Malignant solid abdominal tumours in children; the role of high field MR in diagnosis and treatment

THESIS
submitted for the degree of
Doctor of Medicine
of
The University of London

by
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Submitted 1st June 1991
Resubmitted April 1993
Abstract

Children with solid abdominal tumours are imaged using a combination of modalities including plain film radiography, ultrasound, computed tomography and radionuclides. There is growing concern that, with the exception of ultrasound, these methods expose young children (who may undergo multiple investigations) to a significant dose of ionising radiation. Magnetic Resonance (MR) imaging has recently become available for use in clinical imaging and has the advantage of using radiofrequency (non-ionising) radiation. Therefore it is appropriate to determine whether MR can replace other ionising imaging techniques in the investigation of children with cancer and so reduce the risk of long-term side-effects. The purpose of the work reported in this thesis was to establish the efficacy of MR in the diagnosis, staging and assessment of response to treatment in a number of solid abdominal tumours occurring in children. As children can only be scanned successfully if they remain still during this lengthy and noisy procedure an effective means of sedating children had to be developed and two drug regimens were compared and their effectiveness for sedation are reported.

In 3 clinical studies reported here, MR was used to diagnose, stage and monitor the effects of treatment in children with primary malignant hepatic tumours, renal tumours and neuroblastoma. The results of MR scanning was compared wherever possible with CT scans and surgical/histopathological data. In most cases MR was at least as successful as CT in diagnosing and assessing the extent of disease. The advantages and disadvantages of MR for assessing these tumours are discussed.

In conclusion, we have also established that, with few reservations, MR is a good technique for diagnosing, staging and monitoring the response to treatment of these groups of solid abdominal tumours without the need for contrast agents or ionising radiation. We have also established an effective and reliable method of sedating children enabling high quality scans to be obtained routinely.
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Chapter 1
Introduction and review of the literature
Primary Study Objectives

The primary objectives of the work comprising this thesis were to establish the efficacy of MR in the diagnosis, staging and assessment of response to treatment in 3 groups of solid abdominal tumours occurring in children. The tumours chosen for investigation were primary hepatic tumours (including hepatomas and hepatoblastomas), Wilms' tumour and neuroblastoma as these make up the largest clinical groups of patients referred with abdominal neoplasms. In order to facilitate the investigation of these diseases by MR a safe and reliable method of scanning these children had to be developed as a secondary consideration.

Introduction

Nuclear magnetic resonance (NMR) was discovered independently by Bloch and by Purcell in 1946 and the technique was subsequently applied to spectroscopic chemical analysis. The technical difficulties inherent in the manufacture of large homogeneous magnets, and of applying the technique to moving structures and complex chemical compositions, deterred the application of the technique 'in vivo' for 25 years. In 1971, Damadian (Damadian, 1971) described the difference in relaxation time of normal and tumour tissue in 'in vitro' experiments. During the 1960s and 1970s, with the advent of computerised tomography (CT), algorithms suitable for the production of computerised sectional images were developed. These two advances stimulated the application of magnetic resonance (MR) to imaging, and in 1972, Lauterbur generated the first two-dimensional proton MR image of a water sample (Lauterbur, 1973). Subsequently, images of objects, animals and ultimately humans were produced.

Magnetic Resonance (MR) imaging enables the examination of the internal structure and function of biological tissue without the use of ionising radiation. The technique has been quickly and widely applied to the imaging of the neuraxis in adults (Bradley et al, 1984, Brant-Zawadzki et al, 1984) and in children (Pennock et al, 1986, Brant-Zawadzki et al,
Less work has been directed towards abdominal imaging because respiratory movement and flow cause artifact. Application of MR to children has been limited, partly due to lack of access to these expensive and scarce machines, and partly because it is difficult to maintain safely the long periods of immobility necessary for full diagnostic scans. However, MR has 3 important advantages where children are concerned; 1) ionising radiation is not used 2) extensive preparation, other than adequate sedation, is unnecessary, and 3) high tissue contrast can be generated without the use of intravenous, iodinated contrast agents. Because of their smaller size, faster heart rate and lesser respiratory excursion MR can be applied more easily to children than to adults.

Imaging in patients with malignant disease is necessary for a number of reasons; to aid diagnosis, to stage disease and plan appropriate therapy, to assess response to treatment, to define complications of the disease and its treatment, and to confirm remission or identify relapse. At present a combination of imaging modalities including plain radiography, ultrasound, CT and radionucleide scanning are used.

In the spring of 1988, the first MR scanner in the world dedicated to the imaging of children was installed at the Hospital for Sick Children, Great Ormond Street. The Siemens 'Magnetom' scanner is a high field system, operating at 1.5 Tesla, and is capable of imaging and spectroscopy. The scanner specifications are outlined in the Appendix.

**Review of literature**

CT is now established as the major modality for the sectional imaging of solid abdominal tumours in childhood (Damgaard-Pederson, 1980, Kuhns, 1981, Korobkin et al, 1981, Siegel et al, 1982, Stark et al, 1983a, Giacomantonio et al, 1984, Boechat et al, 1985, Bousvaros et al, 1986, Reiman et al, 1986, Dachman et al, 1987), but it does have disadvantages; 1) CT requires the use of ionising radiation- an important consideration when children require repeated examinations during the course of their illness (The NRPB, 1990) 2) children have less retroperitoneal fat than adults and this reduces the resolution of retroperitoneal structures (Cremin, 1983) 3) venous access in children may be difficult and
hinder administration of intravenous contrast agents. Rapid, bolus injections of contrast cannot be given through the extremely small gauge needles used with small children and neonates, and it is occasionally necessary to use general anaesthesia to achieve adequate enhancement 4) oral contrast agents, which may be difficult to administer and poorly tolerated by a child, are needed to delineate bowel loops 5) CT is not 100% specific or sensitive to tumour diagnosis. New methods of imaging, such as MR, which lacks some of these disadvantages, may complement and/or replace CT. Critical evaluation of MR requires comparison with CT, ultrasonography and other forms of imaging, so that its place in the assessment of paediatric tumours can be defined.

Standard techniques and uses of MR are becoming established for imaging of the adult abdomen and abdominal neoplasia (Glazer, 1988). When imaging paediatric tumours, however, the considerations are different. Children's abdominal tumours tend to be large, so detection of very small lesions is not a primary requirement. The behaviour and, consequently, the signal characteristics of childhood tumours are different; often tumours grow faster and are accompanied by more necrosis and haemorrhage than in adults.

### MR Imaging in Children

Smith (Smith ,1983) reported the early Aberdeen experience of MR imaging of both neurological and non-neurological disease in children. In 28 children examined on a 0.04T system, the images were of similar diagnostic value to CT and were not significantly degraded by respiratory or cardiac motion. Cohen (Cohen et al, 1985 &1986), studied a variety of tumours in children using a 0.15T system, and reported that, so far as the primary tumour mass was concerned, no abnormality shown on CT was missed on MR. MR was superior to CT when demonstrating vessels, bone marrow metastases, and also showed some differences in the internal structure of some abdominal tumours, raising the possibility of specific diagnosis.

Subsequent published MR studies have been refined to examine in greater detail the application to particular tumours, and will be considered in these categories.
Primary Malignant Hepatic Tumours

Clinical background

In the western world, primary tumours of the liver in childhood are uncommon but, after renal tumours and neuroblastoma, are still the third most common solid malignant abdominal tumour. In one large series (Shafford & Pritchard, 1992) approximately 36% were hepatoblastomas, 20% hepatocellular carcinomas, and 9% malignant mesenchymal tumours (including undifferentiated sarcomas and rhabdomyosarcomas). The remainder are benign tumours, most commonly haemangiomas (Bove, 1988). Most children with malignant hepatic tumours have a palpable abdominal mass at presentation. Other signs and symptoms include weight loss, fever and precocious puberty. Jaundice occurs in less than 10%, and is more common in those with pre-existing cirrhosis (Giacomantonio et al, 1984). Children with hepatoblastoma are younger (median 1-2 years), than those with hepatocellular carcinomas or sarcomas, the majority of whom are over 5 years at presentation (Mahour et al, 1983). Serum alpha-fetoprotein (AFP) levels are almost always raised in children with hepatoblastoma and with hepatocellular carcinoma, and those with precocious puberty may have raised serum luteinising hormone (LH), testosterone or human chorionic gonadotrophin (HCG) levels. Some congenital syndromes, including Beckwith-Wiedemann, Sotos' syndrome and von Gierke's glycogen storage disease, are associated with primary liver tumours (Mahour et al, 1983). Pre-existing cirrhosis, due for example to tyrosinaemia, is associated with an increased incidence of hepatocellular carcinoma. Other associated conditions include polyposis coli (familial autosomal dominant) and hepatitis B virus (Shafford & Pritchard, 1992).

The outcome of untreated or incompletely resected primary malignant tumour of the liver is dismal, and the only hope of cure is total surgical removal (Clatworthy et al, 1974, Mahour et al, 1983, Giacomantonio et al, 1984). At presentation, less than half of tumours are resectable (Remischovsky et al, 1974, Lin et al, 1966). If resection is attempted at the time of diagnosis, perioperative mortality is high; in one series reported, 25 perioperative deaths occurred in 85 children and the main cause of death was blood loss (Exelby et al, 1975). More recently, chemotherapy has been used preoperatively and over 70% of previously inoperable
tumours can now be made "operable". Pre-operative chemotherapy has almost certainly contributed to the much improved overall survival of infants and children with primary malignant tumours since the early 1970s (Mahour et al, 1983).

**Imaging**

Options for partial hepatectomy are limited because of the segmental anatomy of the liver. Tumour confined to one lobe of the liver can be treated by simple hemihepatectomy, but if a tumour involves both lobes only trisegmentectomy is possible. "Resectability" has been mostly judged on radiological criteria; the requirements of imaging techniques are a) to demonstrate tumour with high sensitivity, b) to define the relationship of tumour to vascular structures and c) to show extrahepatic disease. A number of techniques have been used to this end, with varying degrees of success. Radionucleide techniques have been largely replaced by computerised tomography, which may be supplemented by ultrasound. Because of the rarity of liver tumours, large series comparing modalities are not available, but aspects of the relative benefits of different imaging modalities are discussed next.

For many years, angiography was most commonly used to determine the intrahepatic extent of tumour and resectability (Bartley et al, 1967, Marks et al, 1979). Angiography is an indirect imaging method, as parenchymal abnormalities are inferred by vascular displacement and abnormalities of the vessel structure. Its major advantage is that vascular anatomy is visualised directly. Correlation with surgical studies has shown that the main error of this technique is underestimation of tumour involving the left lobe of the liver (Marks et al, 1979, Jacobs et al, 1967). The invasive nature of angiography is also a disadvantage, particularly because of the small calibre of vessels in young children. The role of angiography is still controversial and is now only used by surgeons who feel that demonstration of the architecture of the entire arterial system is essential.

Ultrasound assessment of liver tumours in children has been disappointing. Dachman (Dachman et al, 1987) found that using only ultrasound, intra- and extra-hepatic masses could not be reliably distinguished. In another study, tumour margins were not clearly defined, and tumour extent was underestimated by ultrasound (Amendola et al, 1984). A
major problem is that these tumours, which are frequently large, cause considerable anatomical distortion. As a result, familiar landmarks, necessary for adequate staging, are lost. However it is generally agreed that ultrasound is of value for the preliminary assessment of the child with an abdominal mass. In a study assessing the value of ultrasound in the management of 103 children with an abdominal mass, Kohler (Kohler et al, 1984) showed that initial preoperative ultrasound diagnosis was correct in 86% of children with Wilms' Tumour and neuroblastoma, and 71% of 'other diagnoses' which included 2 cases of hepatoblastoma.

The capacity of CT to define the intrahepatic origin of tumour in infants and children has been shown to be reliable when adequately enhanced studies are performed (Korobkin et al, 1981, Amendola et al, 1984, Giacomantonio et al, 1984, Dachman et al, 1987). Of 6 patients with primary liver tumours studied with enhanced CT, Amendola (1984) reported that surgical resectability was correctly predicted in all cases, although one of the 2 patients classified as 'resectable' had residual microscopic tumour at the resection margin. Dachman et al (1987) found that CT definitively indicated the intrahepatic origin of the tumour in 20/21 patients with histologically proven hepatoblastoma. In the exceptional case, the child also had a right adrenal tumour. Few comparative studies of CT and angiography have been performed, but small studies suggest that CT is at least as good in defining tumour extent and, in one patient was able to show (surgically confirmed) nodal disease missed by angiography (Amendola et al, 1984, Giacomantonio et al, 1984).

Specific diagnosis, and differentiation of benign from malignant tumours has been attempted with both CT and ultrasound. In a small survey of 9 children with benign and malignant tumours, ultrasound could not specifically diagnose the histological nature of a mass with complete confidence as there was considerable overlap in the appearances of benign and malignant tumours (Kaude et al, 1980). In a study of 40 children with malignant hepatic tumours, Miller & Greenspan (1985) found that on ultrasound, hepatoblastomas may either be solid (5/8 cases) or partially cystic (3/8 cases). In this series, hepatocellular carcinomas were hypo- or hyper-echogenic, all were multiple tumours and consequently indistinguishable from metastatic disease. 'Ring enhancement', seen on CT in a minority of
hepatocellular carcinomas and some metastases, was of limited diagnostic value. Multiple nodules and intravascular invasion are both more common with hepatocellular carcinoma than hepatoblastoma (Dachman et al, 1987). It is very important to recognise hepatic venous &/or IVC thrombus as pulmonary embolism from detached thrombus this is a potentially lethal complication (Dorman et al, 1985). In a review of CT studies of hepatoblastoma, Dachman et al (1987), described calcification in 8 of 21 patients, and observed that calcification intensified and was seen more often after chemotherapy. He also described tumour inhomogeneity corresponding with macroscopic areas of necrosis and haemorrhage in the resected specimen.

Demonstration of intrahepatic vascular anatomy by CT and ultrasound, a prerequisite for the segmental staging of tumour, has been studied extensively in adults but not in children (Sexton & Zehman, 1983, Pagani, 1983, Mukai et al, 1987a & 1987b). Dynamically-enhanced CT can show the intrahepatic portal and systemic venous anatomy well enough to provide reliable information of segmental involvement in the majority of adult hepatic tumours (Pagani, 1983). However the left hepatic vein is often small and difficult to see, so definition of extent of involvement in the left lobe can be difficult. Sexton & Zehman (1983) comment that when imaging is limited to the transverse plane, an imaginary line between the anterior and posterior divisions of the right portal vein has to be projected to identify the segmental divisions of the right lobe of the liver inferior to the hepatic veins. The value of MR in demonstrating the vascular anatomy of the liver in adults is generally agreed. In 1 study, MR showed the IVC, right and middle hepatic veins, and the main and right portal veins in all patients on a single transverse sequence. The left hepatic vein, left portal vein and the hepatic artery were seen respectively on 98%, 93% and 44% of all scans (Fisher et al, 1985).

Only two studies on the MR imaging of the paediatric liver have been reported, and are now discussed in some detail. Weinreb et al (1986), examined 27 children (3 children with normal livers having abdominal studies for another unspecified reason, and 24 with suspected liver pathology), on a 0.35T system, using T1- and T2-weighted spin-echo sequences. All patients also had CT examinations. MR showed the vascular anatomy more completely than
contrast-enhanced CT in the normal children. The infrahepatic IVC was seen in each case with MR, but in only 60% of children with CT (and under 50% of children less than 6 years.) CT was less reliable than MR in predicting the patency of the IVC. In 2 children the IVC which appeared occluded on contrast-enhanced CT, was later proved patent. This false positive finding was probably due to extrinsic compression of the IVC. Intrahepatic invasion by extrahepatic masses was defined with greater accuracy by MR than CT. In 7 cases CT suggested hepatic invasion by an extrahepatic mass but MR excluded invasion in 3 cases and was equivocal in 4. All 7 masses were shown to be separate from the liver at laparotomy. In 9 patients with intrahepatic disease, MR showed tumour margins better than CT. MR showed more lesions than CT in a single case with multiple intrahepatic nodules. These authors concluded that because it demonstrates parenchymal lesions and vasculature more clearly, without the use of intravenous contrast agents, MR was superior to CT for liver imaging in children.

In a study of 23 children undergoing laparotomy, Boechat et al (1988) attempted to assess tumour resectability, and to define features characteristic of different types of primary liver tumours. MR scans, using standard T1- and T2-weighted spin-echo imaging at 0.3T, and dynamically-enhanced CT examinations were performed in all patients pre- and post-operatively, and 14 children had multiple follow-up scans. Three children subsequently had 'second-look' laparotomies. Both CT and MR diagnosed 4 of 5 benign tumours as non-malignant; MR misdiagnosed a thromosed haemangioma as a hepatoblastoma, and CT misdiagnosed a diffuse haemangioendothelioma as metastatic neuroblastoma. Neither CT nor MR was able, reliably, to distinguish hepatoblastoma from hepatocellular carcinoma, though multiple lesions, invasion of the portal vein, presence of metastases or underlying liver disease favoured the latter diagnosis. In 18 cases of malignant tumour, MR was 100% accurate in predicting tumour resectability, whereas CT overestimated involvement of the left lobe in one instance. In the follow-up studies, 3 patients with unremarkable CT examinations were thought, on MR, to have recurrent disease (serum AFP levels are not reported). In 2 children recurrence was confirmed, while the third had chronic inflammatory changes at the resection
margins. Even in retrospect, these MR scan appearances could not be distinguished from recurrence.

In conclusion, MR studies in children have been promising. As with neuroblastoma and renal tumours, only low field scanning has been reported, and the total number of cases reported are relatively small. These days, most children with hepatic tumour are first treated with chemotherapy, but MR appearances of changes due to chemotherapy have not been reported. High field MR assessment of resectability of primary hepatic tumours and the changes observed during chemotherapy are reported in this thesis.
Renal tumours

Clinical background

Kidney tumours are the commonest cause of an abdominal mass in childhood. In the neonate, they are usually benign and most commonly a mesoblastic nephroma (congenital renal leiomyomatous hamartoma). In the older child, the most frequent tumour is the nephroblastoma (Wilms' tumour [WT]). Other renal tumours, often erroneously classified as WT, are the rhabdoid tumour and the clear cell sarcoma. Rhabdoid tumours constitute approximately 2% of all childhood renal tumours and are associated with brain tumours (primitive neuroectodermal tumours, PNET) while clear cell sarcomas comprise approximately 3%. Renal cell carcinoma and multilocular cystic nephromas also occur but are rare (D'Angio et al, 1980). Because they are the most common, the discussion will mainly concern Wilms' tumour, a disease with a current overall survival of 80-90% (D'Angio et al, 1981).

The majority of children with Wilms' tumours are between 1 and 5 years of age and have an asymptomatic abdominal mass. Less frequently children present with abdominal pain, fever, anorexia, haematuria, hypertension, varicocele or IVC/SVC obstruction (Ritchey et al, 1988). Predisposing conditions include a number of congenital malformations and syndromes such as aniridia, hemihypertrophy, Beckwith-Wiedemann syndrome, WAGR (Wilms-Aniridia-Genitourinary abnormalities-mental Retardation) syndrome, Perlman and Drash syndromes (Pendergrass, 1976). Around 0.5% of patients, especially those with WAGR, have a constitutional deletion of the short arm of chromosome 11 (11p-). Recent evidence strongly suggests that a WT gene is located at band p1.3 of chromosome 11.

Histopathological features are of major prognostic value in Wilms' tumour (Beckwith & Palmer, 1978). About 7-8% of patients have diffuse or focal anaplasia or sarcomatous features, denoted as "Unfavourable Histology" (UH). The remainder are classified as having "Favourable Histology" (FH). Patients with UH are far more difficult to manage successfully than those with FH. Other adverse prognostic features include tumour size, capsular invasion and node involvement (Breslow et al, 1978, Leape et al, 1978).
Unfavourable features associated with relapse of Stage I, FH Wilms' include invasion of the
tumour capsule, the presence of an "inflammatory pseudocapsule", renal sinus invasion and
tumour in the intrarenal vessels (Weeks et al, 1987).

The staging of Wilms' tumour, as determined by the National Wilms' Tumor Study
Group (also used by UKCCSG), is determined by the operative and pathological findings at
the time of diagnosis, and not by imaging criteria, and is summarised in Figure 1.1.
Figure 1.1: National Wilms' Tumor Study Staging System (after D'Angio et al, 1989)

**Stage I**

Tumour is limited to the kidney and is completely excised.

- the surface of the renal capsule is intact, the tumour does not rupture before or during removal, and no residual tumour is apparent beyond the excision margins.

**Stage II**

Tumour extends beyond the kidney but is completely excised.

- there is regional extension of tumour, ie penetration through the outer surface of the renal capsule into the peri-renal soft tissues. Vessels outside the renal substance are infiltrated or contain tumour thrombus. No residual tumour is apparent at or beyond the excision margins. The tumour may have been biopsied or there has been localised flank spill.

**Stage III**

Residual nonhaematogenous tumour confined to the abdomen.

- Any one or more of the following occur.
  a. Lymph nodes on biopsy are found to be involved in the hilum, the periaortic chains or beyond.
  b. There has been diffuse peritoneal contamination by tumour, such as spillage of tumour beyond the flank before or during surgery, or by tumour growth that has penetrated the peritoneal surface.
  c. Implants are found on the peritoneal surfaces.
  d. The tumour extends beyond the surgical margins either grossly or microscopically.
  e. The tumour is not completely resectable because of local infiltration into vital structures.

**Stage IV**

Haematogenous metastases

- deposits beyond Stage III eg. lung, liver, bone and brain.

**Stage V**

Bilateral renal involvement at diagnosis

An attempt should be made to stage each side according to the above criteria on the basis of the extent of the disease before biopsy.
The treatment of Wilms' tumour is determined by stage and histological sub-type, and the mainstay of treatment is nephrectomy, plus chemotherapy, with or without radiotherapy (D'Angio et al, 1981). The role for preoperative chemotherapy and partial nephrectomy has been explored, especially in studies of the International Society of Paediatric Oncology (SIOP) (Lemerle et al, 1976 & 1983). The SIOP studies have shown that preoperative radiotherapy or chemotherapy lessen the risk of intraoperative rupture, which is itself associated with an increased risk of abdominal recurrence (Leape et al, 1978). Preoperative chemotherapy, (preferred to radiotherapy because of its lesser 'late effects'), is used in our institution, in children with tumours thought to be inoperable (ie very large tumours and those invading the IVC, liver or adjacent organs). Since preoperative chemotherapy precludes precise surgical staging, accurate radiological staging of disease is a major priority.

Synchronous bilateral Wilms' tumours (Stage V tumours) occur with a frequency of 4-5% (Breslow & Beckwith, 1982). Review of 162 patients with Stage V disease registered with the NWTS-2 and 3 suggested that the survival of patients managed with resection and chemotherapy did not statistically differ from those treated by biopsy, chemotherapy and second-look surgery (Blute et al, 1987). In this study, bilateral disease was diagnosed preoperatively in only 64% of children and IVC tumour thrombus was diagnosed in 8/10 patients. Bilateral tumours were shown by CT in 40/48 (83%) of cases and in 52/125 (42%) by IVU. These results suggest that current methods of imaging do not diagnose bilateral tumours with sufficient accuracy. Although no management protocols were established by the NWTS studies routine bilateral tumour biopsy, followed by chemotherapy according to the stage of the most advanced lesion, is recommended (Blute et al, 1987). If this causes tumour shrinkage, 'nephron-preserving' surgery ie excisional biopsy or partial nephrectomy, rather than nephrectomy, is favoured. Because management of bilateral disease is different from unilateral tumour, and 'tailor-made' in most cases, the requirements of imaging methods are somewhat different. Ideally 1) bilateral disease must be identified with 100% sensitivity and specificity, 2) disease spread must be accurately diagnosed (node involvement is a poor prognostic factor) and 3) tumour response to chemotherapy must be accurately monitored to help plan the timing and extent of partial resection. If bilateral disease could be accurately
diagnosed without laparotomy, imaging could be used to guide percutaneous biopsy before and after chemotherapy.

Imaging

Prior to the general availability of sectional imaging plain film radiography and urography were the mainstay of diagnosis. However the major problem with urography is the lack of specificity and sensitivity, and its poor performance in the assessment of intraabdominal or intravascular spread of tumour. The urographic appearances of Wilms' tumour vary widely and include non-functioning kidney, a normal kidney and an intra- or extra-renal mass. These appearances are non-specific, and the differential diagnosis includes benign conditions such as hydronephrosis and renal abscess, and malignant tumours (especially neuroblastoma). CT has been shown to be superior to IVU, both in localising and specifying the nature renal masses and in defining spread (Damgaard-Pederson, 1980). Urography is also extremely poor for demonstrating nephroblastomatosis, a condition associated with Wilms' tumours (Fembach et al, 1988).

There are few reported trials comparing CT with ultrasound. However in a retrospective review of 13 children with Wilms' tumour who had real-time ultrasound and enhanced CT prior to surgery, Reiman et al (1986) showed CT to be the more sensitive technique. It was better at identifying bilateral tumours and capsular breach. Not surprisingly, neither technique diagnosed microscopic spread of tumour through the capsule or into the IVC. Only 2 of 5 patients with involved nodes were identified on CT and 1/5 by ultrasound. Microscopic involvement of normal sized nodes was missed by both techniques, and CT failed to identify an involved, enlarged node in one child who had little retroperitoneal fat. Small liver metastases were not diagnosed by either technique in 1 patient. In this study, CT correctly staged 77% of tumours, compared to 23% with ultrasound. De Campo (1986) also found that grey scale ultrasound missed small hepatic metastases in 2/2 cases.

Reports of the effect of tumour extension into blood vessels have been contradictory. Intrarenal vascular invasion is an unfavourable feature for relapse in Stage I disease (Weeks et al, 1987). Leape et al (1978) found that tumour invasion of the renal vein or
IVC was not associated with a poorer outcome whereas Breslow et al (1985) reported an increased risk of relapse in NWTS-2 patients with an intravascular tumour thrombus. Review of NWTS-3 patients with intracaval thrombus concluded that survival rates were determined by stage, and the most important prognostic factor was histological type (Ritchey et al, 1988). However, accurate identification of caval thrombus is necessary to plan treatment and avoid complications. Unrecognised tumour thrombus causing pulmonary embolism is the commonest cause of intraoperative death in the UKCCSG's first Wilms' tumour study (UKW1) (personal communication).

In the past inferior venacavography was used to assess vascular involvement. In many cases, interpretation of results is difficult; extrinsic compression cannot be differentiated from intrinsic tumour. A Valsalva manoeuvre, such as occurs during crying, can force blood into the collateral circulation, mimicking caval obstruction. Additional retrograde studies may be necessary to outline the upper extent of an obstruction (Berdon et al, 1967, Slovis et al, 1981). Ultrasound can successfully evaluate the IVC in many cases and can differentiate between extrinsic compression and intravascular disease. However, in the presence of a large mass the IVC can still be difficult to identify, and for technical reasons the infrahepatic IVC may be difficult to visualise (Slovis et al, 1981, De Campo, 1986). On CT, tumour thrombus may be seen as an intraluminal filling defect or a non-enhancing mass expanding the cava (Marks et al, 1978). However intravenous contrast is required with CT, and false positive results have been reported due to shunting of non-opacified blood through vascular tumours, or to layering of contrast medium after bolus injection into a foot vein (Glazer et al, 1981). In the recent NWTS review (Ritchey et al, 1988), ultrasound and inferior cavography individually diagnosed caval thrombus more accurately then CT (59%, 87% and 42% correct diagnoses, respectively in patients with caval thrombus). Overall, IVC thrombus was missed in 29 of 77 cases (38%), 20 of whom had small thrombi in the infrahepatic portion of the IVC. The most common reason for missing IVC thrombus was failure to perform an appropriate investigation; one third of patients in this group had no preoperative studies or only an IVU.

As for neuroblastoma, attempts have been made to define features diagnostic for Wilms' tumour. On ultrasound, the majority of tumours are large (average diameter of 12 cm),
are usually heterogeneous and may have a hypo- or hyper-echoic rim. Some may be completely homogeneous, with echogenicity comparable with liver parenchyma, and up to 20% contain calcification. Most tumours are obviously totally or partially intrarenal, but some appear to be pedunculated and others of extrarenal origin (Jaffe et al, 1981, De Campo, 1986).

Ultrasound is unable to predict the histological type of a renal tumour. In one study, for instance, anaplastic Wilms' tumours and a mesoblastic nephroma could not be differentiated from favourable histology Wilms' tumour (Jaffe et al, 1981). On unenhanced CT, most tumours are less dense than renal tissue and enhance less with contrast than normal renal parenchyma. Over 50% are heterogeneous, usually due to patchy necrosis, and an easily detected 'pseudocapsule', corresponding histologically with fibrous tissue, may be apparent. With enhancement, a crescent of dense, compressed renal tissue may persist (a 'stasis renogram') (Fishman et al, 1983). However, renal tumours cannot always be differentiated with certainty from other intrabdominal masses either on CT or ultrasound.

Nephroblastomatosis is the term used to describe abnormal persistence of metanephric blastema in the kidney (Hou & Holman, 1961). It is sometimes nodular and sometimes diffuse and may be found in association with Wilms' tumour (Beckwith et al, 1990). Ideally, an imaging modality should be able to differentiate it from discrete tumour, but this has not been the experience with urography, CT or ultrasound (Cormier et al, 1988, Fernbach et al, 1988, White et al, 1992). Ultrasound may show an enlarged kidney or poor definition of the corticomedullary junction, and CT may show non-enhancing cortical plaques. However neither technique is particularly sensitive for this diagnosis and laparotomy with biopsy is more reliable.

Although the histological changes of Wilms' tumour following chemotherapy, including stromal oedema, necrosis and vascular change, have been reported (Guarda et al, 1984), there is little documentation of imaging appearances. Most tumours become smaller during chemotherapy, but they may also (occasionally) respond to treatment with cystic change and no alteration in size (Shimizu et al, 1987). In this case, the ultrasound findings, which were confirmed pathologically, were highly suggestive of tumour necrosis, and clinical assessment of tumour response to treatment would have been misleading. No series
documenting the CT appearances of Wilms' tumour following chemotherapy has been published. As most children present with an abdominal mass, the task of initial assessment still falls to ultrasound (Faerber et al, 1984, Saks et al, 1985, Fernbach, 1991) and Cremin (Cremin, 1987) argues that overall CT has added little to the primary diagnosis of Wilms' tumour.

Reports of the value of MR in the imaging of paediatric renal tumours are limited, and have all been performed at low field strengths. The MR appearances of the normal child's kidney have been described at low field (0.35T), (Dietrich et al, 1986b). These authors examined 15 children, aged from 18 months to 16 years, with no known renal abnormality. The kidney was best demonstrated on coronal T1-weighted spin-echo images. Renal outline and cortico-medullary differentiation is well visualised, the renal cortex being of higher intensity than the medulla and of similar intensity to the liver. The renal artery, vein, ureter and the pelvicalyceal system are predictably of low intensity. In children under 10 years, the renal pyramids are prominent, but high signal intensity from adipose tissue in the renal hilum is not visible. In children older than 12 years, the signal from the hilum progressively increases, corresponding to an increase in fat deposition. On T2-weighted images, corticomedullary differentiation is not well seen, and the kidneys are isointense with spleen and hyperintense compared to the liver. In the same report, the authors examined 43 children with various renal abnormalities, including 3 children with Wilms' tumour. These preliminary findings indicated that MR clearly showed the intrarenal extent of tumour and displacement or involvement of adjacent organs and vessels.

The same group also reported their experience of MR imaging in patients with suspected Wilms' tumours (Kangarloo et al, 1986). Of 4 children examined with T1- and T2-weighted spin-echo sequences at low field, only 2 had tumours. One patient presenting with an abdominal mass was confirmed by MR to have an intrarenal tumour. MR failed to detect a 1cm tumour in a child with Drash syndrome who later had "prophylactic" bilateral nephrectomy. A third child, presenting with a large abdominal mass, was shown to have a solid mass on the left side of the abdomen on ultrasound. MR demonstrated a grossly enlarged left kidney, primarily the result of cortical thickening. Two nodules were apparent on the right
side. At operation the right kidney was found to be studded with multiple nodules on its anterior surface and pathological examination of both the left and right sided lesions was consistent with nodular nephroblastomatosis. In a fourth child scanned following treatment of bilateral Wilms' tumours, no tumour recurrence was seen.

The largest series of children with Wilms' tumour examined by MR has been reported by Belt et al (1986). Fourteen children were examined at low field (0.15T Technicare system), using T1- and T2-weighted spin-echo sequences in all patients and inversion recovery (IR) experiments in a few cases. Direct surgical/pathological correlation was available in 12 patients scanned just before surgery and 4 were reexamined 6-12 months following surgery. Two children were examined post-nephrectomy only. CT scans were also performed in all patients. T1 measurements of 'representative areas' of the tumour were made in 8 cases, using standard computer software. The intrarenal location of tumour was correctly identified by MR in all patients, and the extent more accurately demonstrated than in corresponding CT examinations. Tumour could be easily distinguished from normal renal and perirenal tissue. The renal capsule could not be resolved by MR, so capsular penetration could not be assessed. The majority of tumours were of inhomogeneous signal intensity, shown pathologically to correspond to patchy regions of necrosis and haemorrhage. On T1-weighted sequences, these authors concluded that regions of haemorrhage corresponded with regions of high signal (ie short T1), and necrosis corresponded with areas of low signal (ie long T1), though both gave high signal on T2-weighted spin-echo sequences. Lymph node 'enlargement' was seen in 5 patients on both CT and MR (although actual node size is not reported) but histologically none were involved by tumour. Liver metastases were identified in 4 patients by CT and MR; 2 at presentation which were surgically confirmed and 2 on follow up (although the proportion of patients with liver metastases is high in this series, there was no patient pre-selection). These lesions were difficult to identify on T1-weighted SE images but were well seen on T2-weighted SE and IR sequences.

The IVC was seen by MR in all 12 patients examined preoperatively. Two patients were thought to have caval extension of tumour, and 10 had no intracaval tumour. These
findings were confirmed surgically in all 12 cases. The 2 intracaval thrombi were also detected ultrasonographically but the CT findings were not reported.

Brody et al (1989) have cautioned against the use of MR as the primary staging modality in Wilms' tumour. They reported a single case of a child presenting with a renal tumour who, 4 months after diagnosis, developed cystic hepatic metastases. In this patient, CT and MR of the liver were both normal at the time of diagnosis. However the authors suggest that theoretically small cystic metastases could be missed by MR and that multimodality imaging increases the likelihood of tumour detection.

Drash syndrome is a congenital disorder in which a specific nephropathy is associated with a very high incidence of Wilms' tumour and patients with this condition are regularly screened for tumours (Jadresic et al, 1990). In a report on the value of MR in this condition (Boechat & Kangerloo, 1988), 3 patients were examined. One patient with known bilateral tumours was scanned during chemotherapy. Residual bilateral renal masses of mixed homogeneity were clearly identified. Pathological examination of these masses, following bilateral partial nephrectomy, showed residual tumour at the surgical margin of the left kidney (by implication the mass in right kidney, which was not biopsied, was also residual tumour). In a second patient who subsequently had a "prophylactic" bilateral nephrectomy, poor corticomedullary differentiation was seen, probably secondary to the nephropathy. A small 1cm Wilms' tumour, identified in the resected kidney, had been missed by MR. In the third child, MR scans showed poor corticomedullary differentiation; histopathology of multiple open renal biopsies showed focal glomerulosclerosis (typical of Drash syndrome), but no tumour.

There has been 1 further report of the MR appearances of nephroblastomatosis (Hausegger et al, 1991). In a child with Wilms' tumour, 3 foci of nephroblastomatosis could be detected on imaging. Only 1 focus was seen at ultrasound. The authors state that all 3 could be seen on contrast enhanced MR and CT and that MR was clearer. However review of their published images show that all foci were calcified and appear most obvious on unenhanced CT scans.
No study has been reported directly comparing inferior-venacavography with MR in renal tumours in children. However in a recent paper (Horan et al, 1989) the authors compared the two techniques in renal carcinoma in adults and have shown the sensitivity and specificity to be similar and that the diagnostic yield increases when the techniques are combined.

To summarise, only small numbers of patients with Wilms' tumour have been reported, but MR is of similar accuracy to CT in locating the tumour mass, and is possibly superior in determining tumour extent. Neither technique can distinguish enlarged nodes involved by tumour from those showing 'reactive' changes alone (although none of the patients reported have had malignant involvement of nodes). MR can identify vascular involvement without the use of contrast media. However it is not yet certain whether MR can identify caval vascular involvement missed by CT and ultrasound. Overall, no clear advantage of MR over CT plus ultrasound has been demonstrated, other than important general considerations such as the use of ionising radiation and contrast media.

No reports of the MR appearances of changes induced by chemotherapy are available and no systematic attempt to differentiate Wilms' tumours from neuroblastoma using MR features has been reported. The MR features of nephroblastomatosis have been described in only 2 patients (Dietrich et al, 1986b, Hausegger et al, 1991) and in one of these MR underestimated the extent of the lesions (Dietrich et al, 1986b). The capacity of MR to distinguish concurrent tumours from nodular nephroblastomatosis has not been assessed. No study assessing the value of MR at high field has been conducted. Some of these problems are addressed in this thesis.
Clinical background

Neuroblastoma is one of the most common solid tumours in childhood and accounts for about 8% of all childhood cancers. Although disease survival has improved with modern therapy (Shafford et al, 1984, Pritchard et al, 1987), progress has been marred by the difficulty in comparing results between centres due to the lack of standard criteria for diagnosing, staging and assessing the response of disease to treatment. This problem has been addressed by an international working party, and a consensus has been reached referred to as the International Neuroblastoma Staging System and the International Neuroblastoma Response Criteria (Brodeur et al, 1988), (figures 1.2 & 1.3). Although not a necessary criterion for diagnosis, imaging is required for staging and for assessing tumour resectability and response.
**Figure 1.2; International Staging System for Neuroblastoma** (Brodeur et al, 1988)

**Stage 1:** Localised tumour confined to the area of origin; complete gross excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative macroscopically.

**Stage 2A:** Unilateral tumour with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes negative microscopically.

**Stage 2B:** Unilateral tumour with complete or incomplete gross excision; with positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes negative microscopically.

**Stage 3:** Tumour infiltrating across the midline with or without regional lymph node involvement; or, unilateral tumour with contralateral lymph node involvement; or, midline tumour with bilateral lymph node involvement.

**Stage 4:** Dissemination of tumour to distant lymph nodes, bone, bone marrow, liver, and/or other organs (except as defined in Stage 4S).

**Stage 4S:** Localised primary tumour as defined for Stage 1 or 2 with dissemination limited to liver, skin, and/or bone marrow.

**NB** Arabic numerals are used to distinguish the INSS staging from Evans' stages (Roman numerals).
**Figure 1.3; International Neuroblastoma Response Criteria (Brodeur et al, 1988)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Primary</th>
<th>Metastases</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (clinical remission)</td>
<td>No tumour</td>
<td>No tumour (chest, abdomen, liver bone, bone marrow, nodes etc.)</td>
<td>HVA/VMA normal</td>
</tr>
<tr>
<td>VGPR (very good partial response)</td>
<td>Reduction &gt;90% but &lt;100%</td>
<td>No tumour (as above except bone); no new bone lesions, all preexisting lesions improved</td>
<td>HVA/VMA decreased</td>
</tr>
<tr>
<td>PR (partial response)</td>
<td>Reduction 50%-90%</td>
<td>No new lesions; 50%-90% reduction in measurable sites; 0 to 1 bone marrow samples with tumour; bone lesions same as VGPR</td>
<td>HVA/VMA decreased</td>
</tr>
<tr>
<td>MR (moderate response)</td>
<td>No new lesions; &gt;50% reduction of any measurable lesion (primary or metastases) with &gt;50% reduction in any other; &lt;25% increase in any existing lesion*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR (no response)</td>
<td>No new lesions; &lt;50% reduction but &lt;25% increase in any existing lesion*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD (progressive disease)</td>
<td>Any new lesion; increase of any measurable lesion by &gt;25%; previous negative marrow positive for tumour</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Quantitative assessment does not apply to marrow disease*
Neuroblastoma may present as a mass, or with symptoms due to invasion or compression of adjacent structures such as the spinal cord or optic nerve. The 70% of children who have metastatic disease at diagnosis often present with non-specific symptoms of fever, weight loss, anaemia, bone pain and irritability. Node enlargement, hepatomegaly and skin nodules may be found. Infrequently, neuroblastoma may present as a paraneoplastic syndrome, including myoclonic encephalopathy of infancy or a syndrome characterised by watery diarrhoea, hypokalaemia and achlorhydria, resulting from excess secretion of vasoactive intestinal polypeptide (VIP). Though 80% of patients (>90% with Stage 4 disease), excrete raised amounts of catecholamine metabolites eg vanillyl mandelic acid (VMA) and homo-vanillic acid (HVA), less than 10% of children are hypertensive at presentation.

Treatment of Stage 1 and 2A neuroblastoma is by primary excision. Stage 2B disease is treated with excision followed by 4 courses of chemotherapy. Current treatment of advanced neuroblastoma (Stages 3&4), includes high dose chemotherapy consolidation ("megatherapy") (Pritchard et al, 1982, Shafford et al,1984). In our institution, surgical removal of residual tumour is attempted following induction chemotherapy, and this combined regimen has led to improved survival in advanced disease (Pritchard et al, 1986 & 1987). Analysis of the role of surgery in these patients has suggested that survival is rather better when the primary tumour has been removed. However a more important factor for improved survival is the apparent resolution of metastases following chemotherapy (Matsumura et al, 1988).

Prognostically, the main factors are age and the stage of disease. Of 940 children registered to date (1982-1990) with the European Neuroblastoma Study Group (which includes all tumours of neural crest origin), the overall survival is 45% at 5 years. Five year survival by stage (Evans') is as follows; I 97%, II 90%, III 83%, IV 20%, IVs 63% (personal communication, United Kingdom Children's Cancer Study Group (UKCCSG), February 1990). Thoracic neuroblastomas have an overall survival rate of 61% compared with 20% for abdominal tumours, almost certainly due to the earlier stage of disease at diagnosis and higher proportion of ganglioneuroblastomas.
Other features beside stage have prognostic significance and are shown in Figure 1.4.
**Figure 1.4:** Prognostic features in children with neuroblastoma (Adapted after Pritchard & Kemshead, 1983)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Favourable</th>
<th>Unfavourable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td>1,2,4s*</td>
<td>3,4</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>&lt; 1 year</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>Thoracic</td>
<td>Abdominal except pelvic</td>
</tr>
<tr>
<td></td>
<td>Cervical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pelvic</td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Neuroblastoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>neuroblastoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>†Shimada 'FH'</td>
<td>†Shimada 'UH'</td>
</tr>
<tr>
<td><strong>VIP hypersecretion</strong></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Tumour cell</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-chromosome number</td>
<td>&gt; 50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>-n-myc oncogene copy no.</td>
<td>1</td>
<td>&gt; 1</td>
</tr>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-ferritin</td>
<td>normal</td>
<td>increased</td>
</tr>
<tr>
<td>-neurone-specific enolase</td>
<td>normal</td>
<td>increased</td>
</tr>
<tr>
<td>-lactate dehydrogenase</td>
<td>normal</td>
<td>increased</td>
</tr>
</tbody>
</table>

*INSS classification

**Key**

FH = favourable histology

UH = unfavourable histology

† Shimada et al, 1984 & Joshi et al, 1992
Imaging

Ultrasound is a cheap, readily available and non-ionising form of sectional imaging, but its role in assessing neuroblastoma is still controversial. White (White et al, 1983) found that ultrasound failed to detect the full extent of abdominal disease in up to 50% of patients, mainly due to technical factors. In contrast, Kohler (Kohler et al, 1984) found good correlation between the ultrasound findings and disease stage at surgery, and concluded that diagnostic accuracy of up to 90% could be reached with good equipment in experienced hands. However several reports have suggested that ultrasound is frequently less accurate than CT in documenting the full extent of tumour (Berger et al, 1978, Stark et al, 1983a, White et al, 1983, Faerber et al, 1984) and, because there is no sonographic window, ultrasound cannot assess intrathoracic disease. Saks (Saks et al, 1985) found CT and ultrasound were often complimentary when excessive bowel gas and heavy calcification impaired tumour visualisation by ultrasound and when unopacified loops of bowel and streak artifacts (caused by metallic surgical clips) were a problem with CT.

Though its availability, mobility and practicability make ultrasound the best initial investigation for assessing a child with an abdominal mass (Faerber et al, 1984, Saks et al, 1985), CT is generally established as the most accurate imaging modality for the assessment of disease at the primary site, for determining tumour resectability and for follow-up assessment. Early experience of enhanced CT suggested that it could replace intravenous urography (IVU) and angiography for the identification and assessment of the extent of a mass (Siegel et al, 1982, Faerber et al, 1984). With specific exceptions, this optimism has been justified. In a study of 38 patients, Stark (Stark et al, 1983a) found that CT was the most sensitive single test for the detection and delineation of neuroblastoma at presentation. Staging was validated by surgery in 27/38 patients and by 'multiple imaging' in the remainder. CT alone accurately staged disease in 82% of cases, but when combined with bone marrow biopsy accurately staged 97% of patients. CT was superior to ultrasound for the assessment of posterior mediastinal disease and for assessing the extent of intraabdominal disease. In contrast to Stark's excellent results Saks (Saks et al, 1985) found that neither CT nor ultrasound identified small liver metastases in 2/4 children with neuroblastoma examined by
both modalities at diagnosis. It is not clear why the results of the 2 series should differ so widely, although there is an unusually high proportion of patients with liver metastases in Saks group (and the number of patients is very small).

Accurate imaging is necessary to assess surgical resectability of localised tumours. Some tumours which 'lean over' the midline are also resectable if they do not encircle midline vessels or invade adjacent organs. Since surgical resection without chemotherapy is curative in most of these patients, it is essential that this group is identified. Boechat (Boechat et al, 1985) used contrast enhanced CT to examine 19 children with disease crossing the midline. They found that tumour did not encase the major vessels in 3/19 children and predicted that the tumour was resectable. These findings were confirmed surgically in all 3 children. Tumour appeared to encase major vessels in the remaining 16 children and this was confirmed by surgery or post mortem examination in each case. Golding (Golding et al, 1984) examined 36 patients with advanced neuroblastoma. Intrathecal contrast was given to 9 children on 11 occasions, but the scans were not enhanced with intravenous contrast agents. Seventeen children underwent either primary or delayed surgery (a total of 20 operations). In this group resectability was correctly predicted in 8/9 patients, but direct intraspinal tumour extension was missed in 1 child examined without intrathecal contrast. Non-resectability was predicted correctly in 10/11 patients; one tumour, classified as inoperable because of liver invasion, was successfully resected with a partial hepatic segmentectomy.

Neuroblastoma may recur locally or at distant sites. Although tumour recurrence is often suspected on clinical grounds and rising VMA+/HVA levels, CT has been established as a useful modality for assessing the site of non-skeletal recurrence. In one study, recurrence, as documented by biochemical, clinical, pathological and multiple modality imaging, occurred in 27/52 children on 30 occasions (Stark et al, 1983b). Eighty-five percent of recurrences were confirmed by CT alone, and 100% by CT combined with bone marrow biopsies and localised (spot) radiographic films. Recurrent tumour could not be differentiated from histologically confirmed scar tissue and non-viable tumour in 2/64 examinations.

Intrathecal tumour extension is often clinically silent. Unenhanced CT may miss intraspinal tumour extension, and will certainly not predict the extent of the tumour.
involvement (Golding et al, 1984). With intrathecal contrast, CT can be used to delineate intrathecal extension, and has been recommended with all paraspinal tumours, even when there are no signs of cord compression (Armstrong et al, 1982).

Several studies using CT and US have tried to define features diagnostic of neuroblastoma. Identifying the organ of origin of the tumour is a useful but not conclusive means of differentiating between neuroblastoma and Wilms' tumour. Though most intrabdominal neuroblastomas are suprarenal in origin (Peretz & Lam, 1985), they occasionally arise within the kidney (Peretz & Lam, 1985, Oliphant & Berne, 1988, Rosenfield et al, 1988) and may rarely metastasize to the kidney (Filiatrault et al, 1987). Rosenfield (Rosenfield et al, 1988) reported 6 patients with an apparent intrarenal mass, all histologically confirmed to be undifferentiated neuroblastoma. Three of 6 tumours were not entirely surrounded by renal parenchyma on imaging. Oliphant (Oliphant & Berne, 1988) has suggested that intrarenal neuroblastomas arise by direct extension along the renal pedicle from an extrarenal primary. In his experience (in an unspecified number of cases), patients with neuroblastoma usually have paraaortic and pararenal vascular disease, allowing confident differentiation from primary renal tumours.

In general the ultrasound characteristics of neuroblastoma are non-specific, although most tumours are of heterogeneous echogenicity and have poorly defined margins. Large anechoic areas, probably representing necrotic regions may be present (White et al, 1983) and calcification may occasionally be seen (3/21 tumours in this series [White et al, 1983]). One group of authors suggest a sonographic sign specific for neuroblastoma (found in 4/10 neuroblastomas examined and none of 43 other abdominal tumours) - a smooth, well-defined, hyperechoic lobule lying in a larger mass, which histologically consists of aggregates of neuroblastoma cells, margined by reticulin and collagen and showing no evidence of necrosis, calcification or haemorrhage (Amundson et al, 1987). However this sign is uncommon, has only been independently confirmed in 1 patient when it was found useful for directing guided biopsy (Keller & Buckley, 1987), and is certainly not an adequate criterion for specific diagnosis.
Peretz (Peretz & Lam, 1985), has attempted to characterise the CT appearances of neuroblastoma. Calcification was much more commonly seen in neuroblastoma (80%) than Wilms' tumour (10-20%). After intravenous contrast, a mixed pattern of contrast enhancement was seen with neuroblastoma compared to the 'rim enhancement' characteristic of Wilms' tumours. Elevation and/or encasement of the great vessels was present in all cases (presumably no Stage 1 or 2 tumours were included into this series), and thought to be the single most useful sign differentiating neuroblastoma from Wilms' tumours. However, in this study 2/11 patients with Wilms' also showed 'minimal' elevation of the great vessels in this study and so this sign is not specific to neuroblastoma.

In a study exclusively directed to congenital neuroblastoma, Forman et al (1990) examined the efficacy of a variety of imaging techniques (including ultrasound, CT and MR) in 12 patients. Imaging consisted of 4 prenatal and 11 postnatal ultrasound examinations, 7 CT and 3 MR scans, 4 intravenous urograms and 12 radionucleide scans or skeletal surveys. None of the 3 patients having MR scans were examined by CT.

Of the 11 patients examined by postnatal ultrasound, the primary tumour was seen in 10 and obscured by gas in 1 case. The intrathecal extension of 1 paravertebral tumour was incompletely shown. Seven of these 11 patients had liver metastases and these were apparent in 5 cases and missed in 2.

Of the 7 patients examined by CT, the primary tumour was shown in 6 cases. There were 4 true positive and 3 true negative diagnoses for liver metastases. MR identified the primary tumour in all 3 patients scanned. In 2 of these patients ultrasound was equivocal for the diagnosis and could not exclude adrenal haemorrhage and MR increased the level of diagnostic confidence in favour of neuroblastoma. There was 1 true positive and 2 true negative diagnoses of liver metastases.

Overall the study concluded that, although imperfect, ultrasound was adequate for staging congenital neuroblastoma in view of the relatively benign nature of the disease. The additional imaging findings missed by ultrasound would not have altered the clinical management of these cases as treatment is predominantly of the complications of the disease (such as IVC obstruction).
To summarise, CT has been valuable in identifying the primary site of tumour and in staging disease at presentation. Features specific to neuroblastoma have not been identified, and small hepatic metastases can be missed. Intraspinal tumour will be missed in patients examined without the use of either intrathecal or intravenous contrast. Intravenous enhancement is also necessary to evaluate major vessels and the retroperitoneum adequately. Obviously CT cannot detect distant skeletal or bone marrow metastases and for complete staging bone marrow aspiration and trephine, and radionucleide bone scan are necessary (see below). There is very little literature relating to CT assessment of tumour response to chemotherapy or, to tumour restaging following treatment. Finally, CT is unable to differentiate small regions of scarring from residual disease, nor can it distinguish benign from malignant residual debris, causing some false-positive diagnoses on follow-up scans.

Bone marrow involvement by neuroblastoma is currently assessed by cytological, immunocytological and histopathological examination of bone marrow aspirates and trephine biopsies. Although the sensitivity of the technique can be improved by performing both trephine and aspiration at 2 or more sites (Franklin & Pritchard, 1983) and by using immunohistochemical techniques for detecting tumour cells (Kemshead et al, 1981), the patchiness of marrow involvement, especially after chemotherapy, limits its sensitivity. In contrast, in assessing bony disease, the entire skeleton is surveyed with radionucleide imaging. Well established techniques include scanning with Technetium-labelled methylene diphosphonate (Tc99m-MDP) for the detection of bony metastases and iodine-labelled metaiodobenzylguanidine (1123-mIBG) for the detection of both skeletal and soft tissue metastases (Gilday et al, 1977, Howman-Giles et al, 1979, Podrasky et al, 1982, Geatti et al, 1985, Edeling et al, 1987). However neither technique is 100% sensitive nor specific as both false positives and false negatives occur (Kaufman et al, 1978, Pritchard et al, 1988, Bouvier et al, 1988, Hall-Craggs et al, 1990). Radiolabelled monoclonal antibody has been used to try to improve the specificity of radionucleide techniques. UJ13A recognises a surface antigen expressed by most cells of neuroectodermal origin and labelled antibody has been shown to
localise in both primary and secondary sites of tumour (including bone marrow deposits) (Goldman et al, 1984). However there are problems as false negatives occur, there is uptake by the adrenals and reticuloendothelial system (Goldman et al, 1984) and antibody kinetics vary between patients and on different occasions in the same patient (Lashford et al, 1987). However the technique is promising and because it has important therapeutic implications, studies with other monoclonal antibodies and antibody 'cocktails' are now needed.

Magnetic Resonance Imaging

Three studies assessing the value of MR for staging neuroblastoma have been reported (Cohen et al, 1984 &1986, Fletcher et al, 1985, Dietrich et al, 1987). There has been a further study examining the value of gadolinium enhancement in disease assessment (Komreich et al, 1991) and finally a study has reported examining the accuracy of CT and MR for showing the extent of disease after chemotherapy (Foglia et al, 1989). These studies are now discussed in detail.

Cohen (Cohen et al, 1984), examined 9 children with neuroblastoma (aged 6 months-7 years) using a 0.15T MR system. All children were examined at diagnosis and 8 follow-up studies were performed in 5 children during chemotherapy. Short TR/short TE spin-echo (SE) sequences were performed in the transverse plane in all patients and additional transverse inversion recovery (IR) (TR/TI=1500/400) and long TR/long TE SE sequences in the regions of interest. For comparison, CT scans were also performed in all children at presentation, and following treatment in 6. Three children were treated by primary resection, one child had an open biopsy and another child had resection of tumour following chemotherapy. Four children had no independent assessment of the MR findings. The tumour mass was identified in all patients on both CT and MR. Findings for the 2 techniques correlated so far as tumour extent was concerned. On the initial scans, tumour/tissue margins were shown better by MR in 2 cases and by CT in 1 child, and were equivalent in the remainder. Tumour margins were better shown by CT than MR after chemotherapy (3 patients) and in 1 of these cases, tumour could not be separated from adjacent bowel on the MR scan. Calcification was not identified on MR in any case. MR and CT were comparable in
assessing node and liver involvement. Liver metastases (confirmed by CT and isotope scans in 1 patient and unconfirmed in the second) were seen in 2 patients on T2-weighted sequences which were not apparent on the T1-weighted images. MR showed vascular involvement by tumour more clearly than CT and could therefore predict surgical resectability more reliably.

Changes seen by MR in the signal characteristics of residual tumour after chemotherapy (n=4) were variable; in 1 patient T1 relaxation times shortened and in 3 others it lengthened.

In 1986, Cohen (Cohen et al, 1986) reported their experience of MR examinations at 0.15T in a number of childhood tumours including 17 children with neuroblastoma (presumably including the 9 previously reported as it covered the same time period), and compared the findings with CT. (The methodology of the CT scans, including whether the scans were enhanced, is not described in this paper). Of 14 children examined with both techniques, MR defined tumour more clearly than CT in 5, less clearly in 8 and equally in 1 case. Comparison of neuroblastoma and Wilms' tumours showed that the internal structure of neuroblastic tumours was more uniform, with fewer haemorrhagic and cystic areas. Displacement of major vessels was more common with neuroblastoma, confirming CT and surgical findings. The authors claimed that (in an unspecified number of children) MR did not distinguish small amounts of residual fibrosis from active disease following treatment of Stages 3 and 4 disease but it is unclear whether these findings were surgically corroborated.

At this field strength, the authors comment that images were not significantly degraded by respiration.

Fletcher et al (1985) performed 21 MR studies in 8 children aged 4.5 months-12 years. Five patients had Stage 4, 2 had Stage 4-S neuroblastoma, and 1 child had a retrocrural ganglioneuroblastoma. Five patients were examined at presentation, 1 following chemotherapy, 1 at relapse and the last patient during remission of 4-S disease, 2 years after diagnosis. Short TR/short TE SE, long TR/long TE SE and IR with phase reconstruction sequences were performed in the transverse plane. Fifteen patients also had abdominal CT scans within 3 weeks of corresponding MR studies. The facility to produce multislice MR images was not available, so images could only be compared at preselected levels. In these patients, MR produced images of comparable anatomical detail to CT, but with better contrast.
resolution. When identified, tumour calcification was seen as areas of low signal within the tumour. This study confirmed Cohen's experience (Cohen et al, 1986) that the signal intensity of tumour and kidney was similar on T1-weighted sequences, although renal parenchyma was found to be brighter than tumour in 6 patients on T2-weighted sequences. In the majority of studies, tumour/kidney margins were equally well shown on CT and MR although MR delineated the interface more clearly in 1 case, and less well in 4 studies. Liver/tumour margins were equally well shown on CT and MR. Vascular anatomy and its relationship to tumour was better demonstrated by MR than contrast-enhanced CT. Measurement of tumour T1 and T2 values showed a wide range of initial values. With serial measurement during treatment, an overall decrease in T1 was noted during periods of tumour regression. The visual impression of signal overlap between normal kidney and tumour was confirmed by T1 measurements.

Although neither Fletcher nor Cohen showed any clear advantage for MR over CT in defining tumour extent, both studies were technically limited with images acquired only in the transverse plane. One of the major advantages of MR is its capacity to perform multiplanar imaging, resulting in improved anatomical detail and resolution. In 1987, Dietrich et al (1987) explored the value of variable imaging planes in a study on 17 children with neuroblastoma (aged 6 months-9 years), using a 0.3T Fonar system. In all, 35 MR examinations were carried out (the number at the time of diagnosis is not stated). CT scans were performed at the time of the initial MR scan in all cases. Ultrasound examinations were available in 6 cases, IVU in 4, myelography in 2, radionuclide bone scans in 14 and radiographic skeletal surveys in 3 patients. MR scans were performed in both coronal and axial planes in 13 children. T1-weighted SE sequences were obtained in all patients, and additional long TR/long TE SE in 9 children. Various combinations of imaging were available in all patients. Five children underwent surgery but the timing of this in relationship to the MR scan is not reported.

These authors found that MR clearly showed the site of origin of tumour in all cases (13 adrenal, 1 pelvic, 1 thoracic and 2 intraabdominal paraspinal neuroblastomas), and that, for this purpose, the coronal plane was the most useful. They claimed that MR also showed
the extent of tumour in all 17 patients, as finally determined by multiple imaging (12 patients) or surgery (5 patients). Intraspinal tumour extension and involvement of the posterior mediastinum was also best seen on coronal scans. The overlap of signal intensity between renal medulla and tumour was confirmed on both T1- and T2-weighted sequences, restricting the radiologists' ability to discriminate between tumour and adjacent kidney. In this study, MR successfully demonstrated metastatic disease and showed all lesions within the areas scanned that were shown by all other imaging techniques combined. Bone marrow metastases were seen as areas of low signal intensity in high signal fat on T1-weighted sequences in all 5 patients who had evidence of marrow involvement documented by marrow aspirates and radionucleide scans. Marrow deposits were best seen on coronal scans of the long bones, and by coronal or sagittal scans of the vertebrae.

Complications of treatment were demonstrated by MR in 6 patients. Hydronephrosis (considered to be a complication as it developed only after treatment with radiation and/or chemotherapy), was seen in 2 patients, caval thrombus secondary to an indwelling catheter in a third, and CNS complications of treatment in 3 other children. One had a subdural haemorrhage, the second a parasagittal brain infarct secondary to compression by dural deposits, and the third developed an astrocytoma (although it is debatable whether the latter 2 conditions are complications of treatment). These authors concluded that with multiplanar MR, tumour and vascular definition were sufficient for accurate staging of disease and prediction of surgical resectability. MR was superior to CT in the detection of bone and marrow metastases, and in its capacity to identify intraspinal disease without the use of iodinated contrast agents.

The value of MR demonstration of intraspinal disease has been emphasised by other workers. Siegel (Siegel et al, 1986) reported 2 patients with tumour extension through the intervertebral foramina into the epidural space clearly shown by MR and confirmed by myelography/surgery in 1 child.

There has been very limited experience of the use of gadolinium in the assessment of children's abdominal masses due to the delayed licensing of the contrast agent. A small study has reported the use of gadolinium in 5 children with neuroblastoma (8 examinations)
Two small tumours showed homogeneous and 3 large masses (>10cm) inhomogeneous enhancement. Two children (both with small tumours of under 3 cm) had sequential scans after chemotherapy and in neither case was there and alteration in the pattern of enhancement. The authors state that areas of non-enhancement corresponded to areas of necrosis, haemorrhage and some regions of viable tissue. Although all the children had CT it is not reported whether any underwent surgery or biopsy, hence it is unclear as to how the correspondence was elucidated. The authors found no difference between the enhancement characteristics of neuroblastomas and ganglioneuroblastomas. The numbers reported in this study are very small and insufficient to determine whether gadolinium has a role to play in the assessment of disease or its response to chemotherapy.

In a study of 25 children with neuroblastoma, Foglia et al (1989) examined the diagnostic accuracy of CT and MR for disease assessment after chemotherapy. All these children had advanced disease (stages 3 and 4) and were examined by CT only (14 cases), MR only (8 cases) and 3 patients had both CT and MR. On 26 occasions, imaging and surgery were performed together (ie 26 episodes in 25 patients) although the time delay between them is not specified. A discrepancy between the surgical and imaging findings occured in 10 episodes of which there were 6 discrepancies with 15 CT scans (14 patients), 3 with 8 MR scans and 1 where MR and CT were both performed. These authors state that diagnostic imaging had neither the sensitivity or specificity to be a definitive method of assessing disease after chemotherapy and that surgical assessment was the best method of evaluating tumour.

The capacity of MR to detect bone marrow involvement, noted by Dietrich et al (1987), has also been studied by a group working at high field (1.5T) (Couanet et al, 1988). Forty three MR scans (32 patients) were compared with the results of bone marrow aspirates and 123I-mIBG scans. MR scans were made of the long bones of the legs (37 cases), the vertebrae (34 cases) and the iliac bones (15 cases). These authors report a specificity of 88.9% and sensitivity of 84.4% for the MR detection of marrow involvement. However it is difficult, in their paper, to distinguish between results of studies performed at presentation and those performed during follow-up. Persistence of focal changes, possibly representing fibrosis, during treatment may be a cause of false positives scans on follow up. The 'gold standard'
applied in this study was a marrow aspirate combined with 123/131I mIBG. However false negative results can occur with marrow aspiration (Franklin & Pritchard, 1983) and 123/131I mIBG (Gordon et al, 1990), and might occur even when these studies are combined. In this study, MR detection of marrow involvement seemed highest when long bones were scanned. However the data are not presented in sufficient detail to allow validation of this conclusion.

Corbett et al (1991) reported a prospective comparison of MR, mIBG scintigraphy and posterior iliac crest marrow aspiration and trephine in 19 patients with neuroblastoma (30 examinations). On 10 occasions MR and mIBG scanning showed an abnormality not detected on examination of the bone marrow and on 4 occasions MR was the only modality showing an abnormality. On 16 occasions MR showed more extensive disease than all other methods and these authors conclude that MR shows promise for the detection of marrow involvement. However the results should be viewed with some circumspection as the specificity of MR was not tested and the abnormalities shown by MR were not confirmed as tumour.

Attempts at specific tissue diagnosis have been made with every imaging modality that has become available. As discussed above, Cohen (Cohen et al, 1986) has suggested that neuroblastoma has a more uniform appearance than Wilms' tumour. Measurement of the relaxation times of tumour are non-specific (Fletcher et al, 1985), and values vary widely. This is likely to be related to the inhomogeneous nature of tumours, with varying proportions of different cell populations eg neuroblasts vs ganglion cells vs stroma, and a varying degree of haemorrhage and necrosis. MR spectroscopy (MRS) has been used in an attempt to diagnose neuroblastoma. Maris et al (1985) examined the 31P NMR spectra of the livers of 2 children with Stage 4 and 4-S disease, and found the spectrum differed from normal tissue, in that there were substantially elevated phosphomonoester (PME):ATPβ ratios. However it was not possible to determine whether this was a specific characteristic of neuroblastoma, of tumours in general or just of rapidly proliferating tissue. With spontaneous regression in the child with 4-S disease, and with clinical response to chemotherapy in the child with Stage 4 disease, the PME:ATP ratios tended to return to control levels. Although these results are anecdotal, they suggest that these measurements may prove useful in the future as markers of growth or regression of tumour during treatment.
Naruse et al (1985), examined $^{31}$P NMR spectra in a number of (human) neuroectodermal tumour implants in rats and hamsters, taking measurements before and after administration of a chemotherapy. These authors found that, with very large doses of drugs, ATP peaks decreased and inorganic phosphate (Pi) peaks increased. This effect was not seen at lower doses. The potential of MRS to monitor treatment and the effects of chemotherapy were emphasised.

To summarise, a number of reports suggest that MR is as successful as CT in detecting and delineating intraabdominal disease. It is better than CT at defining vascular anatomy, at detecting bone marrow deposits and in detecting intraspinal tumour. There is a possibility that MRS may be an aid to monitoring the activity of therapy, and (less likely) to establishing specific diagnoses. However all the papers concerned with tumour imaging by MR have involved relatively small numbers of patients, all have been conducted at low to intermediate field strengths, and very few patients in these studies have had surgical or pathological correlation of the imaging findings. No series reporting the experience of a high field strength MR imaging have been published, and there are few reports of changes in seen in tumours after treatment.
Periodic Motion

Periodic motion causes blurring of images and, unique to MR, artifactual ghost-like replicas of moving anatomical structures. The main source of motion artifact when scanning the thorax or abdomen is respiratory motion although other factors such as pulsatile flow and peristalsis also contribute (Ehman et al, 1986).

Two-dimensional (2D) MR images are formed by separate Fourier Transforms of rows and columns of measured data in 2 directions- the phase-encoded (PE) and the frequency-encoded (FE) directions. The spatial information encoded in the FE direction is achieved rapidly, in less than 10 ms. In contrast, separate steps are necessary to obtain spatial information in the PE direction, ie 64, 128, 256 steps depending on the matrix. As each step takes the equivalent of the repetition time (TR), the PE information takes several minutes to acquire using standard spin-echo imaging, during which movement occurs. Respiratory motion introduces a modulation into the PE data, which appears as periodically-displaced ghosts in the PE direction of the resulting image (figure 2.1). Motion in any direction, not just that occurring in the PE direction, causes ghosts (Wood & Henkelman, 1985). To minimise the effects of ghosting, it is necessary to understand what factors effect ghost separation and ghost intensity.

The separation of ghosts, defined as the number of pixels separating 2 ghosts, $Y_G$, is given by:

$$Y_G = \frac{Y_{tot} \times n_{av} \times TR}{T}$$

where

- $Y_{tot}$= total number of pixels across the field of view
- $n_{av}$= number of acquisitions averaging before each new PE step
- $TR$= repetition time
- $T$= period of motion
By increasing ghost separation, fewer appear on the image, and those present are thrown distant from the image. Separation is increased by increasing the TR, number of averages and is greater with more rapid periodic motion.

Ghost intensity depends on the amplitude of motion and the signal intensity of the moving structure (Wood & Henkelman, 1985 &1986, Wood et al, 1988). The physical displacement, measured in terms of the number of pixels traversed rather than the displacement in centimetres, is the parameter determining ghost intensity. Ghost intensity increases with increased intensity of the moving structure, so the most conspicuous ghosts arise from high signal fat of the anterior abdominal wall. Paradoxically, the increased SNR generated by high field systems increases the intensity of ghosts. The high SNR of high field systems allows the number of averages to be reduced and the use of smaller pixels, both of which contribute to increased ghosting.

Methods of suppressing motion artifacts depend on reducing motion, the image intensity of the moving structure or the PE errors induced by the motion and are discussed below.

a) Physical restraint

The simplest method for reducing respiratory motion of the abdomen is the use of a restraining belt. This is uncomfortable, may not be safe in children with large abdominal masses, and only reduces artifact due to respiration without affecting ghosting due to pulsatile flow or peristalsis.

b) Respiratory gating

This is the principle of collecting data during the part of the respiratory cycle when motion is least, usually during end-expiration. This technique depends upon accurate recording of the respiratory cycle. Unfortunately it is much less easily performed than ECG techniques because a) there is no well defined physiological trigger analogous to the R wave, and b) respiration is less regular than the pulse. A pressure sensitive belt, worn around the chest, is the most commonly used triggering device. Ehman et al (1984) investigated the use
of this method in adults, and found the respiratory signal superior to that obtained by either a thermistor placed in a respiratory mask or in a nasal catheter. As data is not collected during most of the cycle, scanning time is inevitably increased by up to 300-400% (Ehman et al, 1984). Unless preconditioning is used, the TR becomes variable, which itself introduces image artifacts similar to ghosts. Gating does reduce both ghosts and blur.

c) Breath-holding

This is a simple and effective method of reducing respiratory motion, and is clinically applicable when fast imaging sequences are used (Edelman et al, 1986, Unger et al, 1988). Ghosts from pulsatile flow may become more conspicuous, but these can be reduced by presaturating flowing blood outside the imaged volume.

d) Restricted Field of View

Surface coils are generally most sensitive to structures adjacent to the coil. If the moving object is distant from the coil, it is less able to create ghosts. This method of restricting the field of view is not applicable to the imaging of large volumes, such as the abdomen, and was unsuitable for our purposes.

e) Fat supression

Short tau inversion recovery (STIR) is a modified inversion recovery sequence where, following a 180° inversion, the 90° imaging experiment is conducted at a time (TI) when signal from fat is passing through the null point (Bydder & Young, 1985). The result is that fat has low signal intensity and consequently ghosts from it should be reduced in intensity.

f) Signal averaging

'Averaging' is the practice of repeating each PE step more than once, and is generally used to increase the SNR. Ghosts occurring in each average will not be identical, and will tend to cancel each other out, thereby reducing systematic noise. Theoretical analysis has shown that the intensity of ghosts is inversely proportional to the number of averages (Wood &
Signal averaging has been shown to be a powerful method of reducing ghosting artifact, particularly in sequences with short repetition times (Stark et al, 1987).

g) Pseudogating

This method separates ghosts so that they are placed away from the image. If \( (n \text{ av} \times \frac{TR}{T}) = 0.5 \), every second ghost falls onto the moving structure, while the others are superimposed one-half field of view away (ie they do not lie on the image). An estimate of \( T \), the period of motion (ie the respiratory rate) is necessary, and the technique is only applicable if the product of the expression \( (n \text{ av} \times \frac{TR}{T}) \) is a multiple of 0.5.

h) Reordering of Phase Encoded Data

Phase-encoding errors can be reduced by reordering the PE steps. When modulation of the PE steps occurs periodically (as with regular breathing), the modulation of the data can be smoothed by reordering the sequence in which the PE steps of data are acquired. This approach has been incorporated into Respiratory Ordering of Phase Encoding data (ROPE) (Bailes et al, 1985), and a number of other sequences. Potentially this method eliminates ghosting with no increase in imaging time, but at the expense of increased blurring.

i) Gradient motion nulling

Gradient motion rephasing introduces additional gradients into an MR sequence to rephase out-of-phase MR signal produced by moving tissue. Rephasing of motion due to velocity or acceleration is relatively simple. Rephasing of higher orders of motion, however, is more complex and may be restricted in practice by the time available between the RF stimulation and data acquisition (TE).

j) Pharmaceuticals

Peristalsis can be suppressed for short periods of time by the use of buscopan or glucagon. Both these drugs have a relatively short time of action and exhibit tachyphylaxis and so it is impractical to use them for the whole duration of the scan.
Of these alternatives signal averaging, cardiac triggering, STIR and pharmacological suppression of peristalsis were used to suppress periodic motion in the studies included in this thesis and are discussed in Chapter 2.

**Monitoring**

As a child in the scanner can neither be well seen, nor heard during data acquisition, vital signs must be closely monitored. Ideally respiratory rate, blood pressure, blood gas oxygenation and expired carbon dioxide, heart rate and ECG, and temperature should all be measured. Several factors must be considered when monitoring devices are selected for use close to a high field strength magnet, 1) ferromagnetic objects are attracted into the magnet, resulting in possibly injury to patients, personnel or the instrument (the 'missile' effect), 2) ferrous materials disturb the homogeneity of the magnetic field, 3) the magnet may disturb the working of the monitoring equipment, eg switching it off, invalidating its calibration etc., 4) monitoring devices may affect the radiofrequency signal received by the scanner. Long leads act as antennae which pick up stray radiofrequency (RF) radiation, causing noise and image degradation (the 'aerial' effect).

Monitoring equipment must be tested to exclude any of these adverse effects. Bar magnets can be used to exclude ferrous material. Phantoms can be scanned with the equipment operational to assess whether any stray RF is causing image noise. Some authors have assessed the use of a variety of monitoring devices at varying field strengths (Roth et al, 1985, McArdle et al, 1986). These groups, working at 0.15T and 0.6T respectively, found that standard equipment for measuring blood pressure, heart rate and body temperature worked satisfactorily without producing significant image artifact. McArdle's group found that noise produced by 2 types of oximeter (Nellcar Pulse Oximeter model N-100 and Ohmeda Biox 3700 Oximeda), significantly degraded images. Several authors (Dietrich & Kangerloo, 1988, Boechat & Kangerloo, 1989) have described the use of the inverted paper cup, placed on the abdomen, to observe respiration. The disadvantage of this simple, cheap device is that
it does not amplify motion and in young children, where respiratory excursion is small, it may be unhelpful or misleading. It is also difficult to place the cup satisfactorily on neonates and young children swaddled in blankets, and the cup often falls off!

In our unit, ECG monitoring is supplied as standard equipment by Siemens (Sirecust 404-1). The electrodes must be placed in a straight line to the left of the sternum (except in cases of dextrocardia). The length of the leads has been established empirically as that causing the least RF noise. The manufacturer will not release details of developmental modifications which makes this equipment suitable for use at high field.

Respiratory apnoea monitors using small surface balloon pressure sensors are widely used in hospital practice, and the Graseby Medical MR 10™ monitor is presently used at HSC, GOS. The casing and batteries contain ferrous material so it is unsuitable for use close to the magnet. We have modified the monitor by stripping the casing of as much metal as possible, and attaching a 2.5m extension tube to the balloon allowing it to be placed outside the central bore of the magnet. Under these conditions, the device does not move into the magnet. The monitor works best with the balloon taped to the upper abdomen, overlying the liver. In most patients, this permits satisfactory monitoring of respiration, though obstructed respiration cannot be differentiated from normal breathing and respiration is still sometimes of too low an amplitude to trigger the monitor in neonates.

An oximeter is the most satisfactory means of monitoring blood oxygenation and pulsatility, and we have investigated the use of the Ohmeda oximeter in our system. The monitor can be placed stably in the magnet room, 2m from the aperture. However, when used at this site, the gradient switching of the scanner electronically turns off the oximeter. If the length of the lead between the sensor and the monitor is increased, the monitor can be placed outside the magnet room (outside the 20 Gauss field). This manoeuvre prevents the monitor switching off, but the noise generated by the aerial effect of the long lead causes severe image degradation. A possible solution to this problem is to create a fibre-optic link between the skin sensor and the monitor placed outside the magnet room.

During general anaesthesia, closer monitoring of physiological functions and blood gases is necessary. Anaesthetic gases are delivered by extension tubing from a piped gas
supply. A standard 'Dinamap' blood pressure monitor, viewed in the scanner control room, with a long extension lead passing to the inflatable cuff attached to the patient, is also used. An Ohmeda 5200 carbon dioxide monitor documents the flux of CO2 in expired gas, but the length of the extension tube invalidates calibration and quantitative measurements are not possible. Oxygen content of inspired gas is measured. Oesophageal stethoscopes monitor respiration, although the noise during sequence acquisition makes it impossible to hear breathing during scanning itself. All tubing between monitors situated in the control room and equipment in the magnet room has to pass through copper shielded U-bend entry ports, designed to prevent stray radiofrequency radiation entering the magnet room.

Although we have tried to monitor patients as completely as possible (making scanning conditions as safe as possible within the constraints described), our technique will remain imperfect until a pulse oximeter suitable for use in a high field system is available. We also have no method of measuring temperature, a particular disadvantage in small infants.

Safety considerations

Several incidents have been reported during MR imaging (Gangarosa et al, 1987). The most serious have been

1) a cardiac arrest in a ventilated child with a cerebellar tumour. The ECG leads had been removed as they were causing interference on the scan. The patient arrested at the end of the scan but was successfully resuscitated

2) a cardiac arrest in a patient with a pacemaker. The patient developed a flat EEG following the arrest, but further details are not available

3) a subretinal haemorrhage leading to unilateral visual loss in a patient with an unrecognised orbital iron filing

4) traumatic external injuries caused by the attraction of ferromagnetic objects into the magnet.

Risks due to MR can be summarised as those due to the static field, to a changing magnetic field, and to RF deposition. Thresholds for health effects determined by 'in vivo'

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studies have been discussed by Budinger (1981). In practice, the major safety issues are as follows;

A) Electrically, magnetically and mechanically activated implants

Patients with implanted pacemakers and neurostimulators should be excluded from the vicinity of an MR scanner. Experiments have shown that even low field strengths can cause switching of reed-relay components within the pacemaker, causing them to switch modes. Higher field strengths can permanently damage relays, and switching RF magnetic signals could be coupled into the prosthesis' circuitry and be superimposed onto its waveform.

B) RF Heating

The radiofrequencies used in NMR cause oscillation of atoms, and heat generation. Energy deposition is measured in terms of specific absorption rate (SAR) and limits of 0.4 W/kg have been recommended by the National Radiological Protection Board (The NRPB, 1983) for whole body exposure, although elsewhere in the world, 4 W/kg is more generally accepted. Reduced ability of animals to perform learnt tasks has been shown when whole body SAR exceeds 4 W/kg (Michaelson, 1980). However in practice, only small sections of the body are irradiated with radiofrequency radiation at any one time, and the limits do not account for concurrent cooling due to blood flow. The limits are more relevant to the imaging of organs without cooling mechanisms, eg. the eye where an excessive rise in temperature may lead to cataract formation, and when the whole body is place within a coil eg. small infants scanned in a head coil.

To reduce the SAR of a sequence, the following manoeuvres can be performed; the slice thickness increased, number of echoes reduced, number of slices reduced, a slice gap introduced or a different sequence type chosen eg gradient-echo in place of a spin-echo.

C) Pregnancy
No consistent teratogenic effects in animals have yet been shown. However most NMR units recommend exclusion of women in the first trimester of pregnancy, during organogenesis, and only restricted exposure during the remainder.

D) Ferromagnetic prostheses

Several types of haemostatic clips have been shown to undergo longitudinal forces and torques in MR imagers (New et al, 1983, Romner et al, 1989). Following placement of haemostatic clips, healing is accompanied by fibrosis and encasement of the clip, in most regions of the body. In the CNS, however, encasement does not occur and New (1983) found in animal models that clips moved sufficiently to cause cerebral injury or haemorrhage in some cases. Movement varies with the composition of the clip; those with high proportions of nickel are not a hazard, but all clips, irrespective of composition, produced image artifact and degradation.

Although there is a theoretical risk of heating in weight-bearing and other surgical prostheses, no adverse effects have been reported.

E) Ferromagnetic objects

Forceful attraction of ferromagnetic objects represent the clearest and most frequent danger in an MR imager. In our own unit, scissors, keys, needles, drawing pins, a ferrous anaesthetic mask, metal vomit bowls, ferrous drip stands and injection pumps have inadvertently been taken into the scanner by staff eg anaesthetists and nurses, who work only occasionally in the unit. 'Walk through' metal detectors may be used to detect metallic objects, but, when the sensitivity of the detector is set to a level sufficient to detect small objects (such as keys or a needle) the alarm sounds continuously. It therefore serves no useful purpose as a screening device. Constant vigilance and supervision are the only means by which these incidents can be prevented.
Chapter 2

Scan methodology and patient preparation
Introduction

At the time of installation of the MR scanner at GOS, there was very little experience anywhere in the world in obtaining high quality scans in children, particularly at high field. The major factors effecting scan quality are a) patient motion and b) artifact due to biological motion (systematic noise). We have attempted to minimise the effects of these factors by using appropriate scan methodology and by trying to prepare patients well for scans, with particular consideration given to the sedation of younger children.

MR scanning technique

There are a number of considerations that need to be made when choosing scan methodology and these include the choice of coil, scan sequences, sequence parameters and methods of reducing the effects of periodic motion. The methods used in scanning the children in the studies included in this thesis are now described. All MR scans were performed on the 1.5T scanner at GOS.

a) Coil

Surface coils have a number of advantages, the most important being inherently better signal to noise ratios (SNR). Wherever possible we used a surface coil (a linearly polarized, receive only head coil) to scan children but use was restricted by the size of the child and limited to those less than about 15 kg. Larger children were scanned in the main circularly polarized transmit/receive body coil as no other appropriate larger surface coil was available at that time.

b) Sequence choice

As discussed in Appendix 2, the image produced is dependent on many factors. Sequences are designed to maximise or 'weight' the influence of one of these factors by careful choice of the sequence type (for example inversion recovery, spin-echo, partial saturation, gradient-echo), time parameters and flip angle. Currently the most commonly used sequences in imaging are;
1) **T1-weighted spin-echo** (short TR/short TE)
2) **T2-weighted spin-echo** (long TR/long TE)
3) **Gradient-echo sequences** eg FLASH, FISP
4) **Short Tau Inversion Recovery** (STIR)

In paediatric imaging, the general consensus has been to use T1-weighted spin-echo imaging in the axial and coronal planes to demonstrate normal and pathological anatomy, and T2-weighted spin-echo imaging to enhance contrast between normal and pathological tissue (Dietrich & Kangerloo, 1988, Boechat & Kangerloo, 1989). STIR and gradient-echo imaging has been used less often in children, although STIR imaging has been used in adults with cancer (Bydder & Young, 1985, Bydder et al, 1985, Dwyer et al, 1988, Dousset et al, 1989). STIR is essentially a T1-weighted sequence, but the degree of T2-weighting can be increased by lengthening the echo time, at the expense of signal loss. Gradient-echo (GE) sequences have the advantage of being fast (a few seconds or minutes), but have low SNRs, and subsequently may require multiple averages, prolonging imaging time, to produce diagnostic images. GE images intrinsically are T2*-weighted, hence are very sensitive to field inhomogeneity, and do not produce real-T2 contrast.

The imaging requirements for different types of malignancies vary depending on the way the tumour behaves e.g. its propensity to invade vessels, and the indication for performing the investigation i.e. for diagnosis or to plan surgical management. In the studies reported here, in keeping with the published experience, conventional T1-weighted spin-echo sequences were performed in all cases in at least 1 plane. Transverse and then usually coronal images were acquired. These images are high in SNR and have good anatomical detail. Blood vessels of sufficiently large size (such as the aorta, IVC, renal arteries and main hepatic veins) are well seen either as black structures where signal void is present or as bright structures when flow enhancement occurs. The sequence parameters used for this sequence were:

\[
\text{TR} = \text{RR interval (ECG triggered sequence)} = \text{approximately 350-450 ms, TE 15 ms, matrix 256x256, slice gap 0, signal averages 4.}
\]
Because of the promising reports of the use of STIR in adult cancer this sequence was performed in all patients after the T1-weighted spin-echo images had been acquired. The advantage of STIR is that it is both T1- and T2-weighted. In our studies, STIR imaging was used for two purposes, -to reduce ghosting and to enhance lesion contrast. Comparison of a STIR and a T2-weighted spin-echo image, obtained in the same patient at the same level, is shown in figure 2.1. As fat is suppressed theoretically there should also be less ghosting artifact from abdominal fat than with non-fat supressed sequences. Although good fat suppression has been achieved with STIR, there is persistent ghosting from the anterior abdominal wall, high signal fluid in the bowel and from peristaltic motion. A disadvantage of the sequence is that following initial inversion and a period of recovery (tau) the imaging experiment is then performed on only partially recovered spins. Hence the SNR is less than with a T2-weighted spin echo using comparable echo times. However the STIR experiment rarely uses echo times as long as those necessary for T2-weighted spin-echo images and this compensates for the SNR considerations. With STIR, relaxation of spins must occur between each imaging experiment so consequently there is a long TR(2.5 - 3 s) and hence the sequence is long. For example with a 256x256 matrix and a TR of 3s, the sequence lasts nearly 13 minutes. A further disadvantage is that a very homogeneous magnetic field is necessary to produce uniform inversion with STIR, if power dependent inversion pulses are used. Since the magnetic field is not perfectly homogeneous, inversion will be imperfect across the slice and this leads to patchy fat supression. With small children the entire imaging volume is within the central, more homogeneous portion of the magnetic field so, from a technical point of view, STIR can be applied more easily than in adults. In our experience, good fat suppression could be obtained in children up to approximately 10 years of age. In older children, as in adults, fat suppression was more erratic. The sequence parameters chosen for the STIR sequence were as follows;

**TR 3000ms, TE 30-40ms, TI 150ms, matrix 256x256, slice gap 0.4, 1 signal average.**

At the onset of the studies it was hoped that a comparison of STIR with T2-weighted spin-echo and gradient echo sequences could be made in each study group. However time constraints did not allow this and additional sequences were performed infrequently.
Whenever possible a conventional T2-weighted spin-echo was performed with the following parameters;

TR 3000ms, TE 88ms, matrix 256x256, slice gap 0.4, 1 signal average.

Gradient echo sequences do not produce contrast in an entirely predictable manner and it tends to vary between different pathologies and patients. As discussed in Appendix 2, contrast may be altered by manipulating the TR, TE and flip angles and, ideally, these should each be optimized for each disease and patient size. Within the time available it was not possible to do this and gradient echo sequences (either FISP or FLASH) were used infrequently.

c) MR scan parameters

i) Signal averages

The time taken to acquire a sequence (T_tot) is;

\[ T_{tot} = TR \times \text{number of PE steps} \times \text{number of averages} \]

The TR of both the T2-weighted spin-echo and STIR sequence are of the order of a few seconds (s), most commonly 3s. With a typical image matrix of 256 PE steps, the time taken for the sequence is;

\[ = 3 \times 256 \times n \text{ av} \]
\[ = 12.8 \text{ min} \times n \text{ av} \]

It is not practicable to increase the averages for these sequences as the scanning time becomes too long. In contrast, for a T1-weighted spin-echo sequence, repetition times of the order of .4-.6s are used. Hence the total scanning time is;

\[ = .5 \times 256 \times n \text{ av} \]
\[ = 2.13 \text{ min} \times n \text{ av} \]

in this case, the number of averages can be increased by a factor of up to 8, with an acceptable total scanning time. The effect of increasing the number of averages is illustrated in figure 2.2;
scans have been acquired with 1, 2, 4, and 8 averages. It can be seen that scan quality improves with increased averaging however 4 averages was felt to produce good image quality within an acceptable scan period (= 8 minutes). This format was adopted as a routine for abdominal scanning.

ii) Cardiac triggering

In 'cardiac triggering', the R wave of the electrocardiograph is used to trigger the start of each cycle of the MR experiment, so that the repetition time (TR) is the R-R interval. As a result, each slice of a multislice sequence is obtained in the same phase of the cardiac cycle, providing the heart rate is regular. Since heart rates of 100-150 are normal in children and infants, the triggered TR interval is usually 0.4-0.6s which is appropriate for T1-weighted spin-echo sequences. T1-weighted spin-echo sequences were performed in the transverse plane with and without triggering in 8 adult volunteers and the first 5 children having abdominal scans. In each case triggering reduced artifact due to flow with an overall improvement in image quality, anatomical definition and spatial resolution. Figure 2.3 compares triggered and untriggered T1-weighted SE sequences of the same transverse section of the abdomen in an adult volunteer. All subsequent transverse T1-weighted abdominal images of the abdomen were acquired with triggering. The images of patients with pronounced sinus arrhythmia are not improved using this technique, as the evolution of the cardiac cycle after the trigger point is variable in time. Consequently slices (for which points are collected at fixed, regular intervals) are acquired at varying parts of diastole and systole for each successive PE step. This effect increases with time from the trigger point and so is worst for slices acquired in the latter part of the cycle.

Although lengthening the TR reduces ghosting (see above) and increases SNR (figure 2.4), because we chose to use ECG triggering, the TR is determined by the pulse rate and is not independently variable.
iii) Respiratory Gating

Respiratory gating depends on accurate monitoring of the respiratory cycle but in the initial experience on the scanner it was found that signal detection was unreliable in our small patients due to the small respiratory excursion and high respiratory frequency. As no satisfactory method of monitoring respiration was devised, respiration-triggered sequences could not be assessed.

iv) Pharmacological procedures

Buscopan and glucagon suppress upper and lower gut motility, but are of limited practical use because of their short duration of action (10-15 mins), tachyphylaxis and, in the case of glucagon, expense. Attempts to reduce peristaltic artifact using these drugs had limited success mainly because a venepuncture in the middle of an examination tended to awaken the child. Each injection prolonged the scan by an average of 10 minutes, as the patient has to be moved out of the core of the magnet, injected, moved back in, and the equipment retuned. As a result of these problems, no systematic analysis of the effect of scanning with and without these agents was undertaken, although the images in the few patients receiving Buscopan had little motion artifact.

v) Scan Matrix

The conventional scan matrix uses 256 steps in each of the frequency- and phase-encoding (PE) directions resulting in symmetrical, square pixels. The PE steps may be reduced, for example to 128, with a consequent reduction in imaging time. However at the time of the studies, only a symmetrical field of view (FOV) was possible and reducing the number of PE steps resulted in reduced spatial resolution and asymmetric pixels. A further manoeuvre is to use a half Fourier data set (see Appendix 2) which halves the imaging time as compared with a full data set. However early experience showed that both these techniques significantly degraded the images and hence a 256x256 matrix with a complete Fourier data set was used routinely.
vi) Slice gap

The introduction of a slice gap reduces the slice-to-slice crosstalk, however it also means that slices are not contiguous. A slice gap of zero was chosen for the T1-weighted images as it was felt essential to obtain contiguous slices for the sequence used to assess anatomy. With both the STIR and T2-weighted spin-echo sequences, the benefit in SNR from having a 0.4-0.5 slice gap outweighed anatomic considerations.

To summarise, scan parameters were chosen to minimise periodic motion artifact within the constraints allowed by using ECG-triggering and 4 signal averages with T1-weighted spin-echo sequences. The only method of reducing artifact with T2-weighted spin-echo imaging was to reduce peristaltic motion pharmacologically but, for logistical reasons, this was not very successful. Ghosting remains a problem with STIR, despite the theoretical considerations that suggest it should reduce the effects of motion on the image.

CT Scanning technique

The majority of CT scans reviewed in the studies were performed at GOS on a 60A Toshiba scanner using established scan protocols and sedation regimens where necessary. CT scans of the abdomen were performed from just above the diaphragm to the pelvis. The pelvis was included where a primary pelvic tumour, massive tumour extension or tumour recurrence (either local or nodal) were suspected. Scans performed at diagnosis were made before and after enhancement with a weight-related dose of an iodinated contrast agent (Iohexol 240). Enhancement was either with a single bolus injection preceding the scan or, particularly when good vascular enhancement was required, by an initial bolus injection followed by a continuous dynamic infusion during the scan was used. At follow up either non-enhanced only or enhanced only scans were performed.

CT scans were performed with 10mm contiguous slices. For logistical reasons none of the scans were personally supervised by the author and the same attention to quality and detail cannot be claimed as for the MR scans.
In a minority of cases, CT scans were from referring hospitals and in these cases a variety of scan protocols were used.

**Ultrasound scans**

All ultrasound scans included in the studies were performed at GOS on an Acuson scanner. Scans were performed by a number of operators (including radiographers and junior radiologists) but all were supervised by a consultant radiologist. Photographic copy of the scans were available for review. No Doppler facilities were available at the time of the studies.

**Scan assessment**

Details of scan review and diagnostic criteria for lymphadenopathy, local tumour extension, hepatic invasion etc. are given in the methodology section of each of the tumour groups investigated.

**Patient Preparation**

**Sedation**

Voluntary patient movement is a common cause of image degradation when scanning children. At high field strength, rapid gradient switching generates noise levels of 90dB (+/- 5dB). The noise may be frightening to an awake child and conversation with him/her is impossible. For successful body scanning, a child must remain immobile for up to 1-2 hours, and must lie completely still for periods of up to 15 minutes during data acquisition. Most young children find it difficult to keep still for any length of time, yet in an MR scanner the child must lie in a confined, enclosed space with restricted parental contact. This problem can be partly overcome by sedating children who are unable to cooperate. A number of different sedation regimens have been described for use in MR, most based on modifications of those already used in CT units. For children up to the ages of 3-7 years, chlora, in doses of 50-100 mg/kg, has been widely advocated (Smith, 1983, Cohen et al, 1986, Dietrich & Kangerloo,
1988), although Ringertz found pentobarbitone more effective (Ringertz et al, 1985). These studies deal with scanning at low field, where the noise generated is a background hum. Because of higher noise levels of a high field system, we found it necessary to adopt drug combinations producing heavier sedation. A comparison of 2 drug regimens and the final drug combination chosen is reported here.

**Patients and Methods**

Two sedation protocols were assessed. Initially, the protocol used for CT scanning at our institution was adopted for all patients irrespective of the type of scan (figure 2.5, Protocol 1). Patient age, the region scanned, drugs administered, the requirement for a supplement of intravenous diazepam (Diazemuls™) (a 'top-up'), and the total examination time were recorded. The quality and success of the examination was assessed and classified as optimal, suboptimal or 'abandoned' at the time of the scan by the supervising radiologist. An examination was considered optimal if motion artifact was confined to the involuntary movements of respiration, cardiac pulsation or bowel peristalsis. If voluntary movement significantly degraded images, and/or if the examination was curtailed because the patient woke up, the examination was classed as suboptimal. Scanning was 'abandoned' when movement produced non-diagnostic images.

Early experience suggested a low rate of success in obtaining satisfactory scans using sedation Protocol 1. A new protocol was therefore devised, (figure 2.5, Protocol 2), and its results compared with Protocol 1 (hence the protocols were sequential and not concurrent). The chi-squared test was used to analyse the statistical significance of the results.

Adverse affects (if any) were recorded at the time of the scan and then the nurse accompanying the child back to the ward was asked to report any late adverse effects thought attributable to sedation.

Children were not sedated when parents refused permission for sedation, when the child was considered old enough (ie over 10 years) and cooperative enough to tolerate the procedure, and when clinicians particularly wished that a younger, compliant child should be
examined without drugs. In these cases, whenever possible, the child was shown the scanner prior to the scan, was warned of the noise, and had a parent present during the scanning procedure. Parents were encouraged to hold the child's feet (hands are inaccessible), and to talk to the child between sequences.

Results

The quality of 375 MR studies was assessed. Comparison of the effects of Protocols 1 and 2 are shown in Table 2.1.

Sedation Protocol 1

Pethco

Thirty-six patients with a mean age of 21 months (range 5 weeks-5 years), were sedated with Pethco alone (a combination of pethidine 25 mg, promethazine 6.25 mg, chlorpromazine 6.25 mg in 1 ml). Optimal scans were obtained in only 66.7% of children scanned. An intravenous supplement of Diazemuls was required in 55% of children.

Droperidol and trimeprazine

Seventy-nine patients with a mean age of 6.2 years (range 10 weeks-17 years), were sedated with droperidol and trimeprazine. Optimal scans were obtained in 74.7% of patients. An intravenous supplement of Diazemuls was required in 44% of children.

Sedation Protocol 2

Pethco and triclofos

Seventy-nine patients, with a mean age of 9.5 months (range 1 week-28 months) were sedated with Pethco combined with triclofos. Optimal scans were obtained in 83.5% of patients scanned. An intravenous supplement of Diazemuls was required in 38% of children.

Trimeprazine and papaveretum

One hundred and twenty seven patients with a mean age of 6.0 years (range 6 months-15 years) were sedated with trimeprazine and papaveretum. Optimal scans were obtained in
85% of children scanned. An intravenous supplement of Diazemuls was required in 46% of children.

Since the age profiles are similar, the results of sedation with Pethco alone can be compared with Pethco and triclofos, and droperidol and trimeprazine can be compared with papaveretum and trimeprazine (Table 2.1). Compared with Pethco only, combination with triclofos increased the proportion of optimal examinations from 67% to 84%, and reduced the number of scans of less than optimal quality from 33% to 16% (0.05>p>0.02), despite an overall increase in examination time. Compared with droperidol and trimeprazine, papaveretum and trimeprazine increased the proportion of optimal scans from 75% to 85% and reduced the number of scans of less than optimal quality from 25% to 15% (0.05>p>0.02) despite increased scanning times.

Alternatively, the 2 protocols can be compared by age group. The results of each protocol in children a) under and b) over 5 years are shown in Table 2.2 and figures 2.6 & 2.7. Modifying the protocol improved the proportion of optimal scans from 71% to 83% for children under 5 years (0.01>p>0.05), and from 75.5% to 88% (0.01>p>0.05) in children over 5 years.

Patients receiving no sedation

Fifty-five children and young adults were scanned unsedated. The mean age for this group was 11.7 years, with an range of 4-20 years (Table 2.3). Intravenous diazepam was given to 3 children (5.5%), and the scans were optimal in each case. Scans had to be abandoned in 6 children aged 4,8,9,9,10 and 15 years.

Miscellaneous

From time to time a number of combinations of drugs other than those described above were used during the period of assessment, because of personal preferences of the prescribing clinician; for example papaveretum with hyoscine and trimeprazine alone.
However the numbers of patients in each of these groups is too small for meaningful comparison.

Unwanted effects

Two patients sedated with Pethco developed upper airway obstruction when laid supine within the scanner. Both children recovered when turned into the 'coma' position and a scan was not attempted. One child with Stage 4s neuroblastoma and extensive hepatic infiltration slept for a prolonged period (24 hours) after being sedated with Pethco and triclofos.

Discussion

The results of this comparison suggest that the drug regimen using heavier sedation significantly improve scan quality. However the 2 protocols were not randomised and ran sequentially and this potentially introduces a learning error favouring the second protocol. However scan techniques and unit staffing were well established at the time of the initiation of the comparison and it is unlikely that experience was a significant factor in improving scan quality.

The reported adverse effects were lower than expected and this may be related to the method of reporting. It is now recognised that sedation does reduce oxygen saturation in children and it would have been preferable to have monitored pO2 levels during and after the scan. At the time of the study this was not possible as a) there was no pulse oximeter compatible with high field scanners and b) there were insufficient oximeters available on the wards to routinely monitor these children.

The difference between sedation and general anaesthesia lies in the potential for patients to be roused by harmful, noxious stimuli. A sedated patient should be able to protect himself from the damaging effects of such stimuli, and should not require the full-time attention of an anaesthetist. In practice, it is difficult to draw such a clear distinction since sedation is designed to prevent arousal to mildly noxious stimuli. In the case of MR scanning
this includes the discomfort of lying still for prolonged periods, and the high noise levels. Since there is considerable individual variation in response to sedative drugs, it is difficult to avoid unwanted side effects in some patients if success is to be achieved in the majority.

The most serious unwanted effect is respiratory depression and, because of this, we tried to avoid the exclusive use of opioids. However, intramuscular opioids give very reliable sedation and allay apprehension so, when the protocol was modified, an injected opioid (papaveretum) was combined with an oral hypnotic in older children. An additional advantage of opioid drugs is that they minimise the distress of venepuncture if an intravenous supplement is necessary. In younger children, triclofos, which has little effect on respiration, was chosen in combination with Pethco (which is a respiratory depressant). Naloxone reverses the respiratory depressive action of narcotic analgesics and, as a precaution, is kept available at all times.

As with any sedation technique, care must be exercised in the choice of patient. Four groups of patients in whom sedation should be used with extreme caution (if at all) are those with:

1. Upper airway abnormalities causing obstruction, including obstructive sleep apnoea syndrome.
2. Abnormalities of the respiratory centre eg. mitochondrial cytopathies and brain stem tumours, or conditions causing desensitisation of the respiratory centre to carbon dioxide eg. chronic lung disease with raised carbon dioxide level.
3. Abnormalities of metabolism or excretion, eg. renal and hepatic dysfunction. This is of particular relevance to children with malignant disease. Hepatic infiltration, such as occurs with 4s neuroblastoma, may reduce the elimination of drugs metabolised by the liver and renal impairment may occur secondary to disease or its treatment. Normal neonates (ie children less than 45 weeks gestational age) are also included in this group as the pharmacokinetics of sedative drugs are extremely variable at this age.
4. Conditions in which a rise in carbon dioxide levels would be detrimental, in particular patients with raised intracranial pressure.
Modifying the sedation protocol has increased the proportion of children successfully scanned in our department. If sedation is inadequate, either the scan has to be abandoned or performed under general anaesthesia. This has cost and time implications, and general anaesthesia may be undesirable in a child undergoing further anaesthetics for other investigative procedures or surgery.

Because of the individual variation in response to sedative drugs, and because the doses used in these protocols are at the upper end of those which may be safely used, adequate monitoring of vital functions is essential.
Table 2.1: Comparison of Sedation Protocols 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Protocol 1</th>
<th>Protocol 2</th>
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</tr>
</thead>
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<td></td>
<td>Arm A</td>
<td>Arm A</td>
<td>Arm B</td>
<td>Arm B</td>
</tr>
<tr>
<td>Pethco</td>
<td>Pethco</td>
<td>Pethco +</td>
<td>Trimeprazine+</td>
<td>Trimeprazine+</td>
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<td>Droperidol</td>
<td>Papaveretum</td>
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<td>79</td>
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<td>6m-15y</td>
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</tr>
<tr>
<td>Head</td>
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<td>Scan quality</td>
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<td></td>
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<tr>
<td>Optimal</td>
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<td>66 (83.5)</td>
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<td>6 (7.6)</td>
<td>11 (13.9)</td>
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<tr>
<td>Aban</td>
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<td>9 (11.4)</td>
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<td>Scan time</td>
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</tr>
<tr>
<td>&lt;30</td>
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<td>4 (5.1)</td>
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<td>5 (13.8)</td>
<td>18 (22.8)</td>
<td>11 (13.9)</td>
<td>24 (18.9)</td>
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Key
Numbers in parentheses = percentages
w = weeks, m = months, y = years
Table 2.2: Comparison of Sedation Protocols 1 and 2 by age

<table>
<thead>
<tr>
<th></th>
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<th>Over 5 years</th>
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<td>Age range</td>
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<td></td>
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<tr>
<td>Head</td>
<td>49</td>
<td>79</td>
<td>25</td>
<td>53</td>
</tr>
<tr>
<td>Spine</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
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<td>7</td>
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<td>Scan quality</td>
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<tr>
<td>Optimal</td>
<td>50 (71.4)</td>
<td>101 (82.8)</td>
<td>34 (75.6)</td>
<td>73 (88)</td>
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<tr>
<td>Subopt</td>
<td>7 (10)</td>
<td>7 (5.7)</td>
<td>6 (13.3)</td>
<td>6 (7.2)</td>
</tr>
<tr>
<td>Aban</td>
<td>13 (18.6)</td>
<td>14 (11.5)</td>
<td>5 (11.1)</td>
<td>4 (4.8)</td>
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Key
Numbers in parentheses = percentages
w = weeks, m = months, y = years
Subopt = suboptimal scan
Aban = abandoned scan
Table 2.3: Patients scanned without sedation

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<td><strong>Region scanned</strong></td>
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<tr>
<td><strong>Head</strong></td>
<td>27 (49.1)</td>
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<tr>
<td><strong>Spine</strong></td>
<td>20 (36.4)</td>
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<tr>
<td><strong>Other</strong></td>
<td>8 (14.5)</td>
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<td><strong>Scan quality</strong></td>
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<tr>
<td><strong>Optimal</strong></td>
<td>38 (69.1)</td>
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<tr>
<td><strong>Subopt</strong></td>
<td>11 (20)</td>
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<tr>
<td><strong>Aban</strong></td>
<td>6 (10.9)</td>
</tr>
<tr>
<td><strong>Scan time (minutes)</strong></td>
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<td>&lt;30</td>
<td>2 (3.6)</td>
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<td>30-60</td>
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<td>61-90</td>
<td>12 (21.8)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>5 (9.1)</td>
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</table>

**Key**
Numbers in parentheses = percentages
y = years
Subopt = suboptimal scan
Aban = abandoned scan
Figure 2.1; 'Ghost' Artifact

Transverse section through the abdomen using a) STIR (TI/TR/TE=150/3000/40ms) and b) T2-weighted SE (TR/TE=3000/85ms) showing 'ghosting' artifact with both sequences. Although signal from fat has been successfully suppressed on the STIR images, high signal from the spleen and to a lesser extent from the liver continues to generate ghost images.
Figure 2.2; Effect of increasing the number of signal averages.

T1-weighted SE (TR/TE=40/15ms) images of a transverse section of the abdomen using 1, 2, 4 and 8 signal averages. With increased signal averages there is increased ghost separation displacing some off the image itself. Paradoxically, the increased SNR generated by increasing the number of averages has also increased the intensity of the ghosts. Overall the image quality is significantly better with 4 averages than 2 or 1.
Figure 2.3; Effect of cardiac triggering

T1-weighted SE images of a transverse section of the abdomen using untriggered (TR/TE=50/15ms) and ECG triggered (TR/TE=49/15ms) sequences. With the triggered sequence there is a reduction in respiratory and flow movement artifact with a concomitant improvement in image quality, anatomical definition and spatial resolution.
Figure 2.4; Effect of changing the repetition time

T1-weighted SE images of a transverse section of the abdomen with increasing repetition times (TR = 11, 30, 50, 70 ms and TE=15ms). With increasing TR values the separation of the 'ghosts' increases and they become displaced further from the image. Another marked effect of increasing the TR is the greatly improved SNR with the longer values. Overall there is an improvement in image quality as the TR increases.
### Figure 2.5: Sedation Protocols

**Protocol 1**

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 months</td>
<td></td>
<td>Feed</td>
</tr>
<tr>
<td>3 months - 8 years</td>
<td>&lt;15 kg</td>
<td>Pethco* 0.1 ml/kg IM</td>
</tr>
<tr>
<td></td>
<td>&gt;15 kg</td>
<td>Trimeprazine 3 mg/kg PO</td>
</tr>
<tr>
<td>&gt;8 years</td>
<td></td>
<td>Nothing or Trimeprazine 3 mg/kg PO +droperidol 0.7 mg/4 kg PO</td>
</tr>
</tbody>
</table>

Drugs administered 40-60 minutes before the scan
Plus diazepam (Diazemuls™), 0.5 mg/kg IV if necessary

**Protocol 2**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month - 2 years</td>
<td>Triclofos 50 mg/kg PO +Pethco* 0.06 ml/kg IM</td>
</tr>
<tr>
<td>2-5 years</td>
<td>Trimeprazine 3 mg/kg PO +papaveretum 250 µg/kg IM</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>Trimeprazine 3 mg/kg PO +papaveretum 400 µg/kg IM</td>
</tr>
</tbody>
</table>

Drugs administered 40-60 minutes before the scan
Plus diazepam (Diazemuls™), 0.2-0.4 mg/kg IV if necessary

* Pethidine 25 mg, Promethazine 6.25 mg, Chlorpromazine 6.25 mg in 1 ml
Figure 2.6: Scan quality using Sedation Protocol 1 compared with Sedation Protocol 2 in children under 5 years.
Figure 2.7: Scan quality using Sedation Protocol 1 compared with Sedation Protocol 2 in children over 5 years.
Chapter 3

Primary Malignant Hepatic Tumours
Introduction

Surgical resection is an important component of the treatment of primary malignant liver tumours in childhood (Clatworthy et al, 1974, Mahour et al, 1983, Giacomantonio et al, 1984). Hence a major role of imaging is to determine tumour resectability which depends on the segmental involvement of liver parenchyma, vascular involvement and the presence of extrahepatic disease. CT, ultrasound and angiography are established methods of assessing tumour resectability (Bartley et al, 1967, Korobkin et al, 1981, Amendola et al, 1984, LaBerge et al, 1984, Miller & Greenspan, 1985, Dachman et al, 1987). However a recent report has suggested that MR (in this study performed at low field), is the most accurate method of diagnosing intrahepatic tumours and predicting tumour resectability (Boechat et al, 1988).

Primary resection of liver tumours is associated with a high perioperative mortality due to haemorrhage (Exelby et al, 1975). In many centres, chemotherapy is now used in some cases to make 'inoperable' tumours resectable. MR appearances of tumours and assessment of resectability after chemotherapy have not been reported.

In this study, we prospectively examined 12 children referred with probable malignant hepatic tumours to examine the value of high field MR for tumour diagnosis and for determining tumour resectability and to observe the MR changes in patients undergoing chemotherapy.

Patients and Methods

Twelve consecutively-referred children with suspected malignant hepatic tumours were examined. Clinical details are shown in Table 3.1; patient 7 also had Beckwith-Wiedemann syndrome. The age range was 7 days-58 months (mean 22.1 months, median 15.5 months), and there were 6 girls. Diagnosis was histologically confirmed in all cases; there were 6 hepatoblastomas and 1 each of the following- hepatoma, embryonal sarcoma, epithelioid haemangio-endothelioma, rhabdomyosarcoma and malignant mesenchymoma. One child was found to have a benign juvenile haemangio-endothelioma.

Surgical details are shown in Table 3.2. Three children were treated by primary surgery; in 1 child the tumour was totally resected, in the second extensive haemorrhage from
the IVC and tumour bed permitted only partial tumour resection, and in the third child disease was found to be inoperable as all 4 segments of the liver were involved by tumour. Eight children were treated by primary chemotherapy and delayed surgery. Five of these children had complete tumour resection, 1 child had a partial resection (disease was found to be inoperable during the dissection), and in 2 children tumours were still inoperable at laparotomy. The remaining child developed pulmonary metastases during chemotherapy. Consequently resection was not attempted and only open biopsy performed.

All children had an abdominal ultrasound examination at diagnosis, and 10 had a CT scan performed at the time of the first MR study. Thirteen CT scans, with and without enhancement with intravenous iodinated contrast agents, were reviewed; 8 scans were performed at GOS and the remainder were from 2 referring hospitals both of which were experienced in the scanning of children with hepatic malignancy (King's College and The Royal Marsden Hospitals).

Twenty-three MR scans were performed; 8 patients had an MR scan at diagnosis and the remainder were examined after chemotherapy. Six patients (numbers 3,4,6,7,8 & 9) had more than 1 scan. Ten children were examined under sedation and 2 with general anaesthesia. Scans were performed using the protocols described in Chapter 2. T1-weighted spin-echo sequences with ECG triggering were performed in at least 2 planes in all cases. STIR sequences were obtained in all patients in at least 1 plane, and T2-weighted SE sequences in 3 children (4 examinations). Gradient echo sequences were obtained in 2 cases.

MR examinations were assessed by 2 radiologists (MHC &/or PF) and the CT scans by a third (CDM). Scans were then reviewed together (by MHC and CDM) and a consensus reached. Features assessed were the appearances and segmental distribution of tumour, presence of extrahepatic disease and visualisation and involvement of blood vessels. Lymph nodes were noted if either over 10 mm in their maximum diameter on the CT or MR scan, or of increased signal intensity on a T2-weighted image on the MR scan (ie signal intensity greater than muscle or liver, equivalent to that of the spleen although generally less than renal parenchyma).
Imaging findings were correlated with surgical/pathological data in 11 patients, and the MR appearances of tumour were correlated with the histological findings of resected tumours (8 patients). The delay between the MR scan and surgery ranged from 1 day- 4 months (mean 24 days, median 7 days). The delay was greater than 24 days in 2 patients (3 and 4 months); one of these children (patient 4) underwent a prolonged course of chemotherapy, developed pulmonary secondaries and had an open biopsy. The second child (patient 11) was born with a mesenchymal hamartoma. Her serum alpha feto protein (AFP) levels gradually rose to levels higher than normal for age and it is likely that either she had a congenital hepatoblastoma or had developed one. Because her clinical and radiological condition remained stable over a 2 year period, she received no chemotherapy and eventually underwent an exploratory laparotomy to assess a) resectability and b) whether liver transplantation was technically feasible.

**Results**

**Primary tumour**

The intrahepatic origin of tumour was clearly identified by both MR and CT in all cases. Ultrasound was predictive in 11/12 cases but failed to identify the intrahepatic origin of a very large tumour in 1 patient.

MR assessment of the segmental distribution of tumour was confirmed in all 11 patients undergoing surgery, whilst CT was incorrect in 2/8 cases. In 1 child, the left hepatic vein was not visualised hence tumour invading across the vein to involve both segments of the left lobe of the liver was not identified. In the second, tumour surrounding and invading the porta was inconspicuous on CT (yet easily seen by MR). MR, by contrast was accurate in both these cases (figures 6.1 & 6.2).

Most tumours (8/12), irrespective of histological type, were inhomogeneous. There were foci of long T1 and T2, corresponding to areas of low attenuation on CT scans, features suggesting cystic change/ necrosis. Four tumours showed foci of short T1; in 2 patients this feature was extensive and correlated histologically with haemorrhagic necrosis (figure 3.3).
However, no short T1 foci were seen in 1 tumour (patient 1) in which widespread necrosis and haemorrhage was noted by the histopathologists.

Four tumours- the 2 haemangio-endotheliomas, a treated hepatoma and 1 hepatoblastoma- were more homogeneous. The only benign tumour (patient 5) was indistinguishable from malignant tumours on MR or CT and was diagnosed as a hepatoblastoma by CT, MR and ultrasound (although later shown to have a normal serum AFP level). The centre of this tumour was very homogeneous on both CT and MR, of low attenuation on CT and high signal on MR (STIR images), features suggesting a fluid centre. However histologically this was the most dense, cellular part of the tumour. Two tumours had distinctive MR appearances; the rhabdomyosarcoma consisted of a botryoid mixed cystic and solid tumour extending through the biliary tree (figure 3.4) and the epithelioid haemangio-endothelial sarcoma appeared lobulated and homogeneous stretching and encasing intrahepatic vessels without invading them (figure 3.5).

Six patients had follow-up MR scans during chemotherapy, however changes in tumour signal characteristics were diverse. All tumours initially reduced in size, correlating with favourable clinical response to treatment. In 2 children, widespread short T1 foci became more confluent with chemotherapy. One of these children had 4 MR scans during chemotherapy (6 courses over 4.5 months) and initial T1 shortening was followed by T1 lengthening. Histological examination of the resected specimen showed extensive fibrosis and little residual viable tumour. Likewise, in a third child prolonged chemotherapy was also associated with a tendency to T1 lengthening. In the patient with a rhabdomyosarcoma, the cystic elements of the tumour resolved leaving solid residual tumour. One hepatoblastoma became very inconspicuous on T2-weighted SE imaging, and had a low intensity centre surrounded by a higher intensity rim on STIR (figure 3.6). Histologically the central region of low intensity correlated with extensive old haemorrhage and haemosiderin deposition in the centre of the tumour which was surrounded by a fibrotic capsule.

**Tumour resectability**

Eleven patients underwent surgical exploration. MR correctly predicted that tumour was resectable in 6 patients and unresectable in 4 but in 1 patient, a cystic, haemorrhagic
tumour (a hepatoblastoma) which was 'operable' on MR criteria (ie involving only 2 segments) was only partially resected at primary surgery because of haemorrhage from a tear in the IVC and from the tumour bed. CT incorrectly classified tumour as 'resectable' in the 2 patients in whom segmental distribution of tumour was underestimated (see above).

**Vascular involvement**

The IVC, porta hepatis, main branches of the portal vein and the hepatic veins were shown by MR in all 12 patients when patent. Portal vein involvement was diagnosed in 4 cases and was surgically confirmed in 2 (the other 2 tumours were not resected). Tumour was seen abutting the IVC in 3 patients and occluding it in 1 child; these findings were surgically confirmed in all 4 cases and were not seen by CT. The IVC was only seen on 3 CT scans, and the hepatic veins and portal veins on 4.

**Extrahepatic disease**

Extrahepatic periportal disease was seen on MR in 5 patients. In the patient with a rhabdomyosarcoma obvious tumour extended into the porta hepatis (figure 3.4). This was also seen on ultrasound and confirmed surgically. Abnormal periportal high signal was seen on STIR or T2-weighted SE images in 4 children due to viable tumour in 1 child, necrotic debris in 1 and inflammatory tissue in 1 child. In the fourth child, follow-up scans during pre-operative chemotherapy showed resolution of the periportal changes and no abnormality was found at surgery. Retroperitoneal or periportal lymph nodes of high signal on STIR sequences and up to 1.5 cm in size were seen in 3 patients. Only reactive changes (no tumour) were identified histologically in these 3 cases. Enlarged retroperitoneal lymph nodes were seen in 1 patient on CT and ultrasound, but were not confirmed surgically.

**Sequence comparison**

High quality T1-weighted SE images with excellent anatomical detail and little motion artifact were obtained in all patients. The T2-weighted SE images suffered from low SNR and ghosting artifact; STIR images were of higher SNR. Liver/tumour contrast was higher (figure 3.6), and abnormal lymph nodes and haemorrhagic fluid levels were more easily seen on the STIR images than T1-weighted SE images. Vascular detail was well shown by both STIR and T1-weighted SE images. Very few gradient-echo sequences were
performed in this series, but tumour/liver contrast was less (figure 3.6) and susceptibility effects also made lesions less conspicuous than on either T2-weighted spin echo or STIR images.

**Discussion**

Accurate assessment of the segmental involvement of liver tumours is essential in determining whether a) a mass is resectable and b) planning the type of resection. Tumours involving only 1 lobe can be treated by lobectomy, whereas involvement of more than 2 segments leaves trisegmentectomy or transplantation as the only options. In this study MR was 100% accurate (and more accurate than CT or US) in defining segmental involvement in the 11 surgically-explored patients, whether treated by primary or delayed surgery. These encouraging results could be attributed to a) high tumour/liver contrast enabling clear definition of tumour margins and b) the clear demonstration of intrahepatic vessels. Intrahepatic and major abdominal blood vessels were shown with remarkable consistency by MR in this study, confirming published data (Fisher at al, 1985, Mukai et al, 1987a ). This enabled definition of 1) the segmental anatomy of the liver, 2) the proximity of tumour to vessels and 3) vascular tumour invasion. Vascular involvement by tumour has surgical implications; disease was unresectable in 1 patient with IVC invasion and surgery was technically more difficult and considerably prolonged in 2 patients with tumour abutting the IVC. There has also been a single report of intraoperative death due to embolism of an IVC tumour thrombus which was not diagnosed preoperatively (Dorman et al, 1986).

Current MR is not capable of distinguishing, reliably, malignant from benign tumours (Boechat et al, 1989). In this study, the only benign tumour was thought to be a hepatoblastoma by all imaging modalities (a similar case was reported in Boechat's series). Two tumours, the rhabdomyosarcoma and epithelioid haemangio-endothelial sarcoma, had very distinctive MR features and with further experience it may become possible to ascribe specific histological diagnoses to these very rare tumours. Serum AFP concentration remains a useful guide to tumour type; a normal level is a strong indicator that an intrahepatic mass is not a hepatocellular malignancy (though it does not exclude a mesenchymal malignancy).
In some cases, signal characteristics of the tumour were helpful in mapping regions of necrosis, a feature which may be useful in monitoring tumour response to chemotherapy. However this observation was not as consistent as in Wilms' tumour (see chapter 5), and the absence of T1-shortening in the tumour does not exclude necrosis.

In this series, high signal in a periportal distribution was a sensitive but non-specific indicator of periportal abnormality and was seen with inflammatory tissue and with viable or necrotic tumour. Only reactive changes were seen histologically when groups of nodes showing high signal on MR were compared with nodes found in the same anatomical distribution at surgery. Hence extrahepatic abnormalities seen on MR must be interpreted with caution to prevent overstaging of resectable disease. CT failed to diagnose extrahepatic tumour in 1 patient, but there were no false positive diagnoses.

T1-weighted SE images provided excellent anatomical definition but the liver/lesion contrast was higher with either STIR or T2-weighted SE images. The quality of STIR images was superior to T2-weighted SE sequences, due mainly to higher SNR and less degradation by motion artifact. Signal intensity increases with increasing T1, T2 and proton density with STIR and where necessary further T2-weighting can be gained by prolonging the echo time. In some vascular/haemorrhagic tumours T2-weighting may be a disadvantage; in one patient imaged after chemotherapy, tumour was less clearly seen on T2-weighted SE images than by STIR possibly due to susceptibility effects of iron causing T2*-shortening and signal loss. Gradient-echo sequences showed lower lesion contrast than either STIR or T2-weighted SE images; in one patient reduced contrast may have been due to loss of signal caused by susceptibility effects occurring in haemorrhagic tumours (figure 3.6). However the numbers are small and more studies are needed.

In this series, only 1 child studied presented with tumour in a fibrotic liver and in this case the mass was clearly seen. However it is recognised that it is difficult to identify tumours in cirrhotic livers with multiple regenerating nodules (Matsui et al, 1989 & 1991). Recent experience in rats with ferrite particulate contrast agent suggests that this may help differentiate hyperplastic nodules (which show decreased signal intensity) from hepatocellular carcinoma (Kawamori et al, 1992).
Conclusions

Diagnosis

MR is accurate for the localization of liver tumours but is not tissue specific and is unable to differentiate benign from malignant masses.

Resectability (Staging)

MR was extremely accurate in predicting segmental involvement and thus resectability of hepatic tumours before or after chemotherapy. However it was unable to differentiate reactive from malignant involvement in periportal tissue or lymph nodes and care must be taken not to overstage disease.

Response to Chemotherapy

Change in size indicated tumour response to therapy. However there is no consistent relationship between tumour signal characteristics and tumour viability and tumour necrosis cannot be identified with certainty.

Overall, taken together, these findings support the use of MR as the primary imaging modality in the assessment of resectability of primary liver tumours.
Table 3.1; Clinical details

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at 1st MR scan</th>
<th>Chemo before 1st scan?</th>
<th>AFP</th>
<th>Histology</th>
</tr>
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<tbody>
<tr>
<td>1. RA</td>
<td>22m</td>
<td>Y</td>
<td>Raised</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>2. MB</td>
<td>7d</td>
<td>N</td>
<td>Raised</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>3. FB</td>
<td>53m</td>
<td>N</td>
<td>Normal</td>
<td>Embryonal sarcoma</td>
</tr>
<tr>
<td>4. AC</td>
<td>7m</td>
<td>Y</td>
<td>Raised</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>5. CC</td>
<td>3m</td>
<td>N</td>
<td>Normal</td>
<td>Juvenile Haemangioendothelioma</td>
</tr>
<tr>
<td>6. EG</td>
<td>38m</td>
<td>N</td>
<td>Normal</td>
<td>Epithelioid Haemangioendothelial sarcoma</td>
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<td>7. JH</td>
<td>28m</td>
<td>N</td>
<td>Normal</td>
<td>Rhabdomyosarcoma</td>
</tr>
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<td>8. SM</td>
<td>14m</td>
<td>N</td>
<td>Raised</td>
<td>Hepatoblastoma</td>
</tr>
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<td>9. JM</td>
<td>10m</td>
<td>N</td>
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<td>Hepatoblastoma</td>
</tr>
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<td>10. MN</td>
<td>58m</td>
<td>Y</td>
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<td>11. KO</td>
<td>22m</td>
<td>N</td>
<td>Raised</td>
<td>Hepatoblastoma in mesenchymal hamartoma</td>
</tr>
<tr>
<td>12. DW</td>
<td>10m</td>
<td>Y</td>
<td>Normal</td>
<td>Anaplastic mesenchymoma</td>
</tr>
</tbody>
</table>

**Key**

N = no chemotherapy given before first scan
Y = chemotherapy started before first scan

AFP = serum alpha fetoprotein concentration (levels given with reference to normal range for age)

d = days  m = months
<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>Prediction of Operability</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>1° chemotherapy + delayed surgery</td>
<td>'Operable'</td>
<td>Total resection</td>
</tr>
<tr>
<td>MB</td>
<td>1° surgery</td>
<td>'Operable'</td>
<td>Partial resection (haemorrhage)</td>
</tr>
<tr>
<td>FB</td>
<td>1° chemotherapy + delayed surgery</td>
<td>'Operable'</td>
<td>Total resection</td>
</tr>
<tr>
<td>AC</td>
<td>1° chemotherapy + biopsy</td>
<td>'Inoperable' (pulmonary 2°s)</td>
<td>Open biopsy</td>
</tr>
<tr>
<td>CC</td>
<td>1° surgery</td>
<td>'Operable'</td>
<td>Total resection</td>
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<td>EG</td>
<td>1° chemotherapy + delayed surgery</td>
<td>'Inoperable'</td>
<td>Partial resection</td>
</tr>
<tr>
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<td>DW</td>
<td>1° chemotherapy + delayed surgery</td>
<td>'Operable'</td>
<td>Total resection</td>
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</tbody>
</table>

**Key**

1° = primary
Figure 3.1; Segmental involvement of the liver by tumour

Transverse a) T1-weighted SE (TR/TE= 450/15 ms) and b) CT scan showing a hepatoblastoma in association with a mesenchymal hamartoma. Tumour is seen in the left side of the liver (arrowed, figures a & b). However the left hepatic vein could not be visualised on the CT scan even with contrast enhancement, so the segmental distribution of tumour could not be precisely described. On the MR scan, the left hepatic vein is easily seen (small arrow, figure a), confirming the involvement of the lateral segment of the left lobe. These findings were confirmed at laparotomy.
Figure 3.2; Peri-portal tumour infiltration

Transverse a) CT scan, b) T1-weighted SE (TR/TE = 450/15 ms) and c) STIR (TI/TR/TE = 150/3000/40 ms) through the upper abdomen of a child with a hepatoma treated with chemotherapy. No definite residual tumour could be seen on the CT scan. On the MR scans, tumour can be seen encasing the main portal vein and the proximal right portal vein. These findings were confirmed operatively and the tumour was unresectable.

a)
Figure 3.2 continued

b)

c)
Figure 3.3; Haemorrhagic necrosis within tumour

Coronal T1-weighted SE (TR/TE=450/15 ms) scan through a large hepatoblastoma. There is extensive high signal (short T1) within the tumour (arrowed) which correlated with haemorrhagic necrosis on histological examination. The tumour is abutting the IVC which is patent. At surgery there was dense adherence of the tumour to the IVC, but no invasion. Some collapse is seen in the right lung.
Figure 3.4; Biliary rhabdomyosarcoma

a) Transverse and b) coronal T1-weighted SE (TR/TE = 450/15 ms) scans through a biliary rhabdomyosarcoma. The tumour is extending along the biliary tract and has the typical characteristics of mixed cystic and solid elements. The tumour is involving the right branch of the portal vein and there is enlargement of the left branch, presumably due to increased flow.

a)
Figure 3.5; Epithelioid haemangio-endothelial sarcoma

a) Transverse and b) coronal T1-weighted SE (TR/TE= 450/15 ms) MR scans and CT scan c) with and d) without contrast enhancement. There is a multifocal solid tumour. The hepatic and portal veins are well shown on the MR scan and show that although the tumour is surrounding the vessels, the veins are neither invaded or compressed by the tumour. On CT the vessels are not seen (despite dynamic enhancement) and the tumour shows central enhancement of the tumour.
Figure 3.5 continued

c)

d)
Figure 3.6; Sequence comparison

A) Before chemotherapy

Transverse scans through a hepatoblastoma using a) T1-weighted SE, b) STIR, c) FLASh 10° and d) FISP 10° sequences. A large tumour is seen occupying the right lobe of the liver. Tumour/liver contrast is greatest with STIR and is poor with both gradient-echo sequences.
Figure 3.6 continued

c)

FLASH 10

FISP 10
Figure 3.6 continued

B) After chemotherapy (same patient)
Transverse scans after chemotherapy and immediately pre-operatively using e) contrast-enhanced CT, f) T1-weighted spin echo, g) T2-weighted SE and h) STIR sequences. The lesion is only poorly seen on the T2-weighted SE images and this is probably due to susceptibility effects caused by products of breakdown of a haemorrhagic tumour.
Chapter 4

a) Wilms' Tumour

b) MR studies of isolated tumour specimens
Part a

Introduction

The purpose of this study was to examine prospectively the value of high field MR, for the diagnosis, staging and assessment of response to chemotherapy in children with primary malignant renal tumours. One series reported (and performed at low field) has systematically compared MR with CT (Belt et al, 1986); other reports are anecdotal (Dietrich & Kangerloo, 1986b, Kangerloo et al, 1986). Belt's study suggested that MR was at least as accurate as, and possibly superior to, CT in the staging of Wilms' tumour. It has not been established whether lymph nodes involved by tumour may be distinguished on MR scans from those showing only reactive changes though it has been shown that reactive lymph nodes may be enlarged and of altered signal intensity (Belt et al, 1986).

In our institution primary surgery is used for 'operable' tumours but pre-operative chemotherapy is preferred when a tumour is considered 'inoperable', to reduce tumour bulk and lessen the risk of operative rupture and spillage (Lemerle et al, 1983). Hence 2 groups of children were examined 1) those having primary nephrectomy and 2) those treated by primary chemotherapy with delayed surgery. In the second group we were able to compare the MR appearances of chemotherapy-treated tumours with surgical/pathological findings.

Patients and Methods

We studied 20 consecutively-referred patients with primary renal tumours. Clinical details are summarised in Table 4.1. There were 6 males and the median age was 27 months (range 3 months to 10 years). Histological diagnosis was available in all cases and showed Wilms' tumour in 18 children (17 'favourable' histology and 1 'unfavourable'), clear cell sarcoma in 1 case, and probable rhabdoid tumour in a child with an associated cerebellar primitive neuroectodermal tumour (PNET). Three children with Wilms' tumours had associated nephroblastomatosis. Ten tumours were right sided and 7 were on the left; 4 of them had Stage I tumours at the time of diagnosis, 11 Stage III and 2 Stage IV. Three children had bilateral disease (Stage V). One additional child, who initially had Stage IV
disease diagnosed 6 years earlier, was referred for assessment of disease relapse in the renal
bed, contralateral kidney and abdominal scar.

Nine patients had primary tumour resection, 10 had surgery following
chemotherapy, and 1 child died during treatment but did not have a post-mortem. There was a
delay of 0 days-9 weeks (median 8.5 days) between the MR scan and surgery, although the
delay was 4 weeks or less in 13/19 patients. Currently, children having pre-operative
chemotherapy have a closed percutaneous tumour biopsy performed at diagnosis and are
staged on the basis of combined imaging and clinical evaluation.

All patients had US imaging on admission using a computed sonography unit
('Acuson'). CT was performed on a Toshiba TCT60A machine before and after intravenous
injection of iohexol as described in Chapter 2.

MR scans were all performed at our institution using sequences described in
Chapter 2. Sixteen children were sedated using the protocols discussed in Chapter 2; 3
children had general anaesthesia to enable CT and MR to be performed sequentially on a
single occasion, and one child had a GA because of inadequate sedation during a previous MR
scan. All children had ECG triggered T1-weighted spin-echo in at least 2 planes. STIR
sequences were performed on 26/30 occasions and T2-weighted SE sequences on 6/30.

Thirty MR scans were performed in 20 patients (see Table 4.2). The first MR scan
was performed at the time of diagnosis in 14 children and after chemotherapy was started in 6.
Follow-up scans were performed in 9 children following further treatment. Twenty-four CT
scans performed in 18 children were assessed; in each case a CT scan was performed at the
time of the initial MR scan. CT and MR were performed within 1 week of each other in all
cases, and in most cases within 2 days.

MR scans were initially viewed by 2 radiologists (MHC or JP) and the CT scans by
a third (CDM), without knowledge of each others' findings. Using criteria described below,
the observers looked specifically for the site and appearances of the primary tumour,
extension beyond the renal capsule, invasion of adjacent organs or the abdominal wall, the
presence of abnormal lymph nodes and tumour extension into the IVC and renal vein. In
19/20 patients, surgical findings could be correlated with imaging findings.
On the MR and CT scans, the primary tumour was examined for its site of origin, the signal and attenuation characteristics and the presence or absence of fluid levels. From the appearances of the primary tumour the observers tried to predict whether or not the tumour contained necrosis, calcification and haemorrhage and this was correlated with the histological findings. On the CT scan haemorrhage was considered to be present if focal areas of high attenuation (although lower than with calcification), with or without fluid levels were seen. Necrosis was identified as focal areas of low attenuation corresponding to fluid, seen with or without fluid levels. On the MR scan, calcification was identified as areas of signal drop-out. Haemorrhage was identified as areas of shortened T1 within the tumour sometimes associated with fluid levels.

Local hepatic invasion was difficult to assess in the presence of very large tumours as displacement of the liver had to be distinguished from true invasion. On both CT and MR invasion was scored as being present if tissue planes were obliterated, there was marked proximity between tumour and large intrahepatic blood vessels and where the residual mass of the liver parenchyma was reduced.

Results

Primary tumours

The renal origin of the tumour was correctly identified by MR in 19/20 cases and by enhanced CT in 17/18. In the remaining patient, examined after chemotherapy, a mass identified on both MR and CT was shown histologically to be nephroblastomatosis with no residual WT. In 3 patients, US failed to identify the renal nature of the tumour; in each of these cases a large intraabdominal mass was associated with large nodes and a diagnosis of neuroblastoma was considered more likely. The extent of the intrarenal tumour was easier to assess on MR than on unenhanced CT, but no better than on enhanced CT. In 4 patients, the margin between intrarenal tumour and normal residual renal tissue was more clearly defined on enhanced CT than on MR.

All tumours appeared heterogeneous on CT scans. Calcification was seen in 6 tumours (4 before chemotherapy), and haemorrhage in 3. Areas of low attenuation, due either
to necrosis or cyst formation, were seen on 18/24 scans. Distension of obstructed renal calyces was seen in 6 patients.

On MR, tumours appeared heterogeneous with mixed signal intensity on T1 and/or T2 weighted sequences on 24/30 scans. Focal high-signal regions of varying size were seen on short TR/short TE SE sequences in 11 tumours examined before and 12 after chemotherapy. In 3 patients, areas of mixed-signal with fluid levels correlated histologically with 'blood lakes' (figure 4.1). These were most obvious on STIR or long TR/long TE sequences. Cystic changes were seen in 4 tumours examined before and 8 after chemotherapy. Fibrous septae were seen in 16 cases, best visualised on STIR. Calyceal distension was seen in 9 patients.

Nine patients, 5 of whom had also been examined before starting chemotherapy, had more than 1 scan. The changes seen in the primary tumour after chemotherapy by MR, with corresponding histological findings are summarised in Table 4.3. Tumour size shrinkage occurred in all cases, with the exception of the child with recurrent disease, whose tumour did not respond to chemotherapy. Tumour size was well shown on CT and MR, but more clearly on MR due to the multiplanar capability. On MR 5/9 tumours became more heterogeneous with treatment, 3 became more cystic (figure 4.2) and 1 tumour became more, and then less cystic. In 4 patients, high signal on short TR/short TE SE sequences became more extensive with treatment. Correlation of MR appearances of tumours with histological findings showed that foci of shortened T1 (seen before or after chemotherapy), correlated with regions of haemorrhage, necrosis, or both (figure 4.3).

Nephroblastomatosis could not be distinguished from residual tumour in any of the 3 cases examined on either the CT or MR scan. On MR, the appearances of nephroblastomatosis included discrete nodules and areas of disorganised tissue with loss of cortico-medullary differentiation, in large kidneys (figure 4.4). Neither CT nor MR identified a 1cm peritoneal nodule of tumour found at laparotomy lying lateral to the kidney in 1 patient.

Liver involvement

No hepatic metastases were identified on US, CT or MR scan, or found at laparotomy in any patient. A comparison of the MR, CT and surgical/pathological findings is
shown in Table 4.4. MR and CT agreed on the presence (5 scans), absence (12 scans) and equivocal nature (2 scans) of hepatic invasion by tumour in 19/24 paired scans (figure 4.5). Of the remaining 5 scans (4 patients), MR correctly identified tumour invasion in one child and absence of invasion in another (delay between MR scanning and surgery 0 and 8 days respectively). In the other 2 patients, the liver appeared invaded on CT and the findings were equivocal or negative on MR scans performed only after chemotherapy (delay between MR scanning and surgery 1 and 43 days); in both cases the liver was found to be adherent to the tumour at surgery, but there was no histological evidence of invasion.

Of 14 patients examined by MR at the time of diagnosis, correlation with surgical/histopathological findings showed 10 true negatives and 2 true positives. Two patients were found to have tumours adherent to, but not invading the liver at delayed surgery. MR had scored liver invasion as positive in 1 case and equivocal in the second. Histopathological correlation was available in 5/6 patients examined by MR only after chemotherapy. There were 2 true negatives and 1 true positive; the other 2 children, scored as negative or equivocal on MR, had adherent but not infiltrated livers. Assessment of the initial MR scan predicted liver involvement more accurately than scans performed after chemotherapy, and MR correctly predicted the absence of tumour infiltration in all 8 patients undergoing 1° nephrectomy.

Extracapsular spread

Macroscopic extracapsular spread of tumour was present in 4 patients, and microscopic spread in another 4. MR correctly identified macroscopic invasion in 3 cases (figure 4.6) and CT in 2; neither modality identified the cases of microscopic infiltration.

Lymph node involvement

Comparison of CT, MR and surgical/histological findings are shown in Table 4.5. In this series all children with clear-cut lymph node enlargement on CT at the time of diagnosis received pre-operative chemotherapy, hence histological confirmation of untreated, enlarged nodes was not available. Enlarged nodes (>1.5cm and up to 4 cm in size) were seen
in 4 patients on MR and in 3 on CT. MR also showed abnormal internal architecture in these
nodes, similar to the 1° tumour and best seen on STIR (figure 4.7). After chemotherapy, the
nodes reduced in size but remained enlarged in 2 patients (2.5 and 1.5 cm maximum
diameters) and viable tumour was found in both cases. In the other 2 patients, the nodes
returned to less than 1.5cm in size and no residual tumour was found.

Lymph nodes of less than 1.5cm in diameter but of abnormally high signal were
found in 9 patients on MR. Histological examination of nodes found in the distribution seen
on the MR scan showed that only reactive changes were present.

Vascular involvement

Vascular architecture was seen more clearly on MR than CT scans in all cases.
Tumour involvement of the IVC was correctly diagnosed in 2 patients by MR and CT.
Extrarenal renal vein infiltration without extension into the IVC (3 patients) was not shown on
either the CT or MR scan. Tumour infiltration of a large intrarenal renal vein, not apparent on
the 'in vivo' scan, was seen on the scan of a resected specimen. In one patient, a flow void was
present around an IVC thrombus, and the signal characteristics of the thrombus were identical
with those of the primary tumour (figure 4.8). These features suggested that 1) the thrombus
was not invading the wall of the IVC, and 2) it consisted of malignant cells rather than
extending thrombus. Both findings were confirmed at primary nephrectomy.

Discussion

In this series, MR clearly highlighted the intrarenal nature of the primary tumour.
Primary tumours were typically heterogeneous on MR and calyceal distension was frequently
seen and may be helpful in identifying a renal origin. In 4 patients, the boundary between
normal kidney and tumour was best shown on enhanced CT. This may be of clinical
relevance in the few patients in whom conservative surgery is contemplated. However, in
future, in cases such as this additional information may be obtained from MR by the use of
gadolinium chelates.
Nephroblastomatosis remains a diagnostic problem and in this study it was not possible to differentiate residual from concurrent nephroblastomatosis. As CT, ultrasound and urography are neither specific or sensitive for this diagnosis (Fembach et al, 1988) biopsy remains the only reliable diagnostic technique.

There was great diversity in the signal characteristics of WT both before and after chemotherapy. In particular, foci of high signal on T1-weighted SE imaging were frequently seen; in 4 patients these foci became more extensive during chemotherapy. Belt et al (1986), reported the presence of both short and prolonged T1 in primary tumours in his series; he concluded that the former represented areas of haemorrhage, and the latter areas of necrosis. In our series, these regions always identified non-viable tumour and careful correlation of MR appearances and histological examination showed conclusively that regions of shortened T1 could be due to haemorrhage, pure necrosis or haemorrhagic-necrosis. The mechanism by which these changes cause T1 shortening is open to speculation. T1-shortening has been shown to occur in mice after whole body irradiation (Bakker & Vriend, 1983). Possible factors include the effect of tumour lysis, which might alter free-water binding or generate paramagnetic substances. Paramagnetic iron may contribute to such an effect. Another possible contributing mechanism is damage to vascular endothelium with subsequent microhaemorrhage, an effect observed in WT after chemotherapy (Guarda et al, 1984).

The IVC was confidently seen on MR in all cases, and displacement and invasion was shown with great clarity however the single case of renal vein invasion was not identified. This study suggests that MR is a reliable technique for identifying tumour invasion of the IVC but not necessarily for smaller vessels. The signal characteristics of IVC thrombus found on MR distinguish organised from tumour thrombus and may help predict whether or not the thrombus is free-floating.

The accuracy of MR in determining lymph node involvement by tumour at presentation cannot be fully assessed in this series as all patients with gross node abnormalities on CT at diagnosis underwent preoperative chemotherapy without initial node biopsy. However lymph node involvement was correctly assessed in all patients undergoing primary resection, and both patients with (proven) tumour involvement of lymph nodes after
chemotherapy were correctly identified. Frequently, small nodes (<2.5 cm) of abnormally high signal on STIR or T2-weighted SE imaging, were seen on MR, but no viable tumour was ever found in these. In this series, as in others (Belt et al., 1986), marginal node enlargement was not a good indicator of tumour involvement. Fortunately, MR can assess lymph node size, signal intensity and homogeneity of internal structure. In 4 patients, gross node enlargement was associated with abnormal signal and structure, such that the signal characteristics of lymph nodes appeared similar to the primary tumour. Following chemotherapy, 2/4 (50%) of these patients showed residual tumour in nodes. The numbers are small but these findings suggest that MR may be an accurate method of identifying involved nodes. However further studies, correlating MR findings with pretreatment histological examination of nodes, are necessary to validate this contention.

Liver infiltration and macroscopic extracapsular tumour spread was accurately identified by MR in most cases. All patients thought to have had liver involvement at diagnosis received preoperative chemotherapy. MR correctly identified both patients with histologically invaded livers, and correctly excluded invasion in all patients undergoing primary nephrectomy. It was less successful at predicting tumour adherence to the liver, without invasion. It is unknown whether tumour adherence after chemotherapy indicates an inflammatory response or treated infiltration. As no laparotomy was performed at the outset in patients undergoing pre-operative chemotherapy, we are unable to assess the sensitivity or specificity of MR in the detection of liver invasion by tumour.

The relationship of masses to adjacent organs and major blood vessels are crucial considerations when determining the correct treatment for a child with an abdominal tumour. Images with the best anatomical detail are therefore needed. In this study, T1-weighted SE images had minimal motion artifact with high spatial resolution and SNR when using ECG triggering and 4 signal averages. Vascular and soft-tissue anatomy were therefore very clearly shown. T2-weighted SE images, with 1 signal average, were consistently disappointing due to motion artifact and low SNR. STIR images were helpful in highlighting lymph node abnormalities and abnormalities of structure within the primary tumour and involved nodes. Because both the tumour and normal renal parenchyma are of high signal on T2-weighted SE
and STIR images, the role of these sequences in showing determining the intrarenal extent of
these tumours is limited. 'Dynamic' gadolinium enhancement combined with fat-saturation (as
has been used in adult renal tumours [Semelka et al, 1991]) of T1-weighted images may be
helpful in more clearly defining tumour boundaries. Further study is needed.

Conclusions

Diagnosis

MR reliably assessed the site of the primary tumour which is the most useful
diagnostic feature for Wilms' tumour, and showed dilated calyces in a minority of cases. The
tumour renal boundary was shown better by CT than MR in a minority of patients, however
this may be an important feature for cases where conservative surgery is being contemplated.

Staging

MR accurately showed liver involvement in most patients but was unable to clearly identify those with adherent as opposed to invasive tumours. The issue of lymph node involvement requires further clarification. Tumour involvement of the IVC was consistently seen with great clarity and reliability by MR.

Response to chemotherapy

Following chemotherapy MR was able to show a decrease in the size of all responding tumours and cystic change in a minority. Because it delineates areas of non-viable tumour (either haemorrhagic and/or necrotic) MR may have a role in monitoring the effects of pre-operative chemotherapy. MR was unable to clearly differentiate residual tumour from concurrent nephroblastomatosis.

Some issues (such as the identification of involved lymph nodes and liver involvement) remains unresolved. The proposed UKCCSG Wilms' tumour study 3 (UKW3),
in which 'operable' tumours will be randomised to primary nephrectomy or primary chemotherapy followed by surgery (± radiotherapy for Stage 3 disease) may provide the opportunity to validate these findings in larger numbers.
Table 4.1: Clinical Details

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at 1st MR scan (m)</th>
<th>Site of renal 1°</th>
<th>Disease Stage at diagnosis</th>
<th>Histology</th>
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<tbody>
<tr>
<td>SB</td>
<td>F</td>
<td>42</td>
<td>Rt</td>
<td>III</td>
<td>UH</td>
</tr>
<tr>
<td>RB</td>
<td>M</td>
<td>8</td>
<td>Lt</td>
<td>I</td>
<td>FH</td>
</tr>
<tr>
<td>HB</td>
<td>F</td>
<td>29</td>
<td>Lt</td>
<td>III</td>
<td>FH</td>
</tr>
<tr>
<td>LC</td>
<td>M</td>
<td>21</td>
<td>Bilateral</td>
<td>V</td>
<td>FH + N’osis</td>
</tr>
<tr>
<td>MC</td>
<td>F</td>
<td>120</td>
<td>Rt</td>
<td>III</td>
<td>FH</td>
</tr>
<tr>
<td>SC</td>
<td>F</td>
<td>20</td>
<td>Bilateral</td>
<td>V</td>
<td>FH + N’osis</td>
</tr>
<tr>
<td>GDo</td>
<td>F</td>
<td>39</td>
<td>Rt</td>
<td>III</td>
<td>FH</td>
</tr>
<tr>
<td>GDy</td>
<td>F</td>
<td>64</td>
<td>Rt</td>
<td>III</td>
<td>Clear cell sarcoma</td>
</tr>
<tr>
<td>KG</td>
<td>F</td>
<td>116</td>
<td>Rt</td>
<td>III</td>
<td>FH</td>
</tr>
<tr>
<td>RH</td>
<td>M</td>
<td>25</td>
<td>Rt</td>
<td>III</td>
<td>FH</td>
</tr>
<tr>
<td>LL</td>
<td>F</td>
<td>25</td>
<td>Lt</td>
<td>III</td>
<td>FH</td>
</tr>
<tr>
<td>JM</td>
<td>F</td>
<td>48</td>
<td>Bilateral</td>
<td>V</td>
<td>FH + N’osis</td>
</tr>
<tr>
<td>MM</td>
<td>M</td>
<td>11</td>
<td>Lt</td>
<td>III</td>
<td>? RTK</td>
</tr>
<tr>
<td>EM</td>
<td>F</td>
<td>4</td>
<td>Rt</td>
<td>I</td>
<td>FH</td>
</tr>
<tr>
<td>OR</td>
<td>M</td>
<td>49</td>
<td>Lt</td>
<td>I</td>
<td>FH</td>
</tr>
<tr>
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<td>F</td>
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<td>III</td>
<td>FH</td>
</tr>
<tr>
<td>JTa</td>
<td>F</td>
<td>97</td>
<td>Lt</td>
<td>IV, relapsed</td>
<td>FH</td>
</tr>
<tr>
<td>ST</td>
<td>F</td>
<td>8</td>
<td>Lt</td>
<td>I</td>
<td>FH</td>
</tr>
<tr>
<td>JTi</td>
<td>M</td>
<td>33</td>
<td>Rt</td>
<td>IV</td>
<td>FH</td>
</tr>
</tbody>
</table>

Key
FH = Favourable histology Wilms' tumour  UH = Unfavourable histology Wilms' tumour
N’osis = Nephroblastomatosis           RTK = rhabdoid tumour of kidney
Table 4.2: MR scans

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>MR scans performed</th>
<th>Number of scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Pre-treatment only</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Pre-treatment + x1 follow-up</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>Pre-treatment + x2 follow-up</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>x1 follow-up only</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>x2 follow-up only</td>
<td>8</td>
</tr>
</tbody>
</table>

Total=20 patients  Total=30 scans
Table 4.3: MR appearances of chemotherapy-induced changes in the primary tumour (n=9)

<table>
<thead>
<tr>
<th>Patient /scan</th>
<th>Chemotherapy (no. of courses)</th>
<th>MR appearances of T\textdegree tumour</th>
<th>Histological findings</th>
<th>MR to surgery</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>3/12.3</td>
<td>Inhomogeneous, solid + cystic, shortened T1 peripherally</td>
<td>Cystic, haemorrhagic-necrosis, anaplasia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>5/16.3</td>
<td>Smaller, increased areas of shortened T1</td>
<td></td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>0</td>
<td>Multiple masses, Solid, septated, 1 nodule with shortened T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>7/24</td>
<td>All masses reduced in size, signal unchanged</td>
<td>Multiple biopsies, nephroblastomatosis only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5a</td>
<td>0</td>
<td>Areas shortened T1 with fluid levels cystic, septae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5b</td>
<td>1/2</td>
<td>Increased areas of T1 shortening, more cystic, smaller mass</td>
<td>Haemorrhagic tumour, foci of necrotic-cystic degeneration. WT</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>7a</td>
<td>0</td>
<td>Inhomogeneous, solid small foci shortened T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7b</td>
<td>4/9</td>
<td>Smaller mass, more cystic, inhomogeneous. Increased foci of T1 shortening</td>
<td>Encysted haemorrhage, small foci necrosis, haemosiderin, WT</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>9a</td>
<td>3/6.6</td>
<td>Large, well-defined rim of shortened T1 around central region of longer T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9b</td>
<td>7/24</td>
<td>Marked shortening of T1 in central region, mass smaller</td>
<td>Solid central mass all necrotic, peripheral haemosiderin and fibrosis. No viable tumour</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Table 4.3 continued;

<table>
<thead>
<tr>
<th>Patient /scan</th>
<th>Chemotherapy (no. of courses over no. weeks)</th>
<th>MR appearances of 1° tumour</th>
<th>Histological findings</th>
<th>MR to surgery interval (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>0</td>
<td>Multiple masses, homogeneous, solid Little normal tissue</td>
<td>Multiple biopsies, 50% nephroblastomatosis 50% WT</td>
<td>11</td>
</tr>
<tr>
<td>12b</td>
<td>7/12.4</td>
<td>All masses reduced in size, no shortened T1 minor cystic changes</td>
<td>Rt nephrectomy, single tumour with haemorrhagic-necrosis, WT. Extensive nephroblastomatosis</td>
<td>156</td>
</tr>
<tr>
<td>16a</td>
<td>0</td>
<td>Inhomogeneous, solid extensive foci T1 shortening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16b</td>
<td>4/10.3</td>
<td>Cystic, T1 shortening unchanged, mass smaller</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16c</td>
<td>7/22.3</td>
<td>No cystic foci, smaller mass, T1 lengthened</td>
<td>Partly necrotic solid tumour, haemosiderin Viable WT</td>
<td>47</td>
</tr>
<tr>
<td>18a</td>
<td>multiple (&gt;30) (recurrent disease)</td>
<td>Homogeneous, solid no short T1</td>
<td>Biopsy, WT</td>
<td>46</td>
</tr>
<tr>
<td>18b</td>
<td>+radiotherapy</td>
<td>Mass larger, more inhomogeneous</td>
<td>Infiltrating mass surgically, no biopsy taken</td>
<td>36</td>
</tr>
<tr>
<td>20a</td>
<td>0</td>
<td>Solid mass, small cystic foci, solitary focus T1 shortening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20b</td>
<td>9/22.3</td>
<td>Mass smaller, cystic small focus persistent short T1</td>
<td>Large foci of cystic-necrosis, haemosiderin little residual WT</td>
<td>69</td>
</tr>
</tbody>
</table>
Table 4.4: Assessment of liver invasion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Chemotherapy?</th>
<th>MR scan</th>
<th>CT scan</th>
<th>Surgical Findings</th>
<th>Histological Findings</th>
<th>MR to surgery interval (d)</th>
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<tbody>
<tr>
<td>a</td>
<td>+C</td>
<td>-</td>
<td>-</td>
<td>- (D)</td>
<td>No invasion</td>
<td>1</td>
</tr>
<tr>
<td>b</td>
<td>+C</td>
<td>-</td>
<td>0</td>
<td>- (D)</td>
<td>No invasion</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>-C</td>
<td>-</td>
<td>-</td>
<td>- (P)</td>
<td>No invasion</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>-C</td>
<td>-</td>
<td>-</td>
<td>- (P)</td>
<td>No invasion</td>
<td>2</td>
</tr>
<tr>
<td>4a</td>
<td>-C</td>
<td>-</td>
<td>-</td>
<td>- (D)</td>
<td>Invaded</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>+C</td>
<td>-</td>
<td>-</td>
<td>- (D)</td>
<td>Invaded</td>
<td>40</td>
</tr>
<tr>
<td>5a</td>
<td>-C</td>
<td>+</td>
<td>+</td>
<td>+ (D)</td>
<td>Invaded</td>
<td>26</td>
</tr>
<tr>
<td>5b</td>
<td>+C</td>
<td>+</td>
<td>0</td>
<td>+ (D)</td>
<td>Invaded</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+C</td>
<td>-</td>
<td>-</td>
<td>- (D)</td>
<td>Invaded</td>
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</tr>
<tr>
<td>7a</td>
<td>-C</td>
<td>+</td>
<td>+</td>
<td>+ (D)</td>
<td>Invaded</td>
<td>48</td>
</tr>
<tr>
<td>7b</td>
<td>+C</td>
<td>+</td>
<td>-</td>
<td>+ (D)</td>
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<td>8</td>
<td>-C</td>
<td>-</td>
<td>-</td>
<td>- (P)</td>
<td>No invasion</td>
<td>0</td>
</tr>
<tr>
<td>9a</td>
<td>+C</td>
<td>-</td>
<td>+</td>
<td>Adh (D)</td>
<td>No invasion</td>
<td>1</td>
</tr>
<tr>
<td>9b</td>
<td>+C</td>
<td>-</td>
<td>?</td>
<td>Adh (D)</td>
<td>No invasion</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>+C</td>
<td>?</td>
<td>+</td>
<td>Adh (D)</td>
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</tr>
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<td>- (P)</td>
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<tr>
<td>12a</td>
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<td>-</td>
<td>-</td>
<td>- (P)</td>
<td>No invasion</td>
<td>11</td>
</tr>
<tr>
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**Key**

**CT and MR scan**

- = No invasion  
+ = Invaded  
? = possibly invaded (equivocal)  
0 = no scan performed

**Chemotherapy**

-C= pre-chemotherapy scan  
+C= post-chemotherapy scan

**Surgery**

P = primary resection  
D = delayed surgery  
adh = tumour adherent to liver
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**Key for table, see over**
### Key for Table 4.5

- C = pre-chemotherapy scan
+ C = post-chemotherapy scan

<table>
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<td>0= normal</td>
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<td>1= Normal size, abnormal signal nodes</td>
<td>1= enlarged (&gt;1.5cm) nodes</td>
</tr>
<tr>
<td>2= Enlarged (&gt;1.5cm), abnormal signal nodes</td>
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<tr>
<td>3= Enlarged, abnormal signal and architecture nodes</td>
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**Surgery**

- = no nodes found
+ = nodes present
P = primary resection
D = delayed surgery

**Histology**

RC = reactive changes
Figure 4.1; Haemorrhagic fluid levels in Wilms' Tumour

Transverse a)T2-weighted SE (TR/TE=3000/88ms) MR scan and b) CT scan of a large haemorrhagic Wilms' Tumour showing multiple fluid levels throughout the tumour.
Figure 4.2; Cystic changes within tumours after treatment with chemotherapy

T1-weighted SE (TR/TE=450/15ms) images a) before (coronal) and b) after (transverse) treatment with chemotherapy. The tumour has decreased in size and has developed multicystic areas (arrowed). (Note the aortic displacement on the earlier scan.)
Figure 4.3; Tumour heterogeneity- areas of shortened T1

Transverse T1-weighted SE (TR/TE=450/15ms) in a tumour which showed marked signal hyperintensity (short T1) in the centre of the mass after treatment with chemotherapy.
Figure 4.4; Residual nephroblastomatosis following chemotherapy for Stage V Wilms' tumours

Transverse a) T1-weighted SE (TR/TE=450/15ms) MR scan and b) unenhanced and c) enhanced CT scans. There is marked loss in the corticomedullary differentiation in the lower poles of both kidneys on the MR scan. Calcified, non-enhancing areas are seen bilaterally in the kidneys on the CT scan. These areas all corresponded with residual nephroblastomatosis; no tumour was found at surgery in either kidney.

a)
Figure 4.4 continued

b)

c)
Figure 4.5; Hepatic invasion

Transverse a) T1-weighted SE (TR/TE=450/15ms) MR scan and b) CT scan at diagnosis and c) T1-weighted SE MR scan after chemotherapy. The huge renal tumour mass is displacing the liver. The liver/tumour border appears poorly defined (arrowed) and the mass is seen closely related to the right portal vein suggesting invasion. After treatment the tumour/liver tissue boundaries remain poorly defined. At surgery the liver was partially resected and invasion was confirmed histologically.

a)

b)
Figure 4.5 continued

c)
Figure 4.6; Macroscopic extracapsular spread

Transverse T1-weighted SE (TR/TE=450/15ms) MR scans in 2 patients who had surgically confirmed macroscopic spread of tumour through the renal capsule to involve the perinephric fat (arrowed).

a)

b)
Figure 4.7: Lymphadenopathy

Transverse a) T1-weighted (TR/TE=450/15ms) SE, b) STIR (TI/TR/TE= 150/3000/40ms) and c) T2-weighted SE (TR/TE=3000/88ms) scans through a large Wilms' tumour with massive retroperitoneal adenopathy. The involved lymph nodes have similar signal characteristics to the primary tumour as seen by a small region of high signal on the T1 image (arrowed) and by the fibrous septae seen on the T2-weighted and STIR images. Repeat scanning [d) STIR ] after chemotherapy showed a marked decrease in the size of the lymph nodes but they still remain enlarged and of high signal (curved arrow). Histologically these nodes showed reactive changes only at delayed nephrectomy. Comparison of the STIR and T2 images shows that the SNR and vascular detail (eg definition of the right renal vein) is greater with the STIR images.
Figure 4.7 continued

c)

--- Image of c) ---

--- Image of d) ---

--- Image of d) ---
Figure 4.8; Tumour invasion of the IVC

a) Coronal T1-weighted SE (TR/TE=450/15ms) MR scan and b) transverse CT scan of a tumour thrombus invading the right renal vein and IVC. On the MR scan the thrombus has the same signal characteristics as the primary tumour suggesting that it consists of tumour and is not an organising thrombus. The thrombus is extending into the right atrium and impinging on the tricuspid valve. A flow void (arrowed) is seen around the thrombus suggesting that it is free floating. These findings were confirmed at surgery.

a) 

b)
Part b

A pictorial essay comparing the MR appearances with the histological findings of resected specimens in Wilms' Tumour.

Introduction

The MR appearances of Wilms' tumours are very heterogeneous; multiple foci with short and long T1 relaxation times, septae and cystic areas are frequently seen. Interpretation of these appearances can only be made with confidence by comparing MR appearances with pathological findings. Patient movement, respiratory and flow motion artifact degrades the spatial resolution of images acquired 'in vivo'. Spatial resolution can be improved by scanning resected tumours and this permits more detailed comparison of the MR appearances with macroscopic and microscopic findings.

Methods

As part of the previous study, the resected specimens of 6 patients (patients 3, 5, 8, 9, 14 and 17) were scanned within 10 minutes of excision, before autolysis occurs. Scans were performed as though in the coronal or sagittal plane using T1-weighted SE (TR=500ms, TE=15ms), and STIR (TI=150ms, TR=3000ms, TE=40ms) or T2-weighted SE (TR=3000ms, TE=88ms) sequences when time allowed. In 5/6 cases, the fresh specimen was immediately sliced in corresponding planes, and in 1 case, the tumour was fixed before slicing. For each slice, 1 cm blocks of tissue were taken from regions of interest seen on the corresponding MR scan. Multiple sections made from the blocks were histologically examined and a 'histological map' of the specimen was constructed. Time constraints imposed because of the need to prepare the tumours for histopathological and cytogenetic examination precluded measurement of relaxation times.
Results

Patient 3

Figure 4.9 a and c; (Photographs) Coronal sections through the kidney (R) and renal tumour (T).

Figure 4.9 b and d; T1-weighted SE MR images of slices corresponding to a) and b) respectively.

Figure 4.9 e; T2-weighted SE image through tumour.

A thin rim of residual renal parenchyma surrounds a large central, predominantly viable tumour (figures a & c). This is seen on the MR scan as a central mass of T1-relaxation approximately equivalent to that of normal renal tissue (figures b & d). Obstructed calyces (C), lined with transitional epithelium, are present in the upper pole of the kidney. A tumour nodule is protruding into 1 calyx ((arrowed, figure a); identical appearances are seen on the MR scan (arrowed, figure b).

A 3x1 cm focus of haemorrhage (curved arrow, figure c) is present in the lower part of the tumour. This is seen as an area of shortened T1 on the SE sequence (curved arrow, figure d). A further area of short T1, but of low signal on T2 imaging (arrowed, figure e), corresponded with a focus of necrotic and partially -necrotic tumour admixed with fresh haemorrhage.
Figure 4.9

a)

b)
Figure 4.9 continued
c)

d)
Figure 4.9 continued
e)
Patient 5

Figure 4.10a; (Photograph) Sagittal section through kidney (K), renal tumour (T) and adjacent section of liver (L).

Figure 4.10b and c; Corresponding MR images using b) T1-weighted SE and c) STIR sequences.

A large tumour is present arising from the upper pole of the right kidney. Within the tumour, there is a well-demarcated central region of necrosis, which is seen as an area of shortened T1 on the T1-weighted SE sequence (large arrows, figures a & b). Surrounding this necrotic centre is a region of viable tumour (V) which is of longer T1 than either residual normal kidney or liver. A multi-cystic area seen on the MR images (curved arrows, figures a and b), corresponds with a focus of necrotic-cystic degeneration. A 2x2.5 cm focus of recent haemorrhage is seen as an area of intermediate T1 on the MR scan (short arrows, figures a & b). In this patient, viable tumour was invading liver parenchyma. On the MR scan, there is extremely close proximity between intrahepatic vessels and the leading edge of the tumour, suggesting tumour invasion.
Figure 4.10 continued

c)
**Patient 8**

**Figure 4.11 a;** (Photograph) Coronal section through renal tumour (T). A tumour thrombus (I) is attached which was removed from the right renal vein and the IVC. Sectioned following fixation.

**Figure 4.11 b and c;** Coronal MR images corresponding macroscopic section, using (b) T1-weighted SE and (c) STIR sequences.

The renal tumour is entirely replacing normal renal parenchyma, and is seen as tissue of intermediate T1-relaxation on the MR image. Close correlation of histology and MR features is not possible in this specimen as fixation distorted fine anatomical structure.

Macroscopically the tumour was lobulated (in an alveolar pattern), with fibrous septae seen between the lobules. This structure is reflected in the MR images. An area of cystic degeneration, seen macroscopically in 1 lobule (arrowed, figure a), correlates with a more heterogeneous MR appearance and within this there are patchy areas of longer T1 which are of higher signal than the bulk of the tumour on STIR (arrowed, figures b & c).

Similarity of the signal characteristics of the thrombus and the renal tumour suggest the thrombus consists of viable tumour. Histologically, viable clear cell sarcoma was present in the tumour and thrombus; no significant degree of haemorrhage or necrosis was present.
Figure 4.11

a)
Figure 4.11 continued
b)
Patient 9

Figure 4.12 a; (Photograph) Coronal section through kidney (R) and upper pole tumour (A & B).

Figure 4.12 b and c; Corresponding T1-weighted SE MR image, scanned (b) 'in vivo' 4 months, and (c) 1 day before resection.

A large tumour mass occupies the upper pole of the kidney. Macroscopically this was heterogeneous (compare regions A and B, figure a), although microscopically both were identical, consisting of non-haemorrhagic necrosis. No viable tumour was present. The tumour is surrounded by a chronic inflammatory pseudocapsule. After 3 courses of chemotherapy (figure b), the tumour showed peripheral T1-shortening. After a further 4 courses, this effect had proceeded centrally (figure c). Close anatomical correlation exists between necrotic tumour demonstrated histologically and the region of shortened T1 seen on the MR scan performed immediately before resection. Hence the changes of the tumour appearance on the MR scan with chemotherapy may reflect peripheral necrosis preceding central necrosis.
Figure 4.12
a)
Figure 4.12 continued

b)

c)
Patient 14

Figure 4.13 a; (Photograph) Coronal section through renal tumour.

Figure 4.13 b and c; Corresponding coronal (b) T1-weighted SE and (c) STIR images through the tumour.

The entire kidney has been replaced by tumour. The lobulated structure of the tumour is well seen on the STIR sequence. The lobules are separated by strands of tissue of low signal intensity on STIR which correspond to strands of fibrous connective tissue. There is a central region of short T1 (arrowed, figure b), which histologically corresponds with necrotic tumour (arrowed, figure a). Most of the tumour mass consisted of viable tumour.
Figure 4.13
a)
Figure 4.13 continued

b)
Patient 17

Figure 4.14 a; (Photograph) Coronal section through a renal tumour (T). A residual rim of the lower pole of the kidney (R) remains.

Figure 4.14 b & c; MR images corresponding to figure a, using (b) T1-weighted SE and (c) STIR sequences.

Most of the kidney is replaced by a bosselated, lobulated tumour (T). No significant necrosis was found but several cystic spaces (C), with a fibrous lining, were present within the tumour. Corresponding regions on the MR scan were of long T1, and of high signal on STIR sequences (arrowed, figures b & c). One tumour lobule (L) appeared macroscopically more heterogeneous than its neighbours and histologically showed multiple small haemorrhagic foci and fibrous strands. On the MR scan, the lobule was also more heterogeneous, showing punctate areas of longer T1 within the mass (small arrow, figure b).
Figure 4.14
a)
Discussion

Anatomical correlation between the macroscopic specimens and MR images was extremely close in all cases. Some features of the specimens, if recognised 'in vivo', may be helpful in determining the renal origin of the tumour. Four tumours had a lobulated structure which led to the formation of triangular spaces within the tumour. In 3/4 cases these were shown to contain fluid, fibrous or necrotic tissue. These triangular shapes, which have not been seen in neuroblastoma or hepatic tumours examined at this institution, were also clearly and easily seen on 'in vivo' scans. Dilated calyces, due to obstruction of residual kidney by tumour, are also helpful in indicating the renal origin of the tumour.

All documented areas of necrosis within the specimens examined, whether haemorrhagic or non-haemorrhagic, were of short T1 on T1-weighted SE images. This contrasts with the experience of Belt et al (1986) who concluded that necrotic tumour was of long T1. The appearances on STIR and T2-weighted SE images were more variable, and were either of higher signal than viable tumour or of mixed signal intensity. The single documented focus of extensively haemorrhagic necrosis was of lower signal intensity on STIR than other foci of non-haemorrhagic necrosis, possibly reflecting haemosiderin deposition.

In conclusion, some imaging features may be helpful in specifying the renal origin of tumours. Foci of short T1 may indicate regions of tumour necrosis, which is of potential benefit in monitoring tumour response to treatment. Indicators, such as this, of good tumour response may be helpful in planning the timing of delayed surgery and, possibly, planning conservative, kidney-preserving operations (as is proposed in UKW3).
Table 4.6; Summary of the MR appearances of necrosis in resected specimens

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<tr>
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<td>High signal rim</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>of lower signal</td>
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</tr>
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<td>8</td>
<td>No necrosis</td>
<td>(no short T1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>foci present)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Necrosis</td>
<td>Short T1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Necrosis</td>
<td>Short T1</td>
<td>Very high signal</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(&gt; viable tumour)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>No necrosis</td>
<td>(no short T1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>foci present)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 5

Neuroblastoma
Introduction

The purpose of this prospective study was to examine the value of high field MR, in the diagnosis, staging and assessment of response to chemotherapy, in children with neuroblastoma. Earlier studies focussed on neuroblastoma were performed at low field and surgical/pathological correlation was not stringent (Cohen et al, 1984 & 1986, Fletcher et al, 1985, Dietrich & Kangerloo, 1986a, Dietrich et al, 1987). In this study we prospectively investigated a consecutive group of 20 children with neuroblastoma. MR and CT scan appearances were compared in most cases, and with surgical and pathological findings where available.

Patients and methods

The clinical details are summarised in Table 5.1. Twenty children, aged 6 days to 9 years 9 months, (mean 30 months, median 19.5 months), 10 of them girls, in whom the diagnosis of neuroblastoma was either established or under consideration, were examined. Sixteen patients had primary tumours in the abdomen, 3 in the posterior mediastinum, and 1 child had a thoraco-abdominal paravertebral tumour. The diagnosis was confirmed by established criteria in all children (Brodeur et al, 1988).

The International Neuroblastoma Staging System (INSS, Brodeur et al, 1988) is essentially a surgical method of staging. In our institution, Stages 1 and 2A disease are treated by primary excision, and Stages 2B-4 with combination chemotherapy and delayed surgical excision. Most patients had advanced disease, the stage being determined on the basis of clinical, pathological, biochemical and imaging findings. One child had Stage 1 disease, 4 had Stage 3, 12 had Stage 4 and 2 had Stage 4s; one child died before being fully staged, but was at least Stage 3.

All MR examinations were performed on the Siemens 'Magnetom' 1.5 Tesla scanner. Seventeen children were examined under sedation, using the protocols discussed in
Chapter 2, but 3 patients required general anaesthesia to enable CT and MR studies to be performed sequentially on a single occasion. All children had ECG and respiratory monitoring during the MR scan. T1-weighted spin-echo (SE) sequences with ECG triggering were obtained in at least 2 planes in all patients, T2-weighted SE sequences were obtained in 7 studies and short tau inversion recovery (STIR) sequences on 20 occasions using parameters described in Chapter 2. Twenty-seven MR studies were performed; the initial examination was performed in 13 children at the time of diagnosis and in the remainder following treatment. Repeat examinations were performed in 7 children following further therapy.

Twenty-three CT examinations, performed in 19 children, were available for comparison with MR studies; a scan could not be performed in 1 child due to inadequate sedation. CT scans were performed at the time of the initial MR scan in these 19 patients and repeated following further treatment in 4 children. Nineteen CT scans were performed at our institution on a 60A Toshiba scanner under sedation using the scan protocol described in Chapter 2, and the remainder were from referring hospitals. Scans were performed before and after enhancement with intravenous contrast on 19 occasions (dynamic enhancement was successful in 14 patients), and 4 scans were unenhanced.

MR scans were initially reported and scored by 2 radiologists (MAHC and/or JPF) and the CT scans by a third (CDM). Neither group knew the other's findings. Finally, all scans were reviewed by 2 radiologists together (MAHC and CDM) and a consensus reached. Using criteria described below, the observers looked specifically for the site and appearance of the primary tumour, the presence and distribution of lymphadenopathy, extent of local tumour invasion, intrathecal tumour extension and the presence of any bone, marrow or other metastases.

MR and CT scans were examined for the presence, site and appearance of a primary tumour. This included an assessment of the presence of calcification within the mass (observed as areas of signal drop-out on the MR scans and of high density on the CT scans) was recorded. Other features of the primary tumour, such as the heterogeneity, signal characteristics and attenuation pattern (in MR and CT scan respectively) and the presence of fluid levels were recorded.
MR and CT scans were assessed for the presence of any abnormal lymphnodes identified separately from the primary mass. Lymphnodes were classified as abnormal on the MR scans if of greater than 15mm in their maximum diameter and/or of abnormal signal intensity on a T2-weighted sequence (either STIR or a T2-weighted spin-echo). Signal was considered to be abnormal if lymphnodes appeared of higher signal than muscle or liver, of signal equivalent to the spleen although usually less bright than the kidneys. Other abnormal features such as evidence of calcification, heterogeneous signal characteristics and the presence of fluid levels were recorded. On CT scans, lymphnodes were classified as abnormal if greater than 15mm in their maximum diameter, showed areas of calcification or of necrosis/haemorrhage. Necrosis was implied when focal areas of low attenuation equivalent to fluid with or without fluid levels were seen and haemorrhage by patchy regions of high density with or without fluid levels (although of lower attenuation than calcification).

Scans were examined for evidence of local tumour invasion into adjacent soft tissues such as the psoas muscles or diaphragmatic crura, and also into the spinal canal. On CT or MR scans, invasion was considered to be present if the normal soft tissue planes were obliterated coupled with evidence of tumour extension into the adjacent soft tissue. This was assessed on the single available transverse plane on the CT scan. On the MR scans, this was assessed using the T1-weighted images acquired in 2 planes as potentially this was thought likely to help improve differentiation of soft tissue displacement from true invasion.

On the MR scan bone was examined for evidence of marrow deposits. These were seen as either multiple, small focal areas of abnormal signal within a vertebral body or abnormal signal from whole vertebral bodies, of low signal on the T1-weighted images and high signal on the T2-weighted sequences (figure 5.1). Cortical destruction and vertebral collapse were noted on the CT scans. Cortical destruction in the absence of vertebral collapse is theoretically difficult to detect on MR, although it usually occurs in the presence of concurrent marrow disease or soft tissue mass which may be obvious.

Tumour was surgically resected in 12 patients (interval from diagnosis to surgery of 6.7 months mean, 6 months median, range 2.5-20 months; interval from MR scan to surgery of 5 weeks mean, 4 weeks median, range 2 days-17 weeks). One child aged 16 days
was examined at post mortem and 1 child with a thoracic mass had a formal exploratory thoracotomy and biopsy. Two children had an open biopsy performed at the time of diagnosis; following chemotherapy no residual mass was seen on imaging in 1 of these and further surgery was not performed. In the second the child died at home following 2 courses of chemotherapy. Surgical data was not available in the remaining 4 children; and in 3 cases surgical intervention was not indicated for either therapeutic or diagnostic purposes. Of these, 1 child with Stage 4S disease and bilateral adrenal tumours was electively treated with chemotherapy only, 2 patients with paraspinal disease had no significant residual mass after chemotherapy and in the remaining patient (who presented with metastatic disease) there was no obvious primary tumour at diagnosis or after treatment.

Results

Primary tumour

The primary site of tumour could be seen on the MR scan in 19/20 cases. In the remaining child, who presented with metastatic disease, a 1cm retrocrural mass which may have represented either the primary tumour or an enlarged lymph node was seen on the MR scan. CT showed 17/19 primary tumours; in one case where the tumour was not seen the quality of the CT scan was marred by movement artifact and in the second the 1cm retrocrural mass identified on the MR scan could not be seen. In one case in a child with bilateral suprarenal primary tumours, MR scans in the coronal plane helped show the both tumours more clearly than CT (figure 5.2). Calcification was seen in 15 primary tumours on CT. On MR, calcification was inferred by areas of signal drop-out within the tumour in only 4 patients; in each case, the tumour was densely calcified on CT (figure 5.3).

Seven of 13 untreated primary tumours appeared as homogeneous, soft tissue masses with signal intensity slightly lower than liver parenchyma on T1-weighted SE imaging. Four tumours showed marked patchy short-T1 elements, in one case associated with fluid levels thought likely to represent intra-tumoral haemorrhage (figure 5.4). Following chemotherapy, 5/11 (45%) tumours showed a low intensity rim surrounding a central region of T1 shortening on T1-weighted images (figure 5.5).
Histological examination of biopsies in 3 patients showed neuroblastoma in 2 and ganglioneuroma/ganglioneuroblastoma in the third. Histological examination of 12 excised specimens (all after chemotherapy) showed undifferentiated neuroblastoma in 5, maturing neuroblasts in 2, mixed poorly- and well-differentiated neuroblasts in 3, complete necrosis in 1 and ganglioneuroblastoma in 1 patient. There was no correlation between the MR and histological appearances (see Table 5.2). There was a delay between the MR scan and surgery (range= 2 days- 4 months, median= 21 days) but even when tumours excised within 3 weeks of the MR scan (n=7) are considered, no correlation is found.

Nodal disease

MR assessment of the extent of nodal disease correlated well with operative findings in 11 of 13 patients undergoing operation or autopsy. Histopathological examination confirmed the presence of involved nodes in 9 patients and uninvolved nodes in 4. MR failed to detect a pulmonary hilar node measuring 0.3x1x0.3 cm in a child with thoracic neuroblastoma and a 1x1x2 cm renal hilar node adjacent to the right adrenal primary tumour in a second case. Histologically, resected nodes consisted of either poorly- or well-differentiated tumour, but in 1 case enlarged nodes showed only reactive changes. In 2 patients, groups of nodes involved by tumour were interspersed with enlarged nodes showing reactive changes. MR was unable to distinguish lymph nodes involved by tumour from those showing only reactive changes, either by size or signal characteristics. (figure 5.6)

Paired MR and CT scans were available on 23 occasions in 19 patients (Table 5.3). On 13 occasions (10 patients), MR and CT showed the same extent of nodal disease and 6 of these had surgery. Surgery confirmed the scan findings in 4/6 but in 2 cases (see above) small involved nodes were missed by both modalities.

On 5 scans (5 patients) MR showed more extensive disease than seen on CT and this was confirmed surgically in all cases. In some cases the additional nodal disease was fairly minor, such as the identification of renal hilar nodes in addition to paraaortic nodes, but in one case (patient 1) extensive small nodes seen in a paraaortic distribution on the MR scan
were not apparent on an high quality enhanced CT scan performed 11 days earlier where poor tissue contrast was due to a paucity of retroperitoneal fat.

In 4 cases, CT was unable to distinguish a mass of contiguous nodes from the primary tumour, which could be separated on MR scan, and in a further child neither CT nor MR could distinguish between primary tumour and adjacent nodes. These 5 scans were performed pre-chemotherapy, when extremely large masses were present. Surgery after chemotherapy indicated that the masses were made up of separate nodal and primary components in 3 patients. The other 2 children died without having surgery.

Local tumour extension

Assessment of local tumour extension into adjacent structures by MR and CT was equivalent on 20/23 scans, and discrepant in 3. In 2 patients, CT suggested involvement of the diaphragmatic crura, and, in a third, liver infiltration. In these 3 patients surgery agreed with the MR findings and the CT abnormalities were not confirmed.

MR correctly assessed tumour extension in 11/13 cases in whom surgical or PM data were available but underestimated tumour extension in the other 2 cases. In one, MR correctly identified invasion of a diaphragmatic crus, but did not identify invasion of psoas, and in the second, MR missed crural involvement. In neither case did CT identify tumour extension missed by MR.

Intrathecal and/or intercostal invasion was observed in 5 patients. MR and enhanced-CT each identified tumour involvement in these patients, but the extent of invasion and the effect on the spinal cord were seen with much greater detail and clarity with MR (figure 5.7). In one child with thoracic disease, small tongues of residual tumour in 3 intercostal spaces identified on the MR scan following chemotherapy correlated precisely with the surgical findings (figure 5.8).

Bone marrow involvement

Ten patients had marrow involvement at presentation, as assessed by marrow aspirates, trephines and/or radionucleide examination. Of these, signal from the vertebral
marrow was abnormal on MR in 6 patients and normal in 4. One child with paravertebral
disease and direct invasion of the spinal canal associated with a collapsed vertebra had normal
iliac marrow aspirates and trephines and died before radionucleide studies could be
performed. On MR several non-contiguous vertebrae showed abnormal signal, highly
suggestive of secondary deposits. CT confirmed the presence of cortical bone destruction of
the collapsed vertebra in this child.

Vascular involvement

The frequency with which vessels were seen by abdominal MR and by enhanced
CT is compared in Table 5.4. When vessels were identified on both CT and MR, there was
good agreement on the degree of vascular displacement and encasement. However, as vessels
were seen more often on MR than CT, the distribution of disease in relationship to the
vasculature could be defined more frequently and clearly on the MR scan. The improved
definition of the tumour/vessel relationship was especially clearly seen with intrathoracic
disease (figure 5.9).

Staging

Table 5.5 summarises disease staging in patients examined at presentation.
Disease stage is compared with the findings of initial MR scans (13 cases) and CT scans (12
cases), and with surgical/histological examination. With Stages 2B-4, surgery is delayed until
after a course of chemotherapy, and does not accurately reflect the extent of local disease at
diagnosis.

MR and CT staging of local disease was in agreement in 10/12 patients and
discrepant in 2. A retrocrural mass was missed by CT in one case (see above), and MR
showed more extensive node involvement than CT in the second, but neither of these children
had surgery. In 3 patients, MR also showed vertebral marrow abnormalities not seen on CT,
upstaging the disease to Stage 4 (but all of these had abnormal bone trephines and aspirates).
With MR findings alone, disease was correctly staged in 9 of 12 patients (75%) fully staged at diagnosis. Understaging in the remainder was due to undetected marrow involvement and/or other distant metastases.

Response to Chemotherapy

Six children were scanned both at diagnosis and following a course of chemotherapy; 4/6 of these tumours were excised. All tumours decreased in size with treatment. The changes in appearances were diverse, ranging from no signal alteration to complex signal changes. There was no consistent correlation between the MR and histological appearances in this limited number of cases.

Sequence choice

High quality MR images were obtained in all patients. The anatomical relationships of disease was most clearly shown on the T1-weighted SE images and in most cases, the extent of the tumour could be identified by combining images in axial and coronal planes. Sagittal images were helpful for assessing liver involvement by large right sided tumours, and involvement of the spinal canal by paraspinal tumours. STIR images were useful for the demonstration of retroperitoneal nodes of abnormally high intensity. Internal tumour structures, such as septae were more easily seen on STIR than on T1- or T2-weighted SE sequences. T2-weighted SE sequences were performed in only 7 patients as problems with this sequence due to low SNR (due to the long echo time), and marked respiratory and peristaltic motion artifact were identified early in the series. Clear tumour boundaries could not be identified, and retroperitoneal structures were frequently obscured. On T2-weighted SE and STIR sequences, tumour was high signal equivalent to renal parenchyma, precluding reliable distinction of tumour/kidney boundaries. Vascular architecture was more clearly shown on STIR than T2-weighted SE sequences (figure 5.10).
Discussion

Certain CT features, such as the site of origin, presence of calcification, and elevation and encasement of the great vessels have been found useful for distinguishing neuroblastoma from Wilms' Tumour (Peretz & Lam, 1985). However none of these characteristics are specific and tumours of renal origin cannot always be distinguished with certainty (Rosenfield et al, 1988). Previous MR studies (Dietrich et al, 1987) have shown that clear definition of the site of origin of tumour is helpful in identifying tumour type. In our study, the primary tumour and its extra-renal site of origin could be defined in all cases, but no features of tumour signal were specific for neuroblastoma. Tumour response to chemotherapy was examined in only 6 patients. In these cases, changes in MR appearance did not correlate with histopathological appearances and persistence of viable tumour could not be predicted by the MR scan.

Stage of disease at presentation is the most important single prognostic variable for neuroblastoma (Evans et al, 1987). Precise staging is therefore of great clinical relevance, guiding the choice of therapy and indicating prognosis. In this study we have compared MR with CT and have validated our observations surgically and pathologically in a higher proportion of patients than in previously reported series. When assessing local disease, MR was at least as good as CT for identifying primary tumours, lymph node involvement, intradural tumour extension and the relationship between tumour and major arteries and the IVC. Although MR occasionally underestimated local tumour extension, CT was unable to identify this additional disease and in no case was tumour stage affected. No systematic attempt was made to examine non-abdominal metastatic disease in this study but vertebral marrow abnormalities were shown incidentally in 7 patients.

Local disease was staged higher by MR than CT in 2 of 12 patients examined at the time of diagnosis. However, marrow involvement, demonstrated by marrow aspirate or trephines, radionucleide scans and MR was also present in each of these cases, identifying Stage 4 disease irrespective of the local tumour extent. Hence there was little overall impact of MR on defining stage in this study. However MR findings could change (assigned) tumour staging if patients thought by other imaging techniques to have Stage 1 or 2 disease, were
shown by MR to have contralateral disease (Stage 3). In this case, inappropriate early surgery might be avoided. Although MR accurately staged disease in 75% of patients staged at diagnosis when used as a single investigation, other staging modalities are still necessary to assess metastatic disease. Radionuclide studies, such as Tc-99mMDP and 123 or 131I mIBG scans, are able to survey the entire body, a task not currently possible using MR in the time available when scanning sedated children.

Operability is affected by the degree of tumour invasion of adjacent tissues, and by the physical characteristics of the tumour. CT is successful in predicting tumour resectability in up to 90% of cases (Golding et al, 1984, Boechat et al, 1985). However in our study, MR was more reliable than CT for showing blood vessels particularly with intrathoracic disease and did not require contrast and this made assessment of vascular involvement easier. Vascular visualisation by CT was adequate when a dynamically-enhanced scan was successfully performed, but, restricted venous access and the small needles used in young children often precludes this type of imaging. Intra thecal disease was also shown more clearly by MR than CT and without the use of contrast. Overall, the more complete description of tumour extent, invasion and vascular involvement is potentially useful to surgeons in helping predict operative findings, such as the presence of residual intercostal/intradural disease.

However, MR is not perfect. Tumour diagnosis was not specific for neuroblastoma, and MR greatly underestimated the frequency of calcification, a useful diagnostic feature of neuroblastoma. Following chemotherapy, the degree of tumour viability and necrosis of either the primary tumour or of lymph nodes could not be predicted, reflecting MR experience with Wilms' tumour (Belt et al, 1986).

Precise anatomical detail is necessary for accurate staging and for planning the appropriate timing of surgery. High field MR generates images high in SNR, enabling improved spatial resolution. In our study, images with minimal motion artifact, high spatial resolution and great anatomical detail were achieved by the use of ECG triggered T1-weighted SE sequences. T2-weighted SE images were frequently non-diagnostic due to low SNR and marked motion artifact. Although signal averaging may partly compensate for these
deficiencies, it is time-consuming. STIR images, which add contrast based on proton density, T1 and T2, and have high SNR, were diagnostically superior to T2 images in the small numbers compared here. Further T2-weighting to the STIR image can be achieved by extending the echo time (at the expense of some signal loss), and with optimised inversion pulses, the slice gap can be reduced to 40% without further significant loss of signal.

Conclusions

Diagnosis

MR is a reliable method for showing the site of the primary tumour and as good as CT. However calcification within the tumour is only infrequently seen and hence the technique is less specific for tumour diagnosis than CT.

Staging

MR is an accurate method for staging local disease. Overall disease staging was only incorrect in cases where distant metastases were present. MR was better than CT for showing the extent of nodal disease and its relationship to blood vessels, and showed intrathecal tumour involvement more clearly. However, when coupled with bone marrow assessment by aspiration and trephine biopsy, MR and CT were equally good for staging disease in this study.

Response to Chemotherapy

MR clearly showed the changes in size and distribution of tumour in response to chemotherapy, but the appearances were not specific for viable as compared with non-viable tumour.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at 1st scan</th>
<th>Site of primary</th>
<th>Surgical correlation</th>
<th>Disease Stage at Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>KB</td>
<td>F</td>
<td>25m</td>
<td>L adrenal</td>
<td>Y</td>
<td>4</td>
</tr>
<tr>
<td>HB</td>
<td>M</td>
<td>8m</td>
<td>Lt posterior mediastinum</td>
<td>N</td>
<td>3</td>
</tr>
<tr>
<td>BC</td>
<td>F</td>
<td>51m</td>
<td>Lt adrenal (resected)</td>
<td>Y</td>
<td>4</td>
</tr>
<tr>
<td>JD</td>
<td>M</td>
<td>23m</td>
<td>Lt adrenal</td>
<td>Y</td>
<td>4</td>
</tr>
<tr>
<td>JG</td>
<td>F</td>
<td>19m</td>
<td>Lt adrenal</td>
<td>Y</td>
<td>4</td>
</tr>
<tr>
<td>RH</td>
<td>M</td>
<td>7w</td>
<td>Rt adrenal</td>
<td>Y</td>
<td>1</td>
</tr>
<tr>
<td>SH</td>
<td>F</td>
<td>7m</td>
<td>Rt thoraco-abdominal</td>
<td>N (Bx)</td>
<td>3</td>
</tr>
<tr>
<td>HK</td>
<td>F</td>
<td>9m</td>
<td>Lt adrenal</td>
<td>N</td>
<td>4</td>
</tr>
<tr>
<td>MK</td>
<td>M</td>
<td>78m</td>
<td>Lt adrenal</td>
<td>Y</td>
<td>4</td>
</tr>
<tr>
<td>GK</td>
<td>F</td>
<td>6d</td>
<td>Lt adrenal</td>
<td>Y (Post Mortem)</td>
<td>4S</td>
</tr>
<tr>
<td>ML</td>
<td>M</td>
<td>29m</td>
<td>Rt adrenal</td>
<td>Y</td>
<td>3</td>
</tr>
<tr>
<td>TL</td>
<td>M</td>
<td>18m</td>
<td>Unknown</td>
<td>N</td>
<td>4</td>
</tr>
<tr>
<td>JM</td>
<td>M</td>
<td>20m</td>
<td>Lt adrenal</td>
<td>Y</td>
<td>4</td>
</tr>
<tr>
<td>CM</td>
<td>F</td>
<td>7w</td>
<td>Bilateral adrenal</td>
<td>N</td>
<td>4S</td>
</tr>
<tr>
<td>PS</td>
<td>M</td>
<td>117m</td>
<td>Lt adrenal</td>
<td>Y</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 5.1 continued

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at 1st scan</th>
<th>Site of primary</th>
<th>Surgical correlation</th>
<th>Disease Stage at Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. JS</td>
<td>F</td>
<td>51m</td>
<td>Posterior mediastinum</td>
<td>Thoracotomy + Bx</td>
<td>3(IS)</td>
</tr>
<tr>
<td>17. GS</td>
<td>F</td>
<td>64m</td>
<td>Rt adrenal</td>
<td>N (Bx)</td>
<td>4</td>
</tr>
<tr>
<td>18. LRT</td>
<td>F</td>
<td>11m</td>
<td>Rt posterior mediastinum</td>
<td>Y</td>
<td>3</td>
</tr>
<tr>
<td>19. PT</td>
<td>M</td>
<td>56m</td>
<td>Rt adrenal</td>
<td>Y</td>
<td>4</td>
</tr>
<tr>
<td>20. MW</td>
<td>M</td>
<td>16m</td>
<td>Rt adrenal</td>
<td>Y</td>
<td>4</td>
</tr>
</tbody>
</table>

Key

Age; d= days, w= weeks, m= months

(Bx) = surgical biopsy obtained

IS = incompletely staged, no radionucleide scan performed
Table 5.2: Correlation of histological appearances with MR imaging of excised primary tumours (n=12)

<table>
<thead>
<tr>
<th>Patient</th>
<th>MR appearances</th>
<th>Histological examination</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Septated, short T1 centrally, long T1 rim on T1 imaging</td>
<td>Haemorrhagic, almost entirely necrotic, no viable tumour</td>
<td>8w</td>
</tr>
<tr>
<td>4</td>
<td>Iso-intense with soft tissue centrally, long T1 rim on T1 imaging</td>
<td>Necrotic and calcified mass, small areas of viable tumour = mixed differentiated and immature cells</td>
<td>3w</td>
</tr>
<tr>
<td>5</td>
<td>Iso-intense with soft tissue on T1 imaging, high signal rim on STIR</td>
<td>&gt;50% necrotic, otherwise differentiated neuroblastoma</td>
<td>8w</td>
</tr>
<tr>
<td>6</td>
<td>Iso-intense with soft tissue on T1 imaging</td>
<td>Haemorrhagic. Viable tumour = undifferentiated neuroblastoma</td>
<td>3w</td>
</tr>
<tr>
<td>9</td>
<td>Short T1 centrally with long T1 rim on T1 imaging, signal drop-out</td>
<td>Calcified tumour, no necrosis. Viable tumour = immature neuroblastomas</td>
<td>6w</td>
</tr>
<tr>
<td>10</td>
<td>Iso-intense with soft tissue on T1 imaging</td>
<td>Viable tumour = undifferentiated neuroblastoma</td>
<td>10d</td>
</tr>
<tr>
<td>11</td>
<td>Long T1 rim, around intermediate T1 centre</td>
<td>40% necrotic, viable tumour = mixed differentiating ganglioneuroblastomas and immature neuroblastomas</td>
<td>7d</td>
</tr>
<tr>
<td>13</td>
<td>Short T1 centrally on T1 imaging</td>
<td>Some fibrosis, no residual viable tumour</td>
<td>8w</td>
</tr>
<tr>
<td>15</td>
<td>Signal drop-out, short T1 centre, long T1 rim on T1 imaging</td>
<td>Minimal necrosis, viable tumour = differentiating neuroblastomas</td>
<td>4m</td>
</tr>
<tr>
<td>Patient</td>
<td>MR appearances</td>
<td>Histological examination</td>
<td>Time</td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>------</td>
</tr>
<tr>
<td>18</td>
<td>Iso-intense with soft tissue on T1 imaging</td>
<td>Focal areas of calcification, viable tumour = immature neuroblastoma, with patches of differentiating tumour</td>
<td>10d</td>
</tr>
<tr>
<td>19</td>
<td>Short T1 centrally with long T1 rim on T1 imaging</td>
<td>Approx 2/3 of tumour necrotic Viable tumour = 50% undifferentiated and 50% undifferentiated</td>
<td>2d</td>
</tr>
<tr>
<td>20</td>
<td>Short T1 rim with central signal drop-out on T1 imaging</td>
<td>Fibrosis, haemorrhage, calcification. Viable tumour = maturing neuroblasts with islands of poorly differentiated cells</td>
<td>2d</td>
</tr>
</tbody>
</table>

**Note**

Time delay = time between MR scan and surgery/ PM.
d= days, w= weeks, m= months
Table 5.3: Nodal disease; MR and CT correlation

23 scans in 19 patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal disease equivalent on MR and CT scans</td>
<td>13 scans (10 patients)*</td>
<td>Surgical correlation in 6</td>
</tr>
<tr>
<td>Nodal disease more extensive on MR than on CT scan</td>
<td>5 scans (5 patients)</td>
<td>Surgical correlation in 5</td>
</tr>
<tr>
<td>Nodes inseperable from $I^o$ tumour on CT scan</td>
<td>4 scans (4 patients)</td>
<td>Surgical correlation in 3</td>
</tr>
<tr>
<td>Nodes inseperable from $I^o$ tumour on CT and MR scans</td>
<td>1 case</td>
<td>(Thoracotomy and biopsy)</td>
</tr>
</tbody>
</table>

NB  * includes same patient scanned on 2 separate occasions
Table 5.4: Frequency of visualisation of vessels on abdominal scans, comparing MR with enhanced CT.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>MR (%)</th>
<th>CT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>IVC</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Coeliac axis</td>
<td>95</td>
<td>8</td>
</tr>
<tr>
<td>SMA</td>
<td>90</td>
<td>42</td>
</tr>
<tr>
<td>SMV</td>
<td>95</td>
<td>25</td>
</tr>
<tr>
<td>Splenic vein</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>Portal vein</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>Lt renal vein</td>
<td>90</td>
<td>25</td>
</tr>
<tr>
<td>Lt renal artery</td>
<td>70</td>
<td>8</td>
</tr>
<tr>
<td>Rt renal vein</td>
<td>95</td>
<td>33</td>
</tr>
<tr>
<td>Rt renal artery</td>
<td>70</td>
<td>8</td>
</tr>
</tbody>
</table>

Analysis of 23 MR and 14 enhanced CT abdominal scans
Table 5.5: Disease Stage (as determined by combined clinical, pathological, biochemical and imaging findings) in patients scanned at presentation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Disease Stage</th>
<th>NMR (n=13)</th>
<th>CT (n=12)</th>
<th>Surg/Path</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>4-BM pos</td>
<td>3/4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>4-BM pos</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>4S</td>
<td>4S</td>
<td>-</td>
<td>4S</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>4-BM pos, distant mets</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>4S</td>
<td>4S</td>
<td>4S</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>4-BM pos</td>
<td>2/4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>3 (no radionucleide studies)</td>
<td>3/4</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>4-BM pos</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Key
BM pos= bone marrow metastases present
Figure 5.1; Bone marrow metastases

Coronal T1-weighted SE (TR/TE=450/15ms) image through a large left suprarenal neuroblastoma. Multiple bone marrow deposits are seen as low signal areas within the vertebrae.
Figure 5.2; Bilateral suprarenal tumours in a child with 4S neuroblastoma

a) Coronal T1-weighted SE (TR/TE=400/15ms) MR scan and b) transverse unenhanced CT scan. The right-sided tumour is more clearly shown on the MR scan in the coronal plane (arrowed) than on the transverse CT scan.

a) 

b)
Figure 5.2 continued

c) Transverse STIR (TI/TR/TE=150/3000/40ms) image through the liver. Multiple nodules of (high signal) metastatic tumour are seen throughout the liver. There is hepatomegaly and medial displacement of the spleen by the left lobe of the liver.

Figure 5.3; Calcified suprarenal neuroblastoma.

Transverse STIR (TI/TR/TE=150/3000/40ms) image through the upper abdomen showing a well defined tumour lying anterior to the right kidney. There is marked signal drop-out in the centre of the tumour due to heavy calcification.
Figure 5.4; Haemorrhagic neuroblastoma

Transverse T1-weighted SE (TR/TE=450/15ms) image through a large right suprarenal neuroblastoma. Several regions of T1-shortening (high signal) are seen through the tumour which also display fluid levels. These appearances corresponded to haemorrhage within the primary tumour.

Figure 5.5; Post-chemotherapy appearances of neuroblastoma

Coronal T1-weighted SE (TR/TE=450/15ms) image through a left suprarenal neuroblastoma after 6 courses of chemotherapy. A dark rim surrounds a central area of high signal. The excised tumour showed total necrosis on histopathological examination.
Figure 5.6; Assessment of tumour viability in lymph nodes after chemotherapy.

Transverse STIR (TI/TR/TE=150/3000/40ms) images through the upper abdomen in 2 children after chemotherapy and immediately pre-operatively. In both cases retroperitoneal nodal masses remain (arrowed). However viable residual tumour was found in case a, whereas no residual viable tumour was found in patient b.

a)  

b)
Figure 5.7; Tumour invasion of the spinal canal; MR v CT.

a) contrast-enhanced CT scan, b) transverse STIR (TI/TR/TE= 150/3000/40ms) and c) sagittal T1-weighted SE (TR/TE=450/15ms) MR scan in a patient with ganglioneuroblastoma. Bone destruction and tumour invasion of the spinal canal with displacement of the cord is shown by both modalities. However the longitudinal extent of the tumour is best seen on the sagittal image and the MR scan did not required the use of contrast agents.
Figure 5.7 continued

c)
Figure 5.8; Tumour invasion of intervertebral foramina

Coronal STIR (TI/TR/TE=150/3000/40ms) image through neuroblastoma involving the posterior mediastinum. Tongues of tumour (arrowed) can be seen passing into the intervertebral foramina. After chemotherapy the mass reduced in size but a repeat scan showed residual tumour in 3 foramina; a finding confirmed at operation.
Figure 5.9: Vascular involvement by neuroblastoma

a) coronal and b) sagittal T1-weighted SE (TR/TE=450/15ms) MR scans of a neuroblastoma of the posterior mediastinum. Encasement and displacement of the aorta by tumour, and tumour crossing the midline is well shown by the scan without the use of a contrast agent.
Figure 5.10; Sequence comparison T2 v STIR

Transverse a) STIR (TI/TR/TE=150/3000/40ms) b) T2-weighted SE (TR/TE=3000/90ms) and c) contrast-enhanced CT scan through a left suprarenal neuroblastoma. Displacement and encasement of the abdominal aorta and the coeliac axis is well shown on the MR scans. Vascular detail is seen better on the STIR than the T2 image. Even with a loading/bolus dose of intravenous contrast, the aorta has not been shown on the CT scan.
Figure 5.10 continued

c)
Chapter 6

General Discussion and Conclusions
General Discussion

Recent technical advances in MR imaging have greatly improved the quality and flexibility of this technique. Improvements have allowed greater spatial resolution, multislice imaging and 'purer' and more flexible sequences. Many of these features are now incorporated into standard MR scanners and this has enabled us to established a method of scanning children with high-field MR which consistently and safely achieves high quality diagnostic scans.

Before discussing the conclusions, a number of weaknesses of the studies are considered;

1) MR and CT scans have not been paired on every occasion
2) MR and CT scans have not been performed immediately before surgery in every patient.
3) The MR scanner is of higher quality than the CT scanner.
4) Each MR scan was supervised by a member of the study team whereas some CT scans were from referring hospitals where protocols were not adhered to.
5) MR sequence comparison has not been rigorous; ideally T1- and T2-weighted SE, STIR and GE sequences should have been performed in every patient in the same plane.
6) Ultrasound scans were performed by a number of individuals. The technique is more operator dependent than either MR or CT. If an abnormality is not identified and recorded at the time of the scan it is not possible to review the findings.

There are a number of reasons why these problems arose;
1) All children with cancer are closely supervised clinically and undergo a battery of radiological, pathological, biochemical and haematological investigations. Children and their families spend long periods of time attending hospitals with the child subjected to a series of unfamiliar and frightening events, and, coupled with the knowledge of a potentially fatal illness, the child, family and their carers are invariably stressed. Addition of another imaging
technique adds to the time and stress of hospital attendance. It is very difficult to impose rigorously a study protocol in this setting.

2) In our busy clinical department (which has other commitments), we have not always been able to arrange investigations to coincide.

3) A diagnostic scan must be obtained to justify scanning a patient. Other (research) objectives, such as obtaining multiple sequences in comparable planes are of secondary importance and, because the period of sedation is finite, cannot always be achieved.

Therefore there are some reservations regarding the comparative imaging in these studies (in particular the CT scans). However, although not state-of-the-art, the CT scans represent good practice and the majority have been performed by staff experienced in scanning and interpreting images in children. Review of the imaging data has confirmed that CT is superior to MR in some aspects, such as showing tumour calcification in neuroblastoma and defining tumour-renal boundaries in Wilms' tumour. In contrast, blood vessels have been shown consistently better by MR than CT in all groups of tumours considered. In some cases this is due to poor contrast enhancement of CT scans, but this reflects the difficulty in obtaining adequate dynamic enhancement in children due to poor venous access and small guage needles and does not represent poor scanning technique or protocols. Consequently, although caution must be exercised when comparing the CT and MR data, it remains useful and valid to do so to a limited degree.

Conclusions

The conclusions of the clinical studies are summarised at the end of each tumour group chapter (pages 82, 105, 160) but the major advantages and disadvantages of MR as a technique for each tumour will be reiterated below. Most children in these studies were examined at the time of diagnosis and in the treatment period immediately afterwards. Therefore no comprehensive study of the value of MR in long term follow-up has been made and the results presented here concern imaging at diagnosis, (including staging), and during early follow-up. In general, information from MR scans was as accurate as CT and obtained
without the use of ionising radiation or intravenous iodinated contrast agents. But MR has some disadvantages compared with CT, namely the longer time of each examination, the failure to recognise calcium and the need to sedate a) more heavily and b) older children.

Primary Malignant Hepatic Tumours

a) Advantages

Of the tumours studied, MR was most clearly superior to CT in the assessment of the resectability of liver tumours. MR was as good as CT at showing the intrahepatic origin of tumour. MR was consistently better than CT for showing 1) which segments of the liver were involved by tumour, 2) the relationship and involvement of blood vessels and 3) the presence of extrahepatic disease. Though MR shows venous anatomy well, some surgeons may continue to require angiography to show arterial blood supply to the liver and tumour.

b) Disadvantages

There are limitations to MR; benign tumours cannot necessarily be distinguished from malignant disease. Malignant and reactive extrahepatic disease (including lymph node abnormalities) could not be distinguished either around the porta hepatis or in the retroperitoneum and cautious appraisal of abnormalities in these areas is necessary to reduce the rate of overstaging.

Wilms' Tumour

a) Advantages

MR reliably assessed the site and size of primary tumours, and macroscopic extracapsular tumour extension was identified in all cases. Vascular invasion of the IVC was well shown by MR and the signal characteristics were helpful in distinguishing organised from tumour thrombus. Following chemotherapy, changes in tumour size were well shown by MR, and the appearance of regions with shortened T1-relaxation times were helpful in
documenting foci of non-viable tumour. This offers a potential role for monitoring chemotherapy.

b) Disadvantages

MR showed no advantage over CT in showing the primary tumour, and in some cases the border between normal kidney and tumour was shown better by contrast-enhanced CT than by MR. Nephroblastomatosis could not be differentiated from residual Wilms' tumour by MR or CT. Unless markedly abnormal architecture was present in lymph nodes, MR could not distinguish between reactive changes and tumour infiltration.

Under the present staging system the influence of extracapsular spread on tumour stage and on treatment depends on combined surgical/pathological findings. Residual macro-or micro-scopic disease following resection upgrades tumour to Stage III and in our experience this cannot be predicted by the imaging findings. Therefore, although MR showed spread reliably, this did not effect final patient management.

Tumour response to chemotherapy was more easily monitored by MR than CT, as areas of non-viable tumour could be identified by MR in several cases. One situation where these advantages might be exploited is in the planning of conservative, nephron-preserving surgery in unilateral or bilateral disease.

**Neuroblastoma**

a) Advantages

MR accurately demonstrated primary tumour and node involvement before and after chemotherapy. Intrathoracic, intraspinal and vascular involvement by tumour were clearly seen on MR scans and in most cases better than with CT.

b) Disadvantages

MR has not answered the problem of differentiating viable tumour from residual necrotic/ reactive tissue in either primary tumour or lymph nodes. MR, in common with all
other imaging modalities, can fail to detect tumour involvement in lymph nodes which are not enlarged. MR is comparatively 'blind' to tumour calcification, a useful diagnostic feature.

In this study we did not conclusively demonstrate that disease was staged higher by MR than CT in any case except in the absence of other methods of assessing cortical bone and marrow involvement. There may be a slight advantage of MR over CT for assessment of lymph nodes following chemotherapy when nodes are smaller and more subtle (as in a single case reported here). This may be because CT suffers from the lack of retroperitoneal fat in children, a problem exacerbated by the effects of chemotherapy and general illness. However study of further surgically validated cases comparing CT and MR is necessary to establish this.

Future Perspectives

Clinical studies

Unresolved issues raised in this thesis include 1) the value of MR in long-term follow-up, 2) the MR appearances of lymph nodes involved by tumour before chemotherapy and 3) the comparative sensitivity of MR, CT and ultrasound in defining tumour involvement of the IVC by renal tumours. MR assessment of bone and bone marrow involvement in childhood cancers was not definitively investigated in this study and no study with parallel histological verification has, as yet, been reported.

In our study of Wilms' tumours, we identified an association between the development of necrosis with shortening of T1-relaxation. The mechanism of this finding is open to speculation and it would be of interest to analyse these changes biochemically and spectroscopically to try to understand what is occurring at a cellular and subcellular level.

Advances in imaging

A disadvantage of MR is the time taken to complete a scan, however there are several possible ways of reducing scan time.
a) Asymmetric field of view (AFOV)

Factors determining scan time are discussed in Appendix 2. Use of the AFOV reduces scan time (in a directly proportional way) by reducing the number of phase-encoding steps. If an ellipsoid structure (such as the abdomen) is scanned, a reduced number of phase-encoding steps are performed along the minor axis of that structure and the field of view is reduced in this dimension. Images are rescaled by Fourier transformation. In essence, the phase-encoding steps of empty space around the structure are not performed, and, for a given number of phase-encoding steps, the matrix equivalent and thus the spatial resolution is better than for an equivalent symmetric FOV. In our studies 256 phase-encoded steps were used with a final matrix of 256x256. If the number of phase-encoding steps is reduced to 128 (and the imaging time halved), a matrix equivalent to 192x256 is produced using an AFOV compared to a matrix of 128x256 using a symmetric FOV. This technique was not available to us during the period of the studies but preliminary assessment in brain imaging has indicated that spatial resolution does not noticeably deteriorate.

b) Echo-planar MR

Echo-planar imaging has been pioneered by Mansfield and his group in Nottingham and is capable of producing images in under 100 msec (Mansfield & Pykett, 1978, Ordidge et al, 1982). The basic concept of the echo planar technique is that successive spin echoes can be used to encode spatial information. The limitation of this technique is the time imposed by T2-decay; the lines of data must be acquired in a time not exceeding T2 (typically the interval between echoes must be 0.5-1 msec). This imposes huge technical demands on the performance of gradient power supplies and on coils even to obtain coarse matrices. An additional problem is that as speed increases, the receiver bandwidth must be broadened to a point where SNR deteriorates. Crooks et al (1988) have developed an echo-planar imager incorporated into a conventional 0.35T MR imager for paediatric use, but as yet the spatial resolution and SNR are grossly inferior to standard imaging techniques. There is also some concern that, as finer matrices are achieved, nerve and muscle depolarisation induced by rapid
gradient switching may become a real hazard (personal communication, Siemens, Research and Development).

c) High frequency ventilation

High frequency ventilation (HFV), ie ventilation at rates above 60 per minute, has been developed and used extensively in neonatal medicine (Greenough & Milner, 1987). This technique enables oxygenation to be maintained with high ventilation rates and small tidal volumes- the chest and abdominal excursion during respiration is much less than with spontaneous respiration or conventional mechanical ventilation. HFV has successfully been exploited for extracorporeal shock wave lithotripsy to reduce the motion of renal and ureteral calculi (Warner et al, 1988). Potentially the technique could be applied to MR imaging to reduce image degradation due to respiratory motion. This in turn would reduce the number of signal averages necessary, with a subsequent reduction in imaging time.

d) Gradient echo imaging

The principles, advantages and disadvantages of gradient echo (GE) imaging are described in Chapter 2. These sequences have been developed as fast imaging techniques but no comparative studies in paediatric imaging have been reported. Image quality depends on the correct choice of imaging parameters (flip angle, TR, TE) which are optimised by systematically varying each of the parameters in turn. Unfortunately, no 'standard' sequence is optimal for all tumours and all sizes of children, so optimising and comparing sequences is very time-consuming. However they do offer faster acquisition of sequences and certainly deserve further investigation. GE sequences are very sensitive to susceptibility effects, and there may be signal loss following haemoglobin breakdown in haemorrhagic tumours.

Magnetopharmaceuticals

Pharmaceutical agents are used with most imaging modalities to accentuate contrast between different tissues. With MR, lesion contrast can usually be optimised by the appropriate choice of sequences but there are occasions when definition of abnormalities is
poor. In these circumstances magnetopharmaceuticals have potential as contrast agents. There is growing experience of the use of these agents in adults (Ferrucci & Stark, 1990, Semelka et al, 1991, Saini, 1992) but as yet there are no reports of their use in the imaging of childhood abdominal tumours.

Contrast agents used in MR are usually paramagnetic compounds (usually incorporating metallic ions) characterised by unpaired electrons. Their effect is to increase T1- and T2-relaxation rates. This has a complex effect on the MR signal which also depends on the pulse sequence chosen. The concentration of the paramagnetic substance also effects the relative changes in T1- and T2- shortening. As with any contrast agent, magnetopharmaceuticals must be stable, pure, non-toxic and readily excretable, and preferably conjugable to tissue- or organ-specific biomolecules.

The observations in this thesis indicate 2 areas where magnetopharmaceuticals may be useful in the imaging of paediatric abdominal tumours, 1) to improve bowel/tumour contrast, particularly when investigating possible local disease recurrence and 2) to improve the definition of the border between tumour and normal kidney in patients with Wilms' tumour where conservative surgery is contemplated.

Bowel contents and tumour may appear isointense. This poses a particular problem when looking for local disease recurrence of either neuroblastoma or renal tumours. Similar problems with CT can sometimes be overcome by using oral contrast agents. Oral gastrointestinal magnetopharmaceuticals may either increase signal from the bowel (eg paramagnetic ferric ammonium citrate) or reduce it (eg air, ferrite particles and perfluorochemicals). Because tumour is generally of high signal on T2-weighted sequences, the 'negative-contrast' agents may be the more useful in identifying tumour/bowel margins. As with oral contrast agents used in CT, it is difficult to get uniform contrast throughout the bowel because of segmentation due to peristalsis. Despite this, these agents warrant further evaluation especially in the long term follow-up of these tumours.

Gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) is concentrated within the kidney producing rapid and sharp differentiation of the renal cortex and medulla. It may be possible to improve renal/tumour definition by the use of early, dynamic scanning after
intravenous injection of Gd-DTPA at a stage where there is enhancement of the kidney but no
enhancement of the tumour. Delayed scanning may produce the relative inverse of this effect.
We are currently assessing the value of this technique. Gadolinium-enhanced MR scanning
combined with fat suppression has shown promise in adults for improving lesion detection and
characterisation (Semelka et al, 1991) but this approach has yet to tried in children.

Spectroscopy

NMR spectroscopy is a unique tool as it is the only method by which body
chemistry can be investigated non-invasively. Its role in diagnostic medicine has recently been
extensively reviewed (Bottomley 1989). Many recent technical advances have allowed
localisation of spectra, acquisition of spectra from smaller volumes and from tissue with lower
substrate concentrations. Despite this, with few exceptions spectroscopy remains a research
tool and certainly in cancer medicine, no clear clinical role has been defined. Abnormalities of
phosphate metabolism have been found in a wide variety of tumours (Bottomley, 1989).
After chemotherapy, radiation or embolisation changes in P-31 spectra from human tumours
almost invariably occur, often before there are any clinical or imaging changes (Ross et al,
1984). Such observations suggest that spectroscopy might prove to be useful as an early
indicator of tumour response to treatment. However some paradoxical features have been
found. Indicators of hypoxia have been found in regressing tumours and also in some that are
not responding to chemotherapy (Griffiths et al, 1983), while tumours responding to treatment
may show more normal high-energy phosphates after therapy (Nidecker et al, 1985, Segebarth
et al, 1987). Further research is necessary to establish whether spectroscopically-detected
changes in tumour metabolism will provide a useful clinical guide to therapeutic efficacy.
Recent advances in proton spectroscopy may be useful for tumour diagnosis and for analysing
the effects of treatment on tumour cell.
Concluding Remarks

As with most new technology, MR was at first enthusiastically embraced but is presently undergoing a period of critical appraisal to determine its appropriate use in clinical practice. Of the specific problems addressed in this thesis, the following has been established;

1) MR is a good technique for the assessment of the primary site of tumour and for the staging of disease in the 3 groups of solid abdominal tumours studied. For these purposes it appears to be as good as CT in most cases with the added advantages of neither using ionising radiation or (in these studies) contrast media. It is particularly good for showing the anatomy of large blood vessels and intraspinal tumour extension. Malignant lymph nodes can not be distinguished with certainty from those showing reactive change only when the nodes are only moderately enlarged. Tumour diagnosis is not specific for cell type in any of the groups studied.

2) An effective method of sedating children has been devised with success rates in excess of other reported series. In the absence of a pulse-oximeter patient monitoring remains inadequate.

3) The sequence choice and methodology used in these studies has produced high quality diagnostic images. The duration of MR scans remains a problem but further sequence manipulation and the use of fast gradient echo sequences (as discussed above) may shorten scans to times comparable with CT scans.

There are many reasons to think that, in the future, MR scanning will be used more to investigate children. The hardware and software of scanners are becoming increasingly sophisticated and many functions have become automated, making scanners increasingly 'user-friendly' and more amenable to use outside a research environment. With increased
availability, the experience of radiologists and radiographers grows resulting in technically
caller examinations, more appropriate use of the technique and more accurate reporting. In the
United States (where there are over 3000 MR scanners) MR now forms part of the routine
service work of most radiology departments (Margulis & Crooks, 1988) and children with
solid tumours are investigated routinely with MR. With increased scanner availability it is
likely that this experience will be mirrored in the UK.
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Acknowledgements

First and foremost I wish to acknowledge the help of Dr Jon Pritchard who has been a patient, diligent and encouraging supervisor. My radiological colleagues Dr J Paul Finn and Dr Claire Dicks-Mireaux have also been instrumental in helping to run and assess the clinical studies.

All clinical research involves a team of people and amongst those involved I wish to thank Janet Leake, Helen Parkhouse, Patrick Duffy, Ed Kiely and Lewis Spitz. I wish to thank our superintendent radiographer Julie Shepherd for help with the radiographic aspects of the work. Dr Alan Connelly has been a patient and clear instructor of physics, and has been instrumental in sequence development in the unit. Thanks are also due to The Department of Medical Photography for printing the illustrations.

Lastly I wish to acknowledge my daughter Elspeth who has constantly enquired into the progress of 'my book' at her bed-time ever since she started talking and has been a great source of encouragement.
Appendix 1
**Magnet**

<table>
<thead>
<tr>
<th>Type</th>
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<tr>
<td>Field strength</td>
<td>Operating strength 1.5 Tesla</td>
</tr>
<tr>
<td></td>
<td>(nominal field strength maximum of 2.0 T)</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>Over 50 cm DSV</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>Over 30 cm DSV</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 ppm</td>
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<td>Over 10 cm DSV</td>
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<tr>
<td></td>
<td>&lt; 0.1 ppm</td>
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<tr>
<td>Stability</td>
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</tr>
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<td>Cryogens</td>
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<tr>
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<td>4.2 K</td>
</tr>
<tr>
<td></td>
<td>liquid nitrogen</td>
</tr>
<tr>
<td></td>
<td>77.4 K</td>
</tr>
</tbody>
</table>

**Passive self shielding**

**Patient tube aperture**

| Diameter               | 69cm                          |
|                       | Diameter within body coil     |
|                       | 55cm                          |
| Length                | 255cm                         |

**Gradient system**

| gradient strength     | 10mT/m                        |
|                       | rise time                     |
|                       | 1.0ms                         |
**Radiofrequency system**

circularly polarised body coil
circularly polarised head coil

**Computer system**

Main computer VAX-11/730

<table>
<thead>
<tr>
<th>Component</th>
<th>Specification</th>
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</thead>
<tbody>
<tr>
<td>architecture</td>
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<tr>
<td>operating system</td>
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<td>main memory</td>
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</tbody>
</table>

Image processor Siemens BSP 11/MR array processor

**Measurement modes**

Field of view (FOV) 50cm DSV 8cm

Matrix 256x256

Resolution

- Pixel size = FOV/Matrix eg 8cm/256 = 0.3mm
- Slice thickness 2-200mm

Reconstruction

- 2D Fast Fourier transformation
- 3D Fast Fourier transformation
Appendix 2

Principles of Nuclear Magnetic Resonance
Introduction

Descriptions of NMR theory frequently contain a mixture of quantum-mechanical and classical physics. For any rigorous analysis of NMR, particularly for spectroscopic techniques and analysis, a quantum mechanical description is necessary, whereby electromagnetic (EM) radiation can be regarded as discrete quanta of energy travelling at the speed of light, and atoms and molecules have certain discrete energy levels. However much of NMR can be understood using a classical physics model, and this is particularly useful when describing many of the practical aspects of NMR, such as the effect of radiofrequency pulses. A brief description of the 2 models will be given.

Certain nuclei eg $^1$H, $^{13}$C, Na, $^{31}$P, Fl spin and, like other spinning objects, they possess angular momentum. Because they bear an electrical charge, these nuclei have magnetic properties and can in essence be considered to behave like miniature bar magnets or magnetic dipoles. When the spin vectors are placed in a magnetic field, they experience a force or torque which causes them to precess around the axis of the field in a fashion similar to a gyroscope precessing around the axis of the earth's gravitational field. The term 'magnetic dipole moment' or 'magnetic moment' is used to describe the turning moment experienced by such a magnetic object when placed in an applied magnetic field, and it describes the properties of magnetic nuclei. Angular momentum and magnetic moment are closely inter-related and this relationship is described below. For the purposes of MR imaging, the proton—the nucleus of the major isotope of hydrogen— is the most useful because of its abundance and favourable magnetic moment.

Quantum mechanical description

Total angular momentum is made up of a number of factors including, for example, spin angular momentum and orbital angular momentum and each of these is quantized. Angular momentum is a vector property and is specified by both magnitude and direction. For any given atomic nucleus, the spin angular momentum is specified by the quantum number $I$ (the spin of the nucleus). The magnitude $p$ of the nuclear spin angular momentum is given by

$$p = \frac{\hbar}{2} \sqrt{I(I+1)}$$
where $\hbar = h/2\pi$, and $h$ is the Planck constant. The value of $I$ may only be an integral, half-integral or zero, depending on the combination of mass number and atomic number. For the proton, $I=1/2$.

The direction of angular momentum can only have a limited number of orientations in respect of a reference direction, and is described by a second quantum number $m_I$. This can have any of $2I+1$ values, i.e. $+1/2$ and $-1/2$ for the proton. Hence the magnitude of angular momentum in a reference direction e.g. $z$, is given by:

$$p_z = m_I \hbar = + \text{ or } -1/2 \hbar$$

The magnetic moment has a magnitude $\mu$, and is related to the angular momentum by

$$\mu = \gamma p,$$

where $\gamma$ is a constant known as the magnetogyric ratio, and is specific to each nuclear isotope.

If a nucleus is placed in a static magnetic field $B_0$, acting along an axis, e.g. the $z$-axis, the interaction between the field and the nuclear moment results in the nucleus acquiring energy $E$, the magnitude of which is given by

$$E = -\mu_z B_0 = -\gamma m_I B_0,$$

for the proton the difference in energy $\Delta E$, between the 2 permissible orientations is

$$\Delta E = \gamma \hbar B_0$$

In the NMR experiment, transitions between the energy states are induced by applying an oscillating magnetic field $B_1$, in the $xy$-plane. For conventional values of $B_0$, the appropriate frequency occurs in the radiofrequency (rf) band, and the $B_1$ field is commonly referred to as the rf field. The $B_1$ field must oscillate with a frequency $\nu_0$ given by

$$\Delta E = h \nu_0$$

therefore

$$\nu_0 = \gamma B_0/2\pi.$$

The angular frequency $\omega_0$, is

$$\omega_0 = 2\pi \nu_0 = \gamma B_0$$

eqn 1
For a population of protons, a balance exists between the 2 permissible energy states determined by the Boltzmann distribution, i.e., a thermal equilibrium determined by the temperature T. The relative numbers in the low and high energy state is given by
\[ N_L = \exp(-\Delta E/kT) \]
\[ N_H = \exp(-\gamma \hbar \text{Bo}/kT) \]
where k is the Boltzmann constant. If the number of nuclei in the high and low energy states were equal, there would be an equal number of transitions between the energy states, and no net absorption of energy would occur when a B1 field were applied. If no energy is absorbed, none is emitted when the applied field ceases so there is no net signal. However, there is a slight excess of protons in the low energy state, allowing small amounts of energy to be absorbed during the NMR experiment. When the strength of the Bo field is increased, the energy difference between the 2 energy states increases. The amount of energy absorbed during application of the B1 field therefore increases, with a subsequent increase in the magnitude of the signal and SNR.

Classical description of NMR

The spinning \(^1\text{H}\) nucleus is considered as a magnetic dipole with angular momentum. When placed in a static magnetic field it will precess around the axis of the field with a characteristic frequency \(\omega_0\), such that
\[ \omega_0 = \gamma \text{Bo} \]
This frequency is known as the Larmor frequency, and is identical to the resonance frequency derived in eqn.1.

Within a magnetic field, the overall effects of the individual dipoles summate to produce the 'macroscopic magnetisation', \(M\). This is the vector sum \(\Sigma\), of the individual magnetic moments. As a large number of vectors precess around the static field axis, their phases will be randomly orientated and the transverse magnetisation of each dipole will be equally and oppositely opposed, hence the transverse magnetisation, in the plane perpendicular to the axis of the main field, will summate to be zero. In the steady state, there is a slight predominance of protons in the low energy state, causing a net longitudinal
magnetisation in the direction of the axis of the static field. In MR, resonance occurs when radiofrequency energy is applied at the Larmor frequency in a direction perpendicular to the reference axis, causing the magnetisation vector to precess from the longitudinal to the transverse plane where it can be detected.

**Signal detection**

When changes occur in the transverse magnetisation, it becomes possible to detect magnetic resonance absorption, as, by Faraday's law of induction, a change in the magnetisation with time will induce a voltage in a receiver coil. Transverse magnetisation can be created by applying an external field (B\textsubscript{1}) rotating synchronously with the precessing spins, acting perpendicular to the main field. This causes the macroscopic magnetisation to rotate about the axis of the applied field. The angle of rotation away from the main field, or 'flip angle' (\(\phi\)), will be determined by the amplitude and duration of the B\textsubscript{1} field, given by:

\[
\phi = \frac{1}{\gamma} B_1 t
\]

where \(t\)=duration (s) \(B_1\)=amplitude of the applied field (T)

The complex motion of precessing spins is difficult to describe, and can be simplified by the concept of the 'rotating frame of reference'. The coordinates of the magnetisation of the spinning dipoles are represented as x, y and z in the laboratory frame of reference. The B\textsubscript{1} field rotates synchronously with the precessing spins. If the axis is considered to be rotating at the Larmor frequency (x', y', z'), then the axes, the B\textsubscript{1} field and the precessing spins on resonance, are static relative to one another. The individual magnetic moments can be described in terms of the net magnetisation vector.

Once the B\textsubscript{1} field has been removed, the precessing spins are subject to the Bo field alone, and will gradually return to the pre-excitation equilibrium. Following a 90° pulse, the transverse magnetisation will be lost and the longitudinal magnetisation return to its equilibrium state. The AC voltage induced in a coil orientated with its axis aligned with the y axis, will be
\[ V \propto M_{xy}^0 \cos wt \]

where \( M_{xy}^0 \) = initial transverse magnetisation following application of the B1 field

\( t = \) time interval between the 90\(^\circ\) pulse and the voltage measurement

The transverse magnetisation decays to zero exponentially with a time constant \( T_2^* \), similarly the detected voltage decays to zero. This is the 'free induction decay', and the processes of decay of the transverse magnetisation and return of the longitudinal magnetisation to its equilibrium state is known as 'relaxation'.

**Relaxation** (Abragam, 1961, Farrar & Becker, 1971)

**T1-relaxation**

In order that nuclei can return to their ground state, they must lose the energy absorbed during excitation, by giving it up to their surroundings or 'lattice'. This is known as 'spin-lattice' relaxation. For energy to be dissipated, stimulating RF fields need to be present, and in normal circumstances these are provided by the dipoles of adjacent neighbouring magnetic nuclei. Relaxation requires a field containing fluctuations at a rate similar to the precessing frequency of the excited protons. In liquids, fluctuations of the field are due to random thermal motion (Brownian motion). The larger the proportion of this field which is fluctuating at the Larmor frequency, the more rapidly relaxation occurs. At the field strength at which most MR systems operate, the frequency of rotation of medium-sized molecules, such as lipids, most closely matches the Larmor frequency. Hence relaxation occurs efficiently ie the T1-relaxation time is short. The rotational frequency of smaller molecules eg water or larger macromolecules eg proteins, is less well matched and relaxation is less efficient (long T1-relaxation times). Because the precessional frequency is proportional to the strength of the external field, it can be seen that T1-relaxation times vary with field strength.

**T2-relaxation**

The term transverse or spin-spin relaxation, is used to describe the process of loss of coherence of the magnetisation in the XY or transverse plane, and is characterised by the time
constant T2. The signal detected in the XY plane is dependent on the phase coherence of the individual isochromats; as this is lost, the signal decays as \( \exp(-t/T2) \). In practice, the loss of signal coherence occurs more rapidly than this due to magnetic field inhomogeneities resulting in different resonance frequencies at different spatial locations. A second time constant T2*, is used to characterise the combination of 'real' T2-relaxation plus inhomogeneity broadening. In order to observe T2 decay, the latter effects can be removed by the use of a spin echo produced by an additional RF pulse (Car & Purcell, 1954, Meiboom & Gill, 1958). Unlike T1 processes, T2 does not involve energy exchange with the surroundings, but is an entropy phenomenon in which the total energy of the spin system does not change, but exchanges between pairs of spins results in a randomisation of the phase. In common with T1-relaxation, T2 decay can be caused by magnetic interactions fluctuating at the Larmor frequency. However, unlike T1 recovery, the transverse component of magnetisation can interact with the z component in the fluctuating field, which is static in both the laboratory and rotating frames of reference (ie a zero frequency component). This mechanism leads to very short T2-relaxation times in solids (of the order of <1 ms), which have extremely long T1 values (≈ minutes). For isotropic, non-viscous liquids, T1 and T2 are equally efficient (ie T1=T2).

Physiological basis of relaxation

MR imaging is concerned with the observation of protons of small mobile molecules, ie water and certain lipids. Most of the signal is derived from protons in water, as numerically these far outweigh the protons in organic compounds. Water protons are not entirely free as a small proportion are bound in layers to the surfaces of macromolecules eg. proteins and polysaccharides. Binding, in turn, effects relaxation times and the mechanism of this is now discussed (Kolata, 1976).

Effects of water binding

For relaxation to occur, energy must be transferred from an excited nucleus to another spin pair or to the surrounding environment. In general these processes involve dipole-dipole interactions which are initiated by the fluctuations in the local magnetic field. Local field
fluctuations are generated by the movement of nuclei or orbital electrons with magnetic moments, in the near vicinity. For the proton in water, the second water proton is the closest nucleus and will effect relaxation. Local field fluctuations contain a range of frequencies which is dependent on the motion of molecules; bound water produces low frequency fluctuations whilst 'free water' contains a greater proportion of high frequency fluctuations. Field fluctuations can be expressed as an autocorrelation function whose time constant, the correlation time \( (t_c) \) is less then \( 10^{-11} \) for free water and up to \( 10^{-8} \) for bound water.

The effect of different frequency components on T1- and T2-relaxation is as follows.

If a 90° RF pulse is applied to a sample \( \mu \), the rate of change of the spin vector, in the laboratory frame of reference, is given by;

\[
d\mu/dt = \gamma \mu AB_L
\]

In the rotating frame of reference, in the presence of a fluctuating local field \( (B_L) \), the various components of the spin vectors are expressed as

\[
d\mu_x/dt = \gamma (B_{Lx}\mu_y - B_{Ly}\mu_x)
\]

\[
d\mu_y/dt = \gamma (B_{Lx}\mu_z - B_{Lz}\mu_x)
\]

\[
d\mu_z/dt = \gamma (B_{Ly}\mu_x - B_{Lx}\mu_y)
\]

As previously discussed, T1 processes are only affected by changes in \( B_{Lx} \) and \( B_{Ly} \), whereas T2 processes are effected by the field acting in all three directions. Since \( z \) is the axis about which precession occurs, the \( z \) and \( z' \) components are the same. In the laboratory frame of reference, fluctuations in this direction will appear as approximately zero frequency. T2-relaxation will therefore occur at frequencies approaching zero, which will not effect T1 processes. T1 and T2-relaxation are both effected by \( x' \) and \( y' \) field fluctuations, which will appear as frequencies approximating the Larmor frequency in the laboratory frame.

The number of protons rotating at each frequency across a range of frequencies is defined as the spectral distribution or density \( J(\omega) \). For tightly bound protons, where the correlation time is long, the spectral density plot is represented as in figure 2.1. The predominance of low frequency field fluctuations dictate that T2-relaxation will be efficient and T1-relaxation inefficient. With intermediate water binding, a higher proportion of frequencies around the Larmor frequency reduces the efficiency of T2-relaxation, but T1-
relaxation becomes more efficient. For free water, there is a broad frequency distribution (figure 2.1), and neither T1- or T2-relaxation is efficient. Hence, as correlation time increases, T2-relaxation efficiency increases, whereas T1 relaxation peaks at around the Larmor frequency, and tails off on either side.

For any sample being examined, the relaxation time observed will be a weighted mean of those in the sample analysed. If 2 states only are assumed to exist (free and bound), the observed T1 may be expressed as

\[
\frac{1}{T_{1\text{obs}}} = \frac{b}{T_{1\text{bound}}} + 1 - b \frac{1}{T_{1\text{free}}}
\]

where \( b \) is the size of the bound water fraction. This equation describes the fast-exchange two state model (FETS) describing the state of water in living tissue.

**Cellular environment**

Cellular content is complex. The types and proportions of organic molecules and ions vary providing a large number of differing physical environments for water molecules. Membrane content differs between different cell populations, affecting the quantity and structure of water present. However, several other factors, in particular the presence of paramagnetic materials and mobile lipids, effect NMR relaxation.

Paramagnetic materials possess an unpaired electron which generates a large atomic magnetic moment. This large local field acts as an alternative source of changing magnetic fields for molecules (mainly water), moving at the resonant frequency, which in turn causes reduction of both T1- and T2-relaxation times. The effect of paramagnetic ions when bound to macromolecules, depends on the accessibility to water; in normal circumstances iron, for example, is sequestered in haemoglobin and myoglobin molecules. However, trauma or other pathology may release sufficient iron to cause significant relaxation of excited nuclei. In terms of imaging, this generates regions of low signal intensity.

**Principles of imaging**

In a uniform magnetic field, nuclei with the same chemical and physical environment, which are spatially separated, will experience the same field strength and will have the same resonance frequency. An FID from the sample will contain a single frequency, and the nuclei
will not be distinguished from each other. If a linear magnetic gradient (Gx) is superimposed on the static field, the nuclei arranged along the gradient will experience different overall field strengths, and will have different resonance frequencies. Hence the FID (a signal varying with time), will consist of a composite of different frequencies. The FID can be analysed by Fourier Transform (which is a mathematical relationship, relating frequency and time), to separate it into the frequencies from which it is composed. The frequency now contains spatial information as it is determined by the position of the nuclei along the gradient. The amplitude of the signal at that particular frequency is also proportional to the spin density at that particular site.

The same principle can be extended to obtaining a slice of a defined width. If a second gradient (Gz) is applied along an axis perpendicular to the imaging plane, the nuclei will again have a spectrum of precessional (Larmor) frequencies. If the applied RF pulse has a restricted bandwidth, only a limited group of nuclei, resonating within that frequency bandwidth will become excited. Nuclei falling on either side of this band will not be stimulated, and will not contribute to the MR signal. As can be seen, the width of the selected slice will vary proportionately with the bandwidth of the applied RF pulse, and inversely proportionately with the gradient strength.

By these manoeuvres, a profile of a selected slice is obtained. To acquire a two-dimensional image, spatial information has to be obtained along the third axis and this has to be done by phase-encoding. A gradient (Gy) is applied after the initial stimulating RF pulse and slice select gradient have been applied, such that nuclei along this y gradient develop different precessional frequencies. When the gradient is turned off, because they have been spinning at different rates, a phase difference will have developed between the nuclei dependent on their position along the gradient, and the nuclei have phase-memory. The Gy gradient is incremented for a number of steps (phase-encoding steps), and analysis of the phase changes of the FID provides the spatial data necessary to reconstruct the image.

**Spin-echo imaging**

During a spin-echo experiment, an initial 90° pulse is produced along the x-axis, tipping the magnetisation into the xy-plane. After a time period t, dephasing of the transverse
magnetisation due to T2* will occur. If a 180° pulse is then applied in the xy plane, it will act to refocus the net magnetisation after a further time t. Dephasing is then attributable to true T2-relaxation and is independent of field inhomogeneity (see figure from S&B p8). The time between each repeat of the 90/180 cycle is denoted the repetition time (TR), and the time between the initial 90° pulse and the echo is the 'echo delay' (TE). Relative T1- and T2-weighting of the sequence is generated by manipulating TR and TE values.

**Gradient-echo imaging**

Spin-echo imaging is time consuming because of the time necessary for refocussing transverse magnetisation. Gradient echo (GE) imaging is used to reduce imaging time by the use of short TRs and small flip angles. For spin-echo imaging with a 90° flip angle, signal reduces with decreasing TR. If an initial pulse of less than 90° is applied, relaxation along the z-axis to the rest position will occur sooner, and there is a point at which the SNR/unit time exceeds that of a spin-echo sequence for a given TR. It is well-recognised that the SNR/unit time can be maintained for any value of TR and T1, if pulse angle is reduced from 90° to the Ernst angle.

In gradient echo imaging with a small flip angle, a 180° pulse cannot be used to create the echo as this would reverse the magnetisation along the z-axis, so an echo is generated by gradient reversal. A negative gradient is applied in the read-out direction, causing dephasing. A positive gradient is then immediately applied which causes rephasing and an echo. Contrast is generated by manipulating TR, TE and flip angle (see below).

**Inversion recovery**

During an inversion recovery sequence, a 180° pulse is given which results in all the magnetisation reversing along the z-axis. Following this pulse, the magnetisation decays along the z-axis, getting smaller, passing through zero, and then growing back to its rest state. If a 90° pulse is applied before the rest state is restored, the resulting transverse magnetisation reflects the rate at which the magnetisation had been decaying in the longitudinal direction, i.e., it is intrinsically T1-weighted. The time between the 180° and 90° pulses is denoted the time from inversion (TI) or tau. In the short tau inversion recovery sequence (STIR), the 90° pulse is timed to occur when signal from fat, which has a relatively short T1, is passing through the
null point. Consequently no longitudinal magnetisation arising from fat is available to be tipped into the transverse plane and so fat does not produce a signal on the final image; it is suppressed. Because the T1 of water is longer, the resulting image is water T1-weighted. In practice, the T1-relaxation time from different fats will vary, and a compromise tau is chosen to maximise signal suppression from subcutaneous fat. Any other tissue with a T1 equivalent to fat will also be suppressed.

Partial saturation

This pulse sequence is also known as saturation recovery or repeated FID. In this sequence repeated 90° pulses are applied to the sample, and the signal measured after each pulse. If a long TR is chosen, complete relaxation occurs between pulses, and the measured signal reflects proton density. If a shorter TR is selected, incomplete relaxation occurs in the z-axis, and the signal develops some T1-weighting. The shorter the TR, the more heavily the sequence becomes T1-weighted. However, signal decreases with shorter TRs and eventually the image quality becomes severely degraded.

Generation of Contrast

Tissue structure and pathology can only be seen if the signal from one structure or abnormal area is different from another, ie there is contrast between them. With MR imaging, differences in water concentration and in the way it is bound, generating differences in the spin density and relaxation times are exploited to produce the image. During the NMR experiment, 3 factors can be manipulated; the repetition time (TR), the echo-delay (TE) and the pulse flip angle (φ). For spin-echo imaging φ is kept constant at 90°, and only TR and TE altered. Whether the net magnetisation is more influenced by spin density, T1 or T2/ T2* relaxation, and subsequently the ‘weighting’ of the image and the contrast generated is determined by the choice of these parameters.

Spin-echo imaging

If a long TR is chosen, longitudinal and transverse magnetisation decay between each pulse sequence. Transverse magnetisation following the 90° pulse is determined by spin
density if a short TE is chosen. With longer echo times, dephasing due to T2-relaxation occurs, and the residual measured transverse magnetisation becomes T2-weighted. The longer the TR, the more complete the relaxation between pulses, ensuring that as much magnetisation as possible is available to be brought down into the xy-plane with the 90° pulse, hence maximising signal.

With intermediate TRs, transverse magnetisation decays but recovery of longitudinal magnetisation (reflecting T1-relaxation) is incomplete. With sequential pulses, a steady state is reached whereby the longitudinal relaxation becomes proportional to \((1 - e^{-TR/T1})\), ie the net magnetisation becomes T1-weighted.

**Gradient-echo imaging**

Two fast imaging GE sequences are available on the Magnetom scanner, Fast Imaging with Steady Precession (FISP), and Fast Low Angle Shot (FLASH). There are basic differences in these sequences and consequently with the contrast generated (Bruder et al, 1988, Buxton et al, 1987, Redpath & Jones, 1988, Winkler et al, 1988).

**FISP**

As TR is reduced, neither longitudinal recovery or decay of transverse magnetisation occurs completely between pulses. In FISP, residual transverse magnetisation is rephased by the application of a rephasing gradient at the end of each pulse sequence and converted into longitudinal magnetisation with subsequent φ pulses. Consequently a steady state is set up. Since magnetic field inhomogeneities are not corrected for, the sequence is T2* and not T2 dependent. With short TRs, where T2* > TR, signal intensity (I) is a function of T1 and T2* expressed as;

\[
I \propto \frac{N(H)(1-e^{-TR/T1})\sin\phi \cdot e^{-TE/T2*}}{1-e^{-TR/T1} \cdot e^{-TR/T2*} \cdot \cos \phi \cdot (e^{-TR/T1} - e^{-TR/T2*})}
\]

With short TRs, the echo amplitude becomes proportional to \(\exp(-TE/T2^*)\), hence tissue with a long T2* (eg cfsf) has a relatively high signal intensity.

If TR>> T2*, allowing time for transverse magnetisation to decay, the equation simplifies to
\[ I \propto \frac{N(H)(1-e^{-TR/T1}).\sin \theta .e^{-TE/T2^*}}{1- \cos \theta .e^{-TR/T1}} \]

and the sequence becomes more T1 dependent.

**FLASH**

In common with other GE sequences, FLASH uses a small flip angle and gradient reversal to generate an echo. In contrast with FISP, however, at the end of each pulse sequence, a spoiler pulse is applied in the slice select direction which causes dephasing of any residual transverse magnetisation. The signal generated then becomes dependent on T1 relaxation, the flip angle and TR. As with FISP, magnetic field inhomogeneities are not corrected for and hence the image is T2* influenced and not T2 weighted.

**Detection of abnormalities**

Identification of abnormalities depends on a number of factors, the most important being (a) spatial resolution, (b) signal to noise ratio (SNR) and (c) the contrast between normal and pathological tissue.

**Spatial resolution**

The dimensions of the imaging voxel determines the maximum attainable spatial resolution. Voxel dimensions are determined by the slice thickness (d), the number of samples in the phase-encoding (Np) and the frequency-encoded (Nf) directions (ie the matrix size), and the field of view (D) with the following relationship;

\[ \text{Voxel volume} = d \times D/Np \times D/Nf = d \times D^2/(Np \times Nf) \]

However, perception of the image is not possible, no matter how good the theoretical spatial resolution, if there is neither adequate signal nor contrast available. Hence actual perceived resolution is also dependent on these factors.

**Signal-to-noise ratios**
Signal-to-noise ratio (SNR) is an important factor for image detection; below a certain level, images appear noisy. The magnet strength (and hence the operating frequency), and a number of factors relating to imaging and the coils used influence SNR for any given MR system.

Several imaging factors influence SNR. If the field of view, slice thickness, signal averages (NEX) and voxel volume are reduced, there is a concomitant reduction in SNR described by the relationship;

$$\text{SNR} \propto \frac{D^2}{(\sqrt{Np} \cdot Nf) \cdot \sqrt{\text{NEX}}}$$

Thus most manoeuvres performed to improve spatial resolution, such as reducing pixel size and slice thickness, also reduce SNR. These can be partly compensated for by increasing signal averages etc, at the expense of increased imaging time. Longer repetition times, shorter echo delay times, larger slice gaps and narrower receiver bandwidths will increase SNR.

Receiver coil design effects SNR; surface coils have inherently greater SNR than circumferential coils, and solenoidal coils produce greater SNR than saddle shaped coils for a given sample volume. Quadrature detection uses 2 separate phase-sensitive detectors, allowing additional detection of signal shifted in phase by 90° in relation to the reference. This improves SNR by a factor of $\sqrt{2}$ compared with a single-phase sensitive detector.

Increasing the sample volume and concentration within the coil increases SNR in a non-linear fashion.

Contrast

If there is no contrast between 2 adjacent objects, they will not be discernible from each other, no matter how high the SNR. Image contrast (C) can be defined as the difference in signal intensity (I) between 2 structures (a and b) as follows;

$$C = \frac{I_a - I_b}{I_b}$$

'Discernibility' or 'conspicuousness' of a structure is related to both contrast and SNR for the reasons outlined above, and this can be described by the contrast to noise ratio (CNR);

$$\text{CNR} = \text{SNR}_a - \text{SNR}_b$$
A further factor effecting object 'discernibility' is its size; in order to be seen small objects require higher CNR than large.

**High field strength imaging**

Most imaging was initially performed on low to intermediate strength magnets. High field strength (>1.5T) is necessary for spectroscopy, so machines capable of both MR imaging and MR spectroscopy have been developed. The main advantage of high field strength to imaging is the improvement in SNR for the reasons discussed previously. To summarise, the magnetic resonance signal is proportional to the difference in the nuclear energy levels which is, in turn, proportional to the magnetic field strength and thus, the operating frequencies. Noise has a more complex relationship to frequency, and the relationship of SNR to frequency is also partly determined by patient resistance. Under operating conditions, SNR becomes roughly proportional to the operating frequency. As the SNR, and consequently the image quality, improves with magnet strength, spatial resolution can be improved without excessive SNR deterioration.

Some authors (Glazer et al, 1988), have argued against the value of high field strength magnets, on the basis that T1-based contrast, which is not related to field strength in a linear fashion, deteriorates with increasing magnet strength. However, T2-based contrast is not field-dependent, and offers an alternative means of detecting pathology, particularly as the intrinsically improved SNR of high field systems improves the quality of T2-weighted images.

In the studies described in this thesis, T1- and T2- weighted spin-echo, gradient-echo and STIR imaging have been investigated to determine the most appropriate sequences to select for imaging of children at high field strengths.

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Figure 2.1 Spectral density plot

The spectral distribution or density $J(w)$ is defined as the number of protons rotating at each frequency across a range of frequencies. The spectral density is plotted against the frequency for a solid, a viscous liquid and a nonviscous liquid.
Primary malignant liver tumors in childhood: assessment of resectability with high-field MR and comparison with CT

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Received and accepted: 17 April 1990

Abstracts. Nine children (mean age 20 months), with proven primary malignant hepatic tumors have been examined prospectively by high-field magnetic resonance (MR) imaging to assess tumor resectability. All patients had comparative ultrasonography (US), 8 patients had X-Ray computed tomography (CT), and surgical correlation was available in 8 patients. The hepatic and portal veins and the inferior vena cava were visualized in all patients on MR and in 4 of 8 patients on CT. MR accurately defined liver parenchymal involvement in all 8 patients who had surgical exploration. CT underestimated disease in 2 cases, and defined tumour margins less clearly than MR. MR identified abnormal extrahepatic tissue when present, but was unable to distinguish viable tumor from necrotic tumor or reactive nodes. High quality short TR/short TE spin echo images were obtained by combining cardiac triggering and signal averaging. Short TI inversion recovery images demonstrated tumor and lymphadenopathy most clearly. We conclude that MR is the imaging method of choice for the assessment of liver tumor resectability in children.

Primary liver tumors constitute an uncommon but lethal group of childhood neoplasms, and surgical removal remains the definitive treatment [1–3]. Resectability is judged largely on radiological criteria, and a variety of imaging techniques has been employed to this end [4, 5]. For many years, X-Ray Computed Tomography (CT) has been accepted as the investigation of choice [1, 6], but a recent study suggests that magnetic resonance (MR) imaging at low field [7] may be a better alternative. Corroborative studies have not been reported and no published data are yet available on the use of high-field MR in the pediatric abdomen. We prospectively examined 9 children with proven malignant liver tumors in order to determine the potential role of high-resolution MRI in the assessment of tumor resectability.

Materials and methods

Nine patients aged 7 days to 5 years (mean 20 months) with histologically-confirmed primary malignant liver tumors were studied. Six had hepatoblastoma, and one each had hepatocellular carcinoma, biliary rhabdomyosarcoma and malignant mesenchymoma. Most patients presented with an abdominal mass or non-specific gastrointestinal symptoms. One patient had Beckwith Wiedemann syndrome and a liver tumor was detected on screening ultrasound (US). The patient with biliary rhabdomyosarcoma presented with obstructive jaundice. Alpha-fetoprotein levels were raised in five patients.

All patients had US imaging on admission, and 8 of these had CT scans. In one patient, MR was performed after US, without comparative CT, in order not to delay initiation of chemotherapy. Five patients received multiple courses of chemotherapy and then had US and CT to monitor tumor response. MR imaging was performed in all patients whenever surgery was contemplated and, in 3 patients, also during chemotherapy. A total of 13 MR examinations were carried out. When used preoperatively, MR and CT were carried out within 6 days of each other. Two patients had visceral angiography.

Real-time US was performed on a computed sonography unit (Acuson) operating at 5 MHz. CT was performed on a Siemens DRH machine or a Toshiba TCT60A using 10 mm contiguous slices with and without intravenous contrast enhancement. MR imaging was performed at HSC on a 1.5T machine (Siemens) with a 64 cm aperture and a circularly-polarized body coil. In 7 patients MR was carried out under sedation: two patients had general anesthesia with mechanical ventilation. Children under 2 years were sedated with chloral hydrate 50 mcg/kg orally and pethidine compound 0.06 ml/kg intramuscularly, while those over 2 years were given tripepramine 3 mg/kg orally and papaveretum 300 mcg/kg by intramuscular injection. Children under 10 kg (3 cases) were examined in an adult head coil and larger children were examined in the body coil (6 cases). All images were obtained with 256 phase encoding steps. Typically, short TR/short TE spin echo sequences were acquired in the axial and coronal planes with ECG triggering and 4 acquisitions. The R-R interval was usually between 400 and 500 ms (TR/TE/ NEX = 450/15 ms/4). Slices were nominally contiguous and slice thickness varied between 5 mm and 10 mm. No respi-
Liver tumors in childhood

Fig. 1 a, b. a Axial short TR/TE spin echo images show extensive parenchymal hepatoblastoma with complex signal changes. The tumor was poorly responsive to chemotherapy. b STIR sequence at the same level as a; the boundary between normal liver and tumor is better-defined than in a (arrow).

Fig. 2 a, b. a CT in child with hepatoblastoma within a mesenchymal hamartoma. Solid tumor (arrow) is present in continuity with a cystic mass. The segmental boundaries are not visualized. b On MR, the left hepatic vein (small arrow) is shown and abnormal signal extends across it to the superior segment of the left lobe (large arrow) – confirmed surgically. STIR sequence TR/TI/TE = 3000/150/30 ms.

Operability

Of 8 patients who had surgical exploration, 3 had successful tumor resection and 5 had inoperable tumor. The center of all 3 resected specimens contained some viable tumor and necrotic tissue and the resection margins were clear. MR correctly predicted operability in all patients. CT was correct in 6, was equivocal in 1. CT incorrectly assessed one patient as operable by failing to identify tumor involvement of the IVC and porta hepatis.

Liver parenchymal involvement

On US, tumors generally appeared as mixed echogenicity structures. The hepatic origin of the masses was correctly suggested in all cases, but tumor size was frequently difficult to assess. The origin of the biliary tumor was correctly identified on US and its cystic nature confirmed. Blood vessels were in general more clearly seen on US than CT.

On MR, all tumors had foci of prolonged T1 and T2, corresponding to low-attenuation areas on CT. In addition, 2 tumors had foci of short T1 corresponding to hemorrhage or necrosis at surgery (Fig. 1a). All patients had tumor in more than 1 segment, and MR correctly predicted the distribution in all 8 patients who had surgery. In 4 of 6 cases, hepatic parenchymal involvement as seen on CT correlated closely with MR, but MR more clearly distinguished normal hepatic parenchyma from tumor. In 2 cases, the tumor margins were poorly defined on CT, and enhancement was unhelpful. In 1 case, involvement of the lateral segments of the left lobe could not be confirmed on CT, due to non-visualization of the left hepatic vein (Figs. 2a, 2b), but this was well shown on MR. One patient with hepatoblastoma, examined after chemotherapy and immediately prior to resection, had residual tumor with low signal on a long TR/long TE spin echo sequence. For this reason, the tumor was inconspicuous. On STIR, the mass had a low-signal center with a high-signal rim. On gross inspection, the resected specimen was markedly hemorrhagic, and numerous hemosiderin-laden macrophages were seen on microscopy.
Vascular involvement

When patent, all the hepatic and portal veins were clearly shown in all 9 patients on MR and in 4 of 8 patients on CT (Fig. 3). Portal vein patency could be inferred on MR by the presence of flow void, and this was confirmed angiographically in 2 cases. The IVC was confidently seen on CT in 3 of 8 patients and was seen on MR in all 9 cases. In one patient, where tumor involved the caudate lobe, occlusion of the IVC with distension of the azygous vein was undetected on CT and ultrasound but was well shown on MR (Fig. 4). At surgery, the lumen of the IVC was occluded due to tumor infiltration and collateral circulation as seen on MR was verified. In another patient, MR showed residual tumor closely applied to the IVC and involving the right portal vein. The IVC was not seen on CT. At surgery, the MR findings were confirmed and adherent tumor-capsule was successfully dissected from the wall of the IVC. In the biliary tumor patient, the right portal vein was invaded by tumor on MR and the left portal vein was enlarged (Fig. 5). The right portal vein was not seen on ultrasound, and this patient did not have CT.

Extrahepatic disease

CT suggested tumor involvement at the porta hepatis in two cases. Retroperitoneal lymphadenopathy was not detected on CT in any case. On MR, disease at the porta hepatis or retroperitoneum was seen in 6 patients (Fig. 4). In the 8 patients who had surgical correlation, viable extrahepatic tumor was found in 2, necrotic tumor in 1, and reactive lymph node enlargement in 3 cases. Corresponding abnormalities were seen on MR in all cases.

Image Quality

Motion artifact on short TR/short TE spin echo sequences was minimal or absent. Parenchymal tumor and lymphadenopathy were more conspicuous on STIR than on the...
other sequences (Fig. 1b). Ghosting was usually present on STIR and long TR/TE sequences. High-intensity ghosts frequently originated from spleen and fluid-filled stomach, but these were generally projected clear of the liver with vertical phase-encoding. On the long TR double echo sequence (TR/TR = 2,500/22/88 ms) ghosting due to abdominal-wall fat resulted in distracting artifact projected across the liver. This was less of a problem on STIR, where fat was suppressed. The gradient echo images suffered from susceptibility artifact due to bowel gas and both tumor and lymph nodes were of lower contrast than on the STIR sequences.

Discussion

Complete excision offers the only hope of cure in pediatric liver cancers, and accurate assessment of disease is vital for appropriate timing of surgery. If tumor is confined to one lobe, simple hemihepatectomy may result in clearance, without chemotherapy. Tumor involvement of both lobes limits the surgical options to trisegmentectomy, at best. In these circumstances, chemotherapy is indicated before resection is attempted.

An imaging technique suitable for assessing resectability should detect parenchymal tumor with high sensitivity, define the relationship of tumor to vascular structures, and detect extrahepatic spread. It is well recognised that MR can provide detailed information on hepatic vascular and segmental anatomy [8, 9]. Whereas there is much debate about the relative merits of MR and CT in adult liver tumors [10–12], our experience indicates that MR is clearly superior in children. We found that CT frequently failed to show normal hepatic veins and the IVC, structures of vital importance in assessing tumor resectability. MR demonstrated these vessels reliably, even in the smallest patients. The ability of MR to show tumor involvement of the IVC, as in patient 1, is of immediate clinical importance, as undetected tumor has been associated with fatal intraoperative embolism [13].

MR accurately defined segmental tumor involvement in all patients for whom surgical correlation was available. The boundaries between normal liver and tumor were generally better shown on MR than on CT, and the STIR sequence was very effective in highlighting parenchymal tumor and abdominal lymph nodes. Although abnormal tissue was seen at the porta hepatis or in the retroperitoneum in 6 of 9 patients, viable tumor was found in only 2 of 8 who had surgery. These data suggest that MR cannot at present distinguish reactive lymph node enlargement from tumor, and abnormal signal at the porta hepatis is not sufficient for the diagnosis of extrahepatic tumor spread. Further work needs to be done if more specific features are to be ascribed to this frequent finding. Boechat et al. [7], in a study of 18 children with malignant liver tumors at low field, found that MR was unable to distinguish between hepatoblastomas and hepatomas on the basis of signal characteristics. We found similar non-specificity of signal on a variety of sequences but the distribution and homogeneity of the biliary tumor was suggestive of the diagnosis.

It has been suggested that motion compensation is unnecessary in pediatric liver imaging at low field [14]. At high field, however, motion artifact is more troublesome, due to the greater signal available from moving structures. Respiratory and cardiac motion combine to degrade images of the upper abdomen [15], but, in our experience, both of these effects can be offset by combining signal averaging [16] and cardiac triggering. Rapid heart rates in children make it practical to average ECG-triggered acquisitions, minimising artifact in short TR/TE spin echo images without prolonging the effective TR. In the coronal and sagittal planes, cardiac triggering optimises image quality in both the chest and abdomen. For long TR sequences, signal averaging becomes impractical due to excessive acquisition times, particularly in children asleep for an unpredictable period. The duration of effective sedation sets an upper limit on the number of sequences which can be run in children.

Originally designed to minimise respiratory artifact by suppressing fat [17], the STIR sequence has not been wholly successful in this regard. It has, however, proved to have advantages over long TR/long TE spin echo sequences for high-contrast imaging of adult liver tumors [18–20]. With magnitude reconstruction, signal intensity increases with increasing T1, T2 and proton density, enhancing sensitivity to increased water content. Good RF homogeneity is essential for successful STIR imaging [20], and this is easier to achieve in smaller patients. Whereas in the limited group of patients described above, critical structures were adequately visualized on STIR and/or long TR spin echo sequences, some information is invariably lost or degraded by artifact, and this must ultimately impact on diagnostic efficacy. It is therefore desirable in all patients to minimise artifact and, in complex or equivocal cases, it may become essential to do so.

The low signal on the T2-weighted sequence after chemotherapy was most likely a manifestation of T2*-shortening due to the magnetic susceptibility effect of insoluble iron. For this reason, tumor was inconspicuous against the low signal in normal liver at high field. On STIR, there was signal loss centrally, but a high-signal rim was obvious, most likely due to prolongation of T1. Susceptibility-induced signal dropout is more likely to occur at high-field than at lower field strengths [21] and this has important implications for the sensitivity of long TR/long TE pulse sequences at 1.5T in these patients. There was no correlation between low signal regions on MR and calcification seen on CT, and in our study MR was ‘blind’ to tumor calcification.

Conclusion

We conclude that MR is the method of choice for the assessment of liver tumor resectability in children. The combination of ECG-triggered short TR/short TE spin echoes and an ungated STIR sequence was sufficient to show parenchymal tumor involvement, vascular and segmental anatomy, and extrahepatic complications. The STIR sequence, although frequently associated with motion artifact, was most effective in highlighting parenchymal dis-
ease and lymph node enlargement. MR could not distin-
guish between reactive lymph node enlargement and ma-
lignant infiltration, but detected the presence of abdomi-
nal nodes with high sensitivity.

Acknowledgements: The authors would like to express their thanks
to Mrs. J. Shephered and Miss C. Young for their help with the radio-
graphic aspects of this work, to Dr. A. Connelly for technical assis-
tance and to Mr. S. Brown and his colleagues in the Department
of Medical Illustration for their help in the preparation of the manu-
script.

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4-S neuroblastoma on high field MR

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Abstract. The appearances of 4-S neuroblastoma imaged with high field strength MR are reported. The correlative pathological findings are described.

Neuroblastoma is one of the most common solid tumours of childhood and there have been a limited number of reports of its appearances on magnetic resonance (MR) [1-3]. We report the first case of 4-S neuroblastoma imaged at high field strength and using a fat nulling short tau inversion recovery sequence (STIR [4]). The correlative pathological findings are described.

Case report

A female infant born by caesarian section at term for fetal distress was found to have hepatosplenomegaly on the first day examination. She became jaundiced over the next 48 h. A spot urinary VMA was grossly elevated and a diagnosis of neuroblastoma was made. Abdominal ultrasound on day 7 showed a grossly enlarged liver containing multiple areas of hyperechogenicity and attenuation of the intrahepatic IVC.

An MR scan using a 1.5 T Siemens "Magnetom" scanner was performed on day 9. Short TR/short TE spin-echo sequences were acquired in the coronal and axial planes, with ECG triggering of the coronal scans. An untriggered STIR sequence was performed in the axial plane. The scans showed a 3 cm left suprarenal mass. Massive hepatosplenomegaly was present with the left lobe extending lateral to the spleen, displacing it medially. The intrahepatic veins and the IVC were compressed. The intrathoracic azygos vein was markedly dilated suggesting collateral flow. On the T1-weighted sequence the liver texture appeared diffusely inhomogenous, containing small patchy areas of high signal. The STIR...
sequence highlighted the liver parenchymal abnormality showing multiple high signal nodules separated by thin dark strands, replacing the normal hepatic tissue (Fig. 1a).

Despite a course of chemotherapy and intensive cardiorespiratory support the patient died aged 16 days from renal failure and disseminated intravascular coagulation. At post-mortem a 3 cm tumour was found in the left suprarenal gland. The liver was grossly enlarged and almost entirely replaced by multiple small tumour nodules separated by thin fibrous septae (Fig. 1b). Extensive patches of necrosis were seen throughout. No tumour was identified in the bone marrow. The disease distribution and histology was of stage IV-S undifferentiated neuroblastoma.

Discussion

The lack of ionising radiation makes MR an attractive imaging option in children, but as yet its place in assessing neuroblastoma is incompletely defined. Promising preliminary results have been reported [1-3]. In this patient MR was able to stage accurately and define the exact extent of the disease as confirmed by the pathological findings. This patient is also the youngest case of neuroblastoma examined by MR described in the literature and illustrates the high quality of examination possible even in the neonatal period.

On a T1-weighted spin echo sequence, the liver parenchyma in this patient showed subtle abnormalities. However the STIR sequence, which combines T1 and T2 weighting around the echo, was valuable on three counts. The lesion contrast was considerably greater and the extensive and diffuse nature of the abnormality was more clearly evident than on the T1-weighted sequence. In addition the nodular structure of the liver was only appreciable on the STIR images. Histologically the nodules were confirmed as tumour separated by thin fibrous septae. The short T1 regions identified on the T1-weighted images corresponded to areas of tumour necrosis.

A number of advantages have been ascribed to the STIR sequence in imaging adult liver tumors [5], but certain features are specific for children. Whereas in adults respiratory artefact is a particular problem, in children hepatomegaly may cause sufficient diaphragmatic splinting to prevent significant degradation of the image. In addition the small size of the paediatric abdomen makes the STIR sequence a technically less demanding experiment.

In conclusion, MRI accurately and clearly identified the abnormalities present as confirmed pathologically. The STIR sequence was optimal in demonstrating the liver parenchymal abnormalities, and shows promise as a supplementary sequence to the short TR/short TE spin echoes in imaging the paediatric abdomen.

Acknowledgement. We wish to thank Dr. J. Pritchard for his permission to report this patient.

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Received: 25 January 1989; accepted: 25 April 1989

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Wilms' Tumour: Pre- and Post-chemotherapy CT Appearances

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Pre-operative chemotherapy is used in our institution for patients with Wilms' Tumours (WT) when surgical 'operability' is in doubt. To date, the computed tomographic (CT) appearances of chemotherapy-induced changes in WT have not been described. We have analysed CT examinations of 18 children undergoing pre-operative chemotherapy to assess the effects of treatment on size, extent and qualitative changes of the tumour.

Clinical response to chemotherapy was associated with a reduction in tumour size of at least 50%. Cystic changes were commonly seen within tumours following chemotherapy. CT did not reliably differentiate lymph nodes involved by tumour from those showing only reactive change. Pre-chemotherapy CT scans were incorrect in predicting liver invasion in 4/18 (22%) cases: of these, two were right-sided tumours, and two were bilateral. Ng, Y.Y., Hall-Craggs, M.A., Dicks-Mireaux, C. & Pritchard, J. (1991). Clinical Radiology 43, 255–259. Wilms' Tumour: Pre- and Post-chemotherapy CT Appearances

Wilms' tumour (WT), a renal embryoma, is one of the most common solid abdominal tumours of childhood (Breslow and Langholz, 1983). With the advent of modern therapy, overall 5 year survival rates have improved to 80–90% over the last 70 years (D'Angio et al., 1976, 1981, 1989; Lemerle et al., 1983).

There are very few reports of the validation of CT staging at presentation (Reiman et al., 1986), and none of radiological assessment of disease following chemotherapy. In our institution, pre-operative chemotherapy is used in children with stage IV and V tumours (D'Angio et al., 1976), and in some with very large tumours. Initial disease stage, therefore, has to be assessed radiologically. We have analysed retrospectively the CT scans of a group of WT patients, performed before and after chemotherapy, and correlated the appearances with surgical and pathological findings.

PATIENTS AND METHODS

Eighteen children with histologically-confirmed WT were included in this study. The age range was 11 months to 9 years and 4 months (median 3 years) and there were 12 girls.

All patients had abdominal CT scans both at presentation and after chemotherapy, just before surgery a total of 36 scans in all. Between the two scans, the chemotherapy consisted of pulsed actinomycin D, vincristine and Adriamycin (stage III, IV and some stage V), or vincristine and actinomycin D (some stage V tumours) for 1–7 months (median 5 months, six courses). Sixteen initial scans were performed before and after enhancement with intravenous contrast medium. Dynamically-enhanced scans only were performed at follow-up. Ten were attempted in all patients except those in whom the inferior vena cava (IVC) had been definitively evaluated on an initial screening ultrasound (US) scan. Enhanced scans only were performed at follow-up. Ten millimetre contiguous slices were taken through the abdomen in all patients. Seventeen lung CT scans and one of the brain, performed at the time of diagnosis, were also available for review.

CT scans were evaluated for location and volume of primary tumour, presence of calcification and other areas of altered attenuation within the tumour mass, local invasion into the liver or adjacent organs, evidence of enlarged lymph nodes, involvement or displacement of the IVC and involvement of the contralateral kidney. The presence of metastases in the lungs, liver and brain were also noted. Liver invasion was scored as 'probably invaded', 'possibly invaded' and 'definitely not invaded'. Invasion was scored as 'probable' where the tumour seemed to be in intimate contact with intrahepatic vessels, and the residual mass of the liver parenchyma was reduced.

Seventeen patients underwent surgery following chemotherapy; the follow-up CT scans were performed within one month of surgery in 11 patients. One child died during treatment and was examined at autopsy. Surgical and pathological findings were correlated with the CT observations.

RESULTS

Primary Tumour

Tumours were bilateral in six patients, right-sided in eight, and left-sided in four. Initial tumour volume varied from 2 to 1700 cm³ (median 600 cm³). Bilateral tumours were consistently smaller than solitary tumours, with median volumes of 353 cm³ for bilateral tumours as compared with 850 cm³ for right-sided, and 1117 cm³ for left-sided tumours. Sixteen had favourable histology tumours, and five had associated nephroblastomatosis.

Tumour volume reduction of 52–99% (median 85%) occurred in 17 of 18 patients, but there was no direct relationship between the degree of shrinkage and duration of chemotherapy. In the remaining child, whose tumour was of unfavourable histology, tumour size decreased by only 26% following four courses of chemotherapy, and this was associated with a poor clinical response to treatment. Disease relapse occurred during
Fig. 1 - (a) Enhanced axial CT scan at presentation showing a large right-sided Wilms' tumour of mixed attenuation. (b) Following 3 months of chemotherapy, the tumour has become smaller, with replacement of the solid component by a multiseptated cystic mass.

Fig. 2 - (a) Initial axial CT scan shows a large right-sided Wilms' tumour of mixed attenuation with 'probable' liver invasion; microscopic infiltration confirmed at pathology. Note lobulated contour of tumour, with a relatively small residual mass of normal liver parenchyma. (b) Following 3 months of chemotherapy, the tumour has reduced markedly in size, with the development of some peripheral calcification.

treatment in the other child with unfavourable histology, associated with an 84% increase in tumour size following a favourable initial response.

Areas of low attenuation developed in 12/18 patients following chemotherapy (Fig. 1). These regions correlated with cystic and necrotic areas within the resected tumours. Four tumours showed no cystic change. There were cystic areas in two tumours before treatment; one tumour became less cystic and the other was unchanged. Eight tumours developed calcification following chemotherapy (Fig. 2), two became more calcified, six were uncalcified, and one partially calcified tumour showed no change. One child did not have an unenhanced scan at presentation, and therefore could not be evaluated for calcification.

**Lymph Node Involvement**

Lymph nodes were considered to be abnormal on CT if >15 mm in any diameter, or of heterogeneous attenuation. The results are summarized in Table 1. Lymph nodes were surgically removed in 12/18 patients. Two of eight patients with enlarged lymph nodes on the pre-chemotherapy CT scan had persistent nodal enlargement following chemotherapy, but neither showed identifiable persistent tumour. However, there was a 2-month interval between the CT and tumour removal in these two patients. Tumour was only found in one of the 'normalized' nodes (12 × 6 mm) which was enlarged at

<table>
<thead>
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<th>Lymph node size</th>
<th>Pre-chemotherapy</th>
<th>Post-chemotherapy</th>
<th>Surgery</th>
<th>Histology</th>
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<tr>
<td>&gt;15 mm</td>
<td>8</td>
<td>2</td>
<td>5</td>
<td>All five normal</td>
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<tr>
<td>Normal (up to 15 mm)</td>
<td>10</td>
<td>16</td>
<td>7</td>
<td>One had tumour, six had no tumour</td>
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diagnosis. Nodal disease was not assessed in the child examined at post-mortem.

In our series, all eight children with enlarged lymph nodes at presentation are alive and disease-free, up to 24 months after therapy. Of those with normal-sized lymph nodes (10 children), four have died: two after pelvic recurrence, one after local relapse, and the fourth child of a treatment complication. One child is receiving chemotherapy for a second abdominal relapse, and the other five are still alive and disease-free, up to 42 months after therapy.

Liver invasion

The results of CT evaluation of liver invasion are summarized in Table 2. CT suggested that none of the left-sided tumours involved the liver, and this was confirmed at surgery. Of eight unilateral right-sided tumours, two did not invade the liver but six were adherent to it. Two of these tumours required wedge resection of the liver together with tumour mass, and the other four were dissected from the liver. Tumour infiltration was confirmed histologically in one patient, excluded in four, whilst in the sixth child, surgical disruption of the capsule precluded assessment of microscopic invasion. None of the bilateral tumours invaded the liver, although two were thought to show 'possible' invasion on the pre-chemotherapy CT scan.

Analysis of pre-treatment CT scans gave a 100% predictive value for absence of liver invasion (8/8 cases). However, four were left-sided tumours and the four bilateral tumours were smaller than average (median 353 cm^3). All three children with 'probable invasion' had adherent livers at surgery (Fig. 3), and one of these showed microscopic infiltration (Fig. 2a). The tumours were adherent to the liver in three of seven children whose CT showed 'possible invasion' (Fig. 4). The other four children with 'possible invasion' had normal livers at surgery (Fig. 5).

There was poor correlation between post-chemotherapy CT and surgical/pathological findings. Fourteen children were thought to have no liver invasion on CT:

<table>
<thead>
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<th>Patient</th>
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<td>Right WT 1</td>
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<td>16</td>
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<td>17</td>
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<td>18</td>
<td>N</td>
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</table>

Y +, 'Probably invaded'; Y -, 'Possibly invaded'; N, 'Not invaded'.
N (adh), adherent, but no tumour infiltration. *
* capsule disrupted.

Fig. 3 - Enhanced axial CT scan showing 'probable' liver invasion, found to have adherent liver at surgery. Note proximity of tumour to intrahepatic vessels.

Fig. 4 - Enhanced axial CT section on a child with a large right-sided tumour showing 'possible' liver invasion. The liver was found to be adherent to tumour at surgery.

Fig. 5 - Enhanced axial CT scan showing a large right-sided Wilms' tumour with 'possible' liver invasion, found to be normal at surgery.
four (29%) were abnormal at surgery/pathology – one was invaded and three were adherent, only 10 were normal. The accuracy of the prediction of 'no liver invasion' was 71% (10/14), and of 'probable' or 'possible' invasion was 50% (2/4).

**Metastases**

Six children had pulmonary nodules at presentation on chest radiography and on CT. All regressed completely following chemotherapy. No liver metastases were detected and one child had a normal CT brain scan.

**IVC Invasion**

Two children had evidence of IVC thrombus on CT and/or US scan at presentation confirmed at the time of delayed surgery. In the remainder, the IVC was normal on both CT scans and at surgery.

**Disease Stage Before and After Chemotherapy**

Five patients each had two laparotomies – one at diagnosis and the other after a median of 6 months' chemotherapy; a sixth child had a laparotomy, but died of a treatment complication 5 weeks later, and underwent autopsy. Since all potential sites of tumour were biopsied at the second laparotomy or autopsy, pre- and post-chemotherapy stage could be compared in these children. Initially, all had biopsy-confirmed stage V disease. CT scan at 0–12 weeks (median 2 weeks) before the second laparotomy/autopsy showed residual non-enhancing masses in 11/12 kidneys (5/6 patients). However, laparotomy confirmed that chemotherapy had eradicated tumour from one kidney in three children, and from both kidneys in two. Coexistent biopsy-proven nephroblastomatosis had confounded interpretation in each case.

**DISCUSSION**

The incidence of intra-operative rupture and the associated increased risk of abdominal recurrence can be reduced by pre-operative chemotherapy (Leape et al., 1978; Lemerle et al., 1983). In our institution, pre-operative chemotherapy is used to facilitate resection in children with tumours judged to be 'inoperable' at diagnosis, and for some of those with very large tumours. In this study we attempted to document radiologic changes ascribed to chemotherapy and to assess how well CT defines the extent of disease following treatment.

In our series a number of tumours developed cystic change and calcification on CT following chemotherapy. Changes in tumour size correlated well with histologic subtype (favourable histology vs unfavourable histology) albeit with small numbers, and also with clinical response to chemotherapy. Pathologically, extensive necrosis and prominent vascular changes have been described after chemotherapy (Guarda et al., 1984) but it is important to emphasize that, occasionally, tumour may respond to treatment with cystic change only and no significant decrease in size (Shimizu et al., 1987).

Following treatment, the CT appearance of lymph nodes was a poor indicator of tumour involvement as microscopic infiltration of normal-sized lymph nodes was not detected, and enlargement was due to reactive change in all cases.

Radiological evaluation of liver invasion by tumour is difficult. The main problem is with large right-sided tumours which either indent or infiltrate the liver. The pre-treatment CT scan is better than the delayed scan as a predictor of post-chemotherapy surgical findings; it can accurately predict absence of liver invasion. In those cases with a 'high probability' of liver invasion, tumour adherence is likely. Problems remain with the 'low probability' group as CT does not accurately identify or exclude tumour adherence. As an initial laparotomy was not performed in most of these children, the significance of 'adherence' at second surgery is unclear. Whether this reflects just an inflammatory reaction or tumour infiltration which has regressed following chemotherapy is open to speculation.

The treatment of WT is determined by stage and histological sub-type (D'Angio et al., 1981). The correlation of CT with initial surgical findings has been evaluated in only small numbers of patients, with an accuracy of only 77% (Reiman et al., 1986). In that study, errors resulted from failure to diagnose lymph node involvement, small liver metastases, and microscopic spread of tumour locally or into the IVC. All of our patients had pre-operative chemotherapy, so we were unable to evaluate the accuracy of CT staging at the time of diagnosis. However, we confirm the lack of specificity and sensitivity of CT in assessment of lymph node involvement and liver invasion. These shortcomings seriously limit the value of CT for staging.

In conclusion, the principal value of CT in children with WT following chemotherapy is to provide objective documentation of clinical response to therapy, thereby helping to identify the best timing for surgery. There are a number of unresolved, and perhaps unresolvable, problems, however: residual nephroblastomatosis cannot be distinguished from WT, liver invasion cannot be identified or excluded with certainty, and lymph node involvement cannot be accurately assessed. Studies evaluating the role of magnetic resonance imaging should be designed with these questions in mind.

**Acknowledgements:** M.A.H.C. is supported by Action Research for the Crippled Child and J.P. by the Imperial Cancer Research Fund.

**REFERENCES**


Sedation in children scanned with high-field magnetic resonance; the experience at The Hospital for Sick Children, Great Ormond Street

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(Received March 1990)

Abstract. Patient movement is the most common cause of image degradation when performing magnetic resonance scans in children. This is a particular problem scanning at high field, as noise levels of up to 90 dB may be reached. Movement can be reduced by adequate sedation. We present the results of two sedation protocols when scanning with a 1.5T Magneton scanner. Optimal scan quality can be achieved in up to 85% of scans using Pentothal combined with triflofos in children aged 1 month–2 years, and trimeprazine combined with papaveretum in children over 2 years. When heavy sedation is used, patient selection must be cautious, and there is a minimum acceptable level of monitoring including close physical observation, electrocardiographic and apex aortic monitoring.

Patient movement is the main cause of image degradation when performing magnetic resonance (MR) scans in children. At our hospital, a Siemens Magnetom MR scanner operating at 1.5 T is used for imaging. Gradual switching during sequences generates noise levels of up to 90dB (0.01dB), which is frightening for children and prevents speech being heard. For a successful abdominal scan, a child must be able to tolerate lying still for 1–2 hours, and must be completely still for periods of up to 15 min during the data acquisition of each sequence. Most young children find it impossible to keep still for any length of time in a scanner; the child lies in a confined, enclosed space with restricted parental contact.

This problem can be partly solved by sedating children who are unable to tolerate these conditions. A number of different sedation regimens have been described for use in MR, most based on modifications of those used in computed tomography (CT) units. Most authors report having to sedate children up to the ages of 3–7 years (Smith, 1983; Cohen et al., 1986; Dietrich & Kangerlo, 1988). Chloral hydrate has been widely advocated in doses of 50–100 mg/kg (Cohen et al., 1986; Dietrich & Kangerlo, 1988), although Ringertz et al. (1985) found pentobarbitone more successful than chloral. These studies have all been performed at low field, when the noise generated is a background hum. Because of the additional problems anticipated with the higher noise levels of a high-field system, a more aggressive approach to sedating children was adopted than that described by other investigators. The sedation protocols devised and the results of sedation are reported.

Patients and methods

Two sedation protocols were assessed. Initially, the protocol used for CT scanning in our hospital was adopted (Protocol 1, Fig. 1). All patients undergoing scans were sedated according to this regimen. Patient age, the region scanned, drugs administered, the requirement for a "top-up" with intravenous diazepam (Diazemuls®), and the total examination time were recorded. The quality of the examination was assessed and classified as optimal, suboptimal or as an abandoned procedure. An examination was considered optimal if a complete diagnostic scan, with insignificant movement artefact was obtained. If movement artefact significantly degraded images, or if the examination was curtailed because the patient awoke, the examination was classified as suboptimal. Scanning was abandoned when movement produced non-diagnostic images.

Early experience of this regimen suggested that the success rate in obtaining satisfactory scans was not adequate. A new protocol was devised (Protocol 2, Fig. 1), and the results of this compared with those of Protocol 1. The g test was used to analyse the statistical significance of the results.

Patients were not sedated when parents refused permission for sedation, when the child was considered old enough (i.e. over 10 years) and co-operative enough to tolerate the procedure and when clinicians particularly wished that a younger, compliant child should be scanned without drugs. In these cases, whenever possible, the child was shown the scanner prior to the scan, was warned of the noise, and had a parent present during the scanning procedure. Parents were encouraged to hold the child's feet (hands are inaccessible), and to talk to the child between sequences.

Results

A total of 375 examinations was assessed and comparison of the results using Protocols 1 and 2 is shown in Table 1.

Protocol 1

Pethco. Thirty-six patients with a mean age of 21 months (range 5–37 months) were sedated with Pethco alone (a combination of 35 mg pethidine, 6.25 mg promethazine and 6.25 mg chlorpromazine in 1 ml). Optimal scans were obtained in 83.5% of children scanned and 55% of patients required an intravenous “top-up” with Diazemuls.

Droperidol and trimeprazine. Seventy-nine patients with a mean age of 6.2 years (range 10 weeks–17 years) were sedated with droperidol and trimeprazine. Optimal scans were obtained in 74.7% of patients and 44% of children required a “top-up” with intravenous Diazemuls in addition to their initial sedation.

Protocol 2

Pethco and triflofos. Seventy-nine patients with a mean age of 9.5 months (range 1 week–28 months) were sedated with Pethco combined with triflofos. Optimal scans were obtained in 83.5% of patients scanned and 38% required a “top-up”.

Trimeprazine and papaveretum. One hundred and twenty-seven patients with a mean age of 6.0 years (range 6 months–15 years) were sedated with trimeprazine and papaveretum. Optimal scans were obtained in 85% of children scanned and additional intravenous Diazemuls was required in 46% of children.

Patients receiving no sedation

Fifty-five children were scanned with no sedation given prior to the procedure. The mean age for this group was 11.7 years, with an range of 4.20 years, and the results are presented in Table 2. Intravenous diazepam was given in three children (5.5%), and the scans were optimal in each case. The abandoned scans occurred in children aged 4, 8, 9, 10 and 15 years.

Since the age profiles are similar, the results of Pethco alone can be compared with Pethco and triflofos, and droperidol and trimeprazine can be compared with papaveretum and trimeprazine. Compared with Pethco alone, combining Pethco with triflofos increased the proportion of optimal examinations from 67% to 84%, and reduced the number of scans of less than optimal quality from 33% to 16% (0.05 < / < 0.02); despite an overall increase in examination time. Compared with trimeprazine and droperidol, papaveretum and trimeprazine increased the proportion of optimal scans from 75% to 85% and reduced the number of scans of less

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The British Journal of Radiology. October 1990

Vol. 63, No. 754

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than optimal quality from 25% to 15% (*P > 0.05 > *P < 0.02), despite increased examination times.

Alternatively, the two protocols can be compared by age group, and the results for each protocol in children under and over 5 years are shown in Table III. Modifying the sedation protocol improved the proportion of optimal examinations from 71% to 83% for children under 5 years (*P < 0.05 > *P < 0.05), and from 75.5% to 88% (*P > 0.05 > *P < 0.05) in children over 5 years.

Unwanted effects

Two patients sedated with Pethco developed upper airway obstruction when placed in the supine position within the scanner. Both children recovered when placed in the "coma" position and a scan was not attempted in either child. One child with Stage 4S neuroblastoma, with extensive hepatic infiltration slept for a prolonged period (24 h), after being sedated with Pethco and trichofon.

Discussion

The difference between sedation and general anaesthesia lies in the potential for patients to be roused by the majority.

The most serious unwanted effect is respiratory depression and, because of this, we tried to avoid the exclusive use of opioids. Nevertheless, intramuscular opioids give very reliable sedation, hence when the protocol was modified, an injected opioid (papaveretum) was combined with an oral hypnotic in older children. In younger children, trichofon, which has little effect on respiration, was chosen in combination with Pethco, a recognized respiratory depressant. Naloxone reverses the respiratory depressive action of narcotics, analgesics, and as a precaution, is kept available at all times.

As with any sedative technique, care must be exercised in the choice of patient. There are four groups of patients in whom sedation should be used with extreme caution.

(1) Those with upper airway abnormalities causing obstruction, including obstructive sleep apnoea syndrome.

(2) Those with abnormalities of the respiratory centre, e.g. mitochondrial cytopathies and brain stem tumours, or conditions causing desensitization of the respiratory centre to carbon dioxide, e.g. chronic lung disease with a raised carbon dioxide level.

(3) Those with abnormalities of metabolism or excretion, e.g. renal and hepatic dysfunction. This group also includes normal neonates (i.e. children less than 45 weeks gestational age), in whom the pharmacokinetics of sedative drugs are extremely variable.

(4) Those with conditions in which a rise in carbon dioxide levels would be detrimental, in particular patients with raised intracranial pressure.

Modifying the sedation protocol has increased the proportion of children successfully scanned. If sedation is inadequate, either the scan has to be abandoned or performed under general anaesthesia. This has cost and time implications, and general anaesthesia may be undesirable in a child undergoing further anaesthesias for other investigative procedures or surgery.

Because of the individual variation in response to sedative drugs, and because the doses used in these protocols are at the upper end of those which may be safely used, adequate monitoring of vital functions is essential. This is very difficult in the setting of a high-field strength MR scanner. We feel that close physical observation, supplemented by electrocardiogram and apnoea monitoring (Graseby Medical MR 10) is the minimum acceptable. Pulse oximetry would be ideal but despite trying several we have not, as yet, found an oximeter which performs reliably within the bore of the magnet, operating at high field.

Table II. Patients scanned without sedation

<table>
<thead>
<tr>
<th>% of examination</th>
<th>Number</th>
<th>Age range</th>
<th>Mean age</th>
<th>Region scanned</th>
<th>Scan quality</th>
<th>Scale time (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abandoned</td>
<td>5 (13.8)</td>
<td>&gt; 90</td>
<td>11 (13.9)</td>
<td>11 (14.4)</td>
<td>22 (28.8)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Suboptimal</td>
<td>5 (13.8)</td>
<td>61-90</td>
<td>16 (20.3)</td>
<td>35 (44.5)</td>
<td>52 (64.9)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Optimal</td>
<td>2 (5.5)</td>
<td>30-60</td>
<td>48 (60.8)</td>
<td>23 (31.6)</td>
<td>47 (57.0)</td>
<td>8 (10.5)</td>
</tr>
<tr>
<td>Others</td>
<td>18 (30)</td>
<td>&gt; 90</td>
<td>48 (60.8)</td>
<td>23 (31.6)</td>
<td>47 (57.0)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Scanned</td>
<td>50 (75.4)</td>
<td>&lt; 30</td>
<td>4 (5.1)</td>
<td>1 (1.3)</td>
<td>4 (5.1)</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Numben</td>
<td>50 (75.4)</td>
<td>&lt; 30</td>
<td>4 (5.1)</td>
<td>1 (1.3)</td>
<td>4 (5.1)</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Completed</td>
<td>27 (49.5)</td>
<td>&gt; 90</td>
<td>11 (13.9)</td>
<td>11 (14.4)</td>
<td>22 (28.8)</td>
<td>7 (8.9)</td>
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</tbody>
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References


