-26%) but overall survival at 5 years was surprisingly good at 55% for intermediate and 31% in advanced stage disease. In some centers, resection is also considered as a bridge to transplantation to avoid drop out on the waiting list or even as an alternative to transplantation with 'salvage transplantation' offered in the case of recurrence. Belghiti and colleagues have shown that patient selection is key to achieving satisfactory outcomes with this approach (23,24).

### Liver transplantation for HCC in Europe

For those patients not suitable for resection due to advanced underlying liver disease the only curative surgical option is liver transplantation. The Milan criteria remain the most widely used means of selecting patients for transplantation in Europe and its application is associated with a five years survival of around 70% (25). According to data from the European Transplant Registry, almost 6,000 liver transplants are performed each year and the primary indication is HCC in around 20% cases (26). The majority of liver transplantation in Europe occurs from deceased donors, therefore the main limitation for transplantation is donor shortage resulting in a prolonged waiting time which, in Europe, is responsible for a dropout rate of between 15% and 35% (27,28). Deceased donor rates vary widely across Europe with Spain having the highest rates of 34.2 per million (in 2008) as compared with 20-25% per million for the most other European countries (26). To reduce the rate of progression beyond Milan criteria, many centers apply 'bridging' interventions including RFA or TA(C)E while on the waiting list. Evidence suggests that this approach is indicated when waiting times are longer than six months but the unpredictability of waits for individual patients often results in wider application (29,30). Post-transplant recurrence may be reduced by effective embolization (31) and the response to pre-transplant loco-regional therapies may also select those patients with a favorable biology (32,33). In patients transplanted after demonstrating a response to

down-staging protocols, histology in the explanted livers was found to be favorable with all residual tumors being well to moderately differentiated and without microvascular invasion (34). Partly based on these findings, the UK transplant criteria for HCC have been extended beyond the Milan Criteria to include those with a period of stability over six months, where the maximum dimension for a single tumor does not exceed 7 cm or five lesions are present with a maximum dimension of 3 cm. Allocation of donor organs in Europe is usually based on MELD score (35). This system results in patients who are sickest in terms of liver disease receiving highest priority. Allocation by MELD may disadvantage patients with HCC and well compensated cirrhosis and therefore patients within the Eurotransplant allocation scheme receive MELD exception points in order to increase priority for transplantation and mitigate the risk of drop out on the waiting list. Other centers in Europe allocate organs in a center specific manner which allows a degree of donor recipient matching although this tends to result in HCC patients receiving more marginal organs which may compromise outcomes (36). Expansion of the donor pool using live donor transplantation or grafts from donors after determination of circulatory death (DDCD) is utilized in some European centers and could potentially increase the number of grafts available for patients with HCC. However numbers of patients undergoing live-donor liver transplantation remains relatively small (300/year) and the use of DDCD grafts results in inferior outcomes due to increased rates of primary non function and biliary structuring disease (26,37).

Despite the improved survival following the implementation of the Milan Criteria, recurrent disease remains a problem and at present there are no evidence-based treatments that have been shown to be effective in post-transplant HCC. Therefore interest has focused on the prevention of recurrence and particularly the role of excess immune suppression which may increase recurrence rates (38). Recently the role of mTOR inhibitors has been examined in the prevention of HCC recurrence. A randomized trial of sirolimus in patients with HCC is underway but yet to report, however a recent meta-analysis suggests that this molecule may have a role in immunosuppressive regimens in HCC patients due to an observed reduction in HCC recurrence (39).

### Ablative therapy

According to the most recent EASL-EORTC practice

guidelines, local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC A tumors not suitable for surgery (4). Percutaneous ethanol injection (PEI) is cheap and has been widely used for over 20 years but there is increasing evidence that radiofrequency thermal ablation (RFTA) may be superior. PEI was introduced as a treatment for HCC in the early 1980s and induces tumor necrosis by causing cellular dehydration, protein denaturation and chemical destruction of blood vessels. It is performed under local anesthetic using ultrasound guidance and requires 4-6 sessions depending on the tumor characteristics. Histological complete necrosis is found in 70% tumors measuring less than 3 cm and the 5-year survival for patients with well compensated cirrhosis ranges from 47-60% (40-42). Although there have been no randomized trials comparing PEI with best supportive care, the historical survival of this group of unresectable patients is in the order of 20% (43). The risks of PEI are small and in one recent series from a single center reporting on 270 patients treated over 20 years, there were no deaths and the most common toxicities were fever, pain and elevation of ALT. The rate of seeding was 1.9%. There have been no randomized trials comparing PEI with surgery but a non-randomized prospective comparison of PEI versus surgery in patients with tumors smaller than 3 cm in size and less than three in number demonstrated almost identical survival at five years of 59.0% for PEI and 61.4% for surgery (44).

A potential disadvantage for PEI is that ethanol does not extend beyond the capsule and there is therefore the risk of not treating the satellite deposits present outside the main tumor rim. Cancer is the cause of death in 60% of Child Pugh A patients following PEI and 28% of recurrences have been reported as occurring solely in the same liver segment (42). For this reason, particularly in tumors greater than 2 cm there has been increasing interest in RFTA which can destroy a rim of tissue around the tumor. The aim of RFTA is to cause local tissue destruction at the tip of an electrode by thermal injury as a result of the deposition of electromagnetic energy. Initially the monopolar electrodes used were only able to induce ablation zones of 1.6 cm but the development of multipronged retractable electrodes has allowed ablation of much larger volumes with a single insertion. As with PEI image guidance is required but many centers use general anesthesia as the procedure is more painful than PEI.

Initial non-randomized trials reported 5-year survivals of 33-40% at five years. The first trial comparing PEI and RFTA randomized 102 patients with HCC less than

5 cm or no more than three tumors less than 3 cm each. Although there was no significant difference in 2-year survival (88% versus 98%) there was a significant difference in terms of 2-year relapse free survival (62% versus 96%) in favor of RFTA. Furthermore, an average of 1.1 sessions of RFTA was required compared to 5.4 for PEI. Longer term survival has now been reported in a prospective trial and found to be 41% at 5 years according to intention to treat. Recurrence rate was 80% but local tumor progression was only 10% and for patients with Childs A cirrhosis and a single tumor five years survival was 61% (45). Subsequently, there have been further randomized trials published (46-49) and three meta-analyses (50-52) and these provide evidence that RFTA is superior to PEI in terms of survival for HCC >2 cm.

However not all lesions are suitable for RFTA and two of the reported trials excluded about 10% patients because the tumor was within 1 cm of the liver hilum, close proximity to the gall bladder or to the gastrointestinal tract and in these circumstances PEI may be the favored option.

Pain is a common side effect of RFTA but the rate of major complications in the reported randomized trials is between 2% and 5% and includes intraperitoneal bleeding, hemothorax, skin burns, and perforated viscous (45-48). The rate of malignant seeding varies between 0% and 3%.

## Transarterial therapy

### *Embolic therapy*

For good performance patients with unifocal disease, not suitable for resection or ablation, or multifocal disease without vascular invasion or extrahepatic spread, transarterial therapy is recommended. Historically, there has been considerable heterogeneity in the approach to transarterial therapy (53) and there have been no large randomized trials against best supportive care. The EASL-EORTC practice guidelines recommend TACE based on the results of two small randomized trials (54,55) and a meta-analysis of seven trials including 545 patients (56). Of the two positive trials, one was performed in Hong Kong and randomized 80 patients to treatment with TACE using an emulsion of cisplatin and lipiodol and gelatin sponge particles or to symptomatic care (SC). The actuarial survival was significantly improved in the treated group (31% at 2 years versus 11% in the untreated group) (55). The second trial, from Barcelona, randomized 112 patients from a screened population of 903 into three groups;

TACE using a doxorubicin/lipiodol emulsion and gelfoam fragments, TAE using gelfoam fragments alone and SC. Again there was a significant difference in two years survival between the TACE group and the SC group (63% versus 27%) (54). However no significant difference in survival was demonstrated between TAE- and TACE-treated patients or between the TAE- and SC-treated patients. More recently drug eluting beads (DEB-TACE) have been evaluated. Doxorubicin is directly loaded onto embolic micro-beads and leaches into the tissue following transarterial injection. The peak plasma concentration and AUC of doxorubicin is reduced compared to conventional lipiodol-based TACE (57) and the systemic toxicity is reduced as a consequence. A randomized comparison of DEB-TACE versus conventional TACE confirmed reduced systemic toxicity with DEB-TACE but a survival benefit has not been demonstrated (58). Overall, the importance of chemotherapy remains questionable and no trial has yet shown a benefit of TACE over bland embolization (TAE). A meta-analysis including 582 patients from five randomized trials demonstrated no difference in survival between TAE and TACE treated patients (12) and a recent randomized comparison of DEB-TACE with bland bead TACE also failed to show any survival advantage for DEB-TACE (59).

### ***Transarterial radioembolization (TARE)***

TARE can be delivered in the form of Iodine-131 labeled lipiodol or using Yttrium-90 conjugated resin or glass microspheres but the lack of randomized trials has prevented TARE becoming established in the therapeutic algorithm. The only reported randomized trial was conducted in France and compared <sup>131</sup>I-Lipiodol with TACE. There was no difference in terms of survival or response but <sup>131</sup>I-Lipiodol was better tolerated (60) and similar findings were reported for a cohort comparison of these two modalities (61). A cohort comparison of <sup>90</sup>Y-microspheres with TACE conducted in 245 patients demonstrated similar survival of around 17 months in the both groups with intermediate stage disease but there was reduced toxicity in the TARE treated patients (62). A potential benefit of TARE over TACE is that there is no embolic effect and TARE appears to be safe in patients with portal vein occlusion (63,64). Randomized trials comparing sorafenib with TARE in patients with liver confined disease but portal vein thrombosis are on-going and may help define the place of TARE in the management of HCC. However the delivery of TARE is not straight forward and

requires expertise and dedicated infrastructure.

In summary, there are a number of locoregional therapies that are used in Europe for liver confined HCC but there are few comprehensive surveys that define their application. A recently published Italian study surveyed 134 centers of which 65% responded. Of 8,959 procedures performed in 2011, 31% were ablations of which about three quarters were RFTA and the remainder PEI. Transarterial treatments accounted for 67% of procedures of which 13% were TAE and the remainder TACE. Of those treated with TACE, DC Beads were used in 46%. Only 16.7% of responding centers performed TARE which constituted 2% of procedures overall (65).

### ***Systemic therapy***

The European Agency for the Evaluation of Medicinal Products (EMA) approved the use of sorafenib for HCC in October 2007. This decision was made in light of the findings of the SHARP trial (66); a multi-center, randomized, placebo-controlled trial which allocated 602 patients with advanced HCC to sorafenib 400 mg BD or placebo. Investigators reported an overall survival benefit of nearly three months with sorafenib (10.7 vs. 7.9 months). Although a multi-center trial, the majority of patients were recruited from Europe, making the results applicable to the population in question here. Importantly, the underlying etiology of liver disease was also reflective of the European population, with Hepatitis C and alcohol being the most frequent causes of underlying liver disease (28% and 24% of all patients recruited respectively). Sorafenib has become established as the standard systemic treatment for patients with advanced HCC, as defined by the BCLC staging system (9). The European Society of Medical Oncology (ESMO) has published clinical practice guidelines which recommend the use of sorafenib in patients with advanced stage HCC and preserved liver function (i.e., Child-Pugh A or B) or intermediate stage patients who have progressed following loco-regional treatments (67). Sorafenib is also indicated in patients with early stage HCC who are ineligible for radical treatment because of poor performance status or co-morbidity (67).

In both the SHARP trial and subsequent Asia-Pacific trial (68), the vast majority of patients had well preserved liver synthetic function confined to Child-Pugh Class A (97% for both studies). GIDEON is a global, prospective, non-interventional study partially undertaken to provide more data from real life clinical use of sorafenib in HCC,

including data from Child-Pugh B patients (69). Additionally, it provides further information on the differences between patient populations and their management according to region. The first interim analysis looked at 511 patients across five different regions, namely Europe, Latin America, USA, Japan and Asia-Pacific. As expected, the etiology of underlying liver disease varied according to region, with HCV infection and alcohol being the commonest in Europe and HBV infection being the commonest in Asia-Pacific. There was also geographical variation in the number of patients who received locoregional treatments (LRT) prior to commencing sorafenib. In Europe only 45% of patients had previous LRT prior to sorafenib treatment as compared to 100% in Japan and 68% in Asia-Pacific (69). Differences were also observed in the underlying disease characteristics by region. In Europe, patients commencing sorafenib tended to have less advanced disease according to BCLC status, with 14%, 22% and 51% of patients having BCLC stage A, B and C disease respectively as compared to 1%, 11% and 74% in the Asia-Pacific population. Additionally, with the exception of Japan, Europe had the greatest proportion of Child-Pugh A patients at 70%, as compared to 60%, 44% and 41% for Asia-Pacific, Latin America and USA respectively.

Following the results of SHARP, Iavarone *et al.* conducted a prospective observational study of all HCC patients treated with sorafenib in six liver centers across Italy (70). Their primary objective was to assess safety, but they also gathered data related to survival and time to radiological progression. In a notable difference to the SHARP trial, they used the modified RECIST (mRECIST) criteria, which consider vascularized tumor dimensions (71). In their population of 296 patients, 75% had BCLC stage C disease and 88% were Child-Pugh Class A. Overall, 56% of patients had received previous LRT treatment, and 38% had not received any previous anti-HCC therapy prior to sorafenib. The incidence of adverse events (AEs) was 91%, with 45% of patients experiencing grade 3/4 AEs. The most common grade 3/4 AEs included fatigue (39%), hand-foot skin reactions (HFSR) (18%) and diarrhea (14%). This is in contrast to the registration trial (66) in which no grade 4 AEs were reported and the grade 3 AEs were most commonly diarrhea (8%) and HFSR (8%) and hypertension (2%). Overall survival data was consistent with previous trials at 10.5 months, and sub-group analysis suggested that survival was improved in BCLC-B patients as compared to BCLC-C (20.7 *vs.* 8.5 months). Time to radiological progression in this population was improved compared to the registration trial (9.2 *vs.* 5.5 months), which may reflect

the use of mRECIST criteria. Despite this, the radiological response rate was similar to the registration trial (8% *vs.* 2% respectively) and the majority of patients (73%) achieved stable disease only. Another notable difference is that 54% of patients required dose reduction due to AEs as compared to 26% in the registration trial. In fact, 26% of all patients received half dose sorafenib for >70% of the treatment period despite a broadly similar patient population in terms of performance status. This may be related to the increased numbers of Child-Pugh B patients, as the GIDEON study also commented on a higher rate of sorafenib discontinuation in Child-Pugh B patients as compared to Child-Pugh A (40% *vs.* 25%) (70). Indeed the results are consistent with a large retrospective audit of 400 patients treated with sorafenib across 13 centers in the UK (72). Again, although the majority of patients were Child-Pugh A (84%), a significant minority had Child-Pugh B disease (16%). Furthermore, in comparison to the SHARP trial, patients in this UK audit received a lower average daily dose of 585 mg and had a shorter time on treatment of 3.2 months.

Ozenne *et al.* have also conducted a retrospective study looking at a cohort of 50 patients with HCC treated with sorafenib at a single center in France (73). In keeping with previous studies, the majority of patients were Child-Pugh Class A (66%) and BCLC-C (76%). They reported grade 3/4 AEs in 18% of their patients, and 38% of patients required dose reduction. Together with the Italian study, this suggests that dose reductions are being used more frequently in clinical practice across Europe than suggested in the registration trial. Although the proportion of patients who discontinued treatment due to AEs was similar between Child Pugh A and B classes, median duration of treatment for Child-Pugh B patients was only 1.8 months. In keeping with previous trials, the majority of patients (67%) demonstrated stable disease with only a minority (11%) demonstrating objective radiological response to treatment. Median overall survival was 5.5 months with a trend towards increased survival in Child-Pugh A patients compared to Child-Pugh B (8.9 *vs.* 2 months). However, Child-Pugh status also correlated with performance status and stage of HCC and, after multivariate analysis, the only factor significantly related to survival was BCLC stage.

Despite the inclusion of some Child-Pugh B patients, the majority of published experience with sorafenib in Europe still pertains to those patients with relatively well preserved liver function. One center in Germany has reported a prospective study of 34 patients with advanced HCC who

were treated with sorafenib regardless of Child-Pugh score (74). Of the 34 patients treated, only four were Child-Pugh C with the remaining patients being split equally between Child-Pugh A and B. High rates of AEs and dose modification were reported (100% and 47% respectively), with the majority of AEs being at Grade 1/2. The toxicity profile is consistent with previous studies and is similar across Child-Pugh groups, with a trend towards an increase rate of diarrhea and skin reactions in Child-Pugh C patients. Worsening liver function was significantly more frequent in Child-Pugh B and C patients (73% and 75% respectively) and all Child-Pugh C patients experienced deterioration in their Child-Pugh score whilst on treatment, with three out of those four patients dying on therapy.

There is little published data pertaining to the use of chemotherapy in advanced HCC in Europe in clinical practice. Gish *et al.* performed the only randomized controlled trial using chemotherapy in a Western population (75). They randomized 445 patients to receive either the thymidylate synthase inhibitor nolatrexed or doxorubicin and found that survival was improved in those patients receiving doxorubicin (7.4 *vs.* 5.1 months). In parallel to the SHARP trial, Abou-Alfa *et al.* compared patients receiving doxorubicin alone to those receiving it in combination with sorafenib in 97 patients recruited across North and South America and Europe (76). Overall survival was improved in the combination group as compared to doxorubicin alone (13.7 *vs.* 6.5 months) and a further trial comparing sorafenib with sorafenib plus doxorubicin is ongoing.

Sorafenib was a major advance but the absolute impact on patient survival is limited and there remains an urgent need to improve outcomes for patients with advanced HCC. Since the approval of sorafenib progress has been disappointing and there have been a series of large phase three that have failed to demonstrate equivalence or superiority of an experimental arm. As with other cancers, the focus for the future will be to understand better, the drivers of oncogenesis in HCC and to develop strategies that target these drivers and prevent the emergence of resistance. Traditionally, diagnosis of HCC has not required histology and this must change in order to increase our molecular understanding of the disease. The relative rarity of HCC in Europe requires functional collaboration between centers within and between member states.

## Conclusions

HCC is a relatively uncommon cancer in Europe yet the

prognosis remains dismal. Reductions in incidence seen in the Far East as a consequence of vaccination and screening have not been observed in Europe, perhaps due to the varied etiology. Improved selection has resulted in better outcomes for transplantation and resection but, for patients treated with palliative intent, the current interventions remain unsatisfactory. Relapse or progression following locoregional therapy is common and the benefit of systemic therapy limited. Major initiatives for the future include early detection so that more patients can be cured, and improved systemic therapy that can increase the cure rate following radical therapy and improve outcome for those with advanced disease.

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