THE OCCURRENCE OF MULTIPLE MYELOMA AT DR GEORGE MUKHARI HOSPITAL, GAUTENG: A RETROSPECTIVE REVIEW (2004-2009)

BY

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DECLARATION

I, Ruth Khutso Rankapole, declare that this dissertation hereby submitted in partial fulfilment of the MMed (Haematology) degree in the Department of Haematology at the University of Limpopo, Medunsa campus, is my own work and that all references used have been duly listed and that neither the whole work nor any part thereof has been, or is to be submitted for another degree at this or any university or tertiary institution or examination body.

Dr Ruth Khutso Rankapole

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DEDICATION

This dissertation is dedicated to my dad, Mr Sefahle Phillemon Rankapole and my late mom, Mrs Rahab Matshero Rankapole for their love and dedication to my education.

To my husband, Mr Thomas Khoza and my two sons, Kulani and Tiyani, for their love, sacrifice, understanding and support.

ABSTRACT

BACKGROUND: Multiple myeloma (MM) is a rare age-related disorder with increasing incidence with advancing age. It is a B-cell malignancy characterised by monoclonal expression and accumulation of abnormal plasma cells in the bone marrow. It comprises about 1% of all malignant tumours worldwide and 10% of haemopoietic neoplasms. MM accounted for 0.43% of newly diagnosed malignancies in South Africa in 1999 and Visser et al (2009), found the incidence to be 0.00054%. Mwambakana in 2000 at Ga-Rankuwa Hospital, now known as Dr George Mukhari Hospital (DGMH), found MM to be the commonest haematological malignancy.

No clear risk factors have been identified in this disease. The natural history of MM is one of progressive bone destruction, refractory cytopenias and end-organ damage. The diagnosis and staging of MM is based on different criteria and systems.

OBJECTIVES: To establish a profile of patients diagnosed with MM at DGMH from 1 January 2004 to 31 December 2009.

METHODS: We conducted a descriptive retrospective review of medical records of patients diagnosed and treated for MM at DGMH from 2004-2009.

RESULTS: Thirty-four patients' records were found. MM was found to be present in these patients as early as the third decade, more females than males were diagnosed and females were surviving longer than their male counterparts. Clinical features were not significantly different from those previously reported. The WHO 2001 diagnostic criteria created by Durie & Salmon and the International Staging System were used more frequently and most patients presented at an advanced stage of the disease.

CONCLUSION: The profile established of MM patients diagnosed and treated would help us to have a high index of suspicion in adult patients on presentation and therefore help us with timeous diagnosis and treatment of these patients. The different treatment modalities should be considered. In future we will be able to establish our own guidelines in diagnosis and management of these patients.

KEYWORDS: Multiple myeloma, profile, diagnostic criteria, staging system, prevalence and survival analysis

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LIST OF ABBREVIATIONS

- ASCT – autologous stem cell transplant
- BCSH – British Committee of Standards in Haematology
- BM – bone marrow
- BMSC's – bone marrow stromal cells
- CD – cluster of differentiation
- CNS – central nervous system
- CRAB – hypercalcaemia, renal insufficiency, anaemia, bone lesions
- CRP – C-reactive protein
- CT – computer tomography
- DGMH – Dr George Mukhari Hospital
- DS – Durie and Salmon
- ECOG – Eastern Cooperative Oncology Group
- ESR – Erythrocyte Sedimentation Rate
- FISH – Fluorescence in situ hybridization
- HIV – human immunodeficiency virus
- Ig – immunoglobulin
- IL – interleukin
- IMWG – International Myeloma Working Group
- ISS – International staging system

- IV – intravenous
- LDH – lactate dehydrogenase
- MGUS – Monoclonal gammopathy of undetermined significance
- MIP – macrophage inflammatory protein
- MM – Multiple Myeloma
- MP – Melphalan and Prednisone
- M-protein – monoclonal protein
- MPT – Melphalan, Prednisone, Thalidomide
- MREC – Medunsa Research & Ethics Committee
- MRI – magnetic resonance imaging
- mSMART – Mayo Stratification of Myeloma and Risk-Adapted Therapy
- NFKβ – nuclear factor kappa β
- NHLS – National Health Laboratory Services
- PET – positron emission tomography
- RANKL – receptor activator nuclear factor kappa β ligand
- R-MP – Lenalidomide, Melphalan, Prednisone
- RSA – Republic of South Africa
- S.A – South Africa
- SEER – Surveillance Epidemiology and End Results
- SMM – smoldering myeloma
- SPE – serum protein electrophoresis
- TGF – transforming growth factor
- TNF – tumour necrosis factor

- U.K – United Kingdom
- U.S – United States
- VAD – Vincristine, Adriamycin, Dexamethasone
- VCAM – vascular cell adhesion molecule
- VEGF – vascular endothelial growth factor
- WHO – World Health Organization

CHAPTER 1: INTRODUCTION

1.1. Study problem

Multiple myeloma (MM) is one of the most frequently seen haematological malignancies at Dr George Mukhari Hospital (DGMH)(1). It is more common in people of African and Afro-Caribbean descent (2). Clinical research on MM in South Africa (S.A) is perceived to be inadequate when compared to data from the United States of America (U.S) or the United Kingdom (U.K) (3).

The Mayo Clinic, in the U.S for example, is one of the world's premier multiple myeloma treatment centres, a world leader in MM research. Mayo researchers identified prognostic factors that predict the course of the disease and developed new systems for classifying this disease (3). In the U.K, the U.K Myeloma Forum and British Committee of Standards in Haematology (BCSH), established guidelines on the diagnosis and management of multiple myeloma in 2005 (11) and 2011 (44). However, in S.A, we do not have a well-established National Cancer Registry which would help in effective disease surveillance done by other countries. This study was done to establish the profile of patients with MM in our institution which included and not limited to 1) demographics, 2) presenting symptoms and signs, 3) criteria used for diagnosis and 4) staging and 5) the 5-year survival rate of patients on treatment was also determined.

1.2. Background

Multiple myeloma or plasma cell myeloma is a B-cell lymphocytic malignancy characterised by monoclonal expression and accumulation of abnormal plasma cells in the bone marrow (4). MM comprises about one percent of all malignant tumours worldwide and 10-15% of haemopoietic neoplasms (5). It is more common in men than women (5) and a median age at diagnosis is 60-65 years with fewer than two percent under 40 years of age (3), and twice as high in blacks than whites. No clear risk factors have been identified in most patients with this disease.

Clinical presentation of MM varies widely with no definitive signs or symptoms seen only in this disease. Some patients are free of symptoms at the time of diagnosis with the disease being detected on routine blood tests (6). The UK Myeloma Forum (11) lists the following as presenting features:

- Symptoms of bone disease: typically persistent, unexplained backache
- Impaired renal function
- Anaemia: typically normochromic, normocytic, and less frequently leukopenia and/or thrombocytopenia
- Hypercalcaemia
- Recurrent or persistent bacterial infection
- Symptoms suggestive of spinal cord or nerve root compression
- Features suggestive of amyloidosis, such as nephrotic syndrome and cardiac failure
- Persistently raised erythrocyte sedimentation rate (ESR) or plasma viscosity as an incidental finding.

The natural history of multiple myeloma is one of progressive bone destruction, refractory cytopenias and end-organ damage in the form of renal and cardiac dysfunction. Deficits in the humoral immune system, use of corticosteroid therapy and progressive leucopenia from bone marrow replacement by the disease, can place patients at increased risk of infectious complications (12).

The diagnosis of multiple myeloma is based on a combination of clinical, pathological and radiological features (5) and is reflected in the diagnostic criteria used. New systems for diagnosis and staging of MM have recently emerged and are primarily derived from the International Myeloma Working Group and Mayo Clinic. In this study we focussed on diagnostic criteria proposed by the World Health Organization (WHO) in 2001 according to Durie and Salmon in 1975 (17) and 2008 according to the International Myeloma Working Group in 2003 (5). The WHO 2001 included only symptomatic patients with progressive disease. The WHO 2008 was more inclusive and it included asymptomatic and symptomatic myeloma.

There was also monoclonal gammopathy of undetermined significance (MGUS); described as a premalignant disorder in which plasma cells also produce monoclonal paraprotein but does not cause symptoms. According to Landgren et al. (14), a prospective study demonstrated that all or almost all cases of MM are preceded by MGUS. The symptoms would manifest as hypercalcaemia, renal failure, anaemia and bone lesions (CRAB).

In a study conducted by Kyle et al. (18), different staging systems for prognostication of the disease were used. The Durie and Salmon staging system derived over 30 years ago, provided an approach to measure the MM tumour burden, which is correlated with

individual clinical, laboratory and X-ray features and the International Staging System (ISS) based on two easily available parameters, serum albumin and β2 microglobulin concentrations. Kyle et al. (18), conducted a review in which clinical and laboratory data were obtained on 1750 previously untreated symptomatic MM patients from 17 institutions worldwide. This system is reproducible in all age groups and in patients on conventional, high dose chemotherapy and those who received stem cell transplantation.

The limitation of the use of these systems i.e. diagnostic and staging, was that there has been significant changes over the years, and this could have created challenges in their consistent implementation.

Currently there is no cure for multiple myeloma. A study by Greipp et al. (7) on 10,750 cases of previously untreated symptomatic myeloma, found that the median survival varies from 29 to 62 months. For decades, the mainstay of therapy has been oral chemotherapy with Melphalan and Prednisone (MP) (10), but in younger cohorts of patients, a median survival of more than 5 years can now be achieved with the introduction of high dose chemotherapy (8, 9).

1.3. Research methodology

This study involved establishing a profile for MM patients at Dr George Mukhari hospital (DGMH). The profile included: demographic information, presenting symptoms, criteria used for diagnosis and staging, and observed survival rate of the patients on treatment.

This study was done with permission from the Medunsa Research & Ethics Committee (MREC).

We have a small Haemato-Oncology Unit that is a subunit of the Department of Internal Medicine that treat and follow up these patients. Most of the patients are treated until they die or lost to follow up.

This was a descriptive study in which medical records of patients diagnosed and treated for multiple myeloma were reviewed for the period 1 January 2004 to 31 December 2009. All patients who met the criteria for diagnosis were included in the study. Data collected was analysed using descriptive statistics in the form of frequency distribution tables and histograms, and Epi Info software. Determination of survival rate was assessed using the Kaplan Meier survival analysis methods.

1.4. Rationale of study

This study would benefit the wider community through early recognition of the disease, reduced delays in diagnosis and improved management of these patients. In future we would be able to establish our own guidelines in collaboration with other institutions in Africa and worldwide, and develop a better disease surveillance.

CHAPTER 2: LITERATURE REVIEW

2.1. Definition and epidemiology

Multiple myeloma (MM) is a form of cancer which affects plasma cells in the bone marrow. Plasma cells normally produce antibodies and are a specialised form of blood cell called a B-lymphocyte. In normal circumstances, the antibody molecules present in the blood vary widely in their structure, reflecting the large number of infections they may be required to combat. In MM a single lymphocyte becomes malignant and produces a very large number of identical cells, also known as a clone, and very large quantities of a single type of antibody are produced; this form of antibody is called a paraprotein and is present in the blood and/or urine in about 99% of cases. Normal antibody levels are reduced in MM, this leads to a susceptibility to infections. The term "multiple myeloma" refers to the spread of the disease throughout the bone marrow at the time of diagnosis and the presence of multiple sites of affected bone (6).

According to Kyle et al. (18), MM is also known as plasma cell myeloma, plasmacytic myeloma, myelomatosis, and Kahler disease. It is a neoplastic disorder characterised by proliferation of a single clone of plasma cells derived from B-cells. This clone of plasma cells proliferates in the bone marrow and frequently invades the adjacent bone, producing skeletal destruction that results in bone pain and fractures. Occasionally, plasma cells infiltrate multiple organs and produce other symptoms. The excessive production of a monoclonal protein (M-protein), a paraprotein, may lead to renal failure from Bence Jones proteinuria or hyperviscosity from excessive amounts of M-protein in the blood.

Fig 2.1 and 2.2 below show bone marrow smear in a myeloma patient with increased number of plasma cells and abnormal forms. A plasma cell is a mature B-lymphocyte that produces immunoglobulins. Plasma cells are rarely found in peripheral blood. They compromise 0.2% to 3% of bone marrow cells. Microscopically as seen below: plasma cells are oval in shape with eccentric, clumped and patchy nuclear chromatin pattern. Their cytoplasm is deeply basophilic with distinct perinuclear zones.

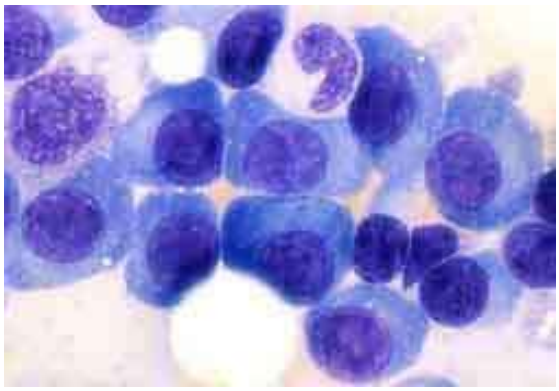


Figure 2.1 Bone marrow plasma cells (picture from Hematopathology University of New Jersey archives)

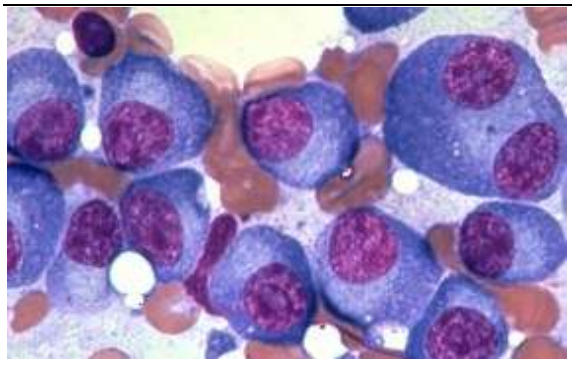


Fig 2.2 Plasma cells and abnormal bi-nucleated form (accessed from www.google.com/images)

MM is the second most common haematological malignancy after non-Hodgkin's lymphoma, comprising 10% of all haematological malignancies and 1% of all cancers. MM is twice more common in African Americans than in white persons and slightly more common in men than in women (18). The incidence is 1-9 per 100000 worldwide with a higher incidence in North America, with 7.1 per 100000 population for men and 4.6 per 100000 for women, and lower in Asia, Japan, China and India (24). The annual incidence, age – adjusted to the 2000 U.S population, is 4.3 cases per 100 000 people, resulting in more than 15 000 new patients in the U.S each year (25, 26).

The aetiology is still uncertain, but increased risk of MM has been noted in survivors of the Hiroshima and Nagasaki disasters, radiation workers, metal workers and following exposure to chemicals and pesticides (19, 20).

The epidemiological studies attempting to establish definite associations between MM and certain infections or autoimmune diseases, have so far, remained inconclusive (4). MM is one of the most established age-related disorders with incidence increasing with advancing age (19, 20). Ninety-eight percent of cases occur over the age of 40 years with a peak incidence in the seventh decade (16). In most series, the median age of diagnosis is about 65 years (18, 21, 22, 23), but it is about a decade less in developing countries. The median age in India is 55-56 years.

2.2. Pathogenesis

The pathogenesis of multiple myeloma is complex and includes mutual interactions affecting the number and function of both malignant cells and normal bone marrow stromal cells.

Bone marrow microenvironment includes the extra cellular matrix and at least five types of stromal cells and these include; fibroblasts, osteoblasts, osteoclasts, vascular endothelial cells and lymphocytes. Reciprocal positive and negative interactions among these cells are mediated by a variety of cytokines and adhesion molecules. Adhesion of myeloma cells to bone marrow stromal cells (BMSCs), through vascular cell adhesion molecule 1 (VCAM-1) interaction, induces the paracrine secretion of cytokines such as interleukin 6 (IL-6), IL-1β, IL-11, tumour necrosis factors (TNFs), transforming growth factor beta (TGF-β) and receptor activator of nuclear factor-kappa B ligand (RANKL) by BMSCs (4). See figure 2.3 and 2.4 below.

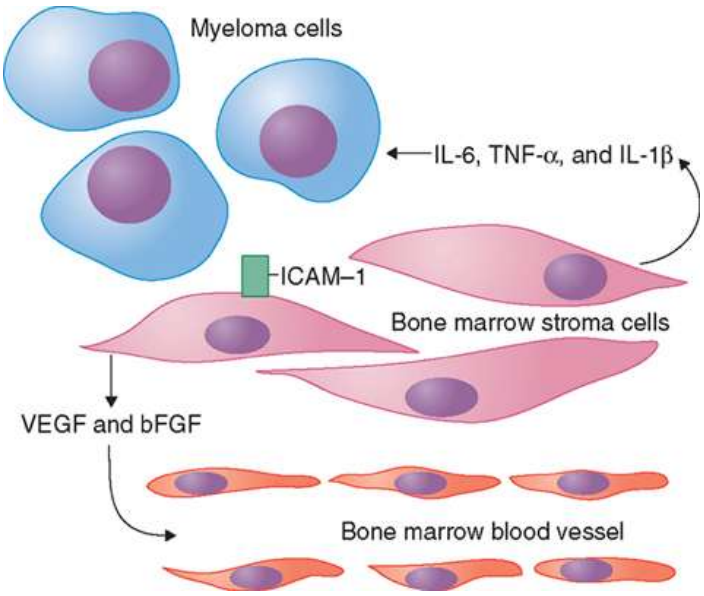


Fig 2.3 Pathogenesis of multiple myeloma (Baz R, Bolwell B)

The production of IL-6 by BMSCs, which is via activation of nuclear factor kappa B (NF-κB), triggers proliferation of myeloma cells, and protects them against dexamethasone-induced apoptosis. Anti-myeloma effects of drugs, such as thalidomide, dexamethasone and bortezomib (proteosome inhibitor), inhibit NF-κB.

Angiogenesis is also increased in some cases of myeloma. Secreted vascular endothelial growth factor (VEGF) from myeloma cells interacts with receptors on endothelial cells to enhance their migration and proliferation. There is also inhibition of T-lymphocyte function through production of inhibitory molecules such as interferon-alpha and reduction of interferon-gamma (4).

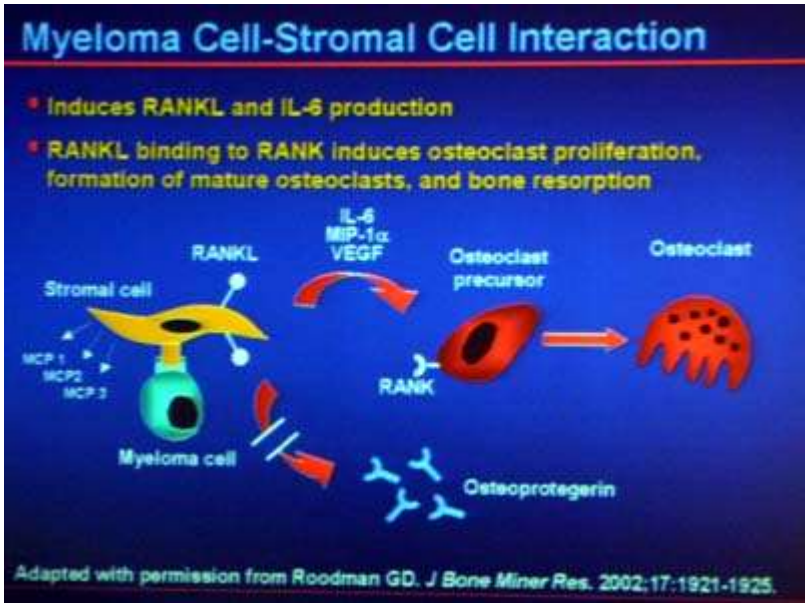


Fig 2.4: Myeloma Cell-Stromal Cell Interaction (taken from www.google/images)

2.3. Biology of bone disease

Bone destruction in myeloma is related to increased osteoclastic activity which is not accompanied by a comparable increase in osteoblast formation. This uncoupling of resorption and formation leads to rapid bone loss, osteoporosis, lytic lesions and fractures. A number of cytokines and growth factors that are produced by either myeloma cells or BMSCs have been implicated in the increased osteoclast formation and activity in myeloma. These cytokines include IL-6, IL-1β, IL-11, TNF-α, TNF-β and more recently, macrophage inflammatory protein 1 alpha (MIP-1α), hepatocyte growth factor and the RANKL pathway.

RANKL interacts with a cellular receptor activator of NF-κβ (RANK), and a soluble decoy receptor of RANKL, named osteoprotegerin (OPG). Following activation of RANK on osteoclasts by its ligand, RANKL, differentiation, proliferation and survival of osteoclasts is enhanced. OPG is reduced in myeloma, while the levels of soluble RANKL are increased. This correlates with the extent of lytic lesions and survival in myeloma. The induction and release of the different cytokines, such as IL-6, IL-1β, TNFs, basic fibroblast growth factor (bFGF) and insulin-like growth factors (IGFs), due to the adherence of myeloma cells to stromal cells, modifies the bone marrow micro environment, enhancing RANKL expression of osteoblasts.

IL-6 also acts as a growth factor for osteoclasts, and as survival factor for myeloma cells. In addition, IL-11 is also produced by both myeloma and stromal cells and exerts its effect through RANKL/RANK/OPG pathway, inducing osteoclastogenesis while inhibiting osteoblast formation (4). Figure 2.5 below illustrates the pathogenesis of bone disease in MM.

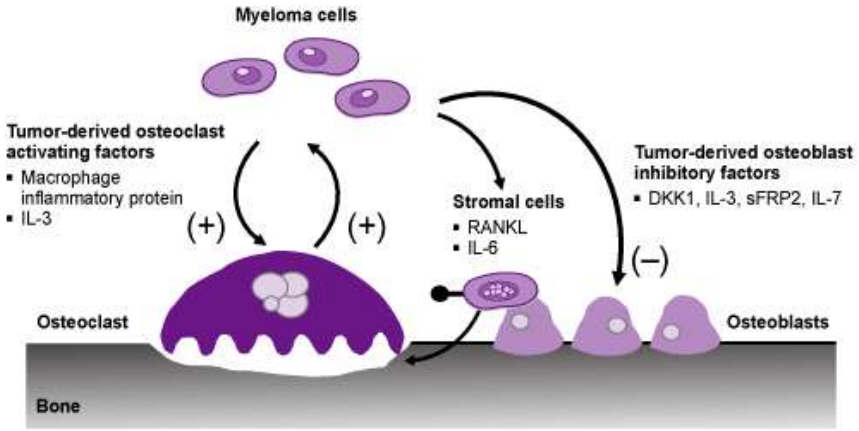


Fig 2.5 Pathogenesis of bone disease in MM (taken from ASH pictures)

2.4. Clinical features

The symptoms and signs of MM are non-specific. The plasma cell infiltration of bone marrow results in bone marrow failure, bone disease, hypercalcaemia and impaired haemopoiesis. In a minority of patients, plasma cell infiltration of soft tissues is seen at presentation, which will also include plasmacytoma that may spread extradurally or cause spinal cord compression (14).

These symptoms and signs include (4, 16):

- Bone pain, especially backache, resulting from vertebral collapse and pathological fractures. Bone pain is the most common symptom and results from osteolytic lesions and pathological fractures- mainly wedging or collapse of vertebral bodies with or without osteoporosis.
- Features of anaemia such as lethargy, fatigue, weakness, dyspnoea, pallor, and tachycardia. Normochromic, normocytic anaemia is a common finding. This may be due to the infiltration of the bone marrow by myeloma cells, chronic inflammation or the use of cytotoxic drugs. Serum erythropoietin levels are usually appropriately raised in those patients with good renal function and inappropriately low in those with poor renal function (4).
- Recurrent infections related to deficient antibody production, abnormal cell mediated immunity and neutropenia. Neutropenia and thrombocytopenia could be due to bone marrow infiltration by plasma cells or cytotoxic drugs. Infections are a major cause of death in these patients.
- Features of renal failure and/or hypercalcaemia such as polydipsia, polyuria, anorexia, vomiting, constipation and mental disturbance.

- Hypercalcaemia is caused by imbalance between bone formation and bone destruction resulting in a continuing loss of calcium from the skeleton. At presentation, around a quarter of patients have hypercalcaemia with associated lytic lesions and/ or osteoporosis. Hypercalcaemia may be severe enough to cause life-threatening dehydration and renal failure. They may also present with uraemia which may or may not be corrected by rehydration and chemotherapy. Renal dysfunction occurs when the tubular absorptive capacity of light chains is exhausted, resulting in interstitial nephritis. Other causes of renal dysfunction are amyloidosis, infection, hyperuricaemia and the use of anti-inflammatory drugs. The infiltration of the kidneys by myeloma cells is rare.
- Abnormal bleeding tendency due to myeloma protein that may interfere with platelet function and coagulation factors. Bleeding may be the result of hyperviscosity, perivascular amyloidosis, acquired coagulopathy or thrombocytopenia
- Amyloidosis which is a condition where an abnormal immunoglobulin deposits in various tissues, occur in 5% with features such as macroglossia, carpal tunnel syndrome and diarrhoea.
- In approximately 2% of cases there is hyperviscosity syndrome with purpura, haemorrhages, visual failure, central nervous system (CNS) symptoms, neuropathies and heart failure.
- Solitary plasmacytoma of bone is a biopsy proven localized bone tumour consisting of monoclonal plasma cells. Complete skeletal radiographs show no other lesions. There are no clinical features of plasma cell myeloma and no evidence of bone marrow plasmacytosis except for the solitary lesion. Patients

may present with bone pain at site of lesion, vertebrae, ribs, skull, pelvis, femur, clavicle and scapula, and also with spinal cord compression. It is more common in men (65%), median age at diagnosis is 55 years. Local control is achieved by radiotherapy in most cases, but up to two thirds of patients eventually evolve to generalized myeloma or additional solitary or multiple plasmacytomas.

- Extraosseous or extramedullary plasmacytomas are localised plasma cell neoplasm that arises in tissues other than bone. Two thirds of patients are male with a median age at diagnosis at 55 years. Approximately 80% occur in the upper respiratory tract, including the oropharynx, nasopharynx, sinuses and larynx. They may occur in numerous other sites, including the gastrointestinal tract, lymphnodes, bladder, CNS, breast, thyroid, testis, parotid and skin. Symptoms are generally related to the tumour mass and include rhinorrhoea, epistaxis and nasal obstruction. Radiographic and morphological assessments show no evidence of bone marrow involvement. There are no clinical features of plasma cell myeloma. The lesions are also eradicated with local radiation therapy. Progression to myeloma is infrequent, occurring in approximately 15% of cases (5, 17).

According to Kyle, et al. (18), the most common presenting symptoms of MM were fatigue, bone pain, recurrent infections and weight loss. Radiographic studies revealed an abnormality in 79% of patients at the time of diagnosis. Lytic lesions were found in about 67% of patients, and approximately 20% each had osteoporosis, pathologic fractures or compression fracture of the spine.

In patients without radiographic abnormalities at the time of diagnosis, lytic lesions, pathologic fractures, compression fractures or osteopaenia developed subsequently

during follow up. In 84% of patients, skeletal lesions developed at some point during the course of their disease.

2.5. Diagnosis of multiple myeloma

Clinical presentation of myeloma can vary widely. There are no definite signs or symptoms which are seen only in this disease. Some patients are free of symptoms at the time of diagnosis, with the disease being detected as a result of routine blood tests (6).

The diagnosis of myeloma depends on the abnormal findings:

- Demonstration of malignant plasma cells on examination of bone marrow or soft tissue
- X-ray showing punched out lesions of bones, osteopaenia or lytic lesions
- Blood serum or urine showing the presence of an abnormal protein (16)
- Presence of end-organ damage, known as an acronym CRAB representing hypercalcaemia, renal insufficiency, anaemia, bone lesions (5, 17).

The work-up for the diagnosis of myeloma is described below in Table 2.1.

TABLE 2.1 The work-up for myeloma (4)

• Full blood count, film and ESR. • Evaluation of kidney function, serum calcium, CRP, β2-microglobulin, LDH, uric acid levels and liver function tests. • Protein electrophoresis and paraprotein quantification, quantitative analysis of the normal immunoglobulins. • 24-hour urine collection for light chain (Bence Jones protein) excretion.

- Serum free light chain and ratio.
- Coagulation screen.
- Bone marrow aspiration and trephine biopsy for morphology, immunophenotyping and cytogenetics.
- A complete skeletal survey. Patients with symptoms or signs of cord compression would require further investigation with computerized tomography (CT) or Magnetic resonance imaging.

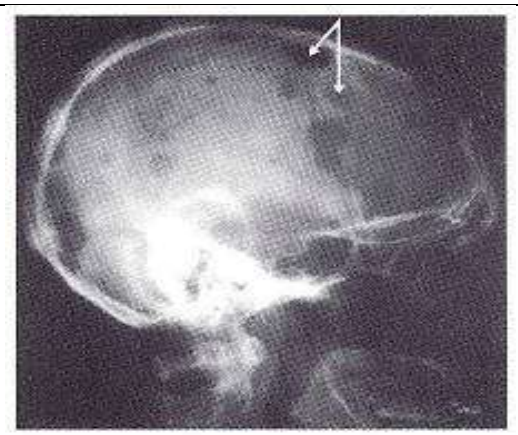


Fig 2.6 skull lytic lesions (www.google.com/images)

Figure 2.6 shows punched out lytic lesions as seen on X-ray of the skull of a patient with MM.

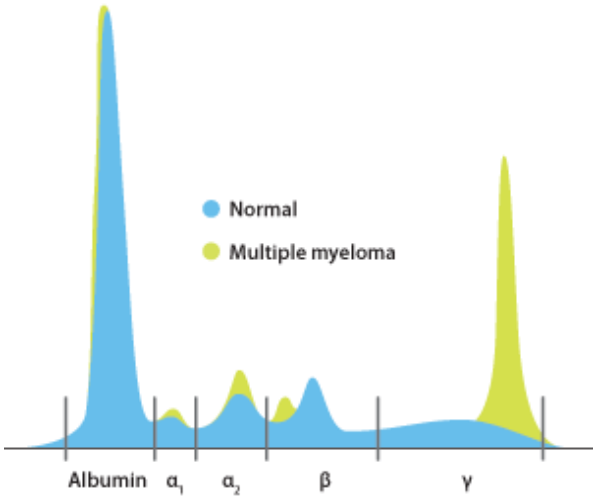


Fig 2.7 serum protein electrophoresis (www.google.com/images)

Figure 2.7 above, shows serum protein electrophoresis of a normal person and that of a myeloma patient. The myeloma patient is represented by a large peak in gamma region of the electrophoresis.

There was also development of antibody able to detect epitopes that were hidden when light chain was bound to heavy chain; quantification of free light chain not bound to heavy chain is now being detected in serum.

The serum free light chain (SFLC) assay involves measurement of both κ and λ free light chain in serum and the κ/λ free light chain (FLC) ratio. In a number of benign conditions, such as immune dysregulation and renal dysfunction, SFLC levels may be abnormal. However, only in plasma cell a monoclonal disorder is the SFLC ratio abnormal. This test provided a new measure of myeloma disease burden, especially in cases where light chain was produced. SFLC measurement is indicated in monitoring patients with AL amyloidosis, oligo-secretory or non-secretory myeloma, myeloma with renal failure where 24 hour Bence Jones protein (BJP) measurements are not reliable and light chain disease-only MM. Emerging data also suggest the role of SFLC as a prognostic marker in MGUS, smoldering myeloma and MM. In MGUS, an abnormal SFLC ratio predicts a higher likelihood of progression to myeloma. (*Munshi C. Investigative tools for diagnosis and management of myeloma. American Society of Hematology 2008*).

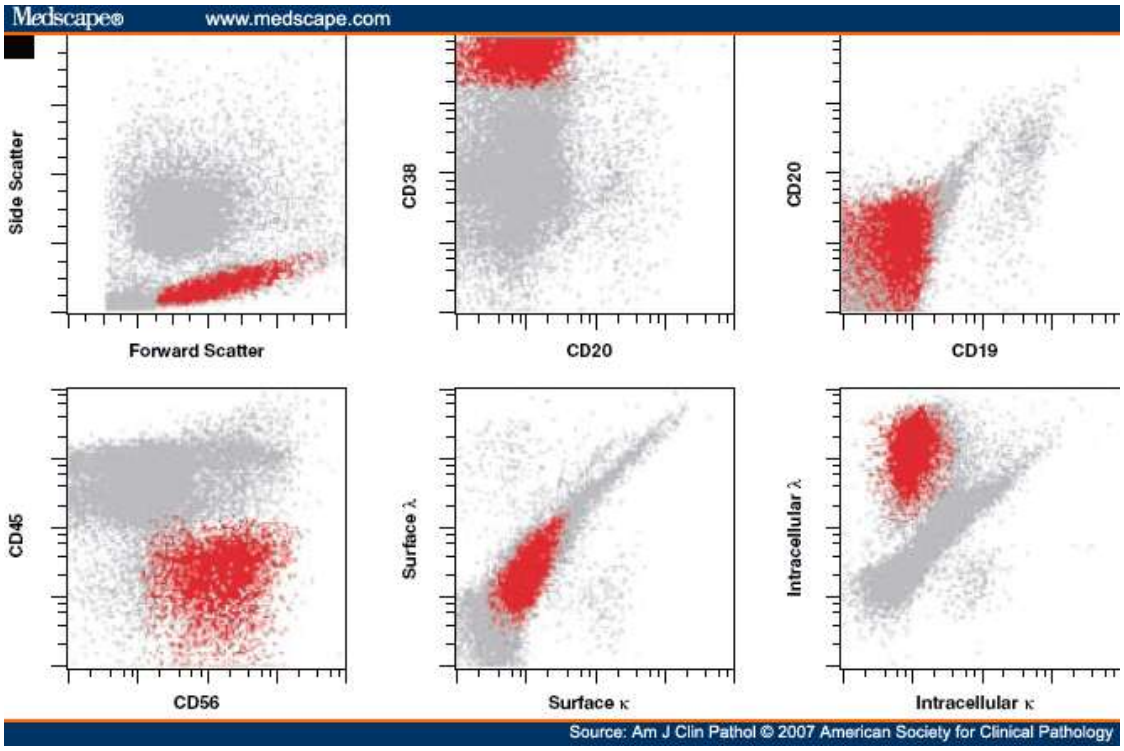


Figure 2.8 Flow cytometry histograms of a bone marrow from a patient with MM.

In Figure 2.8: The neoplastic plasma cells or myeloma cells are painted red and normal B-lymphocytes are grey. These myeloma cells are intermediate in sizes with low side scatter or internal complexity on forward and side scatter histogram. These cells express bright CD38 and are negative for CD19 and CD20. They express CD56 and partial CD45 and also express cytoplasmic lambda.

Plasma cell myelomas typically have monotypic cytoplasmic immunoglobulin (Ig) and lack surface Ig. They usually express CD79a, CD138 and strong CD38, similar to normal plasma cells. In contrast to normal plasma cells, they are nearly always CD19 negative and CD56 is aberrantly expressed in 67-79% of cases. In addition to CD56, myeloma plasma cells may aberrantly express CD117 and CD20 (5).

Additional indicators of higher risk patients are also included in the work up for myeloma. They include elevated serum β2 microglobulin, low serum albumin, elevated lactate dehydrogenase (LDH), high C-reactive protein (CRP), and increased plasma cell proliferative activity, high degree of bone marrow (BM) replacement, plasmablastic morphology and genetics (5).

MGUS should also be excluded as part of the general myeloma work up. Patients may be diagnosed with MGUS if they fulfil the following three criteria:

- Monoclonal paraprotein of less than 30g/l (<3g/dl)
- Plasma cells less than 10% in bone marrow
- No evidence of bone lesions, anaemia, hypercalcaemia or renal insufficiency related to the paraprotein.

At the Mayo Clinic, MGUS transformed into multiple myeloma at the rate of 1-2% a year, or 17%, 34% and 39% at 10, 20 and 25 years, respectively. These patients died of other causes, did not go on to develop MM because they were elderly. Kyle studied the prevalence of myeloma in the Olmsted County, Minnesota, and found that the prevalence of MGUS was 3.2% in people over 50, with a slight male predominance (25). A study conducted in Ghana, showed a prevalence of MGUS of approximately 5.9% in African men over age of 50 (51). In 2009, Landgren and colleagues, demonstrated that monoclonal gammopathy of undetermined significance consistently precedes multiple myeloma (14).

A constellation of radiological, clinical laboratory and pathological findings are combined to provide diagnostic criteria for plasma cell myeloma.

The World Health Organization (WHO) Diagnostic Criterion 2001 **(**17**)** was developed by Durie and Salmon in 1975 and adopted by WHO in 2001**.** In this diagnostic criterion, one major and one minor or three minor criteria (at least bone marrow plasmacytosis and paraprotein should be present) should be present for the diagnosis of multiple myeloma. Table 2.2 below shows the major and minor diagnostic criteria applicable to the diagnosis of MM.

TABLE 2.2 World health organization (WHO) diagnostic criteria 2001

Major criteria:	Minor criteria:
• Bone marrow plasmacytosis of >30% • Plasmacytoma • Large monoclonal globulin on serum protein electrophoresis; >35g/l IgG; >20g/l IgA; >1g/24 hour of kappa or lambda in urine	• Bone marrow infiltration with 10-30% plasma cells • Paraprotein less than the levels defined above • Lytic bone lesions • Immune paresis IgM <0.5g/l, IgA <1g/l or IgG <6g/l

Most recently in 2008, WHO adopted new diagnostic criteria for MM diagnosis, developed by the International Myeloma Working Group (IMWG) in 2003 as depicted below in table 2.3.

TABLE 2.3 World Health Organization diagnostic criteria for plasma cell myeloma 2008 (5)

Symptomatic plasma cell myeloma	Asymptomatic (smoldering) myeloma
• M- Protein in serum or urine (No level of serum or urine M-protein is included. M-protein in most cases is >30g/l of IgG or >25g/l of IgA or >1g/24hr of urine light chain, but some patients with symptomatic myeloma have levels lower than those). • Bone marrow clonal plasma cells or plasmacytoma (Monoclonal plasma cells usually exceed 10% of nucleated cells in the marrow but no minimal level is designated because about 5% of patients with symptomatic myeloma have <10% marrow plasma cells). • Related organ or tissue impairment (CRAB: hypercalcemia, renal insufficiency, anaemia, bone lesions) (The most important criteria for symptomatic myeloma are manifestations of end organ damage including anaemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis or recurrent infections).	• M-protein in serum at myeloma levels (>30g/l) AND/OR • 10% or more clonal plasma cells in bone marrow • No related organ or tissue impairment [end organ damage or bone lesions (CRAB: hypercalcemia, renal insufficiency, anaemia, bone lesions)] or myeloma- related symptoms.

The IMWG provided that three main criteria should be met in order to diagnose MM. The criteria are: 1) abnormal clonal plasma cells in BM, 2) monoclonal protein present in urine and/or blood serum and 3) evidence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, bone lesions which are depicted by acronym, CRAB. The end-organ damage, CRAB, should be linked to MM and not caused by any other disease or disorder. CRAB should also be able to differentiate between asymptomatic and symptomatic myeloma.

The differences between WHO 2001 and 2008, are that CRAB is fundamental in 2008. If any of the CRAB is present, then the diagnosis is symptomatic myeloma irrespective of the level of M-protein or bone marrow plasmacytosis. If the bone marrow plasma cell percentage is ≥10% or the M-protein is ≥30g/l and there is no CRAB, then the diagnosis is asymptomatic myeloma. If the bone marrow plasma cell percentage is <10% and the M-protein is <30g/l, and there is no CRAB, then the diagnosis is MGUS. These diverged from the previous 2001 criteria which relied on the M-protein concentration and the amount of plasma cells. These changes came from the observation that 40% of patients with MM had a serum protein less than 30g/l and 5% of patients with MM had less than 10% bone marrow plasma cells. In about 3%, the M-protein could not be detected in either serum or urine (12) .The disadvantage of CRAB or the end-organ abnormalities, is that it is common in many abnormalities or diseases. It is imperative that these abnormalities (CRAB), are proven to be directly attributable to MM and to rule out other underlying causes.

The distinction of active MM from monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma is important, as only active MM requires treatment. MGUS represents the earliest stage within the spectrum of disease and is defined as the presence of an asymptomatic monoclonal protein without an increase in bone marrow plasma cells. Smoldering myeloma is characterized by the combination of a monoclonal gammopathy and bone marrow plasmacytosis without any other symptom or laboratory abnormality. In some patients, a clear process of progression is evident from asymptomatic MGUS to smoldering myeloma to active MM, while other patients present with de novo active myeloma.

Untreated, the rate of progression from MGUS to active MM is only 1% per year, and early treatment has not been shown to be of benefit in either MGUS or smoldering myeloma (54).

2.6. Treatment and survival

The median survival of patients with MM has been approximately 3 – 4 years (18). However, some patients can live longer than 10 years (23, 27, 28, and 29). Survival of an individual patient with MM depends on variety of patient and disease factors. These can be according to age, disease staging and performance status i.e. whether you are able to perform daily activities without difficulty, as in any other malignancies.

More recently, cytogenetics has been added as one of the prognostic factors. There has been considerable inter- and intra- categorical cytogenetic variations. Therapy is adjusted based on these factors (53). Patients with abnormalities by conventional (metaphase) cytogenetics have a significantly shorter median survival than those without.

Table 2.4 Cytogenetic Prognostic Groups in myeloma (5)

Unfavourable risk:
Deletion 13 or aneuploidy by metaphase analysis
t(4;14) or t(14;16) or t(14;20) by FISH
Deletion 17p13 by FISH
Hypodiploidy
Favourable risk:
Absence of unfavourable risk genetics and presence of Hyperdiploidy
t(11;14) or t(6;14) by FISH

Prognostication based on genetic risk classification is gaining importance. The abnormalities detected by conventional cytogenetics and fluorescence in situ hybridization (FISH) reflect the detected genetic abnormality and the proliferative capacity of the myeloma cell population.

The findings of any abnormality have been initially associated with poor outcome. Until recently, some cytogenetic abnormalities as listed in table 2.4 above are associated with either good or bad outcome.

Survival also depends on disease stage, and since 1975, the Durie-Salmon staging system has been used as the standard for patients with myeloma (30). The Durie-Salmon staging divides patients into 3 stages, namely stage I, II, and III.

TABLE 2.5 Durie & Salmon staging system for multiple myeloma (5)

Stage I: • Hemoglobin level greater than 10g/dl • Calcium level greater than 12mg/dl • Radiograph showing normal bones or solitary plasmacytoma • Low M protein values (i.e. IgG <5g/dl, IgA <3g/dl, urine <4g/24h
Stage II: Findings that fit neither stage I nor stage III criteria
Stage III: • Hemoglobin level less than 8.5 g/dl • Calcium level greater than 12 mg/dl • Radiograph showing advanced lytic bone disease • High M protein value (i.e. IgG >7g/dl, IgA >5g/dl, urine >12g/24h)

Subclassification A involves a creatinine less than 2g/dl

Subclasification B involves a creatinine level greater than 2g/dl

The Durie and Salmon staging system described above on table 2.5 was based upon the levels of haemoglobin, serum calcium, serum creatinine, serum and urine paraprotein, the number and size of bone lesions. In addition, patients without or with serum creatinine of ≥ 2mg/dl were categorized as A or B (24). Its chief limitation has been the categorization of bone lesions which tends to be subjective.

The new International Staging System (ISS) based solely on two readily available tests, the β2-microglobulin and albumin, had replaced the Durie-Salmon staging system. The ISS was a collaborative effort by investigators from 17 institutions worldwide and from data on 11 171 patients (7).

It divides patients into three distinct stages with different outcomes. Patients with stage I, II, III had median survivals of 62, 44 and 29 months, respectively.

TABLE 2.6 International Staging System for plasma cell myeloma

Stage	Criteria
I	Serum β2 microglobulin <3,5 mg/l Serum albumin >3,5g/dl
II	Not stage I or III
III	Serum β2 microglobulin >5,5mg/l

According to Rajkumar and colleagues (55), the ISS allows outcome in clinical trials to be compared with each other more readily. It is easy to assess and is reproducible but has limitations. It is not useful unless the diagnosis of myeloma has already been made. The ISS has no role in MGUS or smoldering myeloma (SMM), and cannot distinguish these two premalignant disorders from myeloma. A patient with MGUS and unrelated renal failure causing elevation of β2 microglobulin can be falsely considered to be stage III myeloma. The ISS does not identify an adverse prognostic group that is sufficiently high risk to warrant a different therapeutic approach. Stage III in the ISS comprises

patients with elevated β2 microglobulin because of tumour burden as well as renal failure.

Rajkumar et al. (53), published prognostic factors and risk stratification in myeloma, involving a combination of cytogenetics, Durie-Salmon staging system and therapeutic implications. This is illustrated on the table 2.7 below.

TABLE 2.7 Prognostic factors and stratification in myeloma

Prognostic determinant	**Standard risk**	**High risk**	**Therapeutic implication**
Host factors	ECOG performance status 0-2 Normal renal function	ECOG performance status 3 or 4 Renal failure(serum creatinine ≥2.0) Advanced age	High-risk patients typically require a decrease in treatment intensity
Tumour burden	Durie-Salmon stage I,II	Durie-Salmon stage III	Limited; some stage 1 patients require no therapy (smoldering myeloma), some require radiation only (if solitary bone lesion)
Tumour biology (disease aggressiveness)	Hyperdiploidy t(11;14) t(6;14)	t(4;14), t(14;16),t(14;20),17p- High LDH, plasma cell proliferative rate, high risk signature on gene expression profiling	Treatment of high risk patients remains unsatisfactory, but bortezomib appears to overcome some high risk features t(4;14)

*ECOG indicates Eastern Cooperative Oncology Group

According to Kumar and colleagues (24), all symptomatic patients should receive treatment. Patients who are asymptomatic or those with smoldering myeloma can be kept on close follow up. Initial supportive treatment includes adequate hydration, bisphosphonates and management of renal failure, correction of anaemia and control of infection (24). Initial therapy is decided based on eligibility for autologous stem cell transplant (ASCT) or not. The specific regimen chosen for initial therapy varies widely. Patients who are not candidates for ASCT because of poor performance status, age, and co-morbidities, standard alkylating chemotherapy is usually effective. Some clinicians prefer MP, while others prefer dexamethasone alone or with thalidomide (52).

Initial chemotherapy for patients with symptomatic MM includes Melphalan and Prednisone (MP), Vincristine, Doxorubicin and Dexamethasone (VAD), alkylator-based combinations, cyclophosphamide with or without prednisone, dexamethasone alone and many other steroid-containing regimens (4).

Melphalan is a chemotherapy drug introduced in the treatment of MM in the early 1960's. This is the drug that is most commonly used, together with prednisone in our institution. It is a bifunctional, alkylating agent. Its toxicity appears to be related to the extent of its interstrand cross-linking with DNA. It also is active against resting and rapidly dividing tumor cells and is used as palliative therapy for MM. It was initially given as a continuous daily dose and from the 1970's, was gradually exchanged for the combination with prednisone (MP- Melphalan + Prednisone). Patients are treated with Melphalan-containing regimen for 12 to 18 months. In approximately 40 percent of patients with newly diagnosed myeloma, intermittent courses of melphalan and prednisone induced remission. The median duration of remission is approximately two years, and the median survival approximately three years. Less than 10% of patients live

longer than 10 years. The principal problem is drug resistance, low frequency of complete remission and inevitable relapse unless death occurred from an unrelated disease or secondary leukaemia (56).

The use of consolidation and maintenance after initial therapy still vary. Most patients will inevitably relapse**.**

Alexanian and colleagues (56) indicated that the survival benefit is meaningful for patients with responsive disease and a realistic goal of treatment is to achieve a partial or complete response that can be sustained for a long period of time with few side effects and management of relapsing disease with treatments that are associated with low morbidity and mortality. They also indicated that it requires vigilant follow up and periodic choices between standard and more intensive therapies.

A study by Blade' et al. (20), found that Melphalan and Prednisone was as effective as combination chemotherapy in both response rate and survival, and they remained the gold standard for MM treatment, particularly in elderly people in whom high dose therapy is not feasible. Although the survival of older patients was shorter than that of younger subjects, the median survival duration was still two years. Again, Kyle et al. (18)) found that the median overall duration of survival was 33 months. The duration of survival was 40.5 months for patients younger than 70 years and 26.4 months for those 70 years or older.

According to Kyle et al. (18), the median survival of patients treated with oral Melphalan plus prednisone chemotherapy was 31 months. The corresponding median survival for patients treated with other regimens was 38 months. A number of

investigators have used MP in addition to the immunomodulatory agent thalidomide (MPT). MPT was first noted to have activity against relapsed or refractory disease. The Italian Multiple Myeloma Network and Intergroupe Francophone du Myėlome randomized trials strongly supported the use of MPT as the standard of care for older patients with newly diagnosed multiple myeloma (63).

VAD and VAD-associated regimens: the combination of vincristine and doxorubicin administered together with high dose oral dexamethasone is the most frequently used first line chemotherapy regimen for myeloma. This regimen is suitable for patients in whom high dose chemotherapy and ASCT are planned as treatment, as they do not damage haemopoietic stem cells (4).

Thalidomide and dexamethasone: this combination produces response rates up to 65% similar to VAD regimens. Unfortunately, venous thromboembolism is seen in 10% of patients. The effect of thalidomide and dexamethasone, in combination with other chemotherapeutic agents, for example, cyclophosphamide, are still being investigated (4). VAD and Bortezomib are also used in treatment of refractory and relapsed disease.

Bortezomib (formerly PS341) is a small molecule that is a potent and selective inhibitor of the 26S proteasome, which is the primary component of the protein degradation pathway of the cell. Bortezomib inhibits proliferation and induces apoptosis of human myeloma cell lines.

It also inhibits the NF-κβ activation, as described in pathogenesis of myeloma, above. Thirty-eight percent to 40% of patients with newly diagnosed myeloma will respond to single-agent bortezomib. The addition of dexamethasone results in overall response rate 67% to 88%.

Several combinations have been explored for induction therapy (64).Lenalidomide (Revlimid) is a novel immunomodulatory agent that is more potent than thalidomide. This drug also adds to the efficacy of steroids in R-MP (lenalidomide, melphalan, and prednisone). MPT has been seen to provide a survival advantage over MP, but thalidomide has been substituted by lenalidomide, due to adverse effects (63).

Patients younger than 65 years of age with newly diagnosed myeloma are eligible for ASCT. These patients are treated with high dose myeloablative chemotherapy (non-Melphalan containing) induction regimen followed by transplant. Myeloma still remains incurable, but both overall and event-free survival is prolonged following ASCT when compared with conventional chemotherapy (52). Survival of patients has generally improved; this can be attributed to active new agents like thalidomide, bortezomib, lenalidomide and optimal use of ASCT and improvements in supportive care (52). Stem cell transplantation is not available in our setting.

Figure 2.9 below shows treatment of newly diagnosed MM patients based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus. This is applicable only to patients who are not eligible for bone marrow transplant.

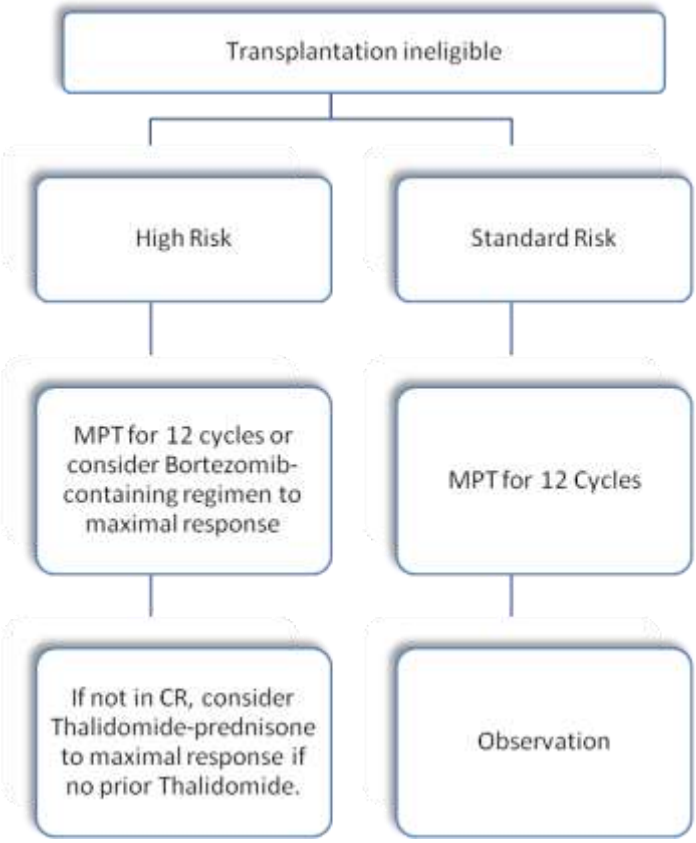


Figure 2.9 mSMART Consensus (64)

Limitations of previous studies included lack of clinical data for individual patients and possible changes in diagnostic practices over time. It could not be ruled out that the observed improved survival was influenced by an increased access to healthcare and earlier detection of the disease over time, also called lead time bias (31). The treatment of myeloma varies considerably across institutions, due to cost and availability of new drugs, and in part may be related to differing treatment philosophies and interpretations of available data, as cited by Rajkumar, et al. (53).

The management of myeloma has evolved over the past two decades from being incurable; the disease is now a chronic illness (24). Patients require careful assessment prior to initiation of treatment and also frequent follow up.

Patients may present late, or elicitation of their symptoms may fail to lead to timely referral for specialist care (32). The main aim of this study is to determine factors that will help in early recognition of the disease, reduce delays in diagnosis and improve the management of these patients.

CHAPTER 3: RESEARCH METHODOLOGY

3.1. Introduction

The aim of this study was to describe the profile of patients diagnosed with multiple myeloma from 1 January 2004 to 31 December 2009 at Dr George Mukhari Tertiary Hospital. The demographic profile, age and gender, presenting symptoms and signs, underlying chronic illnesses, criteria used for diagnosis and staging are described. The 5-year observed survival rate of these patients on treatment was also determined.

3.2. Study setting

The study was conducted at Dr George Mukhari Hospital. It is a tertiary and an academic hospital, which serves as the major teaching hospital for the University of Limpopo – Medunsa campus. It is located 37 km North-West of Pretoria, adjacent to the Ga-Rankuwa Township, Gauteng Province (RSA). It serves as a referral centre for surrounding local areas (Ga-Rankuwa, Mabopane, Soshanguve, Hammanskraal, and Winterveld), North West Province (Brits, Rustenburg) and Limpopo Province (Polokwane to Messina).

The majority of the patients attending DGMH are black. There are 900 beds available, catering all clinical departments. The Haemato-Oncology Unit is a small subunit of the Department of Internal Medicine, conducting an Out-Patient Clinic seeing approximately twenty patients each week and has a ten-bed In-Patient ward. This Unit is run by a professional nurse, two staff nurses and two physicians. The diagnosis and management of patients is the responsibility of the Haemato-Oncology Unit in collaboration with the Department of Haematological Pathology (National Health Laboratory Services).

3.3. Study design

This is a descriptive study in which medical records of patients diagnosed and treated with multiple myeloma between 1 January 2004 and 31 December 2009 were reviewed. The presenting symptoms and signs, with chronic underlying illnesses were based on what was recorded in the patients' files.

The diagnosis and staging were based on laboratory results, radiographs and other tests. The data collection sheet (appendix A) illustrates the data that was collected.

The sample size was 34 patients who met the criteria for the diagnosis of MM during the six-year period.

3.4. Inclusion criteria

All patients who met the criteria for the diagnosis of MM according to World Health Organization (WHO) 2001 or 2008 criteria were included in this study. The diagnosis of multiple myeloma was based on the following findings: 1) increased numbers of plasma cells in the bone marrow or histological proof of plasmacytoma; 2) presence of an M-protein in the serum or urine; 3) bone lesions; 4) immunoparesis; and 5) presence of "CRAB" acronym for hypercalcaemia, renal failure, and anaemia or bone lesions. The criteria are illustrated in Appendix B. Patients with other plasma cell neoplasms, for example, monoclonal gammopathy of undetermined significance, solitary plasmacytoma, and plasma cell leukaemia were excluded from the study.

3.5. Data collection

Data was collected from various sources with permission of the relevant authorities. Files of patients attending the Haemato-Oncology Unit were stored in alphabetical order

in a Multiple Myeloma cabinet and deceased patients' files were filed separately. These files were reviewed with permission of the Superintendent of the Hospital, Head of the Department of Internal Medicine and Sisters in charge. Laboratory results were reviewed from the NHLS (National Health Laboratory System) Laboratory Information System "DISA LAB" using file numbers, with permission of the Laboratory Management. Data was initially captured on an Excel spread sheet. Limitations included the unavailability of a fully detailed medical history, inadequate filing system and files that were lost. These had a great impact on the sample size of our study.

3.6 Data analysis

Descriptive statistics was used for data analysis of the objectives. Frequency distributions were calculated and presented using graph and tables. Before analysis of data, data was coded for ease of computing and Epi Info statistical program was used in the analysis of data. Means, modes and frequencies were computed including Kaplan Meier Survival analysis. .

For objective 1, the demographics, presenting symptoms and signs, criteria used for diagnosis and staging were determined. Thirty four patients were included in this study. The social and occupational histories were excluded due to incomplete records. The presenting symptoms would be what the patients complained of when they were diagnosed. The symptoms were: incidental finding with no symptoms, back pain, bone pain, general weakness, unable to walk, fatigue and headache. The presenting signs were features as examined and investigated for by attending doctor.

These were found to be: fracture, meningioma, osteoarthritis, paraplegia, plasmacytoma, pneumonia, renal failure and vertebral collapse. The underlying chronic illnesses, diabetes mellitus, hypertension, and HIV status were included.

The criteria used for diagnosis, were WHO 2001 or 2008. These involved the following variables: bone marrow plasmacytosis determined by bone marrow aspirate and trephine biopsy where the morphology and number of plasma cells were assessed. Plasmacytoma which was based on biopsy results from bone or any tissue. Monoclonal gammopathy where total protein was measured followed by serum protein electrophoresis which indicated any monoclonal peak; immunofixation and quantification which determined the type and amount of immunoglobulin involved and any decrease in other types of immunoglobulins (immunoparesis).

CRAB was determined if there was high calcium levels, renal failure (high urea and creatinine levels), low haemoglobin levels and lytic lesions on X-rays, bone scans, CT, MRI or PET scans.

The staging systems used, were Durie-Salmon and International staging systems (ISS). These were also determined by checking the laboratory investigations and X-rays. For the ISS, albumin levels and β2 microglobulin were determined. For Durie and Salmon system, haemoglobin, calcium, monoclonal protein levels, and the extent of lytic lesions on X-rays and scan were determined. The laboratory results were also retrieved from the laboratory computer system with permission from the NHLS.

The determination of the survival rate (Objective 2) was assessed using the Kaplan Meier survival analysis method. This survival analysis summarised time to event data with censoring.

Not all patients were observed for the full time to event but should a person die from a cause other than multiple myeloma or lost to follow up before experiencing the event of interest; he or she was censored from the analysis at the time last observed. Survival was calculated from the year of diagnosis until the year of death, lost to follow up, or end of study, whichever occurred first. The primary treatment in the majority of these patients was palliative consisting of Melphalan and prednisone. Vincristine, doxorubicin and dexamethasone were used in one patient who became resistant to melphalan and prednisone. The survival was determined on patients receiving treatment. This analysis did not distinguish the specific types of treatment for individual patients.

Survival analysis was specifically designed to summarise time to event data with censoring. The resulting estimate would not be biased by being based on shorter follow up and fewer deaths, provided that three basic requirements were met. These were: correct recording of time of entry into the study, correct recording of time to event or loss to follow up and the assumption that a patient's chance of being lost or withdrawn was unrelated to the risk of distant recurrence or death from multiple myeloma. If any of these were not met, serious bias in the survival curve would result.

The survival curve was drawn as a step function. The percentage surviving individuals remained unchanged between any two events. At the time zero, all patients were alive, so the survival estimate was 100%. Time zero was the time when each patient entered the study. We did not know whether they would eventually suffer from a recurrence or die from MM, and therefore had to be treated by a mathematical method called censoring. Subjects contributed information to outcome calculations until the last time point of follow-up.

A life table according to the Kaplan-Meier product limit method was drawn to estimate the percentage of patients who survived and did not experience an event. The formula for the calculation of the life-table was calculated according to probability of surviving a given period of time. Time was considered to consist of many small intervals of similar duration (e.g. days).

pk = estimated % surviving beyond a given day k

pk = [no. of patients surviving beyond day k /no. surviving beyond day k + no. dying at day k] × estimated % surviving up to day k

A survival curve was then drawn. At the time zero, all patients were alive, so the survival rate was 100%. The survival curve had a downward step whenever an event occurred. The set of times at which the curve showed a step was the uncensored event times in the data set.

3.7. Reliability, validity, objectivity

When applying quantitative research methods, the merit of the research was acknowledged through the evaluation of the validity and reliability of the work. Reliability was the extent to which a test or measurement gave consistent results. Validity referred to the extent to which a measurement, concept or conclusion was accurate. Reliability and validity in this study was ensured as follows: a detailed description of the research design, method, data collection procedures and analyses were provided in the study to allow replication of research under similar conditions. Validity was not possible without reliability (13).

Validity was ensured by: data being collected by the researcher, herself, results of the patients were retrieved from NHLS (National Health Laboratory Services) computer system (DISA LAB) and the clinical details were retrieved from patient files, which were recorded by qualified personnel (medical doctors, nursing staff).

3.8. Bias

Over diagnosis and misclassification bias were prevented as patients with multiple myeloma in this study were diagnosed according to criteria. If you did not meet the criteria, you were not diagnosed as multiple myeloma. All patients meeting the diagnostic criteria during the period of review were included in the study.

3.9. Ethical consideration

The conducting of research required not only expertise and diligence, but also honesty and integrity. To render the study ethical, the rights to anonymity, confidentiality and consent were observed.

Approval was obtained from Medunsa Research Ethics Committee of the University of Limpopo (Medunsa Campus) before the study commenced. Permission of Superintendent of Dr George Mukhari Hospital for access to patient records was obtained. Permission to access patient results from Laboratory Information System (DISA Lab) was obtained from National Health Laboratory Services (NHLS) management.

Anonymity and confidentiality were maintained throughout the study. All data was kept confidential. Patients were not identified in the study. The file numbers of patients were used, and they were delinked from any personal identifiers to ensure confidentiality. Scientific honesty was also regarded as a very important ethical responsibility when

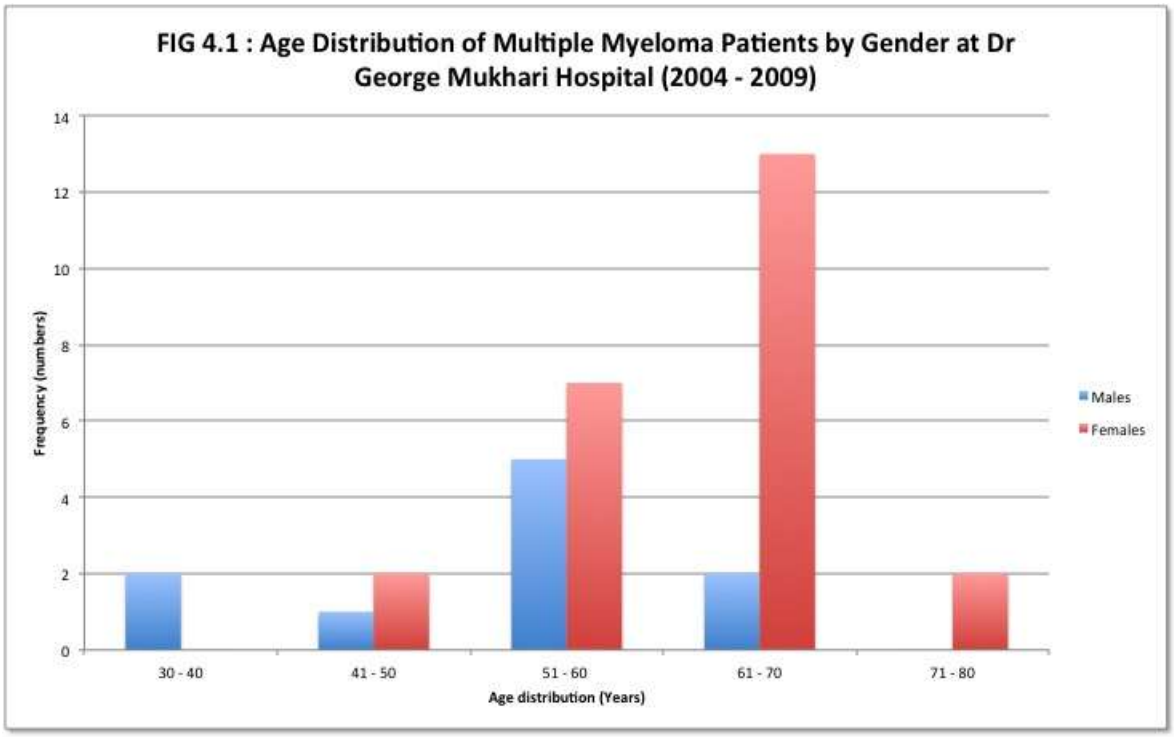
conducting research. Dishonest conducts include manipulation of design and methods, and retention or manipulation of data (Brink 1996:47).The researcher tried to avoid any form of dishonesty by recording truthfully from the records of patients. Manipulation of data could not be done as an independent statistician entered the data from data collection sheets into the Epi Info programme for analysis and also produced the results independently of the researcher to avoid subjective collaboration. The researcher attempted to present the results of the study truthfully and honestly.

All attempts were made for the supervisor or researcher's own perspectives and biases not to influence the findings. No data was misrepresented; credit was given to other authors whose suggestions were used and ideas from other materials were acknowledged (13).

CHAPTER 4: RESULTS

The results of the study showed that of the 34 patients diagnosed and treated for MM from the period between January 2004 to December 2009, 10 were males, constituting 29.4% of the sample and the majority were females constituting 70.6% (24). In terms of race, 32 constituting 94% were Africans and 2 (6%) were undefined or at least no entry could be found on the patient records.

The average age of the patients from the records revealed an age of 59 years for both males and females with a minimum age of 30 and a maximum age of 75. The modal age was found to be 53 years. When age was disaggregated by gender, males had an average age of 53 years, minimum of 30 years and maximum of 67 years. Females on the other hand had an average age of 61 years with 47 and 75 years, as minimum and maximum ages respectively.

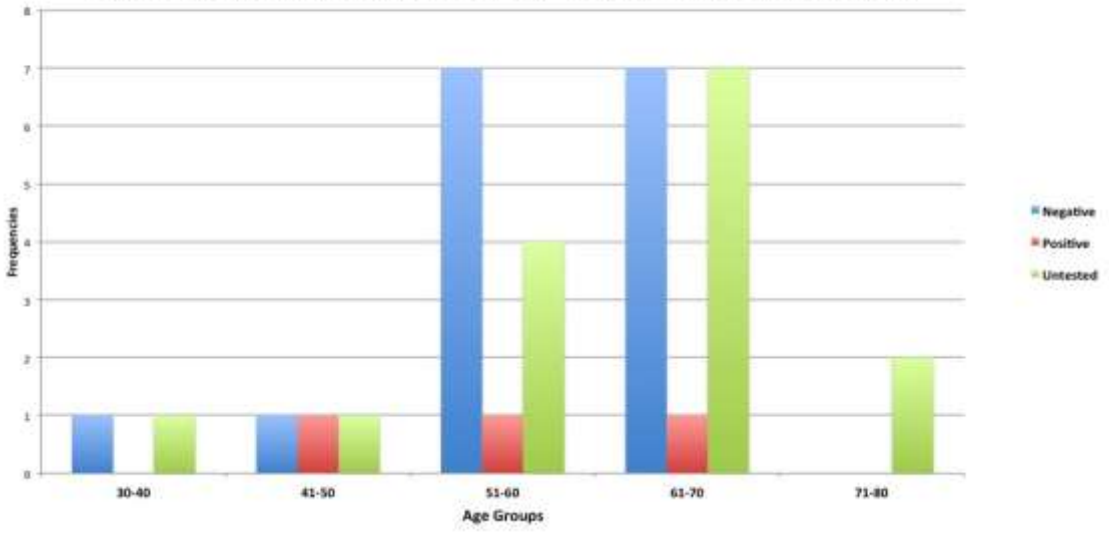


Depicted in Figure 4.1 above, the majority of patients from the records reviewed, 44% were within the 61 – 70 age groups. Of this 44%, males (2) constituted about 6% and females (13) constitute about 38% respectively.

The group ranking second, in which 35% of the patients belonged, was the 51 – 60 years age group. In this group males constituted 15% (5) and females constituted 21% (7). This was subsequently followed by the 41 – 50, 30 – 40 and 71 – 80 years age groups respectively.

Data on marital status, level of education, place of origin, occupation, industry employed, years of experience and employment status were either missing, lacking or incomplete on the patient's records during the review and as such these could not be determined or included in the analysis.

FIGURE 4.2: HIV STATUS AMONGST MULTIPLE MYELOMA PATIENTS ATTENDING DR GEORGE MUKHARI HOSPITAL FROM 2004 - 2009, ACCORDING TO AGE GROUP



In terms of HIV status - of the 34 patients seen - 56% were tested for HIV and 44% were either not tested or results were not recorded in the patient records. Of the 56% patients who were tested or at least data of HIV status was reflected on the records - 8% (3) were found to be HIV positive and 47% (16) were negative. Of the 8% who were HIV positive, all three were women. Figure 4.2 above, showed the HIV status of multiple myeloma patients according to age groups of patients attending at Dr George Mukhari Hospital. HIV positive individuals – one in each group - were observed in the age groups, 41 – 50, 51 – 60 and 61 – 70 years respectively and all were females.

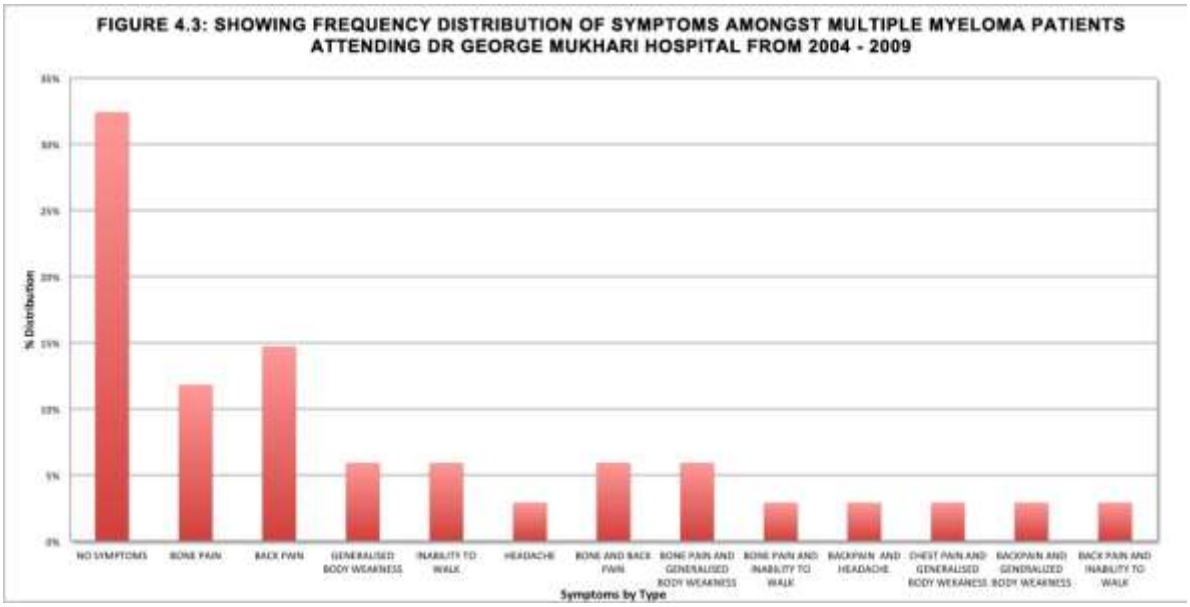


Figure 4.3 above shows the distribution of symptoms amongst patients diagnosed with MM at DGM Hospital for the period 2004 – 2009. Of the 34 patients referred above, majority comprising 11 patients who constituted about 32.4% presented with no symptoms. Five patients constituting about 14.7% presented with bone pain, followed by back pain in 11.8% of the presenting patients. Generalized body weakness and inability to walk ranked the same in about 6% of patients. This was subsequently followed by headache in only one (2.9%) patient.

Some patients presented with more than one symptom. Two patients (6%) presented with both bone and back pain, the other two presented with back pain and generalised body weakness. In each of the following symptoms categories, only one patient was identified, these categories included bone pain and inability to walk, back pain and headache, chest pain and generalized body weakness, back pain and generalised body weakness, and back pain and inability to walk.

Figure 4.4 and 4.5 below show the results of patients' symptoms disaggregated by gender. It reveals that in the majority of patients, back pain comprised about 30% of all symptoms in male patients whereas in females bone pain was the highest of all symptoms at about 16.7%. Lack of symptoms was highest in males presenting at the hospital than females at 30% as compared to 24%.

As has been previously indicated, back pain featured the most in males, followed by generalized body weakness, headache, bone and back pain and back pain and headache at 10% respectively. In females, bone pain was the leading symptom at 12%, followed by back pain, inability to walk, bone pain and generalized body weakness.

FIGURE 4.4: PERCENTAGE DISTRIBUTION OF SYMPTOMS AMONGST MALE PATIENTS DIAGNOSED WITH MULTIPLE MYELOMA AT DR GEORGE MUKHARI HOSPITAL (2004 - 2009)

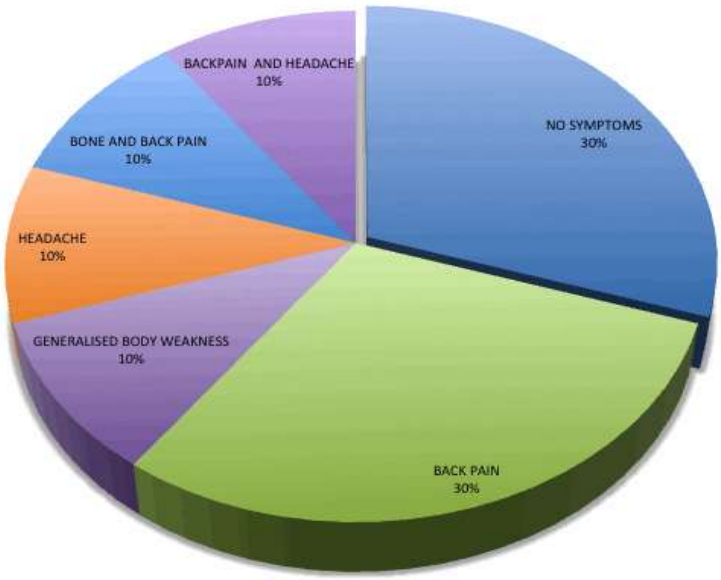


FIGURE 4.5: PERCENTAGE DISTRIBUTION OF SYMPTOMS AMONGST FEMALE PATIENTS DIAGNOSED WITH MULTIPLE MYELOMA AT DR GEORGE MUKHARI HOSPITAL (2004-2009)

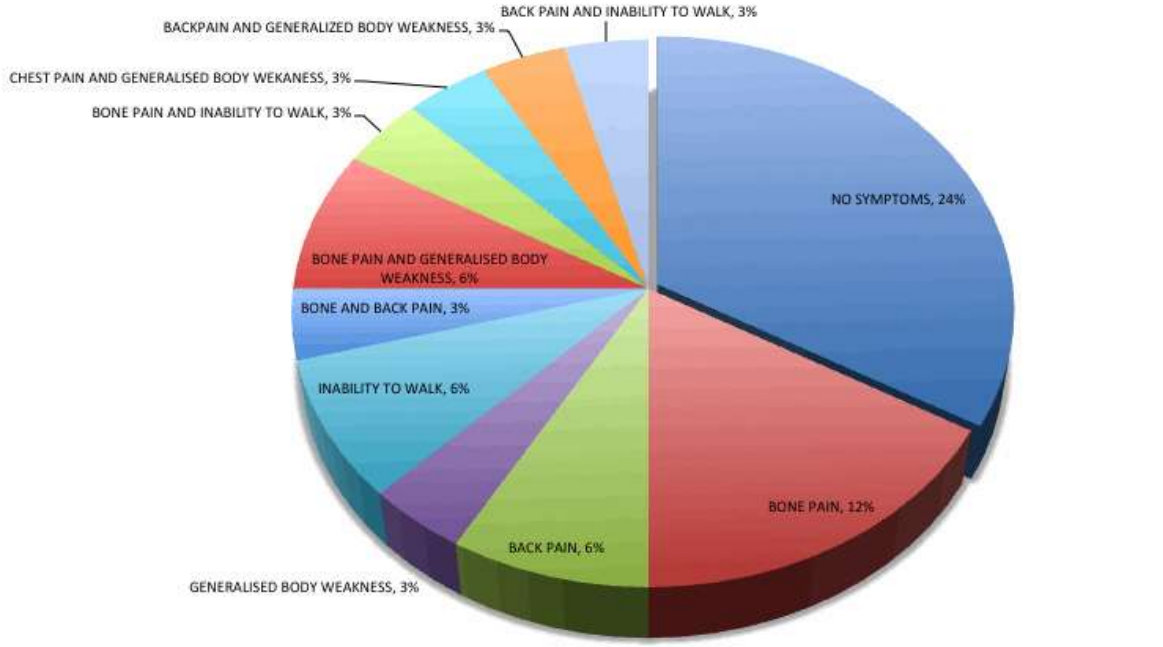
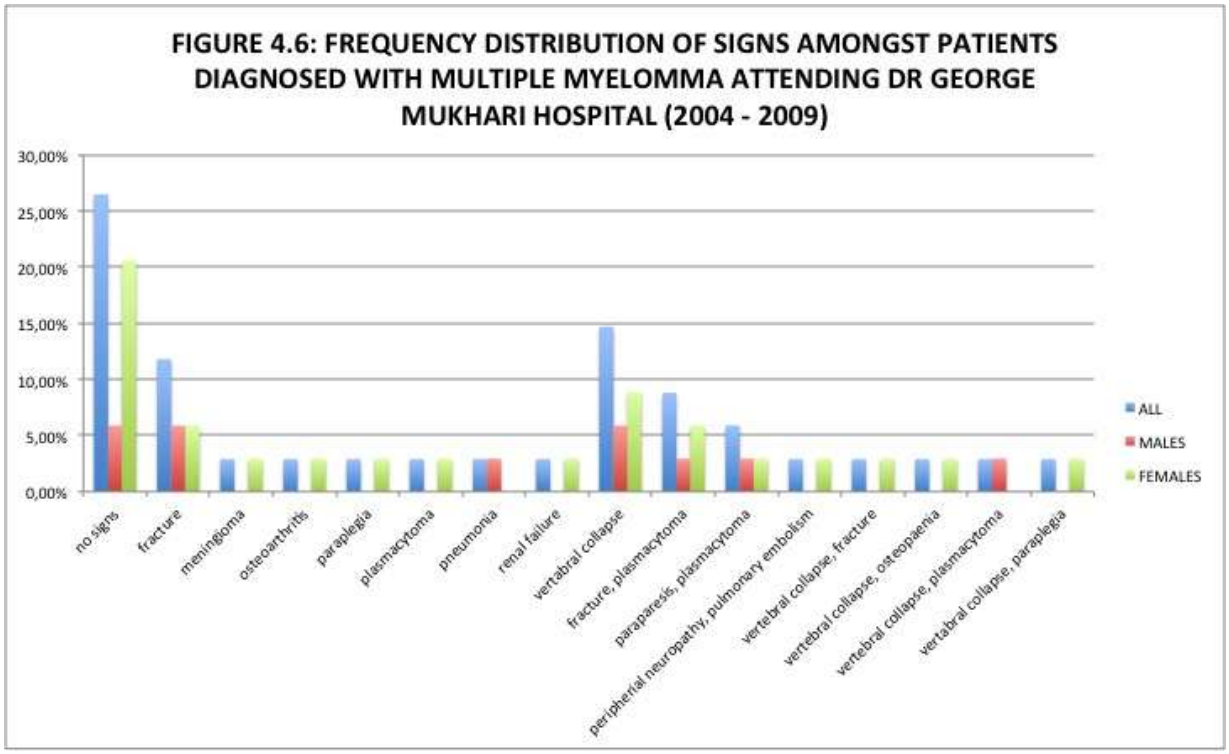


Figure 4.6 below shows the distribution of presenting signs amongst patients diagnosed with MM attending Dr George Mukhari Hospital. These are further disaggregated by gender to show any variation between the two groups.



From the figure above, the majority of patients did not present with any signs and this figure constituted about 26.5%. Of the 26.5%, females were more than males at 20.6% with males only contributing about 6%. This category of signs was followed by vertebral collapse contributing 14.7% of all patients diagnosed with MM attending Dr George Mukhari Hospital for the period under review. Of this group or category, females had the highest proportion of presenting signs than males at 8.8% compared to 5.9%. The third highest proportion of presenting signs amongst these patients included the combination of fracture and plasmacytoma, which in females was also high at about 5.9% as compared to 2.9% in males. A combination of paraparesis and plasmacytoma was the fourth highest presenting signs but both group had similar proportion of 2.9%.

From the figure above, presenting signs in males included the following, fracture, pneumonia, vertebral collapse, fracture and plasmacytoma, paraparesis and plasmacytoma and lastly vertebral collapse and plasmacytoma. Females had all the

types of presenting symptoms with the exception of the following, pneumonia, vertebral collapse and plasmacytoma.

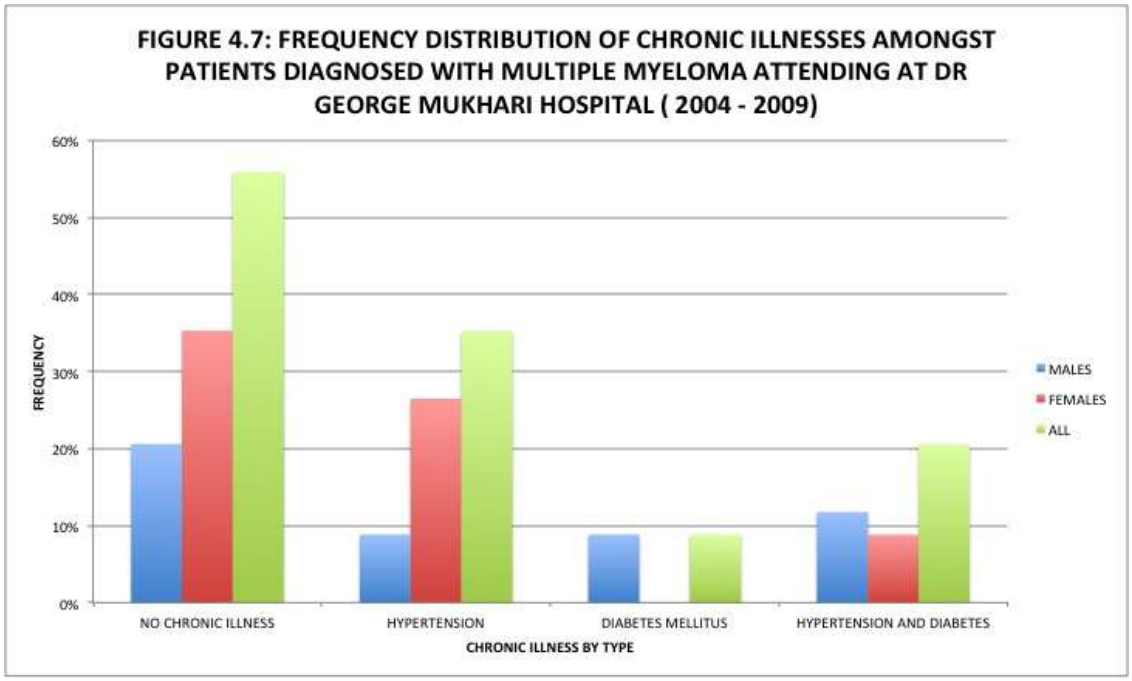


Figure 4.7 above shows the proportion of chronic illnesses in this study. The majority of patients presented with no chronic illnesses and this proportion contributed 56%. Of the 56%, males comprised 21% while females made up 35%. Hypertension was the leading chronic illness amongst these patients at 35%, with males contributing 9% and females 26%. This was followed by the combination of diabetes mellitus and hypertension which comprised 21% of all patients. Of this proportion, males made up 12% while females' contribution was 9%. Diabetes Mellitus was the lowest at 9% and appeared only in male patients.

Figure 4.8 below, shows the type of diagnostic criteria which was used in the diagnosis of MM amongst patients attending DGMH from 2004 – 2009. For the majority of MM

patients, the WHO 2001 diagnostic criteria were used in 94% (32) of patients. For the remaining 6% (2), a combination of WHO 2001 and 2008 was used.

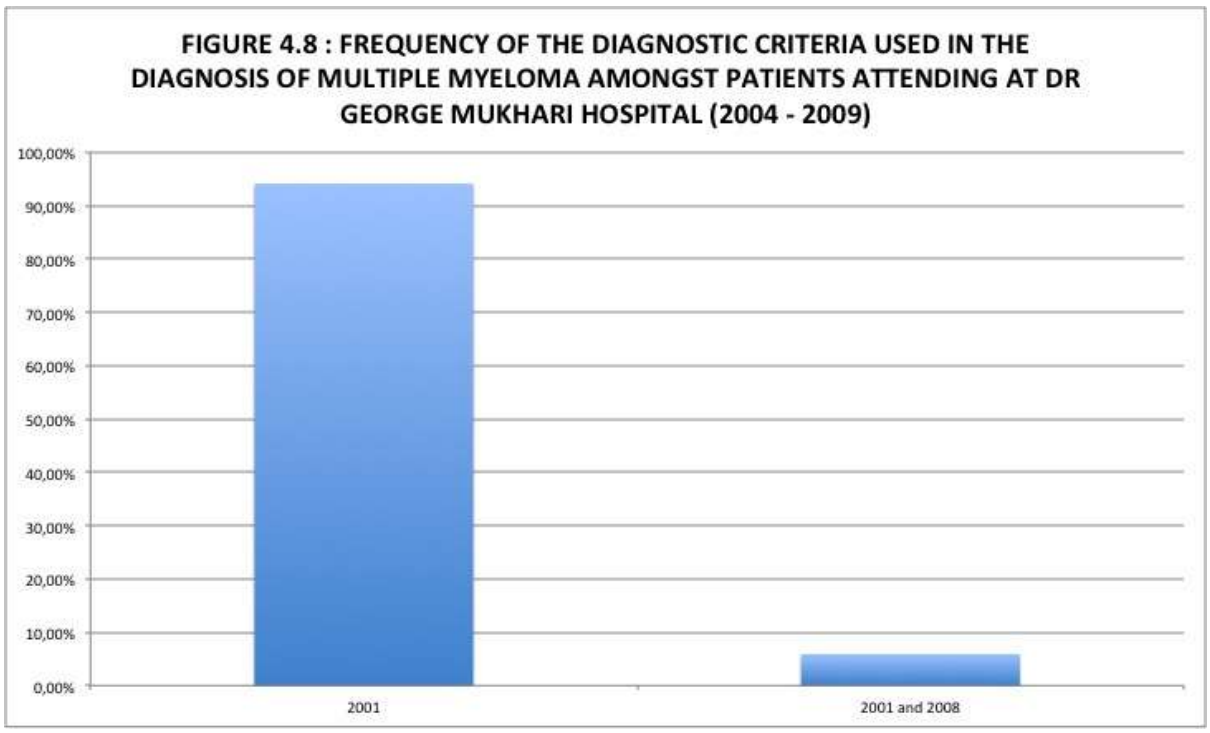


Figure 4.9 below, shows the proportion of major criteria used in the diagnosis. Of the major criteria used, Large Monoclonal Peak was most frequently used. This was used in 41% of instances. This was followed by the combination of BM Plasmacytosis and Large Monoclonal Peak used in 35% of patients. The third highest criterion used was Plasmacytoma and Large Monoclonal Peak and this contributed 11.8% of all diagnostic criteria used. BM Plasmacytosis was used in 5.9% of patients. BM Plasmacytosis and combined BM Plasmacytoma, Plasmacytoma and Large Monoclonal peak were each used in 2.9% of patients.

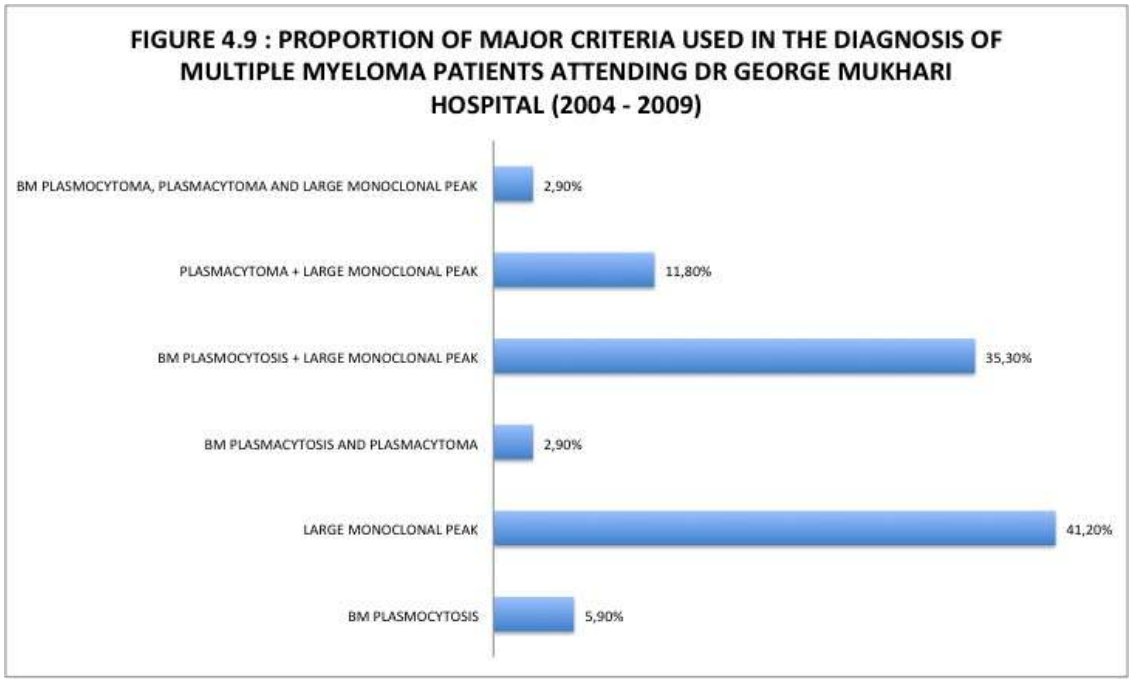


Figure 4.10, shows the proportion of minor criteria used in the diagnosis of MM. Of the minor criteria used, Immunoparesis was the most frequent contributing 26.5%, followed by Lytic Bone Lesion and Immunoparesis at 23.5%, then i) BM Plasmacytosis 10 – 30 & Immunoparesis, ii) BM Plasmacytosis, iii) BM Plasmacytosis 10 – 30, Lytic Bone Lesion & Immunoparesis, iv) BM Plasmacytosis and Lytic Bone Lesion, v) Paraprotein level, Lytic Bone lesion & Immunoparesis and lastly vi) Lytic Bone Lesion at 14.7%, 8.8%, 5.9%, 5.9%, 2.9% and 2.9% respectively.

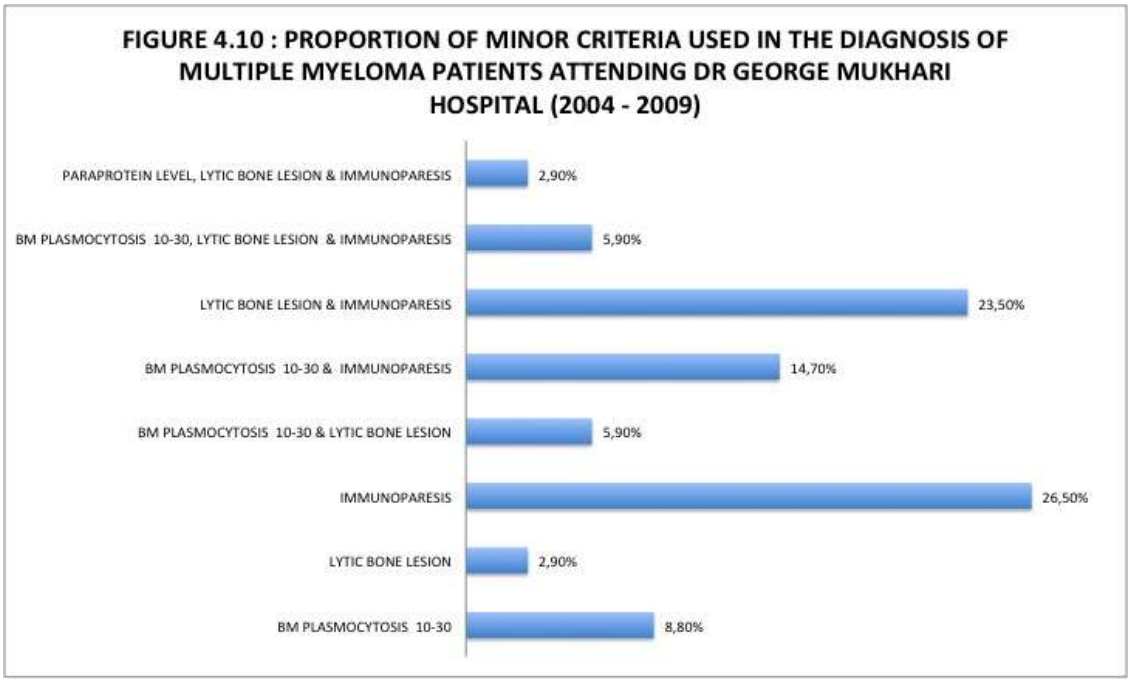


Table 4.1 below, shows the WHO 2001 major and minor criteria used in the diagnosis of MM in this study. With regards to the WHO 2001 diagnostic criteria, diagnosis is and can mostly be made from the combination of the two criteria i.e. one or more of the major criteria combined with one or more of the minor criteria.

		MINOR CRITERIA									
		0	BM PLASMOCYTOSIS 10-30	LYTIC BONE LESION	IMMUNOPARESIS	BM PLASMOCYTOSIS 10-30 & LYTIC BONE LESION	BM PLASMOCYTOSIS 10-30 & IMMUNOPARESIS	LYTIC BONE LESION & IMMUNOPARESIS	BM PLASMOCYTOSIS 10-30, LYTIC BONE LESION & IMMUNOPARESIS	PARAPROTEIN LEVEL, LYTIC BONE LESION & IMMUNOPARESIS	TOTAL
MAJOR CRITERIA	BM PLASMOCYTOSIS	0	0	0	0	0	0	1	0	1	2
	LARGE MONOCLONAL PEAK	1	1	1	3	1	5	0	2	0	14
	BM PLASMACYTOSIS AND PLASMACYTOMA	0	0	0	1	0	0	0	0	0	1
	BM PLASMOCYTOSIS + LARGE MONOCLONAL PEAK	1	0	0	4	1	0	6	0	0	12
	PLASMACYTOMA + LARGE MONOCLONAL PEAK	1	2	0	1	0	0	0	0	0	4
	BM PLASMOCYTOMA, PLASMACYTOMA AND LARGE MONOCLONAL PEAK	0	0	0	0	0	0	1	0	0	1
	TOTAL	3	3	1	9	2	5	8	2	1	34

Table 4.1: Showing the WHO 2001 major and minor criteria used in the diagnosis of MM patients who attended Dr George Mukhari Hospital between 2004 and 2009

Results on the use of the WHO 2001 diagnostic criteria showed that six patients - forming the largest proportion of all patients diagnosed with MM - were diagnosed with BM Plasmacytoma and Large Monoclonal Peak as the major criteria and Lytic Bone Lesion and Immunoparesis as minor criteria. This was followed by diagnosis of five patients, in which Large Monoclonal Peak and BM Plasmacytosis 10 – 30 and Lytic Bone Lesion were the major and minor diagnostic criteria used. BM Plasmacytosis and Large Monoclonal Peak combined with Immunoparesis were the third highest diagnostic criteria used in 4 of the patients. The fourth significant combination comprising three patients was a combination of Large Monoclonal Peak and Immunoparesis as major and minor criteria respectively.

In terms of MM staging (refer to figure 4.11 below), the International Staging System (ISS) for the diagnosis of MM was applied in 28 of the 34 patients representing about 82.4% of all patients diagnosed with MM attending at Dr George Mukhari Hospital between the period under study. Of the 34 patients diagnosed with MM, 38% (13) were categorised as stage III, followed by eight patients categorised as Stage I, comprising 23.5% of the patients. Stage II categorization of MM was seen in seven patients - comprising 20.6% of all patients.

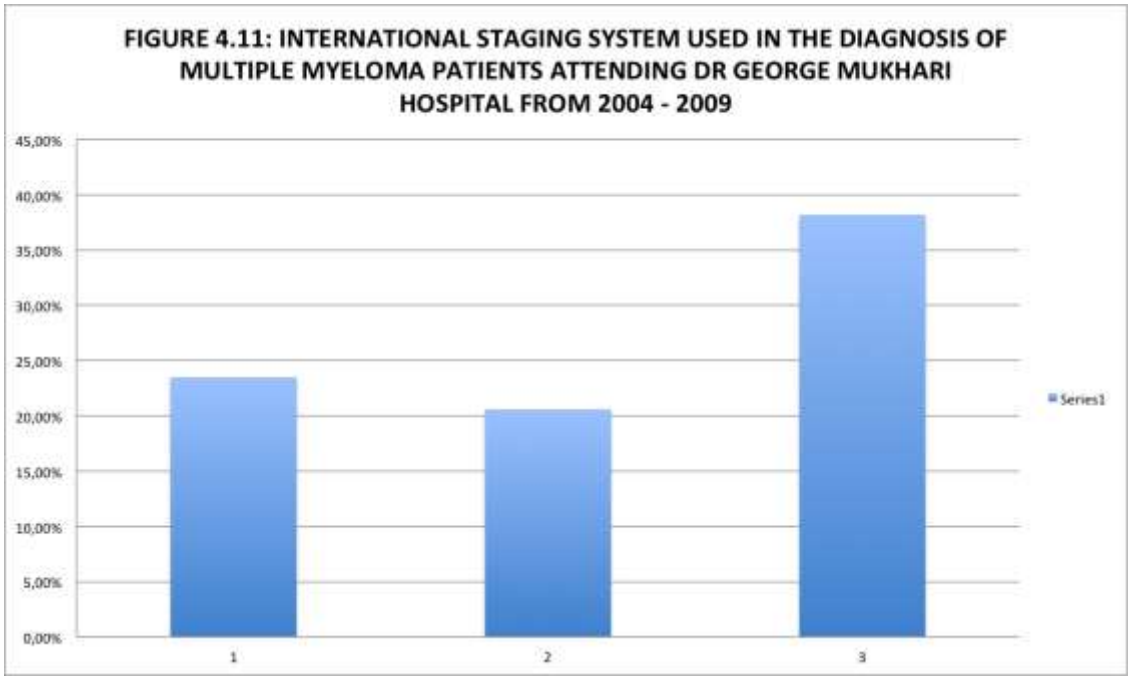


FIGURE 4.11: INTERNATIONAL STAGING SYSTEM USED IN THE DIAGNOSIS OF MULTIPLE MYELOMA PATIENTS ATTENDING DR GEORGE MUKHARI HOSPITAL FROM 2004 - 2009

Figure 4.12 below shows the results of the Durie – Salmon Staging used in the staging of MM amongst patients who attended Dr George Mukhari Hospital within the study period from 2004 to 2009.

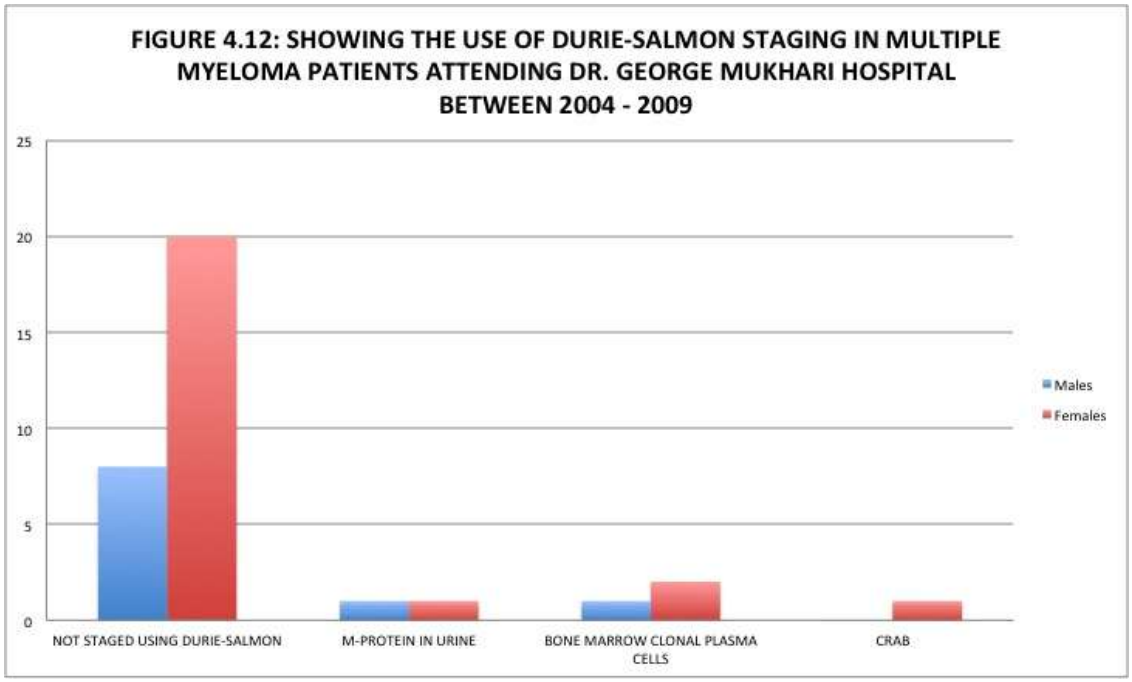


FIGURE 4.12: SHOWING THE USE OF DURIE-SALMON STAGING IN MULTIPLE MYELOMA PATIENTS ATTENDING DR. GEORGE MUKHARI HOSPITAL BETWEEN 2004 - 2009

According to the results, twenty eight patients were not staged using the Durie – Salmon Staging. These patients constitute about 82% of all patients diagnosed with MM at Dr George Mukhari Hospital from 2004 – 2009. Of the 82% of patients who were not staged using the Durie – Salmon Staging, 59% (20) were females and 24% (8) were males. This group was followed by patients diagnosed with bone marrow clonal plasma cells. This group comprised 9% of all patients diagnosed with MM. Of this group 6% (2) were females and 3% (1) were males. M protein in Urine was found in 6% of all patients diagnosed with MM. Of the 6%, 3% (1) were females and another 3% (1) were male. In the last group where CRAB was used, there were no males with only one female in that group. These three groups, namely, M-protein in urine, bone marrow clonal plasma cells and CRAB, are variables included in Durie-Salmon Staging. They were recorded separately in patient files and were therefore not accurately applied for staging. Durie-Salmon staging system was not used in this study, only its variables were indicated.

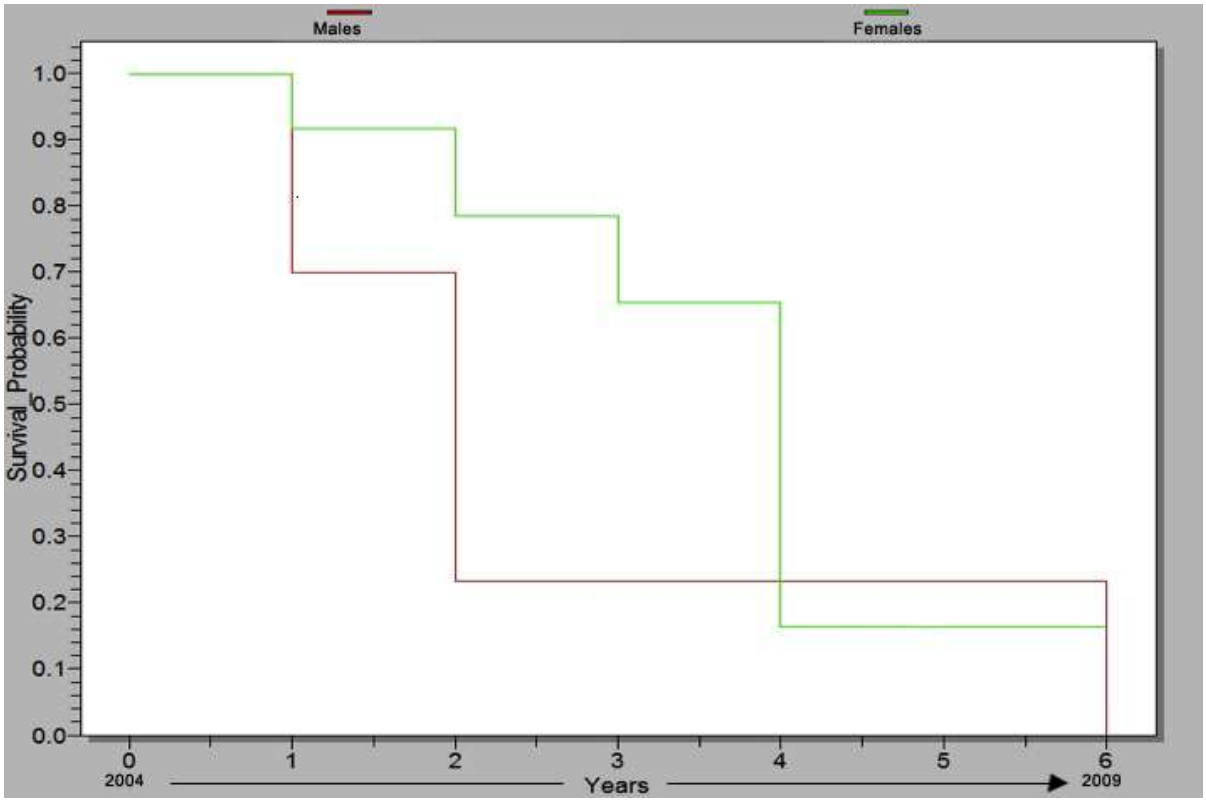


Figure 4.13: Kaplan Meier Survival Analysis

Figure 4.13 above shows the results of the Kaplan Meier Survival Analysis test in which the 34 patients diagnosed with multiple myeloma were followed for 5 years to determine the time to event within the study period. The analysis was disaggregated by gender to determine the variation between the two groups.

In terms of survival by gender, 70% of males (7) and 90% (22) females were respectively alive as at year one, with 3 deaths in male and 2 deaths in female patients. Year two was marked by a sharp decline of 47% of male patients from 70% to 23%, while the female group showed a steady decline of 10% from 90% to 80%. In this year, five males died with only two remaining. With regards to female patients diagnosed with MM in the same year, only 4 patients died with about 18 alive at the time.

No death was witnessed during the third year for the remaining two male patients but within the female participants, 66% of patients were alive (16) at the end of the third year with 3 deaths. In the fourth year, there was no change in the male group but a steep decline in the number of those who are alive decreased from 16 in the previous year to four during that year with 12 patients dead at the end of the year.

In the subsequent year 5, the number of males alive remained the same at two with no death witnessed as in the previous year. In the female patients, the status remained the same as with the previous year with the four patients still remaining from the previous year. By the last year of the study period, all males (2) had died with 16% of all females (4) remaining at the end of that year.

The median survival time, which is the time when half the patients are alive and the other half is dead is two years for males (n=5) and 4 years for females (n=12), with a p value of 0.0436, showing a significant difference between the two groups.

CHAPTER 5: DISCUSSION

5.1. Introduction

Multiple myeloma is a rare, age-related disorder with increasing incidence with advancing age. It accounted for 0.43% of cases of newly diagnosed malignancies in South Africa in 1999; with an absolute number of 257 cases, 130 females and 127 males (66). Visser HF, et al. (2009) found the incidence of myeloma in South African population of 47.8 million in 2009 to be 0.00054% (48). Mwambakana M (2000) at Ga-Rankuwa 2000 found that myeloma was the commonest haematological malignancy seen in this community (1). The national Cancer Registry of South Africa reported from 1993 to 1995 an incidence of approximately 0.2% for all haematological malignancies including myeloma.

Africa is known to lack developed cancer registries. Therefore, it is unable to monitor disease surveillance, incidence and mortality (67). Establishing a profile of patients with myeloma will definitely help in diagnosing patients timeously, monitoring and treating them effectively.

5.2. Demographic profile

Of the 34 patients diagnosed, majority (70.6%) were females. Multiple myeloma (MM) has been shown in review studies to be slightly more common in males than females (18). Our finding may be a reflection of a higher proportion of females in our community or population or that women are more likely to seek medical help and pay attention to cancer signs than men (48, 89).

In terms of race, almost all patients are black Africans. This is in keeping with the proportion of black patients attending DGMH.

The average age of the patients for both males and females was 59 years. The minimum age was 30 and maximum age was 75 in both sexes. The modal age was found to be 53 years. Modal age is more accurate than average age, because it considers also the extremes of ages. The median presenting age will be taken as modal age of 53 years. In most series, the median age of patients at diagnosis is about 65 years (18, 21, 22, 27, and 34).

In industrialized nations, the median age is 62-65 years; it is about a decade lower in developing countries. According to Surveillance Epidemiology and End Results (SEER), USA 2001, about 35% of myeloma patients were younger than 65 years; 28% were in the age group 65-74 years and 37% were older than 75 years. In India the median age is 55-56 years, in China 57.5 years (24, 36, 42, 43). Our median age is consistent with that of other developing countries. Most patients presented in 61-70 years range and the least were in 30-40 and 71-80 years.

Males presented at a younger age than females. The youngest reported age was 30 years. In most series, only 2% of patients are younger than 40 years at presentation. We found 5.8% were younger than 40 years. Thomson (45) established that the normal age of presentation in South Africa was generally in the 6^{th} to 7^{th} decade. He also found that, in the black population, patients presented as early as the 4^{th} decade, and therefore suggested that diagnosis should be considered in any adult age group (45). In a study in India, 12% of patients were also younger than 40 years, compared 2% in Mayo clinic (18).

5.3. Co-morbidities or underlying chronic illness:

Over half (56%) of the patients diagnosed with MM from 2004-2009, were tested for HIV. Only 3% of patients were found to be positive and the other 47% tested negative. Infection with human immunodeficiency virus (HIV) is associated with B-cell abnormalities, for example lymphomas. Monoclonal proteins in non-HIV infected populations were cited by Van Vuuren et al. (58) and that they were also associated with B-cell malignancy or an increased risk of developing B-cell malignancy or multiple myeloma. They also cited that plasma cell neoplasms and an increased incidence of multiple myeloma in HIV infected people had been reported in other studies.

Plasma cell neoplasms, including myelomas have been universally observed, but are not considered HIV-associated neoplasms (58, 59). Young patients (<40 years) who are diagnosed with myeloma, have been found to be HIV infected. In this study only 1 patient, less than 40 years, with HIV, was diagnosed with MM.

The majority of our patients presented with no underlying chronic illness, hypertension or diabetes mellitus. The most common was hypertension in both sexes. Diabetes alone was the least found. Overall prognosis of MM depends on the host and disease related factors. These include poor performance status such as age and significant co-morbidities. Patients in our study, with regards to co-morbidities, had better performance status because there was no underlying illness recorded. The limitation was that we could not validate what was recorded in files of patients. With regard to management of patients, patients with co-morbidities should be considered for reduced dose intensity of chemotherapy, and if they were less than 65 years of age, autologous stem cell transplantation (65).

5.4. Presenting symptoms and signs

Clinical presentation of myeloma has been found to vary widely with no definite signs or symptoms.

Some patients were found to be free of symptoms at the time of diagnosis, with the disease being detected on routine blood tests (6). In this study, 32.4% of patients presented with no symptoms. The most common presentation was bone pain (14.7%) or back pain (11.8%). These are symptoms of bone disease. Generalized body weakness and inability to walk ranked the same at 6%. Some patients presented with more than one symptom. These included headache, generalized body weakness, bone pain, back pain and inability to walk.

Bone pain was found to be the most common presentation in different studies (18, 24, 40). Fatigue was found to be commonly due to anaemia. Studies in India and Mexico found fatigue to be a common presentation (24, 40). These symptoms, as illustrated by figures 4.3, 4.4 and 4.5, are also not significantly different from those reported in other populations (24, 40).

Signs in diagnosis referred to what had been found on examination and investigations by the attending medical practitioner. Most of the patients did not have symptoms and signs on diagnosis as reflected on the figures above. The most common signs were found to be vertebral collapse and fracture which are signs of bone disease. Bone disease had been confirmed to be the most common presenting feature in most studies. Kyle et al. (18), in their review article, found that: conventional radiographs revealed an abnormality in 79% of patients at the time of diagnosis, lytic lesions were found in about 67% of patients, and approximately 20% each had osteoporosis, pathologic

fractures or compression fractures of the spine. In 25% of the 208 patients without radiographic abnormalities at the time of diagnosis, lytic lesions, pathologic fractures, compression fractures or osteopaenia developed subsequently during follow up. In 84% of patients, skeletal lesions developed at some point during the course of the disease.

These were followed by plasmacytomas alone or with other combinations. Plasmacytomas are a collection of abnormal plasma cells in one location and form a tumour and are diagnosed on biopsy of tissue or bone. Plasmacytomas may occur in bone or extramedullary in other tissues and once diagnosed, plasmacytomas of the bone have been found to often or two thirds of patients evolve to multiple myeloma (5). They are classified as major criteria in the diagnosis of MM.

Other signs found were meningioma, osteoarthritis, paraplegia, pneumonia, renal failure, peripheral neuropathy, paraparesis, pulmonary embolism and osteopaenia, alone or in combination. All these symptoms and signs reflected the natural history of MM. These are asymptomatic, progressive bone disease, refractory cytopenias, humoral immune deficit and end-organ damage (12).

5.5. Diagnostic criteria used

The diagnosis of multiple myeloma is based on a combination of clinical, pathological and radiological features as reflected in the criteria used for diagnosis (5). In this study, the WHO diagnostic criteria 2001 were used in almost all patients, except two patients. Diagnosis of MM requires at least one major criterion and one minor criterion, or three minor criteria. One major criterion and one minor criterion were used in all patients. Large monoclonal peak was the most found major criterion in diagnosis. Lytic lesions and immunoparesis were the most frequent minor criteria.

Our study showed that the WHO 2008 was not being used for diagnosis. This could be explained by the fact that most of the patients in our study were diagnosed before or during 2008 and that the new criteria was not yet readily adopted in practice. The criteria for diagnosis have changed over years. The WHO 2008 is more inclusive. Patients would be diagnosed early as MGUS, asymptomatic and symptomatic myeloma. Patients could have been missed because they were asymptomatic at presentation.

5.6. Staging system used in MM patients

Survival of patients is determined by the staging of the disease. The Durie-Salmon staging system has been used since 1975 for MM. It is based on levels of haemoglobin, serum calcium, serum creatinine, serum and urine paraprotein and the number and size of bone lesions. Later on, a new international staging system (ISS) based on two readily available laboratory tests, β2 microglobulin and albumin, was used. The ISS was a collaborative effort by investigators from 17 institutions worldwide and from data on 11,171 patients (7).

In this study 28 of the 34 patients (82.4%) diagnosed at DGMH, ISS was used. Six patients in our study population were not staged only variables used in Durie-Salmon staging system were recorded, such as M-protein in urine, bone marrow clonal plasma cells and CRAB. Information recorded in patients' files was inadequate in this regard. Durie-Salmon was therefore not used and the reason could be: that it involved more variables and some of the variables were not easy to implement, for example, number and size of bone lesions. But early studies showed this staging system to be a reliable practical approach to measure disease bulk. There was correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival.

The majority were staged with ISS which was easy to implement. Most of the patients were at ISS stage III (38%) on diagnosis, followed by stage I (23%) and then stage II (20.6%). ISS stage I, is a low risk group with expected median survival of 62 months; stage II, intermediate risk, with 44 months survival and stage III, high risk group with expected survival of 29 months (7).

According to these results, our patients present late with advanced disease. A study by Visser HF, et al. (48) showed that 42% of patients were stage III on presentation, 55% stage II and only 3% were stage I. They indicated that reasons for the late presentation could be a low level of suspicion by clinicians or just late presentation by patients (48). This could also be the reason for late presentation in our setting, but we still had patients that presented early (stage I), but more still needs to be done to treat patients early.

5.7. Kaplan Meier survival analysis

This was done on 34 patients diagnosed with MM. The patients were followed up for 5 years to determine the time to event within the study period; according to gender (male and females) the variation between these two groups was determined. Most of our patients were on palliative treatment with Melphalan and prednisone, only a few were on VAD (vincristine, doxorubicin, and dexamethasone). Autologous stem cell transplantation is not available in our setting.

The median survival time for males was two years and four years for females. Our study had more females than males; this could have affected the outcome. Females presented at older ages than males and some series had reported advanced age to be a negative prognostic factor.

It is unusual therefore, to find an older age group surviving longer than the young group. However, other studies have shown no effect of age on survival (21, 22, 24, 27).

The results of a study by Turesson I, et al. (46) showed that from a total of 773 patients with MM, 373 men and 400 women, median overall survival of all patients was 22.2 months. Men had a shorter median overall survival than women, 18.6 months and 26.3 months, respectively.

In other studies, the median survival time has been found to be approximately 3-4 years, but some patients can survive longer than 10 years (7, 18, 30). Kyle RA (18) also found that median survival of patients treated with oral Melphalan and prednisone chemotherapy was 31 months, and the corresponding survival of patients on other regimens was 38 months (18). The survival of our patients on Melphalan and prednisone, showed a survival time of more than two years. It would be of benefit if future studies would determine survival time according to treatment, age and staging. Other studies have also indicated the importance of the type of treatment on survival. For example in studies done previously, Melphalan and prednisone were found to be effective combination chemotherapy in both response rate and survival. It was the gold standard treatment in elderly patients in whom high dose therapy was not feasible (10, 20).

Studies have shown that survival of MM had improved over the years. This is partly due to newer treatment regimens that were introduced, Thalidomide, Bortezomib, lenalidomide, etc. Palumbo A et al. (2006) showed that the oral combination of Melphalan, Prednisone and Thalidomide were more effective than standard treatment

for newly diagnosed MM. The advantage was also noted in patient older than 65 years and in younger patients who were unable to undergo transplantation (38).

Limitations of the study:

- Sample size. The sample size was small and may not accurately represent the size in our population. The profile of the patients would be based on a small sample size.
- This was a retrospective review of records. Unfortunately data cannot be validated for accuracy or completeness of records.
- Inadequate patient ascertainment. This was due to incomplete records, inadequate filing of records.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS.

6.1. Conclusion

A total of 34 patients were diagnosed with multiple myeloma at Dr George Mukhari Hospital from 1 January 2004-31 December 2009. Patients that were seen were almost all black Africans. Majority (70.6%) of the patients were females and males were 29.4%. The median age of presentation was 53years. Males presented between 30-67 years with average of 53 years; females between 47-75 years with average of 61 years. Females presented at an older age than males and they survived longer than their male counterparts.

Data on marital status, level of education, place of origin, occupation, industry employed and years of experience were incomplete or missing in the patient records and therefore could not be included. HIV status and underlying chronic illnesses were also recorded, as part of completeness of the profile of these patients. Over half of the patients (56%) were tested for HIV. Only 3% of these patients were positive and the rest were negative. The most common chronic illness found was hypertension in both sexes, followed by combination of hypertension and diabetes and diabetes alone was the least found.

Most of the patients presented with no symptoms and signs. Other features were also non-specific. A high index of suspicion would therefore be needed for early diagnosis. In terms of symptoms, bone and back pain were most common and this was followed by

generalized body weakness. Vertebral collapse and fractures were most common of all presenting signs.

The WHO 2001 criteria for diagnosis of multiple myeloma were commonly used for diagnosis. Large Monoclonal Peak was the major criterion used; immunoparesis and lytic lesions were the minor criteria used. The ISS was the more frequently used staging system in almost all patients. The Durie-Salmon Staging system was never applied accurately during this period of study. The majority of patients presented at stage III ISS, followed by stage I and then II. The median survival of females and males as determined by Kaplan Meier analysis method was 4 and 2 years, respectively, with females surviving longer than males.

6.2. Recommendations

This study was conducted at a tertiary hospital with a small Haemato-Oncology Unit. Therefore the findings cannot necessarily be generalized to the whole population.

1. Multiple myeloma was found to be present as early as the third decade; therefore diagnosis should be considered in all ages.
2. In this setting, myeloma was diagnosed in more females than males, in contrast to previous studies. Clinical features and presentations were found not to be significantly different from those reported in other populations. Patients were found to be asymptomatic, or had non-specific features. Therefore, a high index of suspicion is vital in the diagnosis of these patients.
3. The WHO 2008 is more inclusive, as it also includes asymptomatic and symptomatic myeloma; therefore the use of WHO 2008 diagnostic criteria for

myeloma is strongly encouraged than the WHO 2001, which was more frequently used.

4. Most of the patients presented at a late stage of disease. The median survival was found not to be different from other studies. The survival of the patients in our study, treated with Melphalan and Prednisone, showed a survival of more than two years. Palumbo et al. (65) recommended that patients with co-morbidities should be considered for reduced dose intensity chemotherapy, and if they are less than 65 years of age, autologous stem cell transplantation. Therefore, more active treatment than palliative treatment would benefit our patients even more and therefore is recommended.
5. The completeness of patient records, including full history taking is recommended to facilitate more research.
6. Further studies including the following are recommended: 1. determining survival of patients using age, staging and different treatment regimens 2. complete demographic profiles that include social history should be determined 3. follow up profiles of patients from 2010.

REFERENCES

1. Mwambakana M. The Occurrence of Adult Haematological malignancies at Ga-Rankuwa Hospital. *MMed Dissertation*. Medical University of Southern Africa. May 2000.

2. International Myeloma Working Group. Criteria for the classification of the monoclonal gammopathies, multiple myeloma and related disorders: A report of the International Working Group. *Br J Haematol.* 2003; 121: 749-757.

3. Mayo Clinic. Multiple Myeloma – Diagnosis and Treatment Options at Mayo Clinic: Mayo Foundation for Medical Education and Research; c2001-2010. Available from: http://www.mayoclinic.org/multiple-myeloma/.

4. Terpos E, Rahemtulla A. Myeloma. In: Hoffbrand AV, Catovsky D, Tuddenham EGD, editors. Postgraduate Haematology. 5th Ed. Oxford: Blackwell Publishing; 2005. p. 681-702.

5. McKenna RW, Kyle RA, Kuehl WM, Grogan TM, Harris NL, Coupland RW. Plasma cell neoplasms. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman J, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.4th Ed. Lyon: International Agency for Research on Cancer; 2008.p. 200-208.

6. Campbell K. Multiple Myeloma. London: Leukaemia Research; 2006: p1-12. Available from: http://www.Irf.org.uk/.

7. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade' J, et al. International staging system for multiple myeloma. *Clin Oncol.* 2005; 23: 3412-3420.

8. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High dose chemotherapy with hematopoietic stem cell rescue for multiple myeloma. *N Engl J Med.*2003; 348:1875-1883.

9. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Ross JF, et al. A prospective randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med.*1996; 335: 91-97.

10. Myeloma Trialists' Collaborative Group. Combination chemotherapy versus Melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. *J Clin Oncol*.1998; 16: 3832-3842.

11. Smith A, Wisloff F, Samson D. On behalf of the UK Myeloma Forum, Nordic Myeloma Study Group and British Committee for Standards in Haematology. Guidelines on the diagnosis and management of multiple myeloma. *Br J Haematol*. 2005; 132: 410-451.

12. Bolwell B, Baz R. Multiple Myeloma. The Cleveland Clinic Foundation; c2000–2009: p1-9. Available from: http://www.clevelandclinicmeded.com/.

13. Leedy PD, Ormrod JE. Practical Research: Planning and Design. 5th Ed. Upper Saddle River, NJ, Pearson Education; 2005.

14. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood* 2009; 113:5412-5417.

15. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukaemia* 2009; 23:3-9.

16. Hoffbrand AV, Moss PAH, Petit JE, editors. Essential haematology.5th Ed. Blackwell Publishing: 2006.p.216-229.

17. Grogan TM, Van Camp B, Kyle RA, Müller-Hermelink HK, Harris NL. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: International Agency for Research on Cancer; 2001. P.142-156.

18. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.*2003; 78: 21-33.

19. Gaulier M, Cohen HJ. Multiple myeloma in the elderly. *J Am Geriatr Soc.*1994; 42:653-664.

20. Blade´J, Munoz M, Fontanillas M, San Miguel J, Alcala´A, Maldonado J, et al. Treatment of Multiple Myeloma in Elderly people: Long term results in 178 patients. *Age and Ageing* 1996; 25:357-361.

21. Froom P, Quitt M, Aghai E. Multiple Myeloma in the geriatric patient. *Cancer* 1990; 66: 965-7.

22. Hjorth M, Holmberg E, Turesson J, Westin J, Wislöff F (For the Nordic Myeloma Study Group: NMSG). Multiple Myeloma in young patients (<60 years): Incidence and clinical characteristics. In: Kyle RA, editor. Proceedings of the IV International Workshop on multiple myeloma. Rochester, MN, 1993; 137.

23. Rayner HC, Haynes AP, Thompson JR, Russel N, Fletcher J. Perspectives in multiple myeloma: Survival, prognostic factors and disease complications in a single centre between 1975 and 1988. *Q J Med.* 1991; 290: 517-525.

24. Kumar L, Verma R, Radhakrishan VR. Recent advances in the management of multiple myeloma. *Natl Med J India.* 2010; 23:210-218.

25. Kyle RA, Therreau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ III. Incidence of multiple myeloma in Olmsted Country, Minnesota: Trend over 6 decades. *Cancer* 2004; 101:2667-2674.

26. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. Cancer Statistic, 2005. *Cancer J Clin.* 2005; 55:10-30.

27. Hannisdal E, Kildahl-Anderson O, Grottum KA, Lamvik J. Prognostic factors in multiple myeloma in a population-based trial. *Eur J Haematol.* 1990; 45: 198-202.

28. Palva IP, Ahrenberg P, Ala-Harja K, Almqvist A, Hänninen A, IIvonen M, et al. Treatment of multiple myeloma in old patients. *Eur J Haematol.* 1989; 43:328-331.

29. Cohen HJ, Silberman, Forman W, Bartolucci A, Liu C. Effects of age on responses to treatment and survival of patients with multiple myeloma. *J Am Geriatr Soc.* 1983; 31: 272-277.

30. Durie BG, Salmon SE. A Clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. *Cancer 1975; 36:842-854.*

31. Krislinsson SY, Landgren O, Dickman PW, Derolf AR, Björkholm M. Patterns of survival in multiple myeloma: A population-based study of patients diagnosed in Sweden from 1973-2003. *J Clin. Oncology* 2007 May 20; 25(15):1993-1997.

32. Kariyawassan CC, Hughes DA, Jayatillake MM, Melita AB. Multiple myeloma: Causes and consequences of delay in diagnosis. Q *J Med.* 2007; 100:635-640.

33. Corrado C, Santarelli MT, Bezares R, Saslasky J, Bruno S, Pavlovsky S, the Grupo Argentino de tratamiento de la Leucemia Aguda (GATLA). Effect of age on survival in multiple myeloma. Kyle RA, editor. Proceedings of the IV International Workshop on Multiple Myeloma. Rochester, MN, 1993; 133.

34. Matzner Y, Benbassat J, Polliak A. Prognostic factors in multiple myeloma. *Acta Haematol.* 1978; 60:257-268.

35. Cohen HJ, Bartolucci A. Age and the treatment of multiple myeloma: South eastern Cancer Study Group experience. *Am J Med.* 1985; 79:316-324.

36. Yu-jie MAF, Pei-jing QI, Yan XU, De-hui ZOU, Ya-fei WANG, Yao-zhong ZHAO, et al. Clinical and laboratory features of newly diagnosed multiple myeloma: a retrospective, single-centre analysis. *Chinese Medical Journal* 2007; 120(19): 1727-1729.

37. Kyle RA, Rajkumar SV. Multiple myeloma [published correction appears in *N Engl J Med*. 2005; 352:1163] *N Engl J Med.* 2004; 351:1860-1873.

38. Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma, randomized controlled trial. *The Lancet* 2006 March 11; 367.

39. San Miguel JF, Gutiérrez, Mateo G, Orfao A. Conventional diagnostics in multiple myeloma. *Eur J Cancer*. 2006; 42:1510-1519.

40. Ruiz-Argüelles GJ, Gómez-Rangel JD, Ruiz-Delgado GJ, Aguilar-Romero L. Multiple Myeloma in Mexico: A 20 year experience at a single institution. *Archives of Medical Research* 2004; 35:163-167.

41. Harousseau JL, Dreyling M. On behalf of the ESMO Guidelines Working Group. Multiple Myeloma: ESMO Clinical Recommendations for diagnosis, treatment and follow up. *Annals of Oncology* 2009; 20 (Supplement 4):lv97-lv99.

42. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. *Cancer Statistics* 2008. Comparison of time trends in multiple myeloma, incidence in East Asia, Europe and United States (1973-1990). *Cancer J Clin*.2008;58:71-96.

43. Kumar L, Vikram P, Kochupillai V. Recent advances in the management of multiple myeloma. *Natl Med J. India* 2006; 19:80-89.

44. Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, et al. On behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of multiple myeloma 2011. *Br J Haematol.* 2011; 154:32-75.

45. Thomson Jackie. The approach to the management of multiple myeloma has changed over the past decade. *CME June* 2007; 25(6*)*: 76-78.

46. Turesson I, Velez R, Kristinsson SY, Ladgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: A population-based study. *Clin Oncol J.* 2010 February 10; 28(5): 830-834.

47. Visser HF, Visser A, Nel JM, Moodley V, Pool R. Low secretory multiple myeloma case report. *SA Orthopaedic Journal:* Summer 2009: p76-80.

48. Visser HF, Visser A, Snyckers CH, Pool R, Myburgh JG. Retrospective review of multiple myeloma and immunosecretory disorder cases diagnosed in a tertiary setting. *SA Orthopaedic Journal*: Summer 2009: p38-43.

49. Venter EK, Naude´ F, Meyer BJ. Hypercalcaemia: A finding not to be taken too lightly. *SA Fam Pract.* 2004; 46(1): 33-34.

50. Van Walraren C, Davis D, Forster AJ, Wells GA. Time-dependent bias was common in survival analyses published in leading clinical journals. *Journal of Clinical Epidemiology* 2004 (57):672-682.

51. Landgren O, Katzmann JA, Hsing AW, Pfeiffer RM, Kyle RA, Yeboah ED, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. *Mayo Clin Proc.* 2007; 82(12): 1468-1473.

52. Louw V, Web MJ. Refresher Course: Autologous stem cell transplantation in multiple myeloma. *S Afr J Anaesthesiol Analg.* 2010; 16(1).

53. Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. *Blood* 2011; 118(12):3205-3211.

54. Stoopler ET, Vogl DT, Stadtmauer EA. In: Firriolo FJ, Miller CS, Rhodus NL, editors. Medical management update, multiple myeloma. University of Pennsylvania. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007; 103: 599-609.

55. Rajkumar SV, Buadi F. Multiple myeloma: New staging systems for diagnosis, prognosis and response evaluation. *Best Practice & Research Clinical Haematology* 2007; 20(4):665-680.

56. Alexanian R, Dimopoulos M. The treatment of multiple myeloma. In: Wood AJJ, editor. Drug therapy. 1994 Feb 17: p484-488. Downloaded from www.nejm.org at University of Limpopo on August 24, 2010.

57. Barlogie B, Shaughnessy J, Epstein J, Sanderson R, Anaissie E, Walker R, et al. Plasma Cell Myeloma. In: Lichtman MA, Kipps TJ, Kanshansky K, Beutler E, Seligsohn U, Prchal JT, editors. Williams Hematology. 7th Ed. Mc Graw-Hill Medical Publishing; 2006.p.1501-1524.

58. Van Vuuren MJ, Zemlin AE, Gerishuys JJ. Monoclonal gammopathy and other serum protein electrophoresis patterns in patients with HIV infection in South Africa. *Ann Clin Biochem.* 2010; 47:366-374.

59. Dal Maso L, Franceschi S. Epidemiology of non-Hodgkin lymphomas and other haemolymphopoietic neoplasms in people with AIDS. *Lancet Oncol.* 2003; 4:110-119.

60. International Committee Editors. http://www.icmje.org/Uniform Requirements for Manuscript Biomedical Journals.

61. http://www.lib.monash.edu.au/tutorials/citing/vancouver.html.

62. Last J, editor.2001.International epidemiological association. A dictionary of epidemiology.4th Ed .New York: Oxford University Press

63. Orlowski RZ. Initial therapy of multiple myeloma patients who are not candidates for stem cell transplantation. *American Society of Hematology* 2006:338-346.

64. Dispenzieri A, Rajkumar V, Gertz MA, Fonseca R, Lacy MQ, Bergsagel PL, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART): consensus statement. *Mayo Clin Proc. March* 2007; 82(3): 323-341.

65. Palumbo A, Sezer O, Kyle R, Miguel JS, Orlowski RZ, Moreau P, et al. International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation. *Leukaemia* 2009;doi:10.1038/leu.2009.122: p1-15.

66. Mqoqi N, et al. Incidence of histologically diagnosed cancer in South Africa 1998-1999. *National Cancer Registry of South Africa*. National Health Laboratory Service. Johannesburg. 2004: p1-62.

67. Harding R, Selman L, Agupio G, Dinat N, Downing J, Gwyther L, et al. The prevalence and burden of symptoms amongst cancer patients attending palliative care in two African countries. *Eur J of Cancer.* 2011; 47:51-56.

68. Rajkumar SV. Multiple myeloma: 2011 update on diagnosis, risk stratification and management. *Am J Hematol.* 2011; 86:57-65.

69. Kyle RA, Beard CM, O'Fallon WM, Kurland LT. Incidence of multiple myeloma in Olmsted County, Minnesota: 1978 through 1990, with a review of the trend since 1945. *Nephrol. Dial Transplant* 2010 April 1; 1200-1206.

70. Munshi NC, Anderson KC, Bergsagel PL, Shaughnessy J, Palumbo A, Durie B, et al. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood* 2011 May 5; 117(18):4696-4700.

71. McFarlane H. Multiple myeloma in Jamaica: A study of 40 cases with special reference to the incidence and laboratory diagnosis. *J Clin Pathol.*1966; 19: 268-271.

72. Blade´J, Cibeira MT, De Larrea CF, Rosiñol L. Multiple myeloma: symposium article. *Annals of Oncology* 2010; 21(Supplement 7): vii313-vii319.

73. Birgegård G, Gascón P. Evaluation of anaemia in patients with multiple myeloma and lymphoma: Findings of the European Cancer Anaemia Survey. *Eur J Haematol.*2006; 77: 378-386.

74. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008 March 1; 111(5):2516-2520.

75. Orhan S. Myeloma bone disease: Recent advances in biology, diagnosis and treatment. *The Oncologist* 2009*; 14*: p1-6. Available from *www.TheOncologist.com*.

76. Tamimi W, Alaskar A, Alassiri M, Alsaeed W, Alarifi SA, Alenzi FQ, et al. Monoclonal gammopathy in a tertiary referral hospital. *Clinical Biochemistry* 2010; 43:709-713.

77. Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G. Early mortality after diagnosis of multiple myeloma: Analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002- Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol.*2005; 23:9219-9226.

78. Rajkumar SV, Kyle RA. Multiple myeloma: Diagnosis and treatment. *Mayo Clin Proc.*2005 October; 80(10):1371-1382.

79. Stoopler ET, Volgi DT, Alawi F, Greenberg MS, Sollecito TP, Salazar G, et al. The presence of amyloid in abdominal and oral mucosal tissues in patients initially diagnosed with multiple myeloma: a pilot study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.*2011; 111:326-332.

80. Dmoszyn´ska A. Diagnosis and the current trends in multiple myeloma therapy. *Pol Arch Med.*2008; 118(10):563-566.

81. Collins CD. Multiple myeloma. *Cancer Imaging* 2004; 4:547-553.

82. De La Rubia J, Sanz MA. Treatment of multiple myeloma in the elderly: realities and hope. *Leukaemia & Lymphoma* 2011 January; 52(1):9-14.

83. Turesson I, Velez R´, Kristinsson SY, Landgren O. Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. *Mayo Clin Proc.*2010 March; 85(3): 225-230.

84. Benjamin M, Reddy S, Brawley OW. Myeloma and race: A review of the literature. *Cancer and Metastasis Reviews* 2003; 22:87-93.

85. Dispenzieri A, Zhang L, Katzmann JA, Snyder M, Blood M, DeGoey R, et al. Appraisal of immunoglobulin free light chain as a marker of response. *Blood* 2008 May 15; 111(10):4908-4914.

86. Aboulafi DM. Thalidomide-based treatment for HIV-associated multiple myeloma. *AIDS Read* 2003 Aug; 13(8):383-389.

87. Kumar S. Multiple myeloma- current issues and controversies. *Cancer Treatment Reviews* 2010; 36S2:S3-S11. Available from *www.elsevierhealth.com*.

88. Ong F, Hermans J, Noordijk EM, Kluin-Nelemans JC. Is the Durie and Salmon diagnostic classification system for plasma cell dyscrasias still the best choice? *Ann Hematol.*1995; 70:19-24.

89. Van Osch L, Lechner L, Reubsaet A, De Nooijer J, and De Vries H. Passive cancer detection and medical help seeking for cancer symptoms: (in) adequate behavior and psychosocial determinants. *Eur J Cancer Prev.* 2007 Jun; 16(3):266-274.

APPENDIX A: DATA COLLECTION SHEET

GN number*	
Age	
Gender	
Presenting symptoms and signs	
Criteria used for diagnosis	
Staging system used	
Follow up data	
2004	
2005	
2006	
2007	
2008	
2009	

APPENDIX B: THE DIAGNOSTIC CRITERIA

World health organization (WHO) diagnostic criteria (2001)

Diagnostic criteria: One major and one minor

Or

Three minor criteria

For the diagnosis of multiple myeloma

Major criteria:	Minor criteria:
• bone marrow plasmacytosis of >30% • Plasmacytoma • Large monoclonal globulin on serum protein electrophoresis; >35g/l IgG; >20g/l IgA; >1g/24 hour of kappa or lambda in urine	• bone marrow infiltration with 10-30% plasma cells • Paraprotein less than the levels defined above • Lytic bone lesions • Immune paresis IgM <0.5g/l, IgA <1g/l or IgG <6g/l

World Health Organization diagnostic criteria for plasma cell myeloma (2001)

Symptomatic plasma cell myeloma	Asymptomatic (smoldering) myeloma
• M- Protein in serum or urine (No level of serum or urine M-protein is included. M-protein in most cases is >30g/l of IgG or >25g/l of IgA or >1g/24hr of urine light chain, but some patients with symptomatic myeloma have levels lower than those). • Bone marrow clonal plasma cells or plasmacytoma (Monoclonal plasma cells usually exceed 10% of nucleated cells in the marrow but no minimal level is designated because about 5% of patients with symptomatic myeloma have <10% marrow plasma cells). • Related organ or tissue impairment (CRAB: hypercalcemia, renal	• M-protein in serum at myeloma levels (>30g/l) AND/OR • 10% or more clonal plasma cells in bone marrow • No related organ or tissue impairment [end organ damage or bone lesions (CRAB: hypercalcemia, renal insufficiency, anaemia, bone lesions)] or myeloma- related symptoms.

insufficiency, anaemia, bone lesions) (The most important criteria for symptomatic myeloma are manifestations of end organ damage including anaemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis or recurrent infections).	

World Health Organization diagnostic criteria for plasma cell myeloma 2008