DOWNLOAD PDF PATHOMORPHOLOGIC CHARACTERISTICS OF EARLY-STAGE SMALL HEPATOCELLULAR CARCINOMA

Chapter 1 : Treatment of very early- or early-stage primary liver cancer (hepatocellular carcinoma) | Cochra

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November 21, Abstract Hepatocellular carcinoma HCC is currently the sixth most common type of cancer with a high mortality rate and an increasing incidence worldwide. Its etiology is usually linked to environmental, dietary or life-style factors. HCC most commonly arises in a cirrhotic liver but interestingly an increasing proportion of HCCs develop in the non-fibrotic or minimal fibrotic liver and a shift in the underlying etiology can be observed. Although this process is yet to be completely understood, this changing scenario also has impact on the material seen by pathologists, presenting them with new diagnostic dilemmas. Histopathologic criteria for diagnosing classical, progressed HCC are well established and known, but with an increase in detection of small and early HCCs due to routine screening programs, the diagnosis of these small lesions in core needle biopsies poses a difficult challenge. These lesions can be far more difficult to distinguish from one another than progressed HCC, which is usually a clear cut hematoxylin and eosin diagnosis. Furthermore lesions thought to derive from progenitor cells have recently been reclassified in the WHO. This review summarizes recent developments and tries to put new HCC biomarkers in context with the WHOs reclassification. Furthermore it also addresses the group of tumors known as combined hepatocellular-cholangiocellular carcinomas. Histology , Pathology , Hepatocellular carinoma Core tip: Hepatocellular carcinoma HCC is currently the sixth most common type of cancer with a high mortality rate and an increasing incidence worldwide. HCC most commonly occurs on ground of a cirrhotic liver but interestingly an increasing proportion of HCCs develop in the non-fibrotic or minimal fibrotic. Histopathology of hepatocellular carcinoma. HCC is more common in males than in females and mostly occurs in developing countries. The increasing trend is mainly due to a cohort effect related to infection with hepatitis B and C viruses HBV and HCV , the incidence of which peaked in the s to s. Time trends in incidence of hepatocellular carcinoma of developed countries parallel the timing of HCV spread. In Japan and Europe, where HCV infection spread earlier than in the United States, the incidence of hepatocellular carcinoma has almost reached a plateau and in some areas it is declining; however, in the United States, incidence is still increasing and the infection could have a synergistic effect with other risk factors, such as non-alcoholic fatty liver disease. In most cases, HCC is a multistage disease whose occurrence is linked to environmental, dietary and life-style factors[2]. Although histopathologic criteria for diagnosing classical, progressed hepatocellular carcinoma have not recently changed, diagnosis of small and early lesions has gained of importance due to the increased detection rate of these early lesions in routine screening programs. These lesions can be far more difficult to distinguish from one another than progressed HCC. It occurs predominantly in female patients using oral contraceptives, but has also been described female patients with maturity onset diabetes of the young type 3[6]. In males it is described in patients with glycogen storage disease or androgen treatment. This type is usually beta-catenin mutated and is reported to have a higher risk of malignant transformation[7]. Metabolic syndrome has recently also been described as an emerging risk factor for HCA[6]. In some cases no etiology for the development of a hepatocellular adenoma can be determined. Dysplastic foci Dysplastic foci are uniform lesions and their morphology, cytoplasmatic staining, nuclear size and cellular atypia discriminates them from the surrounding liver tissue. A similar and hard to distinguish lesion is small cell dysplasia. They are usually seen in cirrhotic livers and are also considered premalignant lesions due to their increased proliferation index and low rate of apoptosis[10]. Dysplastic nodules In contrast to dysplastic foci, dysplastic nodules are defined as being larger than 1mm in size. These lesions are usually found in cirrhosis and are generally subdivided into low-grade and high-grade lesions. Both subtypes have been described as possible progenitor lesions to HCC but regression has also been described in literature. Portal tracts and the reticulin network are still present. The borders of the lesions can be rounded but usually do not show compression of

the adjacent liver tissue. In addition, high-grade dysplastic nodules may display the following histological features: Occasional unpaired arteries have also been described in high-grade dysplastic nodules[9 , 11 , 12]. With the remarkable advances of various diagnostic imaging techniques and the establishment of a follow-up system for the high-risk population, the numbers of surgically resected cases of early stage small HCCs and the amount of biopsy material form minute HCCs has increased. Extensive morphologic studies of this material have revealed that many HCCs arise in equivocal nodular lesions, such as dysplastic nodules in the cirrhotic liver and are highly differentiated in the early stages. At the same time, it has been established that well-differentiated HCC in the early stages evolves to advanced and dedifferentiated tumor in a multistep fashion[13 , 14]. An additional characteristic feature of HCC is its frequent occurrence in the form of multiple nodules[15]. In HCC, the simultaneous occurrence of multiple HCCs may reflect either the dissemination of malignant cells from a single primary tumor to form satellite tumor nodules intrahepatic metastasis , or the synchronous development of several independent tumors. The two possible mechanisms of development of multiple HCCs reflect important differences in pathogenesis that appear to have an impact on treatment and prognosis[16]. Differences in prognosis between these two categories probably result from the fact that multiple HCCs developing from intrahepatic metastasis are more aggressive and more poorly differentiated than multiple HCCs that are composed of several independent tumours that emerge more or less simultaneously. Molecular analysis of the HBV integration patterns and genetic changes has indicated independent multicentric development of these nodules[15 , 17 - 20]. During histological assessment, small and early HCCs should be distinguished from advanced disease. While the diagnosis is mostly clear in advanced stage cases, small, early and therefore mostly well-differentiated lesions can be problematic. Due to established screening programs in cirrhotic patients, biopsies of these lesions problematic lesions have increased in number. The international consensus group for hepatocellular carcinoma[21] and the WHO[22] propose the following classification: HCCs of the vaguely nodular type occur more often in cirrhosis, are usually smaller in size and less often show portal vein invasion than the distinctly nodular type. Furthermore they are hypovascular and almost never show intrahepatic metastasis. In resected specimens, they are sometimes difficult to localize, because their margins to the surrounding liver tissue are not well defined and portal tracts are retained within the tumor[11]. The distinctly nodular subtype has a discernible capsule and usually occurs in a cirrhotic liver. Progressed hepatocellular carcinoma can grossly be classified into the following macroscopic groups: The nodular type can either consist of a single or multiple nodules. Single nodules are usually encapsulated and may show extracapsular growth in the vicinity of the primary nodule. The multinodular type is an aggregation of a varying amount of small nodules. The massive type is defined as a large tumor with irregular demarcation. This morphologic appearance can also been seen in advanced stage nodular HCC. The diffuse type is described to have many small nodules in a liver lobe or the whole organ[11]. Rarely a pedunculated or protruded growth can be observed. The most common histologic growth patterns are: Bile production can frequently be observed. Within the tumor cells Mallory-bodies and pale bodies can be also present[22]. Histomorphologic appearance of hepatocellular carcinoma varies greatly from patient to patient and even in a single patient, different stages of intratumoral differentiation and growths patterns can be observed. Some authors postulate a step-wise dedifferentiation of an initially well differentiated small lesion into a larger, less differentiated tumor which leads to intratumoral heterogeneity. The well differentiated lesion is usually replaced by tissue of the dedifferentiated component in advanced disease and therefore leads to a nodule in nodule appearance. Especially in very advanced stage, but sometimes also in small tumors, the initial well-differentiated tumor component may not be discernible[13 , 14 , 24 , 25]. In contrast, progressed HCC shows an expansive and infiltrative histologic growth pattern with complete neovascularization with unpaired arteries and possible vascular infiltration. There are no portal tracts seen within the tumor and all the classical histologic patterns i. The tumors are mostly encapsulated and septae are detected. Encapsulation is reported to be more frequent in tumor arising in a cirrhotic liver than in non-cirrhotic livers[11]. Most of these tumors show satellite nodules within 2 cm of the primary tumor nodule as well as metastasis in the liver.

In HCC, angioarchitecture plays a very important role during tumor growth and is also essential part of modern imaging modalities. These arteries are not associated with a portal tract and therefore have no contact to bile ducts. They also show less elastic fibers compared to normal intrahepatic arteries. Early HCC of the vaguely nodular type has a reduced density of unpaired arteries compared to progressed HCC and therefore appears hypovascular in imaging. Due to the presence of portal tracts within tumor, although less in number than in normal liver tissue, these lesions also receive blood from the portal vein[26 , 27]. Early HCC of the distinctly nodular type as well as progressed-HCC appear hypervascular because of earlier neovascularization with unpaired arteries. Grade I consists of small tumor cells, arranged in trabeculae, with abundant cytoplasm and minimal nuclear irregularity that are almost indistinguishable from normal liver tissue. Grade II tumors have prominent nucleoli, hyperchromatism and some degree of nuclear irregularity. Grade IV has prominent pleomorphism and often anaplastic giant cells. Since HCC is usually quite heterogeneous the eligibility of tumor grading in biopsy specimens is unclear. A study done by Pawlik et al[30] demonstrates that needle core biopsies, especially of progressed HCCs tend to undergrade tumors compared to following surgical resection specimens. This subtype is seen in young patients without liver cirrhosis and with no other known predisposing factors and has a better prognosis than classical HCC[32 , 33]. Grossly it shows many fibrous septae and may have a central scared zone with possible calcification, therefore mimicking focal nodular hyperplasia Figure 2D. Histologically the tumor cells grow in sheets and trabeculae that are separated by collagen fibers which are often hyalinized and show a characteristic lamellar pattern[11]. Cytoplasmatic inclusions such as ground glass pale bodies and cytoplasmatic globules which are PAS-positive and immunoreactive to anti fibrinogen are often seen. The tumor cells are spindle-shaped and show bizarre anaplastic figures. Giant cells are often present, but they can also been seen in other types of HCC. In cases where there is no adjacent classical HCC, these tumor can be difficult to distinguish from leiomyosarcoma and fibrosarcoma[35 , 36]. Scirrhous HCC Scirrhous HCC shows diffuse fibrotic change which can occur after various antitumoral treatments and seldom in untreated tumors. These fibrotic changes often lead to misdiagnosis as cholangiocellular carcinoma or metastasis in preoperative imaging. This type of tumor histologically shows fibrosis along the sinusoid-like blood spaces, with atrophy of the trabeculae. In his series he also describes a unique directly subcapsular location of most of these tumors which leads to a possible pedunculated macroscopy. Clear-cell variant of HCC The clear-cell variant of HCC is usually arranged in a trabecular pattern and is characterized by clear cytoplasm that contains glycogen and a variable amount of fat vesicles[38]. Mostly only parts of the tumor show these clear-cell changes Figure 2A. A male predominance of variable degree is reported of this particular subtype of HCC[11 , 39]. The inflammatory infiltrate usually consists of neutrophils, plasma cells and lymphocytes. Fibrosis usually appears in a pericellular and trabecular form. These patients often suffer from non-alcoholic steatohepatitis but this phenotype of carcinoma is also seen in patients without steatohepatitic changes in the non-neoplastic liver tissue[40].

Chapter 2 : Histopathology of hepatocellular carcinoma

Some surgically resected small hepatocellular carcinoma (HCC) up to 2 cm in diameter have indistinct margins, and it is sometimes difficult to identify the margins of the cancer nodule in the resected specimen.

Treatment of very early- or early-stage primary liver cancer hepatocellular carcinoma Background Hepatocellular carcinoma primary liver cancer arises from the liver cells and is distinct from cancer arising from other parts of the body and spreading to the liver. People with very early- or early-stage hepatocellular carcinoma have single cancer or multiple small cancers confined to the liver, have good liver function, and no restriction of activities. There is significant uncertainty in the management of early-stage hepatocellular carcinoma. Therefore, we searched literature databases for randomised clinical trials RCTs on the topic until September We excluded trials in which participants had previously undergone liver transplantation. Apart from using standard Cochrane methods, which allow comparison of only two treatments at a time, we planned to use advanced methods described in full in the review. Study characteristics of included trials Four trials participants; participants included for one or more analyses compared surgery removal of part of the liver containing cancer versus radiofrequency ablation cancer destruction using heat generated by electric current in people with early hepatocellular carcinoma, eligible to undergo surgery; and 14 trials participants; participants included for various analyses compared different non-surgical interventions in people with early hepatocellular carcinoma, not eligible to undergo surgery. Key results Surgery versus radiofrequency ablation The majority of participants had cirrhotic livers, and the hepatocellular carcinoma was of viral cause. Three trials reported average follow-up range 29 months to 42 months. One trial was funded by a party with vested interests; three trials were funded by parties without any vested.. In people eligible for surgery, there was no evidence of a difference in death between radiofrequency ablation and surgery; although there were fewer deaths due to cancer in the surgery group. There were more serious complications in the the surgery group than in the radiofrequency ablation group. None of the trials reported health-related quality of life. Non-surgical interventions The majority of participants had cirrhotic livers, and the hepatocellular carcinoma was of viral cause. Most trials did not report the portal hypertension status of the participants, and none reported whether the participants received adjuvant antiviral treatment or adjuvant immunotherapy. Eleven trials reported average follow-up range 6 months to 37 months. Trial participants, who were not eligible for surgery, were treated with radiofrequency ablation , laser ablation cancer destruction using laser , microwave ablation cancer destruction using microwaves , percutaneous acetic acid injection cancer destruction using vinegar , percutaneous alcohol injection cancer destruction using alcohol , a combination of radiofrequency ablation with systemic chemotherapy, a combination of radiofrequency ablation with percutaneous alcohol injection, a combination of transarterial chemoembolisation blocking the artery supplying the cancer with beads containing chemotherapy drugs with percutaneous alcohol injection, or a combination of transarterial chemoembolisation with radiofrequency ablation. Five trials were funded by parties without any vested interest; the source of funding was not available in the remaining trials. In people not eligible for surgery, the percentage of people who died during the follow-up period was higher in the percutaneous acetic acid injection and percutaneous alcohol injection groups than in the radiofrequency ablation group. There was no evidence of any difference in the percentage of people who died between any of the remaining comparisons. The percentage of people who died because of cancer was also higher in the percutaneous alcohol injection group than in the radiofrequency ablation group. There was no evidence of any difference in the percentage of people who died because of cancer between any of the remaining comparisons. None of the trials reported health-related quality of life at any time point. Quality of evidence The overall quality of evidence was low or very low because of the way trials were conducted. Therefore, the conclusions made could overestimate the benefits or underestimate the harms of a given treatment. Further high-quality RCTs are needed. The evidence was of low or very low quality. There was no evidence of a difference in all-cause mortality at maximal

follow-up between surgery and radiofrequency ablation in people eligible for surgery. All-cause mortality at maximal follow-up was higher with percutaneous acetic acid injection and percutaneous alcohol injection than with radiofrequency ablation in people not eligible for surgery. There was no evidence of a difference in all-cause mortality at maximal follow-up for the other comparisons. High-quality RCTs designed to assess clinically important differences in all-cause mortality and health-related quality of life, and having an adequate follow-up period approximately five years are needed. Read the full abstract Hepatocellular carcinoma primary liver cancer is classified in many ways. People with very early- or early-stage hepatocellular carcinoma have single tumour or three tumours of maximum diameter of 3 cm or less, Child-Pugh status A to B, and performance status 0 fully functional. Management of hepatocellular carcinoma is uncertain. To assess the comparative benefits and harms of different interventions used in the treatment of early or very early hepatocellular carcinoma through a network meta-analysis and to generate rankings of the available interventions according to their safety and efficacy. However, it was not possible to assess whether the potential effect modifiers were similar across different comparisons. Therefore, we did not perform the network meta-analysis and instead assessed the benefits and harms of different interventions versus each other or versus sham or no intervention using standard Cochrane methodology. We included only RCTs , irrespective of language, blinding , or publication status, in participants with very early- or early-stage hepatocellular carcinoma, irrespective of the presence of cirrhosis, portal hypertension , aetiology of hepatocellular carcinoma, size and number of the tumours, and future remnant liver volume. We excluded trials including participants who were previously liver transplanted. We considered interventions compared with each other, sham, or no intervention. Data collection and analysis: Eighteen trials met the inclusion criteria for this review. Four trials participants; participants included for one or more analyses compared surgery versus radiofrequency ablation in people with early hepatocellular carcinoma, eligible to undergo surgery. Fourteen trials participants; participants included for various analyses compared different non-surgical interventions in people with early hepatocellular carcinoma, not eligible to undergo surgery. Overall, the quality of evidence was low or very low for all outcomes for both comparisons. Surgery versus radiofrequency ablation The majority of participants had cirrhotic livers, and the hepatocellular carcinoma was of viral aetiology. The average follow-up ranged from 29 months to 42 months 3 trials. There was no evidence of a difference in all-cause mortality at maximal follow-up for surgery versus radiofrequency ablation hazard ratio 0. The number of serious adverse events was higher in the surgery group adjusted rate One trial was funded by a party with vested interests; three trials were funded by parties without any vested. Non-surgical interventions The majority of participants had cirrhotic livers, and the hepatocellular carcinoma was of viral aetiology. Most trials did not report the portal hypertension status of the participants, and none of the trials reported whether the participants received adjuvant antiviral treatment or adjuvant immunotherapy. The average follow-up ranged from 6 months to 37 months 11 trials. Trial participants, who were not eligible for surgery, were treated with radiofrequency ablation , laser ablation , microwave ablation , percutaneous acetic acid injection, percutaneous alcohol injection, a combination of radiofrequency ablation with systemic chemotherapy, a combination of radiofrequency ablation with percutaneous alcohol injection, a combination of transarterial chemoembolisation with percutaneous alcohol injection, or a combination of transarterial chemoembolisation with radiofrequency ablation. The mortality at maximal follow-up was higher in the percutaneous acetic acid injection hazard ratio 1. There was no evidence of a difference in all-cause mortality at maximal follow-up for any of the other comparisons. The proportion of people with cancer-related mortality at maximal follow-up was higher in the percutaneous alcohol injection group adjusted proportion There was no evidence of a difference in any of the comparisons that reported serious adverse events number of participants or number of events. You may also be interested in: