Seminars in
ROENTGENOLOGY

Pediatric Interventional Oncology: Endovascular, Percutaneous, and Palliative Procedures

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Introduction

Interventional Oncology (IO) represents an evolution of powerful minimally invasive therapeutic procedures within the discipline of interventional radiology, driven in large part by rapid technological innovation. In modern medical centers, IO is established as the "fourth pillar" of multidisciplinary oncologic care, alongside oncology, surgery, and radiation oncology.[1] Although widespread adoption of IO in the pediatric population has taken longer than in adult practices, there has been increasing interest from patients and providers in employing such minimally invasive and effective approaches to reduce systemic side effects and ensure faster recoveries. The 3 main applications of IO techniques in children with cancer are endovascular, percutaneous, and palliative and supportive procedures/therapy, which are each described in detail.

The toolbox of an IO practitioner builds upon common services for cancer patients such as venous and enteral access, biopsies, and palliative procedures. These basic services often represent the initial point of contact between interventional oncologists and the patients as well as their referring oncologist. Because of the very nature of the therapeutic concepts in IO and their ability to provide quick solutions for increasingly complex problems with symptom relief as a common result, patients view this care with satisfaction and share their impression with the referring physicians. In a way, patient satisfaction has become the most valid argument in IO's struggle for recognition. As such, every biopsy, chest port, or paracentesis provides an opportunity to offer more sophisticated services to manage the oncologic disease, and to educate patients and fellow oncologists about the value of IO.

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Endovascular Procedures

Liver Tumors

Liver tumors are among the rarest malignancies in the pediatric population; the vast majority of cases are due to hepatoblastoma or hepatocellular carcinoma (HCC). Survival data for these tumors are mixed: hepatoblastoma 5-year survival approaches 80% with multimodal treatment while survival for HCC is less than 30%.[2-5] Transarterial chemoembolization is a minimally invasive locoregional treatment option performed by interventional radiologists with level-I evidence as standard of care in adult patients with advanced HCC. This therapeutic approach has been shown in the adult population to prolong disease free progression, downstage and bridge patients for surgical and transplant interventions, and improve overall survival.[6-8] Over 3 decades of prior work as small series have reported that transarterial therapies, including chemoembolization as well as selective internal radioembolization (SIRT) is feasible and effective in children for primary liver tumors, both unresectable hepatoblastoma and HCC.[9]

Endovascular locoregional therapies for pediatric liver tumors include bland transarterial embolization, transarterial chemoembolization, and SIRT, also called transarterial radioembolization. Each of the endovascular approaches utilize the physiologic dual blood supply to the liver made up by the portal vein and hepatic arteries. The liver receives the approximately 75% of its blood supply from the portal vein while liver malignancies, in contrast, receive the majority of blood flow from the hepatic artery. The hepatic arteries feeding can be safely used to inject a wide variety of agents to block the tumor vascular supply and/or deliver drugs/radioisotopes with minimal impact on the normal liver (portal vein) blood supply. Most practices use bland transarterial

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embolization and/or transarterial chemoembolization (Fig. 1); SIRT is also occasionally employed where radioactive yttrium-90 (Y-90) glass or resin microspheres are injected, rather than chemotherapy or embolics, via hepatic arterial catheters at the site of the tumor.

Small studies have shown transarterial chemoembolization is feasible in treating pediatric liver tumors, most of the prior literature is focused on hepatoblastoma.[10-15] One of the earliest reports described 6 hepatoblastoma patients and 3 HCC patients who were unresponsive to systemic chemotherapy and had unresectable disease; all 9 patients responded to transarterial chemoembolization and postembolization surgical resection was feasible in 5 patients.[11] Plasma levels of cisplatin or doxorubicin remained undetectable after embolization, supporting the high locoregional concentration of chemotherapy while minimizing systemic chemotherapy toxicities.[10] In the largest series on transarterial chemoembolization in pediatric HCC, 8 pediatric patients (mean age 12.5 years) with unresectable, transplant-ineligible HCC were treated with a mean of 2.5 transarterial chemoembolization procedures; from this group, 6 patients were successfully bridged to transplantation. Despite encouraging early results in small studies, prospective multi-center assessment of transarterial chemoembolization therapy in the pediatric liver cancer population must be performed to understand how these techniques can be best applied to pediatric oncologic care.

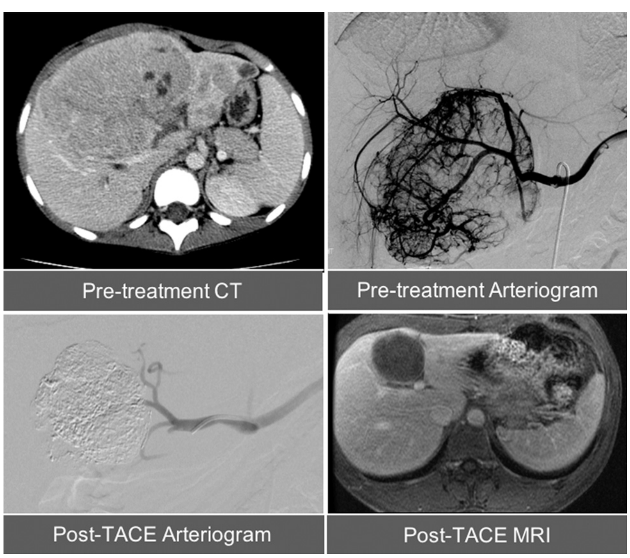

Figure 1 Before and after TACE treatment of liver mass in a 7-year-old male with chronic hepatitis B who presented with abdominal pain and elevated AFP. Contrast enhanced CT reveals a large heterogeneously enhancing primary liver mass. Celiac arteriogram demonstrates markedly increased tumor vascularity with supply from the left hepatic artery and a large inferior branch of the right hepatic artery, which is thought to represent a markedly hypertrophied cystic artery. Additionally, there are other vessels arising from the distal right hepatic artery, which also supplies the tumor. Follow-up arteriogram after increasing AFP 5 months later demonstrates no significant tumor vascularity and excellent chemoembolization result as well as marked reduction of tumor volume. An accessory left hepatic artery arising from the left gastric was found to demonstrate supply to approximately 1.5 cm of hypervascular new tumor which was successfully chemoembolized (not shown). Follow-up MRI 6 months after initial TACE demonstrates nonenhancing lesion that had decreased in size and no residual disease.

Renal Tumors

Wilms tumor is the most common malignant renal tumor in children and the survival for patients with Wilms tumor has improved with systemic chemotherapy and surgical resection, leading to a 5-year survival of over 75%.[16] Yet many patients with Wilms tumor demonstrate unfavorable disease outcome factors such as large tumor size, difficult surgical resection, incomplete excision, peritoneal adhesions, tumor extending to vena cava, metastases, and unfavorable histology.[17-19] While prior experience with endovascular therapies for renal tumors is almost exclusively focused on angiomyolipoma embolization [20] especially in the pediatric population, renewed interest in alternative adjunct treatment strategies such as endovascular chemoembolization for malignant lesions like Wilms has been proposed to maximize survival and outcomes, particularly in patients with poor prognostic factors. In 1 series, 66 patients with advanced Wilms tumor treated with preoperative renal arterial chemoembolization using pirarubicin-vindesine were found to achieve higher rates of complete tumor resection and relapse-free survival in the treatment of advanced Wilms tumor compared to standard therapy alone (systemic chemotherapy and surgery).[21] In patients that received both chemoembolization and modified systemic chemotherapy, a 2-year 100% relapse free survival was observed. The potential advantages in management of advanced Wilms with endovascular intervention include improved complete tumor resection rate of the tumor and longer relapse free survival. A prospective multicenter trial with long-term follow-up is needed to further validate the efficacy of chemoembolization in the treatment of children with Wilms tumor.

Neurologic Tumors

Experience with endovascular embolization treatment approach for head and neck tumors in the pediatric population consist overwhelmingly of juvenile neuroangiofibromas (JNA), a benign but highly vascular tumor that can bleed profusely during surgical resection. Preoperative endovascular embolization of these lesions can be performed with a high rate of technical success, a low complication rate, significantly decreased volume of operative blood loss [22] and aid in preoperative planning.

Similar to JNA, there have been several small series exploring the use of preoperative embolization for intracranial malignancy in children as well. For example, a study of 7 choroid plexus papillomas that underwent successful preoperative embolization found high technical success of 86%.[23] Another study of 8 pediatric patients with intracranial malignancies found that combined endovascular embolization immediately prior to surgical resection led to improved operative times. However, particle embolization was associated with a *higher* complication rate, both from nontarget embolization, vessel rupture, and increased hemorrhage. Hemorrhagic complications were speculated to be secondary to increased pressure and rupture of the distal vasculature.[24] To review available evidence and reach consensus, a large systematic review was performed on the topic of preoperative endovascular embolization for intracranial malignancies reached contradictory findings to prior smaller series.[25] This study reviewed 111 pediatric and adult hemangioblastoma patients who underwent preoperative embolization prior to resection compared to standard of care resection. In the analysis, endovascular embolization was definitively found to be *ineffective* in reducing intraoperative blood loss, reducing surgical risk, or decrease complications; furthermore, in this large series, intracranial endovascular embolization itself introduced significant risk and complications were found to occur in more than 10% patients. So while tumor embolization has had success in head and neck tumor types like JNA, the current literature does not support endovascular embolization for the management of intracranial tumors in children.[25]

Percutaneous Procedures

Percutaneous Biopsy

Image guided percutaneous biopsy is a minimally-invasive technique used to diagnose primary malignancy or metastatic disease, guide treatment by providing tissue for molecular testing and cytogenetics, and follow response to treatment. Interventional radiologists use ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) to guide biopsy needle placement. US and MRI are favorable in the pediatric population due to lack of ionizing radiation. Direct percutaneous access to the lesion may be obtained with the biopsy needle itself or by using coaxial needle technique. Coaxial needle technique is often used, as the coaxial needle maintains stable positioning during multiple needle passes and allows for tract embolization during coaxial needle removal. For lesions that are difficult to visualize with US or contain areas of necrosis, contrast-enhanced US can also be used to improve conspicuity and assist with targeting regions of viable tissue.[26] For lesions in difficult to access locations, the CT gantry may be angled or hydrodissection may be used to displace critical structures to allow successful percutaneous access to the target.[27,28]

Biopsy tract seeding, whereby tumor cells are deposited along the needle path, is a concern following percutaneous biopsy of malignant tumors. Care should be taken to plan biopsy trajectory in collaboration with a surgeon, particularly for percutaneous biopsies of musculoskeletal and liver tumors. Traversing a compartment with biopsy trajectory that will not be violated during surgical resection can have unfortunate consequences, possibly requiring more extensive surgical resection than what was originally clinically indicated. A study in adult patients demonstrated a 2.7% rate of tract seeding following percutaneous biopsy of HCC.[29] Tract cauterization, when employed, has been shown to reduce the incidence of viable tumor cells to 0% following radiofrequency ablation (RFA) for HCC.[30] While at this time, tract cautery function is not available with current biopsy devices, an ablation probe can be placed through the biopsy device to achieve tract ablation.

Image Guided Thermal Ablation

Recent advances in technology have provided multiple percutaneous thermal ablation techniques for treatment of primary benign and malignant tumors and metastatic disease. The most commonly used thermal ablation techniques are microwave ablation, RFA, and cryoablation (Fig. 2). Imaging guidance used for thermal ablation depends upon the location of the target lesion. For example, for lung and bone lesions, CT guidance is typically used. For superficial soft tissue lesions or parenchymal lesions within the liver and kidney, US alone or a combination of US, CT, and/or MRI may be used for guidance. In lesions that are difficult to visualize or contain areas of necrosis, contrast-enhanced US can also be used to improve conspicuity and assist with targeting regions of viable tissue.[26] There is overall limited data on the use of percutaneous thermal ablation techniques in the pediatric population.

A review article from 2014 identified 29 lesions in 28 pediatric patients treated with thermal ablation between 1995 and

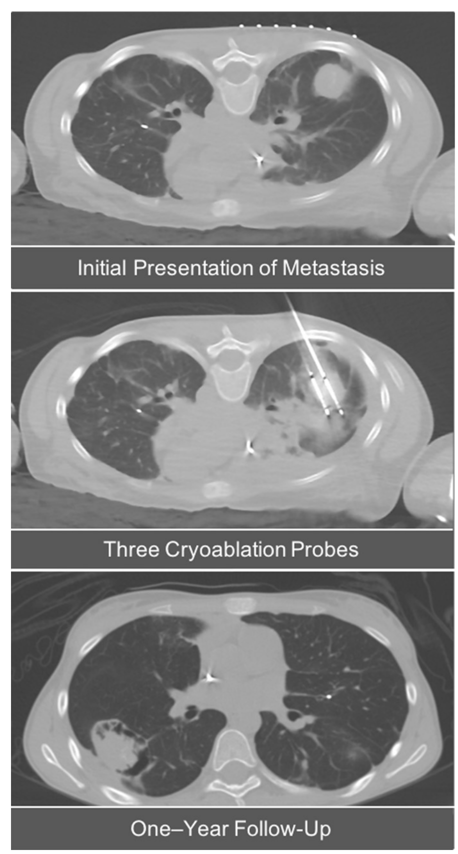

Figure 2 Intraprocedural planning CT in the prone position with posterior skin markers placed in a 14-year-old girl with metastatic osteosarcoma during cryoablation treatment of lung metastasis. Three cryoablation probes were placed percutaneously to create adequate ablation zone. Small pleural effusion developed during freeze-thaw cycles. Post-treatment CT scan approximately 1 year later demonstrated ablation margins and post-treatment changes in the adjacent lung parenchyma and pleura.

2012.[31] Location of lesions treated included liver, lung metastases, bone or soft tissue, kidney, and pancreas. For bone and soft tissue tumors, clinical success was reported as 47%.[31] In 10 children with osteosarcoma, Saumet et al[32] demonstrate a 95% success rate in ablating 22 small metastatic lung lesions (less than 3 cm) using RFA with no local recurrence and minor complication of hemoptysis and pneumothorax. Another study of RFA ablation of lung metastases showed complete ablation of 45% of lung lesions after 1 RFA treatment.[33] In the review article, 7 hepatic lesions were treated in 5 patients, with 100% technical and clinical success.[31] Five retroperitoneal lesions (renal or pancreas) were treated with RFA in 4 patients, with 100% technical success and 75% clinical success.[31] The systematic review demonstrated the limited data on thermal ablation in children. While thermal ablation is feasible in children, to this point, it is often used with palliative intent after traditional treatment has failed.

RFA deposits thermal energy (electromagnetic spectrum between 3 Hz and 300 GHz) into the target tissue resulting coagulation necrosis and tissue damage from the rapidly altermatic current.[34] Grounding pads must be placed on a broad skin surface of the patient, such as the thighs, during treatment to complete the circuit for the transfer of energy. RFA is known to be limited by heat-sink effect whereby flowing blood in adjacent vascular structures dissipates the energy transferred to the tissue and limits the size of the ablation zone. Recently, it has been shown that transarterial chemoembolization followed by RFA results in decreased heat-sink effect and more effective RFA ablation due to decreased blood flow in the target tissue.[35,36]

Microwave ablation deposits thermal energy through molecular oscillation at the higher end of the radiofrequency spectrum and, similar to RFA, causes coagulation necrosis and cell death.[37] Microwave ablation propagates energy more efficiently than RFA with less susceptibility to heat-sink effect, allowing for the creation of larger ablation zones in less time.[38] Microwave ablation as a mono-therapy for treatment of HCCs <3 cm has been shown to be 86.7%-98.5% effective in providing complete treatment response in adults.[39-41]

Cryoablation, in contrast to RFA and microwave ablation, creates cytotoxic temperatures (−24 Celsius and below) through the Joules-Thompson effect as Argon gas in the ablation probe tip is rapidly depressurized and expanded.[42] At cytotoxic temperatures, intracellular and extracellular crystals are formed and cause membrane and organelle damage, leading to cell death.[43] The ice ball is well-visualized during cryoablation treatment by US, CT, and MRI, which allows the operator to guide freeze/thaw cycle timing and to monitor ice ball effect on adjacent critical structures. Cryoablation does not result in coagulation necrosis, therefore has higher rates of post-treatment hemorrhage.[44] A very rare complication following cryoablation of large tumors is "cryoshock,", whereby reperfusion of the necrotic tissue following ablation results in systemic, intravascular spread of cytokines and intracellular materials, which can lead to shock, disseminated intravascular coagulation, and multiorgan failure.[45-47]

Deposition of viable tumors cells along the percutaneous access tract is a concern following ablation. Tract cauterization following ablation can decrease the risk of tract seeding. A 12.5% incidence of viable tumor cells on the ablation probe was found in a study of 40 adult patient when tract cauterization was not performed following RFA for HCC, compared with 0% incidence when tract cauterization was performed.[30]

CT Guided Lung Nodule Marking

Small pulmonary nodules in pediatric oncology patients present diagnostic and therapeutic dilemmas. These small nodules, particularly <10 mm, are often too small for adequate diagnostic yield from a CT guided percutaneous needle biopsy and too small to palpated during surgery. Methylene blue dye can be injected through a needle with CT guidance mixed with contrast, mixed with blood, or full concentration. The Kopans hook needle was originally created for breast lesion localization however can also be placed into the lung parenchyma with CT guidance for nodule localization. Both Kopans hook wire placement and methylene blue dye injection have been used alone in lung marking, however neither is a perfect method alone.[48] Methylene blue injection site can be difficult to localize intraoperatively if the liquid spreads too broadly across the pleural surfaces. Hook wires can become displaced during patient transport or in the operative room during dissection. Methylene blue blood patch alone has been demonstrated to provide 100% diagnostic pathology.[49] More recently, many practitioners use a combined approach with CT-guided lung nodule localization with both methylene blue dye and hook wire placement prior to thoracoscopic wedge resection which has proven to be beneficial (Fig. 3).[48] A recent study by McDaniel et al[50] performed localization of small lung nodules between 1.4 mm and 18 mm using either Kopans needle alone, methylene blue blood patch alone, or the combination of these 2 techniques. Among the 35 patients (40 nodules) included, they demonstrated a technical success rate of 100% with a pathological diagnosis determined in 97.5%.[50] CT-guided nodule localization with microcoils has also been demonstrated to be successful in children.[51] Complications described following needle localization of lung nodules include pneumothorax, pulmonary hemorrhage, and air embolus.

Palliative and Supportive Care

Pain Management

Pain is the most common symptom reported by children with cancer, increasing in severity throughout the course of their illness and peaking at the end of life.[52] While opiates remain at the cornerstone of pain management,[53] a small number of patients require interventional strategies for pain control, including neuroaxial or peripheral nerve blocks, neurolysis, and ablation of painful lesions. Such interventions are used as a last resort in patients with severe pain poorly-controlled by opioids due to tolerance or signs of opioids toxicity or in those with neuropathic pain refractory to opioids.[54] Several small studies and case reports have demonstrated that continuous epidural or peripheral

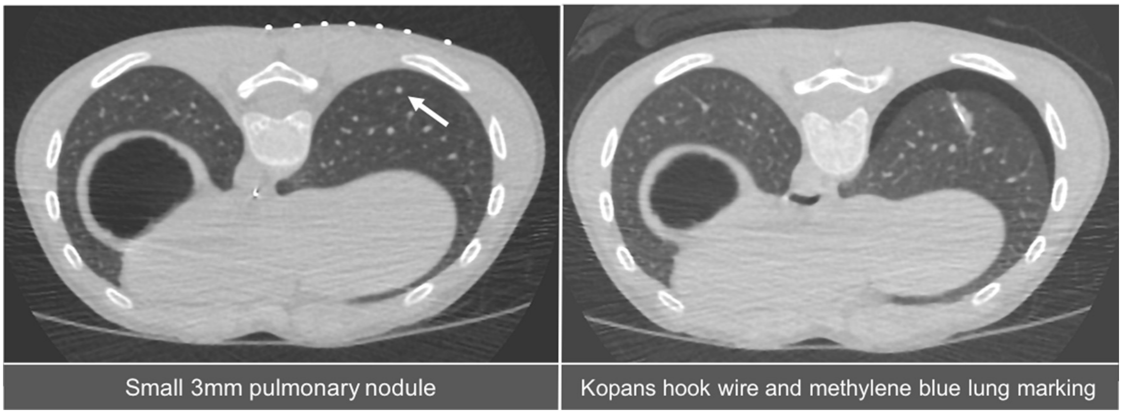

Figure 3 Percutaneous combined CT-guided localization in a 9-year-old boy with history of orbital alveolar rhabdomyosarcoma with small (3 mm) lung nodules concerning for metastases. Surgical resection was recommended because isolated lung nodule metastases are extremely rare. Preoperative CT guided wire placement and methylene blue tattooing of the right lower lobe lung nodule was performed by Peds IR for localization prior to surgical resection. Pathology was consistent with a normal intrapulmonary lymph node, requiring no whole lung radiation treatment.

infusions are effective in reducing pain in children with cancer with minimal risk.[54-63] In a retrospective review of 10 children, Anghelescu et al[57] reported decreased pain and opioid requirements at the end of life using continuous catheter-delivered analgesia without complications for up to 81 days. Safe placement of infusion catheters often requires the use of image guidance, traditionally fluoroscopy, CT, and more recently, US. US-guidance may be advantageous as it allows for real-time accurate estimation of the depth without radiation exposure and has been shown to increased block quality and success, particularly in younger children.[64] Important complications of catheter placement including bleeding, infection, and catheter dislocation can be reduced by using tunneled catheters.[65] While major complications of nerve blockade are rare,[66] patients needing chronic placement may have a higher risk of infection.[67]

Image-guided tumor ablation has become well-established for the palliative management of adults with malignancy,[68] but its application in children has been very limited to date. Most pediatric studies highlight therapeutic outcomes of ablative techniques [31] with less emphasis on their palliative benefits. Case series have demonstrated the safe and effective use of CT-guided RFA and cryoablation to relieve pain in children with benign and malignant lesions.[69-72] Proposed advantages of ablative techniques include more rapid pain reduction, as seen in chondroblastoma patients treated with RFA versus surgical resection,[69] and potential for same site retreatment for recurring pain.

Malignant Effusions

Malignant pleural and peritoneal effusions, although uncommon in children, are associated with poor prognosis and can be a cause of significant morbidity. Therapeutic management of symptomatic patients involves intermittent fluid drainage and shunting as well as options to prevent fluid accumulation. Slowly developing effusions may be aspirated via US-guided thoracentesis[73] or paracentesis for pleural and ascitic fluid, respectively. This approach requires repeated inpatient treatments that can be painful and are considered in patients with short life expectancy. Tunneled pleural or peritoneal catheters are advantageous as long-term drainage solutions. In adults, indwelling catheters are the preferred therapeutic method due to their minimally-invasive approach and ability to be placed and drained in outpatient settings. The safety and efficacy of cuffed PleurX (Becton Dickinson, Franklin Lakes, NJ) tunneled catheters in management of malignant effusions in children was recently demonstrated.[74,75] Leakage around insertion sites and infection pose a small, but important risk.

For pleural effusions, obliteration of the pleural space via pleurodesis can be sought as a more definitive treatment to prevent fluid accumulation. Hoffer et al[76] found decreased respiratory rates and improved aeration following US-guided pleurodesis using doxycycline as a sclerosing agent in 7 children.[76] No studies have applied superior pleurodesis agents like talc poudrage[77] in the pediatric population.

Refractory ascites can be treated using a peritoneovenous shunt that connects a peritoneal and a central venous catheter via a subcutaneous port chamber containing a 1-way valve and pump system that internally drains peritoneal fluid into the venous system. Rahman et al reviewed 31 Denver shunt placements and found resolution of ascites in 91% of patients with one-third of patients having complications including shunt occlusion, pulmonary edema, and infection.[78] An alternative treated to persistent ascites due to portal hypertension is the transjugular intrahepatic portosystemic shunt whereby portal system pressures are reduced via a shunt connecting portal and systemic venous circulations.[79] Serious complications of encephalopathy and shunt occlusion can occur.

Other Supportive Therapies

Management of malignancy-related complications can dramatically improve patient quality of life. Extrinsic tumoral compression of enteric, urinary, and airway luminal structures can not only be a source of great discomfort but also may become acutely life threatening. IR transluminal-directed procedures can alleviate tumor-associated obstruction. Gastrointestinal interventions including percutaneous biliary drainage and stenting[80-82] and gastrostomy tube placement[83] have been shown to safely and effectively alleviate malignant obstruction in children. In children with upper urinary tract obstruction by malignant tumor, temporary nephrostomy placement results in alleviation of obstructive sequelae, including renal failure, with febrile urinary tract infections as the primary complication.[84] Rare airway compromise from tumor obstruction can be relieved using tracheobronchial stenting in combination with other therapies to reduce tumor burden.[85,86]

Conclusion

This review article outlines the important growing role of interventional radiology in the care of pediatric oncology patients. Percutaneous image-guided biopsy provides pathologic diagnosis and helps guide treatment. While there is overall limited data in minimally invasive treatment in children, early studies demonstrate that endovascular treatments and percutaneous thermal ablation techniques are safe and effective in the treatment of benign and malignant tumors in the pediatric population. Endovascular chemoembolization and radioembolization treatments are available for hepatic, renal, and neurologic tumors. Percutaneous thermal ablation has successfully been performed for renal, hepatic, soft tissue, osseous, pancreatic, and pulmonary lesions. When no curative treatment is available, interventional radiology can also contribute to the care of pediatric oncology patients by palliating symptoms with decompressive gastrostomy tubes, biliary drains, nephrostomy tubes, and drainage of pleural fluid or ascites. Multidisciplinary collaboration will continue to contribute to the body of knowledge and expand the role of interventional radiology in pediatric oncology.

What began as a limited, almost abstract idea of a minimally-invasive image-guided tumor therapy has become a comprehensive and creative new specialty, driven by seemingly unlimited technological innovation. The perception of IO has evolved from suspicion, ignorance, or skepticism into something that is fully accepted and demanded by knowledgeable oncologists. Clinicians now refer patients with the expectation that these minimally-invasive therapies will be applied and seamlessly integrated into an individualized, oncologic care plan with partnering disciplines. This gratifying new level of clinical collaboration on equal terms is a result of many years of organized effort by the increasingly organized community of interventionalists to establish the credibility of IO, which is more and more based on prospectively collected clinical evidence as demonstrated in this review article. As a result, the path towards building an IO practice is now open for an entire generation of young practitioners of minimally-invasive, image-guided tumor therapies.

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