Abdominal and pelvic tumours in children

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Abstract

The abdomen and pelvis are common sites of origin for childhood cancers. After haematological malignancies and intracranial tumours, neuroblastoma is the most common childhood cancer most often arising in the adrenal gland. The next most common extracranial tumours are Wilms tumour, arising in the kidney (nephroblastoma), and rhabdomyosarcoma that may arise in a variety of sites, typically in the pelvis. Hepatoblastoma, non-Hodgkin lymphoma and germ cell tumours are other abdominal and pelvic tumours seen in childhood. Many childhood tumours appear to arise from residual embryonic cells, which makes them sensitive to chemotherapy and radiotherapy. Surgery plays a crucial role both in establishing the diagnosis and, in the majority of cases, by resection of the tumour.

Keywords Chemotherapy; hepatoblastoma; neuroblastoma; non-Hodgkin lymphoma; radiotherapy; rhabdomyosarcoma; sacrococcygeal teratoma; Wilms tumour

The abdomen and pelvis are common sites of origin of childhood cancers. After haematological malignancies and intracranial tumours, neuroblastoma is the most common childhood cancer, followed by Wilms tumour and rhabdomyosarcoma.

The outcome of childhood cancers has improved dramatically in recent decades with a multimodality approach to treatment, utilizing surgery, chemotherapy and radiotherapy via clinical trials under the auspices of the Children's Cancer and Leukaemia Group (CCLG), International Society for Paediatric Oncology (SIOP) and the Children's Oncology Group (COG). Despite this, 20% of children and adolescents diagnosed with cancer will still die of their disease. Nonetheless, the outcomes for some patients are now so good that the focus of trials for low-risk disease has shifted to reducing therapy to minimize late effects: 60% of survivors will develop at least one chronic condition related to their previous treatment such as cardiomyopathy, hearing loss, cognitive dysfunction, skeletal growth restriction, infertility, hypothyroidism or secondary malignancies, and up to 25% of these may be severely disabling. The most common childhood abdominal and pelvic tumours will now be discussed.

Adrenal

Neuroblastoma is the most common extracranial solid tumour of childhood. With an incidence of 9.5 per million children, it accounts for 7.8% of all childhood cancers and around 5% of all paediatric cancer related mortality. Neuroblastomas arise anywhere within the sympathetic nervous system; 65% are adrenal in origin.

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Rarer adrenal tumours in childhood include phaeochromocytomas, arising in the adrenal medulla, and adenomas and carcinomas arising from the adrenal cortex. These tumours typically present with symptoms of hypersecretion of hormones. Hence phaeochromocytomas cause hypertension and other symptoms of increased adrenal secretion, whilst adrenal cortical tumours may present with symptoms of Cushing disease or virilization/precocious puberty. At least 10% of childhood phaeochromocytomas are associated with clearly defined hereditary syndromes such as multiple endocrine neoplasia type II (MEN). Of the remaining sporadic cases, at least 25% will be demonstrated to have new gene mutations and these patients should be referred for genetic assessment.

Neuroblastoma

Neuroblastoma is a small round blue cell tumour that arises from cells of neural crest origin. At least 80% of neuroblastomas arise within the abdomen, with 65% situated within the adrenal gland, but they may develop anywhere along the sympathetic chain in the neck, chest or abdomen. Eighty-five per cent of neuroblastomas occur in children under 4 years of age. Its aetiology is unclear. Familial occurrence is rare.

The clinical presentation is varied and often vague. It may present with a mass at the site of origin, but more frequently presentation is late with symptoms of metastatic disease such as bone pain due to bone metastases or anaemia and bruising secondary to extensive bone marrow involvement. Paraspinal tumours may grow through the vertebral foramina causing symptoms of cord compression. Classic but rare manifestations include periorbital bruising 'raccoon eyes' due to orbital involvement, skin invasion causing subcutaneous nodules, 'blueberry muffin' lesions or opsoclonus–myoclonus, a paraneoplastic syndrome where children have symptoms of rapid bursts of chaotic eye movements (opsoclonus), irregular jerking movements, and ataxia.

Diagnosis of neuroblastoma is made by biopsy of the tumour, providing sufficient tissue for biological studies. Cross-sectional imaging of the neck, chest and abdomen is used to assess local tumour extent and metastatic disease. To reduce the radiation burden of recurrent assessments, the overall drive is now towards utilizing MRI rather than CT scans where possible for imaging all paediatric malignancies. Calcification is seen within 90% of tumours and is strongly suggestive of the diagnosis of neuroblastoma. All children should have two site bone marrow aspirates and a bone scan to assess for metastatic disease. Elevated urinary catecholamines are useful in diagnosis and for monitoring response to therapy and recurrence. I^{131}-metaiodobenzylguanadine (MIBG) is a radiolabeled derivative of noradrenalin that is taken up by neuroblastoma tissue at primary and metastatic sites in the majority but not all cases of neuroblastoma. It is useful for detecting occult metastatic disease, response to therapy and recurrence (Figure 1).

Historically, several different staging systems for neuroblastoma were in use around the world, which led to difficulties comparing different trials. Furthermore, a variety of biological factors (MYCN amplification, 11q aberrations, DNA ploidy) have become apparent as relevant to prognosis. The International Neuroblastoma Risk Group Staging System (INRGSS) is based on radiological features, and a comprehensive risk stratification

system of clinical (patient age, tumour stage) and biological variables, all of which are independent prognostic variables of disease progression (Table 1). This gives rise to four risk groups, very low, low, intermediate and high with 17 subgroups (A–R). The new staging system will facilitate international collaboration and development of improved treatment regimens and novel therapies to minimize morbidity in low-risk patients and improve outcomes for high-risk groups.

Increasingly, biological markers are being studied as ways of categorizing disease and stratifying treatment. Approximately 30% of neuroblastomas show amplification of the MYCN oncogene (>10 copies): overall these patients have rapid disease progression with 90% dying regardless of therapy, denoting MYCN amplified disease as high risk. The DNA index refers to the amount of DNA within the nucleus of the cell compared with the expected amount. Hyperdiploidy (DNA index >1) has been shown to correlate with a better response to chemotherapy, lower stage disease at presentation and better overall outcomes.

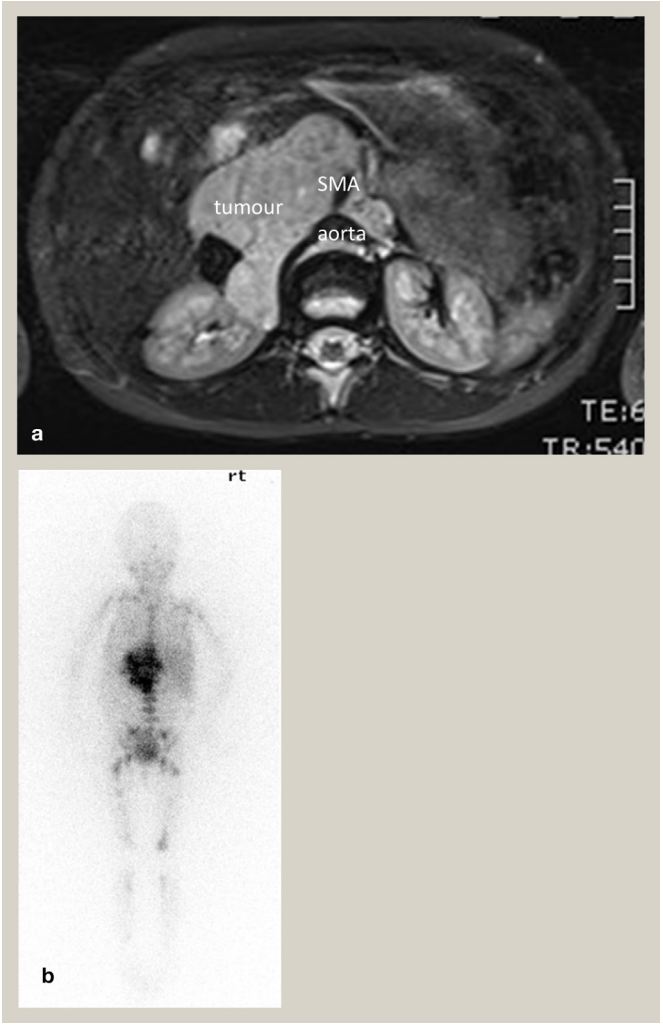

Figure 1 (**a**) MRI scan showing neuroblastoma, arising from the right paraspinal region, encasing the aorta and superior mesenteric artery (SMA). (**b**) MIBG scan (seen from posteriorly) demonstrating a left adrenal neuroblastoma and extensive metastatic disease in the bone and bone marrow. MIBG is excreted in the urine hence the bladder is also strongly positive on the scan.

A variety of other potential biological markers are being investigated and the INRG classification system can evolve to incorporate these when they are demonstrated to have a clear and independent role in influencing outcome and are thus of use in treatment stratification.

Low-risk neuroblastoma may be treated by surgery alone with excellent cure rates. Tumours with no image-defined risk factors (surgical risk factors) may undergo primary resection, whilst tumours with image-defined risk factors (e.g. vessel encasement) will benefit from preoperative chemotherapy to decrease surgical morbidity. Even incompletely resected low-risk disease is considered to require only close monitoring rather than any further treatment. Chemotherapy is indicated only for recurrence or residual symptomatic disease, e.g. cord compression symptoms.

Surgery and chemotherapy, with agents including cyclophosphamide, doxorubicin, cisplatin and etoposide, are the mainstay of treatment for intermediate risk neuroblastoma. Preoperative chemotherapy is given to try to shrink the tumour and decrease its vascularity prior to resection which aims to remove the tumour with clear margins but without damage to adjacent structures.

High-risk neuroblastomas include all MYCN-amplified tumours and metastatic disease, except the specialist subgroup Ms of restricted metastatic disease and favourable biology in patients less than 18 months old, which has a more favourable prognosis. Treatment of high-risk neuroblastoma is multimodality. Patients receive high-dose chemotherapy prior to surgery. Tumours grow encasing surrounding vessels and structures, including the aorta and IVC, making surgical resection very challenging (Figure 1). The benefits of surgical resection of stage 3, and especially stage 4 high-risk tumours remains controversial. There is some good evidence to suggest that >90% resection is as effective as complete resection with less morbidity when performed as part of multimodality treatment. Surgery is followed by further high-dose chemotherapy with bone marrow ablation and stem cell rescue. Retinoic acid, to encourage cell maturation, immunotherapy with antibodies to GD-2, highly expressed on neuroblastoma cells, and radioactive MIBG are then used to eliminate minimal residual disease and consolidate remission.

Localized neuroblastomas detected on fetal or neonatal imaging form a special subgroup that tend to regress spontaneously and can simply be monitored. Non-MYCN-amplified Ms tumours can similarly be managed expectantly though occasionally local symptoms, e.g. liver disease causing such significant enlargement with systemic compromise, require treatment to ameliorate these effects.

Neuroblastoma continues to carry a bleak prognosis overall. Low- and intermediate-risk tumours carry an excellent prognosis approaching 90% survival. Unfortunately the majority of patients present with high-risk disease with survival at most 60% for children under 5 years of age but only 30% for older children.

Kidney

Wilms tumour is the most common renal tumour of childhood and the second most common abdominal tumour accounting for 6–10% of cases of childhood cancer. Mesoblastic nephroma,