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Surgical Treatment of Pulmonary Metastases in Pediatric Solid Tumors

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Abstract

Most children who succumb to solid malignancies do so because of the burden of metastatic disease or due to complications associated with the therapy administered to treat metastatic disease. Approximately one-quarter of children with solid tumors will present with metastatic disease, and an additional 20% ultimately develop metastatic disease, most commonly in the lung. The role of surgery in the treatment of metastatic solid tumors, given its disseminated nature, is not intuitive, yet there are circumstances in which surgical resection of metastatic disease can potentially be curative. However, the utility of surgery is very much dependent on histology, and generally is most appropriate for those malignancies with histologies that are refractory to other adjuvant therapies.

Introduction

In recent decades, significant progress has been made in the treatment of pediatric solid tumors, with current overall survival rates of 75–90% in non-metastatic tumors. Unfortunately, 10–30% of children with solid tumors present with metastases and an additional 15–20% relapse at distant sites¹. Advances in the treatment of metastatic disease, however, have not mirrored those of non-metastatic solid malignancies, with overall survival ranging from 20–70%, depending primarily on histology¹. As metastasis is a disseminated process, treatment depends on effective systemic therapy, but surgical resection can sometimes be therapeutic. In general, the less sensitive the tumor is to adjuvant therapy, the more likely it is that metastasectomy may be beneficial. Although metastasis can occur at a variety of sites, including lymph node, liver, bone, and brain, a clear majority of pediatric solid tumor metastases occur in the lung, and the tumors which have been shown to benefit from metastasectomy have a higher propensity to metastasize to the lung. This chapter will describe metastatic pathogenesis, the history of its surgical treatment, and diagnosis of

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pulmonary metastases, as well as present a histology-specific breakdown of the surgical indications for metastasectomy.

Historical Perspective

In 1961 Richardson published a survey that identified 35 patients who had undergone pulmonary metastasectomy, with a 23% 5-year survival². In subsequent years, through the publication of case reports and larger case series, the following management principles were established: (1) staged bilateral resections are well-tolerated, (2) unnecessary toxic therapy can sometimes be avoided with accurate diagnosis, (3) tumor type is of utmost importance, and (4) the number of metastases and the disease-free interval are not contraindications to metastasectomy³. Further progress was made when wedge resection was popularized by Kilman et al., allowing for resection of multiple bilateral lung lesions with maximal preservation of lung function⁴. Unfortunately, analysis of the outcome of pulmonary metastasectomy was impossible in many of the early series because most series from the 1960s through 2000 grouped multiple histologies together^{2,3,4,5}. Some early series avoided this pitfall⁶ and some brought attention to it by showing the effect of histology on outcome⁷. From this foundation, the literature regarding metastasectomy in pediatric solid tumors has grown substantially in the last two decades, bringing new insights and controversies.

Pathogenesis

The potential for metastasis, the spread of cancer cells to distant sites, is the defining characteristic of malignant neoplasms. Metastases are more common with increasing primary tumor duration and burden, but can occur at any point in primary tumor progression. The metastatic cascade consists of several independent but sequential steps: angiogenesis, tumor cell invasion of adjacent tissue, intravasation, survival in the circulation, arrest at distant sites, endothelial adherence, extravasation, and growth at distant sites. Due to the inherent biologic heterogeneity of solid tumors, one or multiple clones within a primary tumor can progress through this cascade to cause metastasis. Now that we have a better understanding of the many characteristics a tumor cell must acquire in order to metastasize, it becomes even more perplexing why cells of a specific histology consistently form metastases within the same few target organs⁸. In 1889, Paget described the discrepancy between the relative blood supply and frequency of metastases to certain organs using his “seed and soil” hypothesis, which postulated that certain tumor cells, or “seeds”, have affinity for the microenvironment of certain organs, or “soil”. For over a hundred years, very few additional insights were gained about this phenomenon. In recent decades, research has focused first on clearly defining the attributes of the “seeds,” and only during the last 15 years have researchers begun to unravel the intricate interactions between the primary tumor cells and the “soil” of the target organ prior to metastasis. In 2005, Kaplan et al. showed that a pre-metastatic niche in the target organ is pre-populated by vascular endothelial growth factor receptor 1 (VEGFR1)-positive bone marrow precursors, which prepare nests for metastatic cells prior to their arrival at the distant site, and that VEGFR1 inhibition abrogates the formation of these nests, thereby preventing metastasis⁹. Over the last several years, 30- to 100-nm membrane vesicles called exosomes, which contain proteins, lipids, RNA, and DNA, have been described, and their ability to interact with and prepare the pre-metastatic

niche has been demonstrated. In a series of papers well summarized by Hoshino et al., exosomes have been implicated in the following metastatic processes: (1) lateral transfer of information between cancer cells and target organs, (2) localization to and interaction with the pre-metastatic niche, (3) interaction with different target organs depending on their surface integrins, (4) homing to particular cell types in each target organ according to their surface integrins, (5) activation of pro-inflammatory genes in their target cells, (6) redirection of metastasis to alternative organs by using different organotropic exosomes, and (7) inhibition of metastasis by blocking target-organ surface integrins¹⁰. Recent work on exosomes in osteosarcoma, neuroblastoma, and Ewing sarcoma has started to extrapolate this work to pediatric solid tumors^{11,12,13}. Hopefully, a better understanding of the metastatic cascade will result in new therapies and preventive approaches in the future.

Diagnostic and Localization Challenges

Computed tomography (CT) scan became the gold standard for the identification of pulmonary nodules in 1979 when a prospective study by Chang et al. demonstrated the higher sensitivity of this imaging modality over plain chest radiographs¹⁴. CT has become even more sensitive over time with improvements in technology, and CT is still the preferred method of surveillance and identification of pulmonary nodules in children. However, the limitations of CT are still apparent in multiple pediatric solid tumors, including the fact that there are generally no findings pathognomonic for specific histologies, both neoplastic and non-neoplastic.

Although the high sensitivity of CT can be beneficial, its lack of specificity with respect to differentiating malignant from benign nodules can lead to false-positive interpretations, resulting in unnecessary anxiety, surgery, and/or over-treatment if a confirmatory biopsy is not performed. In a 1992 study, Rosenfield et al. showed that less than half of 13 CT-identified lung nodules in pediatric patients with solid tumors were malignant¹⁵. Despite 14 years of advances in CT technology, McCarville et al. reported in 2006 that among children with CT-identified lung nodules, 42% were ultimately found to have only benign lesions at biopsy. Moreover, independent reviewers examining CT scans were only able to correctly identify malignant lesions 57–67% of the time, and agreement between reviewers was poor¹⁶. In osteosarcoma, the opposite problem has been observed. Multiple papers have demonstrated that pre-operative CT underestimates the total number of metastases present in up to 35% of cases^{16, 17,18,19}. However, despite these deficiencies, CT remains the gold standard for the identification of pulmonary nodules in pediatric solid tumors.

Additional difficulties arise when trying to localize the CT-identified lesions for diagnostic or therapeutic resection, particularly if a minimally invasive approach, such as thoracoscopy, is planned. While superficial lesions can be seen intraoperatively on visual inspection and larger, firmer lesions can be palpated with instruments, many deeper, smaller, softer lesions can easily be missed, regardless of the surgical approach. Given that the goal of metastasectomy is localized resection with maximal preservation of normal lung tissue, lobectomies or segmentectomies are not a solution to this problem. Multiple techniques have been used to overcome this problem, including pre-operative marking with wires, coils, or dye, and localization with intraoperative ultrasound^{20,21,22,23}. All of these strategies are

useful, but each has its drawbacks. Dyes spread along the pleura, coils and wires can be inaccurately placed or dislodged, and the accuracy of ultrasound is limited by lesion depth and the amount of air in the lung. Despite the risk of dislodgement, most authors favor pre-operative wire or coil placement when attempting to localize a difficult lesion in the lung. Improvements in coil design may offer a more reliable system in the future²⁴.

Because the management of pulmonary metastases is so dependent on the histology of the primary tumor, each of the major solid tumor histologies will be discussed individually below.

Osteosarcoma

Osteosarcoma is the most common pediatric bone tumor, with 400 new cases per year in the US. Twenty percent of these patients present with metastasis at diagnosis, and another 22% eventually develop metastasis at some point. Pulmonary metastases comprise 85% of these metastases. While the overall survival of patients with osteosarcoma has improved to 75% in recent trials²⁵, survival for metastatic osteosarcoma is still only 17–34%^{26–28}. Over a dozen previous studies have found that complete surgical resection of primary and metastatic disease is essential for survival in osteosarcoma^{26–41}. Good prognostic factors in metastatic osteosarcoma include diagnosis of metastasis after treatment rather than prior to or during chemotherapy, longer disease-free interval between treatment and relapse, fewer metastatic lesions, better histologic response to preoperative chemotherapy, and the ability to clear all metastatic disease surgically. Extra-pulmonary metastasis and metastasis associated with local relapse are associated with a dismal prognosis, with long-term survival of less than 10%, and while chemotherapy at relapse may yield some prolongation of survival, it does not change overall survival^{27, 28, 31–33, 38, 40–43}. However, repeat thoracotomy for subsequent lung-only relapses has been shown to afford some chance of cure if complete resection is possible^{40, 44, 45}. Survivors of single or multiple thoracotomies for metastasectomy generally experience only mild long-term decrease in pulmonary function⁴⁶.

Given the above data, metastasectomy in osteosarcoma should be attempted whenever complete surgical resection of the primary and metastatic sites is possible. The presence of miliary disease and/or hilar node or pleural involvement can be considered relative contraindications, depending on the ability to resect all lesions and maintain adequate pulmonary function. Cases in which extrapleural resection or pneumonectomy can clear all disease may be encountered, but careful pre-operative planning is essential. Patients with metastatic disease and synchronous local recurrence or extra-pulmonary metastasis should only undergo surgery if complete resection of all known disease is possible.

The surgical approach to pulmonary metastasectomy in osteosarcoma is a source of much debate. The use of an open technique with exploration and palpation of both lungs has been supported by overwhelming evidence that complete resection of all detectable disease is necessary for survival, because of the finding that pre-operative CT misses up to a quarter of viable osteosarcoma metastases found by palpation¹⁷, and by evidence that up to 60% of patients with unilateral CT lesions have contralateral metastases at exploration⁴⁷. Unfortunately, no studies to date have attempted to identify the ideal open approach from

among the available options of median sternotomy, transverse sternotomy, synchronous bilateral or staged bilateral thoracotomies using posterolateral muscle-sparing, vertical transaxillary, or lateral incisions. While sternotomy allows access to both lungs at once, the posterior lung and left lower lobe are difficult to evaluate. Despite the exposure that thoracotomy provides, its use necessitates two incisions, and usually two separate surgeries, as it is better tolerated when staged^{17, 19, 48}. A direct prospective comparison of these techniques is likely impossible; however, the authors favor bilateral, staged, postero-lateral, muscle-sparing thoracotomies.

The ability to detect more metastases at thoracotomy is more likely in osteosarcoma than for other soft tissue sarcomas, because the associated osteoid formation allows palpation of lesions down to a size of 1mm. However, it has never been proven that removal of lesions not seen on CT changes patient outcome. Given this, one must consider the following questions: are there patients who could be spared contralateral thoracotomy, and can minimally invasive surgery be used in metastatic osteosarcoma? Karplus and colleagues analyzed 81 patients with unilateral early relapse on CT (<2 years off treatment) who underwent unilateral thoracotomy with 2-year follow-up and found no significant difference between ipsilateral relapse (16%) and contralateral relapse (23%, $p=0.18$)⁴⁹. This is in contrast to Su et al., who found that 6 of 8 (75%) unilateral, early relapse patients had contralateral disease on staged contralateral exploration. Fernandez-Pineda et al. looked at 16 patients presenting with a single pulmonary nodule on CT 4–80 months after treatment who had unilateral thoracotomy; no additional nodules were found during the ipsilateral thoracotomy. Only 3 of 11 patients with a second relapse recurred in the ipsilateral lung⁵⁰. However, if you divide these patients into early and late relapse, all 10 early relapse patients had a second relapse, 7 of whom relapsed on the contralateral side, and 2 of whom recurred contralaterally within 2 months. Only 1 of 6 late relapse patients had a second relapse. The low likelihood of second relapse in late relapse patients was similar in the study by Su et al. (1 of 5 patients). However, 5 of 9 (56%) early relapse patients had additional ipsilateral metastases upon ipsilateral exploration⁴⁷. The available retrospective data show a low incidence of additional metastases at exploration and second ipsi- or contralateral recurrence for late relapse patients, so foregoing contralateral exploration and minimally invasive surgery in late relapse patients with solitary lesions is acceptable. Unfortunately, such circumstances only apply to 5–8% of metastatic osteosarcoma patients, and further prospective trials are needed prior to expanding those indications. The data in early relapse patients are mixed, however, and the topic remains an area of significant controversy. Hopefully, future prospective trials can answer this difficult question.

Wilms Tumor

Approximately ten percent of Wilms tumor patients present with pulmonary metastasis although they still have high overall survival rates³⁵¹⁷. In the United States, these pulmonary nodules have traditionally been treated using whole-lung radiation with very good outcomes⁵², but this therapy is associated with a 5–12% incidence of pulmonary disease within 15 years of treatment and a 15% risk of breast cancer by the age of 40 in female survivors^{53–55}. Initially, Wilms tumor patients were only treated for pulmonary lesions recognizable on plain film, but the higher sensitivity and lack of specificity of CT raise the

question of how to treat patients with pulmonary nodules seen only on CT (“CT-only”). Early studies failed to show any significant difference in overall survival between patients with CT-only pulmonary nodules and patients without lung metastases^{56,57,58}; however, an analysis from the National Wilms Tumor Study (NWTs)-4 and -5 showed better 5-year event free survival (80% vs. 56%; $p=.004$) but not 5-year overall survival for patients with CT-only nodules treated with 3-drug versus 2-drug chemotherapy⁵⁹. Another analysis of NWTs-5 showed that 11 of 42 (26%) patients with CT-only pulmonary nodules who underwent biopsy had benign lung nodules and could avoid additional treatment⁶⁰. In Europe, therapeutic metastasectomy has been used to avoid the long-term effects of lung radiation. An additional analysis of two recent European trials showed that patients with Wilms tumor treated with pulmonary metastasectomy alone had a higher pulmonary relapse rate but similar overall survival when compared to patients who received pulmonary radiation⁶¹. The International Society of Pediatric Oncology (SIOP) protocol 93-01 allowed for pulmonary metastasectomy after initial chemotherapy. If complete remission was achieved by chemotherapy alone or with chemotherapy and surgery, patients continued on similar chemotherapy and did not receive lung radiation. Of 234 patients with lung metastases, 84% achieved complete remission, with 17% requiring surgery. Patients who achieved complete remission with chemotherapy alone or chemotherapy and surgery had good overall survival of 88% and 92%, respectively. Patients who did not achieve complete remission received intensified treatment and lung radiation with an overall survival of 48%⁶². The recently closed Children’s Oncology Group (COG) trial AREN0533, also eliminated lung radiation for patients who achieved complete remission of lung disease after 6 weeks of 3-drug chemotherapy, and encouraged biopsy of lung nodules after initial chemotherapy to ensure that patients did not receive unnecessary lung radiation. Overall, the use of surgery in the diagnosis and treatment of pulmonary disease in Wilms tumor is increasing. The upcoming COG high-risk Wilms tumor trial will incorporate the use of metastasectomy to achieve pulmonary CR after initial chemotherapy, with the goal of obviating the need for lung radiation, as has been done in the SIOP protocol. With the current diagnostic role of surgery, minimally invasive techniques can be used when complete sampling of the lesions is possible.

Hepatoblastoma

Approximately 20% of patients with hepatoblastoma present with pulmonary metastases. Patients with metastases have a much lower survival rate (25–50%) compared to those without^{63, 64}. While early case reports showed the potential for cure following metastasectomy, initial chemotherapy trials also showed the possibility of complete resolution of lung metastases with chemotherapy alone. Two larger Japanese trials showed the importance of this combined approach and emphasized the use of metastasectomy for residual lung disease after chemotherapy^{65, 66}. The strategy of combining chemotherapy and metastasectomy for residual disease is still used in all major hepatoblastoma cooperative trials for patients with pulmonary metastatic disease at diagnosis.

COG reported its experience with 38 patients with hepatoblastoma lung metastases at diagnosis, 9 of whom went on to metastasectomy. There were 8 survivors, 3 of whom developed pulmonary recurrences⁶⁴. In the International Society of Pediatric Oncology Liver

Tumor Study Group (SIOPEL)-1 study, 22 patients had pulmonary metastases at diagnosis and 7 went on to thoracotomy for resection. Four of the seven patients undergoing thoracotomy were long-term survivors⁶³. SIOPEL also studied 59 patients with relapsed hepatoblastoma. Twenty-seven (46%) developed progressive disease in the lung, 31 (52%) were able to achieve a second remission, and 3-year event-free and overall survival were 34% and 43%, respectively⁶⁷. Black et al. showed that serum alpha-fetoprotein (AFP) is a useful marker of relapse in patients who had elevated AFP with their primary disease, allowing possible early detection of recurrence⁶⁸. Although the numbers are small and no risk factor analysis is possible, the survival data show that the complete surgical resection of any primary disease and residual metastatic sites is essential for long-term survival. The resection of any residual disease in the lungs is of utmost importance prior to local control for PRETEXT III and IV patients who require liver transplantation due to the need for post-transplant immunosuppression. Contraindications to metastasectomy include an inability to achieve a complete resection while preserving adequate lung function and the presence of uncontrolled disease at the primary site. Surgical excision of extra-pulmonary metastases should only be undertaken when complete resection is likely, as their presence is associated with a dismal prognosis. The primary goal of hepatoblastoma metastasectomy is complete resection. There is no contraindication to minimally invasive techniques if complete resection can be accomplished.

Neuroblastoma

Among patients with neuroblastoma, pulmonary metastasis at diagnosis is rare. The International Neuroblastoma Risk Group Study most recently reported an incidence of 3.6%⁶⁹. Previous series had estimated the incidence between 0.4% and 3.2%^{70,71}; however, all of these might be underestimates, as detailed lung imaging was not obtained in the majority of these patients. The likelihood of metastasis in general and lung metastases in particular is higher in patients older than 1 year and with *MYCN* amplification (denoting a higher risk group)⁶⁹. Patients with lung metastases are much more likely to have metastases to the CNS and other locations⁷². Regardless of the metastatic burden or location of metastases, surgery should be reserved for diagnosis only. We recommend biopsy of the most easily accessed site, whether primary or metastatic, for initial diagnosis or recurrence.

Rhabdomyosarcoma

Overall survival for metastatic rhabdomyosarcoma (RMS) is poor. One early mixed-histology case series reported that patients with pulmonary metastases from RMS are 35 times more likely to relapse in the lung than patients with lung metastases from other sarcomatous histologies⁴⁴, and other reports confirmed a dismal outcome⁷³. Williams et al. reviewed 17 patients with metastatic RMS and found that 3 patients with embryonal histology, age younger than 10 years, and only lung metastases all survived, but 14 patients who did not have all three of those good prognostic indicators died of disease. The largest European study included 174 patients with metastatic RMS, 55% of whom had metastases to multiple organ systems. Unfavorable primary site, bone or bone marrow involvement, and age <1 or >10 years were independent, unfavorable risk factors. Patients with 0 or 1 of these factors had an overall survival of 47%, whereas overall survival was 9% for those with two

or more risk factors⁷⁴. COG found that only 16% of patients with metastatic RMS have only lung metastases, and that these patients were more likely to have favorable histology, parameningeal primaries, and negative nodes. Patients with only lung metastases had outcomes comparable to those of patients with metastases at other single sites, but patients with 2 or more metastatic sites fared significantly worse. Surprisingly, very few patients with only lung metastases underwent biopsies, and 35% did not receive protocol-directed lung radiation, even though radiation was associated with decreased rates of pulmonary recurrence⁷⁵. A more recent COG report divided patients into groups, as the previous European trial did, and found that patients with 0 or 1 risk factor (age <1 or >10, unfavorable site, bone or bone marrow involvement) had 3-year event free survival of 69%, which is an improvement over earlier trials. Unfortunately, patients with 2 or more risk factors, which constitute the majority of metastatic RMS patients, still only have a 3-year event free survival of 20%⁷⁶. Given the poor outcome and good response to chemotherapy and radiation, metastasectomy in rhabdomyosarcoma should only be performed for diagnosis and minimally invasive techniques can be used when appropriate.

Non-Rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS)

This family of sarcomas includes alveolar soft part sarcoma, synovial sarcoma, chondrosarcoma, and malignant fibrous histiocytoma, among others. These tumors have a propensity to metastasize to the lung, and are generally resistant to chemotherapy and radiation. The rarity of these tumors makes their study difficult. The data for alveolar soft part sarcoma and synovial sarcoma are specifically discussed in the following paragraphs, but based on resistance to other treatments, metastasectomy has been recommended for this family of tumors whenever complete resection of all disease is possible^{77, 78}. CT is the modality of choice for diagnosis of these lung lesions, and because of their consistency, these tumors may be difficult to palpate. Localization techniques described earlier may be advisable for deeper lesions regardless of open or minimally invasive approach.

Alveolar soft part sarcoma has a significant proclivity for lung metastasis. Kayton et al. reviewed 20 patients with alveolar soft part sarcoma. Seven of the patients had lung metastases at diagnosis, but 14 of 20 (70%) of the patients were diagnosed with lung metastases at some point during their course. Despite this high rate of spread and evidence of progression, the 5-year overall survival was 83%, highlighting the slow rate of progression in this disease. One patient underwent 8 thoracotomies for resection of lung metastases and was alive without disease at last follow-up. The authors concluded that liberal application of metastasectomy is justified in this disease⁷⁹. A more recent analysis from Beijing included 64 patients, 56 (87.5%) of whom developed lung metastases at some point. Overall survival for patients with and without lung metastases was 64% and 95%, respectively. These data reinforce the use of therapeutic metastasectomy in this disease.

Synovial sarcoma has a surprisingly good response to chemotherapy compared to the rest of the NRSTS family, but still requires complete resection for cure. Approximately 40% of patients have or develop metastases, and 80% of metastases involve the lung^{80,81}. A study of a 150-patient cohort from England found the overall survival 5 years after the diagnosis of metastasis to be 6%, but with the use of pulmonary metastasectomy, that rate increased to

23%⁸¹. Stanelle et al. analyzed 41 patients with metastatic synovial sarcoma. No patients survived more than 2 years without metastasectomy, but with metastasectomy, the 5-year overall survival was 24%. Survival was significantly more likely with complete resection of the metastases, and palliative debulking did not improve survival. Therefore, therapeutic metastasectomy should be employed in synovial sarcoma whenever complete resection of all metastatic sites is possible.

Ewing Sarcoma

Ewing sarcoma is a chemo- and radiosensitive tumor, which makes the assessment of the utility of surgery more difficult. Early published case series presented conflicting results regarding the benefit of metastasectomy^{7,44,82,83}. In a more recent series, 31 cases of Ewing sarcoma with pulmonary metastasis were analyzed. Only 8 patients underwent pulmonary metastasectomy, but patients who underwent metastasectomy had a 5-year survival of 80%, compared to 0% for patients who had radiation and/or chemotherapy without metastasectomy. That difference seems drastic, but there was no report of or control for disease burden and no explanation of how the decision regarding the choice of therapy was made⁸⁴. As with the earlier reports, this result could have resulted entirely from selection bias. A Polish study, published in 2016, reviewed 38 patients with Ewing sarcoma and isolated lung metastases treated with modern multi-modal therapy from 2000–2014. Twenty patients underwent metastasectomy and 6 received postoperative lung radiation. They divided patients by pulmonary disease burden (Group 1 = solitary nodule <0.5cm or multiple <0.3cm; Group 2 = solitary nodule 0.5–1cm or multiple 0.3–0.5cm; Group 3 = solitary nodule >1cm or multiple >0.5cm), and reclassified the patients after 6 cycles of chemotherapy. Fifteen patients had improvement in their pulmonary disease burden and 11 had complete resolution of all lung nodules. Metastasectomy performed at that time showed that all Group 3 and 63% of Group 2 patients had viable disease, but none of the Group 1 patients had viable disease. Patients with a radiographic response to initial chemotherapy had an improved event-free survival, but no effect of metastasectomy was observed⁸⁵. Given the multitude of conflicting reports hampered by poorly controlled data, there is no reliable evidence that metastasectomy in Ewing sarcoma is of therapeutic benefit. However, with the 47% rate of negative biopsy in patients with small to moderate lung lesions, it can still play an important role in diagnosis, perhaps saving some patients from intensified therapy or lung radiation.

Adrenocortical Carcinoma

Adrenocortical carcinoma is rare chemotherapy- and radiation-resistant tumor. An analysis of one of the largest cohorts to date examined 111 pediatric cases compiled within a national database over a 13-year period⁸⁶. Although pediatric case series examining the effect of pulmonary metastasectomy do not exist, there is ample evidence in the adult literature that this procedure is beneficial and can enhance long-term survival^{87,88}. Case reports confirm the ability of metastasectomy to produce long-term survival in the pediatric population^{89,90}. Pulmonary metastasectomy should be performed in any patient with metastatic adrenocortical carcinoma in whom complete resection is possible. Although there is no contraindication to minimally invasive resection, there are ample data from adults that these

tumors are at high risk of rupture during dissection and removal, and that spillage can lead to implants and carcinomatosis. The implications of spillage are heightened as there is little useful treatment other than surgery, so the surgeon must make every attempt to dissect and remove the tumor intact.

Conclusion

Over the past few decades, significant advances have been made in the treatment of childhood solid tumors. Unfortunately, the survival rates for children with metastatic disease have not improved nearly as much. Although management of metastatic disease relies heavily on systemic therapies, surgery plays an important role in the treatment of several pediatric metastatic solid tumors. In some cases, the surgery is therapeutic, and in some it plays a diagnostic role and guides further systemic treatment. This chapter summarizes the data regarding metastasectomy for the most common pediatric solid tumors. Hopefully, future studies combining surgery and other adjuvant therapies can improve outcome in these difficult disease.

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Table 1

Metastatic Disease and the Benefit of Metastasectomy in Pediatric Solid Tumors.

Tumor Type	Metastasis At Diagnosis	Pulmonary Metastasis	Inc Survival w Metastasectomy	Est. Overall Survival w/ Mets
Osteosarcoma	20% synchronous 40% metachronous	18% 35%	Yes	17–34% 5yr OS
Wilms Tumor	15%	13%	No	86% 5yr OS
Neuroblastoma	60%	4%	No	40% 5yr OS
Hepatoblastoma	24%	17%	Yes	40% 5yr OS
Rhabdomyosarcoma	10–20%	16%	No	56% 3yr OS
Synovial (NRSTS)	16% synchronous 50% metachronous	10% 40%	Yes	24% 5yr OS
Ewing Sarcoma	25%	10%	No	20% 5yr OS
Adrenocortical	21%	10%	Yes	10% 5yr OS