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Extrahepatic spread of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is a major health problem. The treatment of HCC depends on the tumour stage and on the severity of underlying cirrhosis, however, a majority of HCC patients have advanced disease at presentation. In recent years extra-hepatic spread (ES) of HCC seems to have been observed more frequently than in the past even if few data exist in literature on prevalence, clinical presentation and prognosis of patients with HCC ES. Aim of this brief review is underline the main concerns, pitfalls and warnings in practicing with these patients. ES of HCC are not rare, and the probability of finding ES is higher in patients with advanced intra-hepatic HCC. The more frequent ES sites are lung lymph nodes and bones, but also the head and neck district can be affected. The prognosis of HCC patients with ES is poor and sorafenib seems to be the only therapeutic option.

KEY WORDS: Carcinoma, hepatocellular – Neoplasm metastasis - Sorafenib.

Worldwide, hepatocellular carcinoma (HCC) is among the 6 common malignancies with a global mortality estimated to exceed 500000 cases.[1] The incidence of HCC is high in much of the developing world, including sub-Sahara Africa and Southeast Asia.[1-3] Although HCC occurs less frequently in Northern Europe and United States, the incidence has increased in recent years, largely because of chronic hepatitis C virus (HCV) infection.[4]

Cirrhosis, most often due to viral hepatitis, is the dominant risk factor for HCC, and geographical differences are largely due to epidemiological variations in hepatitis B and C infection.[5] Additional cases were associated with cirrhosis due to alcohol and hemochromatosis, as well as idiopathic cirrhosis, non-alcoholic steatohepatitis, diabetes mellitus, autoimmune hepatitis and aflatoxin.[6-10]

HCC presents a gender predilection with a male to female ratio ranging from 3:1 to 9:1. The mean age of presentation of HCC in Europe and the United States is approximately 60 years; whilst in Asia and Africa it is between 20 and 50 years.[11]

In oncology, metastasis formation is the spread of cancer cells from a primary tumour to organs and distant sites in the cancer patient's body. This process is the end result of a complex series of genetic alterations, epigenetic events, and host responses. The tendency of a primary tumour to form metastasis is the hallmark of malignant cancer. Metastasis formation is the final step in tumour progression and has significant diagnostic, prognostic, and therapeutic implications. So, cancer classifications and indication of treatment are critical steps in the management of neoplastic patients. Moreover, the prediction of outcome is relevant to provide adequate information to patients and relatives, both at the time of treatment selection and after the application of therapy.

Tumour staging describes the extent of an individual's tumour burden in the original primary organ and spread throughout the body, and other cofactors such as age or histological grade are only seldom considered. This is common to all malignancies and diseases. However, whereas for most neoplasm

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prognosis and treatment are largely dictated by tumour stage at the time of diagnosis, the scenario is more complex in patients with HCC.[12]

In fact, the natural history of HCC is variable [13, 14] and treatments results reported in literature are difficult to interpret, because survival, as a primary end point, may reflect more the underlying disease (that affect the majority of HCC patients) than progression of HCC.

It is difficult to estimate the real prevalence of HCC extra-hepatic spread (ES); moreover, the prognostic role of ES of HCC is unclear. In this brief review we aim to underline the main concerns, pitfalls and warnings in practicing with HCC patients with ES.

Review criteria

Studies were retrieved from the MEDLINE database using the search terms "hepatocellular carcinoma", "liver cancer" and "primary liver carcinoma" individually and combined with the terms "randomized", "controlled clinical trials", "clinical trials", "phase III studies", "meta-analysis", "cohort study", "prognostic score", "metastases", "extrahepatic spread", "extrahepatic metastases", "outcome", "prognosis", "liver cancer", "staging system", as well as by a manual search and review of reference lists. The search included literature published in English up to 2011.

Staging systems and treatment strategy of HCC

A number of systems [15-23] have been proposed to predict the prognosis for HCC, none of which has been universally adopted.[10, 12, 23] These schema variably incorporate four features that have been recognized as been important determinants of survival: the severity of underlying liver disease, the tumour burden (number and size of nodules, portal invasion,

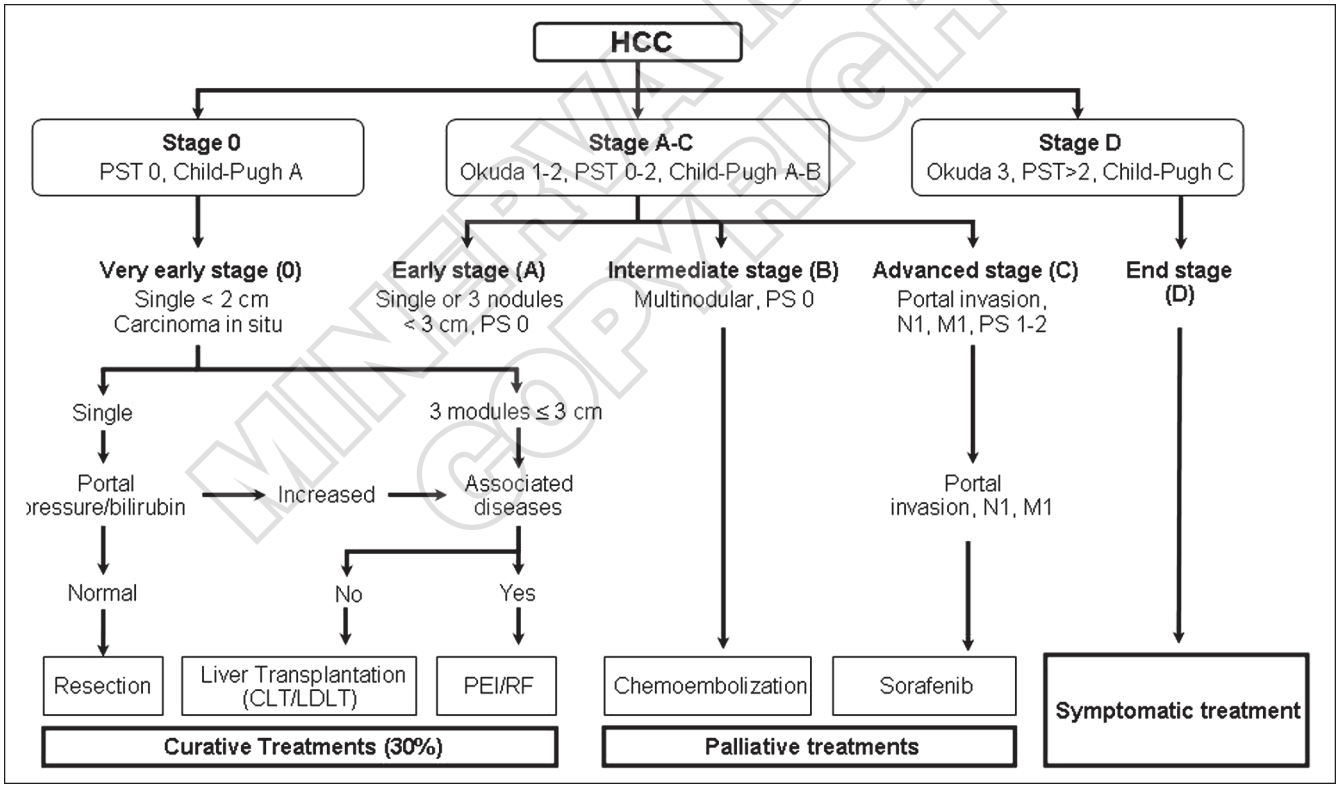

Figure 1.—The Barcelona Clinic Liver Cancer staging system and treatment allocation.
CLT: cadaveric liver transplantation; HCC: hepatocellular carcinoma; LDLT: living donor liver transplantation; PEI: percutaneous ethanol injection; RF: radiofrequency.

ES), the patient's general conditions (performance status), and treatment efficacy. In the absence of an optimum prognostic model, treatment algorithms for patients with HCC in Europe and North America have been prepared on the basis of the Barcelona Clinic Liver Cancer (BCLC) classification.[24]

The BCLC staging classification for HCC classifies patients as having stages of disease from 0 to D [18, 25] (Figure 1). Stage 0 is very early disease, which is defined as a solitary liver cancer that measures ≤2 cm without tumour invasion into surrounding tissues. Stage A is early disease, classified as patients who exhibit preserved liver function with a solitary HCC≤5 cm in size, or up to 3 tumours each of which is ≤3 cm in size. Patients with stage 0 or stage A disease can be effectively treated with curative therapies, such as surgical resection, liver transplantation, or by percutaneous ablation methods, including percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). With these treatments it is possible to obtain complete responses with potential long-term cure, as reflected by a 5-year survival better than 50% to 70%. The BCLC intermediate stage (stage B) consists of asymptomatic patients with well-preserved liver function, and multinodular or large tumour extension, without macrovascular invasion or extra-hepatic spread (ES). Patients with stage B (intermediate) disease can be treated with transarterial embolization (TAE) or transarterial chemoembolization (TACE). Patients with mild related symptoms and/or macrovascular invasion or ES are classified as advanced stage (BCLC stage C) and Sorafenib is considered to be the standard treatment for patients at this stage.[25, 26] Patients with cancer symptoms, related to progressed liver failure, tumour growth with vascular involvement, ES, or physical impairment (performance status ≥2) are classified as stage D (end stage) disease; they do not

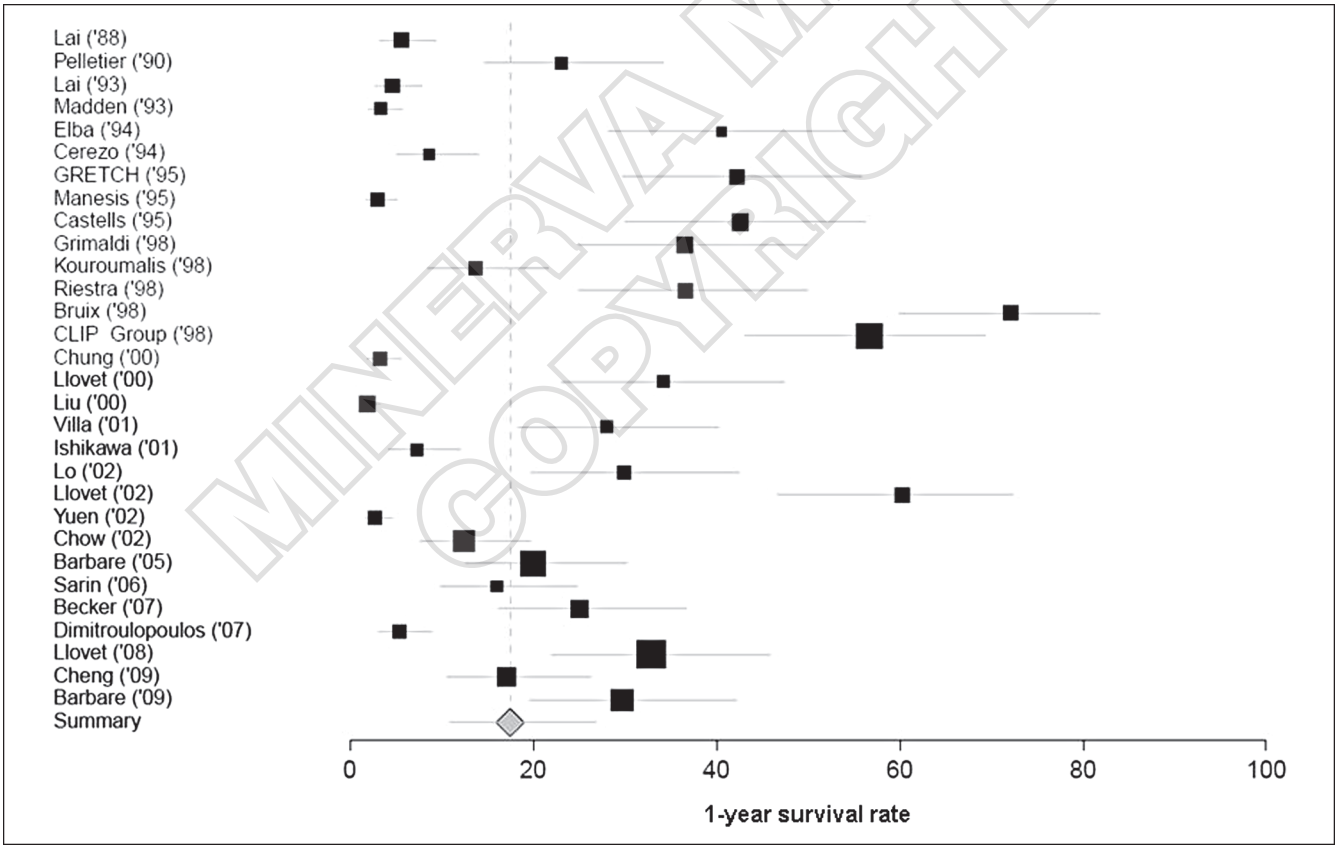

Figure 2.—Forest plot of 1-year survival rates, using random-effects model, of C stage studies in the placebo or untreated arms. Studies are arranged by publication year. Copyright © 2010, John Wiley and Sons. Adapted with permission from Cabibbo G *et al*.[13]

benefit from antitumor treatments and should receive only the best available supportive care.

Extrahepatic spread of HCC

A very recent meta-analysis of survival rate in the placebo or untreated arm of Randomized Clinical Trials (RCTs) of HCC patients, showed the natural history of untreated unresectable HCC[13]. The pooled estimates of the survival rates were 17.5% at 1 year (Figure 2) and 7.3% at 2 years. Moreover, was performed subgroup analyses according to the various BCLC stages; the pooled estimates of BCLC B, C and D stages 1-year survival were 49.6%, 25% (Figure 3) and 11% respectively. However, heterogeneity among studies was highly significant (P<0.0001) both for 1-year and 2-year survival, and persisted when RCTs were stratified according to BCLC classes.

Interestingly, among the 30 RCTs included in the meta-analysis,[25-49] information on the presence of ES was missing from most of RCTs [27-29, 31, 34, 36-38, 40, 43, 44, 46, 50] and ranged from 7% to 68% in the studies reporting it,[25, 26, 35, 41, 42, 45, 47, 49, 51] while in 7 studies [30, 32, 33, 39, 52-54] presence of ES was reason for exclusion of patients from the trial (Table I).

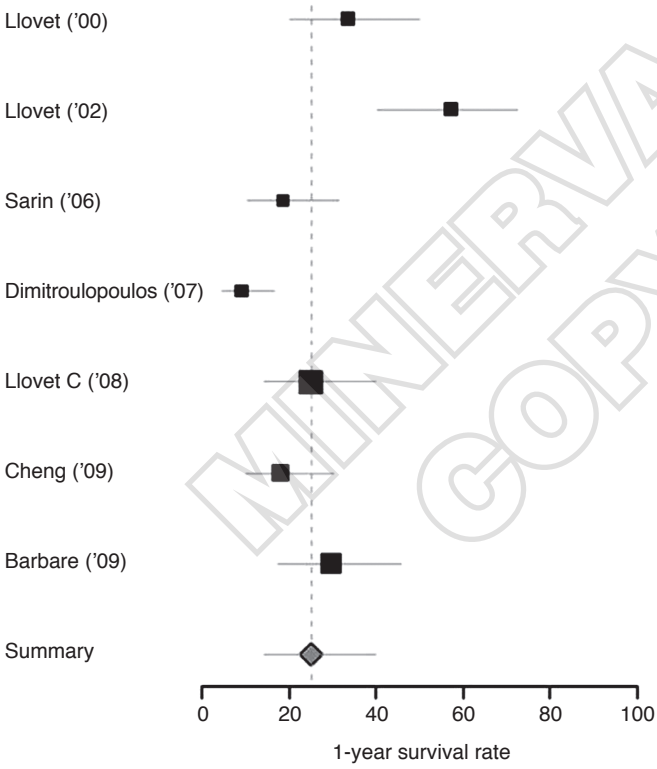

Figure 3.—Forest plot of 1-year survival rates of the placebo or untreated arms of 30 RCTs using random-effects model. Studies are arranged by publication year. Copyright © 2010, John Wiley and Sons. Adapted with permission from Cabibbo G *et al*.[13]

Table II shows summary of studies evaluating and/or comparing several prognostic scores for HCC.[15, 17-23, 55-64] Data on ES were missing in 7 studies,[17, 19-21, 55, 59, 62] while differed greatly in the papers reporting it,[15, 18, 22, 23, 56, 58, 60, 61, 63, 64] ranging from 2.7% to 60%.

A land-mark paper published in 2000, retrospectively studied Computed Tomography (CT) findings in 403 consecutive patients with HCC.[65] In this cohort, 148 patients (37%) with ES of HCC were identified. The most frequent sites of detectable ES were the lung in 81 patients (20%), the abdominal lymph nodes in 60 (15%), the bones in 41 (10%), and adrenal gland in 18 patients (4.4%). In this study no data were showed on impact of ES in the prognosis of patients. However, it clearly demonstrates the importance of intra-hepatic stage of HCC in determining the extra-hepatic staging of disease. In fact, according to TNM staging system, a majority of patients (87%) with extra-hepatic HCC had intra-hepatic stage III (10%) and stage IVA (76%) tumours; 10% of the patients had intra-hepatic stage II tumour, and one patient had stage I tumour.

A retrospective study reviewed clinical records of 482 HCC patients.[66] ES had been detected in 65 patients (13.5%). Among the 65 patients, the frequent metastatic sites were lung (53.8%), bone (38.5%), and lymph node (33.8%). Other metastatic sites were the adrenal gland, peritoneum, skin, brain and muscle. Similarly to the previous study, patients with extra-hepatic metastases had more advanced intrahepatic tumours.

These patients had a prognosis very poor; the 1-year survival rate was 24.9%, and median survival was 7 months.

Another retrospective study [67] also studied patients with ES from a wide cohort of consecutive HCC patients (995). Among these, 151 (15.2%) were found to have ES at the initial diagnosis of primary HCC or developed metastases during the follow-up. The survival rates after diagnosis of ES were 44.1%, 21.7%, 14.2 and 7.1% at 6, 12, 24 and 36 months, respectively.

Table III shows the sites of ES reported in three previous studies.

TABLE I.—*RCTs of hepatocellular carcinoma comparing any treatment of HCC* versus *placebo or no antitumoral treatment.*

Author	Year	Control arm	Treated arm	Reported pts with ES - N. (%)
Lai [27]	1988	46	60	NR
Pelletier [28]	1990	21	21	NR
Lai [29]	1993	36	35	NR
Madden [30]	1993	25	25	8(9)°
Elba [31]	1994	11	11	NR
Martinez Cerezo [32]	1994	16	20	°
GRETCH [33]	1995	46	47	°
Manesis [34]	1995	29	56	NR
Castells [35]	1995	62	58	9 (7.5)
Grimaldi [36]	1998	59	179	NR
Kouroumalis [37]	1998	30	28	NR
Riestra [38]	1998	37	40	NR
Bruix [39]	1998	40	40	°
CLIP Group [40]	1998	240	237	NR
Chung [41]	2000	26	38	27 (40)
Llovet [42]	2000	28	30	7(12)
Liu [43]	2000	58	61	NR
Villa [52]	2001	24	21	°
Ishikawa [50]	2001	20	28	NR
Lo [53]	2002	39	40	°
Llovet [54]	2002	35	77	°
Yuen [51]	2002	35	35	12 (17)
Chow [44]	2002	130	194	NR
Barbare [45]	2005	210	210	72 (17)
Sarin [46]	2006	19	23	NR
Becker [47]	2007	59	60	22 (19) [Lung]
Dimitroulopoulos [48]	2007	30	96	19 (15)
Llovet [25]	2008	303	299	All, 309 (51) Lymph nodes, 154 (25) Lung, 125 (21)
Cheng [26]	2009	76	150	All, 155 (68) Lymph nodes, 72 (32) Lung, 112 (49)
Barbare [49]	2009	137	135	59 (22)

ES: extrahepatic spread; RCTs: randomized controlled trial; NR: not reported
° *Reason for exclusion of patients from the trial*

A part from the papers cited above, the literature shows only case reports on the extra-hepatic metastases from HCC, as in particular for the head and neck district. In fact, metastases from HCC have been reported involving the oral soft tissues and the jaws, being often the first clinical manifestation leading to the diagnosis of HCC.[68-71] To date, about 70 cases of metastases from HCC have been counted for the oral district. Common oral sites of occurrence include the jaws with a predilection for the mandibular bone, and the gingiva. As regards oral soft tissue, the gingiva is the most frequently reported; the early manifestation of HCC gingival metastases resembles a hyperplastic or reactive lesion presenting as polypoid or hemispheric masses having an angiomatous appearance, such as pyogenic granuloma, peripheral giant cell granuloma or fibrous epulis. These lesions could be painful or painless, and bleeding is the most constant early symptom.[72] As the mucosal lesion grows may involve the underlying bon plan.

The most frequently affected mandibular intraosseous locations are the posterior region, the angle, the ramus and the condyle.[73-75] Presence of metastasis in these areas probably is linked to the abundance of hematopoietic tissue, which may enable tumor emboli to implant and proliferate.[71] Patients with HCC metastasis to the jaws are usually symptomatic, with pain, paresthesia and swelling. The in-

TABLE II.—*Cohort studies evaluating and/or comparing several prognostic scores for HCC.*

Author	Year	No. of patients	Reported pts with ES - no. (%)
Okuda [17]	1984	600	NR
CLIP [15]	1998	435	14 (3.2)
Llovet [18]	1999	102	6 (5.8)
Chevret [19]	1999	761	NR
CLIP [48]	2000	196	NR
Schoniger-Hekele [20]	2001	245	NR
Ueno [56]	2001	662	18 (2.7)
Leung [21]	2002	257	15 (5.8)
Levy [57]	2002	926	NR
Vauthey [22]	2002	557	Lymph nodes, 18 (3.2)
Cillo [58]	2004	187	6 (3.2)
Grieco [59]	2005	268	NR
Marrero [60]	2005	239	13 (5)
Cillo [61]	2006	195	8 (4)
Cammà [62]	2008	406	NR
Collette [63]	2008	538	70 (13)
Huitzil-Melendez [64]	2010	187	Lymph nodes, 69 (37) No LN ES, 112 (60)
Tournoux-Facon [23]	2010	687	Chest or bone, 131 (19)

ES: extrahepatic spread; LN: lymph nodes; NR: not reported

TABLE III.—*Summary of extrahepatic spread sites in 3 studies.*

	Studies		
	Katyal *et al.*[65] N. of patients with ES [N.=148]	Natsuizaka *et al.*[66] N. of patients with ES [N.=65]	Uka *et al.*[67] N. of patients with ES [N.=151]
Site of ES – N. (%)			
Lung	81 (55)	35 (54)	63 (42)
Lymph nodes	78 (53)	22 (34)	60 (40)
Bone	41 (28)	25 (38)	51 (34)
Adrenal gland	16 (11)	11 (17)	16 (11)
Peritoneum and/or omentum	16 (11)	6 (9)	1 (0.7)
Brain	3 (2)	5 (8)	-
Rectum	2 (1)	-	-
Spleen	2 (1)	-	-
Diaphragm	1 (1)	-	-
Duodenum	1 (1)	-	-
Esophagus	1 (1)	-	-
Pancreas	1 (1)	-	1 (0.7)
Seminal vesicle	1 (1)	-	-
Bladder	1 (1)	-	-
Skin	-	4 (6.2)	-
Nasal passages	-	-	1 (0.7)

ES: extrahepatic spread

volvement of the overlying oral mucosa occurs when the bone cortex is destroyed by the neoplastic process, resulting in the formation of a mass which often bleeds spontaneously.

Radiographically HCC metastatic to the jaw — or to the gingiva with intra-osseous extension — presents as a radiolucent lesion with ill-defined borders lacking sclerotic limits, having an appearance like that expected in a malignant lesion. However, recently a case of metastasis of HCC into the man-

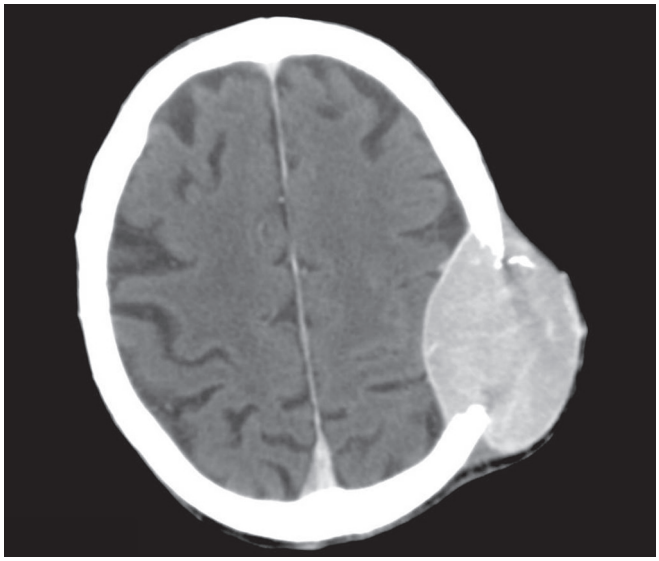

Figure 4.—Contrast-enhanced axial multidetector computed tomography (MDCT) shows an hypervascular skull metastases. Courtesy of Dr. Massimo Galia, Dipartimento di Biotecnologie Mediche e Medicina Legale, Section of Radiological Sciences, University of Palermo, Palermo, Italy.

dible with radiographic findings mimicking a benign radicular cyst has been reported.[76]

Also parotid glands could be a site of metastases from HCC; however, until today only three cases, manifesting as a parotid mass and simulating other parotid neoplasms have been reported in literature.[77]

The pharynx,[78] the tonsil,[70] the esophagus [79] the nasal cavity and maxillary sinus,[80] the skull,[81, 82] the facial subcutaneous tissue,[83] pituitary gland, sphenoid sinus, cavernous sinus,[84] the brain [85] and the orbit [86] are other sites of the head and neck district which could be affected by metastases from HCC.

Even if rarely, metastases from HCC to the skin,[87, 88] the colon;[89] the heart,[90] the kidney,[91] the peritoneum,[92] the gallbladder,[93] the spleen,[94] the pancreas [95] and the epidural space [96] have been also described.

Metastases from HCC may spread through both hematogenous and lymphatic paths.

As regards the bloodborne pathways there are two main routes of tumour metastases spread from the liver to the other districts. The first involves the major vessels of the liver, hepatic artery, and portal veins which are invaded leading to widespread metastasis, frequently to the lungs. The second, described by Batson,[97] consists of a pathway, of rich anastomoses of paravertebral veins (called Batson's plexus - a connection between the azygos and hemiazygos veins and the vertebral venous plexus) that lack valves and may be capable of by-passing other venous systems, such as the pulmonary, caval, and portal. This latter route could explain as some metastases from HCC could involve distant regions without lung involvement.

Treatment of patients with ES

As mentioned above, according to the classification of BCLC, macrovascular invasion and metastasis characterize the advanced stage of HCC.[18]

Previously, no standard systemic therapy existed for the treatment of patients at this stage.[98] Chemotherapy has no activity either intra-venously or intra-arterially, both if tested as a single agent regimen or in combination. In addition, the lack of impact on survival is associated with toxicity that results in impaired quality of life or even in impaired survival; however, two RCTs [25, 26] have now shown that sorafenib, an inhibitor of Raf kinase and vascular endothelial growth factor receptor (VEGFR), improves the overall survival of patients with stage C HCC. Both these studies show benefit in survival, comparing with placebo groups, independently of presence or absence of macrovascular invasion and/or ES. It is important to note that these studies were designed to capture the benefit of the new drug avoiding the confounding effect of deaths unrelated to cancer progression; so, patients included in the RCTs were in compensated cirrhosis.

Symptoms caused by ES were observed more frequently in patients with bone and brain metastases.[77] These patients may benefit from radiation therapy as palliative treatment even if these data were not obtained from RCTs but only by a number of case reports.

In several case reports ES were treated with surgical resection for lymph node, lung, bone or brain metastases, while in other studies HCC patients with ES underwent treatment for the intrahepatic tumor with locoregional therapies.

This approach is controversial and the lack of high-quality studies in this field makes firm conclusions difficult to reach.

We believe that in absence of more solid evidence, patients at advanced stage, with or without ES should be treated with sorafenib.

Conclusions

In recent years ES of HCC are observed more frequently; it is unclear whether this depends on 1) the improving in diagnostic methods; 2) the prolonged survival of patients because of extensive application of surveillance programs [99] and/or effects of treatments, or 3) more attention than in the past in obtaining an accurate staging.

For example, in a recent large multicenter RCT as the SHARP trial,[25] the staging of HCC included bone scan only if bone metastases were clinically suspected.

Since the majority of ES are asymptomatic and, as rarely, they may be in other locations such as skin, salivary glands,[77] oral cavity, seminal vesicle, etc, it is clear how the low proportion of patients with ES in many studies most likely reflect poor compliance with providing accurate tumor staging.

At the present, the prognosis of patients with ES is poor. Many data suggest a 1-year survival rate around 20% in this group of patients.

The prognostic role of ES is still not entirely clear. In fact, in the BCLC classification the presence of ES and/or macrovascular invasion defines the advanced stage. It is also clear that the probability of finding ES is higher in patients with advanced intrahepatic HCC.

The role of sorafenib in the treatment of ES needs to be further investigated.

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