Diagnosis and outcome of Primary Solid Thoracic Tumours in a high tuberculosis prevalent setting

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ABSTRACT

Background and aim
Primary solid thoracic neoplasms (PSTT) have a diverse pathological spectrum, varying prognosis and survival rates and are unusual in children. Early recognition, diagnosis and treatment is key to a good outcome. The aim was to describe the incidence, diagnostic challenges and outcome of PSTT, determine patient demographics, histological spectrum and treatment modalities.

Methodology
32 year retrospective review including all children under 16 years diagnosed with and treated for a thoracic mass at Tygerberg Children's Hospital between 1983 and 2015. Patients with pulmonary metastasis, benign pulmonary tumours and cystic lesions were excluded.

Results
We identified 59 patients, 22 PSST and 37 haematological malignancies (22 lymphoma, 15 leukaemia) that presented with a thoracic mass and were recognised, diagnosed and treated in a tertiary care hospital situated in a middle income country with a high prevalence of HIV and TB. We found the incidence of PSTT to be 0.09 per 100 000 children per year and the median age at presentation was 3.29 (IQR1.4 – 7.02) with a 55% female predominance. Presenting complaints and symptomatology are very non-specific and variable, ranging from cough (55%), tachypnoea (36%), mass (36%), chest pain (23%) and fever (23%). One patient was asymptomatic and none had haemoptysis. Diagnosis was delayed in 36% of cases due to incorrect initial diagnosis and treatment for tuberculosis (23%) and pneumonia (13%). In all cases the CXR suggested a pulmonary abnormality, however invasive testing was required to make an accurate diagnosis, aided by biopsy (68%), surgery (32%) and bronchoscopy (5%). The histological spectrum of PSTT included 6 cases of neuroblastoma (27%), 3 of rhabdomyosarcoma (13%), 3 ganglioneuroblastomas (13%), 2 each of Pleuropulmonary blastoma, Kaposi sarcoma and Ewing's sarcomas (9%) and 1 each of infantile fibrosarcoma, myoepithelioma, undifferentiated sarcoma and osteogenic sarcoma. The stage at diagnosis included 69% early and 31% advanced stage disease. Management included chemotherapy (82%), radiotherapy (23%) and surgery (64%). Overall survival was 64%. Outcome was better with surgical management (83%) compared to non-surgical management (57%).

Conclusion
In this first study reporting on PSTT from a middle income country, we demonstrated that there are numerous challenges in making the diagnosis, and patients are often misdiagnosed as TB or pneumonia. In spite of these challenges the outcome of children with PSTT remains comparable to children living in highly developed countries. Children with pneumonia and TB not responding to treatment, need to be referred for further evaluation to establish an underlying cause, which could include PSTT. These patients all presented with non-specific symptomatology, and diagnosis requires a high index of suspicion. All children with PSTT had abnormal, but not diagnostic chest X-rays and diagnosis was confirmed by invasive testing.

ABSTRAK

Agtergrond en doelstelling
Primêre soliede torakale tumors (PSTT) het ‘n diverse patologiese spektrum, groot variasie in prognose en uitkoms en is buitengewoon in kinders. Vroeë herkenning, diagnose en behandeling is die grondslag van ‘n goeie uitkoms. Die doel is om die insidensie, diagnostiese uitdagings en uitkoms van PSTT te beskryf, asook om meer spesifiek te kyk na die demografie, histologiese spektrum en behandeling van pasiënte.

Metodiek
Hierdie is ‘n retrospektiewe oorsig wat strek oor 32 jaar, vanaf 1983 to 2015, van alle kinders jonger as 16 jaar gediagnoseer en behandel vir ‘n torakale massa by Tygerberg Kinderhospitaal. Pasiënte met pulmonale metastase, nie-kwaadaardige pulmonale tumors en sistiese letsels is uitgesluit.

Resultate
Ons het 59 pasiënte geïdentifiseer wat met ‘n torakale massa gepresenteer het, 22 met PSTT en 37 met hematologiese maligniteite (22 limfoom en 15 leukemie). Hulle is almal gediagnoseer en behandel in ‘n tersiêre vlak hospitaal geleë in ‘n middelinkomste land met ‘n hoë voorkoms van HIV en TB. Die insidensie van PSTT is 0.09 per 100 000 kinders per jaar en die mediane ouderdom ten tye van presentasie was 3.29 (interkwartielvariasiewydte 1.4 – 7.02) met ‘n 55% vroulike oorheersing. Die klagtes en simptome waarmee pasiënte gepresenteer het was baie nie-spesifiek en het gestrek van hoes (55%), tagipnee (36%), ‘n massa (36%), borskaspyn (23%) en koors (23%). Een pasiënt was asimptomaties en geen pasiënte het met hemoptiese gepresenteer nie. Die diagnose is vertraag in 36% van gevalle as gevolg van ‘n oorspronklike verkeerde diagnose en behandeling van tuberkulose (23%) en pneumonie (13%). In alle gevalle het ‘n borskas x-straal ‘n pulmonale abnormaliteit suggereer, maar verdere indringende toetse was nodig om die korrekte diagnose te maak, met die hulp van biopsies (68%), chirurgie (32%) en brongoskopie (5%). Die histologiese spektrum van PSTT het 6 gevalle van neuroblastoom (27%), 3 elk van rhabdomiosarkoom en ganglioneuroblastoom (13%), 2 elk van pleuropulmonale blastoom, Kaposi sarkoom en Ewing’s sarkoom (9%) en 1 elk van infantiele fibrosarkoom, mioepitilioom, ongedifferensieerde sarkoom en osteogene sarkoom (5%) ingesluit. Ten tye van diagnose het 69% van gevalle gepresenteer met vroeë stadium en 31% met gevorde stadium van siekte. Behandeling het chemoterapie (82%), bestraling (23%) en chirurgie (64%) ingesluit en 64% van pasiënte het oorleef. Uitkoms was beter met chirurgiese behandeling (83%) teenoor nie-chirurgiese behandeling (57%).

Gevolgtrekking
In hierdie eerste studie wat verslag lewer oor PSTT in ‘n middelinkomste land, het ons verskeie diagnostiese uitdagings uitgewys en aangetoon dat pasiënte maklik verkeerd gediagnoseer kan word met TB of pneumonie. Ten spyte van hierdie uitdagings, is die uitkoms van pasiënte met PSTT vergelykbaar met die van Eerstewêreldlande. Kinders met pneumonie of TB wat nie kliniese verbetering toon op behandeling nie, moet verwys word vir verdere ondersoeke om ‘n onderliggende oorsaak te bepaal, waarvan PSTT ‘n moontlikheid is. Hierdie pasiënte het almal gepresenteer met nie-spesifieke simptome en ‘n hoë indeks van suspisie is nodig om die diagnose te maak. Al die pasiënte het ‘n abnormale, maar nie diagnostiese, borskas x-straal gehad en die diagnose is bevestig deur indringende toetse.

DEFINITIONS

For the purpose of the study, the following definitions will be used:

- Children: all children from birth to 15 years of age
- Sex: Male or female
- HBTR: Hospital Based Tumour Registry
- TBHCTR: Tygerberg Hospital Children's Tumour Registry. The registry was founded in 1983 and contains data on all patients diagnosed and treated in the Tygerberg Children's Hospital oncology unit
- TB: Tuberculosis
- AFB: Acid Fast Bacilli
- TB MC&S: Testing a specimen for microscopy (AFB) and culture to diagnose TB and sensitivity of the organism if present on culture
- TB Contact: known relative or neighbour with symptoms of pulmonary tuberculosis or that has been diagnosed with pulmonary tuberculosis (PTB) within the last year prior to presentation.
- TB workup: A patient that has been investigated for TB including one or more of the following investigations:
    - CXR
    - Mantoux
    - Gastric washings for Gene Xpert and TB MC&S
    - Sputum for gene Xpert and TB MC&S
    - Fine needle aspiration of a lymph node or mass sent for TB MC&S and on Gene Xpert
    - Bronchoalveolar lavage sent for TB MC&S and or gene Xpert
- Primary Solid Thoracic Tumour (PSTT): Any tumour with its primary lesion in the thoracic cavity including all pulmonary, large airway, soft tissue, bony and mediastinal masses
- Intrathoracic mass: includes all PSTT and haematological mediastinal masses
- Human Immunodeficiency Virus (HIV) status: Classified according to patients exposure to the Immunodeficiency virus/ Exposed, Unexposed, Negative, Infected
- ECM: Routine Health Information. The ECM system is an electronic database of patient records at Tygerberg Hospital, thus it can be used to access all medical records of the patient.
- PIN: Patient identifier number. The number that will be used on all electronic data sheets to identify participants
- CRF: Case report form, the hard copy form used to record data that was collected from the tumour registry and ECM.
- GCP: Good Clinical Practice
- CXR: Chest X-ray
- CT: Computed Tomography
- MRI: Magnetic Resonance Imaging
- PET: Positron Emission Tomography
- US: Ultrasound
- GCP: Good Clinical Practice
- NHLS: National Health Laboratory Service
- High WCC: High WCC was defined as being above the normal limit according to NHLS for age and gender

INTRODUCTION AND LITERATURE REVIEW

Childhood cancer is rare, comprising less than 1% of cases of malignant disease. It is the second most common cause of childhood death in western countries while in Africa it's not even ranked among the top 10 causes of death. Lung and endobronchial neoplasms are very unusual in the paediatric age group and comprises only 0,2% of all malignancies in children.[1,2] Metastases from non-pulmonary tumours are far more common than primary pulmonary neoplasms and in fact outnumber them 5:1. Most primary pulmonary tumours are malignant, with benign neoplasms accounting for approximately 30% of all primary pulmonary lesions in children. Compared to adults, the pathologic spectrum seen in children with primary pulmonary tumours is much more diverse. It includes endocrine tumours, mucoepidermoid tumours, adenocarcinoma, pleuropulmonary blastoma, squamous cell carcinoma and sarcomas.[1,2,3,4] There are various lesions most commonly found in a specific area of the mediastinum, as summarized in the table below. [5]

Anterior mediastinum	Mid-mediastinum	Posterior mediastinum
Teratoma	Lymphoma	Neurogenic tumour
Thymoma	Lymph node enlargement	Duplication of the foregut
Lymphoma	Aneurysm	Neuroenteric cysts
Morgagni Hernia	Congenital anomalies of the great vessels	Bronchogenic cysts
Lymphangioma		Oesophageal lesions
Pericardial cyst		Bochdalek hernia
Intrathoracic goitre		Mediastinal meningocoele

The prognosis and survival rates vary considerably depending on the type of tumour, the location and the stage at diagnosis. As a result of the rarity of these tumours, there is a lack of individual experience with the diagnosis, management and prognosis of these cases, as well as a lack of studies and articles relating to this topic. The true incidence of these tumours are not known.[6] These tumours can present at any age and there is no known etiological factor known that predisposes children and infants to develop these neoplasms. [1,2]

Major improvements in the diagnosis and treatment of childhood cancers over the last 50 years have resulted in a high cure rate of approximately 80% in developed countries. Sadly, the success rate is far lower in South Africa and other developing countries, mostly due to a delay in seeking medical attention or to a lack of access to health care.[7,8]

Hesseling et al conducted a retrospective study in 1995 to determine the disease profile and outcome of 492 children, under the age of 15 years, who were diagnosed with cancer and treated at Tygerberg Children's Hospital from 1983 – 1993[7]. The study found that the most common cancers were leukaemia (22.8%), brain tumours (20,5%), lymphoma (15,2%), nephroblastoma (10%), neuroblastoma (8,5%) and retinoblastoma (5,7%)[7]. Although Hospital Based Tumour Registries (HBTR's) have limitations with regards to the epidemiological information which they can generate, they may provide knowledge about the spectrum of pathology encountered and the outcome of treatment. In this paper where the data was collected from the Tygerberg Hospital Children's Tumour Registry (TBHCTR) there is no specific mention of primary pulmonary tumours. There is however frequency percentages for soft tissue sarcoma (4.7%), germ cell tumours (3,5%), carcinoma (2,8%) and other (0.8%) and primary thoracic / pulmonary tumours will form part of these groups.[7]

An article was published in the SAMJ in 2015 on the incidence of childhood cancer in South Africa. The article was the first report from the South African Children's Tumour Registry (SACTR) which covers the whole of South Africa and provided us with the minimal estimates of cancer incidence over a 21 year period, from 1987 – 2007, in our country. There were 11 699 cases included in the study, and the incidence rate was 45 per million. There was a marked difference in overall incidence rates among ethnic groups which also varied differed markedly among diagnostic groups. This study reported the most common childhood cancer in South Africa to be Leukemia, followed by Lymphoma, CNS

neoplasms, Neuroblastoma and Retinoblastoma. Primary solid thoracic neoplasms are nnot mentioned and will thus fall collectively under the "other" category. [8]

In an article published in 1993 from Canada, a highly industrialised country, a total of 383 cases of primary pulmonary tumours were reported and summarized, including the 9 cases from the above mentioned study[6]. Of these tumours, 92 (24%) were benign and 291 (76%) malignant[6]. Amongst the benign tumours, inflammatory pseudotumours (plasma cell granuloma) were the most common, accounting for 52,2% of the cases. Of the malignant tumours, most were bronchial adenomas which included carcinoid, mucoepidermoid carcinoma and adenoid cystic carcinoma.[6]

In Hancock et al's study, 9 patients (6 boys and 3 girls) were diagnosed with a primary endobronchial or pulmonary parenchymal neoplasm.[6] The average age of diagnosis was nine years and the presenting complaint was variable, ranging from cough and fever to weight loss and pain. Chest X-ray (CXR) also showed various radiological signs varying from atelectasis to an actual mass lesion being visualised. A Computed Tomography (CT) scan was performed in 8 patients and 5 of 6 endobronchial tumours were diagnosed with bronchoscopy and biopsy. The treatment in these cases were thoracotomy and pulmonary resection and laser resection was performed in 2 cases. The various histological diagnoses were bronchial carcinoid (n=3), bronchial mucoepidermoid carcinoma (n=1), inflammatory pseudotumour / plasma cell granuloma (bronchus n= 2 and lung n= 1), fibrosarcoma (n=1) and rhabdomyosarcoma (n=1). The only patient that required postoperative chemotherapy was the child with rhabdomyosarcoma; unfortunately, this child passed away.[6] At an average of 2.4 years post-treatment, 7 (78%) children were alive and well, one had local recurrence of the tumour and one child died.[6] There has always been controversy about the occurrence of malignant degeneration in congenital cystic malformations of the lung. In their review on primary pulmonary neoplasms in 1983, Hartman and Shochat reported that only 4% of pulmonary tumours were associated with congenital cystic maloformations.[9] In this study, however, they found that 4,3% of benign tumours and 8,6% of malignant tumours were associated with previously documented cystic malformations.[6] In summary, this study showed that pulmonary neoplasms are unusual and uncommon in the paediatric population, but early recognition, diagnosis and treatment is key to a good outcome. Sadly, due to the nonspecific nature of the presenting symptoms and signs, the diagnosis and surgical intervention is often delayed. In most cases the prognosis was excellent with complete surgical resection, however, malignancies other than bronchial adenoma are associated with significant mortality.[6,9,10]

There are multiple potential causes for a solid lung mass in a paediatric patient. A solid lung mass is most often caused by an underlying inflammatory, infective or reactive process.[11] Primary pulmonary and large airway neoplasms represent only 0.2% of all malignancies in the paediatric population and they are usually reported as isolated cases.[12] Due to this very low incidence, most health care workers have a very low index of suspicion with regards to these neoplasms, thus the correct diagnosis is often missed or delayed.[2] Early and accurate diagnosis is especially important in malignancies involving the lung and large airways, as a missed or delayed diagnosis can lead to tumour progression to an advanced stage before effective treatment is initiated, which adversely affects the prognosis.[2] Benign neoplasms of the lung and large airways must also be kept in mind as they may be very aggressive and may mimic malignant neoplasms.[2,11,12]

Most primary pulmonary neoplasms in the paediatric population are malignant. The two most common primary pulmonary malignancies in children are pleuropulmonary blastoma (PPB) and carcinoid tumour. There are other more rare malignant neoplasms of the lung such as small cell carcinoma, adenocarcinoma, squamous cell carcinoma and bronchial mucoepidermoid tumour. A pulmonary or airway neoplasm should be considered when a patient's chest radiograph findings and clinical presentation are incongruent, as well as when the chest radiograph findings are unusual or out of the ordinary.[11,13]

In an article published in 2009 on the incidence and outcome of malignant pulmonary tumours using registry data collect over 30 years 160 were identified.[1] From this data the authors calculated that the

incidence of malignant pulmonary tumours were 0.049 per 100 000 people /year and that the incidence had remained stable for the duration of the study. The median age of diagnosis was 16 years. Interestingly, most tumours arose in the lower lobe (37%), followed by the upper lobe (31.2%). With regards to histology, the most common tumours were endocrine tumours (51.6%), then sarcoma (11%) and mucoepidermoid tumour (9%). The overall survival was better in males than in females (>381 vs 288 months) and the 15 year survival was 65%. The tumours with the best outcome and survival were the endocrine and mucoepidermoid tumours. Small cell carcinoma had the worst outcome at a median survival of less than 5 months. The median survival rate for non-surgically treated patients were 14 months with a 10 year survival rate of 32%. This was markedly better in the surgical group which had a 10 year survival rate of 75%. Using multivariate analysis they established that non-surgical treatment and non-endocrine tumour histology are independent factors for predicting death. In this study they concluded that the incidence of paediatric lung cancer remained stable. It also suggested that non-surgical management and non-endocrine tumours are poor prognostic factors. .[1,14,15]

An article reporting on 90 years of experience with regards to primary lung tumours in children and adolescents.[16] was published in 2010. The purpose of this study was to look at the incidence of different primary lung tumours in children and the outcome thereof.[16] The aim of the study was also to contribute to the evidence base of the treatment of malignant pulmonary tumours. They included only primary non-haematological pulmonary tumours. A total of 40 patients were identified and included of which 23 were boys and 17 were girls. The mean age was 9.6 years (3 months to 19 years). A total of 14 different histopathological tumour types were identified, of which the most common types were carcinoid (n=8), inflammatory myofibroblastic (n=7) and pleuropulmonary blastoma (n=6). The mortality rate in this study was 17.5% and the treatment modalities included chemotherapy (23%) and radiotherapy (20%). The conclusion was that primary pulmonary tumours are rare and histopathologically diverse. It was also noted that patients very rarely had a history of exposure to predisposing factors. The mainstay of treatment was surgical resection and the use of adjuvant therapy was dependent on the size of the tumour as well as the histopathological diagnosis.[16]

In a short report on primary intrathoracic tumours in children, a review of 11 cases, published in 1993 and emphasis was placed on the fact that even though these tumours are rare, they need to be kept in mind when compiling a differential diagnosis, since the prognosis of any tumour depends on early detection and appropriate treatment.[5] This research was conducted at the Royal Bromptom National Heart and Lung Hospital in London United Kingdom (U.K.). Over a period of 8 years they saw approximately 4000 children with respiratory problems and of these, 11 were diagnosed with primary intrathoracic tumours. All congenital malformations, metastases and cysts were excluded. Of these 11 children, 6 were boys and 5 were girls. The initial presenting symptoms varied between local and generalised symptoms, however all 11 children had abnormal chest radiographs. CT scans were done in 8 children, which assisted in defining the extent of these lesions. Biopsies were performed in all 11 cases and 8 tumours were found to be malignant. These included 3 neurogenic tumours, 2 lymphomas, one undifferentiated sarcoma, one benign teratoma, an embryonal rhabdomyosarcoma, one squamous cell carcinoma, one plasma cell granuloma and one unclassified endobronchial malignancy. With regards to treatment, 10 patients had surgery and/or chemotherapy and one patient died. Chest radiographs were very useful and were abnormal in all cases. The lateral view was especially valuable in locating the position of the tumour in the mediastinum. To adequately establish the extent of the tumour / disease, further imaging is needed – this may include Magnetic Resonance Imaging (MRI) or Computer tomography of the chest (CT). To manage appropriately, however, accurate histology is required. Therefore it is necessary to obtain a biopsy – either by bronchoscopy, mediastinoscopy or thoracotomy, depending on the site of the lesion. In this series, only one case had a fatal outcome, and that was the patient with pulmonary carcinoma. Since there were significant delays in referral and diagnosis in many of the cases, it is very encouraging that only one patient passed away, as most thoracic tumours appear to have a good prognosis.[5]

STUDY JUSTIFICATION

1. Gaps in the Literature

As a result of the rarity of these tumours, there is a lack of individual experience with the diagnosis, management and prognosis of these cases, as well as a lack of studies and articles relating to this topic. We noted specifically that there has been no studies in South Africa documenting the incidence and other findings with regards to primary thoracic neoplasms, thus the true incidence of these tumours are not known. These tumours can present at any age and there is no known etiological factor known that predisposes children and infants to develop these neoplasms.

Thus we decided to collect data at our institution over the last 32 years to establish the incidence, most common histological type as well as the outcomes. There is thus no data to indicate whether the clinical presentation and stage at presentation differs in our setting compared to a first world setting, where some of the previous research was based. Since TB is so common in our setting, it is thought about much more frequently than intrathoracic masses and may delay diagnosis in our setting. Since our patients often present much later and diagnosis is often delayed, outcome may be poorer than in first world countries, which we will try and establish from our data. The prognosis and survival rates vary considerably depending on the type of tumour, the location and the stage of diagnosis, which we will look at in our setting.

2. Hypothesis

The hypothesis of this study is that primary solid thoracic tumours treated in a tertiary hospital in a region with a high prevalence of tuberculosis and HIV will have poor outcome due to a delay in diagnosis.

3. Problem statement

Intrathoracic masses, specifically primary solid thoracic tumours are rare in the paediatric population and can present in multiple non-specific presentations. This may lead to the treating physician having a very low index of suspicion to diagnose a pulmonary tumour. This study will review all cases of intrathoracic masses, including primary solid thoracic tumours as well as haematological malignancies presenting with mediastinal masses, at Tygerberg Children's hospital from 1983 to 2015. The main focus will be on the diagnosis and histological spectrum of the primary solid thoracic tumours. From this study we would like to determine the incidence of these tumours, the clinical presentations, diagnostic tests performed, reasons for delay in diagnosis, the treatment modalities offered as well as document the different histological diagnoses of the primary solid thoracic tumours.

4. Research question

What is the prevalence of primary solid thoracic tumours, what is the clinical presentation, the diagnostic tests required, the treatment and outcome of children managed with primary solid thoracic tumours at Tygerberg Children's Hospital?

5. Aim of the study

The primary aims of this study is to describe the incidence, diagnostic challenges and outcome of primary solid thoracic tumours at Tygerberg Children's Hospital from 1983 – 2015, looking specifically at the patient demographics of the study population, determining the different histological diagnoses and document the treatment modalities used in the management of these tumours as well as the outcome of all study participants.

6. Primary Outcomes

All cases of primary thoracic neoplasms diagnosed in children aged 0-15 years, recorded in the Tygerberg Hospital Children's Tumour Registry over a 32 year period will be reviewed and analysed to determine the difference in:

1. Demographics and presenting symptoms
2. Histological diagnoses
3. Treatment protocols, including chemotherapy, radiotherapy, surgery and any other modes of treatment.
4. Outcome
5. Relationship of outcome to stage at diagnosis

7. Secondary Outcomes

Secondary outcomes include

1. Concomitant treatment for tuberculosis in patient with pulmonary solid thoracic tumours.
2. Identify amount of patients initially incorrectly diagnosed and treated for another disease.
3. Identify factors which could lead to a delay in diagnosis of children presenting with primary solid thoracic tumours.
4. Compare the outcomes of PSTT to hematological malignancies
5. Compare the age at diagnosis of PSTT to that of hematological malignancies

MATERIALS AND METHODOLOGY

1. Study setting

The study was conducted in Tygerberg Children's hospital (TCH), a 319 bed hospital, situated in the Western Cape of South Africa. TCH is a tertiary care hospital with a dedicated paediatric oncology unit serving approximately half of the children in the Western Cape. The population of the Western Cape is estimated to be approximately 6 million people (2015) of which children younger than 14 years make up 35% of the population. Children with suspected childhood malignancies are referred to the paediatric oncology unit by surrounding regional hospitals or primary health care clinics. The hospital's drainage area includes the Northern Metro sub districts, Khayelitsha, Eastern Tygerberg, West Coast, Cape Winelands and Overberg rural districts. The paediatric oncology unit admits 469 children annually of which 56 had newly diagnosed paediatric malignancies (Annual report 2014-15). TCH is situated in a region with a high incidence of both tuberculosis and HIV.

2. Study Design

A retrospective descriptive analysis including all children with primary thoracic tumours diagnosed and treated at Tygerberg Children's Hospital over a 32 year period.

3. Study Population

The study population includes all children 0-15 years old diagnosed with a primary malignant thoracic mass, including pulmonary, large airway, bony, soft tissue and mediastinal tumours, admitted to the paediatric oncology and/or pulmonology units of Tygerberg Children's Hospital. The following children were excluded from the study:

- Children 16 years of age and older
- Pulmonary metastases from known tumours
- Benign pulmonary tumours
- Children with a pulmonary tumour where the chest is not the primary site of the tumour.
- Pulmonary cystic lesions
- Congenital pulmonary abnormalities

Children 16years and older were excluded from our study since they would have presented at the adult unit and we would thus have no way to adequately and accurately collect the data of these patients. Tygerberg children's hospital admits children up until the age of 12 years and with exception up unti the age of 16 years. Thus patients older than 16 years would not have been captured in our data. Haematological malignancies, acute leukaemia and lymphoma, presenting with a mediastinal mass or with a primary pulmonary lesion were included in data collection. The primary aim of collecting the data from haematological malignancies was to compare their data to those of children presenting with a primary solid thoracic tumours.

4. Data collection:

The patients included in the study were identified from the TCHTR. Clinical data of identified patients was then gleaned from the patient's medical records. The medical records were either available from the paediatric oncology ward or the Tygerberg Children's Hospital medical record department. The data collected was recorded on a case report form (CRF). The data included the demographic data of the patient which included the age, sex, ethnicity and the weight and height of the patient. The HIV status and the degree of immune suppression of the HIV infected children as indicated by the blood lymphocyte CD_4 count and the blood HIV viral load was recorded.
Regarding the manifestations of the malignant pulmonary lesion, the symptoms and signs at presentation, the results of the chest imaging investigations and the diagnostic investigations, including the histopathology of the causative lesion were recorded.

The modalities of the treatment as well as the outcome of the patient were recorded. The disease free interval and time to death subsequent to the diagnosis were calculated in months.
Complications of the treatment were collected including the development of tumour lysis and superior vena cava syndrome.

The tumour registry's records as well as Routine Health Information (ECM) system were used to collect quantitative data. Each patient's hospital number was used to access the hospital's electronic radiology database to obtain radiology reports and the National Health Laboratory System (NHLS) electronic database to obtain the histology and other laboratory reports. However since the study dates back to 1983, many of this data was not available electronically and thus it was obtained from hard copies and written reports recorded in the tumour registry. Each patient enrolled in the study was assigned a unique patient identifier number (PIN). A paper based case report form (CRF) was used to collect the data from the tumour registry and / or ECM. The PIN as well as patient identifiable data was used on the CRF. The collected data was then entered onto an electronic database on the principle investigator's computer, where only the PIN number, thus no identifiable data, was used.

The following data recorded on the case recording form:

- Age
    - At diagnosis
    - At cure / remission
    - At death
- Gender
- Ethnicity.
- Year of presentation
- Date last seen or date of death
- Weight in kilograms
- Height in centimetres
- HIV status
    - Exposed or unexposed
    - Tested: yes or no
    - If Infected
        - CD4 count
        - Viral Load
        - Treatment: Regimen and duration of treatment
- Any other confounding medical disorder
- Symptoms and signs at presentation
- Method of Diagnosis: clinical/radiological/histological
- Stage at diagnosis
- Radiological investigations performed
    - Chest X-ray
    - Ultrasound
    - CT Chest
    - PET CT
    - MRI
    - Bone scan
- Special Investigations: haematological/ microbiology/ tests to exclude tuberculosis
    - Specifically white blood cell count at diagnosis and the relation thereof to the presence of superior vena cava syndrome

  Histopathology of the primary solid thoracic tumour:
    - Histology
    - Stage at diagnosis
    - Site of Tumour
- Management
    - Was patient treated for TB

    - Surgical management: biopsy, de-bulking, resection, tracheostomy
    - Chemotherapy protocol
    - Radiotherapy
- Outcome:
    - alive or dead
    - Cause of death: treatment-related complication or disease-related
- Presence of superior vena cava syndrome at diagnosis
- Presence of tumour lysis syndrome at diagnosis
- Bone marrow aspiration – whether it was done and whether there was infiltration or not

5. Data management:

Paper CRF's were used to obtain and collect data. The data was transcribed from the CRF to an electronic data base (Excel) for analysis. The patient's name was not be included in the electronic data base, only the study number was used. All further analysis was done using the study number only.
All data was handled and managed according to Good Clinical Practice (GCP) requirements and ethical standards. The database was kept on the principle investigator's laptop, which was not accessible to any other person. The database was backed up on a monthly basis and the paper CRFs stored separately in a safe location. As per the South African Research regulations, the data will be stored on a departmental computer for 15 years, or 2 years after publication if successfully published. The research and data collection was performed by Dr C Smit and presented to a statistician for analysis.

6. Data analysis:

All data was presented to a statistician for further analysis and fed back to the researcher in the form of tables. The statistician presented the data as descriptive statics and comparisons were done using non-parametric statistics. Categorical variables were described using frequencies and percentages. Chi-square test was used for associations between categorical variables. The measures of associations depended on whether or not the data was normally distributed. Significance was set at the 5% level or p-value of less than 0.05.

7. Calculation of the proportion of newly diagnosed and the incidence of Primary solid thoracic tumours (PSTT)

The proportion of PSTT expressed on a percentage of newly diagnosed paediatric malignancies was calculated by acquiring the number of newly diagnosed paediatric malignancies form the Tygerberg Children's Hospital Tumour Registry. The number of cases of newly diagnosed paediatric malignancies per year was divided into the number of cases of newly diagnosed PSTT for that specific year and expressed as a proportion with 95th percent confidence intervals.

The incidence of PSTT was calculated as follows. The annual number of children in the Western Cape was obtained from the statistics on Children in South Africa website. As Tygerberg Children's Hospital serves approximately 50% of the children in the Western Cape, the number of children in the Western Cape was halved. This number per year was used to calculate the incidence of PSTT and expressed as the number of PSTT / 100 000 children / year [34]

8. Ethical Considerations

This protocol was submitted to the Stellenbosch University Health Research Ethics Committee for ethics approval (approval number S15/07/15). The following ethical principles were adhered to during the course of this study:

a. Social value:
Primary thoracic neoplasms are extremely rare and often missed or misdiagnosed. Through this study we hope to increase awareness of these rare neoplasms and assist with information to improve the index of suspicion to assist in earlier diagnosis and treatment, which will in turn improve the outcome of these children.

b. Respect for persons
Since this was a retrospective study, only retrospectively collected data was analysed and there was no direct contact between the researcher and patients.

c. Privacy and confidentiality
In order to ensure anonymity, every patient was assigned a PIN. The decoded list, linking the identifiable data to the unique PIN, was kept separate by the principle investigator and will not be available to anyone else to view or access.

All information and data collected was kept in a separate password protected file and this was only known to, and accessed by the researchers. There were no risks for parents, patients or medical personnel involved in the study.

d. Independent review
The protocol was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University, with ethics approval number S15/07/153

e. Informed consent
The HREC committee granted a waiver of individual informed consent since this was a retrospective study of routinely collected data that poses minimal risk to the patient, there was no contact between the researcher and the subjects and it did not adversely affect the right and welfare of the subjects in any way.

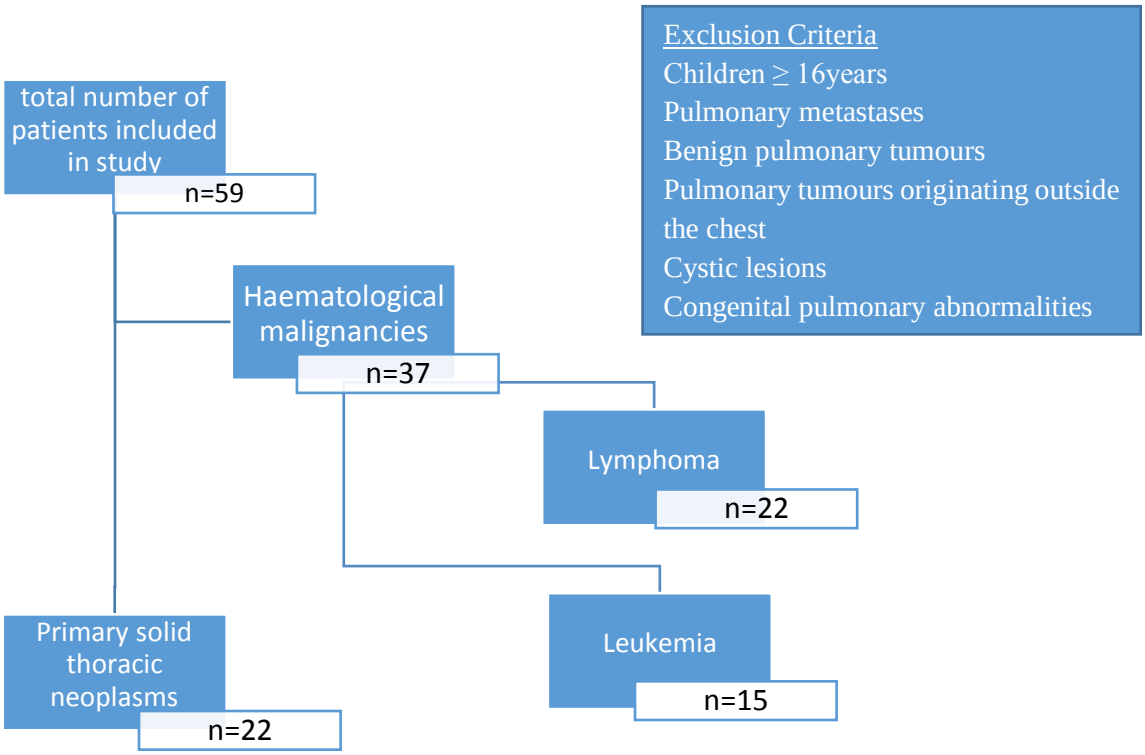
f. Collaborative partnerships
As the researcher I worked closely with my supervisors, advisors and stakeholders. Ethical principles, especially privacy and confidentiality, were strictly adhered to.

9. Strengths and Limitations

In this study, use was made of the Tygerberg Children's Hospital Tumour registry database. Since this data is routinely collected and stored, it is available and relatively complete. However, due to this being a retrospective study, some of the data was not available. This study is the first in Africa to report data regarding primary thoracic tumours in children and will contribute to a relatively small number of papers already published on this subject. The results of this study could potentially have an impact on the quality of patient care by highlighting the importance of having a high index of suspicion of pulmonary solid thoracic tumours, in order to obtain an early diagnosis and improve patient outcomes. It may also encourage health care workers to broaden their differential diagnoses to include cancer in a geographical area with a high burden of tuberculosis. However the data was collected only from the Tygerberg Children's Hospital Tumour registry, thus the results of this project will have a good internal validity but will have only limited external validity.

RESULTS

A total of 59 cases met the inclusion criteria. . Of those, 22 patients had primary solid malignant thoracic tumours (PSTT). The remaining 37 cases had a haematological malignancy which presented initially as a thoracic mass. Of the haematological malignancies 15 (40.5%) had T-cell Acute Lymphoblastic Leukaemia and 22 (59.5%) had Lymphoma (See flow chart Figure 1).



Demographic profile and baseline characteristics

Differences in demographic and baseline characteristics (see Table 1) yielded the following results: The median age for all the children (n=59) at presentation was 6.03 (IQR 2.74 – 9.23) years. For the primary solid thoracic malignancies the median age was 3.29 (IQR 1.24 – 7.62) years. The median age for the leukaemia group was 8.1 (IQR 4.15 – 11.27) years and 6.93 (IQR 1.02 – 11.61) years in the lymphoma group. Of interest was that the children presenting with PSTT were younger than those with a haematological malignancy, but this did not reach statistical significance. The median weight in kg at presentation overall was 18.5 (IQR 12.7 – 24.0). The median weight at presentation in the solid tumour group was markedly lower 13.6 (IQR 9.0 – 19.8) compared to 21.65 (IQR 15.0 – 25.4) in the lymphoma group and 20.9 (IQR 18.0 – 27.0) amongst leukaemia patients. The median weight z-score across all groups were -1 (IQR 0 to -2). The median height at presentation in cm was 114.0 (IQR 95.0 – 127.0) overall, 99.0 (IQR 83.0 – 115.0) among patients with solid tumours, 123.0 (IQR 83.0 – 115.0) in leukaemia patients and 116.0 (IQR 101.0 – 133.0) in patients with lymphoma. The median height z-score median was -1 (IQR 0 to -2) for all groups except the PSTT, which was median -1 (IQR +1 to -2) The lower median in weight and height in the haematological malignancy groups is in keeping with the younger age at diagnosis of the patients with primary solid thoracic tumours.

	Combined Groups (n=59)	Primary solid Thoracic tumours (n=22)	Leukemia group (n=15)	Lymphoma group (n=22)
Age in years	6.03 (IQR 2.74 – 9.23)	3.29 (IQR 1.24 – 7.62)	8.1 (IQR 4.15 –11.27)	6.93 (IQR 1.02 – 11.61)
Weight in kg	18.5 (IQR 12.7 – 24.0)	13.6 (IQR 9.0 – 19.8)	21.65 (IQR 15.0 – 25.4)	20.9 (IQR 18.0 – 27.0)
Weight z-score	-1 (IQR 0 - -2)	-1 (IQR 0 - -2)	-1 (IQR 0 - -2)	-1 (IQR 0 - -2)
Height in cm	114.0 (IQR 95.0 – 127.0)	99.0 (IQR 83.0 – 115.0)	123.0 (IQR 96.0 – 127.0)	116.0 (IQR 101.0 – 133.0)
Weight z-score	-1 (IQR 0 - -2)	-1 (IQR +1 - -2)	-1 (IQR 0 - -2)	-1 (IQR 0 - -2)

Table 1: Age distribution of study participants
Abbreviations: IQR: Inter quartile range, kg: kilograms, cm: centimetre

As described in table 3, the ethnic distribution of the patients presenting with a PSTT was 41% (n=9) Coloured, 36% (n=8) Caucasian and 23% (n=5) Black. These proportions did not significantly differ from those presenting with haematological malignancies. Of the children presenting with PSTT 55% (n=12) were female and 45% (n=10), which differs from the male predominance seen in children presenting with haematological malignancies. (Table 2)

Weight and height z-scores of all primary thoracic neoplasms									
		Overall		Solid tumours		Leukaemia		Lymphoma	
	z-score	N	% of total	n	% of total	N	% of total	n	% of total
Weight									
	>+3	1	1,7	1	4.5	0	0	0	0
	+3	1	1,7	0	0	1	6.6	0	0
	+2	2	3	1	4.5	0	0	1	4.5
	+1	2	3	1	4.5	1	6.6	0	0
	0	14	24	4	18	2	13	8	36
	-1	14	24	5	23	4	26	5	23
	-2	8	13	1	4.5	3	20	4	18
	-3	3	5	1	4.5	0	0	2	9
	<-3	4	7	3	13	0	0	1	4.5
	Unknown	10	17	5	23	4	26	1	4.5
Height									
	>+3	0	0	0	0	0	0	0	0
	+3	0	0	0	0	0	0	0	0
	+2	1	1,7	0	0	1	6.6	0	0
	+1	6	10	4	18	1	6.6	1	4.5
	0	13	22	3	13	3	20	7	32
	-1	11	18	4	18	4	26	3	13
	-2	6	10	0	0	1	6.6	5	23
	-3	7	12	2	9	1	6.6	4	18
	<-3	2	3	2	9	0	0	0	0
	Unknown	13	22	7	32	4	26	2	9

Table 2: All study patients' Heights and weights as per z-score

Clinical Presentation

The differences in clinical presentation varied remarkably amongst the patients. (Table3). The most common presenting symptom amongst patients with primary solid thoracic neoplasms was cough 55% (n=12), followed by tachypnoea in 36% (n=8). The next common feature were non-specific symptoms 32% (n=7), chest pain 23% (n=5) and fever 23% (n=5). Weight loss was a symptom in 18% (n=4) and 14% (n=3) presented with anorexia, dyspnoea and or a respiratory distress. Only 13% (n=2) presented with a lower respiratory tract infection. We found that only 2% (n=1) of our patients were asymptomatic and no patients included in this study presented with haemoptysis.

The presenting symptoms were similarly non-specific in children presenting with haematological malignancies. The most common presenting symptom amongst patients with leukemia was cough 53% (n=8), followed by other symptoms in 47% (n=7). The next common feature was fever and weight loss, both 33% (n=7), tachypnoea, anorexia, respiratory distress and a mass 27% (n=4). Dyspnoea and lower respiratory tract infection was a symptom in 13% (n=2) and 7% (n=1) presented with chest pain. We found that no patients included in this group presented with haemoptysis and none of them were asymptomatic. The most common clinical presenting symptom amongst the patients with lymphoma was also cough 45% (n=10), followed by other symptoms in 36% (n=8). A further 32% (n=7) of patients presented with fever and 27% (n=6) with respiratory distress or a mass. Tachypnoea and weight loss were the presenting symptoms in 23% (n=5) of patients, 14% (n=3) presented with anorexia, 9% (n=2) with dyspnoea and 5% (n=1) with chest pain. No patients in this group presented with a lower respiratory tract infection, and none were asymptomatic or had haemoptysis.

Demographics and clinical characteristics of all primary thoracic neoplasms									
		Overall		Solid tumours		Leukaemia		Lymphoma	
		n	% of total	n	% of total	n	% of total	n	% of total
Gender									
	Male	35	59	10	45	11	73	14	64
	Female	24	41	12	55	4	27	8	36
Race									
	White	16	27	8	36	5	33	3	14
	Black	13	22	5	23	2	13	6	27
	Coloured	30	51	9	41	8	53	13	59
Age									
	< 1yr	5	8	5	23	0	23	0	0
	1 - 5yr	21	36	9	40	6	40	6	27
	5 - 10 yr	20	34	5	23	5	23	10	45
	10 - 15 yr	13	22	3	14	4	14	6	27
HIV									
	HIV infected	4	7	2	9	0	0	2	9
	HIV negative	12	20	4	18	2	13	6	27
	HIV status unknown	43	72	16	72	13	87	16	64
TB									
	TB	2	3	2	9	0	0	0	0
	No TB	50	85	17	77	14	93	19	86
	Unknown	7	12	4	14	1	7	3	14
Symptoms									
	Cough	30	51	12	55	8	53	10	45
	Tachypnoea	17	29	8	36	4	27	5	23
	Mass	18	31	8	36	4	27	6	27
	Other	22	37	7	32	7	47	8	36
	Chest pain	7	12	5	23	1	7	1	5
	Fever	17	29	5	23	5	33	7	32
	Weight loss	14	24	4	18	5	33	5	23
	Anorexia	10	17	3	14	4	27	3	14
	Respiratory distress	13	22	3	14	4	27	6	27
	Dyspnoea	7	12	3	14	2	13	2	9
	Respiratory tract infection	4	7	2	9	2	13	0	0
	Asymptomatic	1	2	1	5	0	0	0	0
	Haemoptysis	0	0	0	0	0	0	0	0

Table 3: Demographics and clinical characteristics of all primary thoracic neoplasms
Abbreviations: HIV: Human Immunodeficiency Virus; TB: Tuberculosis, yr: years

Associated Clinical Syndromes

Demographics and clinical characteristics of all primary thoracic neoplasms								
		Overall		Solid tumours		Leukaemia		Lymphoma	
		n	% of total	n	% of total	n	% of total	n	% of total
Gender									
	Male	35	59	10	45	11	73	14	64
	Female	24	41	12	55	4	27	8	36
Race									
	White	16	27	8	36	5	33	3	14
	Black	13	22	5	23	2	13	6	27
	Coloured	30	51	9	41	8	53	13	59
Age									
	< 1yr	5	8	5	23	0	23	0	0
	1 - 5yr	21	36	9	40	6	40	6	27
	5 - 10 yr	20	34	5	23	5	23	10	45
	10 - 15 yr	13	22	3	14	4	14	6	27
HIV									
	HIV infected	4	7	2	9	0	0	2	9
	HIV negative	12	20	4	18	2	13	6	27
	HIV status unknown	43	72	16	72	13	87	16	64
TB									
	TB	2	3	2	9	0	0	0	0
	No TB	50	85	17	77	14	93	19	86
	Unknown	7	12	4	14	1	7	3	14
Symptoms									
	Cough	30	51	12	55	8	53	10	45
	Tachypnoea	17	29	8	36	4	27	5	23
	Mass	18	31	8	36	4	27	6	27
	Other	22	37	7	32	7	47	8	36
	Chest pain	7	12	5	23	1	7	1	5
	Fever	17	29	5	23	5	33	7	32
	Weight loss	14	24	4	18	5	33	5	23
	Anorexia	10	17	3	14	4	27	3	14
	Respiratory distress	13	22	3	14	4	27	6	27
	Dyspnoea	7	12	3	14	2	13	2	9
	Respiratory tract infection	4	7	2	9	2	13	0	0
	Asymptomatic	1	2	1	5	0	0	0	0
	Haemoptysis	0	0	0	0	0	0	0	0

Table 3 illustrates the findings with regards to HIV status. Unfortunately the status was not documented in many of the study participants as they were not tested for HIV, especially those that were diagnosed and managed in the 1980's and early 1990's. Amongst patients with primary malignant thoracic neoplasms 72% (n=16) had an unknown HIV status, 18% (n=4) were HIV negative and 9% (n=2) were confirmed HIV positive. The 2 HIV positive patients both had Kaposi sarcoma, which is an HIV defining illness. The remaining 2 HIV positive patients had lymphoma and no patients with leukemia had HIV.

We specifically looked at associated / concomitant Tuberculosis (TB) in our study patients, which is illustrated in table 3. We found that in the PSTT group 77% (n=17) had a negative TB workup, in 14% (n=3) the outcome of TB tests were not recorded. In 2 cases children with PSTT were treated for pulmonary TB of which only one case was proven to be TB. Amongst the patients with haematological malignancies, no patients had confirmed TB, the outcome of TB investigations was not recorded in 7% (n=1) of leukemia and 14% (n=3) of lymphoma patients.

Initial incorrect diagnosis and management as either Tuberculosis or Lower respiratory tract infection

	Overall (n=59)		Solid tumours (n=22)		Leukaemia (n=15)		Lymphoma (n=22)	
	n	% of total	n	% of total	N	% of total	n	% of total
Correct diagnosis	41	69	14	64	12	80	15	68
Incorrect diagnosis	18	31	8	36	3	20	7	32
TB	11	19	5	23	0	0	6	27
LRTI	7	11	3	13	3	20	1	5

Table 4: initial diagnosis and management
Abbreviations: TB: Tuberculosis, LRTI: Lower Respiratory Tract Infection

We looked specifically at the PSTT group to establish what percentage of our patients were initially incorrectly diagnosed and treated as either having pulmonary tuberculosis or a lower respiratory tract infection. Out of the 22 patients, 64% (n=14) had the correct diagnosis made at first presentation. In 36% (n=8) cases the patients were initially incorrectly diagnosed and treated. Tuberculosis was diagnosed in 23% (n=5) and 13% (n=3) was treated for a lower respiratory tract infection as shown in table 4 above. Amongst lymphoma patients 27% (n=6) was initially misdiagnosed as TB and 5% (n=1) as pneumonia. It is clear that both patients who presented with either PSTT or mediastinal lymphoma were incorrectly treated for tuberculosis while this did not occur in with mediastinal leukaemia.

We looked for the presence of tumour lysis syndrome and superior vena cava syndrome, however as expected it was restricted to the leukaemia and lymphoma groups and none of the patients with primary solid thoracic tumours presented with these clinical syndromes, as indicated in table 5. This table also includes the results of the bone marrow aspiration and trephine bone marrow biopsies. In the primary solid thoracic tumour group 64% (n=14) of patients had a normal bone marrow aspiration, a bone marrow was not done in 18% (n=14) of patients and in 18% (n=4) of our patients that information could not be found. This data suggest that in children with a PSTT a bone marrow aspiration and trephine bone marrow biopsy did not contribute to the diagnosis. In haematological malignancies a bone marrow aspiration is of much more value and was diagnostic in 100% (n=15) of leukemia patients, and assisted with the diagnosis in 27% (n=6) of patients with lymphoma.

Presence of tumour lysis syndrome, superior vena cava syndrome, bone marrow infiltration and White blood cell count at diagnosis								
	Overall		Solid tumours		Leukaemia		Lymphoma	
	n	% of total	n	% of total	n	% of total	n	% of total
Tumour lysis syndrome								
yes	9	15	0	0	6	40	3	14
no	41	69	21	95	8	53	12	55
unknown	9	15	1	5	1	7	7	32
bone marrow infiltration								
yes	21	36	0	0	15	100	6	27
no	28	47	14	64	0	0	14	64
not done	4	7	4	18	0	0	0	0
unknown	6	10	4	18	0	0	2	9
superior vena cava syndrome								
yes	3	5	0	0	2	14	1	5
no	56	95	22	100	13	86	21	95
unknown	0	0	0	0	0	0	0	0
WCC at diagnosis								
High	28	47	7	32	11	73	10	45
Low	3	5	2	9	0	0	1	5
Normal	17	29	5	23	4	27	8	36
Unknown	11	19	8	36	0	0	3	14

Table 5: Presence of tumour lysis syndrome, superior vena cava syndrome, bone marrow infiltration and White blood cell count at diagnosis
Abbreviations: WCC: White cell count
High WCC was defined as: Being above the normal limit according to NHLS for age and gender

Diagnosis

We looked at the precise methodology used to make the diagnosis and these results are summarized below in table 6. Radiology proved to be the most frequently used special investigation and was used to assist in the diagnosis in 97% (n=57) of patients. Biopsies assisted in the diagnosis in 83% (n=49) of patients, surgery in 14% (n=8) and bronchoscopy in 8% (n=5) of the cases. In the primary solid thoracic tumour group 95% (n=21) of patients were diagnosed radiologically, assisted by biopsies in 68% (n=15), surgery in 32% (n=7) and bronchoscopy in 5% (n=1).

Looking at the specific radiological tools used to make the diagnosis in the primary solid thoracic tumour group, 100% (n=22) of patients had a CXR, 64% (n=14) had a CT chest, 45% (n=10) a chest US, 18% (n=4) a MRI chest, 15% (n=9) a bone scan and no patients had a PET scan. When compared to the patients with haematological malignancies there was a trend to use chest ultrasound (45%), radio-isotope bone scans (36%) and MRI scan of the chest (18%) more frequently. Comparing frequency of diagnostic investigations across groups indicated that MRI ($p = 0.03$), chest ultrasound ($p = 0.029$) and bone scan ($p = 0.005$) were used more frequently in PSTT than in haematological malignancies.

Diagnostic investigations used in the diagnosis										
		Overall		Primary solid thoracic tumours		Haematological malignancies Leukemia		Lymphoma		P value
		n	% of Total	n	% of Total	n	% of Total	n	% of Total	
Radiologically		57	97	21	95	15	100	21	95	
	CXR	57	97	22	100	15	100	20	91	>0.05
	CT chest	31	53	14	64	3	20	14	64	>0.05
	US	17	29	10	45	1	7	6	27	0.029
	Bone scan	9	15	8	36	0	0	1	5	0.005
	MRI chest	6	10	4	18	1	7	1	5	0.03
	PET scan	3	5	0	0	0	0	3	14	>0.05
Biopsy		49	83	14	64	15	100	19	86	>0.05
Surgery		8	14	7	31	0	0	1	5	>0.05
Bronchoscopy		5	8	1	5	7	7	3	14	>0.05

Table 6: Diagnostic investigations used in the diagnosis
Abbreviations: CXR: chest x-ray, CT: Computed Tomography, US: Ultrasound, MRI: Magnetic Resonance Imaging, PET: Positron Emission Tomography

CXR Findings

The CXR descriptions of the primary solid thoracic tumour group are presented in table 7 below.

Histology	Pt nr	CXR abnormalities
Neuroblastoma	1	Large extra pulmonary soft tissue mass posteriorly with calcification, not involving the spine
	2	Posterior mediastinal mass
	3	Large homogenous mass left superior mediastinal region with compression of left main bronchus
	4	Right posterior mediastinal mass
	5	Solid tumour in the upper 2/3 of the left chest with erosion of the 2nd, 3rd, 4th and 5th ribs, possibly extending bilaterally across the mediastinum
	6	Posterior mediastinal mass
Rhabdomyosarcoma	7	Solid mass lesion in the right lung with mediastinal shift and a small pleural effusion
	8	Right sided pleural effusion and mediastinal mass with mediastinal shift to the left with anterior and posterior compression of the trachea and right main bronchus
	9	Soft tissue mass, lung fields clear
Ganglioneuroblastoma	10	Massive tumour in the right thorax with erosion of the 5th rib
	11	Large tumour in right hemithorax
	12	Right sided posterior mediastinal mass with mediastinal shift to the left
Pleuropulmonary blastoma	13	Mass lesion in the right lung with a pleural effusion
	14	Left sided pleural effusion with left sided cystic tumour
Kaposi Sarcoma	15	Right par tracheal soft tissue mass
	16	Left pneumothorax, ARDS picture, lymphadenopathy
Ewing's sarcoma	17	Mass in the left lung, mediastinum shifted to the right with splaying of the ribs on the left
	18	Left chest wall mass with mediastinal shift to the right and bony destruction of the 8th rib
Infantile Fibrosarcoma	19	Soft Tissue mass in the left thoracic wall extending in between the ribs, but no pulmonary involvement
Myoepithelioma	20	Soft tissue mass, lung fields clear
Undifferentiated sarcoma	21	Mass in left lung involving left upper and lower lobe and lingula with compression of left main bronchus
Osteogenic sarcoma	22	Lesion on the 9th rib on the left as well as a paravertebral lesion

Table 7: Description of CXR abnormalities of Primary solid thoracic tumours
Abbreviations: CXR: chest x-ray

Histological Subtypes

The most common primary solid thoracic tumour that we encountered was neuroblastoma 37% (n=6). There were 13% (n=3) respectively of rhabdomyosarcoma and ganglioneuroblastoma. Nine percent (n=2) of patients each of Kaposi's sarcoma, pleuropulmonary blastoma and Ewing's sarcoma respectively. Myoepithelioma was present in 5% (n=1) of patients, as was infantile fibrosarcoma, undifferentiated sarcoma and osteogenic sarcoma. Of these primary solid thoracic tumours, 36% (n=8) were mediastinal masses, 32% (n=7) were pulmonary tumours, 14% (n=4) were found in the thoracic wall and 9% (n=2) had a rib as primary site, 5% (n=1). In 1 (5%) case the location was paratracheal and 5% (n=1) was located in the thoracic spine. Early disease was present in 55% (n=12) of patients and 27% (n=6) presented with advanced disease. Data on the staging of disease at diagnosis could not be found in 18% (n=4) of patients in the primary thoracic malignancy group. (Table 8)

Summary of histology, management and outcome of solid primary thoracic tumours		
	n	% of total
Histology		
Neuroblastoma	6	27
Rhabdomyosarcoma	3	13
Ganglioneuroblastoma	3	13
Pleuropulmonary blastoma	2	9
Kaposi's sarcoma	2	9
Ewing's sarcoma	2	9
Infantile fibrosarcoma	1	5
Myoepithelioma	1	5
Undifferentiated sarcoma	1	5
Osteogenic sarcoma	1	5
Site		
Mediastinum	8	36
Pulmonary	7	32
Thoracic wall	3	14
Rib	2	9
Para tracheal	1	5
Thoracic spine	1	5
Stage		
stage 1	4	18
stage 2	8	36
stage 3	4	18
stage 4	2	9
unknown	4	18

Table 8: Histology, site and stage of primary solid thoracic tumours

Table 9 shows the data of the 37% (n=22) of our patients that presented with lymphoma. Histologically they were subdivided into 73% (n=16) non-Hodgkin's Lymphoma and 27% (n=6) Hodgkin's lymphoma. Amongst the patients with non-Hodgkin's Lymphoma 55% (n=12) had T-cell lymphoblastic lymphoma, 9% (n=2) had large cell anaplastic lymphoma, 4,5% (n=1) patients had Burkitt Lymphoma and 4,5% (n=1) had diffuse large B-cell lymphoma. In the Hodgkin's Lymphoma group the histology was subdivided into the following histological types with each being present in 9% (n=2) of cases: nodular sclerosing, mixed cellularity and lymphocyte rich Hodgkin's lymphoma. The

most common tumour site in 86% (n=19) was mediastinal. However in 5% (n=1) of patients the primary tumour site was thoracic, 5% (n=1) was found on the chest wall and pleura respectively. The majority of patients in this group, 77% (n=17), presented with advanced disease of which 64% (n=14) had stage 3 disease at diagnosis, 13% (n=3) stage 4 disease and in 5% (n=1) stage at diagnosis was not known. Overall 18% (n=4) of patients presented with what we described as early disease of which 5% (n=1) had stage 1 disease and 13% (n=3) had stage 2 disease at diagnosis.

Summary of histology, site and stage of diagnosis of lymphoma group			
		n	% of total
Non-Hodgkin's Lymphoma		16	73
	T-cell Lymphoblastic	12	75
	Large cell anaplastic	2	13
	Burkitt	1	6
	Diffuse large B-cell	1	6
Hodgkin's Lymphoma		6	27
	Nodular Sclerosing	2	33
	Mixed Cellularity	2	33
	Lymphocyte Rich	2	33
Site			
	Mediastinum	19	86
	Thoracic	1	5
	Thoracic wall	1	5
	Pleura	1	5
Stage			
	stage 1	1	5
	stage 2	3	14
	stage 3	14	64
	stage 4	3	14
	Unknown	1	5

Table 9: Lymphoma: histology, site and stage at diagnosis of the lymphoma group patients

Management

Table 10 below summarizes the various treatment modalities used in our study participants. Amongst the primary solid thoracic tumour group 64% (n=14) had surgery, 82% (n=18) had chemotherapy and 23% (n=5) had radiation as part of their management protocol. All patients with haematological malignancies had chemotherapy, which was the sole management in leukemia. Amongst patients with lymphoma 9% (n=2) had surgery and 14% (n=3) had radiation as part of management.

Combined therapy was received in 60% (n=13) of patients with PSTT, 41% (n=9) receiving the combination of chemotherapy and surgery, 14% (n=3) receiving chemotherapy, radiotherapy and surgery and only 5% (n-1) receiving the combination of chemotherapy and radiotherapy, as indicated in table 11. A single treatment modality was used in 27% (n=6) of patients, 23% (n=5) receiving only chemotherapy and only 5% (n=1) receiving surgery alone. In our study there were 13% (n=3) patients that did not receive any treatment at all. 2 of these patients underwent spontaneous regression and the other died very soon after admission and diagnosis, before any treatment could be started.

Site, management and outcome of all primary thoracic neoplasms								
		Overall		Solid tumours		Leukaemia		Lymphoma	
		n	% of total	n	% of total	n	% of total	n	% of total
Site									
	Mediastinum	27	45	8	36	0	0	19	86
	Pulmonary	7	12	7	32	0	0	0	0
	Thoracic wall	4	7	3	14	0	0	1	5
	Rib	2	3	2	9	0	0	0	0
	Para tracheal	1	2	1	5	0	0	0	0
	Thoracic spine	1	2	1	5	0	0	0	0
	Bone marrow	15	25	0	0	15	100	0	0
	Pleura	0	0	0	0	0	0	1	5
Surgery									
	Surgery	16	27	14	64	0	0	2	9
	No surgery	43	73	8	36	15	100	20	91
Chemotherapy									
	Chemotherapy	55	93	18	82	15	100	22	100
	No chemotherapy	3	5	3	14	0	0	0	0
	Unknown	1	2	1	5	0	0	0	0
Radiation									
	Radiation	15	25	5	23	7	47	3	14
	No Radiation	43	73	16	21	8	53	19	86
	Unknown	1	2	1	5	0	0	0	0
Outcome									
	Alive	36	61	14	64	9	60	13	59
	Demised	17	29	5	23	6	40	6	27
	Unknown	6	10	3	14	0	0	3	14
Relapse									
	Yes	4	14	2	9	3	20	3	14
	No	45	78	17	77	12	80	6	27
	Unknown	5	9	3	14	0	0	3	14
Cause of death									
	Disease related	12	71	4	80	5	83	3	50
	Treatment related	5	29	1	20	1	17	3	50

Table 10: Site, management and outcome of all primary thoracic neoplasms

	PSTT number (n=22)	PSTT percentage
Single treatment modality	6	27
Chemotherapy only	5	23
Surgery only	1	5
Radiotherapy only	0	0
No treatment received	3	13
Combined therapy	13	60
Chemotherapy and surgery	9	41
Chemotherapy and radiation	1	5
Chemotherapy, surgery and radiation	3	14

Table 11: Various treatment modalities and combinations of treatment received

Previous data showed a better outcome and higher survival rate with surgery compared to patients that did not undergo surgery. Since surgery is the mainstay of treatment in solid tumours we compared the outcome of patients that had surgery to those that did not. In the primary solid thoracic tumour group (n=22), 64% (n=14) had surgery as part of their management and 36% (n=8) did not. Unfortunately we did not know the outcome of 3 patients, thus they were excluded, which left us with n=19 patients. Of these patients 63% (n=12) had surgical management and 37% (n=7) did not have surgery as part of their management. 83% (n=10) of patients that had surgery survived and 17% (n=2) demised compared with the non-surgical group where 57% (n=4) survived and 43% (n=3) died, as indicated in table 12. However this difference was not statistically significant (p=0.21).

Primary solid thoracic neoplasm	Total number (n=19)		Surgery (n=12)		No Surgery (n=7)		Pvalue
	N	% of total	n	% of total	n	% of total	
Alive	14	74	10	83	4	57	0.21
Demised	5	26	2	17	3	43	

Table 12: Comparison of outcome in PSTT patients looking at surgical management versus no surgical management

Outcome

Information regarding the outcomes, relapse rate and cause of death in the study population can be seen below in Table 13. Of the 22 patients with primary thoracic neoplasms 64% (n=14) survived, 23% (n=5) demised and data was not available on 14% (n=3) of patients. In the primary solid thoracic tumour group 77% (n=17) were cured, in 14% (n=13) we did not have data on outcome and 9% (n=2) relapsed. Of the patients that died from PSTT 80% (n=4) died of disease related causes while 20% (n=1) died from a treatment related cause. The other 77% (n=17) of patients were either alive or data was not available. Amongst the leukemia group 60% (n=9) survived and 40% (n=6) demised, 83% (n=5) due to disease related and 17% (n=1) due to treatment related complications. A total of 59% (n=13) of patients with lymphoma survived, 27% (n=6) demised (50% (n=3) each of tumour related and disease related complications) and outcome was unknown in 14% (n=3). Comparing outcome between the primary solid thoracic malignancies and the other tumours, survival was not statistically significant (p=0.5).

Commenting on stage at diagnosis was difficult, since all PSTT do not have a classic staging system due to rarity of disease, some are classified as stage 1 to 4, others just as localized or advanced. Due to that reason we have commented on stage as being either early or advanced. When taking the stage of disease into account it was found that amongst 22 patients with primary solid thoracic tumours, 55% (n=12) were diagnosed with early stage disease. Of these patients 75% (n=9) survived and 16% (n=2) demised and in 8% (n=1) the outcome was not known. In comparison 27% (n=6) of patients were diagnosed with an advanced stage of disease, of these 50% (n=3) survived, 33% (n=2) passed away,

16.5% of patients (n=1) had no documented outcome and in 18% (n=4) of patients the initial stage at diagnosis was not known. This data is documented in table 14 below.

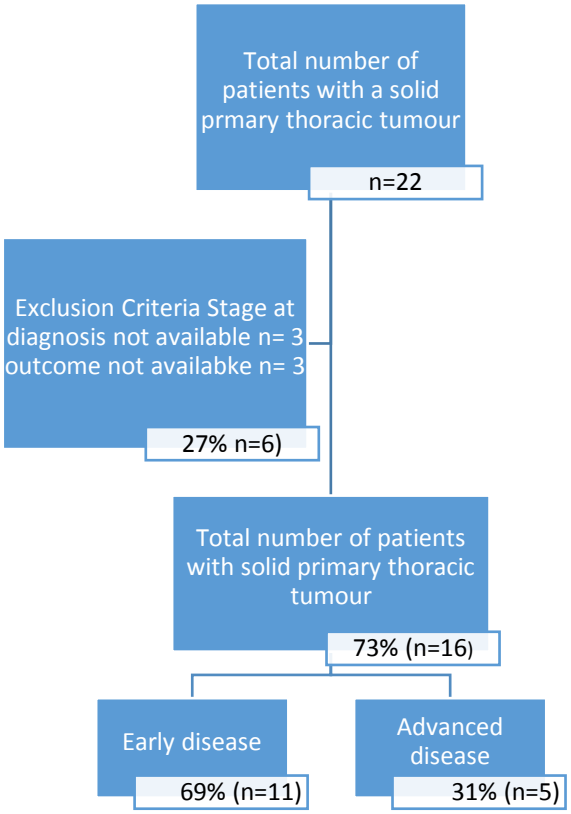
Site, management and outcome of all primary thoracic neoplasms								
		Overall		Solid tumours		Leukaemia		Lymphoma	
		n	% of total	n	% of total	n	% of total	n	% of total
Site									
	Mediastinum	27	45	8	36	0	0	19	86
	Pulmonary	7	12	7	32	0	0	0	0
	Thoracic wall	4	7	3	14	0	0	1	5
	Rib	2	3	2	9	0	0	0	0
	Para tracheal	1	2	1	5	0	0	0	0
	Thoracic spine	1	2	1	5	0	0	0	0
	Bone marrow	15	25	0	0	15	100	0	0
	Pleura	0	0	0	0	0	0	1	5
Surgery									
	Surgery	16	27	14	64	0	0	2	9
	No surgery	43	73	8	36	15	100	20	91
Chemotherapy									
	Chemotherapy	55	93	18	82	15	100	22	100
	No chemotherapy	3	5	3	14	0	0	0	0
	Unknown	1	2	1	5	0	0	0	0
Radiation									
	Radiation	15	25	5	23	7	47	3	14
	No Radiation	43	73	16	21	8	53	19	86
	Unknown	1	2	1	5	0	0	0	0
Outcome									
	Alive	36	61	14	64	9	60	13	59
	Demised	17	29	5	23	6	40	6	27
	Unknown	6	10	3	14	0	0	3	14
Relapse									
	Yes	4	14	2	9	3	20	3	14
	No	45	78	17	77	12	80	6	27
	Unknown	5	9	3	14	0	0	3	14
Cause of death									
	Disease related	12	71	4	80	5	83	3	50
	Treatment related	5	29	1	20	1	17	3	50

Table 13: Site, management and outcome of primary malignant thoracic neoplasms

Stage at diagnosis of primary thoracic neoplasm	Total number (n=22)		Alive (n=14)		Demised (n=5)		Unknown (n=3)	
	n	% of total	N	% of total	N	% of total	n	% of total
Early disease	12	55	9	75	2	16	1	8
Advanced disease	6	27	3	50	2	33	1	16.5
Unknown stage	4	18	2	50	1	25	1	25

Table 14: Outcome of primary thoracic neoplasms according to stage

We then excluded all patients with unknown variables being either stage at diagnosis or outcome and reviewed the data again looking specifically at outcomes.



After excluding patients with missing data, we included 16 patients in the primary solid thoracic tumour group and compared outcomes with stage at diagnosis. 69% (n=11) of patients were diagnosed with early stage disease amongst which 82% (n=9) survived and 18% (n=2) passed away. A further 31% (n=5) presented with advanced disease, 60% (n=3) of these patients survived and 40% (n=2) demised. However this was not statistically significant (p=0.35) (See Table 15.)

Stage at diagnosis of primary thoracic neoplasm	Total number (n=16)		Alive (n=12)		Demised (n=4)		P value
	n	% of total	N	% of total	n	% of total	
Early disease	11	69	9	82	2	18	
Advanced disease	5	31	3	60	2	40	0.35

Table 15: Outcome of primary thoracic neoplasms according to stage, excluding those with unknown data

Comparison between the patients with Primary Solid Thoracic Tumours and those with Haematological malignancies:

When comparing various aspects between the PSST (primary solid thoracic tumours) and Haematological malignancies that presented with mediastinal masses, which include Leukemia (n=15) and lymphoma (n=22), the following was observed. The age at presentation was much younger in the PSTT group, 3.29 (IQR 1.24 – 7.62) compared to the haematological malignancies. The median age of presentation in leukemia was 8.1 (IQR 4.15 – 11.27) and in lymphoma it was 6.93 (IQR 1.02 – 11.61). The median weight was similar in all groups, -1 (IQR 0 to -2).

The clinical presentation amongst all groups was very nonspecific and varied widely, however cough was the most common presenting symptom across all groups and interestingly no patients in this study presented with haemoptysis. A total of 97% (n=57) patients had a CXR at diagnosis. The CXR assisted in, but did not confirm the diagnosis in any cases. MRI (p = 0.03), chest ultrasound (p = 0.029) and bone scan (p = 0.005) were used more frequently in PSTT than in haematological malignancies.

Initial incorrect diagnosis was a problem amongst all groups with 31% (n=18) of patients overall being incorrectly diagnosed at presentation, 19% (11) incorrectly diagnosed as having tuberculosis, which included 23% (n=5) of patients with primary solid thoracic tumours compared to 27% (n=6) of patients with lymphoma. Furthermore 12% (n=7) of patients were initially incorrectly treated for a lower respiratory tract infection. 13% (n=3) of those with PSTT, 20% (n=3) of those with leukemia and 5% (n=1) of those with lymphoma.

In patients diagnosed with early stage lymphoma, the prognosis is excellent, as reflected by the 100% survival in patients presenting with stage 1 or 2 lymphoma. In primary solid thoracic tumours however, the outcome is better if diagnosed earlier, but not as significantly as in the lymphoma group.

Proportion of childhood cancers and prevalence of PSTT

There were 1577 new malignancies diagnosed over the period from 1983 – 2015. The average number of new cases of malignancies diagnosed per year was 47.8 (95^{th} CI 44.6 – 50.9). The average number of cases of PSTT per year were 0.9 (95^{th} CI 0 – 0.13). The percentage of PSTT over time was 0.02% (95^{th} CI 0 – 0.03%). The incidence of PSTT over the time period from 1983 – 2015 was 0.09 per 100 000 children per year (95^{th} CI 0.08 – 0.1).

DISCUSSION

This study shows that in a retrospective study of cases reported over a 32 year period, 22 primary solid thoracic tumours (PSTT) were recognised, diagnosed and treated in a tertiary care hospital situated in a middle income country with a high prevalence of tuberculosis (TB) and HIV. Of the cases studied, the correct diagnosis was however delayed in 36% of cases. Pulmonary tuberculosis was incorrectly diagnosed and treated in 23% of patients, while 13% were initially managed as a lower respiratory tract infection. The outcome of children treated for PSTT in this study was comparable to those reported from highly developed countries.[1,6] When compared to children with haematological malignancies presenting with thoracic mediastinal masses, the children with PSTT were younger, more likely to have tuberculosis, required a different set of diagnostic investigations and had a poorer outcome, even if the PSTT presented at an early stage. This study emphasises that PSTT can be successfully diagnosed and treated in middle income countries in spite of the challenges in diagnosis due to the high prevalence of infectious diseases, especially TB and HIV.

Although there are limited studies in the literature calculating the incidence of PSTT, a study conducted over 30 years in a highly developed country that included 160 cases of PSTT, estimated the incidence of PSTT to be 0.049 /100 000 people / year.[1] In our study we found the incidence to be 0.09 per 100 000 children per year. It is surprising that the prevalence of PSTT is slightly higher than the published incidence, as the high incidence of TB in the region results in an incorrect diagnosis of TB in patients with PSTT in approximately 1 in 5 cases. Further, this study only reports on children referred to a tertiary hospital which is likely to be an underestimation of the true incidence in the region.

Primary thoracic malignancies are rare in children. This study revealed that the most common primary solid thoracic tumour in our setting is neuroblastoma, followed by rhabdomyosarcoma and ganglioneuroblastoma. In a study published in the early 1990's a total of 383 primary pulmonary tumours were reported.[6] Of these 383 tumours 24% were benign and 76% malignant. Of the malignant tumours (n=291) bronchial adenoma (40.5%) bronchogenic carcinoma (16.8%) and pulmonary blastoma (15.5%) were the most common. Also included in this study were mediastinal lymphoma patients who comprised 1.0% of the cases.[6] In our study were the haematological malignancies were separated from the PSTT, however we documented 22 cases of lymphoma over the 32 year study period. This difference in the proportion of cases is most likely due to sampling of different populations. The high proportion of bronchial adenoma and bronchogenic carcinoma cases indicates that this sample was collected from a thoracic surgery database while our study collected cases primarily from an oncology database, which can explain the difference in the pathology reported. Previous data reports that 4% of primary pulmonary tumours were associated with congenital cystic malformations[6], however we were not able to find a single case of this association.

Kaposi sarcoma and lymphoma are known to be associated with HIV disease and in 5% of the cases in our study this association was present. In the 2 cases with Kaposi sarcoma of the airways both were initially misdiagnosed and treated for pulmonary tuberculosis. This is not surprising as the overlap in clinical presentation between pulmonary tuberculosis and HIV related lung disease is well documented.[22]

Multiple previous studies noted an obvious gender difference reporting that female gender has been associated with a 1.5-fold increase in the relative risk for PSTT.[1] The reason for this risk amongst females is unexplained. Although our study reports a 55% female predominance, it was not statistically significant and we were unable to confirm this risk. The reason for this may be the small sample of 22 cases of PSTT we collected over the 32 years of the study. PSTT presented at a younger age 3.29 (IQR 1.24 – 7.02) years compared to leukaemia, 8.1 (IQR 4.15 – 11.227), and lymphoma, 6.93 (IQR 1. 02 – 11.61) years. This difference was not statically significant. The average age in this study of 3.29 years is considerably less than the average reported age of 9-16 years.[1,6,16] The age difference is explained by the difference in the histology of the PSTT reported in the different studies.

All studies reviewed indicated that presenting complaints and symptomatology are very non-specific and variable, ranging from cough and fever, to weight loss and pain.[5,6,9,10] This is similar to our study in which cough (55%), tachypnoea (36%) and chest pain (23%) were the most common presenting symptoms. Although 24-27.9% of benign pulmonary tumours are asymptomatic, this is rare in pulmonary malignant tumours were only 6% were asymptomatic.[6,13] In our study only a single case of PSTT was asymptomatic. This patient had stage 2 neuroblastoma and was diagnosed on pre-operative CXR for unrelated elective surgery. Another form of presentation was non-resolving lower respiratory tract infection (9%). Haemoptysis (9%) is also associated with malignant pulmonary tumours but this was not found in our study.[13]

The most useful tool to raise the suspicion of a primary pulmonary tumour remains the chest radiograph. In all cases the CXR suggested a pulmonary abnormality.[5] Although chest computer tomography and chest magnetic resonance imaging are useful in assisting with the diagnosis, an appropriate diagnosis depends on accurate histology.[13] Similarly, in our study invasive testing was required to make an accurate diagnosis in all the cases. This included biopsy (64%), thoracic surgery (31%) and bronchoscopy (5%). This data suggests that chest imaging needs to be followed by invasive diagnostic tests to establish the exact diagnosis.

In a previous study by Neville et al they found that only 25% of patients presented with localized disease[1], however in our study we found that 69% of patients presented with early stage of disease and 31% presented with advanced disease. Presenting with advanced stage disease reduces and possibly eliminates the opportunity for resection, which impacts negatively on survival. In our study all the cases requiring surgery (n=18) also required chemotherapy. This contrasts with the study by Neville et al where surgery was the only form of therapy in the majority of cases.[1] The reason for this difference in therapeutic approach is due to the difference in the underlying pathology and histological diagnoses. According to oncology management protocols for the various histological diagnoses in our study, the majority of our cases of PSTT required chemotherapy as part of the management.

The survival rates in previous studies were variable. Hancock et al reported a 78% survival rate at an average of 2.4 years post treatment.[6] Neville et al documented a 15 year survival rate of 65% and they showed that survival was better in male than in female patients.[1] Their study showed a marked difference in survival between patients treated surgically compared to those who received non-surgical treatment. The median survival rate for non-surgically treated patients was 14 months with a 10-year survival rate of 32%. This was markedly better in the surgical group which had a 10-year survival rate of 75%.[1] Looking at the data published by yu et al they showed a mortality rate of 17.5%.[16] Our study showed that 64% of patients with primary solid thoracic tumours survived, 23% died and the outcome of 14% was unknown. After excluding those with an unknown outcome, the survival rate of those patients presenting with early disease was 69% compared to 31% in those presenting with advanced stage disease. Patients with lymphoma in our study diagnosed with early stage disease had a 100% survival. As expected, the mainstay of management of primary solid thoracic tumours is surgical. Transthoracic surgery was performed in 64% of the cases. The outcome of patients treated surgically indicated 83% survival, compared to 57% survival in patients treated non-surgically. However this was not statistically significant (p=0.21).

This study was performed in a referral tertiary care hospital in a middle income country. It is likely that PSTT remained initially unrecognised in the referral region resulting in under-diagnosis. This would be compounded by the fact that a large proportion of symptomatic children with PSTT would, in a region with a high prevalence of TB and HIV, be diagnosed and treated for TB, thus contributing to the underdiagnoses. Being a retrospective study with the data collected from a paediatric cancer registry, as well as having not included adolescent patients older than 16 years, makes it difficult to compare our study with studies which mostly included adolescent patients or where data was collected from a cardiothoracic database rather than an oncological one. Over the 32 year period of the study the imaging techniques have changed considerably which improved the possibilities of making the diagnosis of PSTT.

In this first study reporting on PSTT from a middle income country, we demonstrated that there are numerous challenges in making the diagnosis. In spite of these challenges the outcome of children with PSTT remains comparable to children living in highly developed countries. Further studies are required from low and middle income countries with a high prevalence of TB and HIV to improve the external validity of this study.

RECOMMENDATIONS

1. Further prospective studies are required to confirm the findings of this study in countries with a high prevalence of TB and HIV.
2. The value of modern imaging tools needs to be evaluated in diagnosing primary solid thoracic tumors
3. Educational programs are needed to increase the awareness of PSTT and to raise the index of suspicion amongst health care workers.
4. Lower respiratory tract infections and pulmonary TB not responding to treatment need to be referred to tertiary care hospitals for further evaluation, and to possibly consider a workup for PSTT.

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