FOCUS ON: ONCOLOGY

Anaesthesia and paediatric oncology

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Summary
Children with cancer present unique challenges to all concerned with their management. The disease process and its treatment can have a profound impact on the patient’s physiological and psychological state. Anaesthetists are often involved in the diagnosis, treatment and emergency resuscitation of these patients.

This article aims to review the anaesthetic issues associated with childhood malignancy and the increasing role played by the anaesthetist as part of the multidisciplinary team caring for these children. There is particular focus on the anaesthetic techniques used for radiotherapy and short painful procedures within this patient population.

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Introduction
In the UK there are about 1500 new cases of childhood cancer diagnosed each year. Cancer accounts for about 20% of the deaths in children aged 1–14 years1 and one third of all childhood cancers are leukaemias. Acute lymphoblastic leukaemia (ALL) is by far the most common representing 80% of all childhood leukaemias and 25% of all childhood cancers. It commonly occurs between 1 and 6 years with a peak incidence at 2–3 years. Lymphomas are much less common and account for less than 10% of childhood cancers. Brain and spinal tumours account for 25% of childhood cancers. These are most commonly astrocytomas, primitive neuroectodermal tumours and ependymomas. Embryonal tumours make up about 15% of childhood cancers. These tumours arise due to proliferation of tissue normally only seen in the developing embryo and include: medulloblastoma, neuroblastoma (proliferation of sympathetic nervous system tissues), retinoblastoma, Wilm’s tumour (nephroblastoma), hepatoblastoma and embryonal rhabdomyosarcoma in soft tissue. Rarer cancers include bone tumours, soft tissue sarcomas and germ cell and gonadal tumours.

Cancer is about one fifth more common in boys. Childhood cancers have a much better response and survival rate than adult cancers. Overall the 5-year survival rate is about 75% this increases to around 80% in ALL. Chemotherapy, radiotherapy and surgery are the principle methods used in the treatment of cancer. Surgery may be in the form of curative resection or tumour debulking. Cytotoxic drugs target tumour cells throughout the body. They damage DNA through a variety of mechanisms,
causing cell death or preventing cell replication. They are classified according to their mode of action but have certain side effects in common which include myelosuppression, nausea and vomiting, and alopecia.

Radiotherapy provides local disease control and can provide synergistic cytotoxicity when used in combination with chemotherapy. Radiotherapy generates free radicals that damage DNA thus interfering with cell function. Well vascularised and oxygenated tissues are more sensitive as they have a rich oxygen supply for free radical formation. Rapidly proliferating tissues are more susceptible, for example skin and mucosa, which accounts for the common side effects of local erythema and desquamation. Radiotherapy is used as a primary therapy, as an adjuvant or neoadjuvant therapy either alone or in combination with chemotherapy, and also in the setting of symptom palliation.

Anaesthetic implications of childhood cancer

The disease process itself may have implications for the anaesthetist. This is dependent on the disease type and its site of presentation. A thorough history and examination is extremely important for all paediatric cancer patients. Particular emphasis should be placed on the anatomical effects of the cancer. Also the systemic effects of the cancerous process must be considered and appropriately investigated.

Airway pathology

Tumours directly involving the airway are relatively rare in children. However enlarged tonsils and adenoids secondary to leukaemic infiltration are quite common. These may cause obstructive sleep apnoea with the associated anaesthetic problems. Cervical adenopathy can be large enough to cause airway compromise and leukaemic infiltration of retropharyngeal lymph nodes may present as stridor. Immunocompromised children may also present with opportunistic infections of the upper airway causing life-threatening airflow obstruction. Mucositis associated with chemotherapy may cause bleeding and painful blistered mucosa within the oral cavity. The injury to the digestive mucosa extends throughout the gut hence intestinal motility maybe affected. There has been a report of hyperkalaemia with suxamethonium use in a patient with extensive mucositis. The proposed mechanism is similar to the hyperkalaemic response seen in thermal injuries.

Mediastinal pathology

One of the most significant oncological anaesthetic problems is the child that has a mediastinal mass. Hodgkin’s lymphoma, T-cell ALL and T-cell non-Hodgkin’s lymphoma can have massive anterior mediastinal masses at presentation. Masses in the anterior mediastinum can cause severe tracheobronchial compression. There may also be compression of the heart and great vessels (see Fig. 1). The compression of the trachea may extend well below the level of the carina hence endotracheal intubation may not be sufficient to by-pass the obstruction. The induction of anaesthesia in such circumstances can lead to complete airway obstruction, reduction or loss of cardiac output which may not be treatable. There are numerous reports of sudden death under anaesthesia in such patients.

These children may be completely asymptomatic hence a screening chest radiograph should be performed in all children prior to anaesthesia. If a mass is seen a CT scan of the chest should be performed if possible. Studies comparing the degree of tracheal compression with the incidence of airway complication have led to the recommendation that anaesthesia be avoided in those patients with tracheal areas less than 50% of predicted. Echocardiography and ultrasound scanning are valuable in the assessment of myocardial and great vessel compression and also the presence of pericardial effusions.

Children with large anterior mediastinal masses should only be anaesthetised in centres with paediatric cardiothoracic services. There may be a need for emergency rigid bronchoscopy, tracheostomy, thoracotomy or median sternotomy. There should be the capability to perform femoral–femoral bypass. Often it is possible to establish a diagnosis from peripheral blood films, pleural fluid aspirate or bone marrow aspirate. If this is not possible it may well be safer for these children to start treatment prior to tissue diagnosis in order to reduce the tumour mass. The type of treatment given is guided by the most likely diagnosis given the patient’s age and the radiographic appearance of the mass. These masses will often regress extremely quickly following the commencement of chemotherapy and anaesthesia may be provided more safely within a few days.

Abdominal pathology

Wilm’s tumours and abdominal neuroblastomas can be massive at presentation. They can cause
diaphragmatic splinting making ventilation under anaesthesia problematic. Despite being of near normal weight these children are often quite cachectic due to these tumours. All abdominal pathology as well as chemotherapy may have detrimental effects on gastric emptying.

Intracranial pathology

Supratentorial brain tumours may be associated with raised intracranial pressure with all its implications for the anaesthetist. Leukaemic infiltration of the meninges may cause marked increase in intracranial pressure.

Systemic effects of cancer

Anaemia is one of the most common problems encountered in children with cancer. It can lead to reduced oxygen delivery to the tissues. Haemoglobin levels above 7 g/dL are usually adequate if normal cardiovascular compensatory mechanisms
exist. However, children may not be able to compensate if they have chemotherapy-induced myocardial dysfunction.

Cancer can have a number of effects on coagulation and while these may not have direct anaesthetic implications, they may need correction prior to any invasive procedures performed by oncologists or surgeons. Disseminated intravascular coagulation (DIC) is present in up to 15% of patients with malignancy. It is due to a generalised activation of the coagulation system. It more commonly takes on a chronic form which is asymptomatic and associated with modest reductions in platelet count and fibrinogen levels, and increased fibrinogen degradation products with minimal changes to prothrombin time or activated partial thromboplastin time. The acute form is rarer but can be associated with life-threatening haemorrhage or thrombosis. This is particularly seen in acute promyelocytic leukaemia (AML-M3). Asparaginase a chemotherapy agent used in remission induction for acute leukaemia may also cause DIC. Platelet disorders-both quantitative and qualitative-can be secondary to myelosuppression as complications of chemotherapy or radiotherapy, or due to extensive bone marrow involvement by the disease process itself. This can often be exacerbated by a reduction in clotting factor production either due to liver involvement or vitamin K deficiency.

Neuroblastomas can secrete catecholamines and cause systemic hypertension. Surges in blood pressure are associated with abdominal palpation. Wilm’s tumours can extend into the inferior vena cava and the renal vein leading to renovascular disorders and systemic hypertension.

Cytotoxic agents and radiotherapy

Both chemotherapy and radiotherapy have a vast array of adverse effects. Those causing cardiac and pulmonary toxicity are of particular relevance to the anaesthetist.

Cardiac toxicity

Cardiotoxic syndromes associated with cytotoxic agents include: myocardial depression, myocardial ischaemia, hypotension, hypertension, myocardiitis, endomyocardial fibrosis and arrhythmias. The commonly implicated drugs are doxorubicin (Adriamycin), daunorubicin, fluorouracil and cyclophosphamide.

The anthracycline class of drugs which include doxorubicin and daunorubicin are associated with the most problems. They can cause acute rhythm and conduction disturbances such as supraventricular tachycardias and heart block and are also associated with a chronic cardiomyopathy. Children and adolescents with previous anthracycline treatment and normal cardiac function at rest have been seen to have certain changes in function under anaesthesia. These changes include decreased in fractional shortening, a marker of left-ventricular systolic function, and stroke–volume index. Delayed cardiotoxicity, sometimes years later, has been seen after anthracycline therapy. A number of risk factors predispose a patient to cardiotoxicity. These include cumulative drug dose, total dose on any given day of treatment, rate and route of administration, drug combination and dosing schedule. Patient factors include age less than 1 year, previous anthracycline chemotherapy, previous or current mediastinal radiation, history of pre-existing cardiovascular disorders and electrolyte abnormalities particularly hypokalaemia and hypomagnesaemia. Children receiving cardiotoxic chemotherapy should have surveillance echocardiography both during and after treatment. It is very useful to have this information available prior to anaesthesia.

Radiation therapy to the thorax can damage the pericardium, myocardium, heart valves and coronary vessels. The risk is increased with concomitant doxorubicin therapy. Radiation-induced pericardial disease with pericarditis or effusion, can develop from 2 months to years after treatment.

Pulmonary toxicity

The adverse respiratory effects of cytotoxic agents can be early or late in onset. Early complications include interstitial pneumonitis (methotrexate, bleomycin, paclitaxel), acute non-cardiogenic pulmonary oedema (bleomycin, interleukin-2), bronchospasm (vinblastine, methotrexate) and pleural effusion (methotrexate). Late onset disease is more common and usually manifests as pulmonary fibrosis (bleomycin, mitomycin, balsulfan). Bleomycin is of particular importance as it results in toxicity in approximately 10% of patients. Up to 70% of children treated with bleomycin for rhabdomyosarcoma demonstrate significant restrictive changes on pulmonary function tests (PFTs). Bleomycin can lead to broncholitis obliterans with organising pneumonia (BOOP), eosinophilic hypersensitivity and more commonly bleomycin-induced pneumonitis (BIP) which can progress to pulmonary fibrosis. BIP presents with progressive dyspnoea, basal crackles, bilateral infiltrates on chest X-ray and a restrictive pattern on PFTs. It is a diagnosis of
exclusion once infection, metastasis and lymphangiitis have been discounted. Treatment is to stop the agent and give steroids.\textsuperscript{14}

The risk of bleomycin-induced lung damage is increased by increasing total drug dose, the presence of renal failure and radiation therapy. There is some evidence to suggest that the damage produced is exacerbated by the administration of supplemental oxygen as bleomycin-associated lung injury is mediated via oxidant pathways. High fractions of inspired oxygen can provoke lung injury many years after drug exposure. It is important to maintain concentrations of inspired oxygen as low as is safely possible in patients with a history of bleomycin therapy.

Radiation-induced pulmonary injury manifests as radiation-induced pneumonitis. Its severity is related to the total volume of lung exposed to treatment, the total dose and the size of the individual fractions of dose. Risk factors include concurrent or previous chemotherapy, previous radiotherapy and the withdrawal of steroids. It has a worse prognosis the earlier the onset.\textsuperscript{15}

Certain agents can have effects on renal and hepatic function. These should be monitored throughout the duration of treatment. Non-steroidal anti-inflammatory drugs should be avoided in patients receiving nephrotoxic chemotherapy.

**Tumour lysis syndrome**

This syndrome can occur as a result of massive tumour breakdown when treatment is first initiated. It has also been reported to occur spontaneously during surgery in untreated patients with massive lymphoproliferative tumours.\textsuperscript{16,17} It has been reported to occur initiated. It has also been reported to occur

Tumour lysis syndrome most commonly occurs with high-grade lymphomas and acute leukaemias. It must be remembered that steroids have potent anti-cancer properties, hence the inadvertent administration of steroids to these patients must be avoided. The syndrome results from the sudden release of intracellular contents into the systemic circulation when there is rapid destruction of tumour cells. Metabolic derangements include hyperkalaemia, hypocalcaemia, hyperuricaemia and hyperphosphataemia. These can lead to renal failure, cardiac arrhythmias, seizures, tetany and sudden death. The emergency treatment involves control of the hyperkalaemia, correction of the hypocalcaemia and hyperhydration to prevent urate nephropathy. Due to the rapid release from destroyed tumour cells, the rise in serum potassium is much more rapid in tumour lysis syndrome than that seen in renal failure. Continuous haemodialfiltration may be required. These patients should be managed on an intensive care unit.

All patients at risk of tumour lysis syndrome should have preventative measures initiated prior to chemotherapy. These include hyperhydration, the administration of allopurinol or uricozyme and alkalinization of the urine. A more recent advance in management is the drug rasburicase, which is a recombinant urate oxidase enzyme. This has proved very effective in prophylaxis in high-risk paediatric patients.\textsuperscript{18} It is prudent to delay any anaesthetic interventions until these preventative measures have been established.

**The septic child**

Children with neoplasia account for 12.8% of all cases of severe sepsis in children aged 1–9 years and 17.4% in those aged 10–19 years. The mortality is 16% in those with cancer as opposed to 10% in those without. It is higher in those who have undergone bone marrow transplantation.\textsuperscript{19} Children with leukaemia or lymphoma differ from those with solid tumours with regards to their predisposition to sepsis. Leukaemia is a disease of the bone marrow and involves more intensive myeloablative therapy compared to the treatment of solid tumours. A more prolonged period of immune dysfunction, in particular neutropenia renders them more susceptible to opportunistic infections for longer periods.

Anaesthetists are often involved in the initial management and stabilisation of the patients prior to their transfer to definitive care. It is vital that good communication exists between the paediatric and anaesthetic teams in order that those children with established or pending septic shock be recognised and managed in a multidisciplinary fashion. An ABC approach should be adopted. Signs of sepsis include increased respiratory rate, tachycardia, delayed capillary refill, cool peripheries and altered mental state. Hypotension is a late and pre-terminal sign of circulatory failure. The child should be administered high flow oxygen and venous or intra-osseous access established. At this point blood should be sent for routine haematology, biochemistry and blood cultures. An initial fluid bolus of 20 mL/kg of 0.9% saline or 4.5% human albumin (or gelatin-based colloid) should be given and the response noted. Subsequent fluid boluses should be with colloid. The oncologists should advise with regard to the most appropriate broad spectrum antibiotics on an individual patient basis.
Children often require several boluses of fluid to achieve relative stability. After 40 mL/kg it is necessary to consider inotropes and ideally to monitor central venous pressure. Intubation should be considered after three boluses of 20 mL/kg of fluid have been given. Positive pressure ventilation improves oxygenation and prevents/treats pulmonary oedema. Paediatric intensive care services should be contacted early in order that they can guide treatment and begin to organise patient transfer.

The role of the anaesthetist

Anaesthetists form part of the multidisciplinary team caring for children with malignancy. They are involved at every stage of the child’s journey including diagnosis, treatment, disease surveillance, pain management and at times resuscitation on the intensive care unit.

Regular and at times daily visits to the hospital can have profound psychological effects on both the child and their parents. The disruption to their normal routine must be limited as much as possible. This includes clear guidelines with regard to starvation and morning sessions to allow return to school or nursery in the afternoon. Full explanations should be given to parents and their involvement at induction of anaesthesia encouraged.

Anaesthesia is often conducted in isolated sites such as radiotherapy suites, day-case oncology units and radiology/imaging departments. The personnel involved in anaesthetising and recovering these patients should have the appropriate paediatric training. Wherever possible the environment should be as ‘child-friendly’ as possible. At all times there should be full paediatric resuscitation facilities available.

Anaesthesia for radiotherapy

Radiotherapy in paediatric patients is indicated for three main groups of cancers: brain tumours, commonly gliomas and medulloblastomas; tumours outside the central nervous system, e.g. neuroblastoma, lymphoma, rhabdomyoscarcoma; leukaemia, e.g. cranial irradiation in ALL.

The goals of radiotherapy are to deliver a high dose of irradiation to the treatment area whilst sparing healthy tissue. The precise control of patient movement is therefore vital and general anaesthesia is indicated in younger children. Children over 5 years will often tolerate radiotherapy without anaesthesia with suitable preparation, including play therapy. The ideal anaesthetic for radiotherapy should be rapid in onset, of brief duration with prompt recovery, and assure immobility and a patent airway in a variety of positions. There have been no randomised studies in paediatric patients to demonstrate the superiority of any anaesthetic technique.

In our institution we employ a technique of total intravenous anaesthesia by means of a propofol infusion. The appeal of propofol is that it has rapid onset and awakening; it has a low incidence of side effects and in addition has antiemetic properties. The technique avoids repeated instrumentation of the airway and daily exposure to volatile agents. Opioid analgesia is not required as radiotherapy is not painful and opioids are associated with hypoventilation and apnoea. To facilitate vascular access nearly all children scheduled for a prolonged course of radiotherapy should have a long-term central venous device inserted, e.g. Portacath™ or Hickman™ line. A course of radiotherapy maybe from 10 days (e.g. abdominal neuroblastoma) to 7 weeks, (in some brain tumours). The total dose is fractionated to reduce the incidence of side effects.

If the area to be irradiated involves the head or cervical spine a mould needs to be made of the patients head. This mould will subsequently ensure the accuracy of the treatments. The mould is made using a sheet of thermoplastic. Whilst warm this is draped over the patient, as it cools it hardens around the contours of the child head (see Fig. 2). There are pre-made holes in the sheet for the nostrils and mouth. As the sheet hardens it is important that the child can maintain their airway without obstruction. If the mould is made correctly it is very rare for the child to need any artificial

![Figure 2](image)
airway device, however we do insert a bite block to act as spacer between the teeth when making the mould. If the child subsequently needs an oropharyngeal airway or a LMA there will then be enough space between the teeth for insertion.

The radiotherapy suites are often in the most geographically isolated areas of a hospital. Pipeline gases and vacuum are not always available. It is important to ensure there is full resuscitation equipment and backup sources of oxygen and suction available prior to inducing anaesthesia. For simplicity we use a self-inflating resuscitation bag and mask system with a portable monitor rather than an anaesthetic machine.

A parent accompanies the child to the radiotherapy suite. With appropriate communication the child’s waiting time in this predominantly adult outpatient setting can be kept to a minimum. Induction takes place within the treatment room with the child either on the trolley or on the parent’s knee. The aim is to maintain spontaneous respiration at all times. A bolus of 3–5 mg/kg of propofol is given via a pump over 1–2 min (more rapid injection is associated with apnoea). A continuous infusion of propofol is commenced typically at a rate of 10 mg/kg/h and is adjusted to response. The patient is transferred onto the treatment table. They are carefully positioned and the mould applied (see Fig. 3a). The child is continuously observed to confirm an unobstructed respiratory pattern. A capnography catheter is positioned perinasally on the mould to produce a reliable waveform on the monitor and supplemental oxygen can be delivered by taping a facemask to the mould.

The requirement for children to be positioned prone for radiotherapy has almost disappeared due to improvements in conformation radiotherapy techniques. However the technique described works equally well for prone patients. Children having abdominal or peripheral radiotherapy do not require a mould for treatment. Their head is supported to one side with a foam wedge, again an artificial airway is very seldom required.

The monitor is positioned so that it can be viewed via a closed-circuit TV camera, whilst another camera observes the child. During the treatment the anaesthetic team observe the child and monitor via TV screens in the control room (see Fig. 3b). Although the value for end-tidal carbon dioxide is not accurate using this method, it does give a reliable trend of adequate ventilation and respiratory pattern. At the end of the procedure the patient is transferred for recovery in a designated area within the radiotherapy suite. Emergency drugs, a self-inflating resuscitation bag and advanced airway equipment together with portable suction should be available at all times.

This technique is associated with a short awakening time and rapid psycho-motor recovery. Patients can be rapidly transferred back to ward and are usually eating within 20 min of the end of the procedure. Studies have shown that using this technique mean awakening time is 4 min and discharge home can be as soon as 30 min.

Other methods for anaesthesia for radiotherapy include the use of ketamine or inhalational agents. Ketamine can be administered intravenously or less commonly now intramuscularly. It is however associated with excess salivation and increases in intracranial pressure. Methods using inhalational agents usually require repeated instrumentation of the airway with a LMA or endotracheal tube. There are also issues with regards to adequate scavenging of anaesthetic gases.

**Anaesthesia for short painful procedures**

Short painful procedures include lumbar puncture, bone marrow aspirate and trephine biopsy. The

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**Figure 3** (a) Patient in position for radiotherapy treatment, in this case for an optic chiasm glioma. (b) Inside the control room views of the child, anaesthetic monitor and infusion pump are displayed on closed-circuit TV screens.
number of these procedures being performed has increased. This reflects the increasing use of intrathecal methotrexate rather than radiotherapy in central nervous system prophylaxis and the move towards ‘risk-directed’ treatment strategies. This approach requires regular bone marrow aspirations during treatment in order to assess the patient’s response to current therapy and plan subsequent chemotherapy regimes.

The aims of anaesthesia for these interventions are to provide analgesia and amnesia whilst ensuring minimal side effects and disruption to the child’s routine. This is achieved using either a total intravenous anaesthesia technique or a combination of intravenous and inhalational agents. There is evidence that the recovery and side effect profile is more favourable with an intravenous technique. In our institution we use a combination of propofol and remifentanil to facilitate anaesthesia for these procedures.

The child should be fasted as per local protocol. Platelet count and clotting should be checked prior to the procedure and any abnormalities corrected. Each haematology unit will have their own policy but typically the platelet count should be above $50 \times 10^9/L$ for lumbar puncture and $20 \times 10^9/L$ for bone marrow aspiration.

The majority of these children will have long-term intravenous access. Children with Porta-caths$^\text{TM}$ will require them to be accessed prior to induction. Using a clean technique, anaesthesia is induced with propofol 3 mg/kg then remifentanil 1 mcg/kg via the indwelling central access. Oxygen is administered via an anaesthetic breathing circuit and ventilation is assisted as necessary. The patient is then positioned in the lateral position. Supplemental injections of remifentanil 0.5 mcg/kg or propofol 0.5–1 mg/kg are given if the patient moves or shows signs of response to stimuli. This technique ensures a rapid induction, minimal movement during the procedure and eliminates the need for scavenging. Propofol only intravenous techniques have also been described. The advantage of adding remifentanil is that it has a propofol-sparing effect and diminishes movement to stimuli. However, it does increase the incidence of apnoeas and the need for assisted ventilation for a short period after induction.

Inhalational anaesthetic techniques are associated with a longer induction and more delayed recovery and a higher incidence of nausea and vomiting. Again scavenging of anaesthetic gases using open paediatric circuits is an issue with implications for staff exposure during high volume, rapid turnover lists.

### Anaesthesia for long-term central venous access

Children should have central access secured as early as possible in their course of treatment. It facilitates not only the administration of chemotherapy agents but also reduces the anxiety associated with repeated anaesthetics. However, it is precisely because these lines are inserted early in the course of treatment that the anaesthetist must be alert to potential hazards. These include the presence of a mediastinal mass; the risk of tumour lysis syndrome, DIC associated with asparaginase and the risk of infection if the white cell count is low (this usually reaches a nadir at 5–10 days post dose with recovery by day 21).

The anaesthetic technique used should preferably include endotracheal intubation and positive pressure ventilation. This avoids the distortion to the anatomy of the great vessels in the neck caused by an LMA. There is also a serious risk of air embolism if these patients are spontaneously breathing.

### Conclusion

Children with malignancy represent a unique patient group. Although they often require anaesthesia for relatively minor procedures, the potential for serious deterioration under anaesthesia is very real. Anaesthetists form part of a multidisciplinary team involved in the care of these children who often undergo long and protracted treatment regimes. The anaesthetic techniques employed must be safe but at the same time aim to have minimal impact on the child’s normal daily routine.

### References


