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Abstract

Interventional radiologists continue to expand the diagnostic and therapeutic options available for pediatric oncology patients. Percutaneous radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) are performed safely in children, providing new adjuncts in the armamentarium of therapies for childhood cancer. Percutaneous image-guided radiofrequency ablation (RFA) provides a viable and effective therapeutic option in the treatment of benign and malignant solid tumors in a variety of locations to include the skeleton, liver, spleen, kidney, adrenal gland, lung, and pancreas. Primary and metastatic malignancies as large as 8 cm in children are now effectively treated with RFA. The most common indications for RFA in children include hepatoblastoma, hepatocellular carcinoma (HCC), metastatic osteosarcoma, and Wilms tumor. TACE is an additional therapy, safely performed in children, providing effective therapy options for children with multifocal hepatoblastoma, paraganglioma, neuroblastoma, HCC, osteogenic sarcoma, and Wilms tumor. When TACE and surgery are combined, blood loss and operative time are reduced, while providing more efficacious therapy when combined to surgery alone. In conclusion, RFA and TACE provide children with safe and effective options for treatment of pediatric malignancy.

Interventional radiologists continue to expand the diagnostic and therapeutic options available for pediatric oncology patients. Pediatric oncologists and surgeons increasingly rely

on partnership with pediatric interventional radiology for precise and effective percutaneous biopsy, tumor ablation, drainage, and vascular access procedures. With specific reference to image-guided therapy procedures and protocols, discussions of percutaneous radiofrequency ablation and transarterial chemoembolization in children will be the focus of this chapter.

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Radiofrequency Tumor Ablation

Percutaneous image-guided radiofrequency ablation (RFA) provides a viable and effective therapeutic option in the treatment of benign and malignant solid tumors in a variety of locations to include the skeleton, liver, spleen, kidney, adrenal gland, lung, and pancreas [1–31]. In these applications, the basic concepts of radiofrequency tumor ablation are similar: delivery of localized and contained heat induces focal coagulative necrosis and cell death. Cytotoxicity is best induced when regional temperatures are maintained between 50 °C and 100 °C. In the recent decade, the majority of RFA experience documented in pediatric and adult medical literature focuses on primary applications of RFA in the treatment of hepatocellular carcinoma (HCC) and osteoid osteoma [1–6]. Percutaneous RFA has expanding indications in the treatment of pediatric malignancy, most evolving in the treatment of multifocal, recurrent, or metastatic malignancies of bone, liver, kidney, and face with successful treatment of children as young as 1 year old [8–12]. This section will review details of pediatric unique care issues in percutaneous RFA with respect to general patient care and organ-specific RFA applications in the treatment of pediatric malignancy.

General Procedural Issues

Although adult percutaneous RFA in organs such as the liver, lung, and kidney may be successfully performed in adults with conscious sedation, children do not tolerate similar pain experiences, and thus, general anesthesia is required for RFA procedures in children. In the authors' clinical experience, pain, even with general anesthesia, can be significant enough to cause elevations in blood pressure and heart rate when the RFA heat contacts sensitive structures such as the pleura during lung RF ablation.

The use of prophylactic antibiotics is variable among authors and in specific tissue applications, especially when treating focal hepatic and renal

malignancies [2, 5, 6, 8]. In the authors' pediatric experience, a single dose of preprocedural antibiotics is administered when treating focal liver, bone, and lung lesions, and to date, none of our cases have been complicated by abscess formation or sepsis.

The potential for skin burns exists with RFA due to heat distribution at the skin site of grounding pads used with monopolar RFA systems or if coaxial needles are not fully withdrawn adjacent to the insulated portion of the RFA needle. Thermal burns are best avoided with the use of large surface area foil-grounding pads, placed with the longest surface edge facing the RFA electrode, at a distance of 25–50 cm from the electrode [22]. In larger children, the thigh is often recommended as a good location for placement of up to four large (100 cm² each) foil pads. In young children, the thighs may be too small for placement of large foil pads. As an alternative large surface area structure, the buttocks serve well as a site for the foil pads when RFA is performed in the upper body.

Young children present with smaller body surface areas than their adult counterparts. Algorithms have been published that predict the range of core temperature elevation with RFA [13]. Given the relatively greater ratio of tumor volume to body surface area, the potential exists of greater total body-heating effect when large surface areas are treated with RF in children [8, 13]. In the authors' experience, total body temperature elevation has not been encountered in the treatment of focal liver tumors. On the other hand, body core temperature elevation as high as 40°C has been documented when treating large metastatic lung lesions, responding well to the use of a hypothermic blanket. When treating large volume tumors (5–8 cm diameter), patients are placed on a hypothermic blanket prior to beginning the RFA procedure. The use of a hypothermic blanket as cool as 20°C maintains body temperature at or below 38°C during prolonged RFA treatment of large volume malignancy in the chest [8, 13].

Pain control is critical in children, requiring a plan for each specific organ system and lesion being treated with RFA. In bone, liver, and lung, pain from RFA usually requires the

administration of intravenous narcotic analgesics for effective pain management. Pain following RFA is reported to be greatest 12–24 h following treatment, usually subsiding after a few days and is well managed with narcotic analgesia [8].

Hepatic Tumor Ablation

Hepatoblastoma and hepatocellular carcinoma are the most common hepatic malignancies in children [14–16]. In adults, the primary focus of hepatic tumor RFA is in treatment of hepatocellular carcinoma (HCC) or metastatic disease from organs such as the colon, pancreas, lung, and breast [1, 2, 5, 6]. Radiofrequency ablation treatment of hepatic malignancy (hepatoblastoma, HCC, metastatic leiomyosarcoma) in children has been sporadically reported [8–10]. Hepatoblastoma patients that present the greatest clinical challenge are those with Beckwith-Wiedemann, with multiple hepatoblastomas developing over time. These patients are ideal candidates for RFA, given the risks of repeated surgeries for resection (Fig. 62.1). A percutaneous approach is used in the majority of reported pediatric hepatic tumor RF ablations. Overlapping RFA burns is performed in larger tumors, each site reaching a target temperature of at least 60°C over 12 min.

In the treatment of focal liver tumors, the authors would apply guidelines similar to adult literature, such that we expect complete tumor RFA in 90 % of patients with tumors smaller than 2.5 cm. Tumors 2.5–3.5 cm can be ablated in 70–90 % of cases; ablation of tumors 3.5–5.0 cm will be effectively ablated in 50–70 % of cases [2, 5, 25]. In large tumors (greater than 3.5 cm), and with conditions such as Beckwith-Wiedemann with recurrent hepatoblastoma, palliative RF ablation is a reasonable goal, if treatment can prolong life expectancy with limited systemic symptoms and few minor complications. Radiofrequency ablation, in combination with chemoembolization, is effective in the treatment of adult patients with HCC larger than 3.5 cm [27] and should be considered in similar situations in the pediatric patient.

Lung and Renal Malignancy Ablation

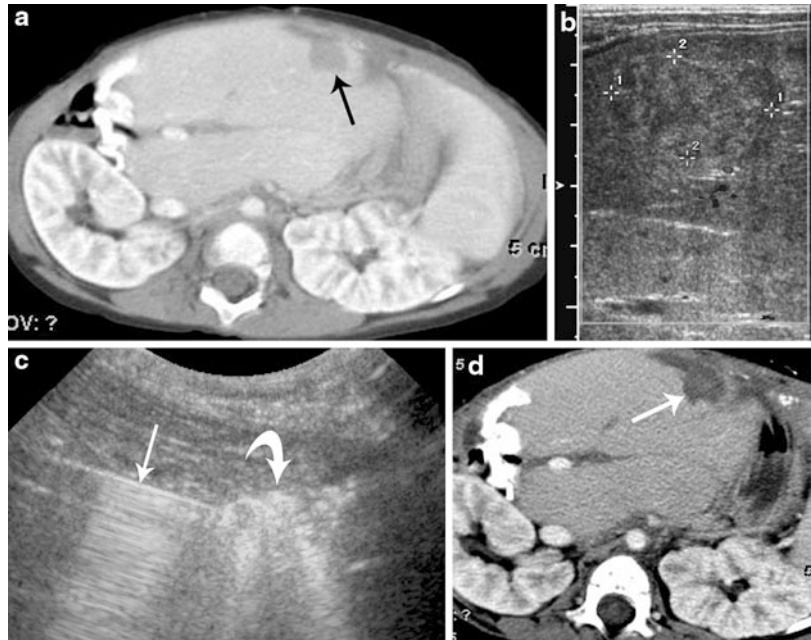
Radiofrequency ablation is an effective percutaneous option for treatment of solid lung malignancies in adults and children. The most common indication for lung RFA in children is metastasis such as osteogenic sarcoma primarily for patients who are not operative candidates [2, 8, 9, 28–30]. Both ultrasound and CT guidance for lung RF ablation cases have been utilized for metastatic lesions as large as 8 cm (Fig. 62.2), with CT most useful when lung precludes an effective sonographic window. In large bilateral lung tumor ablations, core body temperature elevations are maintained at 38–39°C with the use of a hypothermic blanket system (Medi-Therm II; Gaymar, Orchard Park, NY), with blanket cooling temperatures as low as 20°C [8]. Although initial experience shows that RFA ablation in the pediatric lung is well tolerated, the potential for fatal complications is reported in adult lung RFA treatment [28, 29].

The limited reported experience with percutaneous RFA of Wilms tumor and renal cell carcinoma developing in children with von Hippel-Lindau disease is promising [8, 19–21]. In these situations, percutaneous RFA is well tolerated, providing an effective nephron-sparing alternative to surgery especially for recurrent and multifocal Wilms tumor and Wilms tumor in patients with solitary kidney. Recent literature has shown that RF ablation of renal lesions during renal artery balloon occlusion results in larger effective zones of ablation, with a higher rate of infarction of normal renal tissue peripheral to the treated focus [31].

RFA Conclusion

Radiofrequency tumor ablation in children is rapidly evolving and is proving to offer effective therapeutic options in a variety of pediatric disorders. Radiofrequency ablation is well tolerated in children with few complications. As the pediatric experience grows, new opportunities for interdisciplinary treatment regimens that include

Fig. 62.1 Two-year-old male with Beckwith-Wiedemann syndrome and focal HB, treated with RFA. (a) Pretreatment CT (arrow indicates the focal HB). (b) Ultrasound with cursors 1 and 2 delineating the focal HB. (c) Sonogram during RF ablation with watercooled electrode (straight arrow)-inducing echogenic RF coagulation necrosis (curved arrow) in the tumor. (d) CT image at 1 month follow-up demonstrating complete ablation (arrow) of the focal HB



RF ablation will develop, defining clear roles for this versatile minimally invasive therapy.

Chemoembolization in Children

Chemoembolization is uncommonly performed in children. Reports are confined to case reports and case studies, with no randomized controlled studies available [32]. Pediatric chemoembolization has been performed for primary and metastatic hepatic malignancies (Fig. 62.3), osteogenic sarcoma, and Wilms tumor [33–44].

The basic principles of transarterial chemoembolization (TACE) are the same in both children and adults. Direct injection of the chemotherapeutic agent into the tumor allows for a greater concentration of the drug into the tumor with fewer systemic toxicities, while the embolization provides a longer dwell time and produces ischemia.

Pediatric Liver TACE

Indications for hepatic TACE in children include primary liver malignancies (predominately hepatoblastoma (HB) and hepatocellular

carcinoma (HCC)) and metastatic disease such as sarcomas or neuroblastoma [33–44]. Hepatoblastoma accounts for 1 % of all pediatric malignancies [38]. While overall survival from HB is 63 %, a 90 % cure rate is possible if the tumor is resectable and the patient has no metastatic disease at diagnosis [36]. Complete surgical resection is the key [33]. Unfortunately, the tumor is initially unresectable in approximately 50 % [40, 42]. Systemic chemotherapy may shrink the tumor and allow later resection in up to 70 % of those patients [35, 36]. Unresectable patients receiving orthotopic liver transplantation (OLT) have a survival of 20–40 % and a recurrence rate of 50 % [35]. Otherwise, the outcome is dismal in tumors that remain unresectable. Due to toxicities of systemic chemotherapy, several investigators have attempted TACE to provide a greater tumor response while avoiding these complications [32, 33, 35–42]. The indications for TACE are not well established. TACE has been advocated for treating unresectable patients after failed systemic chemotherapy, for replacing primary systemic chemotherapy, as a bridge to OLT, and for palliative care [32, 35–40]. Initial attempts at TACE with HB were in patients with unresectable tumors despite systemic

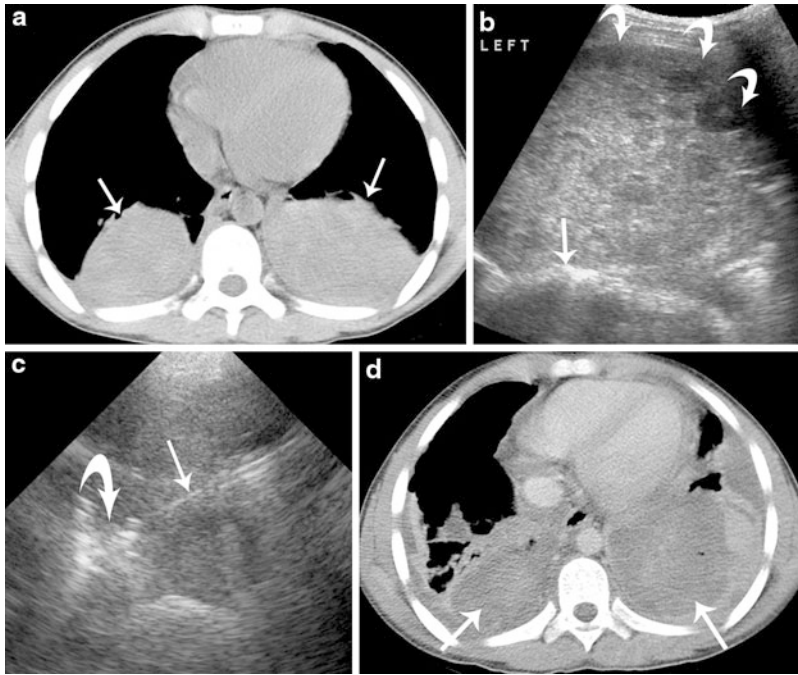


Fig. 62.2 Twelve-year-old male undergoing palliative RFA for bilateral pulmonary metastatic osteosarcoma. (a) CT image of the chest demonstrating bilateral pulmonary metastatic lesions (arrows), measuring 5 cm (right) and 8 cm (left). (b) Sonogram of the osteosarcoma (curved arrows) adjacent to normal lung (straight arrow) prior to

RFA. (c) Sonogram during US-guided RF ablation (straight arrow-RF electrode) of the left metastatic lesion, demonstrating early coagulation necrosis echogenicity (curved arrow) during RFA. (d) CT image during second palliative RFA session demonstrating significant bilateral necrosis following the first RFA (arrows)

chemotherapy. Subsequently, TACE has been studied as the primary treatment for liver-only disease.

Arcement et al. reported on seven patients with unresectable HB treated by TACE [36]. These patients received cisplatin (90–150 mg/m²) and/or adriamycin (30 mg/m²) with gelatin sponge embolization in five of these patients. Lipiodol was not included in the TACE. One of these patients had significant reduction in the tumor size, but none became resectable. Three patients survived to the point of receiving OLT, with two still alive at the conclusion of the study. An additional patient was alive and awaiting OLT at 18 months. They concluded that TACE could be used as a bridge to OLT in unresectable patients who do not respond to systemic chemotherapy.

Malogolowkin et al. treated six children with HB, all of which remained unresectable after

systemic chemotherapy [35]. Their protocol consisted of cisplatin (100 mg) and doxorubicin (30 mg), with one patient also receiving mitomycin (30 mg). This was mixed with bovine collagen (Angiostat, Regional Therapeutics, Inc, Pacific Palisades, CA) as an embolic agent and nonionic contrast to a volume of 8.75 ml. They did not use lipiodol and limited treatment to no more than 70 % of total liver volume and a maximum injected volume of 8.75 ml. All six children had a partial response (>50 % reduction in tumor volume). Three patients became resectable by imaging criteria, although two of these had residual microscopic disease. The patient with complete resection died of a recurrence in the residual liver. Both of the patients with microscopic residual disease survived, one after additional systemic chemotherapy and one after OLT.

Czanderna et al. reported on four patients with unresectable HB treated with TACE [39].

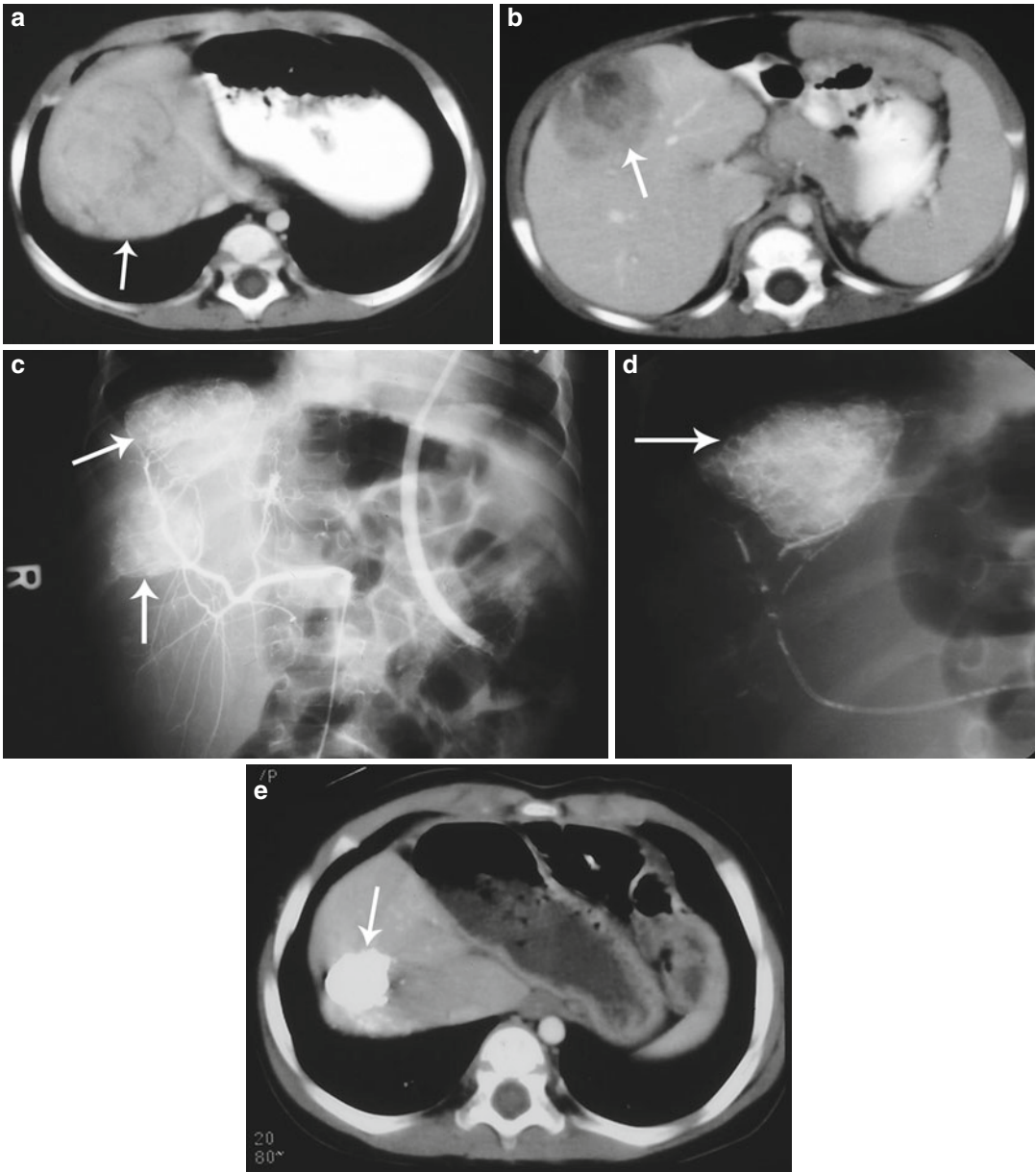


Fig. 62.3 Nine-month-old male with residual hepatoblastoma following partial hepatectomy, effectively treated with TACE (with no recurrence). (a) and (b) CT images demonstrating the two residual foci of HB (arrows). (c) Arteriogram with arrows indicating two foci

of HB with well-defined arterial supply. (d) Microcatheter access with lipiodol contrast defining one of two foci treated with TACE (arrow). (e) Posttreatment CT demonstrating dense contrast in shrunken and necrotic focus (arrow) of previously treated HB

All patients had received systemic chemotherapy, using cisplatin (60 mg/m^2), doxorubicin (30 mg/m^2), and mitomycin (20 mg/m^2) mixed with 10 ml or less of lipiodol, and embolized with gelatin sponge. Patients received 1–3 courses of

treatment. Three of the patients had a reduction in volume of between 25 % and 33 % and a decrease AFP 83–99 %. One patient died of systemic myelotoxicity before response could be assessed. One patient received OLT, and two were

resected. One patient died after resection, presumably as a cardiac complication from prior systemic chemotherapy.

Xuewu and colleagues reported on eight patients with unresectable HB [38]. They performed 1–3 TACE procedures on each patient with adriamycin (20 mg/m²), vincristine (1.5 mg/m²), and cisplatin (40 mg/m²) mixed with 5–10 ml of lipiodol. They performed coil embolization afterward. Six of the eight (75 %) became resectable after the first TACE procedure, and the two others became resectable after further TACE procedures. One patient died of pneumonia. Six had surgery, and one patient refused surgery but elected to have TACE 3 times and no longer has detectable disease. All were disease-free 15–49 months after TACE.

Li et al. reported on 16 patients with unresectable HB treated with TACE [37]. Their protocol included cisplatin (40–50 mg/m²), adriamycin (20–30 mg/m²), and lipiodol. After infusing the chemotherapy, embolization was performed with gelatin sponge particles. Total treatment was limited to <70 % of the liver volume and no more than 10 ml of solution. Patients received 1–3 treatments. The tumors demonstrated a 19–82 % reduction in size (mean = 59.2 %), with reduction in the alpha fetoprotein (AFP) of 29–99 % (mean = 60 %). The tumor became completely resectable in 13/16 patients, with the additional 3/16 patients having a partial resection 4 weeks after the last TACE. Survival at 1, 2, and 5 years was 87.5 %, 68.7 %, and 50 %, respectively, with all receiving systemic chemotherapy after surgery. No patients had chemotoxicity from the TACE. The authors thought TACE may be a first-line treatment in patients without metastatic disease.

Ohtsuka and colleagues were the first to report on using TACE as the primary treatment for HB without metastatic disease [40]. They did not limit TACE to unresectable patients, with seven children in their study. Four patients were without metastatic disease and did not receive systemic chemotherapy. The three children with metastases received systemic chemotherapy prior to TACE. TACE used pirarubicin (30 mg/m²) mixed with lipiodol (1 ml/maximum

tumor diameter with 15 ml being the maximum volume given) and gelatin sponge embolization. Tumor volume reduced by 12–57 %. Complications included transient liver insufficiency in one patient who recovered in 6 days and pulmonary artery embolization of lipiodol in one patient who recovered in 2 weeks (lipiodol volume of 0.8 ml/maximum tumor diameter). They stated they believe the optimum lipiodol volume is 0.6 ml/maximum tumor diameter. All patients without metastatic disease at diagnosis had subsequent resection and were disease-free at the time of the report. The patients with metastatic disease all died, two of their metastatic disease and one from a secondary malignancy.

A similar study by Oue and colleagues had eight patients with HB [42]. Six patients had primary TACE and two had prior systemic chemotherapy before TACE. Only one patient had metastatic disease at diagnosis. This patient received systemic chemotherapy. The additional patient with systemic chemotherapy received it at an outside hospital prior to referral for TACE. TACE consisted of adriamycin (20–30 mg/m²) and cisplatin (4–60 mg/m²) mixed with lipiodol followed by gelatin sponge embolization. Tumor shrinkage varied from 0.9 % to 45 % with a mean of 25.8 %; after resection, pathology showed 71.1 % necrosis. All patients received systemic chemotherapy after surgery. Of the eight patients, six were disease-free and alive at the time of the report, although three received bone marrow transplantation due to elevated AFP levels. Two patients died of metastatic disease.

A case report by Xianliang et al. demonstrated a patient with an unresectable tumor treated solely by TACE and systemic chemotherapy [41]. The original tumor occupied 90 % of the total liver volume. TACE consisted of doxorubicin (20 mg/m²), vincristine (1.5 mg/m²), and cisplatin (40 mg/m²) in 10 ml of lipiodol followed by coil embolization. Tumor volume reduction was 75 % after the first TACE, and after three TACE sessions, no discernable residual tumor was present. He then had six courses of systemic chemotherapy (vincristine and cisplatin) followed by an additional TACE. His disease-free survival was 33 months at the time of the study.

These reports and an additional case report demonstrate that TACE has utility in treating patients with HB [33]. Response rates seem to be better when lipiodol is used in the TACE procedure. The role of TACE as a primary treatment option after failed systemic chemotherapy, bridge to OLT, or for palliation cannot be known due to the lack of randomized control trials.

While HB is the most reported liver tumor in pediatric TACE, other tumors have been treated with this technique. Hepatocellular carcinoma (HCC), sarcomas, neuroblastoma, and a paraganglioma have been treated as well with TACE [34–36, 39, 43, 44]. In one study, three patients with HCC and two patients with undifferentiated sarcoma were treated with TACE [35]. All HCC patients had a partial response. Two became resectable with one survivor. The other resectable patient had microscopic residual, received two additional course of TACE, and died of liver failure. There was no response in the sarcoma patients, both of which died. Arcement in the same study as above had seven patients with HCC [36]. Four received intra-arterial chemotherapy. All of these patients died, two after OLT. Three patients had gelatin sponge embolization after intra-arterial chemotherapy. One patient had OLT and was alive at 14 months. A single patient with HCC was treated by TACE in another study; this patient died from pulmonary embolization of lipiodol [39]. There is a case report on TACE for neuroblastoma; this patient had Stage 4S and was treated with TACE due to the large mass effect from the tumor causing pulmonary and hepatic compromise [43]. This patient received 10 mg of cisplatin and 7 mg of doxorubicin with polyvinyl alcohol particle embolization. The tumor reduced in volume by 50 % and improved symptoms. Another case report showed TACE for metastatic paraganglioma [34]. This patient had anemia unresponsive to erythropoietin and iron supplementation from a paraneoplastic syndrome and would not receive blood products due to religious beliefs. He had intra-arterial infusion of 5-fluorouracil and then two rounds of TACE with doxorubicin and cisplatin mixed with

lipiodol. Gelatin sponge embolization was then performed. His hemoglobin increased from 5.6 mg/dL to 17 mg/dL. He died of a postsurgical complication after resection of his primary chest mass.

TACE for Osteogenic Sarcoma

Osteogenic sarcoma is the most common primary bone malignancy in children. Limb salvage surgery is the preferred treatment, supplemented with chemotherapy. Intra-arterial administration of the chemotherapy directed into bone tumors has been described [45]. In addition, case series have been published describing TACE in patients with osteogenic sarcoma [46, 47]. In one series, pirarubicin (30–50 mg) and cisplatin (40–80 mg) were infused into the arteries supplying the primary tumor followed by gelatin sponge embolization [46]. Limb salvage surgery was then performed within a week. In this series of 47 patients, the authors found that there was significantly less blood loss, the operating time was less, and the resection was easier as the tumors had developed a pseudocapsule of fibrous edematous tissue in 43/47 patients. Mean tumor necrosis was 82.9 %. Follow-up was short, and it is unknown what will be the effect on local recurrence. The only complication was skin blistering in three patients.

Another study of 32 patients received an infusion of methotrexate (1–2 gm), pharmorubicin (30–50 mg), and cisplatin (60–100 mg) [47]. The embolic agents included adriablastine gelatin microspheres, anhydrous alcohol with lipiodol, common bletilla tuber with lipiodol, and gelatin sponge. Necrosis occurred in 85.5 % of patients with extent being 81.6–87.9 %, although gelatin sponge results were significantly lower than the others. All patients also received systemic chemotherapy and had limb salvage surgery. The surgery was aided by the stable to decreased tumor size and less blood loss. Survival at 1, 2, and 5 years was 95.5 %, 72 %, and 42 %, respectively. Local recurrence occurred in three between 3 and 6 months after the procedure.

TACE for Wilms Tumor

Two reports are published on TACE for Wilms tumor, although both are on the same patient population [48, 49]. They treated 24 patients with TACE and compared them to a control group of 20. Their protocol was doxorubicin (20 mg/m²), cisplatin (50 mg/m²) mixed with lipiodol (0.5 ml/kg), and saline (5–15 ml) with gelatin sponge embolization. Mean tumor size reduction was 48.2 %. At 2-year follow-up, their conclusion was that TACE and surgery was superior to surgery alone. Survival at 2 years was 83.3 % in the TACE group and 10 % in the surgical group. At 1 year, 16.6 % of the TACE group was alive and disease-free as compared to the control group with only 40 %. Pathological specimens showed tumor cell necrosis, degeneration, and apoptosis; increased interstitial fibrous tissue hyperplasia; and lymphocyte infiltration [49].

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