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INTERVENTIONAL ONCOLOGY (DC MADOFF, SECTION EDITOR)

Role of Interventional Radiology in Pediatric Cancer Patients

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Abstract

Purpose of Review Pediatric interventional radiology (IR) is a growing subspecialty. Here, we review the current role of IR in children with cancer, which uses imaging such as ultrasound, fluoroscopy, and computed tomography to perform minimally invasive procedures. These include biopsy, needle localization, central venous access, thermal ablation, transarterial chemoembolization, transarterial radioembolization with yttrium-90, non-tunneled/tunneled drainage catheter placement, and lymphatic interventions.

Recent Findings Although locoregional therapies for the treatment of cancer in adults are common, they are less common in children, perhaps due to the relative rarity of cancer in children, their typically better performance status, and paucity of comorbidities. Preliminary results from small-scale studies for ablation, transarterial chemoembolization, and transarterial radioembolization with yttrium-90 used in the front-line armamentarium of curative therapy are encouraging.

Summary Pediatric IR offers an array of minimally invasive procedures intended to diagnose and treat pediatric cancer patients. However, more research is required to determine the efficacy of locoregional therapy in children and to define the clinical scenarios where benefit is likely to be optimized.

Keywords Pediatric · Children · Malignancy · Cancer · Oncology · Interventional radiology · Ablation · Transarterial chemoembolization · Transarterial radioembolization with yttrium-90, Y90 · Lymphatic embolization

Introduction

Interventional radiology (IR) uses imaging such as ultrasound, fluoroscopy, and computed tomography to perform minimally invasive procedures to decrease the morbidity and mortality of traditional surgery. Pediatric IR is a growing subspecialty, and over the last 40 years, it has become part of standard medical care [1, 2]. Approximately 15,000 children in the USA are diagnosed with cancer each year [3]; the subspecialty of pediatric interventional radiology offers an array of procedures intended to diagnose, treat, and provide supportive care.

Radiation Safety

As children are more sensitive to radiation and have longer lifetimes to express changes, a concentrated effort is being made to reduce medical radiation in children [4•, 5•]. The Image Gently, Step Lightly campaign recommends a checklist of goals, including using sonography, "step lightly" by minimizing fluoroscopy time, collimating, lowering the frame rate, using last image hold, and using digital zoom whenever possible. Patient shielding is not routinely recommended as collimation is the best method of reducing extraneous dose; there is some evidence that shielding may actually increase internal backscatter [6].

Often, the smaller body habitus of pediatric patients lends itself to ultrasound guidance. Ultrasound allows real-time

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imaging guidance without radiation exposure, decreasing the risk of these procedures in the pediatric population.

Sedation

Compared with the majority of adult IR practices, pediatric IR requires deep sedation or general anesthesia for most procedures both to limit motion and for patient comfort [7, 8]. Our institution utilizes an independent anesthesia or sedation team for these services. Whenever possible, multiple procedures are combined to decrease the number of anesthesia occurrences.

Diagnosis

Biopsy

For the initial diagnosis of a tumor, percutaneous needle biopsy (PNB) is often requested. The safety and efficacy of PNB in both adult and pediatric patients has been confirmed and demonstrates excellent results with few complications. With the advent of precision medicine, PNB is often also utilized for molecular studies, for both standard of care and research purposes, and therefore the tissue sample needs to be of sufficient quality/quantity for both histologic diagnosis and any additional molecular studies. Percutaneous needle biopsy is also used for staging to identify the residual or recurrent disease and to obtain microbiologic analysis in patients with known or suspected infection [9].

Prior to biopsy, a review of cross-sectional imaging including ultrasound, computed tomography, magnetic resonance imaging, or positron emission tomography is reviewed to identify a safe pathway and to determine the best area to target within the lesion for the greatest diagnostic yield (i.e., most enhancing or fluorodeoxyglucose-avid region). A multidisciplinary conversation with the referring physician and pathologist may be useful to guide the approximate amount of tissue that will be needed for diagnosis and any additional molecular studies. In addition, real-time touch prep or frozen specimen evaluation can be used to increase the adequacy of the tissue.

When ultrasound is utilized (Fig. 1), a thorough ultrasound scanning immediately prior to the biopsy should be performed to identify a safe approach to the lesion, identify vascular structures, as well as determine more viable portions of the mass. At our institution, the targeted biopsy is always performed with a coaxial system to obtain more than one sample and/or to avoid tract seeding [10]. Post biopsy embolization with Gelfoam (Pfizer, New York, NY) pledgets and/or slurry is routinely performed to minimize blood loss.

Needle Localization

Computed tomography-guided localization of pulmonary nodules prior to video-assisted thoracoscopic surgical resection can be performed in children to distinguish malignant and benign etiologies. In children who have had prior chemotherapy and are immunocompromised, infection is a top differential in these patients. Often, imaging findings are not specific to a diagnosis.

In some forms of childhood cancer, such as osteosarcoma, there is a survival benefit when pulmonary metastases are resected. In addition, the chemotherapy regimen may be modified based on the histopathologic findings.

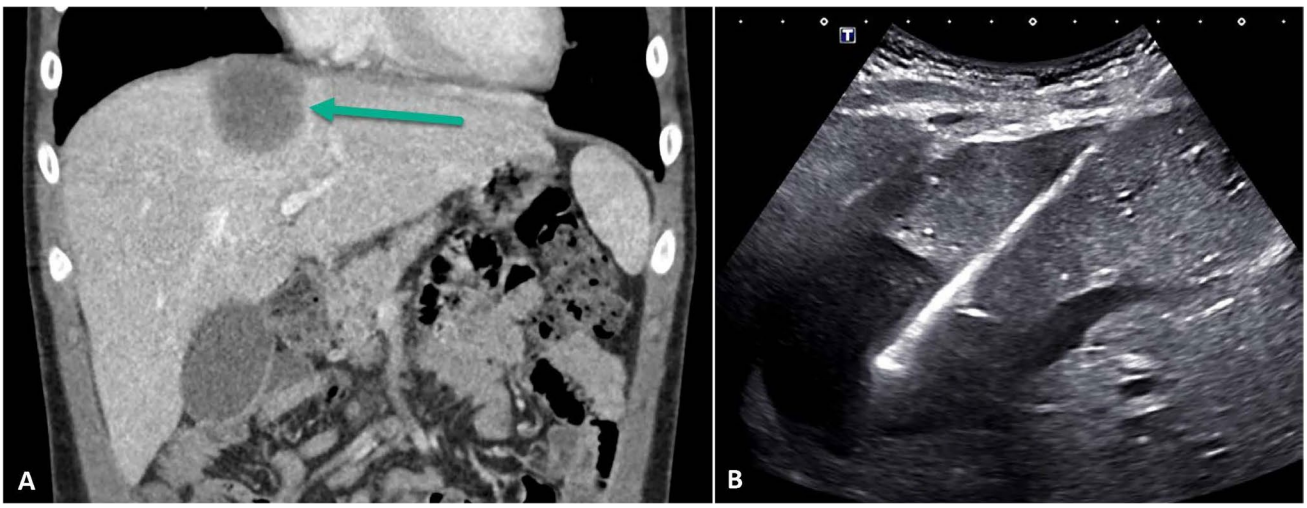

Fig. 1 Images of a 14-year-old male status post heart transplant with an enlarging liver lesion. Pre-biopsy computed tomography demonstrating a mass in the dome of the liver (green arrow) (**A**); ultrasound-guided liver biopsy (**B**) confirmed the preliminary diagnosis of post-transplant lymphoproliferative disease

We use a combination method, which utilizes methylene blue mixed with autologous blood and hook wire localization (Kopans breast localization needle, Cook Medical, Bloomington, IN) [11]. If the nodule is subpleural, both the methylene blue/autologous blood patch and hook needle are applied approximately 1–2 cm deep to the nodule (Fig. 2). This avoids methylene blue in the pleural space as well as dislodgement of the hook wire with respirations.

Central Venous Access

Port Placement

Central venous access is required for most pediatric cancer patients. There is a reduced complication rate of image-guided percutaneous port placement compared with the landmark technique [12–14].

Compared with tunneled central lines, implantable venous ports are associated with lower rates of central line-associated bloodstream infection and a lower likelihood of requiring revision or replacement over the course of therapy [15]. Although each patient is evaluated individually, our suggested weight for placement of a 5F single lumen venous port is approximately 10 kg, and for placement of a 9.5F dual lumen venous port is approximately 30 kg. The most common indications for dual lumen ports are non-Hodgkin lymphoma and sarcomas (Fig. 3). These patients often require intense chemotherapy with the need for pain medications and total parenteral nutrition, which are not compatible with other medications.

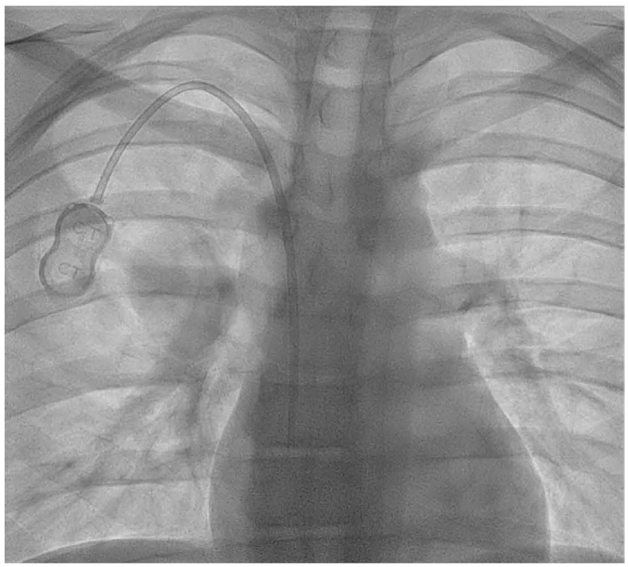

Fig. 3 Image showing a double lumen port in a 16-year-old male with a history of osteosarcoma

The use of prophylactic antibiotics is controversial; however, we do not use prophylactic antibiotics unless the patient is neutropenic with an absolute neutrophil count of < 1000.

The right internal jugular vein is the preferred vein of interventional radiologists with a short, straight route to the superior vena cava/heart. Access to the internal jugular vein with image guidance avoids pneumothorax and reduces the rate of symptomatic central venous stenoses [16]. To obtain a smooth curve of the catheter, a lateral venous access

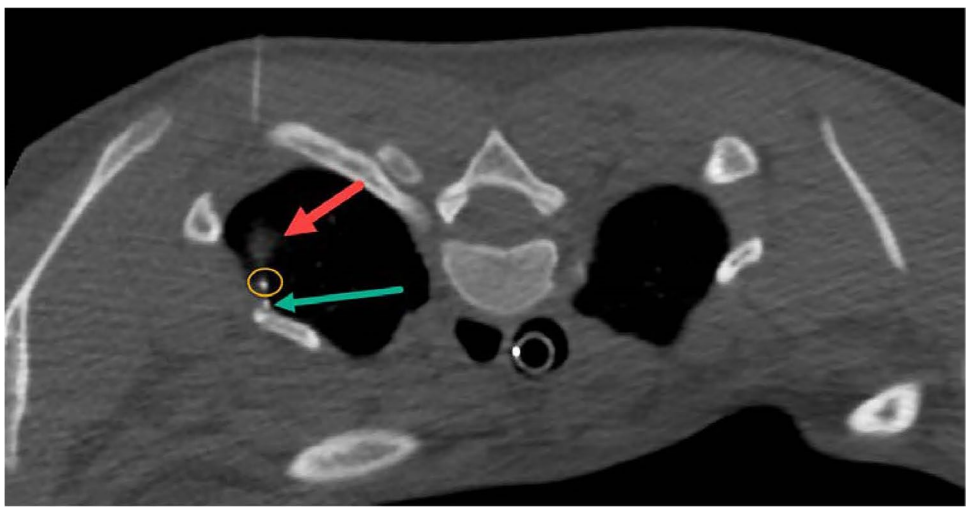

Fig. 2 Computed tomography scan of a 12-year-old female with a history of pulmonary metastatic osteosarcoma of the lower extremity with a new lung nodule after 4 years in remission. Prone computed tomography scan demonstrating Kopans wire across the 2 mm lesion (yellow circle) with the hooked wire tip across the contralateral pleura (thin green arrow), as requested by the surgical team. Methylene blue blood patch is denoted by a thick red arrow, approximately 1 cm from the pleural surface. Thoracoscopic surgical wedge resection was performed immediately to follow and confirmed metastatic osteosarcoma

approach (Fig. 4) is used as close to the clavicle as possible which also minimizes catheter tip movement with neck motion.

Locoregional Therapy

Thermal Ablation

Thermal ablation uses an applicator that is inserted percutaneously into a tumor with image guidance to deliver heat or cold energy and includes radiofrequency ablation, microwave ablation, and cryoablation. The term "tumor ablation" is defined as the direct application of thermal therapies to a specific focal tumor(s) in an attempt to achieve eradication or substantial tumor reduction [17]. These techniques may also have an impact on the immune system of patients by activating a tumor-associated antigen-specific T-cell response [18•, 19, 20]. Thermal ablation has been widely used in adults as a minimally invasive tumor treatment for both control of tumor and pain management (Fig. 5). It can be performed in almost every organ including the liver, kidney, lung, musculoskeletal system, and pancreas [18•].

These procedures tend to be offered to patients who are poor surgical candidates with comorbidities. However, data are limited in children, perhaps due to the overall rarity of cancer and typically higher performance status with less comorbidities compared with adults. Of note, liver ablation is more effective in cirrhotic livers; however, most pediatric liver malignancy is in the setting of normal liver tissue [21].

Small studies have reported that ablation is feasible in children with primary, recurrent, or metastatic tumors in organs throughout the body, but larger multi-center studies are needed to establish efficacy [18•, 22].

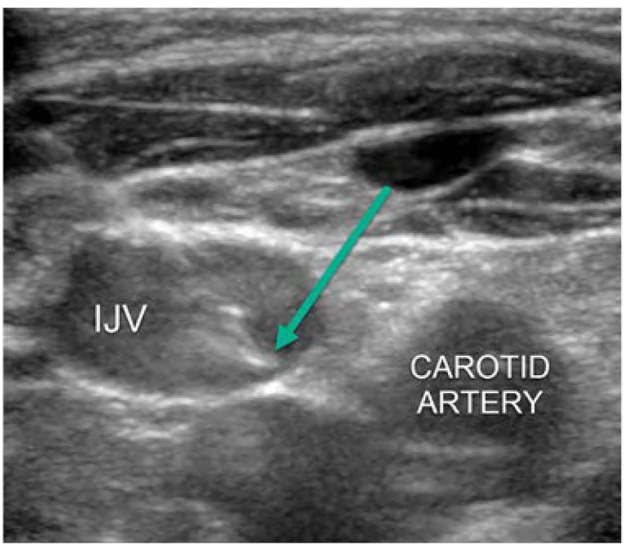

Fig. 4 Image showing right internal jugular vein (IJV) puncture demonstrating the needle tip (green arrow) via a lateral approach

Transarterial Locoregional Arterial Therapies for Pediatric Liver Tumors

Primary liver malignancies account for 1 to 2% of childhood cancers and include hepatoblastoma (HB), hepatocellular carcinoma (HCC), undifferentiated embryonal sarcoma of the liver (UESL), and rhabdoid tumor of the liver (RTL) [23]. Surgical resection is the foundation of cure and is the most important factor for the long-term survival of children with primary liver tumors [24]; however, only one-third of patients have resectable lesions at diagnosis. Effective standard-of-care chemotherapy regimens that decrease tumor size and facilitate conventional resection have only been established for HB [25] and have not been described for HCC, UESL, or RTL. The outcome for patients with unresectable tumor after chemotherapy and for those with recurrent disease continues to be dismal with limited options and guarded outcomes [26••, 27••]. Orthotopic liver transplantation (OLT) has been established as efficacious in children with HB and in adults with HCC [28]. However, OLT patients will require life-long medical therapy with potential episodes of rejection and occurrence of the post-transplant lymphoproliferative disease. "Novel" therapies are needed to downstage/bridge patients to surgery or OLT [27••]. Liver tumors receive blood predominantly from the hepatic artery, in contrast to the normal liver which derives most of its blood supply from the portal circulation. This is the basis of transarterial therapy via the hepatic artery.

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) is the most common standard of care for the treatment of locally advanced HCC in adults. Transarterial chemoembolization is a minimally invasive local treatment option that capitalizes on the combined antitumor effects of prolonged dwell time cytotoxic chemotherapy and the ischemia caused by occlusion of the supplying hepatic arteries. In adults with unresectable HCC, TACE offers a significant survival benefit compared with best supportive care. Approximately 80 to 90% of eligible adult patients are successfully bridged to OLT by local tumor control with TACE [29, 30]. It has been reported that TACE is safe and effective for both HB and HCC patients who were bridged to surgical resection or OLT with a low incidence of severe complications [24, 26••, 31, 32••]. A landmark study by Malogolowkin et al. describes 11 patients with HB, HCC, and UESL who were treated with TACE where five of the 11 patients were downstaged to surgery; three of the 11 patients were alive with no evidence of disease at 31–73 months [26••]. Another study describes eight

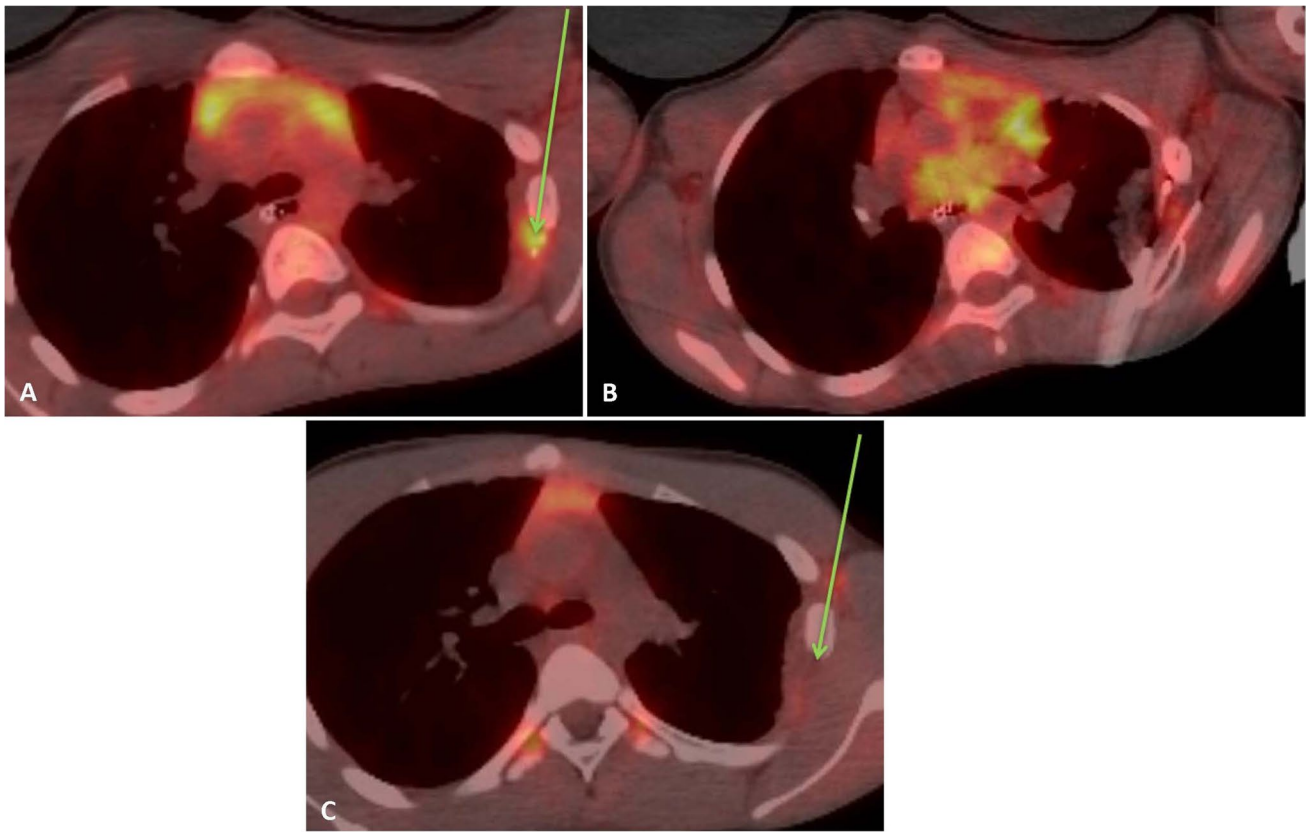

Fig. 5 Positron emission tomography (PET)/computed tomography (CT) of a 14-year-old male with a history of recurrent left chest wall desmoid tumor who presented with pain. Pre-procedure PET/CT demonstrated abnormal fluorodeoxyglucose uptake in the left chest wall (green arrow) (**A**), PET/CT guided placement of cryoablation probes using a split dose technique demonstrated iceball formation around the site (**B**), follow-up PET/CT 6 months post ablation demonstrated significantly decreased activity in the treated area (green arrow) (**C**). The patient had no complaints of pain at follow-up and had returned to playing baseball

patients with HCC who were treated with TACE where six of the eight patients were bridged to transplant; five of the six patients were alive at 3.4–11 years after the first TACE [32••].

Transarterial Radioembolization with yttrium-90

Transarterial radioembolization with yttrium-90 (TARE-Y90) is commonly used in adults with liver tumors and demonstrates durable local control, good long-term outcomes, and equivalent if not superior tumor responses and tolerability when compared with TACE [33]. Transarterial radioembolization uses radioembolic microspheres to carry yttrium-90 to liver tumors via the hepatic artery, where they lodge in the capillary network to deliver cytotoxic radiation via beta decay. Rather than occluding the hepatic artery, in contradistinction to TACE, there is the preservation of blood flow which promotes radiation injury [34]. In children with unresectable liver tumors, TARE-Y90 may offer an alternative therapy to decrease tumor size and allow for surgical resection, as a bridge to liver transplant (Fig. 6), or as a less toxic palliative treatment. Limited data in children demonstrate that TARE-Y90 is both feasible and safe for both palliation or as part of primary pediatric liver tumor curative therapy [27••, 35••, 36••]. Two small studies describe TARE-Y90 used successfully in children as part of therapy with curative intent, which led to hepatic resection in two patients with HB [27••] and two patients with HCC [36••].

In addition to tumor control, preliminary data support future liver remnant hypertrophy, which was seen in five patients treated with intent to cure with a mean percent increase in future liver remnant of 49% (range 16–76%) (Fig. 7); five of five patients went on to hepatic resection [27••, Aguado A unpublished data].

Supportive Care

Drainage Catheter Placement

Percutaneous image-guided drainage catheters can be placed for postoperative collections as well as for organs

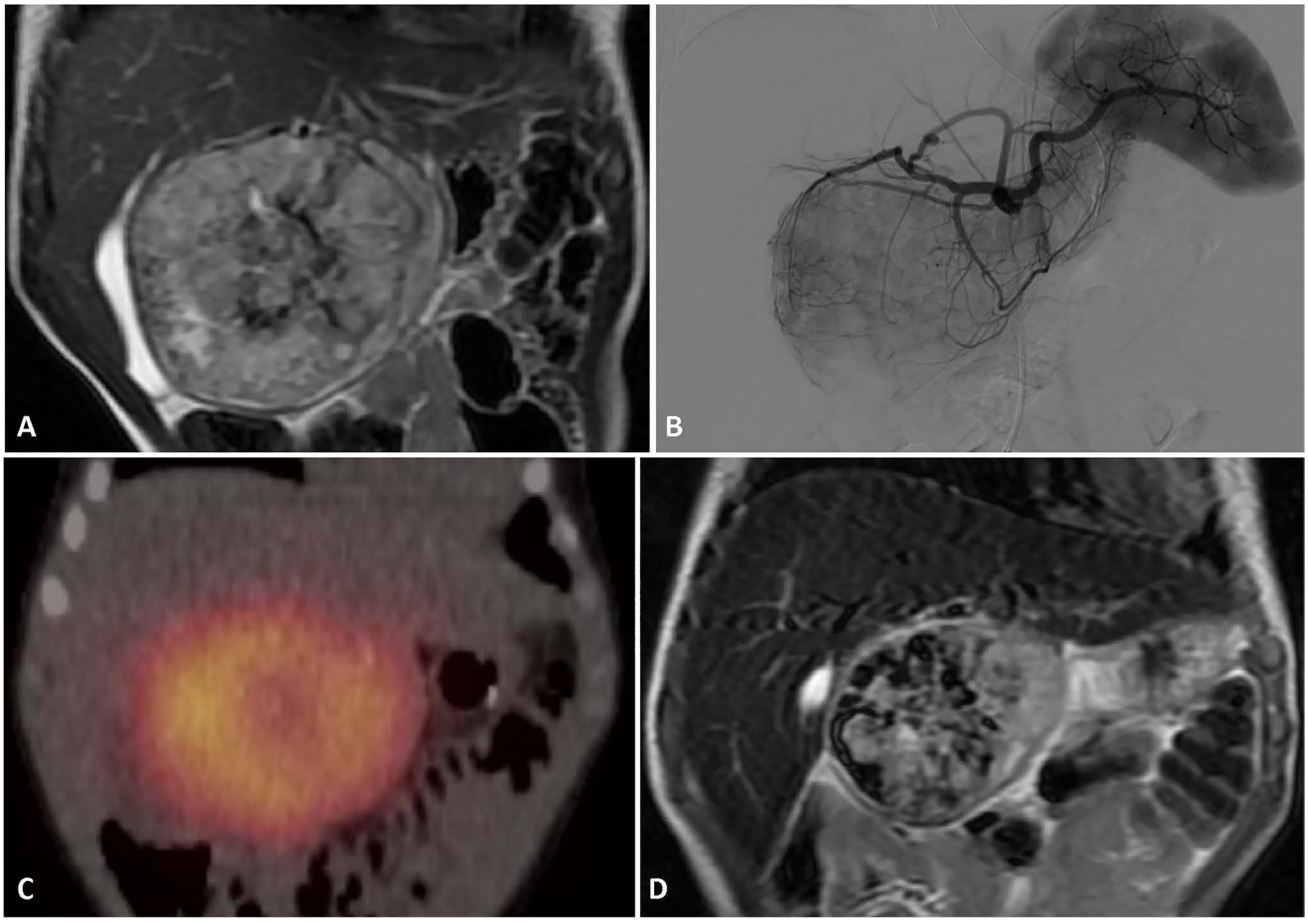

Fig. 6 Images of a 2-year-old male with PRETEXT III multifocal hepatoblastoma. Post chemotherapy T2-weighted magnetic resonance image (**A**), mapping angiogram demonstrating a central hypervascular tumor with supply from the right and replaced left hepatic arteries (**B**), immediate post-transarterial radioembolization with yttrium-90 (TARE-Y90) single-photon emission computed tomography/computed tomography showing deposition of Y90 in the liver tumor (**C**), magnetic resonance image 3 weeks post TARE-Y90 (timed with the fourth cycle of chemotherapy that was continued 2 days post TARE-Y90), which demonstrated a 40% reduction in tumor volume (**D**). Patient went on liver resection 5 weeks post TARE-Y90; explant demonstrated 85–90% necrosis of tumor

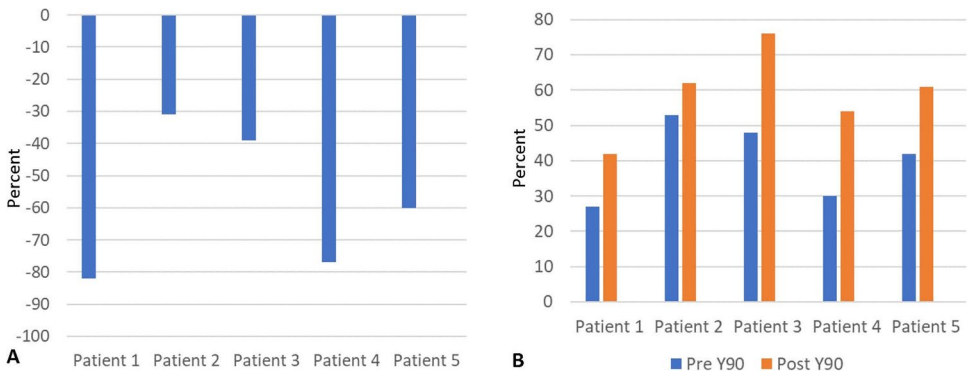

Fig. 7 Graph showing percent tumor volume decrease within 1-month post-transarterial radioembolization with yttrium-90 (TARE-Y90) with a 54% mean reduction in tumor volume (range 30–82%) (**A**); graph showing percent future liver remnant (FLR) pre- and post TARE-Y90 within 1 month with a mean % FLR increase of 49% (range 16–76%) (**B**). Y90, yttrium-90

such as the liver or kidneys (Fig. 8) requiring drainage from outlet obstruction. Interventional radiology-placed drains are often the first-line treatment for infected or symptomatic fluid collections in the absence of indications for immediate surgery. If infected collections are complex, adjuvant intracavitary thrombolytic therapy can be used to facilitate drainage [37].

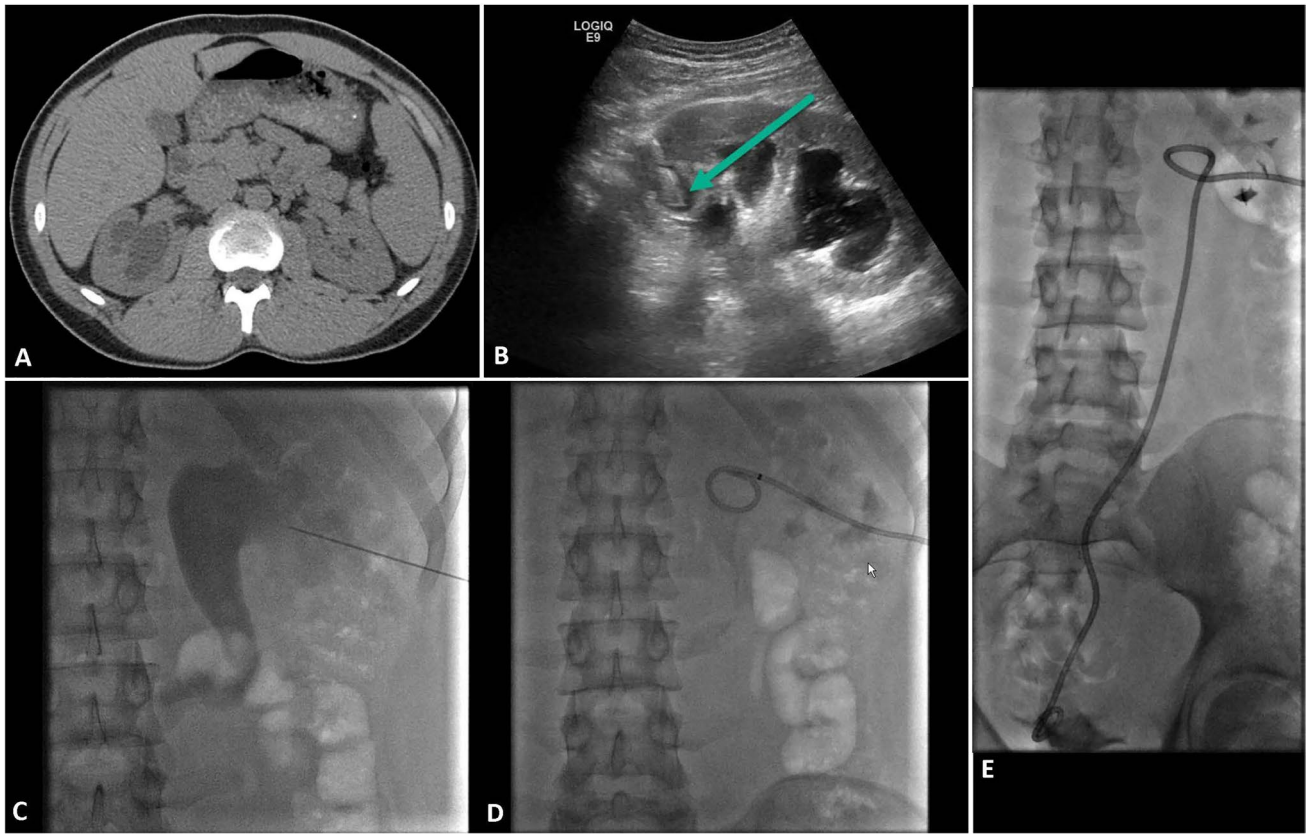

Fig. 8 Images of a 17-year-old male with pelvic paraganglioma that caused right ureteral obstruction. Pre-procedure computed tomography demonstrates moderate-to-severe right hydronephrosis (**A**), ultrasound demonstrates needle within a lower pole calyx (**B**), limited antegrade nephrostogram confirms moderate-to-severe hydronephrosis (**C**) with the placement of a pigtail nephrostomy tube (**D**), which was later converted to a nephroureteral tube

Tunneled Drainage Catheter Placement

Malignant ascites and pleural effusion are common manifestations of advanced malignancy and are typically refractive to conservative treatment and portend a poor prognosis. They can significantly impact the quality of life, and symptomatic control is often required. Improvement of symptoms can improve performance status and overall sense of well-being. While treatment options include aspiration, recurrence rates are high. Although pleurodesis is an effective treatment for malignant effusion, it is painful, requires hospitalization, and concerns have been raised about the risk of acute respiratory distress, respiratory failure, and death following talc administration [38]. Studies show that tunneled catheter placement supports patient convenience and comfort. Patients and families can be taught to drain ascitic or pleural fluid on their own, reducing the number of trips to the hospital for repeated paracentesis or thoracentesis and allowing more autonomy. A small subset of patients with malignant pleural effusion will also undergo autopleurodesis with a durable resolution of symptoms [39, 40].

Lymphatic Interventions

Different types of surgical procedures, including resection and OLT, can injure the lymphatic ducts and lymph nodes, resulting in postoperative lymphatic leakage (PLL), a difficult to treat and potentially life-threatening complication [41]. Postoperative lymphatic leakage can occur anywhere in the body along the lymphatic chain, leading to pathological accumulation of lymph or chyle (i.e., chylous ascites, chylothorax) [42••]. Refractory PLL can significantly affect postoperative recovery times, wound healing, and quality of life. High-output PLL increases morbidity and mortality among patients due to lymphocytopenia, protein loss, fat loss, malnutrition, respiratory distress, and immune suppression. When conservative management fails, lymphangiography and embolization can provide an alternative therapy to surgery (Fig. 9) [43].

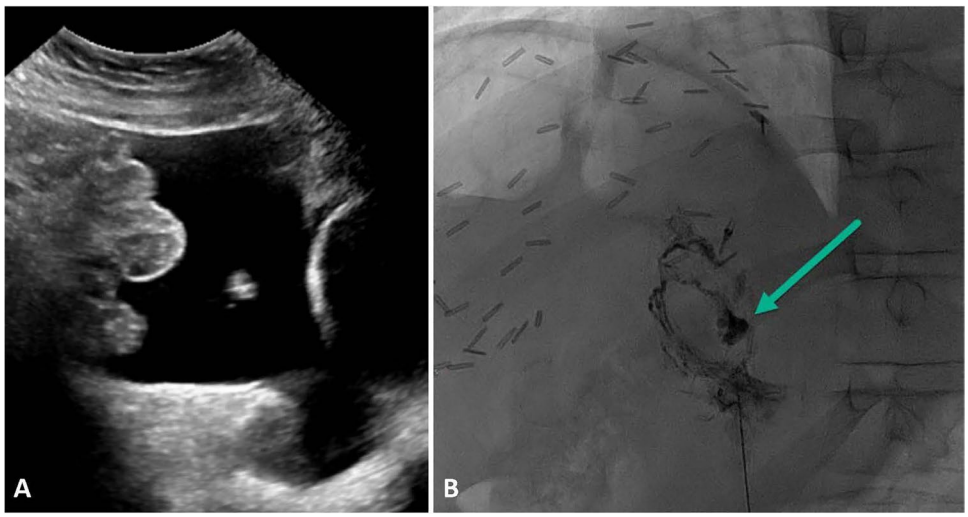

Fig. 9 Images of a 9-year-old female with a history of undifferentiated embryonal sarcoma of the liver status post liver transplant with chylous ascites. Pre-procedure ultrasound demonstrated diffuse ascites (**A**); liver lymphangiogram demonstrated a frank leak from the surface of the liver, which was embolized with n-Butyl cyanoacrylate glue. High-output chylous ascites resolved within a few days. Case courtesy of Drs. Deborah Rabinowitz and Maxim Itkin

Conclusion

Pediatric interventional oncology offers an array of minimally invasive procedures intended to diagnose and treat pediatric cancer patients. As a growing subspecialty, more research is required to determine the efficacy of locoregional therapy in children and to define the clinical scenarios where benefit is likely to be optimized.

Declarations

Conflict of Interest Allison Aguado, MD, declares she has no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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