SPECIAL INTEREST ARTICLE

Staged intraperitoneal brachytherapy and hyperthermic intraperitoneal chemotherapy in an adolescent: novel anesthetic challenges for pediatric anesthetists

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Summary
Newer techniques that have found a place in cancer management in adults are offered far less commonly in pediatric patients. We present a case of a patient with recurrent Wilms’ tumor managed with a novel combination of cytoreductive surgery, intraperitoneal brachytherapy, and subsequent hyperthermic intraperitoneal chemotherapy. Each stage presents challenges that the pediatric anesthetist is unlikely to have faced before. Such cases require flexibility and thorough planning to manage the combination of major surgery, remote anesthesia with brachytherapy and hyperthermic chemotherapy with its potential for metabolic derangement, significant fluid shifts, analgesic care, and potential exposure of staff to cytotoxic agents. Comprehensive care can be offered in pediatric centers.

Case details
A 16-year-old, 44-kg adolescent presented with a third recurrence of Wilms’ tumor. He originally presented at the age of 3 and was treated with a left nephrectomy and primary resection of his tumor, followed by chemotherapy and external beam radiation therapy. Eleven years later he presented with an abdominal wall tumor which was again resected and followed by radiotherapy and chemotherapy.

On this occasion, he presented with a 7 cm retro-vesical mass (Figure 1). His disease was unresponsive to fourth-line chemotherapy and he had reached maximal permissible dosage for external beam radiotherapy. Without a different approach, he would survive no more than a few months. A management plan was offered including resection of the new mass with microscopic margins, then five fractions of intra-abdominal brachytherapy to be followed with hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin 4 days after resection.

Preoperatively, the patient had mildly impaired renal function (creatinine 175 micromol/l), mild left ventricular dysfunction (left ventricular fractional shortening 28%), and moderate pain managed with oxycodone 5 mg orally as required. The patient was particularly anxious about anesthesia and had previously responded poorly to premedication.

Initial anesthesia planning was for two separate general anesthetics (initial resection and then HIPEC) supplemented with a 5-day thoracic epidural infusion. For the first procedure, the patient was given oral premedication and proceeded to an uneventful induction with propofol, fentanyl, and sevoflurane utilizing a central venous access device already in situ. Two large bore venous and an arterial cannula were placed in addition to a urinary catheter. A thoracic epidural catheter was placed at the T8/T9 level after induction of anesthesia.

Surgery proceeded uneventfully taking 11 h in total to achieve tumor resection, widespread cytoreductive surgery, placement of the brachytherapy guide system, and external diversion of his single ureter. In the face of
modest blood loss, the patient required 25 ml·kg⁻¹ of packed red blood cells, 15 ml·kg⁻¹ of fresh frozen plasma (FFP), 10 ml·kg⁻¹ of platelets, and 10 ml·kg⁻¹ of cryoprecipitate. The custom-made brachytherapy applicator system was substantially larger than anticipated, taking up a significant proportion of the abdomino-pelvic bed. Due to concerns about the risk of intra-abdominal compartment syndrome in a patient with a single kidney, the decision was made to leave the abdomen open until HIPEC (Figures 2 and 3). The patient was left intubated and remained ventilated while awaiting his second operation. The epidural was removed in view of this altered management plan.

Over the next 3 days, the patient underwent five brachytherapy treatments which required transport of the patient to the co-located adult tertiary center. On the fourth day after the initial resection, the patient returned to the operating suite for removal of the brachytherapy guides and HIPEC with cisplatin. The same venous access was used for this case and nasopharyngeal temperature monitoring was used with a target temperature under 39°C.

For this procedure, active attempts at patient warming were avoided in the lead up to introduction of heated cisplatin. The cisplatin was maintained at 41°C with a specialized recirculation system (Belmont Hyperthermia Pump, Belmont Instrument Corp, MA, USA). As the patient’s temperature increased, ice was intermittently placed over the great vessels of the neck and in both axillae. This ensured that NP temperature remained less than 38.5°C at all times. All theater staff maintained practices for safe handling of chemotherapeutic agents under supervision of oncology staff.

Following HIPEC, his single ureter was reimplanted into his bladder. At the end of the procedure, the patient was returned to the pediatric intensive care unit. He was extubated uneventfully the next day.

His subsequent recovery was complicated by a cisplatin-induced tubulopathy causing moderate hypercalcemia (peak: 3.31 mmol·l⁻¹ on day 7) and hypophosphatemia (trough: 0.74 mmol·l⁻¹ on day 5). His creatinine rose to 296 micromol·l⁻¹ on postoperative day 9 and subsequently returned to preoperative levels. He also developed a Superior Mesenteric Artery syndrome which manifested as enteral feed intolerance. Diagnosed 17 days after HIPEC, this resolved slowly over 8 weeks with conservative management and a period of parenteral nutrition.

Other postoperative issues included arterial hypertension possibly due to a steroid-effect, significant abdominal pain, and anxiety and depression leading to the involvement of psychology services and initiation of a selective serotonin reuptake inhibitor. He was discharged to outpatient care after an 89-day hospital admission. Although this was very challenging for the family and the patient, particularly with respect to the associated psychological impact, they speak positively about the decision to pursue a course that has resulted in survival well beyond the initial prognosis at recurrence.

Introduction

This case involves the use of multiple novel therapies with significant impacts on anesthesia care. Identified anesthetic challenges for this multiday plan included: (i) Initial major abdominal resection with peritomectomy and significant postoperative analgesic requirements; (ii) Planning for brachytherapy sessions in a co-located facility (including plans for emergent laparotomy in the event of system failure); and (iii) Anaesthesia for HIPEC.

There is very little published information on the combination of cytoreductive surgery (CRS) and HIPEC in pediatric patients and no reports of brachytherapy used in this manner between the two operative procedures. Adult practice more commonly involves CRS and HIPEC during the same procedure.

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is well described in the management of adult peritoneal carcinomatosis. Rather than pursuing only surgical debulking, the aim is to remove all visible tumor at surgery and supplement this with the delivery of topical, heated (41–43°C) chemotherapy in the intraperitoneal space. This is generally performed at the same procedure.

CRS with HIPEC for pediatric malignancies associated with peritoneal carcinomatosis is presently confined to very few centers. However, there are reports of promising outcomes in desmoplastic small round cell tumor, where 1-year survival is usually reported in the range of 30% to 55% and Hayes-Jordan et al. (1,2) have reported 1-year survival of 89%. The same group has recently published results in patients with ovarian carcinoma with five of eight patients still alive 2–6 years after their treatment (3). Their most recent report of 50 patients includes patients with a variety of sarcomas and 2 patients with Wilms’ tumors. Those with complete cytoreduction from CRS had a median survival of 31.4 months vs 7.1 months in those without successful tumor load reduction. This early success suggests that these approaches are likely to enter practice in other centers, though still in a particular subset of patients.

This case provides an example of such treatment with an additional novel phase of management: tumor bed brachytherapy delivered via intraperitoneal guides. The
pediatric anesthetist presented with such a case needs a thorough understanding of the challenges in all three phases.

Cytoreductive surgery

CRS aims to remove macroscopic tumor from parietal and visceral peritoneum. It may also involve resection of intra-abdominal organs. As it is not always possible to remove all macroscopic tumors, the surgical goal is to resect until the remaining nodules are less than 2.5 mm in diameter. This maximizes the ability of subsequent chemotherapy to penetrate remaining tumor nodules and improve survival rates (4–6). Anesthetic challenges include prolonged surgery and significant fluid and blood loss with a potential need for massive transfusion.

Developing evidence for anesthetic approaches to CRS is difficult even in adults given its application in the care of rare cancers. This problem is more acute in pediatric oncology surgery. From their survey of 29 adult major surgical centers, Bell et al. confirmed routine use of invasive arterial pressure monitoring and central venous catheters for patient monitoring. Thirteen of 29 centers utilized some form of cardiac output monitoring. Other centers report use of a pulmonary arterial catheter or PiCCO (7).

CRS involves substantial fluid losses secondary to the extensive raw peritoneal surface area involved. In some cases, drainage of ascites may also contribute to fluid loss. In adults, intraoperative fluid turnover has been shown to be greater than the 6–8 ml·kg⁻¹·h⁻¹ commonly described for major intra-abdominal surgery. Schmidt et al. (5) retrospectively reviewed 78 patients having CRS with HIPEC and found their median fluid requirement was 11.9 ml·kg⁻¹·h⁻¹.

In adult reports, it is emphasized that there is a risk of hypothermia during the CRS phase due to the significant fluid turnover and extensive intra-abdominal exposure. Warming intravenous fluids and utilization of forced air warmers have been recommended (8).

There is also significant risk of coagulopathy secondary to massive blood transfusion. This risk relates to the degree of tumor resection and peritoneal stripping with resultant blood loss. In the survey of adult anesthetic practice by Bell et al., 27 of 29 (93%) centers guided management of coagulopathy by standard laboratory parameters including APTT, PT, and INR (8). At that time 6 of 29 centers (21%) were using bedside thromboelastography intraoperatively. A significant proportion of patients will require blood products including coagulation factor replacement in addition to packed red blood cell (PRBC) transfusions (7–9).

Careful fluid management is also vital in providing a degree of renal protection. In adult patients where CRS is combined with HIPEC, there are additional insults to the kidneys, including raised intra-abdominal pressures and nephrotoxicity from chemotherapy itself (8,10). Some authors describe the use of furosemide or low doses of dopamine to maintain urine output. The value of these interventions is debatable as prospective research indicates that maintaining normovolemia and adequate urine output alone is associated with unaltered creatinine values (11). Albumin may fall significantly during debulking surgery, particularly where there is ascites to drain (9). Despite this, it is not clear if albumin replacement has any advantages for fluid management in these patients (8).

Brachytherapy

Brachytherapy is a form of radiation therapy delivered with a source close to the site to be treated, rather than utilizing external beam radiation. It is typically used to deliver high-dose radiotherapy directly to tumors within deep body cavities, e.g., cervix, uterus, esophagus, or bronchus. It is also feasible where the tumor can be accessed by a needle or catheter, making it an option for prostate, breast, and head and neck malignancies. Brachytherapy can be further classified according to the manner of placement of the radiation source as contact or interstitial, by the dose rate (low, medium, high, or pulse) or the duration of the therapy as some radioactive sources are intended to be permanent while other methods involve temporary placement.

Delivery of radiation therapy via a sealed source close to the treatment area has the advantage of delivering a highly concentrated dose in a well-localized area with rapid fall off as the distance from the source of alpha and beta radiation increases. Delivery requires specialized systems and guides and is usually carried out in specialized facilities. Once in place it is vital to ensure the guides do not move as this will compromise the dose to the tumor bed.

There is no specific literature to guide intraoperative care of the pediatric patient having brachytherapy as this treatment has so far been utilized in very few cases. By contrast, brachytherapy is used in a number of different adult oncology settings. In prostate cancer where low-dose permanent seeds are implanted, positioning of the radioactive source is aided by minimizing intravenous fluids (12). Regional anesthetic approaches may be preferred in adult brachytherapy for lower body malignancies although there is no evidence they are associated with superior treatment outcomes (13–16).
Brachytherapy in children almost always requires anesthesia to allow tumor access. Additional risks to patients, carers, and staff then relate to delivery of anesthetic care in an area remote to the main operating suite and the unlikely but potentially catastrophic situation of needing to urgently remove a stuck sealed source. Radiotherapy facilities are often not initially planned to function as spaces for delivery of anesthesia and the location of necessary equipment may be compromised (Figure 4).

All episodes of insertion and treatment with a radioactive source require consideration of radiation exposure. There is a remote risk that the radioactive source may require urgent removal from the patient if it gets stuck in the delivery system, though this complication has not been reported in the literature to date. Such loss of control of the radiation source requires a specific retrieval plan with acknowledgment of potential risks to the patient of local tissue damage and to staff involved in the source retrieval, which would have required urgent laparotomy in this case.

**Heated Intraperitoneal Chemotherapy (HIPEC)**

HIPEC is a treatment modality more often employed in adult tumors with mitomycin C and platinum-based agents such as oxaliplatin most commonly used. The chemotherapeutic agents utilized need to meet a key goal: maximal concentration in peritoneal tumor and minimal systemic absorption. Heating the agents results in an increase in peritoneal concentration with a fall in both systemic and portal blood concentrations (17). Peritoneal cavity concentrations are also higher than those elsewhere because the body’s clearance of the drug from the systemic circulation exceeds the relatively slow clearance of the agents from the peritoneal cavity into the systemic circulation (11). Toxicities for end organs may still occur though the development of these is likely.
to be after the surgery. Commonly used agents like the platinum analogs are associated with nephrotoxicity, gastrointestinal upset, and neurotoxicity as in other chemotherapy regimens.

The delivery of chemotherapeutic agents in the surgical field may be completed in an essentially closed fashion or with the abdomen open with a contained area created with some height above the level of the abdomen. This technique is referred to as the open or “coliseum” technique (Figure 5) (7). It allows surgical handling of abdominal contents during the surgery and is thought to provide better distribution of chemotherapeutic agent throughout the peritoneal cavity compared to the closed technique. The inflow and outflow tubing for circulation of chemotherapeutic agents needs to be managed by some form of pump capable of reliably warming the chemotherapy solution. Temperatures within the peritoneal cavity should be measured at multiple locations to ensure uniform circulation of heated agent. Dwell time for the chemotherapy varies from 60 to 120 min (7,18). Specific protocols for the handling and disposal of chemotherapeutic agents are essential.

Hyperthermia itself is a key derangement that may occur. Without correction it may cause consumptive coagulopathy, injuries to the kidneys or liver, peripheral neuropathies, seizures, and arrhythmias (19). Dangerous hyperthermia may be prevented by inducing some cooling prior to introduction of the chemotherapeutic agents. This may be accomplished by decreasing the room temperature and avoiding warming of IV fluids or surface air. If core temperature starts to rise during HIPEC, placement of ice over major vessels (axillary or carotid) can be utilized. Research into practice at different institutions indicated that an average of 39.2°C was the mean accepted core temperature (8). Altering the temperature of the infusate is rarely employed.

HIPEC induces a hyperdynamic state (20). During the hyperthermic phase, there is an increase in heart rate, cardiac index, and oxygen consumption (20,21). This is partly related to heat stress induced by hyperthermia with resultant vasodilatation. The fall in peripheral vascular resistance requires an increase in cardiac output. Inotropes or vasopressors may be required to maintain acceptable hemodynamics and there are reports of the use of a variety of agents including norepinephrine and dopamine (11,7). Carbon dioxide production will tend to rise during the treatment, and without adjustment of ventilatory parameters, endtidal carbon dioxide may increase (20).

There is potential direct cardiotoxicity of cisplatin and selective renal magnesium loss as well (11). Coupled with QT interval dispersion during cisplatin therapy, this requires careful attention to magnesium levels in plasma. There is one case report of amiodarone-refractory pulseless ventricular tachycardia after intraperitoneal cisplatin (22).

There is a high risk of renal dysfunction due to a combination of factors including nephrotoxicity of chemotherapeutic agents such as cisplatin and mitomycin, significant fluid shifts, and raised abdominal compartment pressures. Renal protection depends principally on careful attention to volume status. While there are reports of some institutions utilizing dopamine or diuretics such as frusemide or mannitol to maintain urine output, there is little evidence to suggest this

Figure 4 In a radiotherapy suite, the working space for an anesthetist may be compromised by shielding requirements and hardware such as the brachytherapy delivery system seen in the foreground.

Figure 5 HIPEC open coliseum technique with the edges of the abdomen secured to retaining plastic. Multiple delivery circuits are visible along with four separate temperature probes to ensure adequate circulation of chemotherapeutic agents.
results in improved outcomes (7,8,20). Rates of postoperative renal dysfunction are reported as being anywhere from 1% to 10% (8,10).

Abdominal compartment hypertension during the infusate stage can further reduce cardiac output secondary to compression of the inferior vena cava and an increase in splanchnic vascular resistance. It is a particular feature of closed infusion systems rather than the coliseum approach. The volume of perfusate and use of peritoneal expanders by the surgeons will also impact on intra-abdominal pressure. Maintaining perfusion pressure is therefore a priority utilizing adequate intravascular filling or use of vasopressors or both. Muscle relaxation may also help (23,24).

The postoperative phase

The key challenges in early postoperative management are provision of adequate analgesia and the risk of organ dysfunction in multiple systems. Due to their extensive abdominal surgery patients are thought to be at risk for anastomotic leakage, bowel perforation, bile leakage, fistula formation, bleeding, pancreatitis, deep vein thrombosis, and pulmonary embolism.

Vasodilation is common after HIPEC, therefore necessitating careful monitoring, thorough attention to fluid requirements, and possibly use of vasopressor agents such as noradrenaline. Increased fluid replacement requirements may continue through this postoperative phase and require continuing assessment of fluid responsiveness.

Thromboembolism risk is an important consideration (18). This applies in all patients as the presence of malignancy and prolonged surgery constitute significant risk factors. Prevention may include graduated compression stockings and chemoprophylaxis. Postoperative feeding may be an issue although oral feeding is usually established between 7 and 11 days after surgery.

Particular toxicities related to the chemotherapeutic agent utilized should also be considered. For platinum analogs such as cisplatin or oxaliplatin, nephrotoxicity and electrolyte disturbances such as hypomagnesaemia and hypocalcaemia may be significant early considerations, along with gastrointestinal disturbances.

Analgesia is a key component of enhancing postoperative recovery. In the adult literature, thoracic epidural is stated by some authors to be the best option for combined CRS/HIPEC procedures (8,18). In the case reported above, the initial intention was to provide epidural analgesia to facilitate extubation prior to brachytherapy. Once the surgical plan was altered and long-term intubation was decided upon, the epidural was removed.

One argument in favor of a neuraxial approach is improved postoperative respiratory status. In the retrospective study by Schmidt et al. (9), 56 (72%) of 78 patients had a thoracic epidural. About 59% of these patients had a period of postoperative ventilation compared to 86% in those without an epidural. Those without an epidural were ventilated for a median of 10.3 h compared to 3.1 h in patients with an epidural.

Epidural analgesia may also be associated with earlier recovery of gastrointestinal function (25). In the event of postoperative coagulation disturbance, the timing of epidural removal requires careful planning. While there was concern in this case that postprocedural coagulopathy may increase the risks of an epidural, the common usage in adult practice suggests this option should be considered. There are no available outcome studies evaluating the benefits of regional analgesia compared to parenteral opioids in this patient group.

Safety considerations for staff during HIPEC

Exposure of operating staff to chemotherapeutic agents remains a concern during HIPEC although this is less of a concern with closed delivery techniques (26). One small study in which mitomycin C exposure of the surgeon and perfusionist during open HIPEC was assessed was unable to demonstrate a significant safety hazard to those in the operating room (27). This study, while only assessing exposure levels over 10 cases, did suggest that latex gloves were a sufficient barrier to prevent skin absorption. This team also reported a standard approach of using a smoke evacuation device in the surgical field. Some centers report an institutional practice of prohibiting pregnant women, those attempting to become pregnant, those with a history of miscarriages, immunosuppressed staff, or those with a hematological condition from participating in HIPEC cases (26–29). As each facility delivering cytotoxic therapy will have practice guidelines regarding use of these agents, as well as safety procedures in place in the case of small or large spills, perioperative teams should review this local information prior to the procedure. Understanding of safe procedures and responses in emergency situations with cytotoxic agents must be confirmed with all involved staff.

Considerations of location

A final point to consider in planning such novel treatment plans is the ideal location for the sequence of procedures to take place. Access to brachytherapy facilities
for our institution is provided by the co-located adult hospital. For this patient, it was decided to undertake all other procedural care and inpatient management at The Children’s Hospital at Westmead because of the expected reliance on many supporting pediatric services. These services included a pediatric intensive care, nephrology, pain management service, and pediatric hematology. The involvement of specialist pediatric allied health, social work, and psychology services were a major part of recovery for this patient.

There are no published opinions on the best location (in terms of pediatric vs adult centers) for pediatric patients undergoing HIPEC or brachytherapy. There is evidence that even for clinical care situations where there is a greater caseload of adult patients than pediatric patients, those cared for in pediatric centers have better outcomes. This applies to pediatric trauma patients and functional outcomes (30,31), appendicitis management (32), interhospital transport (33), and leukemia (34,35). Even in surgical care where pediatric surgeons have less exposure to a particular technique, such as pancreaticoduodenectomy, there is evidence that outcomes are better if the patient is cared for in a pediatric center (36).

Developing medical techniques that require expensive medical infrastructure tend to find a role in adult practice prior to pediatric practice. Examples on the horizon include intraoperative MRI, hybrid angiography suites, and robotic surgery. Expensive infrastructure is likely to be used in far lower numbers in pediatric health care. For many centers this will require collaborative relationships with adult institutions. It then becomes necessary to include planning for pediatric support services, interfacility transport, and the psychological and social support available as standard care in pediatric centers. This will require consideration on a case-by-case basis. Novel cancer therapies such as HIPEC and brachytherapy are another example where a strong argument can be made that overall care of the patient is better at a pediatric center.

**Conclusion**

Novel techniques in surgical management of malignancy are likely to enter pediatric practice as they transfer from adult care. Many of the issues in adult care are likely to continue to be issues in particular blood loss, difficult fluid management, hemodynamic disturbance, and temperature management in the case of HIPEC. Postoperative analgesia is also a significant challenge. However, as peritoneal carcinomatosis is not as common in pediatric patients and the malignancy lineages are different additional therapeutic variations, such as the intervening brachytherapy in this case, may also challenge the pediatric anesthetist further. Clear communication of the anticipated plan and course with the surgical and oncology teams is vital in this setting, as well as a flexibility of approach. At all steps in the planning, careful consideration of potential risks to staff must also be considered.

**Ethics approval**

Ethics approval and patient and family consent were obtained for this report.

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**Conflicts of interest**

The authors have no disclosures or conflicts of interest to report.

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A.D. Weatherall

8

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