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April 2, 2013

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Please find enclosed the edited manuscript in Word format (file name: 2691).

Title: Management of Hepatocellular Carcinoma: enlightening the gray zones

Author: Andrea Mancuso

Name of Journal: *World Journal of Hepaology*

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

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2: I introduced "HCC Management" as Running Title
3: I corrected Tel and Fax number as you suggested
4: I introduced an Abstract as you suggested.
5: I introduced Key words.
6: I introduced Core Tip.
7: I corrected the References citation as you suggested.
8: I put Figurs at the end of the paper.
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3 References and typesetting were corrected

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Sincerely yours,

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Management of Hepatocellular Carcinoma: Enlightening the gray zones.

RUNNING TITLE: HCC Management

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Abstract

Management of hepatocellular carcinoma (HCC) has been continuously evolving during recent years. HCC is a worldwide clinical and social issue and typically a complicates cirrhosis. The incidence of HCC

Commento [WL3]: no less than 200 words

is increasing, not only in the general population of patients with cirrhosis, but particularly in some subgroups of patients, like those with HIV infection or thalassemia. Since a 3% annual HCC incidence has been estimated in cirrhosis, a bi-annual screening is generally suggested.

The diagnostic criteria of HCC has recently had a dramatic evolution during recent years. HCC diagnosis is now made only on radiological criteria in the majority of the cases.

In the context of cirrhosis, the universally accepted criteria for HCC diagnosis is contrast enhancement in arterial phase and washout in venous/late phase at imaging, the so called "typical pattern". However, recently updated guidelines slightly differ in diagnostic criteria.

Apart from liver transplant (LT), the only cure of both HCC and underlying liver cirrhosis, all the other treatments have to match with higher rate of HCC recurrence. The latter can be classified into curative (resection and percutaneous ablation) and palliative treatments.

The aim of this paper was to review the current knowledge on management of HCC and to enlighten the areas of uncertainty.

Key words: HCC; Management; TACE; OLT; Surgery; Management

Commento [WL4]: Please list 5-10 key words for each paper, selected mainly from Index Medicus, which reflect the content of the study. Each key word is separated by a semicolon.

Core tip: Management of hepatocellular carcinoma (HCC) has been continuously evolving during recent years. However, albeit overall similar, the main Societies of Hepatology differently defined their own guidelines. In fact, despite an evident agreement in the general lines of HCC management, some gray zones still persist (1 - 4). The aim of this paper was to review the current knowledge on management of HCC and to enlighten the areas of uncertainty.

Commento [WL5]: Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

Management of hepatocellular carcinoma (HCC) has been continuously evolving during recent years. However, albeit overall similar, the main Societies of Hepatology differently defined their own guidelines. In fact, despite an evident agreement in the general lines of HCC management, some gray zones still persist [1 - 4] . The aim of this paper was to review the current knowledge on management of HCC and to enlighten the areas of uncertainty.

Commento [WL6]: The Authors should put the number of the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the citied author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]".

Epidemiology

HCC is a worldwide clinical and social issue. Actually, it is the sixth most common cancer and the third cause of cancer-related death. Incidence increases with advancing age, with a median age at onset of about 70 year-old in developed countries and there is a male preponderance, with a male to female ratio of about 2.4 [5, 6].

HCC is typically a complication of cirrhosis, although it can rarely develop in the absence of cirrhosis [1 - 4]. Known underlying diseases at risk for HCC development are chronic viral hepatitis C and B, alcoholic hepatitis, non- alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, Budd-Chiari syndrome (BCS). Diagnostic algorithm follows the same radiological criteria for HCC (see above) despite the different aetiologies of underlying liver disease. However, an exception is HCC developing in BCS. In fact, the radiological pattern of regenerative nodules in BCS is similar to that of HCC [7]. Moreover, as a consequence of the hindered hepatic venous outflow, radiological criteria for HCC can be altered [8, 9]. Finally, although the risk of procedure-related bleeding is probably increased (10), generally diagnosis of HCC in BCS still needs histological confirmation [8, 9].

Overall, the incidence of HCC is increasing, not only in the general population of patients with cirrhosis [8, 9], but particularly in some subgroups of patients, like those with HIV infection or

thalassemia. In fact, in both HIV and thalassemia, a recent significant outcome improvement due to, respectively, iron chelating drugs in the latter and HAART in the former, has allowed the appearance of the complication of the underlying hepatic disease [13 - 18].

Screening and recall policy

Surveillance of HCC is important simply because as little is HCC size at diagnosis as high is the probability of curative treatment. Since a 3% annual HCC incidence has been estimated in cirrhosis [19], a bi-annual screening is generally suggested [1 - 4]. Although less stringent, there is a risk of HCC development also in non-cirrhotic chronic hepatitis and treated viral hepatitis, for which an annual screening is generally performed [1 - 4]. Ultrasound (US) is the test of choice for surveillance. In fact, US is a cheap and safe test, due to the absence of contrast medium and radioactivity [20 - 23]. Moreover, differently from CT and MR, US does not expose to the risk of false positive results. However, CT or MR should be preferred for surveillance of patients for which US is not adequate because of technical reasons or in liver transplantation waiting list [1 - 4].

Once hepatic nodules are discovered at US screening, the further work-up depends on the size [1 - 4]. Nodules < 1 cm should prompt a strict US surveillance every 3 or 4 months for the first year and, in the absence of size increase, every six months after one year, like patients with cirrhosis without liver nodules. In fact, hepatic nodules < 1 cm rarely are HCC. Moreover, for such little size nodules, diagnostic value of either CT and MR is inadequate.

Nodules between 1 and 2 cm in size should be studied with CT and MR and, in case of non diagnostic imaging, undergo nodule biopsy. Moreover, a second biopsy should be contemplated in case of inconclusive findings at histology, nodule growth or change in enhancement pattern.

Nodules > 2 cm should undergo CT and MR and, in case of atypical imaging findings, nodule biopsy [1 - 4].

HCC Diagnosis Update

The diagnostic criteria of HCC has recently had a dramatic evolution during recent years [24, 1, 2, 3, 4]. In fact, till the first half of the past decade, the Golden Standard for HCC diagnosis was histology. Then, since radiological diagnostic criteria have been shaped and established [1], HCC diagnosis is now made only on radiological criteria in the majority of the cases [1 - 4]. In the context of cirrhosis, the universally accepted criteria for HCC diagnosis is contrast enhancement in arterial phase and washout in venous/late phase at imaging, the so called "typical pattern" (Figures). However, recently updated guidelines slightly differ in diagnostic criteria [2 - 4].

Hepatic lesions > 1 cm with typical pattern at one imaging (CT or MR) have diagnosis of HCC in both the American Association for the Study of Liver Disease (AASLD) 2011 and European Association for the Study of the Liver (EASL) 2012 guidelines [2, 4]. However, EASL 2012 guidelines specify that for lesions between 1 and 2 cm the concordance of typical pattern at two imaging (CT and MR) should be advices in suboptimal settings (technology, local skills) (4). Both AASLD 2011 and EASL 2012 guidelines suggest lesion biopsy in the absence of typical pattern. Finally, both AASLD 2011 and EASL 2012 guidelines exclude from diagnostic criteria contrast-enhanced US (CEUS) and alpha-fetoprotein value [2, 4].

Japanese Society of Hepatology (JSH) 2012 guidelines agree with the diagnostic value of typical pattern at one imaging (CT, MR, CEUS) regardless of the size, and maintains the diagnostic value of CEUS and biochemistry (AFP > 200 ng/dl, PIVKA-II > 40, AFP L3 > 15%) (3). However, the main difference between JSH 2012 and both AASLD 2011 and EASL 2012 guidelines is that the former consider a diagnostic criteria the lesion hypo-intensity in hepatic image of Gd-EOB-MR [2 - 4].

HCC Treatment

Apart from liver transplant (LT), the only cure of both HCC and underlying liver cirrhosis, all the other treatments have to match with higher rate of HCC recurrence. The latter can be classified into curative (resection and percutaneous ablation) and palliative treatments[2 - 4].

Resection is considered the First-Line treatment for patients with solitary tumours and preserved liver function (normal bilirubin and, either HVPG ≤10 mmHg, PLT >100000 or no varices at endoscopy). Resection can also be performed for multi-focal HCC inside Milan criteria or in case of mild portal hypertension when patients are not suitable for OLT, although it is debated if such patients could benefit from other locoregional therapies, avoiding the risk of surgery and of liver de-compensation after surgery. In fact, perioperative mortality in cirrhotics after HCC resection is about 2–3%. Moreover, there is a risk of tumor recurrence after surgery of about 70% at 5 years, enclosing both true recurrence and the novo tumours [25 - 39].

Percutaneous local ablation, namely radiofrequency ablation (RFA) and ethanol injection (EI) are the standard of care for BCLC O-A not suitable for surgery. Although RFA is recommended in most instances as the main ablative therapy in tumors less than 5 cm, the probability of complete necrosis is very high for little tumors (< 2 cm) and progressively decreases with the increase of tumor size. In tumours ≤ 2 cm both RF and EI achieve complete responses in more than 90%, making percutaneous local ablation competitive with resection. EI is better indicated when RFA in not technically feasible. This is the case of tumors overflowing the liver margin or near organs, just like gallbladder or bowel, because of the risk of thermal injury and perforation, or when tumor is adjacent to a main vessel, because of the concern of thermal dispersion and inefficacy of RFA [40 - 64].

Trans-arterial chemoembolization (TACE) is the recommended treatment for BCLC stage B multinodular asymptomatic tumors without vascular invasion or extrahepatic spread. Drug-eluting beads have similar efficacy to gealfoam-lipiodol with probably less adverse events. Both should be discoraged in decompensated liver disease and in case of macroscopic vascular invasion or extrahepatic spread [65 -

[80]. An alternative to TACE is radioembolization. However, radioembolization , although promising and with advantage of being indicated also in the case of portal vein neoplastic thrombosis, is expensive and further data are needed. In fact, to our knowledge there are not well designed studies comparing radioembolization with neither TACE nor Sorafenib [81 - 84].

Liver transplantation (LT) is actually a consolidated therapeutic option for HCC because it cures both tumor and underlying cirrhosis [1 - 4]. However, the indication of LT for HCC treatment has evolved over recent years [85 - 109]. Moreover, initial experiences tended to offer LT as the last therapeutic chance when resection was not feasible. In fact, till the first half of nineties, the discouraging results of some experiences had questioned the possibility of LT efficacy as HCC treatment. In 1996, the publication of a pivotal prospective study on less than 50 patients, transplanted for HCC under predefined criteria (single HCC $\leq$ 5 cm or 3 HCC $\leq$ 3 cm each), the so called "Milan criteria", showed a 4 year survival of 75% [85]. Subsequent experiences of LT for HCC inside the Milan criteria, confirmed a survival rate exceeding 70% at 5 years, with a recurrence in less than 15%. Due to these data, LT is now the first-line treatment for one HCC $\leq$ 5 cm or 3 HCC $\leq$ 3 cm each [1 - 4].

Although all published guidelines go on considering the Milan criteria as the only fence inside which LT should be considered as treatment of HCC [2 - 4], the possibility of an extension of Milan criteria as indication for LT is already a debated issue. In fact, while it is universally recognized that LT for HCC inside Milan criteria guaranties an acceptable outcome, numerous heterogeneous experiences explore the possibility of extending the Milan criteria.

A line of experiences studies the applicability of the University of California San Francisco (UCSF) criteria, that is single nodule $\leq$6.5 cm or 2–3 nodules $\leq$4.5 cm and total diameter $\leq$8 cm. In fact, UCSF criteria on explant identified retrospectively a cohort of patients whose survival was not significantly different from those of patient transplanted for HCC inside the Milan criteria [93]. The same results had other retrospective experiences by other groups using UCSF criteria. Moreover, a recent prospective

study showed a 5 year survival not significantly different in patients transplanted for HCC inside Milan and UCSF criteria [103].

A recent multicenter restrospective study on over 1700 found that HCC inside the "Up-to-seven" criteria at explant (those HCCs having the number 7 as the sum of the size of the larger tumor and the number of tumors) and without microvascular invasion had a 5 year survival not significantly different from those inside the Milan criteria, while survival was significantly worst in case of HCC inside the "Up-to-seven" criteria and with microvascular invasion [104].

Another line of studies suggest that Down-staging for HCC exceeding conventional criteria could be effective for extending LT without worsening survival. These studies are heterogeneous in design, inclusion criteria and philosophy. In fact, while some suggests to offer LT to those patients who achieve an effective downstaging, so selecting patients with a less aggressive HCC and likely reducing the probability of HCC recurrence after LT, others indicate LT for those HCC without an effective downstaging, as a rescue treatment [107 - 109].

Despite all the above studies, guidelines still give indication to LT only to HCC inside Milan criteria [2 - 4]. However, as published experiences show, many center actually perform LT outside the Milan criteria, using criteria different from centre to centre [85 - 109].

Whatever the criteria adopted, a significant problem of HCC candidates for LT is the problem of drop out, that is patients who do not reach the goal of LT because of progression of HCC or of causes unrelated to HCC. Many studies have investigated the risk of drop out that remains difficult to define, although some factors, like tumor multinodularity, neoadjuvant treatment failures, elevated AFP or MELD some, have been correlated with a higher probability of drop out. From an opposite point of view, given the organ shortage, some patients with single HCC <2 cm may benefit from alternative treatments and avoid LT at least until recurrence occours, highlighting the possibility of salvage transplantation in low risk

population. Moreover, it is still uncertain which is the role of LT after surgery and high risk of recurrence at pathology [2 - 4].

Living donor liver transplantation (LDLT) is an alternative option if waiting list is long and offers the possibility of a LT after a short time. However, there is a donor risk of death of about 0.3% and of life threatening complications of about 2%. In fact, LDLT should be restricted to centers of excellence [110 - 120].

The mainstay of palliative therapy for advanced HCC is Sorafenib, which is indicated in advanced HCC (BCLC C) or HCC progressing upon loco-regional therapies in patients with well preserved liver function and good Performance Status. Registrative studies have shown a three months increase in median overall survival of Sorafenib compared to placebo. Moreover, adverse events are frequent a can be severe (Diarrea, Hand-foot skin-reaction) [121 - 125].

The role of Sorafenib in some subgroup of patients is debated. In fact, while some experiences report encouraging results of sorafenib therapy after HCC recurrence post OLT, others suggests that adverse events could affect sorafenib efficacy [126 - 135]. Moreover, our preliminary experience on HCC in HIV positive patient report a high incidence of hepatotoxicity. In both the subgroup the possibility of drug interections should be investigated.

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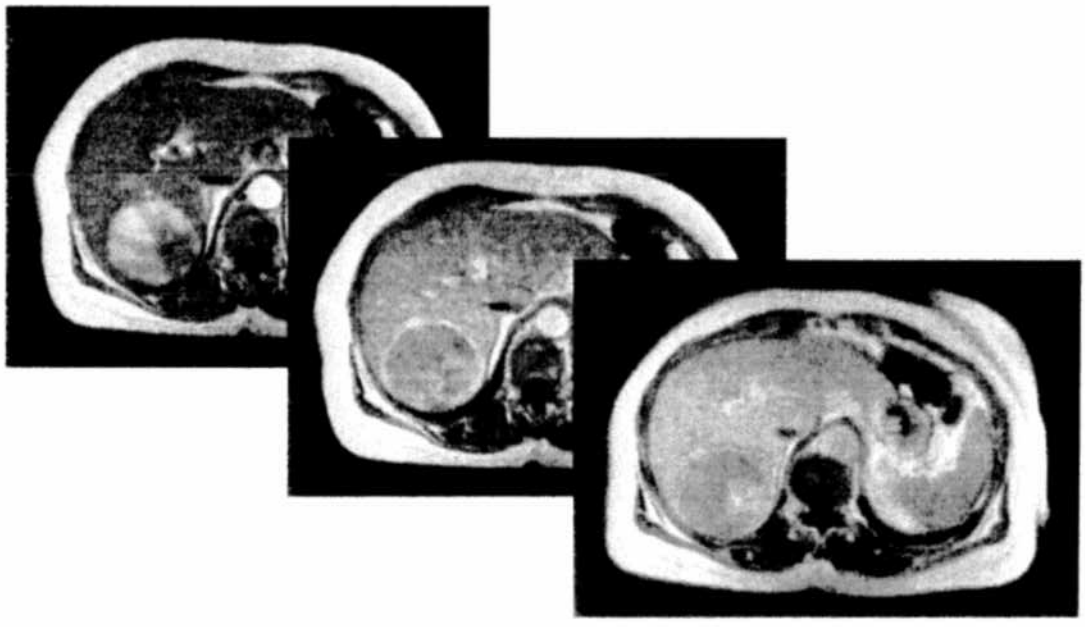

Fig 1: Typical HCC at MRI: contrast enhancement in arterial phase and washout in venous/late phase.

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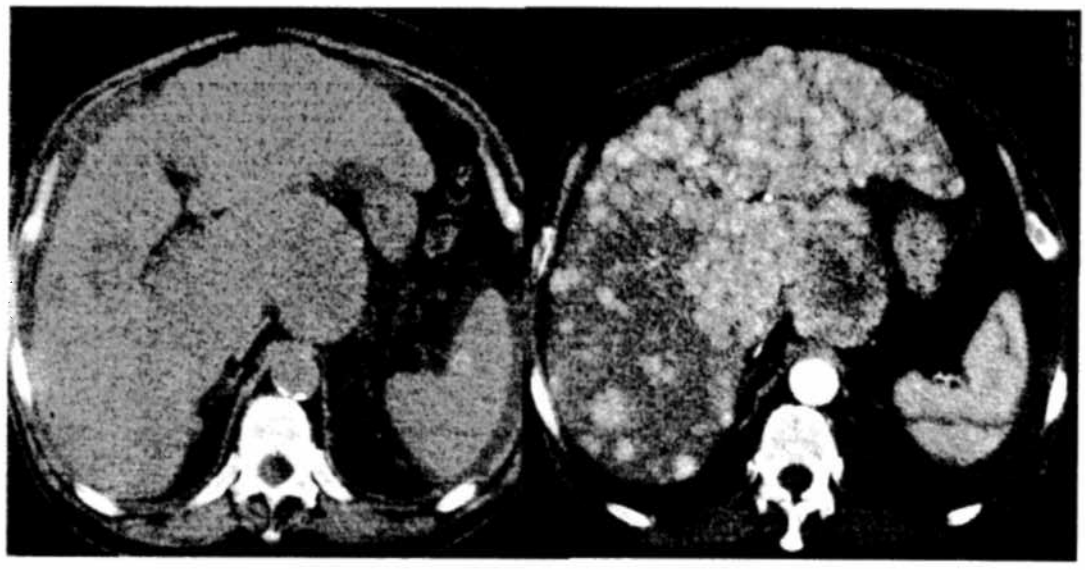

Fig 2A: multi-nodular HCC, basal and arterial CT phase

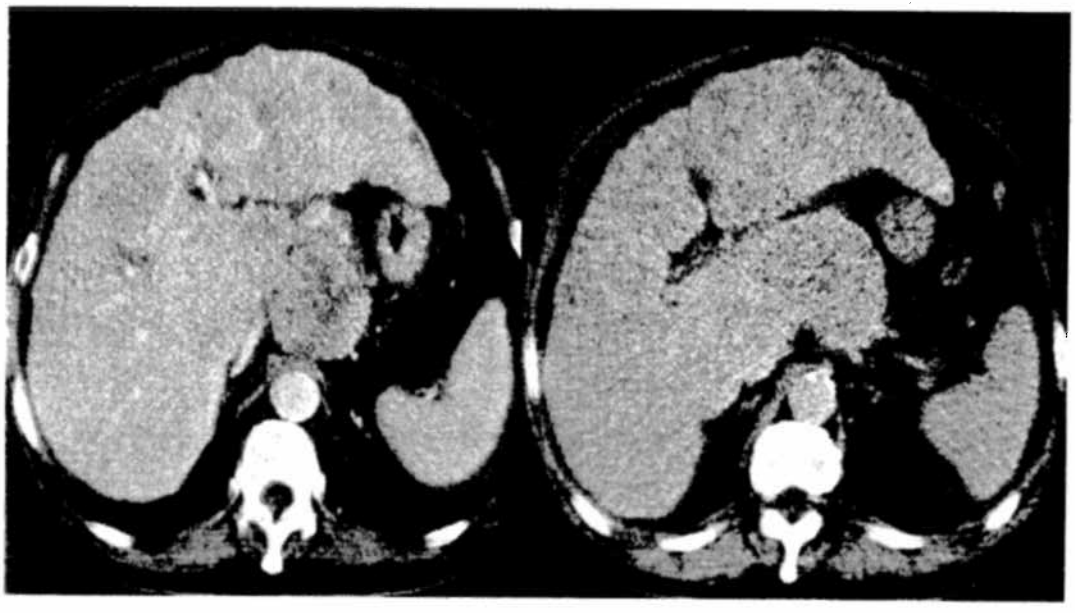

Fig 2B: multi-nodular HCC: venous and late CT phase

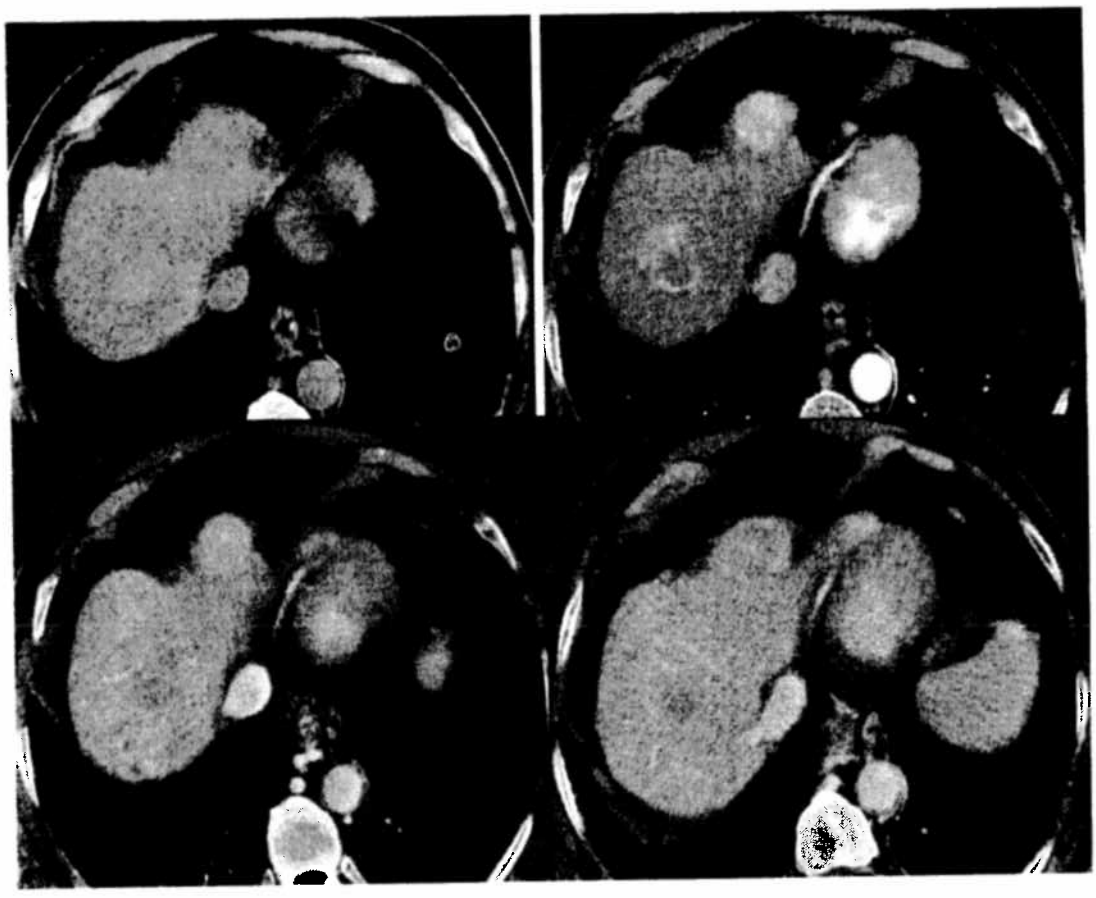

Figure 3: A new Typical HCC found at CT during follow up another HCC treated with RFA (central lesion). Note that also in the treated lesion there is a marginal area of vital HCC.