available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

The role of anatomic and functional staging in myeloma: Description of Durie/Salmon plus staging system

*Brian G.M. Durie**

Cedars-Sinai Outpatient Cancer Center at the Samuel Oschin Comprehensive Cancer Institute, Division of Hematology/Oncology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

ARTICLE INFO

Article history:
Received 21 November 2005
Accepted 21 November 2005
Available online 13 June 2006

Keywords:
Multiple myeloma
Staging
Imaging
Durie/Salmon
PET Scan
MRI

ABSTRACT

Staging is the cornerstone of baseline myeloma evaluation. New imaging techniques such as magnetic resonance imaging (MRI), whole body FDG-PET scanning and whole body CT (combined with PET directly or by fusion) offer the opportunity to precisely stage patients by anatomic and functional techniques. The new Durie/Salmon PLUS staging system integrates these new imaging techniques into a new generation of anatomic and functional myeloma staging. It is possible to discriminate between the impact of tumour burden (myeloma cell mass) and other prognostic factors. This refined classification by stage and prognostic category is increasingly important in clinical trials. The value of clinical staging in patient management is emphasized both in discrimination of early disease status and clearer identification of poorer risk of Stage II and III disease. Wider use of newer imaging will undoubtedly enhance analysis of new trials incorporating novel agents.

1. Introduction

Multiple myeloma is a heterogeneous disease, which can present with or without overt symptomatology.[1] The heterogeneity relates both to the intrinsic biology of the myeloma cells and bone marrow microenvironment as well as systemic host responses to the myeloma.[2] The patient age, health status and the time of presentation to the healthcare system all impact outcome.

In an effort to standardize treatment approaches it is essential to characterize the disease as clearly as possible at the time of diagnosis. The Durie/Salmon myeloma staging system was introduced in 1975 to permit easy clinical staging which correlated with measured myeloma cell mass.[3] This system has been widely used over the past 30 years. Despite the fact that classification based upon the number and extent of bone lesions found on X-ray is observer-dependent, the system has proved to be remarkably reliable.[4,5] Nonetheless, the availability of much more sensitive imaging techniques has required the integration of computed tomography, magnetic resonance imaging and FDG-PET scanning into routine anatomic and functional staging.[6–9] This has been accomplished by the development of the Durie/Salmon PLUS myeloma staging system (Table 1). The data supporting this new Durie/Salmon PLUS myeloma staging system and ways in which it can be implemented are discussed here in detail.

2. Limitations of anatomic staging using standard radiographs

Multiple myeloma can produce both localized lytic lesions and diffuse osteopenia evident on standard radiographs. Fracture of weakened areas is common. Early myeloma may not reveal observable changes on X-ray. Other imaging techniques show evidence of active myeloma in approximately 20% of patients with negative X-rays.[8,9] In addition, osteopenia may or may not be due to myeloma and can require further characterization. In some cases it may be difficult to

* Present address: 8201 Beverly Boulevard, Los Angeles, CA, 90048, USA. Tel.: +1 323 966 3572; fax: +1 323 966 3685.
E-mail address: bdurie@aptiumoncology.com.

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.11.037

Table 1 – Anatomic/Functional staging

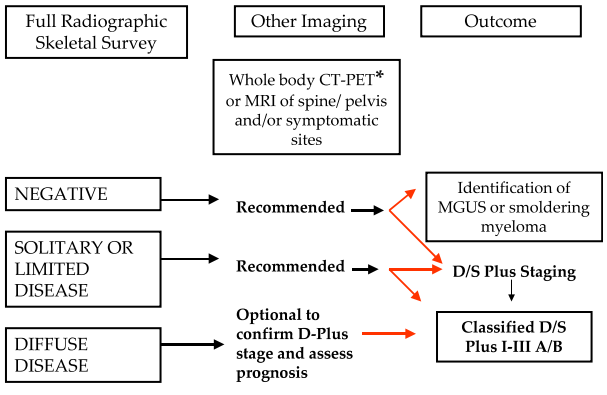
Durie/Salmon PLUS myeloma staging system		Integration of imaging
Durie/Salmon STAGE	Plus upstage	MRI/PET* Number of lesions
I B		I 0–4
II A or B		II 5–20
III A or B		III >20
see Refs. [4,7,9,10,14]		B:creatinine >2 and/or EMD on PET or MRI

determine if bone collapse or fracture is a true pathologic process secondary to myeloma.

The ideal baseline diagnostic evaluation to overcome the limitations of standard radiography is summarized in Table 2. The diagnosis and disease stage are usually clear-cut for patients with multiple lytic lesions and/or severe osteopenia with fractures. The diagnostic and staging challenges emerge in patients with earlier disease. The goal is to provide systematic guidance for detection of early bone destruction or loss with screening of the whole body or the major areas of potential involvement in the axial skeleton. The problem is both technical and financial in that extensive imaging is costly. There is thus, a strong requirement to show the clinical impact of the new imaging approaches. Obvious advantages of more precise anatomic and functional staging include:

- Correct staging using current imaging technology
- Avoidance of unnecessary treatment for patients with MGUS and/or smoldering myeloma[1]
- Early treatments for patients with impending overt bone disease
- Identification of poorer risk subgroups
- Accurate staging for patients with oligo-secretory or non-secretory myeloma
- Specific advantages of Durie/Salmon plus Staging are summarized in Table 3.

Table 2 – Ideal baseline diagnostic evaluation for staging and prognosis



*Recommendations:

- Whole body CT-PET is ideal. Whole body FDG-PET combined with localized CT is also excellent.
- MRI with T1-weighted STIR and gadolinium enhancement encompassing the whole spine and pelvis is a reasonable alternative and is the basis for the new DS-Plus Staging. MRI of symptomatic sites and/or areas of special concern is helpful, but does not constitute baseline staging.

3. Role of computed tomography (CT)

CT is the ideal tool for detection of early bone destruction.[4,6] Use of CT has enhanced the diagnosis of localized bone problems for many years. With the more recent availability of wide field and whole body techniques,[7,8] larger screening and assessment are possible (see Table 2). The combined use with FDG-PET is discussed below.[9] Incorporation of FDG-PET helps overcome the difficulty in determining the age or activity status of lesions identified on CT. Since myeloma lesions frequently don't heal, despite eradication of myeloma in a particular area, CT scan typically shows persistent bone lesions throughout the course of the disease. Both MRI and FDG-PET reflect the myeloma activity over time. However, CT alone cannot assess continued activity of myeloma in areas of prior bone destruction (See Tables 3 and 4).

4. The role of magnetic resonance imaging (MRI)

The use of MRI has added enormously to the ability to identify and monitor marrow infiltration with myeloma.[10–13] MRI is

Table 3 – Advantages of Duries/Salmon Plus Staging

- Direct confirmation of active myeloma for stage I patients with negative x-rays
- Cell mass assessment and staging for patients with hyposecretory or non secretory disease
- Identification of poor risk patients with >20 focal lesions and/or extramedullary disease
- Overall, direct assessment of the patient versus assignment of risk based upon statistical proabability related to cytogenetic or other factors. This facilitates immediate clinical decision-making.

Table 4 – Comparison of staging systems

		Original Durie/Salmon myeloma staging system	Durie/ Salmon plus		International staging system (ISS)
		Median survival* (months)	Median survival** (months)		Median survival* (months)
STAGE I	A	69	72	I	62
	B	22	20		
STAGE II	A	58	61	II	44
	B	34	28		
STAGE III	A	45	40	III	29
	B	24	19		

* See Ref. [5].
** See Ref. [9].

especially helpful for the evaluation of the axial skeleton. Infiltration at the site(s) of osteopenia or questionable lytic disease is diagnostically important. However, it is important to note that the MRI predominately reflects marrow infiltration, which may or may not be associated with bone destruction. Abnormal MRIs occur in patients with early smoldering disease. An abnormal MRI does not necessarily equate with a need for immediate therapy. Conversely, in patients with documented active myeloma, the number of lesions on MRI correlates very well with the treatment outcome and overall survival.[14] This excellent correlation with survival outcome is the primary reason for the inclusion of MRI into the Durie/Salmon PLUS system (see Table 3).

Advantages of MRI include gadolinium enhancement of areas of myeloma, which can thus be distinguished from other morphologic displacements, and the different settings (e.g. STIR [sagittal T_1-weighted inversion recovery]), which allow discrimination of fatty tissue (e.g. following radiation therapy), vascular abnormalities and degenerative changes. Disadvantages include the time and expense required to scan large portions of the body. The most common and recommended approach is to scan the spine and pelvis for screening purposes. Other areas can be encompassed if symptomatic. Larger field screening of limb girdle areas and extremities can be utilized with detailed follow-up for areas of concern. An additional disadvantage of the MRI is for serial monitoring. It takes 9–12 months for lesions evident on MRI to resolve and be clearly indicative of response.[11,14] Thus although very accurate, MRI is cumbersome for routine screening and not ideal for serial monitoring.

5. Whole body FDG-PET

This relatively new technique has several advantages for whole body screening.[7,9,14–16] Firstly, it is possible to scan the whole body in a reasonable time frame. Since fluro-[F18]-deoxy glucose is taken up and retained by areas of active myeloma - one can assess both the location and activity of myeloma lesions. By considering the level of FDG uptake (SUV: Standardized Uptake Values, which take into account injected FDG dose and body weight) one can generally distinguish between active myeloma and other pathologies. One must be alert for areas of infection or abscesses since such lesions can have substantial FDG uptake.[17] However, fever, pain and other clinical abnormalities are usually obvious clues to the presence of sepsis. Nonetheless, this is an important caution or caveat, and other diagnostic evaluation including biopsy may be required to confirm the correct pathology.

The currently available data indicate utility of whole body FDG-PET in several settings:

- *MGUS is FDG negative.*[9,14,15] MGUS and low level smoldering myeloma are consistently negative on scan. Conversely only very low-level myeloma is not detectable on FDG-PET. Technetium-99 sesta MIBI imaging may be especially helpful in this setting to detect indolent disease.[18–22] Whole body technetium-99msesta MIBI has been used as an alternative to FDG-PET with one study showing rather similar results.[18] Interesting and important nuances include the enhanced uptake of technetium-99m sesta MIBI by drug resistant myeloma cells versus enhanced uptake of FDG by metabolically active myeloma cells.[9,19]
- *Active myeloma is FGD positive.*[9,14,15] Untreated myeloma patients manifest both focal and diffuse abnormalities on FDG-PET. Patients with and without high-risk extramedullary disease are also identified. FDG-PET identifies active myeloma and allows enumeration of sites of focal disease for classification within the new Durie/Salmon PLUS myeloma staging system.
- *Systemic intramedullary and extramedullary disease can be monitored with FDG-PET.*[9,14,15] FDG-PET uptake decreases rapidly with effective therapy. Uptake can decrease within hours and within a few days to 3–4 weeks reduced uptake reflects ongoing response. Conversely, as noted above[11,14] there is a substantial time lag of 9–12 months in the reversal of MRI abnormalities with successful therapy.
- *Persistent FDG-PET positivity correlates with likely earlier relapse.*[9] In the post transplant setting a persistent positive scan is a poor prognostic factor and correlates with likely relapse in $\leqslant$6 months. Importantly this can occur when bone marrow and M-component markers are negative.
- *CT-PET is the ideal screening technology.*[7] Since FDG-PET uptake indicates active myeloma and CT shows bone destruction, combined whole body CT-PET is an excellent method to evaluate myeloma.[7,9,14,15]

6. Development of the Durie/Salmon PLUS staging system (Table 1)

The new system takes advantage of currently available imaging techniques. The Durie/Salmon PLUS system overcomes two major disadvantages of the original Durie/Salmon system.

1. *Better classification of early disease.* Using CT-PET and/or MRI patients with definite active myeloma are distinguished from those with MGUS or smoldering disease. This is important for individual patients and to clarify protocol design.
2. *Discrimination among patients with stage II and III disease.* Using the new imaging techniques, good and poorer prognosis stage II and III patients can be distinguished. This is especially true for those with >20 focal lesions on MRI and/or PET and/or presence of extramedullary disease which identify the patients with the poorest prognosis.

7. The need for a multifaceted approach to staging and prognostic factor classification

Myeloma is heterogeneous at both the cellular and clinical levels.[23–25] Therefore, no single system can encompass all patients. Table 4 shows a comparison of staging and prognostic factor systems. Some patients are hypo or non-secretory. For such patients high tumour burden is accompanied by low serum B_2 microglobulin. ISS staging can therefore be misleading. Very indolent myeloma is not FDG avid and may not be detected with FDG-PET.[9] However, such disease is usually detected by MRI[26] and/or MIBI imaging.[18,22] Early disease has low serum B2 microglobulin, but can be associated with

abnormal cytogenetic findings identifying a poor prognosis subset.[23,24] The clinician and clinical researcher must be alert to these nuances of heterogeneity. An advantage of the Durie/Salmon PLUS staging system is that it can form the basis for ancillary or complementary prognostic factor classification. For example, cytogenetic abnormalities can identify both low and high myeloma cell mass patients with drug resistant and/or especially high-risk features.[14,23,24] High levels of soluble receptor activator of NFkB ligand/ osteoprotegerin ratio predict particularly poor survival and have been proposed as useful for prognostic sub-classification.[25] Using anatomic/ functional and prognostic factor staging systems in a complementary fashion is ideal.

8. Current and future role of imaging in myeloma

It is essential to integrate new imaging technology into myeloma staging in a systematic fashion. The Durie/Salmon PLUS myeloma staging system (Table 1) provides a reliable method for both staging and prognostic classification. The anatomic/ functional staging is a direct approach, which serves as a basis for immediate clinical assessment and as a basis for clinical decision-making. A single focal lesion can be irradiated. Multiple lesions require a systemic approach. Both MRI and FDG-PET are included and can be used in a flexible fashion as feasible. Whole body FDG-PET (or CT-PET) is more efficient for whole body screening. MRI is especially helpful for evaluation of axial disease and also more indolent disease likely to be less FDG avid. Another alternative is technetium-99m sesta MIBI imaging for evaluation of more indolent disease.[20–22]

It is conceptually useful to plan immediate therapy and/or clinical trials based upon combined information about myeloma tumour burden and risk factors. The A/B framework for the Durie/Salmon PLUS system is amenable to the addition of genetic, proteomic and cytokine-based prognostic stratification.[25] It has already been shown that integration of PET information positively impacts clinical care overall.[27] It is reasonable to anticipate that refined individual decision-making can be derived from a complementary combination of anatomic/ functional staging and prognostic factor classification. Novel therapies will target cell mass and prognostic factor subsets to allow evolution of personalized approaches to myeloma care.

Conflict of interest statement

None declared.

REFERENCES

1. Durie BGM, Kyle RA, et al. Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. *Hematol J* 2003;**4**:379–98.
2. Durie BGM, Jacobson J, et al. Magnitude of response with myeloma frontline therapy does not predict outcome: importance of time to progression in Southwest Oncology Group chemotherapy trials. *J Clin Oncol* 2004;**22**(10):1857–63.
3. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. *Cancer* 1975;**36**:842–54.
4. Gahrton G, Durie BGM, et al. Multiple Myeloma and Related Disorders. The role of imaging in myeloma. *Arnold* 2004;**10**:155–63.
5. Greipp PR, Durie BGM, et al. International Staging System for multiple myeloma. *J Clin Oncol* 2005;**23**(15):3412–20.
6. Kyle RA, Schreiman JS, et al. Computer tomography in diagnosis and management of multiple myeloma and its variants. *Arch Int Med* 1985;**145**:1451–2.
7. Antoch G, Vogt FM, Freudenberg LS, et al. Whole-body dual-modality PET/CT and whole-body MRI for tumour staging in oncology. *JAMA* 2003;**290**:3199–206.
8. Modic MT, Obuchowski N. Whole-body CT screening for cancer and coronary disease: does it pass the test?. *Cleveland Clin J Med* 2004;**71**(1):47–56.
9. Durie BGM, Waxman AD, et al. Whole Body F-FDG PET identifies high-risk myeloma. *J Nucl Med* 2002;**43**:1457–63.
10. Bauer A, Stabler A, et al. Magnetic resonance imaging as a supplement for the clinical staging system of Durie and Salmon?. *Cancer* 2002;**95**(6):1334–5.
11. Walker R, Jones-Jackson L, et al. Diagnostic imaging of multiple myeloma- FDG PET and MRI complementary for tracking short vs long term tumour response [abstract #758]. *Blood* 2004;**104**(11):217a.
12. Kusumoto S, Jinnai I, Itoh K, et al. Magnetic resonance imaging patterns in patients with multiple myeloma. *Br J of Haematol* 1997;**99**:649–55.
13. Mariette X, Zagdanski AM, Guermazi A, et al. Prognostic value of vertebral sessions detected by magnetic resonance imaging in patients with stage I multiple myeloma. *Br J of Haematol* 1999;**104**:723–9.
14. Walker R, Barlogie B, et al. Prospective evaluation of 460 patients from total therapy II—identification of characteristics on baseline MRI examinations of prognostic significance—importance of focal lesions (FL) in multiple myeloma (MM). *Hematol J* 2003;**4**:S171.. Abstract 188.
15. Schirmeister H, Bommer M, et al. Initial results in the assessment of multiple myeloma using 18 F-FDG PET. *Eur J Nucl Med* 2002;**29**:361–6.
16. Walker RC, Barlogie B, Shaughnessy J. DKK1 in myeloma: correlation with FDG-PET. *New Engl J Med* 2004;**350**(14): 1465–6.
17. Miceli M, Atoui R, Walker R, et al. Diagnosis of deep septic thrombophlebitis in cancer patients by fluorine-18 flurodeoxyglucose positron emission tomography scanning: a preliminary report. *J Clin Oncol* 2004;**22**(10):1949–56.
18. Mileshkin L, Blum R, Seymour JF, et al. A comparison of fluorine-18 fluoro-deoxyglucose PET and technetium-99m sestamibi in assessing patients with multiple myeloma. *Europ J Haematol* 2004;**72**(1):32–7.
19. Fonti R, Vecchio S, Zannetti A, et al. Functional imaging of multidrug resistant phenotype by 99mTcMIBI scan in patients with multiple myeloma 2004;**19**(2):165–170.
20. Durie BGM et al. Technetium-99m-MIBI scanning in multiple myeloma (MM): comparison with PET (FDG) imaging. *Blood* 1996;**88**:10.. Abstract 1559.
21. Tirovola EB, Biassoni L, Britton KE, et al. The use of 99mTc-MIBI scanning in multiple myeloma. *Br J Cancer* 1996;**74**:1815–20.
22. Durie BGM, Waxman AD, D'Agnolo A. A whole-body Tc-99m-MIBI scanning in the evaluation of multiple myeloma (MM). *J Nucl Med* 1998;**39**:138.
23. Jaksic W, Trudel S, Chang H, et al. Clinical outcomes in t(4;14) multiple myeloma: a chemotherapy-sensitive disease characterized by rapid relapse and alkylating agent resistance. *J Clin Oncol* 2005;**23**(28):7069–73.

24. Dewald GW, Therneau T, et al. Relationship of patient survival and chromosome anomalies detected in metaphase and/or interphase cells at diagnosis of myeloma. *Blood* 2005;**106**(10):3553–8.
25. Terpos E, Szydlo R, Apperley JF, et al. Soluble receptor activator of nuclear factor kB ligand-osteoprotegerin ratio predicts survival in multiple myeloma: proposal for a novel prognostic index. *Blood* 2003;**102**(3):1064–9.
26. Chim CS, Ooi GC, et al. Unusual presentations of hematologic malignancies: role of MRI and FDG-PET in evaluation of solitary plasmacytoma. *J Clinic Oncol* 2004;**22**(7):1328–30.
27. Hillner BE et al. Clinical decisions associated with positron emission tomography in a prospective cohort of patients with suspected or known cancer at one United States center. *J Clinic Oncol* 2004;**22**(20):4147–56.