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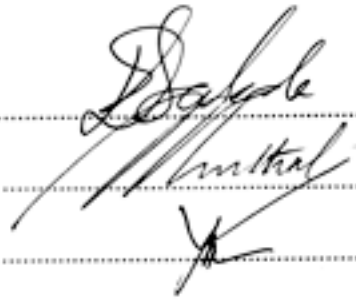
DECLARATION

I hereby declare that this dissertation herein presented for the degree of Master of Medicine in Orthopaedic Surgery has not been previously submitted wholly or in part for any other degree at this or any other University nor is it being currently submitted for any other degree.



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Approved by .....(Co-supervisor)

STATEMENT

I hereby testify that this study is entirely the result of my own independent investigations. The various sources to which I have referred are clearly cited in the text and the references.

Signed:.....(Candidate)

Date:.....8/8/14

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LIST OF ABBREVIATIONS

CDH	…….....	Cancer Diseases Hospital
CT	……..	Computerised Tomography
ESR	…….....	Erythrocyte Sedimentation Rate
GPPF	……	Graduate Proposal Presentation Forum
LDH	……	Lactate Dehydrogenase
MGUS	……	Monoclonal Gammopathy of Undetermined Significance
MRI	……	Magnetic Resonance Imaging
NHL	.....	Non-Hodgkin's Lymphoma
NOS	.....	Not Otherwise Specified
PET	……	Positron Emission Tomography
SMM	……	Smouldering Multiple Myeloma
SPSS	……	Statistical Package for the Software Sciences
UNZAREC / UNZABREC	……	University of Zambia Biomedical Research Ethics Committee
UTH	……	University Teaching Hospital
ZMW	……	Zambian Kwacha (Rebased)

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ABSTRACT

This was a retrospective cross-sectional survey of patients who presented to The University Teaching Hospital with histologically confirmed primary malignant bone tumours from the 1st of January 2008 to the 31st of December 2012. There were a total of hundred and fifty three (153) patients seen in total. Sixty six (43%) were females while 87 (57%) were males. The youngest patient was three years while the oldest patient was 78 years old. The average age of the patients was 31.6 years. Almost 69% of the patients were aged 40 years and below. The age distribution of primary malignant bone tumours showed a bimodal pattern of distribution with 35.1% of the patients having presented with tumour between the ages of 11 to 20 years; the second peak was observed between the ages of 51 to 60 years involving 10.6% of the patients with primary malignant bone tumours. The majority (35%) of the patients came from Lusaka Province, while the least came from North Western Province (2.0%). The highest number of patients (thirty nine) (25.5%) was recorded in 2012 and the lowest number 20 (13%) was recorded in 2011.Based National Cancer Registry data, from 2008 to 2011, the overall proportion of patients with primary malignant bone tumours compared to all the other cancers recorded at UTH ranged between 1.7 to 2.8%. The majority, eighty-four (55.3%), of the patients had osteosarcoma, followed, in descending order, by multiple myeloma 42 (27.6%), chondrosarcoma 11 (7.2%), Ewing's sarcoma 8 (5.3%), fibrosarcoma 3 (2.0%) and lymphoma 2 (1.3%). The majority of patients (35.5%) reported pain and swelling alone as a presenting complaint. 19.8% of the patients presented with pathological fractures. The single and most commonly reported anatomic site was from multiple myeloma which has a general skeletal involvement (27%); the second most commonly involved site was the femur 23.7%, followed by the tibia 17.1%, and the humerus 7.5%. Notwithstanding the inconclusive nature of the information on geographic distribution of tumours, the findings in the study paralleled those reported in literature.

Chapter 1

Background to the Study

1.1 Introduction

Historically the largest contributor to Zambia's disease burden has been infectious diseases, however the burden of disease from malignancy has seen an upward trend (Bowa et al. 2005). Malignant neoplasms have not been well characterized in Zambia partly due to the under-utilization of the national cancer registry in terms of cancer reporting (Bowa et al. 2005). Retrospective studies (Bowa et al. 2005; Chintu et al. 1995) conducted at the University Teaching Hospital have demonstrated an increase in malignancies, especially the HIV related malignancies. Despite demonstrating a rise in HIV related childhood malignancies, the relative proportion of primary malignant bone tumours at UTH was low (Chintu et al. 1995).

Primary bone cancer includes malignancies directly originating from bone tissue. This is different from secondary bone tumours in which case the neoplastic elements arise primarily from other non-osseous sites within the body and secondarily spread to bone. Secondary bone tumours generally have a poorer prognosis and are much more common than their primary bone tumour counterparts (Bramer & Somford 2010; Negash et al. 2009).

Globally, primary malignant bone tumours are relatively rare (Fletcher & Unni 2002; Katchy et al. 2005; Baena-Ocampo et al. 2009; Negash et al. 2009; Bramer & Somford 2010; Jain et al. 2011). Wherever primary malignant bone tumours occur they tend to pose serious challenges in terms of diagnosis, morbidity and mortality, and therein lies their importance (Bahebeck et al. 2003; Baena-Ocampo et al. 2009; Negash et al. 2009).

The World Health Organisation has classified bone tumours based on the histological character of the neoplastic cells (Fletcher & Unni 2002; Kuchenbecker et al. 2010).

These tumours are classified on the basis of their histological picture; therefore primary bone cancers are named on the basis of their resemblance to the parent tissue or type of stroma that the tumour produces (Bramer & Somford 2010).

The aetiology of primary malignant bone tumours has not been well established but these tumours have been observed to show variations in incidence, site and age distributions within and outside national geographic boundaries (Parkin et al. 1993; Katchy et al. 2005).

Consideration has been given to the possible role of the environment in the causation of these tumours but this has not yet been proven using epidemiological means (Parkin et al. 1993; Katchy et al. 2005). Patients often present with variable and vague symptoms including pain, swelling, and fracture, sometimes with reports of incidental antecedent traumatic events.

Due to the, sometimes vague, symptoms, it's not uncommon for physicians to miss the diagnosis (Bramer & Somford 2010). Neoplasms affecting the skeleton are being observed more often in orthopaedic practice (Omololu et al. 2002).

This study reviewed the pattern of primary bone cancer as observed at the University Teaching Hospital from the 1st of January 2008 to the 31st of December 2012.

1.2 Problem Statement

Primary malignant bone tumours present a diagnostic and therapeutic challenge and are a cause for significant morbidity and mortality among those afflicted; however the pattern of distribution of primary bone tumours was not well documented at the University Teaching Hospital.

1.3 Study Justification

Based on anecdotal evidence, it was observed that there were a significant number of patients who presented to The University Teaching Hospital with primary bone cancers. There was no published work clearly describing primary malignant bone tumours at The University Teaching Hospital.

An orthopaedic bone tumour register recorded 35 cases of primary malignant bone tumours in 2010 alone at the University Teaching Hospital. Knowledge of the distribution of primary bone cancers will help clinicians and hospital administrators both at The University Teaching Hospital and Cancer Diseases Hospital to allocate resources to meet the specific needs of bone cancer patients. This information is also likely to serve as a basis for other studies. Understanding The University Teaching Hospital distribution of primary bone cancers is

fundamental in the development of a clear scope of interventions aimed at early detection, treatment and rehabilitation of sufferers and survivors.

1.4 Research Question

What was the pattern of disease of primary bone cancers at the University Teaching Hospital from 1st January 2008 to 31st December 2012?

1.5 Objectives of the Study

The main objective of this study is to establish the pattern of primary malignant bone tumour distribution of at the University Teaching Hospital. The specific objectives of the study are to:

1. To outline the socio-demographic characteristics of patients presenting with primary malignant bone tumours with respect to age, gender and geographic origin.
2. To determine frequency of primary malignant bone tumours at UTH
3. To determine the hospital prevalence of primary malignant bone tumours including their histological distribution
4. To determine the clinical presentation of primary malignant bone tumours

Chapter 2

Literature Review

2.1 General Description

In general cancer ranks second as a cause for mortalities in developed countries and the third leading cause of death in developing countries (Baena-Ocampo et al. 2009). It was estimated that by the year 2002 there would have been 10.6 million new cases of cancer, 6.7 million deaths from cancer and an overall 24.6 million people affected by cancer (Baena-Ocampo et al. 2009). According to Bramer & Somford (2010, pp. 247) primary malignant bone tumours occur in the United States of America at a rate of 9 new cases per million-population per year with slightly more male cases than female.

The mortality rate in the U.S.A is 4 persons per million people per year and the male to female ratio is 5:4 (Bramer & Somford 2010). While cancer ranks high among the causes for mortalities both in the developing and developed countries, the World Health Organization (WHO) reports that primary bone malignancies are rare, accounting for around 0.2% of all cancers. They occur at a rate of a tenth (1/10) of their soft tissue counterparts (Fletcher & Unni 2002; Negash et al. 2009). A 10 year study done in Kuwait by Katchy et al., (2005, pp. 407-408) involving 142 patients, 76 of whom had primary malignant bone tumours, confirmed that malignant bone tumours are indeed relatively uncommon and the primary malignant bone tumour incidence for the duration of the study varied between 0.5 to 5.5 per million population per year.

Notwithstanding their rarity, primary bone cancers pose serious challenges in terms of diagnosis, morbidity and mortality (Bahebeck et al. 2003; Baena-Ocampo et al. 2009). These patients tend to present with pain, swelling, pathological fracture or a combination of features (Katchy et al. 2005; Bramer & Somford 2010).

2.2 Geographic Distribution

According to a study conducted in Sweden, the geographic and sex distribution of primary malignant bone tumours is understood to be quite variable suggesting that geography possibly

affects the occurrence of primary malignant bone tumours (Larsson & Lorentzon 2010). However, the findings of a study done in Mexico City were reflective of the similarity in distribution and epidemiology of primary malignant bone tumours as they are in other developed and underdeveloped countries. It was, therefore suggested that the risk and occurrence of primary bone tumours is independent of geo-location (Baena-Ocampo et al. 2009).

Notwithstanding the foregoing but similar to the study findings in Sweden by Larsson and Lorentzon (2010, pp. 594-597), some of the primary malignant bone tumours have been observed to show variations in incidence, site and age distributions within and outside national geographic boundaries based on a study done in Kuwait. (Katchy et al. 2005). The incidence rate for bone sarcomas in North America and Europe is approximately 0.8 new cases per 100,000 population per year in males. Somewhat higher figures in incidence rates are observed in Argentina, Brazil and Israel (Fletcher & Unni 2002). Incidence rate variations that have been noted to occur with geographic variation have been on account of higher incidence rates of osteogenic sarcoma (Fletcher & Unni 2002).

A 6year retrospective study done in Mexico City involving 566 cases of both malignant and benign bone tumours showed that benign primary bone tumours accounted for 71.6% of the total primary bone tumour burden whereas 28.4% were due to primary bone malignancy (Baena-Ocampo et al. 2009).

2.3 Age Distribution

Age stratified frequencies including incidence rates of bone sarcomas are bimodal with the first and highest peak occurring in the second decade of life whereas the second peak tends to occur in patients above the age of 60 years. This was reported by WHO, observed in Kuwait and southern India (Fletcher & Unni 2002; Jain et al. 2011; Katchy et al. 2005). In Mexico it was shown that the average patient age at presentation was 25 years and the median age at presentation was 36 years. The malignant primary bone tumours also showed a bimodal frequency involving the age groups 11 to 20 years (51, 32%) and 41 to 50 years (25, 15.5%) in Mexico City (Baena-Ocampo et al. 2009). In a study conducted in southern India involving 104 patients the mean age of presentation was 26.87%.

The weighted risk of developing bone sarcomas in the second decade of life in comparison to that of developing the same in patients older than 60 years are almost the same but there have been more cases reported in the second decade (Fletcher & Unni 2002). In Kuwait the age and sex distribution had a bimodal curve of distribution in conformity with the general findings in most other studies for primary malignant bone tumours. These peaked between 10 and 19 years of age with a higher frequency among males (Katchy et al. 2005). The majority of patients including male and female were also aged between 10 and 19 years (Katchy et al. 2005).

In Cameroon the youngest reported patient was 20 months old and the oldest was 89 years. The age distribution was such that the mean age at presentation for osteosarcoma was 22 years, 37 years for malignant non-Hodgkin's bone lymphoma, 35 years for fibrosarcoma and chondrosarcoma. While the mean age in Ewing sarcoma was 16 years (Bahebeck et al. 2003).

2.4 Sex Distribution

In the Mexico City study of primary malignant bone tumours men were affected in 53.7% of the cases and women in 46.3% of the cases. In the same study there was no difference in the distribution of osteosarcoma between males and females, however there was a difference in distribution of chondrosarcoma, lymphoma, and Ewing sarcoma, it tended to affect males than females (Baena-Ocampo et al. 2009).

In Sweden men were affected in 53.7% of the cases and women in 46.3% of the cases (Larsson & Lorentzon 2010). In the Kuwait study there were 58 male and 18 female patients with primary malignant bone tumours, the male incidence rate was between 0 and 7.2 per million while the female specific incidence rate ranged from 0 to 4.6 per million per year (Katchy et al. 2005). Bahebeck and colleagues (2003) did not stratify for their findings in Cameroon in order of gender.

2.5 Anatomic Site Distribution

The bone tumour age distribution peaked in children and adolescents with the malignant bone tumours mostly affecting the femur, vertebra and tibia (Larsson & Lorentzon 2010). Including benign tumours, the femur was the most commonly involved bone (39.9%), then followed by the tibia (17.7%), and the humerus (11.8%) (Larsson & Lorentzon 2010). In

Mexico City, the commonly affected sites were as follows; femur 77 (47.8%), vertebrae 29 (18%), tibia 18 (11.2%), and the humerus 17 (10.6%) (Baena-Ocampo et al. 2009). In Cameroon, the affected anatomic sites included the tibia (17.5%), the femur (9%) and the spine (9%). The pelvic ring, scapular-ring and the humerus had the following distribution respectively; (2%), (3%) and (2%). The forearm frequency was 1.5%, the hand, wrist and foot and ankle were affected in less than 1% of the cases (Bahebeck et al. 2003).(Baena-Ocampo et al. 2009)

2.6 Histolopathological Distribution

In North America and Europe, histologically stratified cancer registry data shows that osteosarcoma is the commonest primary bone cancer (35%); the second most common primary bone malignancy is chondrosarcoma (25%), which is followed by Ewing's Sarcoma (16%) (Fletcher & Unni 2002). In the work of Baena-Ocampo and colleagues (2009) in which 161 patients with primary malignant bone tumours were identified, the distribution of the tumours was as follows; osteosarcoma 75 (46.6%), chondrosarcoma 14 (9%), multiple myeloma 13 (8%), plasmacytoma 11 (6.8%), lymphoma 9 (5.6%) and Ewing sarcoma 4 (2.5%).

A study done in Sweden also revealed that the most common primary bone cancers included; osteosarcoma (46.6%), chondrosarcoma (8.7%) and multiple myeloma (8.1%) (Larsson & Lorentzon 2010). The frequency of occurrence of the primary malignant bone tumours in Kuwait was as follows; Ewing's sarcoma/PNET 23(30.3%), multiple myeloma 19 (25.0%), osteosarcoma 16(21.0%), chondrosarcoma 6(7.9%), Non-Hodgkin's lymphoma 5(6.5%), Chordoma 3(3.9%), Sarcoma (not otherwise specified) 1(1.3%), hemangiopericytoma 2(2.6%), malignant giant cell tumour 1(1.3%) (Katchy et al. 2005).

In Cameroon there were 10 histopathological variants of primary bone cancers identified. The primary malignant bone tumours that were identified included; Osteosarcoma 48 (39%), malignant non-Hodgkin’s lymphoma of the bone 33 (27%), fibrosarcoma18 (15%), chondrosarcoma 9 (7%) and Ewing's sarcoma7 (6%). The other five types of tumours were malignant haemangiopericytoma, solitary plasmacytoma, haemangioendothelioma, malignant histocytofibromas and multiple myeloma; these were quite rare in Cameroon (Bahebeck et al.

2003). The annualized frequency of primary malignant bone tumours was 9 to 15 tumours per year (Bahebeck et al. 2003).

2.7 World Health Organization Classification of Primary Bone Tumours

The WHO classification of bone tumours (table 1) has classified bone tumours on the basis of their biological behaviour and the type of matrix that the tumour produces (Morphology code of the International Classification of Diseases for Oncology (ICD-O) {726} and the Systematized Nomenclature of Medicine, n.d. cited in Fletcher C.D.M., Unni K.K., Mertens F. (Eds.), 2002, p.226).

Table 1: The WHO Classification of Bone Tumours

TYPE	BENIGN		MALIGNANT	
Chondrogenic	Osteochondroma		Chondrosarcoma	Central
	Chondroma	Enchondroma		Primary
		Periosteal chondroma		Secondary
		Multiple Chondromatosis		Peripheral
	Chondroblastoma			Dedifferentiated
	Chondromyxoid Fibroma			Mesenchymal
				Clear Cell
Osteogenic	Osteoid osteoma		Osteosarcoma	
	Osteoblastoma		Conventional	Chondroblastic
				Fibroblastic
				Osteoblastic
			Telangiectatic	
			Small cell	
			Low grade Central	
			Secondary	
			Parosteal	
			Periosteal	

TYPE	BENIGN	MALIGNANT
		High grade surface
Fibrogenic	Desmoplastic Fibroma	Fibrosarcoma
Fibrohistiocytic Tumours	Benign fibrous histiocytoma	Malignant fibrous histiocytoma
Ewing sarcoma		Ewing sarcoma
Haematopoietic Tumours		Plasma cell myeloma
		Malignant lymphoma
Giant cell Tumour	Giant cell tumour	Malignancy in giant cell tumour
Notochordal tumours	Chordoma	
Vascular Tumours	Haemangioma	Angiosarcoma
Smooth muscle Tumours	Leiomyoma	Leiomyosarcoma
Lipogenic Tumours	Lipoma	Liposarcoma
Neural Tumours	Neurilammoma	
Miscellaneous Tumours		Metastatic Malignancy
Miscellaneous Tumours		Adamantinoma
Miscellaneous Lesions	Aneurysmal bone cyst	
	Simple bone cyst	

TYPE	BENIGN	MALIGNANT
		Fibrous dysplasia
		Osteofibrous dysplasia
		Langerhans cell histiocytosis
		Erdheim-Chester disease
		Chest wall harmatoma
Joint Lesions		Synovial chondromatosis

2.8 Grading and Staging of Malignant Bone Tumours

Primary malignant bone tumours exhibit a varied biological behaviour with some being locally aggressive and having a low metastatic potential while most others exhibit a higher tendency to metastasize and recur locally. The commonest site for metastatic spread is the lung (Bramer & Somford 2010). Biologic behaviour of primary malignant bone tumours is predicted by using grading and staging systems (Bramer & Somford 2010). Grading of tumours takes into account their cellularity, number of mitoses, and the pattern of their histological growth (Bramer & Somford 2010).

On the basis of their grade, tumours are consequently divided into low and high-grade categories. A bone tumour staging system, which incorporates the grading system is utilized for the purposes of categorizing bone tumours and predicting their biologic behaviour, evaluating treatment modality requirements, predicting outcomes and comparing groups of tumours (Bramer & Somford 2010).

The Enneking staging system (Table 2) below is the most commonly used staging system for bone tumours. It takes into consideration the grade, local extent and possibility for distant spread of the tumour (Bramer & Somford 2010). This system is meant to incorporate the most crucial prognostic factors into a system of progressive stages that helps to guide management.

Stages IA and IIA lesions are contained in well defined anatomical compartments which are determined by natural physical anatomical barriers to tumour growth, e.g. bone, articular cartilage, fascial septa or joint capsules. Stages IB and IIB lesions by and large extend beyond the anatomic compartment of origin and are thus referred to as being extra compartmental. Stage III refers to metastatic lesions regardless of size or grade of the primary tumour. Lymph node and distant metastasis both yield poor outcomes and thus no distinction is made between the two of them in the Enneking system.

Table 2: Enneking system for staging malignant musculoskeletal tumours

STAGE		SITE	GRADE	METASTASIS	HISTOLOGICAL FEATURES
I	A	Intracompartmental	Low	NO	Well differentiated Few Mitoses Moderate cytological atypia Low metastatic risk (<25%)
	B	Extracompartmental			
II	A	Intracompartmental	High	NO	Poorly differentiated High mitotic rate High cell-to-matrix ratio
	B	Extracompartmental			
III		ANY	ANY	YES	

Chapter 3

Research Methodology

3.1 Study Design

This was a retrospective cross-sectional survey of patients who presented with primary malignant bone tumours to The University Teaching Hospital from January 1 2008 to December 31st 2012. All records of patients with histologically confirmed primary malignant bone tumours that presented to UTH during the study period were included in this survey.

By definition, primary malignant bone tumours are tumours whose neoplastic element originates from any of the cellular components of bone and have the capacity to spread locally and to distant sites (Fletcher & Unni 2002). Details pertaining to demographic characteristics and clinical presentation were collected using a standard data collection sheet.

3.2 Study Site

The site for the study was The University Teaching Hospital in Lusaka, which is Zambia's largest and final referral hospital. UTH has a bed capacity of 1800 beds and a bed occupancy rate beyond 100% (Chintu et al. 1995). The patient data was obtained from the following sources:

The Zambia National Cancer Registry,

ii. The University Teaching Hospital Main Records department

iii. The histopathology laboratory registers

iv. The University Teaching Hospital ward Bone Tumour register

iv. The Cancer Diseases Hospital Database

3.3 Case Definition

Cases were being defined as all patients of any age and gender with histologically confirmed primary malignant bone tumours arising from the axial or appendicular skeleton with the exclusion of tumours arising from the head.

3.4 Inclusion Criteria

Records of patients of all ages and gender who presented to the University Teaching Hospital during the period of the study (1st January 2008 to 31st December 2012) were included. Further the patient should have been diagnosed by a surgeon as having a primary malignant bone tumour involving any region of the skeleton from the cervical spine downwards with histological evidence of a primary malignant bone tumour. Patients with histological evidence of primary bone cancer but incomplete records with respect to the other parameters were included in the study.

3.5 Exclusion Criteria

All patients lacking histological confirmation of primary malignant bone tumours were excluded.

3.6 Data Collection

The investigator with the assistance of 2 data assistants did the data collection, and the data was tabulated. The data sources were categorised into primary and secondary sources with the primary sources of data being the actual patient records at The University Teaching Hospital. The secondary sources of data included the various institutional registers and databases from The University Teaching Hospital and Cancer Diseases Hospital. Secondary data was collected for the purposes of identifying and retrieving the primary data sources.

The data was de-identified by removing all the patient specific identifiers. This was done after complete patient records were obtained and unique study-specific identification numbers assigned. The study identification numbers were 4 digit codes that were uniquely assigned to patients. Upon obtaining of a complete record the patient's records were filed back in the main records department. For the purposes of patient confidentiality no records were taken out of the hospital or the Main Records Department.

Patient records were manually scrutinised for consistency primarily with respect to patient-specific identifiers including name, age, gender, hospital record number and laboratory number.

The collected data was collated entered on an Excel spread sheet, exported and analysed using Statistical Package for Social Sciences (SPSS). Redundancies and duplicates were eliminated manually and by electronic means.

The data collected included the following:

i. The patients' full name

ii. The hospital record/file number

iii. The age of the patient in years

iv. The gender of the patient

v. The clinical presentation (pain, swelling, pathological fracture, incidental finding)

vi. The anatomic site affected by the tumour

vii. The histological diagnosis according to the WHO classification of bone tumours.

viii. The geographic origin of the patient (provincial domicile and not ethnicity).

Data has been presented in form of graphs and tables. Age was categorized into 10-year periods resulting into the creation of ordered categorical variables with respect to age.

3.7 Sampling

The sampling method used was purposive sampling. The sampling frame included patients of any gender and age with clinical and histopathological evidence of primary bone malignancy. These should have been attended to at UTH during the period of the study.

3.8 Data Analysis

Univariate analysis of socio-demographic factors was done. A Chi square test was used to study association between categorical variables. A P-Value of less than 0.05 was considered significant.

3.9 Ethical Considerations

The research was initiated by the development of a research proposal. The proposal was presented and approved at the Graduate Proposal Presentation Forum, followed by an application to the University of Zambia Biomedical Research Ethics for approval to conduct

the study. The study did not involve any interaction with human participants; therefore a waiver for patient informed consent was applied for and approved by the University of Zambia Biomedical Research Ethics Committee. Formal request was sought from The University Teaching Hospital management for the conduct of this study at the institution and The Cancer diseases Hospital for the use of their tumour database. All information pertaining to patient identity was kept secure and only accessed on retrieving the appropriate records.