Chapter 4
Solid Tumors Outside of the Central Nervous System

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Solid tumors which occur outside of the central nervous system (CNS) have some similar, relevant characteristics important in the pediatric intensive care unit (PICU). In addition to tumors which arise in the anterior mediastinum, there are other disease-specific complications documented in this section. Many of the critical care issues focus on the postsurgical care of children after having (often) large tumors removed from the chest, the abdomen, or the pelvis. In this chapter, three distinct solid tumors will be discussed, highlighting these critical care issues. Furthermore, focus on the emerging "fast-track" or early recovery after surgery (ERAS) concepts in the perioperative period for children appears to improve surgical outcomes in some patient populations.

Anterior Mediastinal Masses

Anterior mediastinal masses present a unique clinical dilemma for surgeons, oncologists, interventional radiologists, anesthesiologists, and intensivists. With a new mass in the anterior mediastinum, a biopsy is often needed for the definitive diagnosis, to initiate appropriate therapy. However, depending on the size and location of the mass, the anesthesia risk of obtaining a tissue biopsy may outweigh the benefit of obtaining tissue prior to initiating a potential therapy. Because of this unusual risk-benefit analysis, the approach to anterior mediastinal masses requires a thoughtful, multidisciplinary approach.

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In children, the leading causes of anterior mediastinal mass are lymphoma (Hodgkin's and non-Hodgkin's), leukemia, thymoma, histiocytosis, and neuroblastoma, all with varying treatment strategies [1–3]. Typically, the sedation and anesthesia needed for obtaining appropriate tissue for diagnosis are done in an operating room or interventional radiology suite. However, it is important for the pediatric intensivist to understand the rationale for sedation and anesthesia, as complications will impact the post-biopsy course in the PICU.

Airway and Cardiovascular Compromise

Symptomatic tracheal compression is a significant concern to anesthesia providers and is thought to be an increased risk of airway compromise intraoperatively. It has been demonstrated that children with >50% decrease in tracheal cross-sectional area are more likely to be symptomatic [4] and are at highest risk of developing intraoperative airway complications [5, 6]. Conversely, children with <50% decrease in the cross-sectional area of the trachea are less likely to have intraoperative airway compromise [7, 8].

From a physiologic standpoint, anterior mediastinal masses grow and develop in the same space with not only the trachea and main stem bronchi but also major components of the cardiovascular system. Thin-walled structures that are more responsive to changes in intrapleural pressures are particularly at risk: superior vena cava, right atrium, and pulmonary artery. With this in mind, maintaining a spontaneously breathing patient with negative intrapleural pressures is important, as the inspiratory muscle tone, elastic recoil of the chest wall, and displacement of the diaphragm serve to maintain functional residual capacity [9].

Developing the anesthesia plan in a multidisciplinary fashion serves to best address the diagnostic needs and the anesthesia risks of getting tissue. To that end, patients with anterior mediastinal masses can be divided into three broad categories for anesthesia [9]:

- *Low risk*: Asymptomatic of mildly symptomatic, without postural symptoms or radiographic evidence of significant compression of structures
- *Intermediate risk*: Mild to moderate postural symptoms, tracheal compression <50%
- *High risk*: Severe postural symptoms, stridor, cyanosis, tracheal compression >50% or tracheal compression with associated bronchial compression, pericardial effusion or SVC syndrome

With each incremental increase of risk, increased attention needs to be paid to both the possible increased risks and the potential risk mitigation strategies:

- *Awake intubation*: For patients requiring general anesthesia with an anterior mediastinal mass, the preferred method to secure the airway is via awake, fiberoptic bronchoscopy [10]. Attention is to be paid to minimize laryngospasm with

topical anesthetics and with rescue plan in case of airway loss or hemodynamic collapse during or after intubation.

- *Reinforced endotracheal tube*: For patients with both tracheal and bronchial compression from an anterior mediastinal mass, a reinforced endotracheal tube may be passed beyond the obstruction in order to ventilate the patient [9]. However, reinforced endotracheal tubes may have unusual complications should the patient bite down on the tube or the reinforcement dissect into the lumen of the tube [11–13].
- *Rigid bronchoscopy*: Like the use of the reinforced endotracheal tube, the rigid bronchoscopy can be useful in patients with both tracheal and bronchial obstruction from an anterior mediastinal mass [14]. A rigid bronchoscope may be a particularly useful temporizing method to maintain oxygenation and ventilation should the need for emergent cardiopulmonary bypass arise.
- *Cardiopulmonary bypass*: In addition to the rescue availability of cardiopulmonary bypass (CPB), CPB has been used prophylactically in select patients thought to be at greatest risk of cardiovascular collapse following induction of anesthesia with an anterior mediastinal mass [15–17]. This may be particularly true in adults, who are less responsive to changes in positioning compared to pediatric patients [16].
- *Prone positioning*: This may be more useful in children than in adolescents and adults with anterior mediastinal mass. As older patients have a more ossified thoracic cage compared to children, the impact of prone positioning may not have the same effect in either the intubated or the extubated patient [14].
- *Heliox*: Heliox is a mixture of helium with oxygen at 70/30 and may be a useful adjuvant for use during a procedure both to obtain tissue from an anterior mediastinal mass [18] and to facilitate the extubation of a patient with an anterior mediastinal mass [19].
- In a long-standing mass, which may lead to some degree of laryngomalacia, the laminar flow from the heliox mixture may aid in delivering flows to the distal airways, beyond the residual obstruction.

Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor in children, with approximately 650 new cases per year and an incidence of 10.5 cases/million/year for children younger than 15 years of age [20, 21]. It is most predominantly seen in children younger than 5 years of age. Derived from neural crest cells, neuroblastoma involves organs of the sympathetic nervous system, with the adrenal glands being the most common primary site.

Prognosis is highly variable based on risk group. Patients are stratified to low risk, intermediate risk, and high risk based on tumor stage, age at diagnosis, presence of the oncogene, MYC-N amplification, histology, tumor differentiation, DNA ploidy, and 11q aberration. High-risk features include age greater than 18 months at

the time of diagnosis, MYC-N amplification, and metastatic disease. Patients with low- and intermediate-risk disease have an overall survival rate greater than 90%, while those with high-risk disease have an overall survival rate of less than 50% [20, 22].

Neuroblastoma treatment depends heavily on the risk group of the patient. In patients with low-risk disease, surgical resection, if possible, is often curative, with no need for systemic chemotherapy. Infants younger than 12 months with localized disease, Stage 4S, may also have spontaneous regression of disease without need for surgery or chemotherapy. These patients can be observed alone with overall survival rate of approximately 100% at 3 years. Intermediate-risk patients are treated with multiagent chemotherapy and surgical resection if possible [21].

High-risk patients, who represent about 50% of all patients with neuroblastoma, are difficult to treat and have much lower long-term survival compared to low- and intermediate-risk patients [20]. Regimens to treat these patients consist of induction, local control, consolidation, and maintenance therapy. Children's Oncology Group (COG) induction consists of alternating cycles of chemotherapy with multiple agents, including topotecan, cyclophosphamide, vincristine, doxorubicin, cisplatin, and etoposide. Local control includes surgical resection and/or radiation therapy. Consolidation often consists of high-dose, myeloablative chemotherapy with autologous stem cell rescue [23]. Maintenance therapy is designed to prevent relapse after patients achieve a clinical remission. In recent years, immunotherapy has been used either alone or with isotretinoin as maintenance therapy for patients in remission. Immunotherapy consists of anti-GD2 monoclonal antibodies such as humanized 3F8 (Hu3F8) and chimeric 14.18 (dinutuximab) [22]. These antibodies have become an important component of treatment for neuroblastoma.

Immunotherapy for Neuroblastoma

A major new component to neuroblastoma therapy, in addition to chemotherapy, surgery, and radiation, is immunotherapy. Several different antibodies exist to target ganglioside GD2, which is expressed on the surface of neuroblastoma cells [24]. These immunotherapies have been incorporated into neuroblastoma treatment as an important component of maintenance therapy but require careful monitoring during and following infusion due to their side-effect profile. Dinutuximab is a commercially available chimeric human-murine monoclonal antibody to GD2. A similar monoclonal antibody, Hu3F8, is used at Memorial Sloan Kettering Cancer Center (MSKCC). These antibodies are associated with infusion-related side effects that are important for pediatric critical care practitioners. Dinutuximab is infused in the inpatient setting, sometimes in the PICU, with infusions from 10 to 20 hours for 4 consecutive days. Hu3F8 is given in the outpatient setting over 30 minutes every other day for a total of three doses per cycle.

During the infusion, pain is the most common adverse event, with grades 3–4 pain in the abdomen, back, and extremities occurring in about 50% of patients [25]. GD2 is expressed on neuroblastoma cells, but also on peripheral nerve cells, leading to severe pain during infusion often requiring high doses of opioids for management. Respiratory depression requiring reversal of narcotics with naloxone can occur due to the opioid doses needed to achieve adequate pain control. In some cases, adequate pain control can only be achieved with continuous infusions of analgesics such as opioids with dexmedetomidine, lidocaine, or ketamine, each of which has adverse effects of which the critical care physician should be aware. Opioids with dexmedetomidine can lead to hypotension and bradycardia [26]. Continuous lidocaine infusion is generally safe but has a narrow therapeutic window, with toxicity leading to CNS depression [27]. Ketamine infusions are well tolerated without hallucinations or respiratory compromise but can lead to dysphoria and nystagmus [28, 29]. These alternative or adjuvant analgesics improve pain control and may also decrease opioid use.

These antibodies are also immunogenic and can generate anaphylactic-like hypersensitivity responses, bronchospasm, urticaria, hypotension, hypertension, and capillary leak [25]. Anaphylaxis and anaphylactoid reactions can be treated with epinephrine. Bronchospasm responds to short-acting beta-agonists such as albuterol. Rash and urticaria are managed with antihistamines. Hypotension and capillary leak respond to fluid resuscitation. In patients receiving both antihistamines and opioids, the hypotension can be more profound, requiring multiple fluid boluses, although patients generally tolerate the periods of hypotension and maintain perfusion and mentation while receiving fluids.

Hypertension is seen acutely with pain but can also be a later effect with Hu3F8 and has been linked to posterior reversible encephalopathy syndrome (PRES) [30]. PRES can present with headache, altered mental status, visual disturbances, and seizure. It is diagnosed based on clinical and radiographic findings. Patients with PRES frequently require management in the PICU for close neurological monitoring. Treatment involves blood pressure control, optimization of electrolytes, and antiepileptic medications as needed for seizures [31].

Spinal Cord Compression

Neuroblastoma can extend from the sympathetic chain into the spinal canal and cause peripheral nerve root or spinal cord compression. Additionally, leptomeningeal disease or osseous metastases can lead to spinal cord compression. Spinal cord compression in neuroblastoma is seen in about 10–15% of cases, most frequently in progressive, terminal disease, but it can be a presenting symptom in 1–4% on cases [32]. Spinal cord compression requires rapid treatment to prevent permanent neurologic sequelae, although even with treatment up to 50% of patients have residual neurologic deficits [33]. Treatment modalities include neurosurgical decompression, radiation therapy, high-dose systemic glucocorticoids, and

chemotherapy. The best treatment modality to prevent long-term neurologic sequelae remains unclear, and each treatment modality is associated with short- and long-term complications.

Chemotherapy can be used for treatment of intraspinal neuroblastoma, but does not provide immediate relief of spinal cord compression symptoms. Neurosurgical decompression provides the most immediate relief of symptoms, but it is not clear if there is any difference in long-term outcomes in these patients. Radiation can also provide rapid relief of symptoms but is associated with long-term side effects, especially in young, developing children. For patients who have disease progression and subsequent spinal cord compression despite chemotherapy, neurosurgery or radiation therapy is an appropriate treatment [33]. Glucocorticoids can reduce edema and provide rapid relief of symptoms but also have not necessarily been shown to impact long-term outcomes [33]. Treatment of these patients often involves multidisciplinary teams including the PICU, neurosurgery, and oncology to determine the best approach for each patient.

Surgery and Surgical Complications

Surgical resection is an important component of neuroblastoma treatment. The surgeries are often long, technically difficult cases that involve dissection of tissue in the thorax, abdomen, and sometimes the spine. Average operative time is around 8.5 hours, and average estimated blood loss is around 30 cc/kg [34]. These procedures involve retroperitoneal lymph node dissection, hepatic lobe biopsy, and dissection of the tumor from major surrounding vasculature including the renal arteries, mesenteric arteries, and the aorta. Additionally, most of the surgeries are done via a thoracoabdominal approach leading to placement of a thoracostomy tube and manipulation of the diaphragm. Fluid shifts following surgery can result in hemodynamic instability (hypotension, decreased urine output, and poor perfusion). Patients often require multiple fluid boluses in the first 24–48 hours postoperatively, and around 33% of patients require vasoactive medications for fluid refractory hemodynamic instability. Patients may remain intubated following surgery for 1–4 days (average 1.5 days). In a minority of patients, around 3%, the best surgical procedure requires nephrectomy. Additional surgical complications include small bowel obstruction (3%), systemic or local infection postoperatively (3%), and clinically significant intraoperative bleeding (6%) [34].

Metastatic Osteosarcoma

Osteogenic sarcoma is the most common bone tumor in children and young adults [35]. Though the overall survival in osteosarcoma is roughly 75% [36], metastatic disease to the lung can occur within the first 12 months after initiation of treatment

[37]. Relapse of osteosarcoma in the lung occurs in greater than 30% of patients [38]. The survival in children with metastatic disease to the lung has as low as a 40% and 22% 3-year and 5-year survival, respectively [39]. As a result, children with metastatic disease to the lung are in need of complete resection in order to maximize survival benefit. Systemic therapies are not as reliable a treatment modality for improving survival, as the ability to achieve complete resection is the most relevant prognostic factor for long-term survival [40]. Children undergoing open thoracotomy for metastatic disease resection represent an important patient population for many PICUs. While not solely a PICU issue, the comprehensive care from preoperative planning through discharge provides an important framework for discussion of the multidisciplinary, comprehensive care plan which can be so effective for children undergoing major surgery, both in the chest and in the abdomen.

Surgical Approach

The surgical approach to patients with pulmonary metastatic disease varies based on several clinical factors. While the majority of patients presenting with pulmonary metastatic disease have bilateral pulmonary disease, there may be between 24% and 40% of patients who present with unilateral disease [38]. For those presenting with bilateral pulmonary disease, it remains controversial as to approach this as a single-stage operation via median sternotomy or staged thoracotomies [38, 39].

The most common approach to either unilateral or bilateral metastatic disease is via thoracotomy. Postoperative complications from thoracotomy surgery include pleural pain, bleeding, respiratory failure, and need for mechanical ventilation [39]. Management of these predictable issues often falls to the multidisciplinary team caring for the patient in the PICU or acute care ward. For patients undergoing thoracotomy surgery, thoracic epidural pain management has proven to be a safe and effective mode of nonsystemic pain relief [41, 42]. Avoidance of systemic narcotics and sedatives has significant advantages in the “fast-track” surgical approach to perioperative care (discussed below) and at reducing the risk for oversedation and the development of delirium in the postoperative period [43]. While the majority of patients undergoing thoracotomy do not have other significant postoperative issues beyond pain, those who have intraoperative bleeding complications may continue to have significant bleeding postoperatively requiring frequent blood transfusion or even re-exploration to stop active bleeding [39].

Desmoplastic Round Blue Cell Tumor

Desmoplastic round blue cell tumors (DSRCT) represent a very small percentage of solid tumors in children. In fact, a recent publication found a total of 450 cases in the literature since its discovery in 1989 [44]. However, the novel approach to this

rare tumor gives insight into the future of multimodality treatment of solid tumors which may be relevant to those who care for critically ill children.

Sharing some biological similarities to both Ewing sarcoma and Wilms tumor, DSRCT is thought to originate in the peritoneum and spread locally to the intraperitoneal organs. Without surgical debulking, it is universally fatal [45]. The most generally accepted treatment regimens involve Ewing-like regimen involving cyclophosphamide or ifosfamide, doxorubicin, and vincristine, surgical cytoreduction, and radiotherapy [44–46]. The surgical cytoreduction can be a big surgery. As the tumors can be as large as 40 cm, and invading multiple intraperitoneal organs, the cases can be quite long (up to 12 hours), with complications consistent with other long surgeries that have significant fluid shifts [45, 47, 48]. Surgery entails resection of tumor implants commonly found on the omentum, diaphragm, spleen, Morrison's pouch, abdominal wall peritoneum, small bowel mesentery, and pelvis [47, 48]. Pain, fluid shifts, systemic inflammatory response, wound dehiscence, and surgical site infections are all possible following this surgery [48].

In addition to the standard regimen of systemic chemotherapy, cytoreduction therapy, and radiation, there have been a variety of studies aimed at addressing the residual intraperitoneal nodules [44, 47, 48]. The use of hyperthermic intraperitoneal chemotherapy (HIPEC) in some uterine cancers has shown some efficacy [49, 50]. The same approach has been explored in the use of hyperthermic cisplatin or oxaliplatin +/− mitomycin and/or irinotecan in DSRCT [51, 52]. The data as of yet are inconclusive, and the use of HIPEC is best used in the framework of a clinical trial. The early studies of the use of HIPEC had clinically relevant side effects to the pediatric intensivist with renal failure and urinary tract infection complications [48]. Another potential therapy targeting residual intraperitoneal tumor in DSRCT is the use of immunotherapy remote from the tumor debulking surgery. The efficacy of intraperitoneal ^{131}I-8H9, which targets surface cell antigen 4Ig-B7H3 expressed in DSRCT, is currently being evaluated. In this protocol, an intraperitoneal catheter is placed during the debulking surgery, and intraperitoneal 8H9 is instilled via surgically placed intraperitoneal catheter as an adjunct to the systemic chemotherapy, cytoreductive surgery, and radiotherapy (Abstract presented at Connective Tissue Oncology Society Annual Meeting, 2016).

Enhanced Recovery After Surgery

Enhanced recovery after surgery (ERAS) programs are designed to utilize a multidisciplinary team to optimize recovery for postoperative patients, leading to increased patient (and caregiver) satisfaction, efficient use of hospital resources, and reduced hospital length of stay without increasing the rate of readmission [53]. The concepts for ERAS derive from the experience of adult patients undergoing elective colonic surgery [54], elective rectal and pelvic surgery [55], and pancreaticoduodenectomy [56]. The elements of the adult-derived ERAS programs highlight the surgical experience in totality, from preadmission counseling through maximization of

intraoperative pain management with mid-thoracic epidural anesthesia/analgesia and short-acting anesthetic agents, careful use of intraoperative fluids, postoperative mobilization plan, nonnarcotic pain management, prevention of nausea and vomiting, minimizing drains and catheters, and stimulation of gut motility [57]. These principles have been documented in children undergoing large abdominal surgeries for inflammatory bowel disease [53] and can be applied to our patients undergoing surgery for metastatic osteosarcoma, neuroblastoma, and DSRCT as well as other common thoracic and abdominal surgeries performed on children with solid tumors.

Applying these concepts to children has been retrospectively documented for relatively common surgical procedures such as appendectomy [58], renal surgery [59, 60], and even cardiac surgery [61]. Furthermore, these concepts have also been evaluated in prospective studies in ambulatory surgeries [62], as well as in pediatric colorectal surgery specifically [53].

Though there may be institution-dependent variation, our experience at MSKCC has been positive, with all elective surgeries now being screened for participation in ERAS. Areas of focus include preoperative, intraoperative, and postoperative, although there are several elements of ERAS that span the entirety of the perioperative period, from preadmission screening to follow-up after discharge. Several elements are critical for success:

- Active patient involvement
- Audit of compliance and outcomes
- Multidisciplinary team involvement

Preoperative

ERAS is intended to encompass the entirety of the surgical experience for patients and their families. The elements in the preoperative arena are:

- Targeted patient and parent education and selective bowel preparation
- Reduced fasting duration
- Carbohydrate “preload” drinks
- After admission and before the initiation of surgery, non-opioid analgesia and regional anesthesia barring any contraindications
- Active patient and parent involvement
- Appropriate management of expectations from the multidisciplinary team.

Intraoperative

Intraoperatively, the surgical and anesthesiology teams work together to improve the perioperative experience. Important aspects of the intraoperative experience include:

- Actively warming of the patients to maintain normothermia.
  - The use of Bair Hugger and warmed intravenous fluids as necessary
- Goal-directed fluid therapy to minimize water and sodium overload.
- Maximizing regional anesthesia so as to decrease opioid use.
- Alternatively, non-opioid infusions can be used with anesthetic inhalational agents to provide appropriate sedation and analgesia for the case.
- Postoperative nausea and vomiting protocols that include dexamethasone and ondansetron.
- Close attention to the need (or lack of need) for postoperative drains to remain in place, including nasogastric tubes.

Postoperative

Postoperative care focuses on return of normal function. The multidisciplinary team works together to achieve the goal of timely, appropriate discharge while meeting the postoperative needs of the patient. The important elements include:

- Minimizing intravenous fluids
- Initiating early oral nutrition when appropriate
- Early indwelling urinary catheter removal
- Early ambulation to aid in reducing postoperative ileus and delirium

Throughout the perioperative period, there is also a focus on active patient involvement (including clear discharge criteria), active multidisciplinary team involvement, and continued auditing of compliance and outcomes for quality improvement. This comprehensive team approach involves representation from hospital administration, nursing, advanced practice providers, anesthesia, surgery, pediatrics, child life, physical and occupational therapy, nutrition, and the pediatric ERAS coordinator. In studies in routine pediatric surgery, length of stay was reduced, as well as reduced post-discharge convalescence [53, 62]. Whether these results are reproducible in a pediatric oncology population is a question actively being investigated.

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