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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

Reiterative Radiofrequency Ablation in the Management of Pediatric Patients with Hepatoblastoma Metastases to the Lung, Liver, or Bone

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Abstract
Background and Purpose Conventional treatments of systemic chemotherapy and surgical resection for recurrent or metastatic hepatoblastoma (HB) may be inhibitive for the pediatric patient and family who have already been through extensive therapies. This single-institution case series evaluates the safety and efficacy of percutaneous radiofrequency ablation (RFA) in the management of metastatic HB.
Materials and Methods Between March 2008 and February 2015, RFA was used as part of multidisciplinary management for HB recurrence or metastasis in 5 children (median 5.0 years old) in an attempt to provide locoregional control and preclude additional surgery. Combined local treatments of 38 metachronous metastases included surgical metastasectomy (14 lesions: 7 lung, 7 liver), percutaneous RFA (23 lesions: 21 lung, 1 liver, 1 bone), and stereotactic radiotherapy (1 liver lesion).
Results For lesions treated with RFA (median diameter 6 mm, range 3–15 mm), local control was achieved in 22/23 metastases (95.6%) with median follow-up of 30.1 months after RFA (range 18.9–65.7). Median hospitalization was 3 days (2–7), with major complications limited to 1 pneumothorax requiring temporary small-caliber chest tube. Four children remain in complete remission with median follow-up of 67 months (range 41.2–88.8) after primary tumor resection, with mean disease-free survival of 31.7 months after last local treatment. One child succumbed to rapidly progressive disease 12 months after RFA (23.9 months after primary tumor resection).
Conclusion RFA provides a safe and effective reiterative treatment option in the multidisciplinary management of children with metastatic HB.

Keywords Hepatoblastoma · Pediatric · Radiofrequency · Ablation · Metastasis

Abbreviations

HB Hepatoblastoma
RFA Radiofrequency ablation

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Introduction

Although the occurrence of hepatoblastoma (HB) is rare [1, 2], the prognosis remains dismal for patients with recurrent or extra-hepatic disease [3–13]. Treatment of recurrence or advanced metastasis focuses on chemotherapy in combination with complete surgical resection

[6, 9, 14–18], which may require reiterative surgical treatment [9, 17, 19].

In adults, radiofrequency ablation (RFA) is a recognized minimally invasive therapy for the treatment of recurrent and metastatic disease under 3 cm [20]. There is little published literature on percutaneous ablation in children [21–26], with less on the efficacy for HB metastases [27–30]. Furthermore, the potential for reiterative RFA treatments in children with HB metastases has not been evaluated.

This is a single-institution, retrospective cohort study of patients younger than 20 years of age treated for metastatic HB by systemic chemotherapy in association with local treatments that included at least one session of RFA. The aim of this study is to report our experience for RFA in children with metastatic HB disease as a component of multidisciplinary management.

Materials and Methods

Ethics

We retrospectively reviewed the medical files of all children with metastatic HB treated with at least one session of RFA. All procedures performed were in accordance with ethical standards of the institution and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Institution board review approval and written consent were followed in accordance with our institution's policy. For this type of study, formal consent was not required.

Patients

All patients under the age of 20 years old treated with RFA of HB metastases between March 2008 and February 2015 are reported. RFA indications were discussed at multidisciplinary meetings with a goal to achieve complete treatment of all metastatic lesions. RFA was pursued for small and isolated nodules to avoid or preclude additional surgery. Inclusion criteria were: (1) prior resection of primary tumor with pathological HB confirmation, (2) CT imaging identifying an isolated nodule with size less than 3 cm, (3) nodule deemed technically treatable based on imaging and patient's conditions. Technical RFA exclusions included metastasis within 2 cm of the hepatic or lung hilum, with laboratory exclusion criteria INR > 1.5 and platelet count $< 100{,}000/\text{mm}^3$. Formal consent was obtained from parents/guardians. The diagnosis of recurrence was based upon increasing alpha-fetoprotein (AFP) and correlative imaging findings of lesion enlargement and/or response to chemotherapy. Pre-RFA biopsy was performed only in children without a prior biopsy confirmation of metastatic disease.

Procedure

All RFA procedures were performed by staff interventional radiologists with greater than 5 years of experience, using either CT guidance for lung and bone metastases (General Electric Healthcare, Little Chalfont, Buckinghamshire, UK) or US guidance for liver metastases (General Electric Healthcare, Little Chalfont, Buckinghamshire, UK). For CT-guided procedures, a low-dose pediatric radiation algorithm was followed standardized to weight (80–120 kV, 57.5–70 mAs, 5 mm slice width, 16 feed/rotation, 27.50 pitch, 1.375:1 acquisition mode). General anesthesia was administered for all patients. RFA was performed using an internal cooling electrode needle (Covidien, Boulder, Colorado). Needle trajectory was chosen to ensure treatment coverage, minimize normal parenchyma traversed, and avoid crossing vascular structures or pleural fissures. Hepatic and osseous ablation was considered successful when post-ablation thermal measurements reached greater than 65 degrees Celsius at the center of the ablated area. Given temperature and tissue density variabilities after pulmonary ablation, a technically successful end point for pulmonary nodule ablation was considered when a penumbra of ground glass opacification, representing the zone of coagulation necrosis, encompassed the nodule and at least 5 mm beyond imaged borders.

Follow-Up

Post-ablation complications were classified as minor (pain, fever, pneumothorax not requiring chest tube) or major (symptomatic hemorrhage, abscess, pneumothorax requiring chest tube, mortality). All patients had a planned post-procedure hospitalization of 3–4 days and were discharged if no complication presented or once complications resolved. Evaluation for incomplete local treatment or new metastasis was performed with standard screening serum AFP and scheduled CT or MRI. Technically effective local treatment was considered if follow-up imaging demonstrated a fibrotic scar encompassing the metastasis and absence of new nodular tumor development.

Results

RFA was employed for metastatic recurrences in 5 children (median 5.0 ± 6.2 years old). Patient demographics and tumor details are listed in Table 1. All patients had already undergone treatment including chemotherapy and surgical resection of the primary tumor, with a total of 38 metachronous metastases developing after primary surgical resection. The RFA-treated lesion represented either the first, second, or third recurrence of disease after previous systemic chemotherapy or surgical metastasectomy. The mean time to metastasis after primary liver tumor resection for the first, second, and third metastatic occurrences was 7.1, 15.3, and 20.5 months, respectively. Pathological confirmation of metastatic status was performed by surgical metastasectomies in 3 patients or percutaneous biopsy in 2 patients. (Table 2 identifies percutaneous biopsy).

Multidisciplinary treatment strategies with the goal to achieve complete remission of all metachronous metastases employed systemic chemotherapy in association with reiterative local treatments by surgery, radiotherapy, and/or RFA (Table 2). Overall, 4 of 5 patients underwent surgical resection of 14 metastases (7 lung, 7 liver) in 10 separate surgical interventions. Surgical resection was considered first-line local therapy to make initial confirmation of metastatic status ($n = 11$), or because RFA was contraindicated ($n = 2$; one pulmonary hilar location and one liver metastasis over 3 cm in diameter). RFA was selected to avoid additional systemic chemotherapy or surgery for 5 patients with a total of 23 metastases (21 lung, 1 liver, and 1 bone metastases). Of lesions treated by RFA, the median diameter was 6 mm (range 3–15 mm). A total of 8 RFA procedures were performed to treat these 23 metastases, with a maximum of 7 lesions (median 2.5, range 1–7) treated during the same procedural setting to limit anesthesia induction and improve patient experience. Stereotactic radiotherapy (45 Gy, 25 fractions) was selected for a liver hilum lymph node due to contraindications to both surgery and RFA. All patients received chemotherapy, with various combinations of cisplatin, carboplatin, etoposide, vincristine, irinotecan, temozolomide, temsirolimus, and rapamycin.

For all 23 RFA treatments, a 95.6% local control rate (22/23) was obtained after median follow-up of 30.1 months after RFA treatment (range 18.9–65.7). Local recurrence occurred in a patient with a bone metastasis, who succumbed to rapidly progressive new distal metastasis that precluded further local re-treatment. Two other patients developed new metastatic lesions that were located at a distance from the RFA treatment site, which were subsequently successfully treated with surgical metastasectomy due to contraindications for RFA (solitary hilar lung metastasis and solitary liver metastasis with diameter greater than 3 cm).

Procedural complications were limited to one major pneumothorax that required a small-caliber chest tube for 7 days, and three minor complications comprised of 2 unilateral pneumothoraces that did not require chest tube placement and one minor skin burn. Of patients that underwent pulmonary nodule RFA, no patient or family reported decreased pulmonary function. Post-procedure hospitalization ranged 3–7 days (median 4 days), with conservative discharge criteria to ensure patient's guardians would be comfortable reassuming care at home.

Other than the patient with rapidly progressive metastatic disease, the remaining four patients are still alive and considered in complete remission based on screening imaging evaluation with median follow-up of 67.0 months (range 41.2–88.8) after primary tumor surgery and mean disease-free survival of 31.7 months (range 18.1–42.4 months) after last local treatment (Table 3). Among these 4 patients, the AFP level is unmeasurable in 3 patients, but remains elevated above 50 ng/ml in 1 patient despite persistent disease-free survival by imaging.

Discussion

Although international collaborative efforts have attempted to standardize the therapeutic approach to metastatic HB by risk stratification and tumor-specific factors [31–33], the prognosis of advanced, recurrent, or metastatic HB is still

Table 1 Patient demographics, tumor presentation, and initial clinical management

Patients	Sex	Dx Age	Histological subtype	PRETEXT staging	Synchronous disease	Initial AFP (ng/ml)	Initial chemoregimen	AFP after chemo and surgery
1	F	17 years	Atypical	4	None	136,611	CDDP, Doxo	< 10
2	M	2 years	Epithelial[f]	2	None	230,000	CDDP	< 10
3	F	1 years 5 months	Atypical	3	Lung (2)	1,000,000	CDDP, Doxo, Carbo	< 10
4	M	3 years 2 months	Epithelial[fe]	2	Ascites	110,000	CDDP, Doxo	< 10
5	M	10 years	SCUD	4	Hemoperitoneum	8000	CDDP, Doxo	< 10

f fetal predominance, *fe* fetal and embryonic contingents, *SCUD* small cell undetermined, *AFP* alpha-fetoprotein, *CDDP* cisplatin, *Doxo* doxorubicin, *Carbo* carboplatin

Table 2 Local treatment details by patient

Patients	1st met occurrence					2nd met occurrence				3rd met occurrence			
	Time since primary tumor resection (months)	Location (n metastases)	*n* metastases resected in n surgical interventions)	*n* metastases ablated (in n RFA procedures)	*n* metastases irradiated (in n sessions)	Time since primary tumor resection (months)	Location (*n* metastases)	*n* metastases resected (in n surgical interventions)	*n* metastases ablated (in n RFA procedures)	Time since primary tumor resection (months)	Location (*n* metastases)	*n* metastases resected (in *n* surgical interventions)	*n* metastases ablated (in *n* RFA procedures)
1	4.1	Bone[a] ($n = 1$)	–	1[b] (1)	–	9.1	Lung ($n = 2$)	2 (1)	–	15.3	Widespread disease	–	–
2	7.0	Lung ($n = 2$) Liver ($n = 1$)	3 (2)	–	–	21.7	Bil. lungs ($n = 13$) Liver ($n = 1$)	1 (1)	13 (3)	22.8	Liver ($n = 1$)	1 (1)	–
3	8.3	Lung ($n = 1$)	1 (1)	–	–	19.5	Bil. lungs ($n = 3$)	–	3 (1)	34.7	Lung (1)	1 (1)	–
4	7.1	Liver ($n = 1$)	1 (1)	–	–	11.1	Liver (3)	3 (1)	–	18.3	Bil. lung ($n = 6$)	1 (1)	5 (2)
5	18.6	Liver[a] ($n = 1$) Lymph node ($n = 1$)		1 (1)	1 (25)	–	–	–	–	–	–	–	–

[a]Histopathology confirmed by biopsy

[b]Local recurrence at the RFA site

Table 3 Details of last clinical and imaging follow-up

Patients	Clinical and imaging assessments at last follow-up evaluation							
	Time elapsed since primary tumor resection (months)	Time elapsed since last local treatment (months)	Impression from last surveillance imaging	Final AFP (ng/ml)	Total number of metastases treated by RFA, resection, or radiation therapy	Total metastases resected (in *n* surgical interventions)	Total metastases ablated (in *n* RFA procedures)	Total metastases irradiated (in *n* sessions)
1	23.9	11.4	PD[a]	> 10,000	Bone[a] ($n = 1$) Lung ($n = 2$)	2 (1)	1 (1)	–
2	88.8	42.4	CR	1	Lung ($n = 15$) Liver ($n = 3$)	5 (4)	13 (3)	–
3	84.4	40.7	CR	2.8	Lung ($n = 5$)	2 (2)	3 (1)	–
4	41.2	18.1	CR	51.3	Lung ($n = 6$) Liver ($n = 4$)	5 (3)	5 (2)	–
5	49.6	25.6	CR	1	Liver ($n = 1$) Lymph node ($n = 1$)	–	1 (1)	1 (25)

CR complete remission, *PD* progressive disease with mortality

[a]Lesion with untreatable PD leading to death

poor [4, 6, 9–11]. While liver transplantation has proven to extend survival in patients with unresectable hepatic disease, chemotherapy with complete surgical excision of primary and metastatic lesions still provides the cornerstone of curative treatment for oligometastatic recurrent and metastatic disease [6–14]. For some patients, however, surgical resection may be less appealing due to comorbidities, cumulative sequelae of prior surgeries, or desire to avoid invasive surgical procedure for small or isolated lesions. RFA allows definitive cure for tumors less than 2–3 cm, can be applied for multiple lesions during the same procedure, and can be repeated in the event of recurrent or new metastatic lesions [20, 34].

In our institution, RFA was pursued after multidisciplinary consensus to provide curative treatment for small oligometastatic disease to avoid or preclude surgical intervention (Figs. 1, 2). RFA was well tolerated and technically straightforward, with short procedure time and very minimal post-procedure pain. Radiation exposure was limited using pediatric CT scanning protocols to decrease the radiation dose, or by employing ultrasound guidance when possible. The median hospitalization duration of four non-ICU days was relatively short compared to surgical metastasectomy that often includes ICU stay.

Our results validate the utility and safety of RFA as a local treatment control option for oligometastatic HB. Furthermore, RFA may be successfully applied in the same patient for multiple lesions separated by space or time. All five patients treated with RFA also received a combination of treatments for other disease locations that included systemic chemotherapy plus either surgery or radiation therapy. Through this collaborative approach, four of our 5 patients are currently considered in remission with a mean disease-free survival of 31.7 months (range 18.1–42.4) since the last locoregional treatment. While all patients did have new recurrence at a site distal to the initial lesion treated with RFA, these new recurrences were successfully treated with additional reiterative RFA treatment that precluded additional surgery. This pattern of repetitive recurrence is well documented for metastatic HB, and reiterative locoregional treatment is the recommended standard of care [4, 11, 13, 16, 17].

The multidisciplinary criteria to select among locoregional treatment options of surgery, RFA, and radiation therapy are not yet clearly evident. Given the heterogeneous presentation of metastatic HB, a multidisciplinary discussion can help identify an optimal approach to each patient on a case-by-case basis that selectively applies the most appropriate local treatment (surgical metastasectomy, RFA, radiation therapy) in conjunction with systemic chemotherapy. In our multidisciplinary discussions, decisions were based upon assessment of metastasis size, number, and location, as well as the general health of the patient. In the reported patients, RFA treatment was pursued for small and isolated nodules to avoid additional surgery for oligometastatic recurrence measuring less than 3 cm that was deemed technically treatable based on imaging and patient's conditions. Lastly, the role of adjuvant chemotherapy with RFA is uncertain and would require further evaluation in studies with larger patient cohorts.

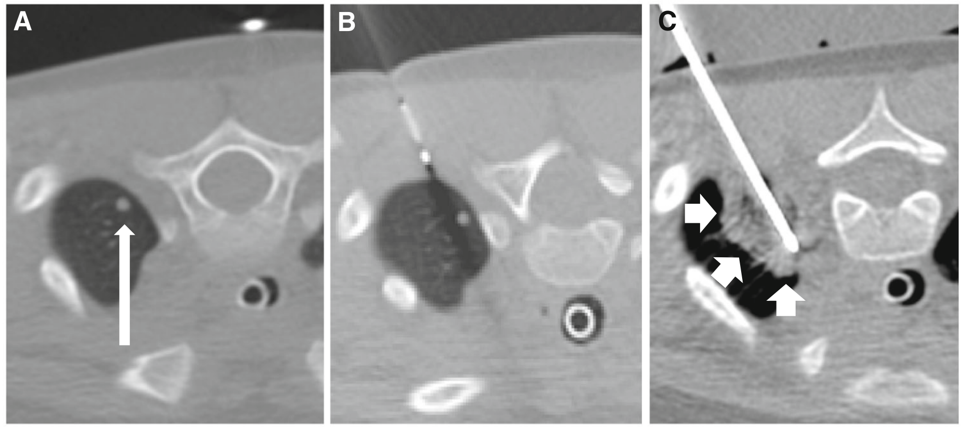

Fig. 1 RFA of a left apical lung metastasis. **A** Pretreatment CT (arrow points to 5 mm nodule). **B** RFA needle approach. **C** Arrows outline pulmonary ablation zone

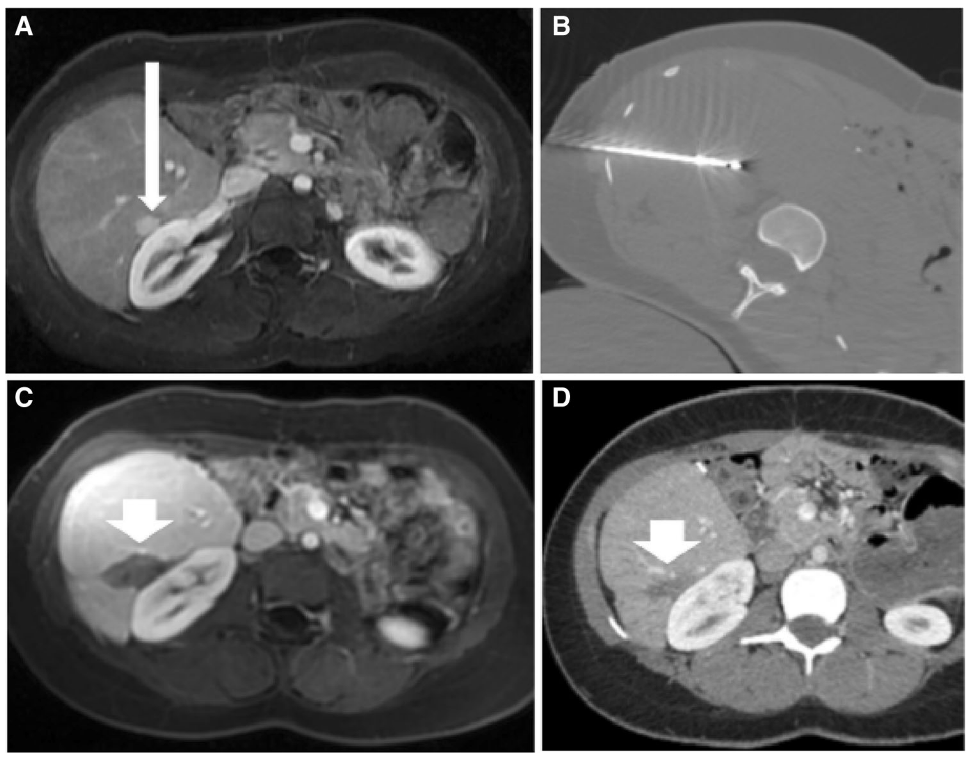

Fig. 2 RFA of a right hepatic metastasis. **A** Pretreatment gadolinium contrast-enhanced MRI. Arrow points to 10 mm nodule. **B** Intraprocedural CT image to demonstrate RFA needle approach. **C** Post-procedure imaging follow-up at 3 months with gadolinium contrast-enhanced MRI. Arrow points to ablated region without evidence for local recurrence. **D** Post-procedure contrast CT at 2 years. Arrow points to ablation scar without evidence for local recurrence

The main limitations in our retrospective study include small cohort size, variability of chemotherapeutic regimens, and follow-up of less than 5 years. We acknowledge the concern for RFA to comprehensively address pulmonary metastatic tumor burden. Surgical exploration with manual palpation has been suggested to have superior ability to detect microscopic pathologic nodules compared to CT [35–37]; however, CT-guided ablation should not be dismissed given the uncertain clinical relevance of palpable nodules [37] and the continued improvements in image resolution to detect punctate nodules. Furthermore, in the event of non-visible microscopic pathologic nodules, RFA can be safely applied reiteratively over time to the same region of the lung with limited damage to lung parenchyma [34, 38]. In our patient cohort, no recurrent lung disease presented at the site of RFA.

Conclusion

Radiofrequency ablation for metastatic HB provides a safe and efficacious local curative treatment option that may be well suited for patients in whom surgical resection is clinically contraindicated or psychosocially unappealing. Furthermore, RFA treatment may be applied reiteratively in this patient population known to present with repetitive recurrences.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Darbari A, Sabin KM, Sahpiro CN, et al. Epidemiology of primary hepatic malignancies in U.S. children. Hepatology. 2003;38(3):560–6.
2. Mann JR, Kasthuri N, Raafat F, et al. Malignant hepatic tumours in children: incidence, clinical features, and aetiology. Pediatr Perinat Epidemiol. 1990;4(3):276–89.
3. Browne M, Sher D, Grant D, et al. Survival after liver transplantation for hepatoblastoma: a 2-center experience. J Pediatr Surg. 2008;43(11):1973–81.
4. Zsiros J, Maibach R, Shafford E, et al. Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol. 2010;28(15):2584–90.
5. Tannuri AC, Cristofani LM, Teixeira RA, et al. New concepts and outcomes for children with hepatoblastoma based on the experience of a tertiary center over the last 21 years. Clinics (Sao Paolo). 2015;70:387–92.
6. Fuchs J, Rydzynski J, Schweinitz DV, et al. Pretreatment prognostic factors and treatment results in children with hepatoblastoma. A report from the German Cooperative Pediatric Liver Tumor Study HB 94. Cancer. 2002;95(1):172–82.
7. Ismail H, Broniszczak D, Kalicinski P, et al. Changing treatment and outcome of children with hepatoblastoma: analysis of a single center experience over the last 20 years. J Pediatr Surg. 2012;47(7):1331–9.
8. Kremer N, Walther AE, Tiao GM. Management of hepatoblastoma: an update. Curr Opin Pediatr. 2014;26(3):362–9.
9. Semeraro M, Branchereau S, Maibach R, et al. Relapses in hepatoblastoma patients: clinical characteristics and outcome-experience of the international childhood liver tumor strategy group (SIOPEL). Eur J Cancer. 2013;49(4):915–22.
10. Katzenstein HM, London WB, Douglass EC, et al. Treatment of unresectable and metastatic hepatoblastoma: a paediatric oncology group phase II study. J Clin Oncol. 2002;20:3438–44.
11. Matsunaga T, Sasaki F, Ohira M, et al. Analysis of treatment outcome for children with recurrent or metastatic hepatoblastoma. Pediatr Surg Int. 2003;19:142–6.
12. Horton JD, Lee S, Brown SR, et al. Survival trends in children with hepatoblastoma. Pediatr Surg Int. 2009;25(5):407–12.
13. Meyers RL, Katzenstein HM, Krailo M, et al. Surgical resection of pulmonary metastatic lesions in children with hepatoblastoma. J Pediatr Surg. 2007;42(12):2050–6.
14. Pham TH, Iqbal CW, Grams JM, et al. Outcomes of primary liver cancer in children: an appraisal of experience. J Pediatr Surg. 2007;42(5):834–9.
15. Yada K, Ishibashi H, Mori H, et al. The role of surgical treatment in the multidisciplinary therapy for hepatoblastoma. Hepatogastroenterology. 2014;61(131):553–6.
16. Trobaugh-Lotrario AD, Feusner JH. Relapsed hepatoblastoma. Pediatr Blood Cancer. 2012;59:813–7.
17. Shi Y, Geller JI, Ma IT, et al. Relapsed hepatoblastoma confined to the lung is effectively treated with pulmonary metastasectomy. J Pediatr Surg. 2016;51(4):525–9.
18. Carcellar A, Blanchard H, Champagne J, et al. Surgical resection and chemotherapy improve survival rate for patients with hepatoblastoma. J Pediatr Surg. 2001;36:755–9.
19. Wanaguru D, Shun A, Price N, Karpelowsky J. Outcomes of pulmonary metastases in hepatoblastoma–is the prognosis always poor? J Pediatr Surg. 2013;48(12):2474–8.
20. de Baere T, Auperin A, Deschamps F, et al. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. Ann Oncol. 2015;26(5):987–91.
21. Botsa E, Poulou LS, Koutsogiannis I, et al. CT-guided radiofrequency ablation in children. Pediatr Radiol. 2014;44(11):1421–5.
22. Gomez FM, Patel PA, Stuart S, Roebuck D. Systematic review of ablation techniques for the treatment of malignant or aggressive benign lesions in children. Pediatr Radiol. 2014;44:1281–9.
23. Saumet L, Deschamps F, Marec-Berard P, et al. Radiofrequency ablation of metastases from osteosarcoma in patients under 25 years: the SCFE experience. Pediatr Hematol Oncol. 2015;32(1):41–9.
24. Hoffer FA. Interventional oncology: the future. Pediatr Radiol. 2011;41:S201–6.
25. Hoffer FA, Daw NC, Xiong X, et al. A phase 1/pilot study of radiofrequency ablation for the treatment of recurrent pediatric solid tumors. Cancer. 2009;115(6):1328–37.
26. Yevich S, Gaspar N, Tselikas L, et al. Percutaneous computed tomography-guided thermal ablation of pulmonary osteosarcoma metastases in children. Ann Surg Oncol. 2016;23(4):1380–6.
27. Dunn CL, McLean TW, Lucas JT, Clark H. Successful radiofrequency ablation for recurrent pulmonary hepatoblastoma. Pediatr Blood Cancer. 2015;62(12):2242.
28. Van Laarhoven S, van Baren R, Tamminga RY, et al. Radiofrequency ablation in the treatment of liver tumors in children. J Pediatr Surg. 2012;47(3):e7–12.
29. Liu B, Zhou L, Huang G, et al. First experience of ultrasound-guided percutaneous ablation for recurrent hepatoblastoma after liver resection in children. Sci Rep. 2015;18(5):16805.
30. Ye J, Shu Q, Li M, Jiang TA. Percutaneous radiofrequency ablation for treatment of hepatoblastoma recurrence. Pediatr Radiol. 2008;38:1021–3.
31. Maibach R, Roebuck D, Brugieres L, et al. Prognostic stratification for children with hepatoblastoma: the SIOPEL experience. Eur J Cancer. 2012;48(10):1543–9.
32. Czauderna P, Haeberle B, Hiyama E, et al. The children's hepatic tumors international collaboration (CHIC): novel global rare tumor database yields new prognostic factors in hepatoblastoma and becomes a research model. Eur J Cancer. 2016;52:92–101.
33. Czauderna P, Lopez-Terrada D, Hiyama E, et al. Hepatoblastoma state of the art: pathology, genetics, risk stratification, and chemotherapy. Curr Opin Pediatr. 2014;26(1):19–28.
34. Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours; a prospective, intention to treat, multicenter clinical trial (the RAPTURE) study. Lancet Oncol. 2008;9(7):621–8.
35. Cerfolio RJ, McCarthy T, Bryant AS. Non-imaged pulmonary nodules discovered during thoracotomy for metastasectomy by lung palpation. Eur J Cardiothorac Surg. 2009;35(5):786–91.
36. Kayton ML, Huvos AG, Casher J, et al. Computed tomographic scan of the chest underestimates the number of metastatic lesions in osteosarcoma. J Ped Surg. 2006;41(1):200–6.
37. Karplus G, McCarville MB, Smeltzer MP, et al. Should contralateral exploratory thoracotomy be advocated for children with osteosarcoma and early unilateral pulmonary metastases? J Pediatr Surg. 2009;44(4):665–71.
38. de Baere T, Palussiere J, Auperin A, et al. Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. Radiology. 2006;240:587–96.