

ORIGINAL RESEARCH

Open Access



The role of thoracoscopic lung biopsy in the management of children with solid organ malignancies and suspected lung metastases in a developing country

Mark Wagener^{1,2*} , Nasheeta Peer³ and Mahomed Hoosen Sheik-Gafoor^{1,2}

Abstract

Background: Accurate diagnosis of lung lesions appearing on computed tomographic (CT) imaging in children with solid organ malignancies can be difficult. Therefore, this study aimed to determine, in a developing country setting, (1) the utility of thoracoscopic lung biopsy for assessment of suspected lung metastases in solid organ malignancies, and (2) the pathology of biopsied lesions suspected to be malignancies. The electronic records of all patients with solid organ malignancies who underwent thoracoscopic lung biopsies for suspected metastases at a tertiary hospital in South Africa between January 2012 and December 2017 were analysed retrospectively.

Results: A total of 29 thoracoscopic biopsies were taken from 25 patients. In eight biopsies (27.6%), viable metastatic tumour was identified; in one, a completely necrotic tumour was found. Seven patients (28.0%) were found to have infective aetiologies which required alternative therapies: of these, three patients had tuberculosis; three had bronchopneumonia and one had a fungal lung infection. Other findings included haemorrhagic infarction ($n = 1$); non-specific fibrosis ($n = 1$) and reactive lymph node ($n = 1$). In ten biopsies (34.5%), no lesion was found on thoracoscopy.

Conclusions: Thoracoscopy was found to improve the management of children with solid organ malignancies and suspected metastases. Thoracoscopy enabled many patients to avoid additional chemotherapy and radiotherapy and its negative consequences and enabled therapy for specific benign pathologies including infections.

Keywords: Thoracoscopic lung biopsy, Video-assisted thoracoscopic surgery (VATS), Solid organ malignancy, Children, Nephroblastoma, Lung metastases

Background

Solid organ malignancies in children, including nephroblastoma, neuroblastoma, hepatoblastoma, rhabdomyosarcoma and germ cell tumours, may present with metastases at diagnosis or relapse at distant sites. Metastases to the lungs are particularly common in

nephroblastoma and hepatoblastoma, with studies from our centre showing 15–30% of children with nephroblastoma having lung metastases at diagnosis [1, 2].

The presence of lung metastases influences treatment and prognosis with treatment including additional chemotherapy and subsequent radiotherapy, both of which can have serious and debilitating complications. The negative effects of further chemotherapy predominantly relate to the addition of doxorubicin for nephroblastoma, which can cause congestive cardiac failure [3]. The negative effects of radiotherapy are well documented and include skeletal deformities, renal toxicity,

* Correspondence: mark.wagener2@gmail.com

¹Department of Paediatric Surgery, Inkosi Albert Luthuli Central Hospital, 800 Vusi Mzimela Road, Cato Manor, Durban, KwaZulu-Natal 4091, South Africa

²Department of Paediatric Surgery, University of KwaZulu-Natal, Durban, South Africa

Full list of author information is available at the end of the article

gonadal toxicity, interstitial pneumonitis and secondary malignancies [4]. Therefore, considering the severe adverse effects of these treatments, it is crucial to ensure that the diagnosis of lung metastases is accurate to warrant such serious therapies.

Amongst the initial investigations conducted to identify suspected lung metastases is computed tomography (CT) scanning, which is also used as the modality of choice to monitor the response of lesions to chemotherapy and radiotherapy. However, whilst CT is highly sensitive in detecting lung lesions, it lacks specificity [5, 6]. In children with solid organ malignancies, not all lesions detected on cross-sectional imaging may be metastases; some may represent benign pathologies. Benign pathologies represent 30-70% of lesions biopsied in these children, with a spectrum of pathologies including infective aetiologies, non-specific inflammation, granulomas and fibrosis [5, 6]. Notably, in developing country settings, it was speculated that such lesions would have an even broader differential diagnosis, including multiple infective aetiologies. Accurate diagnosis then becomes important not only to avoid unnecessary additional chemotherapy and radiotherapy but also to provide the appropriate treatment if infection is diagnosed.

In view of this, there has been a trend towards confirming diagnoses of lung lesions detected on cross sectional imaging in children with solid organ malignancies. Use of thoracoscopy has emerged as a minimally invasive, low risk and precise means of providing an accurate diagnosis [7–12]. In addition to providing a diagnosis, thorascopic removal of lung lesion may have therapeutic advantages in the cases where single or few metastases can be removed completely [13, 14]. Nevertheless, despite its usefulness, thorascopic lung biopsy and resection of metastases in children with solid organ malignancies has not yet been broadly applied in paediatric surgical oncology globally, particularly in developing country settings.

Although centres in developed countries have explored the utility of thorascopic lung biopsies in children with suspected lung metastases, these cannot be extrapolated to developing regions where the differential diagnoses may be broader. Although the role of thorascopic lung biopsy has been investigated in a developing country setting, this did not include evaluation of children with suspected pulmonary metastases [15]. Thus, there is a lack of evidence on this topic from developing countries, including South Africa. The spectrum of causes for lesions in the lung of children with suspected metastases remains untested in South Africa and required exploration. Therefore, the aim of this retrospective study was to determine (1) the utility of thoracoscopy and biopsy in diagnosing patients with suspected lung metastases but atypical imaging; (2) the

aetiology of biopsied lesions and (3) the value of lung biopsy in a treatment algorithm. In addition, we aim to describe our method of thorascopic lung biopsy.

Method

Study design, sample selection and data extraction

A retrospective electronic chart review of patients who fulfilled the inclusion criteria was undertaken at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa. This tertiary hospital is the main provider of specialised paediatric oncology services for the province's 11 million population.

Records were retrieved for all patients with solid organ malignancies who underwent thorascopic lung biopsies for suspected metastases between January 2012 and December 2017. Participants in this study included both new patients who presented with metastases and known patients with pulmonary relapse.

Data were extracted from the electronic records by a clinician and included the following: age, primary diagnosis, timing of biopsy, result of biopsy and outcome. Data were then inserted into an Excel spreadsheet, version 15.27 (Microsoft, USA), for analysis.

Patient selection process for thoracoscopy

At IALCH, all children with solid organ malignancies undergo CT of the chest at diagnosis, at intervals during their treatment and on completion of treatment. They are subsequently followed up with plain chest radiographs. High resolution 1 mm thickness slice CT imaging is used to diagnose lung lesions and direct management. The latter includes selecting patients for thorascopic lung biopsy and planning surgery. A prerequisite for lesions on CT imaging to be selected for thorascopic lung biopsies was that they had to be peripheral, accessible thorascopically and were either atypical lesions or lesions that persisted after initial chemotherapy. With regard to management, lesions detected on CT imaging, but not plain X-ray, were classified as stage 4 disease. These patients were treated with 3 drug chemotherapy (addition of doxorubicin) and lung irradiation, based on National Wilms Tumour Studies (NWTS) –4 and –5 data which showed improved event free survival for these children [16].

Thorascopic procedure

Surgical method used for thoracoscopy was standard in all patients. The patient had a general anaesthetic and was placed in the lateral decubitus position with a roll underneath the chest. Bilateral lung ventilation was used. Open insertion of a 5 mm port for the telescope was done in the mid-axillary line (with the usual position being just below the scapula), two further 3 mm ports were inserted so as to triangulate the lesion. The ipsilateral

thorax was inflated with carbon dioxide (CO₂). Pressures of up to 5 mmHg and flow of 2 l/min was used. Biopsies were taken using ligating loops. Extension of port sites to mini thoracotomies was used for larger lesions, with use of a linear stapler to excise the lesions. Neither tracers nor routine post-operative intercostal drain insertion were used.

This standard technique for thoracoscopy was used in all patients. Two patients required extensions of their port incisions and extra-corporal excision of their lesions using linear stapler.

Specimens were sent in formalin for histopathological analysis.

Results

Amongst 25 patients on whom thorascopies were performed, 22 had a primary diagnosis of nephroblastoma (88%); a single patient each had a hepatoblastoma, ovarian tumour and adrenal carcinoma (Fig. 1). Thirteen patients (52%) had suspected lung metastases at diagnosis whilst 12 (48%) developed suspicious lung lesions either during the course of their treatment or after completion. The mean age of these patients was 4.6 years (range 1 to 9 years), of whom 12 were female and 13 male.

A total of 29 thorascopic biopsies were taken from 25 patients. Three patients had 2 metachronous biopsies; 1 patient had 3 synchronous biopsies. On histology, viable metastatic tumours were identified in seven patients (28.0%) and eight biopsies (27.6%), with a completely necrotic tumour found in a single patient (Fig. 2). Another seven patients (28.0%) were diagnosed with infective aetiologies which required alternative therapies: three patients were found to have tuberculosis; three had bronchopneumonia and one had a fungal lung infection. Other findings included haemorrhagic infarction (1

biopsy), non-specific fibrosis (1 biopsy) and reactive lymph node (1 biopsy). In nine patients (36.0%), no lesion was found on thoracoscopy, with a total of 10 thorascopic biopsies showing no lesions (34.5%); one patient had two metachronous thoracoscopy procedures that showed no lesions.

Of the 8 biopsies where metastatic tumour was found, two had reported tumour free margins (25%); three had positive margins and in another three the margins were not reported on.

Amongst the patients with the most common primary diagnosis, i.e., nephroblastoma ($n = 22$), a diagnosis of lung metastases was confirmed in six patients on histology (27.3%). The other patients had no lesion ($n = 8$), pneumonia ($n = 2$), tuberculosis ($n = 3$) (Fig. 3), reactive lymph node ($n = 1$), non-specific fibrosis ($n = 1$) and haemorrhagic infarction ($n = 1$).

Four patients developed post-operative pneumothorax. One patient developed an expanding pneumothorax which was successfully managed with an intercostal drain insertion and subsequently resolved. In the other three patients, the pneumothorax resolved spontaneously. No further complications occurred.

Discussion

In this study, of the 25 patients with solid organ malignancies, seven (28%) had a diagnosis of pulmonary metastases confirmed on thoracoscopy. The other 18 patients with suspected lung metastases on CT imaging either had non-malignant pathologies or no lesions were detected. Thoracoscopy and the subsequent histopathological analyses of biopsied specimens enabled the diagnoses and curative treatment of infective aetiologies in seven patients (28%).

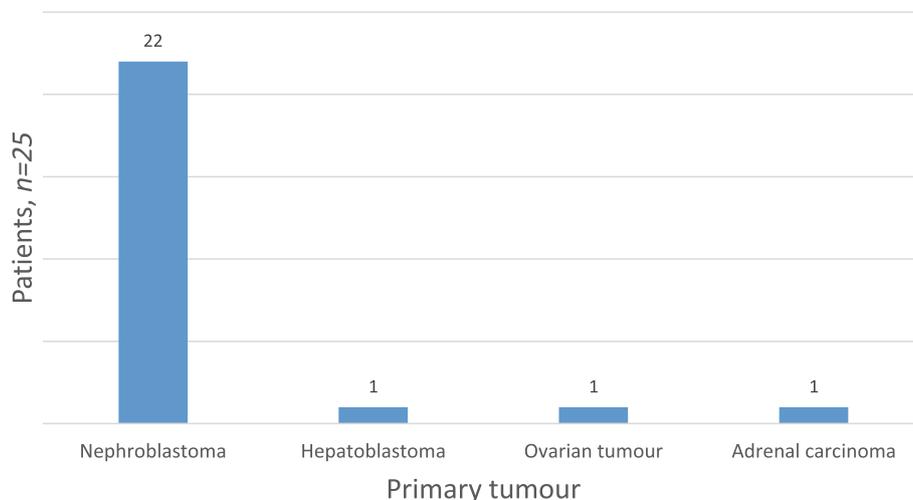
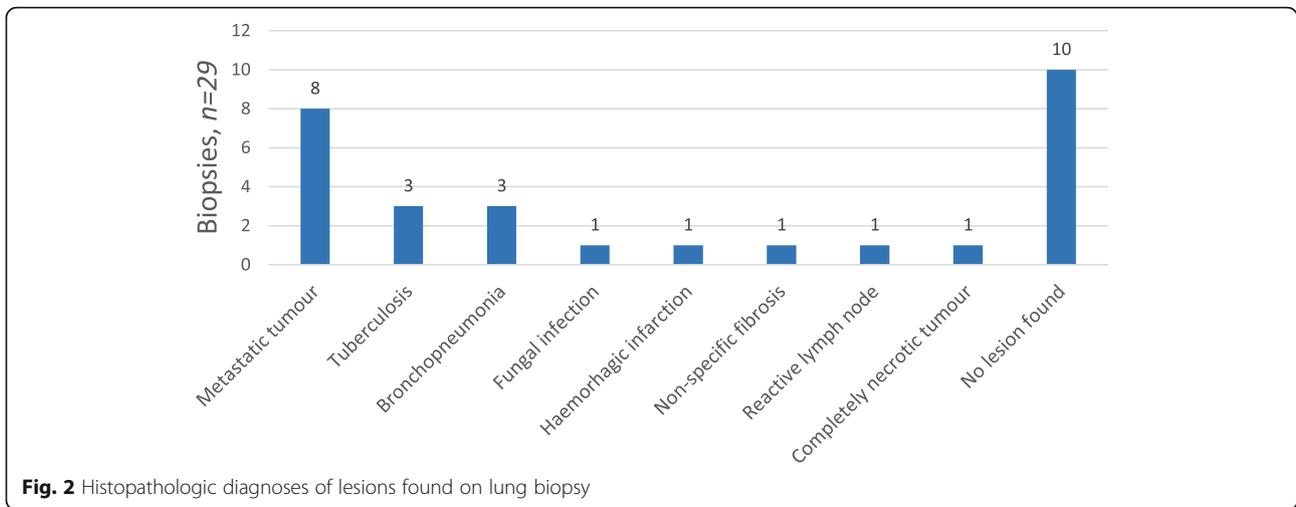


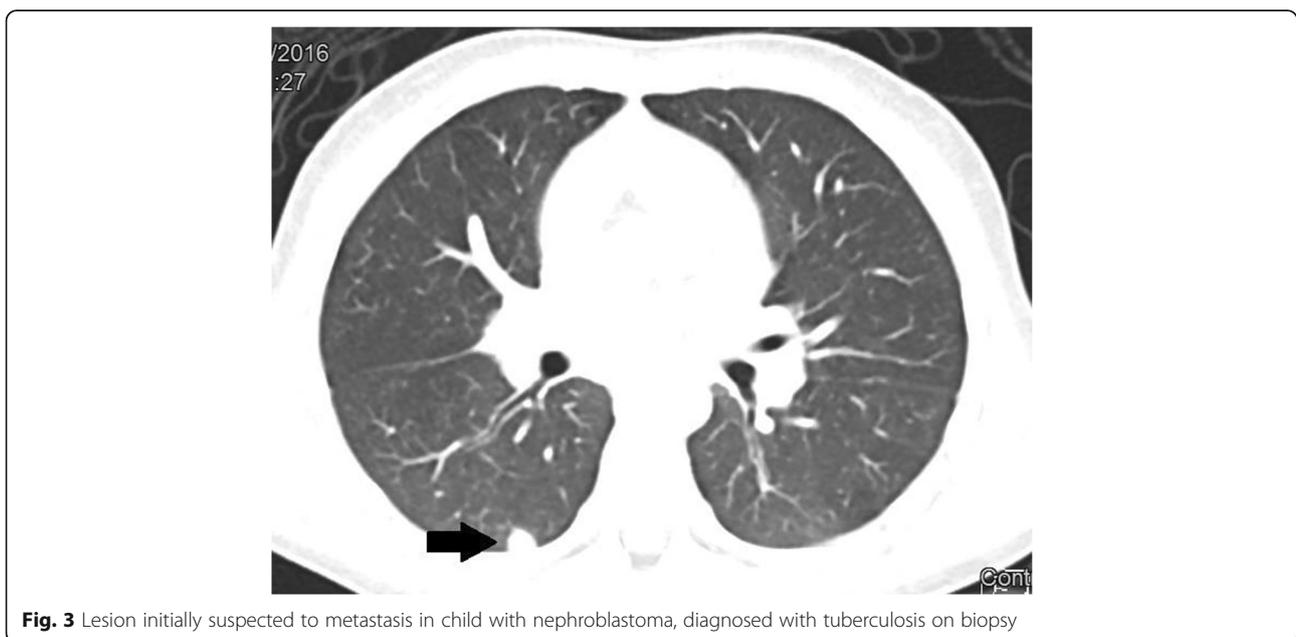
Fig. 1 Primary tumour of study patients who underwent thorascopic lung biopsies



Notably, the majority of patients (72%) were spared from undergoing intensified chemotherapy and radiation and the potential harmful effects of these treatments. This highlights that the introduction of thoracoscopic lung biopsy to confirm diagnosis has improved the management of these challenging patients.

Historically, patients with solid organ malignancies and suspected pulmonary metastases have posed both a diagnostic and therapeutic challenge. The interpretation of lung lesions identified on CT scan is difficult because of the wide range of possible differential diagnoses including infective and other benign aetiologies. The need for additional chemotherapy and radiotherapy with their associated complications poses a further challenge.

The majority of patients in our case series who were eligible for thoracoscopy had nephroblastoma, which is the 4th most common childhood malignancy in South Africa and accounts for 12% of paediatric malignancies in the South African Children’s Tumour Registry [17]. As mentioned, previous studies from our centre show that 15-30% of children with nephroblastoma have lung metastases at diagnosis [1, 2]. In this study, just over a quarter (27.3%) of patients with nephroblastoma who underwent thoracoscopic lung biopsies were found to have a metastatic lesion. This highlights that thoracoscopic lung biopsy is particularly useful in these patients in our setting. Almost three-quarter of patients with nephroblastoma and suspected lung metastases were



able to avoid unnecessary chemotherapy and radiation because of accurate diagnoses following thoracoscopy.

Alternatives to this approach, i.e., CT imaging followed by thoracoscopy include positron emission tomography-computed tomography (PET-CT) in order to determine if a lung lesion is benign or malignant [10]. Despite being less invasive, this modality may be less sensitive than biopsy, especially in the case of small lesions. Moreover, it will fail to accurately diagnose the specific nature of benign pathology which may be easily treatable. Considering the high proportion of treatable benign pathology diagnosed thoracoscopically in our setting, the surgical approach may be more prudent locally.

The use of thoracoscopic lung biopsy may also have therapeutic advantages in the presence of metastatic lesions. However, of the eight patients where metastatic tumour was found, only two were shown to have negative margins. Therefore, to date, thoracoscopy remains predominantly a diagnostic tool in our practice. Similar to other centres [10], we avoid surgery for therapeutic purposes in children with progressive pulmonary disease who are on treatment because of poor prognostic outcomes. Biopsies in such cases are usually only undertaken when the diagnosis is in doubt.

Nevertheless, if surgery is undertaken as part of therapy for lung metastases, it is important to achieve complete removal with free margins [13, 14, 18]. In these instances, metastatectomy is done in patients where imaging is highly suggestive of metastases and the patient has shown an inadequate response to chemotherapy [10]. Thoracoscopy has been shown to be a reliable method of achieving this goal when metastases are small and few in number [6, 9–12]. Additionally, minimally invasive surgery can potentially be performed as a synchronous bilateral procedure for bilateral metastases where the procedure would normally be staged if an open approach was used [12].

Much of the appeal of thoracoscopic biopsy of lung metastases is to avoid lung radiotherapy which has significant long-term adverse consequences. These include 5–12% of pulmonary disease within 15 years of treatment and 15% risk of breast cancer by age 40 in female survivors [4]. The International Society of Paediatric Oncology (SIOP) and Children's Oncology Group (COG) guidelines both currently allow for the use of metastatectomy [19, 20]. The SIOP protocol 93-01 involves the omission of radiotherapy if metastases are cleared with chemotherapy alone or chemotherapy and surgery. Using this approach, it has been shown that the majority of patients with lung metastases at diagnosis can avoid radiotherapy with an overall survival of 88% for patients who had clearance of lung metastases with chemotherapy alone and 92% for patients who had clearance of metastases with chemotherapy plus surgery [21]. This practice, however, remains controversial.

Thoracoscopic surgery for suspected lung metastases is a developing entity and its place in treatment protocols has not been clearly established. Most authors agree on the following indications: uncertain diagnosis, persistence after initial chemotherapy and pulmonary relapse [10]. Our practice has followed this trend.

A limitation of our work is we are currently restricted to biopsies of lesions visible on the surface of the lung or superficially situated within the lung parenchyma. Thus, we are not able to biopsy suspicious lesions that are deep. Fortunately, the majority of metastatic lesions occur in the periphery of the lung and are thus more accessible for biopsy. Technologies that may assist in lesion detection include image-guided labelling with coils or dye; radionuclide labelling and intra-operative ultrasound [10, 12, 22–24]. The future may involve us incorporating these into our practice thus enabling sampling of a greater number of suspicious lung lesions.

Of additional concern was the number of patients with lesions on CT scanning that were not seen at thoracoscopy; this comprised over a third of patients who underwent thoracoscopy (36%, $n = 9$). This is a problem that has been recognised in the literature [10, 12]. It is possible that lesions are missed on thoracoscopy due to lack of tactile ability or due to lesions lying deeper in the lung parenchyma and therefore not visualised. Techniques mentioned above may be used to improve detection of these lesions; however, these are not currently used in our practice.

Conclusions

Thoracoscopic lung biopsy improves the management of children with solid organ malignancies and suspected lung metastases or atypical features on cross sectional imaging. For future research, we would like to introduce pre-operative, image-guided labelling of lesions and intra-operative ultrasound and assess whether this improves the diagnostic yield from thoracoscopic biopsy.

Abbreviations

CT: Computed tomography; IALCH: Inkosi Albert Luthuli Central Hospital; NWTs: National Wilms Tumour Studies; CO₂: Carbon dioxide; PET-CT: Positron emission tomography-computed tomography; SIOP: International Society of Paediatric Oncology; COG: Children's Oncology Group

Acknowledgements

None.

Authors' contributions

MW came up with the idea for the study. MW and MHSG designed the study. MW acquired the data. MW analysed and interpreted the data. MW drafted the initial manuscript. NP and MHSG performed critical revision of the manuscript. All authors read and approved the final manuscript.

Funding

No funding was required for this research.

Availability of data and materials

Data and material is available on request.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (ref. no. BE302/18). Since this was a retrospective chart review, consent for participation is not applicable.

Consent for publication

The manuscript has been read and approved for submission by all the named authors and consent is given for publication.

Competing interests

The authors declare no competing interests.

Author details

¹Department of Paediatric Surgery, Inkosi Albert Luthuli Central Hospital, 800 Vusi Mzimela Road, Cato Manor, Durban, KwaZulu-Natal 4091, South Africa.

²Department of Paediatric Surgery, University of KwaZulu-Natal, Durban, South Africa. ³Non-communicable Diseases Research Unit, South African Medical Research Council, 491 Peter Mokaba Road, Durban, KwaZulu-Natal 4091, South Africa.

Received: 10 December 2020 Accepted: 25 August 2021

Published online: 09 November 2021

References

- Aronson DC, Maharaj A, Sheik-Gafoor MH, Hadley GP. The results of treatment of children with metastatic Wilms tumours (WT) in an African setting: do liver metastases have a negative impact on survival? *Pediatr Blood Cancer*. 2012;59(2):391–4. <https://doi.org/10.1002/pbc.24080>.
- Hadley GP, Bösenberg A. Surgery for Wilms' tumour. The effect of neoadjuvant chemotherapy. *Pediatr Surg Int*. 1995;10(5):362–5.
- Green DM, Grigoriev YA, Nan B, Takashima JR, Norkool PA, D'Angio GJ, et al. Congestive heart failure after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study group. *J Clin Oncol*. 2001;19(7):1926–34. <https://doi.org/10.1200/JCO.2001.19.7.1926>.
- Paulino AC, Wen BC, Brown CK, Tannous R, Mayr NA, Zhen WK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. *Int J Radiat Oncol Biol Phys*. 2000;46(5):1239–46. [https://doi.org/10.1016/S0360-3016\(99\)00534-9](https://doi.org/10.1016/S0360-3016(99)00534-9).
- Ehrlich PF, Hamilton TE, Grundy P, Ritchey M, Haase G, Shamberger RC. The value of surgery in directing therapy for patients with Wilms' tumor with pulmonary disease. A Report from the National Wilms' Tumor Study Group (National Wilms' Tumor Study 5). *J Pediatr Surg*. 2006;41(1):162–7. <https://doi.org/10.1016/j.jpedsurg.2005.10.020>.
- Burdine J, Joyce LD, Plunkett MB, Inampudi S, Kaye MG, Dunn DH. Feasibility and value of video-assisted thoracoscopic surgery wedge excision of small pulmonary nodules in patients with malignancy. *Chest*. 2002;122(4):1467–70. <https://doi.org/10.1378/chest.122.4.1467>.
- Rotheberg S. Thoracoscopic lung surgery in infants and children: the state of the art. *Pediatr Allergy, Immunol Pulmonol*. 2011;24(3):139–44. <https://doi.org/10.1089/ped.2011.0100>.
- Ure BM, Schmidt AI, Jesch NK. Thoracoscopic surgery in infants and children. *Eur J Pediatr Surg*. 2005;15(5):314–8. <https://doi.org/10.1055/s-2005-865793>.
- Guye E, Lardy H, Piolat C, Bawab F, Becmeur F, Dyon JF, et al. Thoracoscopy and solid tumors in children: a multicenter study. *J Laparoendosc Adv Surg Tech*. 2007;17(6):825–9. <https://doi.org/10.1089/lap.2007.0043>.
- Fuchs J, Seitz G, Handgrettinger R, Schäfer J, Warmann SW. Surgical treatment of lung metastases in patients with embryonal pediatric solid tumors: an update. *Semin Pediatr Surg*. 2012;21(1):79–87. <https://doi.org/10.1053/j.sempedsurg.2011.10.008>.
- Fuchs J. The role of minimally invasive surgery in pediatric solid tumors. *Pediatr Surg Int*. 2015;31(3):213–28. <https://doi.org/10.1007/s00383-015-3660-9>.
- Heaton TE, Davidoff AM. Surgical treatment of pulmonary metastases in pediatric solid tumors. *Semin Pediatr Surg*. 2016;25(5):311–7. <https://doi.org/10.1053/j.sempedsurg.2016.09.001>.
- Abel RM, Brown J, Moreland B, Parikh D. Pulmonary metastasectomy for pediatric solid tumors. *Pediatr Surg Int*. 2004;20(8):630–2. <https://doi.org/10.1007/s00383-002-0927-8>.
- Tronc F, Conter C, Marec-Berard P, Bossard N, Remontet L, Orsini A, et al. Prognostic factors and long-term results of pulmonary metastasectomy for pediatric histologies. *Eur J Cardiothorac Surg*. 2008;34(6):1240–6. <https://doi.org/10.1016/j.ejcts.2008.07.039>.
- Oak S, Akhtar N, Viswanath N, Pathak R. Video-assisted thoracoscopic lung biopsy in children. *J Indian Assoc Pediatr Surg*. 2006;11(4):231. <https://doi.org/10.4103/0971-9261.29607>.
- Grundy PE, Green DM, Dirks AC, Berend AE, Breslow NE, Anderson JR, et al. Clinical significance of pulmonary nodules detected by CT and Not CXR in patients treated for favorable histology Wilms tumor on national Wilms tumor studies-4 and -5: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59(4):631–5. <https://doi.org/10.1002/pbc.24123>.
- Stefan DC, Stones DK. The South African Paediatric Tumour Registry – 25 years of activity. *S Afr Med J*. 2012;102(7):605–6. <https://doi.org/10.7196/SA MJ.5719>.
- Warmann SW, Furtwangler R, Blumenstock G, et al. Tumor biology influences the prognosis of nephroblastoma patients with primary pulmonary metastases: results from SIOP 93-01/GPOH and SIOP 2001/GPOH. *Ann Surg*. 2011;254(1):155–62. <https://doi.org/10.1097/SLA.0b013e318222015e>.
- Godzinski J. The current status of treatment of Wilms' tumor as per the SIOP trials. *J Indian Assoc Pediatr Surg*. 2015;20(1):16–20. <https://doi.org/10.4103/0971-9261.145439>.
- Irtan S, Ehrlich PF, Pritchard-Jones K. Wilms tumor: "State-of-the-art" update. *Semin Pediatr Surg*. 2016;25(5):250–6. <https://doi.org/10.1053/j.sempedsurg.2016.09.003>.
- Verschuur A, Van Tinteren H, Graf N, Bergeron C, Sandstedt B, de Kraker J. Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. *J Clin Oncol*. 2012;30(28):3533–9. <https://doi.org/10.1200/JCO.2011.35.8747>.
- McConnell PI, Feola P, Meyers RL. Methylene blue-stained autologous blood for needle localization and thoracoscopic resection of deep pulmonary nodules. *J Pediatr Surg*. 2002;37(12):1729–31. <https://doi.org/10.1053/jpsu.2002.36707>.
- Eichfeld U, Dietrich A, Ott R, Kloepfel R. Video-assisted thoracoscopic surgery for pulmonary nodules after computed tomography-guided marking with a spiral wire. *Ann Thorac Surg*. 2005;79(1):313–7. <https://doi.org/10.1016/j.athoracsur.2003.10.122>.
- McDaniel JD, Racadio JM, Patel MN, Johnson ND, Kukreja K. CT-guided localization of pulmonary nodules in children prior to video-assisted thoracoscopic surgical resection utilizing a combination of two previously described techniques. *Pediatr Radiol*. 2018;48:626–31.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen® journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)