ROLE OF PET CT IN MULTIPLE MYELOMA

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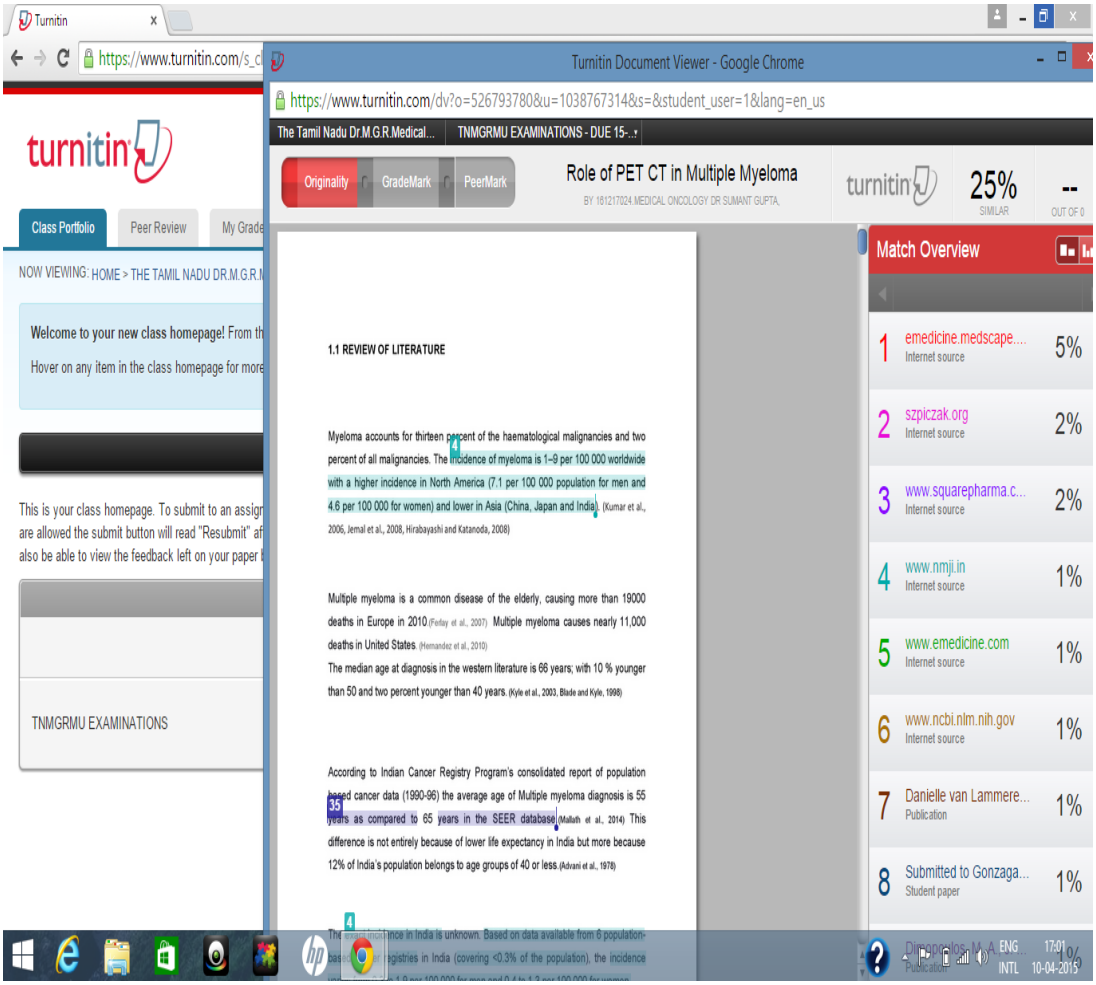
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Role of PET CT in Multiple Myeloma
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1.1 REVIEW OF LITERATURE
Myeloma accounts for thirteen percent of the haematological malignancies and two percent of all malignancies. The incidence of myeloma is 1–9 per 100 000 worldwide with a higher incidence in North America (7.1 per 100 000 population for men and 4.6 per 100 000 for women) and lower in Asia (China, Japan and India). (Kumar et al., 2006, Jemal et al., 2008, Hirabayashi and Katanoda, 2008)
Multiple myeloma is a common disease of the elderly, causing more than 19000 deaths in Europe in 2010 (Ferlay et al., 2007). Multiple myeloma causes nearly 11,000 deaths in United States. (Hernandez et al., 2010)
The median age at diagnosis in the western literature is 66 years; with 10 % younger than 50 and two percent younger than 40 years. (Kyle et al., 2003, Blade and Kyle, 1998)
According to Indian Cancer Registry Program's consolidated report of population based cancer data (1990-96) the average age of Multiple myeloma diagnosis is 55 years as compared to 65 years in the SEER database (Malluth et al., 2014) This difference is not entirely because of lower life expectancy in India but more because 12% of India's population belongs to age groups of 40 or less. (Advani et al., 1978)
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CERTIFICATE

This is to certify that the dissertation entitled **"ROLE OF PET CT IN MULTIPLE MYELOMA"** is a bonafide work done by **Dr. SUMANT GUPTA** in the Department of Medical Oncology, College of Oncological sciences, Adyar, Chennai, in partial fulfilment of the University rules and regulations for award of Doctor of Medicine in Medical Oncology under my guidance and supervision during the academic year 2012 to 2015.

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The Institute Thesis Review Committee (IRTC) reviewed and approved the dissertation entitled **"ROLE OF PET CT IN MULTIPLE MYELOMA".**

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ABBREVIATIONS

MM	Multiple Myeloma
EP	Extramedullary Plasmacytoma
SP	Solitary Plasmacytoma
sCR	Stringent Complete Remission
CR	Complete Remission
PR	Partial Remission
SD	Stable Disease
PD	Progressive Disease
PET	Positron Emission Tomography
CT	Computed Tomography
SUV	Standardised Uptake Value

SUMMARY

Myeloma accounts for thirteen percent of the haematological malignancies and two percent of all malignancies. According to Indian Cancer Registry Program's consolidated report of population based cancer data (1990-96) the average age of Multiple myeloma diagnosis is 55 years.

Conventionally, the investigations for diagnosis and remission status in MM is a cumbersome and painful procedure involving bone marrow studies, multiple blood investigations and skeletal survey with conventional radiography. In this study we tried to compare the whole body PET CT scan to correlate disease burden in both multiple myeloma and plasmacytoma as measured by PET/CT scan with standard staging and prognostic parameters and also to evaluate response to induction therapy using PET based SUV changes.

In our study we analysed the results of all myeloma patients who reported to our Institute from 1st Jan 2013 to 31st December 2014 and we had done PET scans for willing patients at the time of diagnosis and then at the end of planned induction therapy if they had achieved VGPR or better response.

We had total of 31 patients who underwent PET CT scan as part of the study, Of these three patients were upstaged to MM as they had multiple plasmacytomas and went on to receive treatment as MM. Of the treated cases of MM, 7 patients had VGPR or better response and they went ahead and got an end of treatment PET CT scan. The two patients who had stringent CR as per conventional criteria had no metabolic activity on the PET scan whereas the other two patients with CR response, one had absent metabolic activity while one had faint SUV of 1.2 and taken as CR.

Of three cases with Plasmacytoma who underwent end of treatment PET CT scan, one had metabolic CR on PET while other two had small unicentric activity with SUV of 1 and 1.3 and they were kept under follow up.

The overall survival and Event free survival at a median of 15 months in all the patients (n=112) was 76% and 43.1% respectively, following induction with novel agents.

Although the numbers were very small and the follow up was limited, PET CT scan appears to be a promising investigation in diagnosis and staging MM as well as in establishing the remission status. Further continuation of the study and bigger patient population is required for more detailed analysis.

CHAPTER 1

INTRODUCTION

1.1 REVIEW OF LITERATURE

Myeloma accounts for thirteen percent of the haematological malignancies and two percent of all malignancies. The incidence of myeloma is 1–9 per 100 000 worldwide with a higher incidence in North America (7.1 per 100 000 population for men and 4.6 per 100 000 for women) and lower in Asia (China, Japan and India). (Kumar et al., 2006, Jemal et al., 2008, Hirabayashi and Katanoda, 2008)

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According to Indian Cancer Registry Program's consolidated report of population based cancer data (1990-96) the average age of Multiple myeloma diagnosis is 55 years as compared to 65 years in the SEER database.(Mallath et al., 2014) This difference is not entirely because of lower life expectancy in India but more because 12% of India's population belongs to age groups of 40 or less.(Advani et al., 1978)

The exact incidence in India is unknown. Based on data available from 6 population-based cancer registries in India (covering <0.3% of the population), the incidence varies from 0.3 to 1.9 per 100 000 for men and 0.4 to 1.3 per 100 000 for women. The incidence as per MMTR(Madras Metropolitan Tumor Registry) is around 1 per 100,00 populations. (Swaminathan et al., 2011)

In a study from India, the percentage of subtypes was IgG 67.6%, IgA 18.5 while light chain disease was 12.8% respectively. (Kumar et al., 2006) Another Study from Aligarh Muslim University, India showed that the average incidence of Myeloma in India is 1.28 per 100,000 populations. The rates for males and females are 2.02 per 100,000 and 0.71 per 100,000 persons per year respectively. The average incidence rates for Muslims for slightly higher than that for Hindus in the study. The highest incidence rate of 14.39% was in the age group of 65 years and above. (Bisati et al., 1992)

A. Definition Of Multiple Myeloma

Multiple myeloma (MM) is characterized by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. This clone of plasma cells proliferates in the bone marrow and often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. (Kariyawasan et al., 2007)

Conventionally diagnosis of MM was established using radiographs in addition to bone marrow studies and biochemical investigations. These investigations aid at distinguishing between the spectrum of plasma cell disorders ranging from Monoclonal Gammopathy of Undetermined Significance (MGUS) to symptomatic MM.

The diagnosis of multiple myeloma as per the IMWG Consensus Guidelines 2014 should include complete hemogram with differential count and peripheral smear. Biochemical investigations including serum calcium and creatinine, M protein and immunofixation, quantitation of immunoglobulins. In addition, routine urinalysis, 24 h urine collection for proteinuria, electrophoresis and immunofixation along with quantification of both urine M-component level and Serum Free Light Chain (SFLC) assay. Along with this skeletal survey using X Rays is mandatory whereas MRI Scan and PET scan are optional as per physician's discretion. (Appendix 6)

B. Spectrum Of Disease

MM is the consequence from malignant proliferation of clonal mature B cells. Plasma cell malignancies, however, account for a variety of clinical presentations ranging from asymptomatic plasma cell disorders such as monoclonal gammopathy of uncertain significance (MGUS) or smoldering myeloma (SMM), neither of these require therapy. MM and the more aggressive variant plasma cell leukemia which requires immediate therapy.

MGUS is characterised by M component in serum of less than 3g/L and bone marrow clonal plasma cells of less than 10% with no evidence of end organ damage(CRAB)

Asymptomatic MM or Smoldering MM (SMM) is characterized by an excess of monoclonal protein in the blood and urine. but the patient does not exhibit any of the “CRAB” criteria.

The solitary plasmacytoma (SP) is characterized with accumulation of malignant monoclonal plasma cells without a systemic plasma cell proliferative disease. It is a uncommon malignant disease of plasma cells and represents 5% to 10% of all plasma cell neoplasms as per the literature. It can be subclassified into two groups regarding to location; defined as solitary plasmacytoma of the bone (SBP) and extramedullary plasmacytoma (EP) (Kilciksiz et al., 2012)

Extramedullary plasmacytomas (EP) are seen in approximately 7 percent of patients with MM at the time of diagnosis, and an additional 6 percent of patients will develop EP later in the disease course. (Varettoni et al., 2010, Blade et al., 2011)

Symptomatic MM is the other end of spectrum and is discussed in detail.

C. Diagnostic Investigations

The 2009 IMWG guidelines for standardising investigative work-up in patients with suspected MM include the following: (Dimopoulos et al., 2009)

- Serum and urine evaluation monoclonal protein
- Serum free light chain(SFLC) assay
- Bone marrow studies (Bone marrow aspiration and biopsy)
- Serum beta2-microglobulin, serum albumin, and LDH levels
- Cytogenetics
- FISH for defined cytogenetic abnormalities
- Skeletal survey
- MRI

Routine blood investigations include the following:

- Complete Hemogram
- ESR
- Comprehensive biochemistry (eg, levels of total protein, albumin and globulin, BUN, creatinine, uric acid)
- 24-hour urine collection for quantification of the Bence Jones protein (ie, lambda light chains), protein, and creatinine clearance; proteinuria greater than 1 g of protein in 24 hours is a major criterion
- CRP
- Serum viscosity

The 2011 NCCN Clinical Practice Guidelines on Oncology, Myeloma version recommend the use of SFLC assay as well as FISH for 1q21 amplification as part of the initial diagnostic workup. (Anderson et al., 2009)

D. Imaging Investigations

- Skeletal survey for the evaluation of bony lesions; including the skull, long bones, pelvis and spine
- MRI for spinal lesions, paraspinal involvement, and early cord compression
- PET scanning in conjunction with MRI potentially useful (Dimopoulos et al., 2011)

E Pathophysiology

MM is characterized by neoplastic proliferation of plasma cells involving more than 10% of the bone marrow. Increasing evidence suggests that the bone marrow microenvironment of tumor cells plays a pivotal role in the pathogenesis of myelomas. (Raab et al., 2009)

The neoplastic cells of MM, plasma cells, and plasmacytoid lymphocytes are the most mature type of B-lymphocytes. B-cell maturation is linked with a programmed rearrangement of DNA sequences in the process of encoding the structure of mature immunoglobulins. It is characterized by excessive production of monoclonal immunoglobulin G (IgG), immunoglobulin A (IgA), and/or light chains, which can be evaluated with serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP).

Cytogenetics wise MM karyotype is complex with an average of 11 numeric and structural abnormalities per cell. PAX 5 and IRF4 gene have recently been implicated in yhe pathology of MM.(Sato et al., 2015)

The role of cytokines in the pathogenesis of MM is an important area of research. Interleukin (IL)–6 is also an important factor promoting the in vitro growth of myeloma cells. Other cytokines are tumor necrosis factor, ILGF1, SDF 1 and IL-1b.(Cho and Lee, 2014)

The pathobiology of MM leads to the clinical manifestations in term of bony, haematological, renal, neurological as well as general processes.

Skeletal processes

Excessive plasma cell proliferation leads to skeletal destruction with osteolytic bony lesions, low hemoglobin and hypercalcemia. The hypercalcemia is due to bony involvement and possibly humoral involvement. Solitary plasmacytomas (seen in 2-10% of patients) lead to high serum calcium levels through production of the osteoclast-activating factor.

Bony destruction and its replacement by clonal neoplastic plasma cells may lead to pain, spinal cord compression, and even pathologic fracture. The mechanism of spinal cord compression symptoms may be the development of an epidural mass with compressive symptoms, a compression fracture of a vertebral body destroyed by multiple myeloma, or, rarely, an extradural mass. In cases of pathologic fractures, the bone lesion is typically lytic in nature.

Hematologic processes

Involvement of the bone marrow with neoplastic plasma cells leads to cytopenias which may further lead on to complications of anemia, bleeding disorders or infections. Specific to bleeding, M protein can interact specifically with clotting factors, leading to defective aggregation.

Renal processes

The mechanisms of renal impairment in MM are due to direct tubular injury, amyloidosis, or involvement by plasmacytoma.(Ludwig et al., 2007) MM can manifest with renal complications including hypercalcemic nephropathy, hyperuricemia due to renal infiltration of plasma cells resulting in myeloma, light-chain nephropathy,amyloidosis, and glomerulosclerosis. (Zucchelli et al., 1988)

Neurologic processes

The neurological manifestations may be due to nerve compressions secondary to skeletal destructions, compression by plasmacytomas or amyloid infiltration of nerves

General processes

Hyperviscosity syndrome is infrequently seen in MM and is seen in IgG and IgA myeloma subtypes. It may involve sludging in the capillaries and micro circulation, which may result in purpura, retinal hemorrhage, papilledema, coronary ischemia, or even florid central nervous system (CNS) symptoms leading to confusion, vertigo,seizure. Cryoglobulinemia can cause Raynaud phenomenon, thrombosis, and even gangrene in the extremities.

F. Diagnostic Criteria

Revised International Myeloma Working Group (IMWG) diagnostic criteria for multiple myeloma 2014 (Ocio et al., 2014)

Clonal bone marrow plasma cells equal to atleast 10% or biopsy-proven bony or extramedullary plasmacytoma and/or any one or more of the following myeloma defining events:*

Myeloma defining events:

Evidence of end organ damage that is attributable to the underlying plasma cell proliferation, specifically:

- Hypercalcaemia
- Renal insufficiency manifesting with a creatinine clearance <40 mL per min or serum creatinine (>2 mg/dL)
- Anaemia: haemoglobin value of less than 12 g/dl or 2 g/dl below the normal lab cut off.
- Bone lesions, either one or more osteolytic lesions on skeletal radiography, CT, or PET scan.

Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage =60%
- Involved : Uninvolved serum free light chain ratio =100
- >1 focal lesions on MRI studies (>5mm)

These changes are based on the identification by the IMWG of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be detrimental to these patients.(Ocio et al., 2014)

G. Treatment Options In A New Case Of Multiple Myeloma

In patients with symptomatic MM, treatment is required whereas in asymptomatic patients with MM, treatment is delayed until disease clinically progresses or until serum or urine levels of M protein substantially increase as per the aforementioned diagnostic criteria.

Initial evaluation is done also to assess whether the patient is a candidate for Autologous Bone Marrow Transplantation. Eligibility depends primarily on the patient's age and comorbidities. Typically an age of 65 years is used as a cut-off point for transplant eligibility. This divides the treatment of MM into four groups

- Potential Transplant Eligible: Newly Diagnosed
- High-Risk Transplant Eligible
- Newly diagnosed elderly patients who are not eligible for transplant
- Relapsed and Refractory disease

Potential Transplant Eligible: Newly Diagnosed

VAD (vincristine, doxorubicin [Adriamycin], and dexamethasone) chemotherapy, conventionally had been used to reduce the tumor burden in MM as a preparatory regimen for autologous bone marrow transplantation as it is stem cell sparing. VAD is administered as a 4-day continuous iv infusion of vincristine and doxorubicin, with 4 days of oral dexamethasone.

Many researchers felt that the high-dose steroids in VAD were in fact responsible for much of its efficacy. Because in some cases, high-dose dexamethasone can produce significant clinical responses.(Alexanian et al., 1990)

In a matched case control study enrolling 200 patients, it was observed that the response rates with VAD were inferior than that with Thalidomide and dexamethasone regimen, 76% vs 52%, respectively. (Cavo et al., 2005)

Novel Agents

Novel therapeutic agents specifically targeting the mechanism whereby MM cells grow and survive in the bone marrow milieu, can overcome resistance to standard dose as well as high dose therapies. The immunomodulatory agents – *Thalidomide* and its more potent analogue *Lenalidomide* are known for their anti-angiogenic activity in the bone marrow. They also abrogate the adhesion of MM cells to bone marrow

stromal cells (BMSC) and block MM growth and survival factors like IL-6, TNF alpha, VEGF and FGF. They also modulate immune responses through NK cells. Importantly recent studies have shown that Lenalidomide binds to cereblon the substrate recognising subunit of Ubiquitin ligase complex. This causes degradation of two related transcription factors from IKAROS family Zinc finger IKZF1 and IKZF3, with special role in B and T cell differentiation and myeloma cell survival.(Ogura, 2015)

Bortezomib is first in class proteosome inhibitor used in MM for blockade of NF Kappa B activation and related IL-6 production by BMSC. It also acts directly on MM cells to induce apoptosis through caspase 8 and 9 activation. This caspase activity also causes synergism with dexamethasone and acts in the microenvironment to inhibit the binding of MM cells to BMSC, secretion of MM promoting cytokines and BM angiogenesis.(Varga et al., 2014)

Thalidomide has proven efficacy in MM. The superiority of induction chemotherapy containing thalidomide based regimens was demonstrated in a randomized trial that compared VAD with thalidomide plus steroids (dexamethasone), thalidomide and doxorubicin plus dexamethasone; and thalidomide plus VAD. (Cavo et al., 2005)

Thalidomide has a well-established role as the first-line therapy, either as a single agent or in combination with steroids or as a second agent in

patients with MM. The toxicity of this drug is mainly sensory neuropathy, and strict contraception has to be followed as it is teratogenic.

Another analogue of thalidomide, **Lenalidomide** is now established as a standard component of MM therapy. In July 2013, a phase 3 trial of lenalidomide (Revlimid) met the main goal of improving progression-free survival in patients with newly diagnosed MM. The drug was also approved for second line treatment MM, mantle cell lymphoma, and also transfusion-dependent anemia caused by myelodysplastic syndromes.

In the study, treatment with lenalidomide combined with dexamethasome in patients with newly diagnosed MM resulted in a significant improvement in survival compared to treatment with a regimen consisting of melphalan, prednisone and thalidomide (MPT). (Wang et al., 2008)

In another randomized trial incorporating lenalidomide along with high-dose dexamethasone (LD) versus lenalidomide plus low-dose dexamethasone (Ld) in newly diagnosed cases of myeloma, Rajkumar, et al., found that the overall response rate (ORR) for LD was superior (82%) to that for Ld (70%), although there was an improvement in the VGPR-or-better response in the LD arm (44% vs 26%) which was done as an unplanned sub group analysis.(Stadtmauer et al., 2009)

However, on further analysis there was no difference in progression-free survival between the 2 arms. Overall survival also continued to favour the Ld arm. But in patients younger than 65 years, there was no benefit in survival for Ld over LD emphasizing that although Ld was better in the elderly due to its lesser toxicity, still the CR rates were better in LD group. (Stadtmauer et al., 2009)

In all major lenalidomide trials, patients tolerated the treatment well with minimal nausea. Patients usually experience total alopecia, but other adverse effects (eg, peripheral neurotoxicity, constipation) were comparatively mild. Cytopenias are usually expected, but not severe enough to cause hospitalization for infection or transfusion.

Bortezomib, a proteosome inhibitor showed a striking activity against MM. Objective responses as high as 27.7% in patients with relapsed and heavily pretreated MM (Richardson et al., 2003)led to its approval by the US Food and Drug Administration (FDA) in 2003. Subsequent to its approval, subsequent studies showed Response rates in the tune of 80% when bortezomib was combined with other drugs like Melphalan and Thalidomide.

A randomized trial compared bortezomib plus dexamethasone with conventional VAD for induction, showing response rates of 80% for the bortezomib plus dexamethasone arm versus 62.8% for the VAD arm. The superiority of bortezomib regimens was shown in post transplant relapses.

These regimens also showed better and deeper responses which was independent of beta-2 microglobulin levels (ISS Stage) or adverse cytogenetic risk groups.

In tune with these results superior responses were seen when bortezomib was combined to other approved agents as in VTD (bortezomib, thalidomide, and dexamethasone). VTD on comparison with thalidomide plus dexamethasone (TD) in a large phase III study showed 93% RR in the VTD arm versus 80% in theTD arm.

Further studies confirmed the role of Bortezomib in the initial non-intensive management of multiple myeloma. (Harousseau et al., 2010)

Bortezomib has shown important promise in patients with plasma cell leukemia and renal failure. The predominant adverse effects are peripheral neuropathy, hypotension, and thrombocytopenia. Despite the excellent results, the exact timing and combinations of bortezomib regimens in the treatment plan of patients with newly diagnosed multiple myeloma is still evolving.

Varicella-zoster virus reactivation occurs in upto 10%-60% of patients with MM who are treated with bortezomib. Antiviral prophylaxis with acyclovir has been found effective for preventing these reactivations. (Vickrey et al., 2009)

The FDA approved administration of bortezomib by the subcutaneous route in January 2012. A study by Moreau et al found that the efficacy of subcutaneous bortezomib is not inferior to the efficacy of standard intravenous administration and that the safety profile of the subcutaneous administration is improved.

Overall, the data on these novel agents are very encouraging and promising but we will need further studies to help define the exact timing and role of novel agents in the treatment of MM.

Table 1: Key Trials of Novel Agents in Newly Diagnosed MM

Drug	Study	Phase	N	Regimen	ORR	Ref
Thalidomide	Rajkumar MM003	III	470	Thal+ Dexa	69%	ASH 2006
Thalidomide	Palumbo	III	129	MPT	76%	Lancet 2006
Thalidomide	Wang	II	36	Thal + Bort + Dexa	92%	ASH 2005
Lenalidomide	Rajkumar E4A03 Arm A	III	223	Len +Standard Dose Dexa	1 yr OS 87%	Lancet 2007
Lenalidomide	Rajkumar E4A03 Arm B	III	222	Len + Low dose Dexa	1 yr OS 96%	Lancet 2007
Bortezomib	Jagganath	II	48	Bort +/- Dexa	90%	BrJH 2005
Bortezomib	Barlogie	II	303	TT3+Bort	90%	ASCO 2007

High-Risk Transplant Eligible

High risk myeloma has been defined as advanced-stage disease (stage III according to the International Staging System); those with poor cytogenetics, for example t (4:14), t (14:16), and t (14:20), deletion of chromosome 13, inactivation of *TP53*; and those with a complex karyotype.

This subgroup has about 25% of all the newly diagnosed cases of MM. The expected median survival of 2 years or less is seen in these patients. Although these patients respond to conventional MM therapies, these individuals tend to relapse rapidly. This subgroup is usually treated with a novel agent containing doublet or triplet followed by consolidation with high dose chemotherapy and stem cell rescue.

With the advent of novel agents like, thalidomide, lenalidomide, and bortezomib there has been a substantial improved in the outcomes in these high-risk patients. In fact, these novel agents to an extent appear to overcome the influence contributed by high-risk cytogenetics. (Jagannath et al., 2007, Sagaster et al., 2007)

Newly diagnosed elderly patients who are not transplant eligible

All the protocols which are used in transplant eligible patients can be given to this group of transplant ineligible cases but the usual regimens discussed are not given to transplantable cases as they are myelotoxic.

The gold standard has been the MP regimen as far back as the 1950s. This regimen typically consists of melphalan 8 mg/m^2 and prednisone 100 mg given on days 1-4, with courses repeated at 4- to 6-week intervals. A meta-analysis of 4930 patients from 20 randomized trials compared MP to other drug combinations and showed a significantly higher response rate (60%) with this combination, with a response duration of 18 months and overall survival of 24 to 36 months.(Klein et al., 2011)

A 3-arm randomised study reviewed MPT (MP plus thalidomide) versus MP versus VAD based induction, followed by high-dose chemotherapy and autologous transplantation in 447 patients between ages 65 and 75 years, with OS as the primary endpoint. The overall response rate in the MP plus thalidomide arm and transplantation arm was similar.(Mateos et al., 2013)

MP plus thalidomide is now recommended as first-line treatment. MP plus lenalidomide has also shown promise.(American Society of Hematology.)

Patients with refractory disease or relapse

Patients who have disease relapse can be treated with any of the agents to which they have not had previous exposure. If the relapse has occurred

after more than 6 months then even re-challenge with the same agents can be tried.

Bortezomib was initially used as a salvage therapy in initial phase III randomized trial showing response rates of upto 38% relative to 18% in patients receiving dexamethasone only. Median PFS was 6.22 months in the bortezomib arm versus 3.49 months in the dexamethasone-only group. As per the 2014 NCCN MM guidelines, adding cyclophosphamide and dexamethasone to bortezomib (VCD) is a recommended combination for salvage therapy.(Richardson et al., 2003)

On July 20, 2012, the US FDA approved carfilzomib (Kyprolis) for patients with MM who have earlier received atleast two lines of treatment including bortezomib and an immunomodulatory agent and had demonstrated disease progression on or within 60 days of therapy completion. This approval was following a phase 2b, single-arm, multicenter clinical study of 266 patients which demonstrated an overall response rate (ORR) of 22.9% with a median duration of 7.8 months.

Another study showed that pomalidomide, another newer novel agent, had promising response rates in double refractory MM.(Lacy et al., 2011). Following this in February 2013, pomalidomide was approved by the FDA for use in patients with MM who had undergone at least 2 previous lines of therapy (including lenalidomide and bortezomib) and has had disease

progression on or within 60 days of completion of the last therapy.(Leleu et al., 2013)

H. Pet Scan & Multiple Myeloma

The most widely used system for the staging of multiple myeloma is the Durie and Salmon myeloma staging system, established in 1975. This system for the first time determined that the detection of bone lesions by X rays best correlated with measurable myeloma cell mass.(Rajkumar and Kyle, 2005) However, MRI and PET/CT, have shown considerable promise in the diagnosis and assessment of therapy in patients with multiple myeloma. Although the Durie-Salmon Plus staging system, established in 2006, does state that focal lesions should be identified, quantified, and reported as seen on MRI, bone scanning, or PET/CT, the adoption of this practice has been slow. (Durie et al., 2006)

The plain X-Ray has been used to detect MM lytic lesions if there is more than 30% destruction of the bony trabeculae, the IMWG recommends whole body X Rays (WBXR) for the diagnostic work up of MM, 80% newly detected patients present with lesions most commonly involving the vertebrae, ribs and skull.(Terpos et al., 2011)

MRI is the most sensitive modality to pick up bone disease in MM MRI detects bone involvement in patients with myeloma much earlier than

the myeloma-related bone destruction, with no radiation exposure. It is the gold standard for the imaging of axial skeleton, for the evaluation of painful lesions, and for distinguishing benign versus malignant osteoporotic vertebral fractures. MRI has the ability to detect spinal cord or nerve compression and presence of soft tissue masses, and it is recommended for the workup of solitary bone plasmacytoma.(Dimopoulos et al., 2015)

Positron Emission Tomography (PET) is a nuclear imaging using positron emitting radionucleotide tracer (like 18-FDG) and a Computed Tomography Scan (CT scan) to derive a three dimensional functional imaging.

Over the last decade PET/CT has become an important diagnostic tool of imaging in the practice of Oncology underlining a new era of co-ordination between radiology and nuclear medicine. The role of PET/CT scan in the management of many cancers is still evolving in practice. The current recommendations in some cancers like lung and lymphomas are clearly defined for which there is now strong evidence.(LeBlanc, 2014)

Historically, the concept was introduced in late 1950s by David E Kuhl,et al in USA. The current PET/CT scanners commercially available since 2000 are attributed to Dr David Townsend and Dr Nutt. (Townsend et al., 2003)

Recent studies of FDG PET/CT used to diagnose, stage, and manage multiple myeloma have yielded promising results, in an important study, Sensitivity of FDG PET in detecting myelomatous involvement was 85% and specificity was 92%. (Bredella et al., 2005)

The Role of PET Scan in Multiple Myeloma is point of great interest and debate as according to WHO Classification Multiple Myeloma is incorporated in B Cell neoplasms and PET Scan has a definitive role in lymphomas which are again B Cell neoplasms as per the International working Group on Lymphomas. (Cheson et al., 2007)

With the availability of newer therapeutic options in MM, interest in the evaluation of the depth of response to therapy, particularly CR, has increased. The International Myeloma Working Group has recently proposed the addition of the “stringent CR” category, which requires normalization of the free light chain ratio and/or absence of residual clonal cells in the BM by immunofluorescence or immunohistochemistry.

In addition to accurate staging, FDG PET/CT also influences the intended management of multiple myeloma patients. In a study by Hillner et al. that assessed the impact of FDG PET in 18 different cancer types, the intended management for multiple myeloma was changed from treatment to nontreatment or vice versa in 48.7% of myeloma patients, which was the

highest rate among all of the cancer types studied as part of the National Oncologic PET Registry. (Hillner et al., 2008)

The possible and potential roles of PET CT Scan in various aspects of Multiple Myeloma are discussed below

The Value of FDG PET/CT in Diagnosis, Staging, and Intended Management

The spectrum of disease of Plasma cell disorders range from Monoclonal Gammopathy of Undetermined Significance (MGUS) to symptomatic MM.

The role of PET CT Scan in MGUS is limited to absence of SUV in MGUS patients. Smoldering myeloma is characterized by an excess of monoclonal protein in the blood and urine. but the patient does not exhibit any of the “CRAB” symptoms of multiple myeloma.(Caers et al., 2014) The presence of focal lesions detected by PET CT Scan can play an important role in this subgroup to differentiate it from full blown multiple myeloma. (Caers et al., 2014)

The most important role of PET CT Scan in the evaluation of solitary plasmacytoma has been detecting other focal lesions and upstaging to multiple myeloma which changes the management protocol and prognosis. In addition FDG-PET has value for staging and RT planning in plasmacytoma

and potentially could have a role in response-assessment after RT. Slow resolution of FDG uptake post treatment does not necessarily imply an adverse prognosis. (Kim et al., 2009)

It has been shown that the number of focal lesions on PET and the presence of extramedullary disease adversely impacted event-free and overall survival. (Bredella et al., 2005)

In a study of newly diagnosed multiple myeloma patients conducted by Nanni et al. FDG PET/CT detected additional lesions in 16 of 28 patients compared with whole-body radiography. More than three focal lesions on PET/CT Scan had conferred adverse prognosis in Multiple Myeloma and is proposed to be a stronger indicator than chromosomal translocation by FISH. (Nanni et al., 2006)

Both FDG PET and FDG PET/CT have been shown to detect lytic lesions and stage multiple myeloma patients. In a prospective study of 46 newly diagnosed multiple myeloma patients, FDG PET was superior at detecting lesions in 46% of patients, whereas whole-body radiography was superior in only 8% of patients (Zamagni et al., 2007)

The Value of FDG PET/CT in Assessment of Response and Management

Incorporation of novel agents prior to autologous stem cell transplantation (ASCT) for multiple myeloma (MM) has increased rates of complete response (CR), a gain which has resulted in extended progression-free survival (PFS) and overall survival (OS). (Kumar et al., 2008, Stewart et al., 2009, Cavo et al., 2010). Although attainment of CR according to conventionally defined criteria and sustained CR remain important prognostic factors and primary endpoints of ongoing clinical trials, more sensitive techniques than negative immunofixation are needed to better evaluate the increasing depth of response afforded by novel agent-based therapies. (Cavo et al., 2011, Barlogie et al., 2008)

In a study involving 239 patients, FDG PET/CT was performed at baseline and after initial therapy before stem cell transplantation. The presence of more than three FDG-avid focal lesions at baseline was an independent parameter associated with inferior overall and event-free survival. The 30-month estimate of event-free survival for patients with more than three lesions was 66% versus 87% in patients with three or fewer lesions.

Another smaller study with 15 plasmacytoma patients treated with radiotherapy showed 64% of the FDG PET/CT studies normalized after

therapy, and patients remained disease-free during follow-up. (Kim et al., 2009)

The Value of FDG PET/CT in Autologous Stem Cell Transplantation Assessment

Most importantly, the complete lack of FDG activity prior to transplantation conferred superior outcome in both low and high-risk microarray defined subgroups; conversely, the presence of FDG active site was associated with poor outcome and indicates the need for alternative strategies. (Hillner et al., 2008)

In this context, elimination of minimal residual disease (MRD), as detected at the BM level by multiparametric flow cytometry or PCR, has been shown to more carefully prognosticate for improved clinical outcomes in comparison with standard techniques that assess CR. (Paiva et al., 2008) In addition, imaging techniques, such as magnetic resonance imaging (MRI) to detect the absence of focal lesions (FLs) potentially harboring viable monoclonal plasma cells.(Nanni et al., 2006, Walker et al., 2007) It has been proposed as an additional tool to increase the definition level of CR and its impact on prognosis.

More sensitive tools, such as multiparametric flow cytometry and PCR, are able to more carefully detect the presence of MRD at the BM level,

but fail to identify the persistence of focal lesions- FL(s) potentially harbouring nonsecretory MM cells or sites of active disease outside of the medullary cavity of the bone. In a report by Zamagni, et al 23% of the patients in CR had a persistence of PET/CT FLs. (Zamagni et al., 2011)

In this prospective study, authors showed that FDG PET/CT assessment after thalidomide-dexamethasone induction therapy and autologous stem cell transplantation is a reliable predictor of prognosis. The presence of at least three focal lesions, SUVmax greater than 4.2, and presence of extramedullary disease adversely affected progression-free survival. SUVmax greater than 4.2 and extramedullary disease were also correlated with shorter overall survival, with an overall survival rate of 77% and a 4-year rate of 66%. The 4-year overall survival of patients with negative PET/ CT findings 3 months after double autologous stem cell transplantation was superior to those with positive FDG PET/CT findings, with progression-free survival 66% and overall survival 89%. The presence of extramedullary disease, SUV greater than 4.2, and positive PET/CT findings 3 months after double autologous stem cell transplantation were shown in a multivariate analysis to be associated with shorter progression-free survival. (Zamagni et al., 2007)

1.2 AIMS AND OBJECTIVES

1. To analyse clinical features, staging and response in patients over a two year period.

2. To correlate disease burden in both multiple myeloma and plasmacytoma as measured by PET/CT scan with standard staging and prognostic parameters.

3. To evaluate response to induction therapy using PET based SUV changes and to compare conventional assessment of CR with PET Scan.

CHAPTER 2

MATERIALS & METHODS

2.1 RETROSPECTIVE DATA

From 1st January 2013 to 1st January 2015 all consecutive patients of Multiple Myeloma (MM) and Plasmacytoma coming to Cancer Institute for treatment were eligible for analysis. A total of 124 patients were enrolled out of which only 113 were analysable**.**

All patients underwent a detailed history and clinical examination in addition to blood tests, bone marrow studies and radiological examination as per the protocol attached. (Appendix 6)

Patient inclusion criteria

i. All new untreated cases of Multiple Myeloma and plasmacytoma
ii. Adequate renal function
iii. Adequate liver
iv. Ability to give an informed consent for treatment

Patient exclusion criteria

i. Patients who have any severe and/or uncontrolled medical conditions.

ii. Patients with a history of renal disease.

iii. Patients with other known active malignancy

iv. Previously treated patient.

Treatment of patients

Patients with solitary plasmacytoma were treated with radiation and in this subgroup repeat PET CT Scan was done after 3 months of completion of radiation therapy. All patients with Multiple Myeloma received 4-6 cycles of induction chemotherapy with the following protocols;

- Thalidomide 100mg p.o. once a day with Dexamethasone 40 mg p.o. once a week
- Lenolidamide 25mg p.o. once a day with Dexamethasone 40 mg p.o. once a week
- Bortezomib 1.3mg/m^2 i.v. or s.c. either weekly once or day 1,3,8,11 in a 4 weekly cycle along with Dexamethasone 40 mg p.o. once a week
- In non transplant eligible group of patients Melphalan was used along with Steroids in compromised doses.

In some cases palliative Radiotherapy was used for symptomatic relief.

2.2 PET CT GROUP DATA

Material

In this group all consecutive patients of MM and Plasmacytoma coming to Cancer Institute for treatment from 1st Jan 2014 to 1st Jan 2015 were considered for inclusion if they were willing to sign informed consent and meeting the proposed inclusion criteria.

Any patient who was deemed unfit by the treating physician or those who were in the exclusion criteria described above were excluded from the study

The PET CT Scan was done at the time of diagnosis and was repeated for all patients who achieved a VGPR or CR after Induction Chemotherapy to correlate the IMWG Criteria based response with PET CT based response.

All patients planned for autologous stem cell therapy underwent PET CT Scan irrespective whether they had an upfront PET CT Scan.

All newly diagnosed untreated cases of Multiple Myeloma and Plasmacytoma who consented for the study underwent detailed clinical examination and history as per the Performa attached

Patients had a baseline assessment in the form of

i. Hemogram with ESR
ii. Renal function Test
iii. Liver Function Test
iv. Serum calcium levels
v. Serum Electrophoresis
vi. Quantitative immunoglobulin levels
vii. Bone marrow aspiration and biopsy
viii. Skeletal survey
ix. LDH
x. Beta 2 microglobulin
xi. Serum free light chain studies (in light chain myeloma)
xii. Serum Albumin Levels
xiii. PET/CT Scan with 18-FDG radiotracer (as per SOP Attached)

Treatment of patients

Patients with solitary plasmacytoma were treated with radiation and in this subgroup repeat PET CT Scan was done after 3 months of completion of radiation therapy.

All patients with Multiple Myeloma received 4-6 cycles of induction chemotherapy with the following protocols;

- Lenolidamide 25mg p.o. once a day with Dexamethasone 40 mg p.o. once a week
- Bortezomib 1.3mg/m^2 i.v. or s.c. either weekly once or day 1,3,8,11 in a 4 weekly cycle along with Dexamethasone 40 mg p.o. once a week

Methodology

PET CT Scans were done using Discovery VCT 64 Slice PET CT Scanner (Manufactured by GE Healthcare, India).

Patient Preparation consisted of minimum 4 hour of fasting state along with normal creatinine values (less than 2 mg %). Patients were also advised to skip oral hypoglycemic agents on the day of the scan and to avoid any rigorous exercise before the examination.

8-10 millicurie of FDG-F18 was given by intravenous route over 5 minutes and after 45 min patient was shifted to the PET CT Machine gantry for scanning. Patient also receives intravenous CT Contrast (omnapague) at the rate of 1 ml/kg body weight. Patient then underwent whole body PET and CT Scan from cortex to mid thigh using a continuous spiral technique and an 64 -slice helical CT with a gantry rotation speed of 0.5 s. CT scan data were collected using the following parameters: 250-350 mAs, 120 KeV, a section width of 3.75 mm, and a table Speed of 78 mm/sec, later PET scan was carried out by 3min/bed by keeping both hands down in the first part of study. CT attenuation-corrected FDG-PET images were reconstructed using an ordered subset expectation maximization algorithm (28 subsets, 2 iterations). Images were displayed in a 128 x 128 matrix (pixel size 3.75 x3.75 mm, slice thickness 3.75 mm). CT and FDG-PET scan data were accurately coregistered using commercial software (Xeleris and ADW processors). For quality assurance of measurements, obtained serum glucose, recorded average SUV in the liver as an additional quality assurance mechanism and Used screen-saves or other documentation to improve reproducibility in defining ROIs between baseline and follow-up studies

The results are then assessed after reconstruction of images as per the software. FDG imaging protocols acquired slices with a thickness of 2 to 3 mm. Hypermetabolic lesions were shown as false colour-coded pixels onto the gray-value coded CT images. Standardized Uptake Values (SUVmax)

were calculated by the software for each hypermetabolic region detected in the image. CT Scan provided a quantification of size of the lesion, since PET imaging does not provide a precise anatomical estimate of its extent.

Statistical Analysis

Statistical analysis was carried out using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). This included descriptive analysis of demographic and clinical parameters. Categorical variables were summarized by frequency (percentage), and the quantitative variables were summarized by mean and standard deviation or median and range. Association for two way tables was assessed using the chi-square test.(P value ,0.05 was considered statistically significant)

Progression free survival (PFS) was estimated using Kaplan Meier method and outcomes compared across patient parameters and treatment regimens used.

CHAPTER 3

RESULTS

3.1 ANALYSIS OF PATIENTS BETWEEN 2013-2015

One hundred and twenty four consecutive patients diagnosed as Multiple Myeloma (MM) or Plasmacytoma from 1st Jan 2013 to 31st December 2014 were evaluated. Twelve patients were excluded from the final analysis as they had received prior treatment for myeloma outside before coming to our centre. The final number of previously untreated patients were one hundred and twelve (n=112), ninety six had MM and eight patients had solitary plasmacytoma, three patients had multiple plasmacytomas and five had plasma cell leukemia. The median follow up of all patients is 15 months.

Gender

Sixty one patients were males while 51 were female (M: F=1.2:1) showing a slight male preponderance.

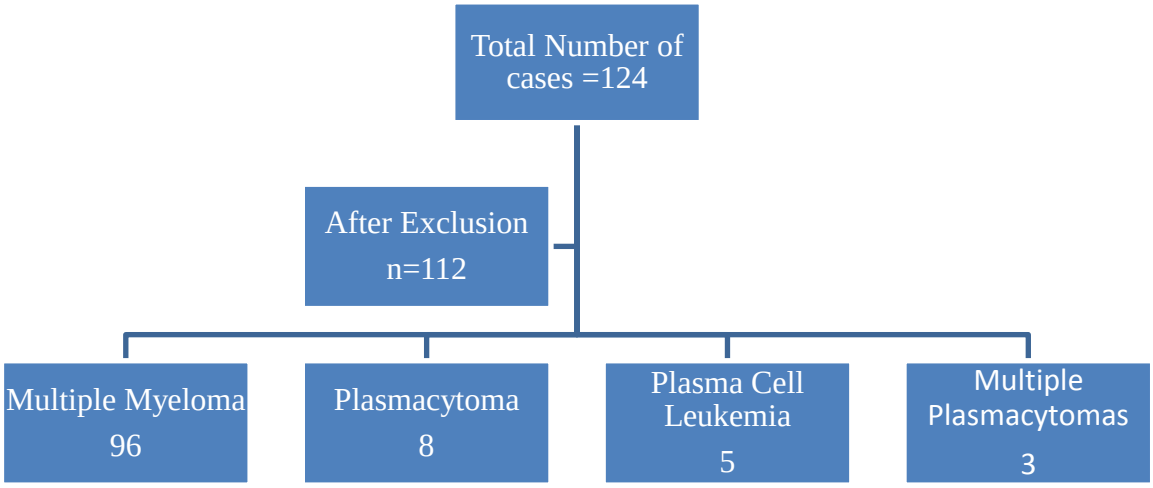

Fig 1: Patients

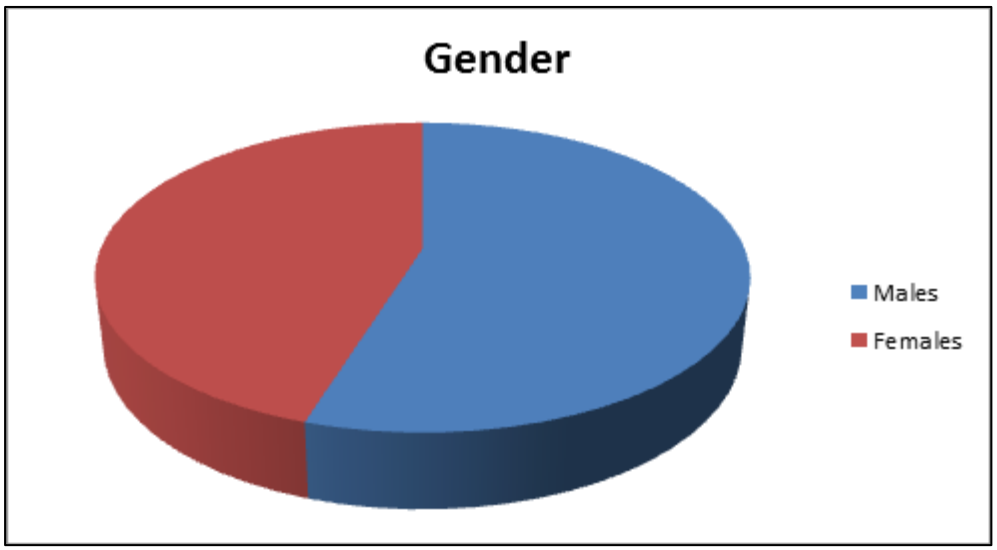

Fig 2: Gender

Age

Median age was 56 years (range 27-81 years). The proportion of patients in the age range 21-40 years was 4.2% (n=5), 65.4% (n=73) were in the range of 41-60 and 40.4% (n=34) were more than 61 years old .

Clinical Presentation

The signs and symptoms at presentation are shown (Table 2). The predominant symptom was pain in the back in 97% patients, 22% presented with paraparesis while 12.5% had fractures. 15% presented with renal failure. Fatigue was presenting complaint in 22.1% patients while 11.5% had active infections when they first came to hospital.

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Table 2: Presenting Signs &Symptoms

Back Pain/ Bony Pains	109	97.23%
Paraparesis	25	22.1%
Fatigue	25	22.1%
Infections	13	11.5%
Renal failure	17	15%
Fractures	14	12.5%

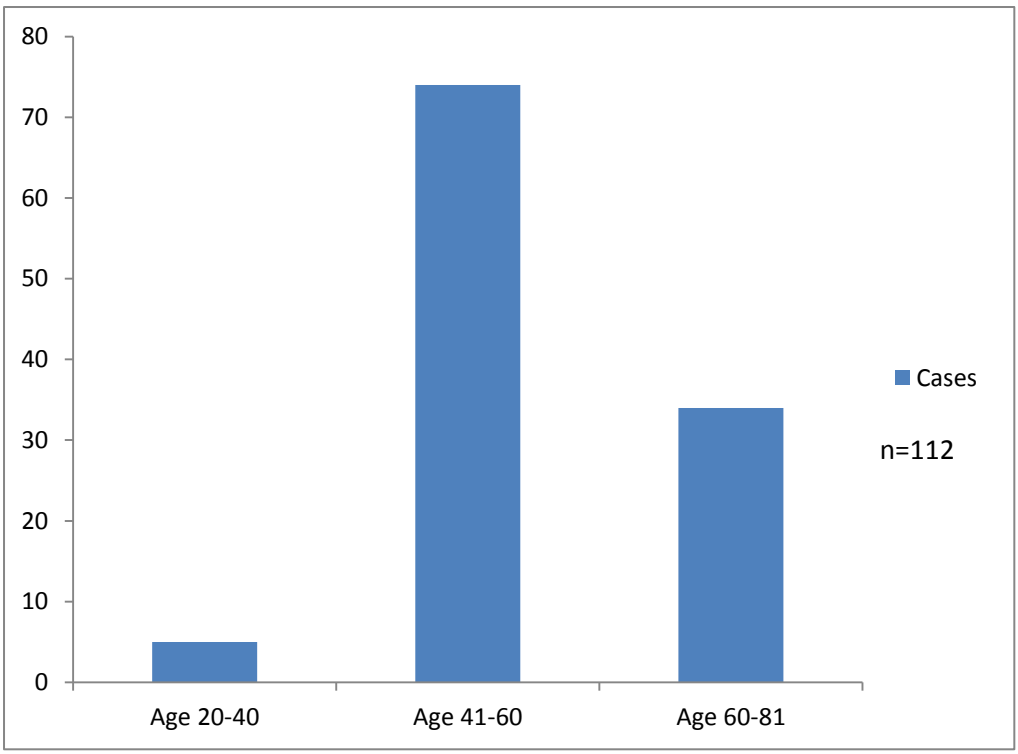

Fig 3: Age

The median duration of symptoms was 3 months (range 1-13 months). The median ECOG performance status of patients in the cohort was 2.

Associated diseases, like Type 2 Diabetes Mellitus and Hypertension were present in 36 patients (32%). One patient had hepatitis C positivity.

Table 3: Associated Diseases

T2DM	27	24.1%
Hypertension	24	21.4%
Hepatitis C	1	0.8%

Laboratory Parameters

Hemoglobin: The Median haemoglobin was 8.5 g/dl (range 4.2-14.5 g/dl). The value of Hb was less than 10 g/dl in 82 patients (73.2%), between 10-12 g/dl in 21 patients (18.8%) and more than 12 g/dl in 9 patients (8%).

Total Leukocyte Count (TLC): The median TLC was 6700 10^9/L (range 1500-20000 10^9/L). Seventeen (15%) patients had an abnormal TLC value with 11 patients having values more than 11000 10^9/L and 6 patients having values less than 4000 10^9/L.

Table 4: Laboratory Parameters

Parameter	Median	Range
Hemoglobin	8.5 gm/dl	4.2-14.5 gm/dl
Total Leucocyte Count	6700 x 10^9	1500-20000 x 10^9
Platelet Count	2.35 lakh	0.15-5 lakh
ESR	111 mm/ 1^{st} hr	10-200 mm/ 1^{st} hr
Creatinine	0.9 mg/dl	0.4-12 mg/dl
Calcium	9 mg/dl	6.1-15 mg/dl
LDH	522 u/ml	218-2024 u/ml
Albumin	3 g/dl	1.6-6.3 g/dl
Sr Protein electrophoresis " M Protein"	2.95 mg/dl	1.95-7.3 mg/dl

Platelets: The median platelet count was 2.35 lakhs (range 0.15 to 5 lakhs), 24 (21.2%) patients had thrombocytopenia (less than 1.5 lakh).

Peripheral Smear: 5 patients had presence of plasma cells in the blood with median value of 34% (range 28%-68%).

ESR: The median ESR was 111 mm/1^{st} hr (range 10-200 mm/1^{st} hr), 103 patients (91%) patients had abnormal values, while the rest were normal.

Biochemistry

Serum Creatinine: The median serum creatinine level was 0.9 mg/dl, 24 patients (21.4%) had value above 1.4 mg/dl (Range: 0.4-12 mg/dl).

Calcium: The median Calcium was 9 mg/dl (Range: 6.1-15 mg/dl), 10 patients (8.8%) had elevated Calcium levels above 11 mg/dl.

LDH: LDH values were available in only 52 patients and, median was 522 U/ml (range 218-2024 U/ml). Twenty (38%) patients had high LDH values (more than 400).

Albumin: Serum Albumin was available in 100 (89%) patients with a median level of 3 gm/dl (range 1.6- 6.3 mg/dl). Seventy six (75.4%) patients had albumin levels less than 3.4 mg/dl.

Serum Protein Electrophoresis: One hundred eight of 112 patients had protein electrophoresis performed. The median value of M band was 2.95 mg/dl (range 1.95-7.3 mg/dl), It was normal in 27 patients. In the seventy seven patients with normal M band, 2 had solitary plasmacytoma and rest 25 patients had elevated kappa/lambda ratio on serum free light chain assay (SFLC).

Bone Marrow Examination

Bone Marrow Examination was performed in all patients. Ninety eight (87.5%) patients had an abnormal bone marrow. In 25 patients only scattered plasma cell were present and was confirmed using immunohistochemistry using CD 138 antibody. In the remaining 73 patients the extent of plasma cell infiltration was 20-100%. Of this 5 patients had plasma cell leukemia . The remaining 14 patients (12.5%) had a normal bone marrow study of which plasmacytoma (n=12) and MM (n=2). Both the MM had elevated lambda chain on SFLC assay.

Radiology

Skeletal survey showed 14(12%) patients to have a single bone abnormality while 98 (88%) patients had multiple bony lesions.

Magnetic Resonance Imaging (MRI) of the spine was done in all cases with suspected paraparesis or on physician's discretion (n=25), 12 patients had fracture in the vertebrae, 24 patients had radiological features of cord compression.

Stage of Disease

Durie and Salmon Staging System was used to stage the MM patients (n=99), 82 patients were DSS Stage IIIA (83%) and 17 were DSS IIIB (17%).

Treatment

All patients except those who had solitary plasmacytoma (n=8) were treated as for MM. Seventy nine (n=104) received chemotherapy (Table 5), these included bortezomib, lenalidomide, thalidomide and melphalan together with steroids (Dexamethasone at 40 mg orally every week was given with Bortezomib, Thalidomide and lenalidomide while Prednisolone was given with melphalan. Of the remaining 25 patients 19 patients succumbed to the disease before any definite systemic therapy could be initiated and 6 refused to have any treatment.

Table 5: Treatment

Bortezomib	40	51%
Lenalidamide	26	32%
Melphalan	4	5%
Thalidomide	9	12%

Twenty six patients also received radiation for palliation of bone pain during the induction treatment with radiation (dose 20 – 30 Gy). Adequate pain relief was achieved in all the patients.

Overall, seventy nine of the patients with MM who were initiated on chemotherapy, only sixty patients were only eligible for analysis. Twelve were still on treatment at the time of analysis, four died due to complications,

two were lost to follow up while one died due to cardiac dysfunction unrelated to treatment.

A median of 4 cycles of treatment was administered to the evaluable patients (range 3-12 cycles)

Assessment of Response

Evaluation of response was assessed using the International Myeloma Working Group (IMWG) Criteria (IMWG Consensus, 2009), complete response (CR) including stringent CR was observed in 36.5%, Very good partial response (VGPR) in 25%, partial response (PR) in 10% and progressive disease in 28.5% patients. Table 6.

Table 6: Overall Response to treatment (n=60)

	CR	**VGPR**	**PR**	**PD**
Bortezomib	14 (43.8%)	6 (18.8%)	2 (6.3%)	10(31.3%)
Lenalidomide	6 (35.3%)	5 (29.4%)	2 (11.8%)	4 (23.5%)
Thalidomide	2 (25%)	3 (37.5%)	1 (12.5%)	2 (25%)
Melphalan	0	1 (33.3%)	1 (33.3%)	1(33.3%)
Total	*22(36.5%)*	*15 (25%)*	*6 (10%)*	*17(28.5%)*

High dose chemotherapy with autologous peripheral blood stem cells rescue

All patients who achieved more than very good partial response (VGPR) to the MM treatment were considered for consolidation with high dose chemotherapy with melphalan and supported with autologous peripheral blood stem cell rescue, if they were less than 60 years old, with intact organ functions and deemed fit by the treating physician.

In the 60 patients who were evaluable, 29 (48%) patients were deemed transplant eligible while 31 (52%) were ineligible high dose chemotherapy.

Out of these twenty nine eligible patients, 18 (60%) were planned for high dose chemotherapy. Fourteen (47%) underwent high dose chemotherapy, 4 (13%) patients could not have adequate collection of stem cells and so further treatment was not given.

The remaining 11 patients were not treated with high dose chemotherapy as 3 did not achieve VGPR, 4 patients refused and other 4 patients deemed unfit for high dose therapy by the treating physician.

Solitary Plasmacytoma

There were 8 patients who presented with solitary plasmacytomas, 3 had spinal lesions, 2 in the upper extremity, and 1 each in the mandibular, sternal and iliac bones.

All patients with solitary plasmacytomas received radiation as the primary modality of treatment. Six (75%) patients are still in CR, 1 has progressed to Multiple Myeloma and 1 was lost to follow up.

All patients (n=5) who presented with Plasma Cell Leukemia did not respond to treatment progressed and died.

Survival

At a median follow up of 15 months the Overall Survival (OS) was 76% and Event Free Survival (EFS) was 43.1%.

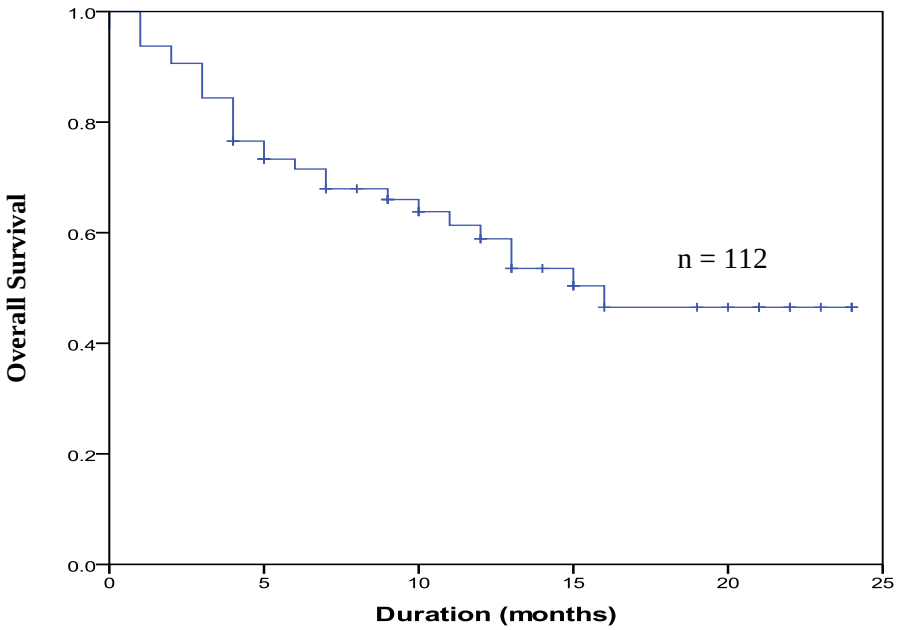

Fig 4: Overall Event Free Survival

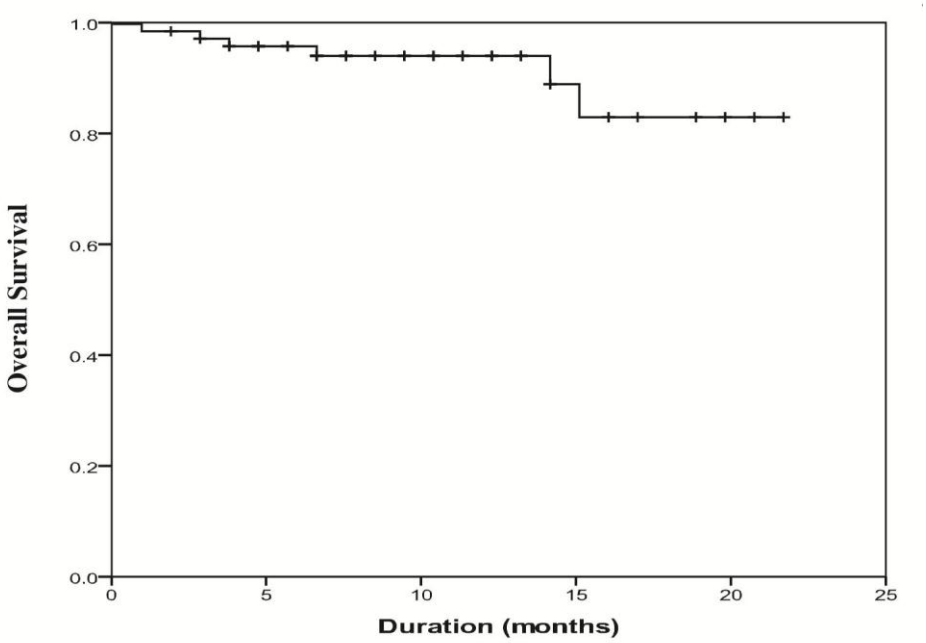

Fig.5 Overall survival

3.2 THE ROLE OF PET CT SCAN IN THE MANAGEMENT OF MULTIPLE MYELOMA

All patients (n=54) who presented to the Cancer institute (WIA) in 2014 were open for enrolment into the study if they were consented and were eligible. Thirty one (57%) patients agreed to participate in the study.

Of the thirty one patients 28 had PET CT scan at the time of diagnosis while 3 had prior to high dose chemotherapy. Of the 31 patients had MM, 5 had solitary Plasmacytoma while 4 had multiple plasmacytomas but were treated for MM. In all we had 38 PET Ct scans, 28 upfront and in ten patients post treatment for remission status.

Gender: Seventeen patients were male while 14 were female with a M:F ratio of 1.2:1.

Age: Median age was 55 years (range: 42-77 years), 24 patients (77.5%) were younger than 60 years at the time of diagnosis.

Clinical Presentations

The signs and symptoms of the 31 patients are described in table 7

Table 7: Presenting signs and symptoms

Back Pain/ Bony Pains	30	96.5%
Paraparesis	6	19.4%
Fatigue	7	22.6%
Anemia	27	77.5%
Renal failure	2	6.5%
Fractures	1	3.2%

The median duration of symptoms prior to diagnosis was 3 months (range 1-12 months), the median ECOG performance status was 2. Associated disease like diabetes mellitus and hypertension were present in 9 patients (29%).

Table 8: Associated Diseases

Type 2 Diabetes Mellitus	6	19.5%
Hypertension	7	22.5%

Laboratory Parameters

Hemoglobin: The Median haemoglobin was 10.5 g/dl (range 4.2-12.7 g/dl). Only 4 patients had Hb value of more than 12 g/dl whereas 27 (77.4%) had anemia.

Total Leukocyte Count (TLC): The median TLC was 7454 10^9/L (range 3500-15000 10^9/L). Nine (29%) patients had abnormal TCC vaues, 4 having TLC more than 11000 10^9/L and 5 having lower than 4000 10^9/L.

Platelets: The median platelet count was 2.3 lakhs (range 0.7-3.9 lakhs). Five patients (16%) had thrombocytopenia.

Peripheral Smear: All patients had normal peripheral smear.

ESR: The median ESR was 99 mm/1st hr (range 120-180 mm/1st hr), 30 patients (97%) had an abnormal ESR value.

Biochemistry

Serum Creatinine: The median serum creatinine level was 1.61 mg/dl (range 0.5-12 mg/dl), 4 (13%) had value above the normal (1.4 mg/dl).

Calcium: The median Calcium was 10.6 mg/dl (Range: 7.2-12 mg/dl). Eight (26%) had elevated Calcium levels above the normal (11 mg/dl).

LDH The median was 670 U/ml (range 320-1600 U/ml). Twenty six (84%) patients had high LDH values (more than 400).

Albumin: Median value of serum albumin was 3.17 mg/dl (range 1.3-5 mg /dl).

Beta 2 Microglobulin The median value was 6.6mgm/dl (range 2.9-11.3 mgm/dl).

Serum Electrophoresis: Serum electrophoresis was performed in all cases (n=31). Twenty four (77%) had abnormal M protein, with median value of 4.6 mg/dl (range 1.4-6.4 mg/dl). Seven patients (23%) had no detectable M protein, 5 patients had solitary plasmacytomas while two had MM. In the two cases with MM and normal M band the SFLC ratio was deranged.

Immunoglobulin levels were done in all the cases 29 patients (93.5%) had increased Immunoglobulin G (Ig G) levels with median value of 1400 mg/dl (Range 35-2953mg/dl) while 2 patients had (6.5%) increased IgA (388 U and 798 mg/dl).

Table 9: Laboratory Parameters

Parameter	Median Value	Range
Hemoglobin	10.5 g/dl	4.5-12.7 g/dl
Total Leucocyte Count	7454 10^9/L	3500-15000 10^9/L
Platelet count	2.3 lakhs	0.7 – 3.9 lakhs
ESR	99 mm/1st hr	20-180 mm/1st hr
Serum Creatinine	1.61 mg/dl	0.5-12 mg/dl
Calcium	10.6 mg/dl	7.2-12 mg/dl
Albumin	3.17 mg/dl	1.3-5 mg/dl
Beta 2 microglobulin	6.6 microgm/dl	2.9-11.3 microgm/dl
M protein	4.6 mg/dl	1.4-6.4 mg/dl

Bone Marrow Study

Bone marrow examination was performed in all patients (n=31), 26 patients (83%) had an abnormal bone marrow. In one patient only scattered plasma cells were present and were confirmed by immunohistochemistry using CD 138 antibody. In the remaining 25 patients the extent of plasma cell infiltration in the bone marrow ranged from 30% - 100%. The remaining five patients with normal bone marrow had solitary plasmacytomas.

Skeletal Survey

Four patients (13%) had only single lesion on whole body X-rays while 27 (83%) had multiple bone lesions.

Staging

Both ISS and Durie Salmon Staging system were used for all patients with MM (n=26). According to the ISS Staging system 5 patients were stage I, 9 were stage II and 12 were stage III. According to the Durie Salmon Staging (DSS) system all patients were stage III with 23 being IIIA and 3 being stage IIIB.

PET CT Scan

Of the twenty eight patients who had pre treatment PET CT Scans, three patients (10.7%) were upstaged to MM as they had multiple

plasmacytomas. These patients did not have bone marrow plasmacytosis or fulfilled the CRAB criteria used for diagnosis of symptomatic MM. Skeletal survey did not detect additional bony abnormalities.

Table 10: Multiple Plasmacytoma patient characteristics

UHID	Hb(g/dl)	Calcium (mg/dl)	Creatinine (mg/dl)	Bone Disese	Bone Marrow	PET			
						FL	SUV	EM	BMU
58272	10	7.8	1	Nil	Normal	7	7	Y	N
49322	5	11	0.9	Nil	Normal	6	12	Y	Y
43567	12	10	0.5	Nil	Normal	8	9	Y	N

FL= Number of focal lesions, SUV=Standardised Uptake Value, EM= Extramedullary disease, BMU= Bone marrow uptake.

The first patient, had metabolically avid disease with multiple lytic lesions with soft tissue components in the skull, medial end of right clavicle, ramus of mandible, sternum, pleural based lesion where the SUV range was 3.1- 7.

The second patient, presented with 14.7x13.1x6 cm mass near D11 (SUV 12), multiple peripancreatic lymph nodes (SUV 8.2), diffuse marrow uptake and multiple skeletal lesions (SUV Range 6.1-12).

The third patient had multiple bony lesions along with pleural and 3rd rib soft tissue lesion measuring 3x1 cm with maximum SUV of 9.(SUV Range 5.1-9)

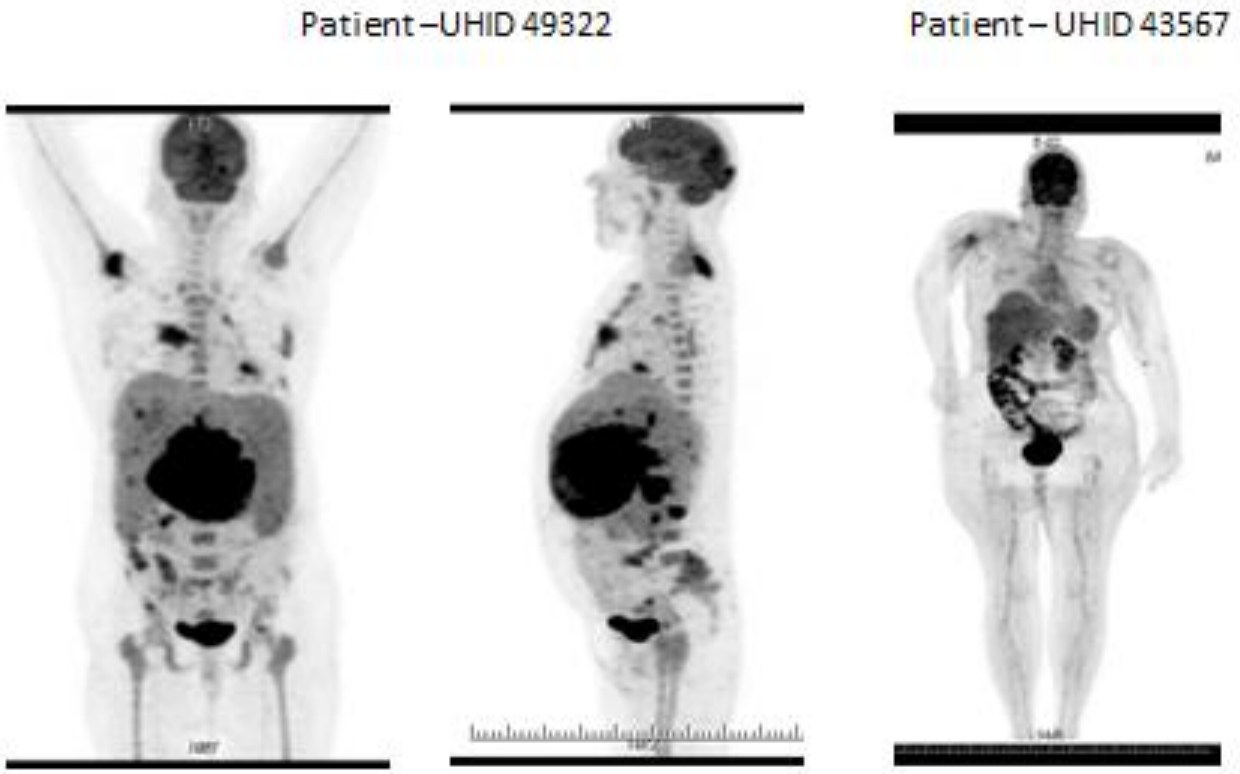

Fig. 6 Pre Treatment PET CT Scans

Treatment

Thirty of the thirty one patients received treatment and one patient died before therapy could be initiated.

Table 11: Treatment

Chemotherapy Only	15
Radiotherapy Only	6
Both Modalities	9
No treatment	1

Of the patients who received chemotherapy (n=24), 9 (37%) were treated with Lenalidomide and dexamethasone, 14 (60%) received Bortezomib and dexamethasone and one (3%) had Thalidomide with dexamethasone.

At the time of analysis 16 patients had completed the planned treatment.

Table 12: Overall Response to treatment- Chemotherapy (n=16)

	CR	**VGPR**	**PR**	**PD**
Bortezomib	5 (30.5%)	2 (13%)	0	4 (25%)
Lenalidomide	1 (6.5%)	1 (6.5%)	1(6.5%)	1(6.5%)
Thalidomide	1 (6.5%)	0	0	0
Total	*7 (43.5%)*	*3 (18.5%)*	*1 (6.5%)*	*5 (31.5%)*

In the evaluable 16 patients, 6 had not achieved the desired response, 2 were unwilling for EOT PET CT Scan and one was lost to follow up in CR.

Patients with Solitary Plasmacytomas (n=5) received radiation to the site of disease and 3 were in remission while two had further progression of disease. All the three patients who are in CR underwent PET CT Scans.

At the end of all treatment 7 patients had PET CT scans at the time of diagnosis and at the end of proposed therapy for comparison of response (4 had MM and 3 had plasmacyoma)

Table 13: Comparison of Response

Prior to treatment PET CT							End of treatment PET CT			
UHID	**FL**	**SUV Mean**	**SUV range**	**EM**	**BMU**	**Status Post treatment**	**FL**	**SUVmax**	**Extramed**	**BMU**
59964	5	5	2.1-7	N	N	CR	0	0	N	N
72274	5	4.6	1.2-6	N	Y	sCR	0	0	N	N
73710	6	5.8	3.1-8	N	N	CR	1	1.2	N	N
73431	4	5.1	4-6.6	N	N	sCR	0	0	N	N
70589	1	3.1	-	N	N	CR	1	1.3	N	N
45679	1	7	-	N	N	CR	0	0	N	N
72788	1	4.2	-	N	N	CR	1	1	N	N

FL= Number of focal lesions, SUV=Standardised Uptake Value, EM= Extramedullary disease, BMU= Bone marrow uptake.

The three patients who had PET CT scan prior to high dose chemotherapy were in metabolic CR (Patient number 1, 2 and 4). Patient number 3 had a residual uptake of 1.2 SUV with lesion measuring less than 1.6 cm and was in conventional CR.

Patient number 5, 6 and 7 were plasmacytomas are on follow up.

In the patients who achieved conventional stringent CR the PET CT scan showed no metabolic activity (2 and 4). But in patient number 3 we had Cr by conventional means but PET CT showed residual metabolic activity, although the significance is doubtful.

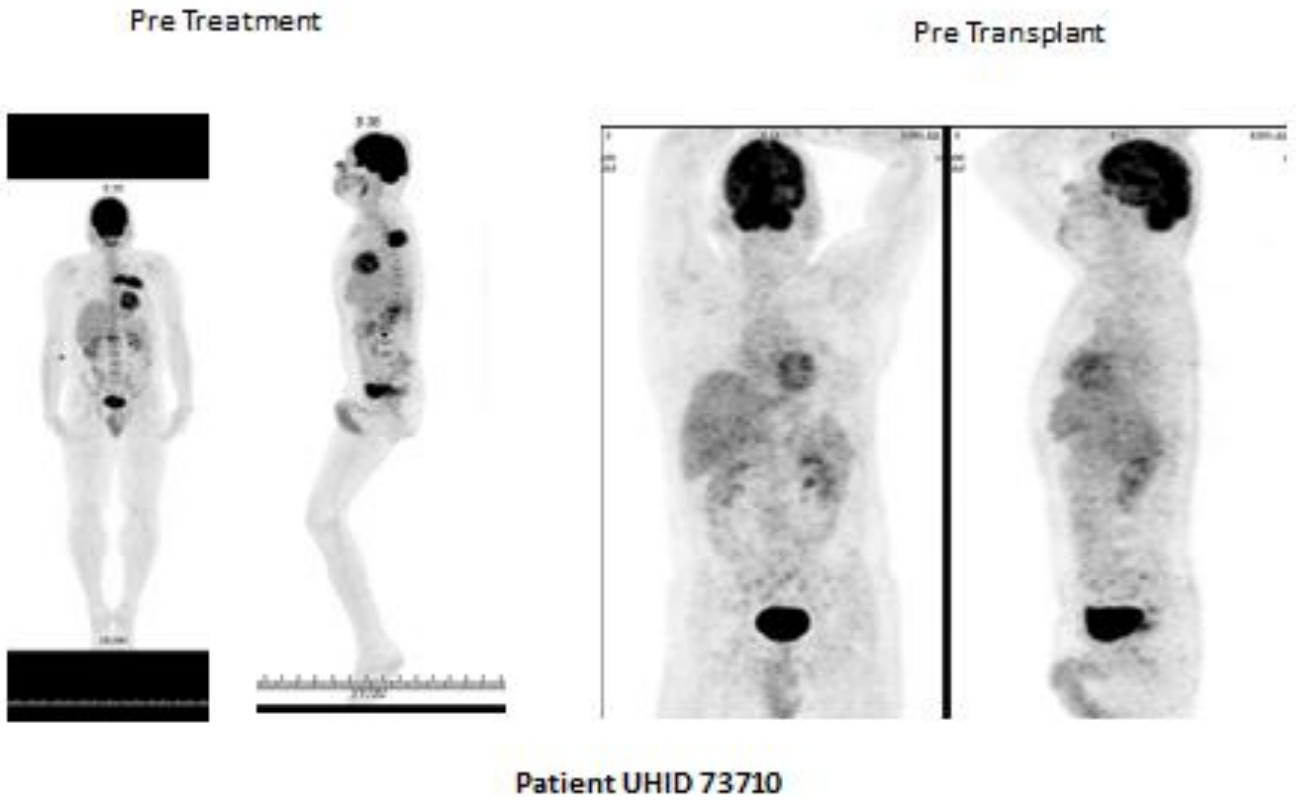

Fig. 7: Pre treatment and Pre transplant PET CT Scans

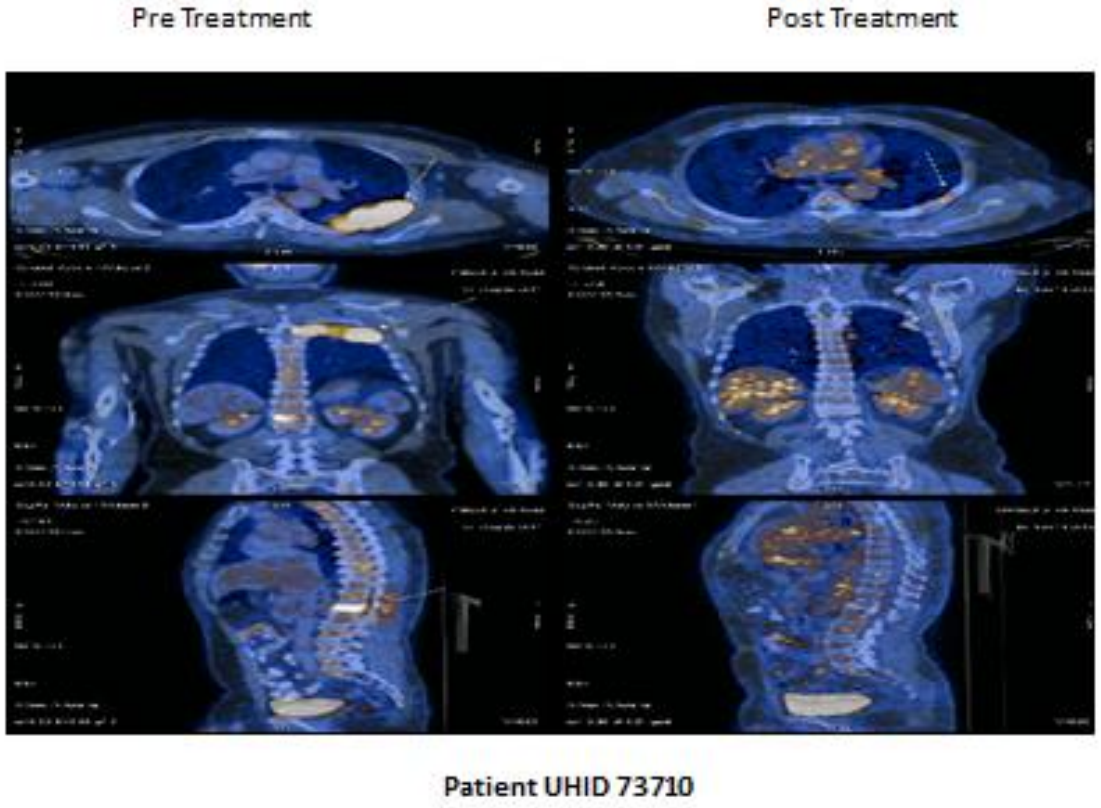

Fig.8: Pre treatment and Pre transplant PET CT Scans

PET CT Factors & Survival

In the PET CT Group we analysed the number of focal lesions whether less than 3 or more than 3, SUV max of the lesion and presence of extramedullary disease.

Table 14: Characteristics on PET CT scan (n=28)

Characteristic Feature		Number of Patients
No. Of FL	**<3**	7
	>3	21
SUV max	**<4.2**	6
	>4.2	22
Extramedullary Disease		12
Multiple Plasmacytomas		4

Number of Focal Lesions ranged from 1 to 9 with mean number of 5.2.

SUVmax: Standardised Uptake Values at the point of maximum activity were taken and the mean value was 5.8 (Range 3.1 to 12). 6 patients had value less than 4.5 while 22 had higher values.

Extramedullary Disease 12 patients had extramedullary disease out of which 6 had lung/pleural based lesions, 3 had GI lesions, 2 had scapular and one each in forearm, rib and paraspinal mass. 2 patients had more than one site of extramedullary disease.

On analysis none of these factors given below

- Number of focal lesions
- SUV max
- Extramedullary Disease

had any significant survival outcome in our study. In the sub group of patients who had less than three focal lesions there was EFS advantage of 3 months but it was not statistically significant.

Table 15: Overall survival and PET characteristics

Variable	Values	No of Patients	Mean EFS (months)	P value
SUV	<4.5	5	9.4	0.6
	>4.5	23	10.9	
Extramedullary Disease	Yes	9	11	0.9
	No	19	8.9	
Number of lesions	<3	6	14	0.8
	>3	23	11	

CHAPTER 4

DISCUSSION

The incidence of Multiple Myeloma in India varies from 0.4-1.9/100,000 population for males and 0.4-1.3/100,000 population for females.(Takiar et al., 2010) The incidence as per Madras Metropolitan Tumor Registry (MMTR) is 0.82/100,000 population for males and 0.52/100,000 population for females. (Swaminathan et al., 2011) .As per Indian Cancer Registry Programme's consolidated report (1990-96) the average age of diagnosis with MM is 55 years as compared to 65 years in SEER database. (Mallath et al., 2014)

In this study the median age at presentation was 56 years which is similar to that reported in Indian data. Data from Kerala had shown a similar median age of 61 years in South Indian population.(Nair et al., 1993) The incidence of MM in the patients under 40 years is 4.2% in this study which is similar to rates reported by Kayle et al. in western population (Kyle, 1975).

The overall male to female ratio in this cohort was 1.2:1 which is different from the reported rates of 2:1 in the Delhi Cancer Registry but is similar to the 1.6:1 ratio in the SEER database.

Clinical Presentation

Bone pain was the most common symptom in our patient group accounting for 97% of all presenting complaints. This is slightly higher than that from other parts of the country but substantially higher than reported by Kyle et al (68%). (Kyle et al., 2003)

The incidence of paraparesis and fractures in our study group was 22.1% and 12.5% respectively which when compared to western population was significantly higher (less than 5%)(Chakraborti and Miller, 2010)

Labaratory parameters at presentation

Presence of CRAB (hypercalcemia, renal failure, anaemia & bone disease) is a diagnostic feature of MM with bone marrow plasmacytosis (>10%). The occurrence of these features are variable in the published literature.

In this study the frequency of anaemia was 83% which was higher than 62% reported in the AIIMS study and the west. (Kyle et al., 2003)

Renal failure in this study was 15% which was less than 32% reported from Kyle et al and 22% reported in a series from Mumbai. (Advani et al., 1978)

The incidence of hypercalcemia was 9% which was similar to the other Indian studies (10-11%) except that from Mumbai which was reported at 22%.(Advani et al., 1978)

Serum M protein was present in 76% of patients which was less than that of AIIMS experience of 85.5%.(Kumar et al., 2006) Ig G myeloma is the commonest form of myeloma in all series. (Kumar et al., 2006) (Advani et al., 1978, Gupta et al., 2009)/

Table 16: Comparative Data from Indian and western studies.

	Our Study	Kumar (AIIMS)	Kyle(Mayo)	Advani	Gupta
Cases	112	534	869	231	146
Median Age	56	55.4	61.5	51	51
Age<40	4.2%	11.7%	4%	13%	12%
Males	54.5%	69%	61%	69%	69.7%
Bone Pains	97%	84%	68%	81%	79%
Anemia	83.1%	62.4%	62%	59%	40%
Renal Failure	15%	31.3%	32%	22%	37%
Hypercalcemia	9%	10.3%	30%	28%	11%
Skeletal abn (WBXR)	95.5%	93.7%	79%	-	96%

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Treatment and Response

In the last decade novel agents (Thalidomide, Lenalidomide and Bortezomib) have become the standard of care for newly diagnosed MM. Thalidomide was initially extensively used, however, it had toxicities like teratogenicity, Deep vein thrombosis (DVT) and neuropathy. To overcome this lenalidomide was developed which was 50,000 times more potent in inhibiting TNF alpha effects than thalidomide and also less toxic.

In this study 79 patients were treated according to the protocol. In the cohort of 112 patients 80 patients were transplant eligible while 32 were ineligible due to age, co existent severe medical conditions or had solitary plasmacytoma. The median follow up was 15 months. Of these patients 79 were treated with chemotherapy as the main modality of treatment and 60 patients were assessable at the time of analysis with 51.5% patients achieving VGPR or above and 10% having Partial response. The overall response rate (CR+VGPR+PR) was 61.6%, the ORR was inferior to that observed in the West using these two drug induction protocols (80-91%).The data from The Mayo Clinic in the Lenalidomide Dexa study had a CR+VGPR rates of 56% at 21 months which were similar to 51.5% in our study but again our treatment protocols were variable and median duration of follow up was only 15 months.(Rajkumar, 2013)

PET CT Scan

Currently, the most widely used system for staging MM is that of Durie and Salmon—a system based on readily available clinical and hematologic parameters such as haemoglobin levels, M protein level, calcium levels, percentage of diffuse infiltration of bone marrow by plasma cell & number of osteolytic bone lesions traditionally defined by skeletal radiography (Durie and Salmon, 1975). The updated version, Durie and Salmon PLUS (DSS+), includes the addition of more advanced imaging modalities such as 18F-FDG PET/CT or MRI.(Durie et al., 2003) The clinical and hematologic parameters included in the Durie and Salmon staging system may simply represent or correlate with the underlying tumour burden, which may be a more direct predictor of disease progression and patient survival.

^{18}F-FDG PET/CT evaluates glucose metabolism activity and provides biochemical and functional information in contrast to only anatomical details obtained by CT and MRI. ^{18}F-FDG-PET/CT imaging combines whole-body functional imaging of PET and morphologic imaging with CT in a single study.

It is possible to quantitatively express the degree of 18F-FDG uptake as the standardized uptake volume (SUV) with the usual cut-off value of 2.5 for lesions measured ≥1 cm in size. To avoid false-negative results, it has been recommended that for lesions <5 mm in diameter, any amount

of 18F-FDG uptake is positive regardless of SUV, whereas for lesions 0.5-1 cm should be considered indeterminate if SUV is <2.5.(Larson et al., 1999)

In the cohort of 31 patients in the current study the SUV values ranged from 3.1 to 12 with a mean value of about 5.8 which is significant as the original reports described a historical cut off value of SUV as 4.5 with long term outcome.(Zamagni et al., 2011)

The number of focal lesions detected on PET scan in our analysis ranged from 1 to 9 with a mean of 5.2 lesions, the presence of more than 3 ^{18}F-FDG-avid focal lesions is an independent parameter associated with decreased overall and event-free survival. Thus, in a study a 30-month estimate of event-free survival of 66% was detected in patients with >3 focal lesions vs 87% in those with ≤3 focal lesions.(Bartel et al., 2009)

Twelve patients in our study had extramedullary disease, of which 6 had lung/pleural based lesions, 3 had GI lesions, 2 had scapular and one each in forearm, rib and paraspinal mass. 2 patients had more than one site of extramedullary disease, Haznedar et al studied 61 newly diagnosed patients with myeloma and reported that both the presence of extramedullary lesions and the increased value of SUV_{max} predicted poor prognosis with shorter overall survival.(Haznedar et al., 2011)

Despite being known prognostic PET based variables, i.e, number of focal lesions, extramedullary disease and SUV values, they had no statistically significant co-relation with survival in this study. This may be due to the small number of patients and we need to extend the study to confirm these findings.

We had 10 patients who had post treatment scans and of these 7 patients had also undergone pre treatment imaging. Three had plasmacytomas and 7 were MM.

The three plasmacytoma cases had received radiation as the primary modality of treatment and 1 patient had no SUV while other two had SUV of 1.2 and 1.3 only which was attributed to post RT changes. Several retrospective studies indicate that in patients with a normal ^{18}F-FDG-PET scan after radiotherapy, it remains negative during the follow-up. Whereas normal post treatment PET scan in patients who had positive findings before therapy correlated with complete remission. (Kim et al., 2009)

In the MM patients in this study all 7 were taken up for autologous stem cell transplantation and all had no SUV uptake on PET Scan prior to treatment with high dose chemotherapy confirming CR. Complete ^{18}F-FDG suppression detected in focal lesions before transplantation predicted significantly better outcomes in the Total 3 study.(Bartel et al., 2009)

At present, there are no uniform criteria for visual or quantitative evaluation or both of ^{18}F-FDG-PET/CT in MM. In addition, there is also a lack of inter-observer reproducibility in ^{18}F-FDG-PET/CT image interpretation. To use PET/CT as a valid prognostic tool, it is necessary to develop a consensus regarding a protocol for ^{18}F-FDG-PET/CT as well as a uniform protocol for response criteria similar to that in solid tumours and lymphomas.(Wahl et al., 2009)

Future Directions

The main drawback of PET CT Scan described in the Indian context has been the false positive results due to tuberculosis. (Nazar et al., 2012)

Recently, newer radiolabeled agents have been developed to increase the sensitivity and specificity of PET scan, C-MET (methionine) is a radiolabeled positron emitting amino acid that images amino acid metabolism. The plasma cells are known to have high amino acid activity. (Nazar et al., 2012) In a series it was found that C-MET PET Scan was better than 18-FDG PET CT Scan with overall accuracy of 93% and specificity of 100%(Nanni et al., 2007) but larger numbers and longer follow up are needed.

CONCLUSION

- PET CT Scan is a reliable tool in the diagnosis and staging of Multiple Myeloma and Plasmacytoma
- In this study it was valuable in only three patients compared to conventional criteria.
- It predicted correctly stringent CR (sCR) in all patients when evaluated at the end of all treatment.
- There was no correlation of PET scan results and outcome measures.
- Though our study limited by small numbers and short follow up failed to demonstrate any statistically significant prognostic variable but larger trials have shown that PET CT scan can be used for this purpose.
- This study has to be extended for a definite assessment of the role of PET CT scan in Multiple Myeloma .
- Newer advances like C-MET labelled PET CT scans and better software computations may make PET CT scan an essential part of diagnostic and prognostic work up in Plasma Cell Disorders

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APPENDIX 1

ECOG PERFORMANCE STATUS

Description	**Scale**
Normal activity	0
Symptomatic but ambulatory self-care	1
Ambulatory more than 50% of the time	2
Ambulatory 50% or less time, nursing care needed	3
Bedridden, may need hospitalization	4

APPENDIX 2

CANCER INSTITUTE MM PROFORMA

Sl no.	**NAME**								
AGE yrs	SEX male 1/female 2								
DAT dd/mm/yyyy									
DUR OF SYMPT (Months)									
OP.NUMBER							**year**		
Performance status 0 1 2 3 4									
Presenting features									
Back pain 1 / 0					Paraperesis 1 / 0				
Fatigue 1 / 0					Fracture 1 / 0				
DOE 1 / 0					Hyperviscosity 1 / 0				
Renal failure 1 / 0					Infection 1 / 0				
Bone pain 1 / 0									
Others									
Co-morbidities: HT/DM/IHD/ Liver/ CKD Autoimmune/HIV/Psych/ other mention									
Hemoglobin			WBC				Plt		
LDH							ESR		
Urea			Creat				Calcium		
Albumin			Beta2 Micro						
DC									
Bones involved					Single/ Multiple				

MRI spine	
Bone marrow	% of plasma cells
IHC in BM	
M protein level	
Serum FLC K L ratio	
Quantitative Immglobulin levels	IgG IgA IgM
Stage Salmon Durie	
Stage ISS:	
Cytogenetics:	
HIV 1/0	HBV 1/0	HCV 1/0
Prior trt 1/0	Details:	

First line trt	Chemo1/ RT2/ Combi3

Transplant eligible/ ineligible			If ineligible, reason					
First line therapy:								
Bortezomib 1/0 Len 1/0 Thal 1/0 None 1/0								
Melph 1/0 Endoxan 1/0 Steroids 1/0								
Dat start 1st line								
Dat of last cycle								
Protocol 1st line			Vd 1			VTD2		
Ld3		CRd4			VRd5		VMP 6	
MPR 7		Td8			MPT9		MP 10	
Cyclopred11		CTD 12						
No cycles **given:**								
Reason for stopping 1st line before 4-6 cycles		Planned trt given 1				Toxicity 2		
		Death 3				PD 4		
		Lost fup 5						
Protocol change 1/0				Changed protocol no.				
Dose modified 1/0			Reason			Toxicity 1/0		
Started low age/PS 1/0			Other reasons					
Status Interim:		1CR/2VGPR/3PR/4PD/5unknown						
Status end 1st line:		1CR/2VGPR/3PR/4PD/5unknown						
Date of end trt assess:								
Radiotherapy given 1/0				Dose GY:				
Details of radiotherapy		Palliation spine/ palliation other						

	Single site/ multiple site								
Dose RT									
Response pain	Responded/ not responded								
Follow up details									
Relapse or progressive disease on fup 1/0									
If yes: date of progr									
Date last fup									
Event defn for	1 regular fup censored/ 2 lost fup in CR censored/ 3 progression/ 6 death due to other reasons/ 7 death due to disease								
Cause of death	1 not dead/ 2 disease/ 3 other								
"event date"									
Status of disease at last fup	CR 1/ progr disease lost fup 2/ progr dis adv supp care3/ PR 4								
Status life at last fup	**1 alive/ dead 2**								

APPENDIX 3

DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 amended by the 29th World Medical Assembly Tokyo, Japan, October 1975, and the 35th World Medical Assembly, Venice, Italy, October 1983and the 41st World Medical Assembly, Hong-Kong, September 1989

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare or animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I - BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II-MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent Committee (1,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III - NON-THERAPEUTIC MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX 4

PATIENT INFORMATION SHEET

Title of the Study: Role of PET CT Scan in Multiple Myeloma

a. What is this document?

You are invited to participate in a research study. The document provides you with information about the research study to help you make an informed decision about your participation.

b. What is the purpose of this research activity?

Your doctor would have told you that you are suffering from a type of cancer which is called as Multiple Myeloma and is caused by excessive collection of plasma cells in your body which are a type of white blood cells.

This disease needs to be confirmed and staged so that appropriate treatment can be started for the same. The usual investigations will include some blood, urine tests along with X Rays and bone marrow studies. We are at present looking at the role of PET CT Scan in your disease and are trying to establish whether it might stage your disease better than the normal available tests and also whether it can correctly predict the response to the treatment that will be offered to you.

c. Why have I been Chosen?

You have been diagnosed as having Multiple Myeloma and your doctor feels that this study is suitable for your disease and condition.

d. Do I have to take part?

Participation in this study is entirely voluntary. If you decide to take part you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving any reason. This will not affect the quality of care you receive.

e. What will happen to me if I take part?

If you agree to take part you will undergo a 18 FDG PET CT Scan which is a simple imaging test. You will be requested to come at the PET CT Centre in our hospital with three hours fasting and then a injection of radiaoactive contrast will be given in your vein. Following half an hour of which you will have a whole body PET CT Scan.

The entire process will take 30-45 minutes and will be pain free and safe.

f. What are the complications of this test?

There are no specific side effects or complications; it is like any other imaging test. The radiation exposure is around 20-25 milli sevart which is safe for humans. As with all contrast agents there are less than 1% of chances of contrast agent reaction which is usually mild and manageable.

g. What are the advantages of taking part?

This will help us to improve the understanding of cancer and may help in designing better treatment strategies for this disease.

h. What will happen to the results of this research study?

Doctors at the Cancer Institute will review the progress of the research, and the results will be published in a peer reviewed journal. However individual patient details will not be identified in any report or publication.

i. Who is conducting this research study?

The research is conducted at the Cancer Institute, Chennai. The following doctors can be contacted if you have any concerns during the study

Dr. T. S. Ganesan
Professor
Department of Medical Oncology

Dr. Sumant Gupta
Senior Resident
Department of Medical Oncology

APPENDIX 5

PATIENT CONSENT FORM

Study Title: Role of PET CT Scan in Multiple Myeloma
Study Centre Cancer Institute (WIA) Chennai

Please Mark 'Y' for Yes and 'N' for No in the box

1 I confirm that I have read and understood the Patient Information Sheet for the above study and have had the opportunity to ask questions and discuss it with my doctor. ☐

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that the information will be held by the Cancer institute (WIA) Chennai and that the Institute may use the data generated from the study for the publication in journals or presentations in conferences. ☐

4. I Also understand that my confidentiality will be protected ☐

5. I agree to take part in the above study. ☐

Signature (or Thumb Impression) of the Subject/Legally Acceptable Representative:

_____

Date: _____ / _____ / _____

Signatory's Name: _____

Signature of the Investigator _____

Date: _____ / _____ / _____

Study Investigator's Name _____

Signature of the Witness _____

Date _____ / _____ / _____

Name of the Witness _____

APPENDIX 6

INTERNATIONAL MYELOMA WORKING GROUP

CONSENSUS GUIDELINES

Diagnostic Criteria for Plasma Cell Diseases

Diagnosis	Diagnostic Criteria
MGUS	All three criteria must be met:
	Serum monoclonal protein (IgG or IgA) < 3 g/100 mL
	Clonal bone marrow plasma cells < 10%
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
Smoldering (asymptomatic) MM	Both criteria must be met:
	Serum monoclonal protein (IgG or IgA) ≥ 3 g/100 mL and/or clonal bone marrow plasma cells ≥ 10%
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
MM (symptomatic)	All three criteria must be met:
	Clonal bone marrow plasma cells ≥ 10%*
	Presence of serum and/or urinary monoclonal protein (except inpatients with true nonsecretory MM)
	Evidence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder, specifically:
	Hypercalcemia: serum calcium ≥ 11.5 mg/100 mL

Diagnosis	Diagnostic Criteria
	Renal insufficiency: serum creatinine > 1.73 mmol/L
	Anemia: normochromic, normocytic with hemoglobin value > 2 g/100 mL below lower limit of normal or hemoglobin value < 10 g/100 mL
	Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures
Solitary plasmacytoma	All four criteria must be met:
	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells
	Normal bone marrow with no evidence of clonal plasma cells
	Normal skeletal survey and MRI of spine and pelvis (except for primary solitary lesion)
	Absence of myeloma-related organ damage (CRAB) that can be attributed to plasma-cell proliferative disorder
Other plasma-cell diseases	Waldenstrom's macroglobulinemia
	Systemic AL amyloidosis
	Monoclonal Ig deposition disease
	POEMS syndrome

Adapted from Kyle Leukemia 2009.

Abbreviations: AL, amyloid light chain; CRAB, hypercalcemia, renal failure, anemia, or bone lesions; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MRI, magnetic resonance imaging; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes.

↵* Monoclonal plasma cells usually account for ≥ 10% of all nucleated cells, but they may range from < 5% to almost 100% (InternationalMyeloma Working Group: Br J Haematol 121:749-757, 2003).

Abbreviations: ADL, Activities of Daily Living; FISH, fluorescent in situ hybridization; GEP, gene expression profiling; IADL, Instrumental Activities of Daily Living; LDH, lactate dehydrogenase; MM, multiple myeloma; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography.

Diagnostic Work-Up for Patients With MM

	Description
First-level investigations to make diagnosis	
History and physical examination	
Blood and urine	Complete blood count and differential; chemistry, including creatinine and calcium; serum protein electrophoresis and immunofixation, quantification of immunoglobulin; 24-hour urine collection for proteinuria, electrophoresis, and immunofixation
	Serum free light chains
Bone marrow	Aspirate and trephine biopsy with plasma cells phenotyping
Imaging	Skeletal survey
Second-level investigations to assess prognosis	
Blood	Albumin, β_2-microglobulin, LDH
	Serum free light chains
Cytogenetic	Metaphase karyotype
FISH	t(4;14), t(11;14), t(14;16), t(14;20), chromosome 13 deletion, 17p13 deletion, and chromosome 1 abnormalities

	Description
Third-level investigations required before starting therapy or enrollment ontoclinical trials	
Performance status	Karnofsky performance status and WHO scale
Patient status	Assessment of comorbidity, frailty, and disability (cumulative illness rating scale or Charlson score; ADL and IADL score)
Organ function	Cardiac, pulmonary, hepatic, GI, and renal function
Infectious disease	Hepatitis B and C, HIV
Additional pretreatment investigations	
Imaging	MRI PET/CT
Prognostic	GEP

Abbreviations: ADL, Activities of Daily Living; FISH, fluorescent in situ hybridization; GEP, gene expression profiling; IADL, Instrumental Activities of Daily Living; LDH, lactate dehydrogenase; MM, multiple myeloma; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography.

Response Assessment

Response	IMWG criteria
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow3 by immunohistochemistry or immunofluorescence4
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow3
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	> 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,5 a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30% In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA
No change/Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA
Progressive disease5	Increase of > 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be> 0.5 g/dL)6 Urine M-component and/or (the absolute increase must be >200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Bone marrow plasma cell percentage; the absolute percentage must be > 10%7 Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to

	the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).6 It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice Development of new soft tissue plasmacytomas or bone lesions Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] Decrease in haemoglobin of > 2 g/dL [1.25 mmol/L] Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]
Relapse from CR5 (To be used only if the end point studied is DFS)8	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of > 5% plasma cells in the bone marrow7 Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

1. BGM Durie *et al*. International uniform response criteria for multiple myeloma. *Leukemia* (2006) 1-7.

Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473; and Kyle RA, Rajkumar SV. Leukemia 2008;23:3-9.

Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

3. Confirmation with repeat bone marrow biopsy not needed.

4. Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

5. All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

6. For progressive disease, serum M-component increases of >1 gm/Dl are sufficient to define relapse if starting M-component is >5 g/Dl.

7. Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

8. For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease

APPENDIX 7

CHEMOTHERAPY TEMPLATES

DEPARTMENT OF MEDICAL ONCOLOGY, CANCER INSTITUTE (WIA)

Bortezomib/ Dexamethasone
TRANSPLANT INELIGIBLE

Name		Date	
UHID	Age	Sex	
Height	Weight	BSA	IBW
BP:	Pulse:	Consent taken:	
Hemogram (day1)			
LFT (day 1)			
RFT (day 1)			

Velcade and Dexamethasone Q28 day- transplant ineligible 6-8 cycles till maximum response and then maintenance	
Bortezomib 1.3mg/m2 s/c	Day 1,8.15.22
Dexamethasone oral 40 mg	Days 1,8,15,22
Acivir 400 mg PO BID	Till end of therapy with bortezomiob

CYCLE NO.....DAY NO.....DATE.....

PREMEDICATIONS: none

Chemotherapy		Calculated dose	Doctors signature	Nurses Signature
Inj Bortezomib	1.3 mg/m2 D1,8,15,22,S/C			
Dexamethasone	40 mg PO D1,8,15,22			

Post chemotherapy advice		
Tablet Ranitidine	150mg BD X 3 days	
Tablet Domperidone	10mg TDS x 3 days	

Resident Incharge Signature	Consultant signature	3rd yr resident	Pharmasist

DEPARTMENT OF MEDICAL ONCOLOGY, CANCER INSTITUTE (WIA)

Lenalidomide /Dexamethasone

Name		Date	
UHID	Age	Sex	
Height	Weight	BSA	IBW
BP:	Pulse:	Consent taken:	
Hemogram (day1)			
LFT (day 1)			
RFT (day 1)			

Lenalidomide and Dexamethasone Q28 days; 3-4 cycles for pre transplant and consider stem cell harvest. Continue for 1 year in transplant ineligible and then switch to maintenance	
Lenalidomide 25 mg	Daily for 21 days (3weeks on and last 1week stop medicine in each cycle)
Dexamethasone oral 40 mg	Days 1,8,15,22
Ecospirin 75 mg	Po daily till end of therapy with lenalidomide

CYCLE NO.....DAY NO.....DATE.....

PREMEDICATIONS: none

Chemotherapy		Calculated dose	Doctor's Signature	Nurses signature
Lenalidomide	25 mg PO Daily for 21 days			
Dexamethasone	40 mg D1,D8,D15,D22			

Post chemotherapy advice	
Tablet Ranitidine	150mg BD X 3 days
Tablet Domperidone	10mg TDS x 3 days

Resident Incharge	Consultant Signature	3rd yr Resident Signature	Pharmasist

DEPARTMENT OF MEDICAL ONCOLOGY, CANCER INSTITUTE (WIA)

Thalidomide/ Dexamethasone

Name		Date	
UHID	Age	Sex	
Height	Weight	BSA	IBW
BP:	Pulse:	Consent taken:	
Hemogram (day1)			
LFT (day 1)			
RFT (day 1)			

Thal dex for myeloma Q 28 days; Continue for 4-6 cycles in transplant eligible prior to ASCT	
Thalidomide 100 mg	Daily for 28 days
Dexamethasone oral 40 mg	Days 1,8,15,22
Ecospirin 75 mg	Po daily till end of therapy with thalidomide

CYCLE NO.....DAY NO.....DATE.....

PREMEDICATIONS: none

Day	Chemotherapy	Calculated Dose	Doctor's Signature	Nurses Signature
Daily for 28 days	Thalidomide 100 mg			
D1,8,15,22	Dexamethasone 40 mg			

Resident in charge (dose calculated by)	Consultant (verified by)	3rd yr resident (verified by)	Pharmacist (verified by)

DEPARTMENT OF MEDICAL ONCOLOGY, CANCER INSTITUTE (WIA)

MPT

Name		Date	
UHID	Age	Sex	
Height	Weight	BSA	IBW
BP:	Pulse:	Consent taken:	
Hemogram (day1)			
LFT (day 1)			
RFT (day 1)			

MPT for myeloma Q 42 days; Continue for 6 months to 1 year in transplant ineligible and then switch to maintenance	
Melphalan 9 mg / m2 PO	D1-4
Thalidomide 100 mg	Daily for 42 days
Prednisolone 2mg/kg oral (Max 100 mg per day)	D1-4
Ecospirin 75 mg	Po daily till end of therapy with thalidomide
Melphalan is available as 2 mg tablets, hence doses to be rounded to nearest 2 mg	

CYCLE NO.....DAY NO.....DATE.....

PREMEDICATIONS: none

Chemotherapy		Calculated dose	Doctor's Signature	Nurses Signature
Melphalan	9 mg / m2 PO D 1-4			
Thalidomide	100 mg DAILY FOR 42 DAYS			
Prednisolone	2mg/kg oral (Max 100 mg per day) D 1-4			
Ecospirine	75 mg, Po daily till end of therapy with thalidomide			

Post chemotherapy advice		
Tablet Ranitidine	150mg BD X 3 days	
Tablet Domperidone	10mg TDS x 3 days	

Resident Incharge	Consultant Signature	3rd yr Resident Signature	Pharmasist