LIVER TUMOURS- DIAGNOSIS, STAGING AND MANAGEMENT: A RADIOLOGIST'S PERSPECTIVE

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INTRODUCTION

A variety of imaging modalities is currently available for the investigation of liver tumours including ultrasound, angiography, computed tomography (CT), magnetic resonance imaging (MR) and nuclear medicine, all of which are capable of detecting lesions within the liver. In some situations, a single test may be sufficient to demonstrate the extent of the problem for management purposes but in many cases, several of the available modalities have to be used in an effective combination. **Detection** of the intra-hepatic lesion alone, however, is not sufficient. The nature of the lesion must also be determined - **characterisation** of the abnormality. Where resection is considered the best therapy, assessment must include an accurate **localisation** of the lesion in relation to the segmental anatomy of the liver and its relationship to major vascular structures, since it is on the basis of this information that surgical resections are planned. There also has to be an evaluation of the whole abdomen and chest to ensure that there are no other diseases which would preclude curative resection-**staging**. Even considering all the imaging modalities available, there is a limitation in that the peritoneal surfaces are not clearly evaluated and small lymph nodes affected by malignant disease may not be detected. Where radiological tests suggest no contraindication to surgical resection, laparoscopy and laparoscopic ultrasound can allow an evaluation of the peritoneal surfaces and the targeting of biopsies where necessary. An extensive resection may be inappropriate if the remaining liver appears too small to support liver function and consequently **hepatic volumetric measurements**[1] are helpful in assessing suitability for surgery.

COMMON ISSUES

While overall metastases represent the most common malignant tumours of the liver, this is not the case in those patients who have pre-existing cirrhosis. In that context, hepatocellular carcinoma (HCC) is the most common malignancy and on a world-wide basis, HCC is the most common primary malignant tumour of the liver, the majority having underlying cirrhosis. Although far less frequently encountered than HCC, cholangiocarcinoma is the second most common primary malignant tumour of the liver. This tumour has a number of well-recognised associated conditions including primary sclerosing cholangitis and ulcerative colitis. Liver metastases, hepatocellular carcinoma and cholangiocarcinoma together represent the three common malignant lesions of the liver and it is the diagnosis, staging and management of these diseases which form the basis of this paper.

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CHARACTERISATION

In the course of radiological imaging of the liver, a number of benign lesions will be detected and since they may mimic malignant disease, differentiation must be made. The most common problems are: *hemangiomas, cysts, focal nodular hyperplasia* and *adenomas.* Hemangiomas are more common in women and more frequently in the postmenopausal period. They may be single or multiple. Typically hyperechoic on ultrasound examination, they are frequently subcapsular in position and have a characteristic posterior acoustic enhancement. Calcification is seen in 10-20%. MR scanning shows these lesions to be hyperintense on T2 weighted images and they may appear lobulated. On CT scanning, they have a low attenuation and a clear margin. After intravenous contrast injection, they show a characteristic 'filling-in', beginning with a globular enhancement at the periphery of the lesion and over a period of 10-15 minutes progressively filling in. Delayed scans are helpful. When the lesions are large, there may be incomplete in-filling due to central necrosis or fibrosis, and occasionally the lesions may thrombose exhibiting atypical findings and thereby causing confusion in diagnosis. While generally asymptomatic, haemangiomas may enlarge especially in pregnancy and thrombose when they may give rise to pain.

Hepatic cysts rarely cause confusion as they have a clear-cut margin on ultrasound and no internal echoes. On CT scanning, they are of water density and show no enhancement following intravenous contrast administration. Like haemangiomas, they are hyperintense on T2-weighted MR images. However, occasionally, inflammatory cysts and cystic metastases may have similar appearances. The clinical picture, history and study of the cyst contents obtained by cyst aspiration unless hydatid disease is suspected, will contribute to the differentiation of these lesions.

Focal nodular hyperplasia**,** also more commonly seen in women and associated with the oral contraceptive pill, may be detected as a space-occupying lesion within the liver. These lesions, which may be single or multiple, occur in the 30-40 age group, may be hypo, hyper- or iso-echoic and have a clear cut outline on ultrasound. On CT, they are of low attenuation, non-encapsulated and classically have a central scar, a feature also shared with many primary liver tumours. After intravenous contrast administration, there is enhancement of these vascular lesions. Differentiation has to be made from hepatic adenomas also more common in women and associated with the oral contraceptive pill. These lesions tend to be hyperechoic on ultrasound and on CT scanning, are of low attenuation and have a capsule. There may be evidence of internal haemorrhage or necrosis. Following intravenous contrast, they show peripheral enhancement. On MR imaging, they are hyperintense on

T1 weighted images. Although designated 'benign', hepatic adenomas should be removed as they have a propensity to bleed and a potential for malignant change. The overall accuracy is enhanced when clinical information such as the age and sex of the patient, a history of hepatitis or a primary malignancy elsewhere, and any history of steroid or oral contraceptive use, is available. Tumour markers, notably the alpha-fetoprotein (AFP) level and the carcinoembryonic antigen (CEA) level may also be useful.

In the majority of cases, the nature of an intrahepatic lesion, can be accurately characterised by a combination of imaging tests, biochemical data and clinical information. From time to time, however, biopsy of a lesion of uncertain aetiology, using ultrasound or CT guidance, may be required but the necessity for this should be weighed against the potential complications of bleeding from vascular lesions such as hepatocellular carcinomas and haemangiomas, and the seeding of tumour cells along the needle track or within the peritoneum particularly where curative resection or liver transplantation is under consideration.

HEPATOCELLULAR CARCINOMA

For the most part, HCC is superimposed on a background of cirrhosis. The liver contour may be irregular and lobulated. Atrophy of the right lobe and segment 4, are common features and marked hypertrophy of segments 1, 2 and 3 may be evident. Gallstones are also frequently seen. Splenomegaly and numerous venous collaterals reflect portal hypertension. Most HCCs demonstrated in the West are large at presentation and readily identified on ultrasound, MR or CT scanning. They may be single and possibly encapsulated (Figure 1), diffuse or multifocal. Involvement

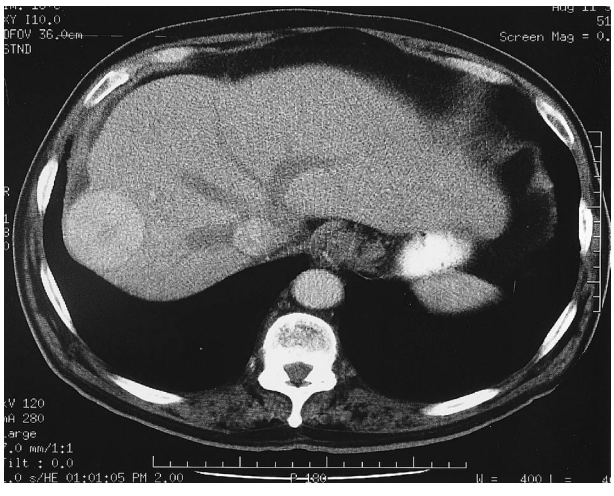

FIGURE 1
CT scan: an encapsulated HCC in a cirrhotic liver.

of a portal vein branch by tumour is a common occurrence, and usually precludes any form of surgical management. The majority are vascular showing marked enhancement during CT with intravenous contrast injection. Most HCCs are unsuitable for surgical resection on account of the site and size of the lesion in conjunction with the fact that there is a background of cirrhosis. Intra-arterial chemoembolisation can be used with good effect in some patients.[2] Single encapsulated lesions show the best results but chemoembolisation has little effect on tumour thrombus in the portal system. The use of percutaneous alcohol ablation[3] is confined to treatment of small (< 5 cms) HCCs.

Detection of a small hepatocellular carcinoma may prove to be a challenge even with the range of imaging modalities available. The background cirrhotic changes with distortion of the normal anatomy, portal venous flow alterations and the formation of regenerative nodules, contribute to the difficulty. In chronic hepatitis, where the AFP level may be elevated beyond normal limits, detection and differentiation from regenerative nodules may be difficult. To address this problem, a battery of tests is currently advocated including ultrasound,[4] contrast enhanced CT, CT arterio-portography (CTAP), Lipiodol CT, angiography and contrast enhanced MR. The size of this list reflects the fact that no single test is ideal. Where doubt remains after intensive imaging, laparoscopy and laparoscopic ultrasound may be useful. Serial follow-up scanning may be required. Ultrasound is a useful tool in the follow-up of liver lesions but has been shown to be limited in the detection of small HCCs in end-stage cirrhosis.[5] It is operator-dependent and it may be more appropriate to use a combination of biochemical assays and serial CT or MR studies which are less operator-dependent modalities, to obtain more reproducible results for comparative purposes.

Although in the seventies, liver transplantation was used as a means of managing HCCs, the recurrence rate approached 100% at five years, and consequently, the use of transplantation as a means of treating HCCs lost favour. However there is a renewed interest in using liver transplantation where cirrhosis is associated with small tumours. Approximately 5% explanted livers are found to harbour small previously undetected HCCs and the subsequent survival of these patients is not adversely affected. In those patients in whom transplantation is under consideration, it is clearly important to be aware of the presence of malignancy, but also whether the lesion has breached the capsule or invaded the portal vein, factors which would influence the surgical decision to proceed with transplantation. Those patients who might be deemed 'resectable' are those who may benefit from transplantation.

HEPATIC METASTASES

Recent technological innovations have led to higher definition imaging: the advent of improved duplex/colour Doppler imaging has simplified the non-invasive assessment of hepatic vascular structures as well as tumour vascularisation. As liver imaging is being recognised as having clinically distinct tasks, and as different imaging strategies are required for particular settings, the role of ultrasonography has become more clearly defined in the various stages of patient management.

In many centres ultrasonography is used routinely in the initial assessment to detect the presence of liver tumours, because of its non-invasiveness, low cost and availability. CT and MR are both more sensitive in tumour detection and for staging purposes; ultrasound has limitations. For those patients with metastases confined to the liver who are considered suitable for curative resection, the survival rate is significantly better than those with non-resectable disease. Unfortunately the majority of patients with liver metastases are not suitable for surgery, mainly on account of the extent and distribution of disease within the liver. An accurate evaluation of the extent of disease is essential

pre-operatively. It is recognised that, even with the use of state-of-the art preoperative imaging facilities, some patients classified as 'resectable' will not be considered suitable candidates at the time of surgery. Currently available imaging studies understage metastatic disease. Extrahepatic disease particularly peritoneal spread and metastatic disease within small lymph nodes, will not be identified. Early detection of liver metastases measuring only a few millimetres in size is desirable in order that more patients can benefit from curative surgery. Spiral CT arterial portography is considered to be in the lead in detection of small liver lesions but (superpara-magnetic iron oxide) SPIO enhanced MR scanning is set to challenge its lead.[6] Both of these techniques now regularly identify subcentimetre lesions. MR is judged best in characterising liver lesions but characterisation of small nodules is a problem since classical features associated with specific lesions, have not developed at this early stage and serum tumour markers will not be evident. None of the preoperative techniques allows the detection of microscopic metastases.

Neither CTAP nor SPIO-enhanced MR is accurate in the assessment of extrahepatic disease. This is best evaluated by laparoscopic and intra-operative examination, which provide complementary information to the imaging studies. It is our practice in the Royal Infirmary of Edinburgh, to use a combination of CT portography (CTAP) and laparoscopy. CT portography involves the percutaneous introduction of a catheter, under local anaesthesia, into the superior mesenteric artery. Contrast introduced during CT scanning, enhances the portal system and normal liver parenchyma. Liver tumours, whether primary or secondary, supplied by the hepatic artery, are not enhanced and appear as defects against the enhanced liver tissue. Spiral CT scanning technology allows volumetric data acquisition in a single breath-hold. Together with CTAP, in which the margins of lesions are particularly clearly defined and where there is a high contrast difference between the hepatic venous structures and the parenchyma, it lends itself to accurate segmental localisation, and to the creation of 3D reconstructions and volumetric measurements. Hepatic volumetry can be carried out and it provides a pre-operative assessment of the volume of functioning liver and an estimate of the volume of the potential liver remnant, should liver resection be considered (Fig 2).

Scintigraphic detection of metastatic disease has improved in recent years. The development of radioimmunodetection techniques may in the future allow more accurate staging. Although labelled antibody techniques for tumour scanning date back to the mid-seventies, monoclonal antibody (MoAb) imaging has been available for clinical application only in the last few years. The concept is similar to nuclear medicine studies. A monospecific antibody to a tumour-associated antigen is tagged with a radioactive moiety and injected into the patient. Distribution of the antibody can then be imaged to identify focal areas of uptake. A number of different antibody carriers and radionuclide tags are under investigation. The antibody component of the complex is designed to attach selectively to antigen receptors on the tumour cell surface. Aggregates of the complex then appear as areas of increased uptake or 'hot spots' on the photoscans, outlining tumour deposits.

At the present time MoAb is more likely to be used as a complementary technique to improve tumour detection in areas where CT and MR are still less than optimal. It

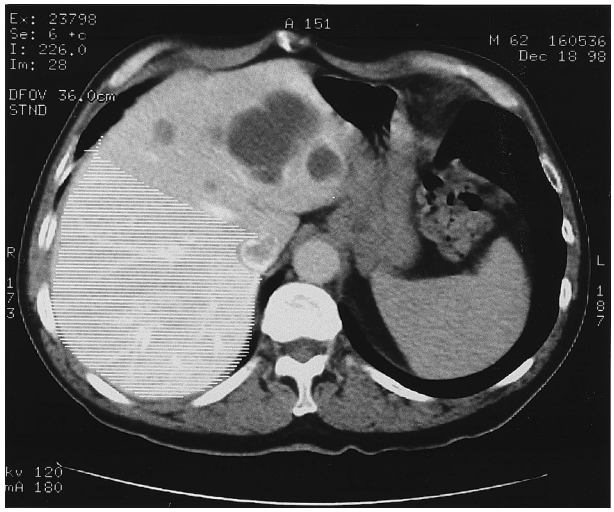

FIGURE 2
CT scan: volumetric measuring of the potential liver remnant should an extended left hepatectomy be considered to remove the metastatic disease

appears to be more sensitive than CT scanning in the detection of colorectal cancer and may be useful in depicting small peritoneal deposits. It is still limited in the detection of hepatic metastases because of the background uptake in the liver. However this technique may be useful in identifying sites of disease not visualised with CT. Metastatic disease in the lungs, bones, and extra-abdominal lymph nodes and brain have also been identified by MoAb imaging. Further studies are still required to improve the technique.

Radiolabelled monoclonal antibodies to CEA or tumour-associated glycoprotein can be used to detect liver metastases in colorectal cancer, and this technique has a higher sensitivity than CT scanning in the detection of extrahepatic metastases. False positives, however, do occur and further refinements are required. Immunoscintigraphy may be helpful in locating metastases when the serum CEA concentrations rise. While radiolabelled antibodies can detect the primary disease, they are of greater value in tumour staging, in detecting recurrent tumour and occult metastatic disease. A single injection of the radiotracer allows the whole body to be imaged. Five per cent of patients with colorectal carcinoma will have lung or bone secondaries at the time of presentation. Immunoscintography may have a role in the future in the preliminary staging assessment. It is currently considered that the most important role for immunoscintigraphy is in the follow-up of patients with colorectal cancers for detection of recurrent disease[7].

Where the disease is confined to the liver but is not suitable for surgical resection, alternative local techniques designed to destroy liver tumours may be used. These include: cryosurgery, interstitial therapies, percutaneous alcohol, focussed ultrasound, insertion of radiofrequency electrodes and hepatic artery perfusion therapy.

CHOLANGIOCARCINOMA

Cholangiocarcinoma frequently presents with obstructive jaundice and consequently only requires to be differentiated from other intrahepatic mass lesions when it arises from a small peripheral duct location and does not exhibit its usual presentation. This 'intrahepatic' variety is uncommon, the

perihilar site being the most common location affected. Complete cholangiography, either obtained by endoscopic or percutaneous means, or using a combination of the two, is necessary to assess the extent of ductal involvement. Approximately 30-40% will have an associated intrahepatic mass which may show peripheral enhancement on CT scanning with intravenous contrast administration. MR scanning is also an effective tool in assessment of cholangiocarcinomas, providing information regarding the parenchymal extent of disease as well as offering Magnetic Resonance Cholangiopancreatography (MRCP) to demonstrate the strictured duct system and Magnetic Resonance Angiography (MRA) to visualise the vascular structures in the upper abdomen. Bile duct cancer superimposed on the chronic changes of sclerosing cholangitis is difficult to detect, not only on imaging studies but also with regard to the acquisition of tissue for pathological confirmation. Lobar atrophy is commonly seen, a feature attributed to portal vein branch involvement or to chronic biliary dilatation. Compensatory hypertrophy of the disease-free liver may be seen. For the majority of patients, the site and ductal extent of the disease preclude curative resection. In some cases, an extensive resection would be required to ensure a curative procedure but the small size of the liver remnant would lead to post-operative liver failure.

The exciting innovative technique of portal vein embolisation,[8] may be used to stimulate atrophy in the tumour-bearing area and hypertrophy in the tumour-free liver. The procedure can mimic the changes frequently seen in cholangiocarcinoma where tumour involvement of a lobar portal vein has resulted in atrophy of that lobe with compensatory hypertrophy in the contralateral lobe (Figure 3). The embolisation is performed under local anaesthesia, using a technique similar to percutaneous biliary drainage procedures. It is well-tolerated by the patients and has few reported complications. Within a few weeks of the embolisation, hypertrophy is demonstrated in 60% and may render some patients 'resectable' where previously considered 'unresectable'. It has implications in the resection of hepatic metastases and cholangiocarcinoma but is of less value in the cirrhotic patients with HCC since cirrhotic liver fails to undergo hyperplasia in the same way as non-cirrhotic tissue.

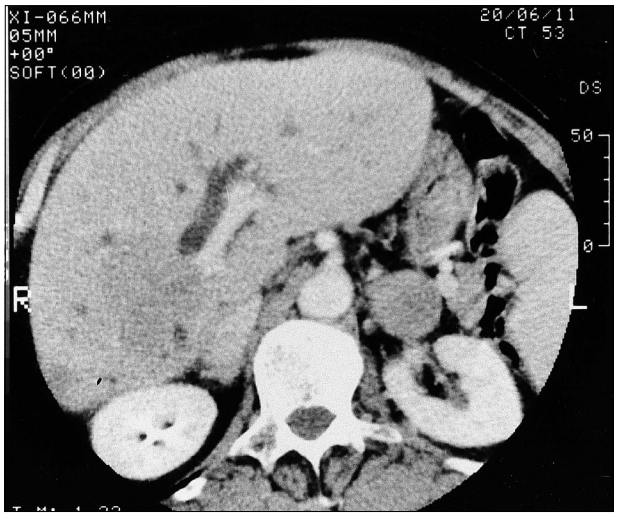

FIGURE 3
CT scan: right lobe shrinkage and left lobe hypertrophy as a result of a cholangiocarcinoma involving the right portal vein

CONCLUSIONS

Radiological imaging technology has seen major advances in recent years. Ultrasound scanners continue to develop and Doppler imaging of the hepatic vasculature is widely used in liver imaging, particularly following transplantation. Spiral CT scanning offers volumetric data acquisition and with that, the option of 3D reconstructions and hepatic volumetry. These latter options are also available with MR scanning. New promising MR contrast agents are currently under evaluation and for the future, MR offers a non-radiation imaging modality with MRCP and MRA capabilities.

Nuclear medicine has been placed on the back burner having been largely superseded by cross-sectional imaging but work continues in the field of immunoscintigraphy and with further refinements, this area may re-emerge as one of value in the future.

There are still several areas of difficulty for imaging techniques, notably the detection of small HCCs in the cirrhotic liver, as is shown by the percentage of tumours discovered in explanted livers, and in the detection of cholangiocarcinoma in patients with sclerosing cholangitis. However progress has been made in the last ten years, and in general, the patient found to have a liver tumour can be accurately assessed using the available tools and the most effective management and treatment strategy implemented. It is unfortunate that, for the most part, patients present at a point where their disease has advanced beyond the stage of cure. Portal vein embolisation may improve the number of patients who are offered surgery but to make a real impact on the survival of patients with these common ailments, effective screening programmes[9] will be required.

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