出國報告（出國類別：其他）

赴加拿大出席第 60 屆美國核醫學會年會公差報告

服務機關：核能研究所
姓名職稱：翁茂琦　助理工程師
羅彩月　副研究員
張志賢　副研究員
派赴國家：加拿大
出國期間：102 年 6 月 7 日~102 年 6 月 14 日
報告日期：102 年 7 月 15 日

摘　要

本次公差主要是赴加拿大溫哥華參加 102 年 6 月 8~12 日召開之第 60 屆美國核醫學會年會（2013 Annual Meeting of Society of Nuclear Medicine and Molecular Imaging，簡稱 SNMMI），張貼及解說本所發表之壁報論文共計 11 篇，並參加研討會各項主題課程，作爲提昇核能研究所（以下簡稱本所）相關研發計畫成果及未來申請計畫方向之參考。出差期程自今年 6 月 7 日至 6 月 14 日，共計 8 日。

美國核醫學會年會（SNMMI）爲全球知名之核子醫學研發相關年會之一，每年皆有來自各國之研究人員參與本項核醫學會年會盛會，探討的主題從臨床之新技術及案例交流，診斷用核醫藥物之研究及治療用核醫藥物及同位素之最新方向，網羅最新核醫藥物及相關醫療設施之研發現況及未來之趨勢，對本所核醫藥物之發展可以提供很有價值之參考資訊。今年 SNMMI 除了美國之外，來自全世界各地 49 個國家從事核醫相關之基礎及臨床研究人員超過 5,000 人與會，論文發表總共有投稿 1,974 篇，其中口頭報告有 795 篇（含技術人員與學生口頭報告 126 篇），共分成 149 個口頭報告場次，海報發表有 1,179 篇；本所於本次會議共發表 11 篇。

本次公差，收穫頗豐，在第 60 屆美國核醫學會年會獲得世界核醫發展之最新資訊及方向，並與國內外與會人員有良好的交流，盼能建立未來合作契機。

目　　次

一、目　的

本次公差主要目的爲赴加拿大溫哥華參加 102 年 6 月 8~12 日召開之第 60 屆美國核醫學會年會（2013 Annual Meeting of Society of Nuclear Medicine and Molecular Imaging，簡稱 SNMMI），會議主題爲核醫藥物於癌症診斷、治療、心血管及腦中樞神經等領域之研發、應用現況及未來發展研討，美國 FDA 亦於會議中成立診療核醫藥物的最新審查法規與經驗之獨立議程；此會議對奈米癌症藥物研發、核醫治療、核醫分子影像及腦中樞神經技術病變診斷、相關診療研究應用有許多最新研發成果發表。

核能研究所（以下簡稱本所）目前正積極開發腦神經診斷用核醫藥物、治療用核醫藥物等研發，爲瞭解先進國家在核醫藥方面技術開發現況與未來市場拓展之規劃，本所同位素應用組羅彩月博士、張志賢博士及翁茂琦先生奉派參加 SNMMI，張貼及解說本所發表之壁報論文共計 11 篇，將我國在核醫方向之努力與研發成果向國際社會介紹，並參加研討會各項主題課程，作爲提昇本所相關研發計畫成果及未來申請計畫方向之參考。出差期程自今年 6 月 7 日至 6 月 14 日，共計 8 日。

二、過　程

參加第 60 屆美國核醫學會年會（2013 Annual Meeting of Society of Nuclear Medicine and Molecular Imaging）年會，代表本所張貼及解說壁報論文。

月	日	星期	地點	工作紀要
6	7	五	溫哥華	去程：台北至溫哥華
	8	六	溫哥華	參加第 60 屆美國核醫學會年會（2013 Annual Meeting of Society of Nuclear Medicine and Molecular Imaging）年會，代表本所張貼及解說壁報論文。
	9	日	溫哥華	
	10	一	溫哥華	
	11	二	溫哥華	
	12	三	溫哥華	
	13-14	四-五	台北	旅途：溫哥華至台北

三、心　得

第 60 屆美國核醫學會年會（2013 Annual Meeting of Society of Nuclear Medicine and Molecular Imaging，簡稱 SNMMI）由美國核醫分子影像學會（Society of Nuclear Medicine and Molecular Imaging）主辦，於今年 6 月 8-12 號加拿大溫哥華舉行，會議議程及主題如附錄一。與往年不同，今年的核醫學會年會，除了介紹核醫領域的創新發展之外，也廣納各種分子影像技術之課程與成果，彰顯分子影像技術在核子醫學重要時代的來臨。

繼去年中（2012）Prof. Michael J. Welch 過世之後，Prof. Henry N. Wagner Jr.也不幸於去年底逝世，享年 85 歲。Welch 教授過去主要服務於聖路易斯華盛頓大學，爲美國科學院院士。Wagner 教授是核醫學領域的開創者，榮獲約翰霍普金斯大學醫學與放射學榮譽教授，曾擔任 SNMMI 主席，並被尊稱爲“核子醫學之父”。大會爲了紀念他，今年首度以 Henry Wagner 作爲專題演講的命名（演講者：Dr. Val Lewington），與本所定期舉辦積彭講座相似。核子醫學界的兩大巨星相繼隕落令人唏噓，然而年輕一輩人才輩出，核醫界逐漸世代交替，又十足讓眾人歡欣鼓舞。

今年會議除了美國之外，來自全世界各地 49 個國家從事核醫相關之基礎及臨床研究人員超過 5,000 人與會，論文發表總共有投稿 1,974 篇，其中口頭報告有 795 篇（含技術人員與學生口頭報告 126 篇），共分成 149 個口頭報告場次，海報發表共有 1,179 篇。台灣共發表 32 篇，其中口頭論文爲 4 篇，壁報論文爲 28 篇。本所於本次會議發表共 11 篇，如表一。國內學、研單位發表情形（如表二）：陽明大學/榮總有 10 篇，台灣大學/醫院有 5 篇，長庚大學/醫院 3 篇，國防大學/三總 2 篇，其他單位 5 篇。鄰近國家發表情形方面，中國有 144 篇（口頭 46 壁報 98），日本有 175 篇（口頭 67 壁報 108），韓國有 157 篇（口頭 53 壁報 104）。

今年 SNMMI 台灣各學、研單位皆指派多人參加，本所與會人員有同位素應用組張志賢博士、羅彩月博士及翁茂琦先生，所外與會人員包括台大醫院曾凱元主任、秀傳醫院洪光威主任、亞東醫院吳彥雯主任、林口長庚醫院閻紫宸主任及國防大學馬國興教授等，此外陽明大學及長庚大學亦有學生參與盛會。

表一、核能研究所發表論文明細

序號	作者	論著名稱	口頭或海報
1	陳亮丞 等	Biodistribution study of ^{188}Re-HSA microsphere in GP7TB hepatoma model via intraarterial route.	海報
2	游佳瑜 等	Preparation and stability of radiolabeling human serum albumin (HSA) microspheres with ^{188}Re(I)-tricarbonyl technology	海報
3	何宗澧 等	The cytotoxicity evaluation of ^{188}Re-human serum albumin (HSA) microspheres in GP7TB hepatoma cell line.	海報
4	陳亮丞 等	Therapeutic efficacy of ^{188}Re-liposome compared with 5-FU in CT26-luc lung-metastatic mice model via intravenous route	海報
5	林亮廷 等	Tumor suppressive profiling in Rhenium-188 embedded PEGylated liposome treated NSCLC animal model	海報
6	李銘忻 等	An automatic synthesis module for Ga-68-DOTATATE labeling and compliant with the GMP	海報
7	羅彩月 等	Development of in-situ forming thermosensitive hydrogel for radiotherapy combined with chemotherapy in a mouse model of hepatocellular carcinoma	海報
8	羅彩月 等	Biodegradable drug delivery system for hepatoma therapy	海報
9	林萬鈺、羅彩月	Therapeutic efficacy of Re-188-MN-16ET/Lipiodol in an animal model of hepatocellular carcinoma	海報
10	洪振傑、黃蜂運、林萬鈺、羅彩月、謝柏蒼	Evaluation of the hepatic tumor therapeutic efficacy of a C/GP/Dox/^{188}Re-Sn colloid	海報
11	夏建忠、林武智等	Evaluation of the pharmacokinetics of ^{111}In-labeled immuno gold nanoparticle in an EGFR-expression tumor-bearing mouse model	海報

表二、國內學、研單位參與發表情形

發表單位	篇數*	發表單位	篇數	發表單位	篇數
核能研究所	11 (7)	中台大學	2 (2)	中興大學	1 (0)
陽明大學	10 (9)	國防大學	2 (1)	中原大學	1 (0)
台北榮總	8 (1)	台中榮總	2 (1)	台中慈濟醫院	1 (0)
台灣大學/醫院	7 (5)	花蓮門諾醫院	1 (1)	臺北科技大學	1 (0)
長庚大學/醫院	3 (3)	亞東醫院	1 (1)	新光醫院	1 (0)
三軍總醫院	3 (1)	清華大學	1 (0)		

*註：篇數欄位表示方式爲：總發表篇數（第一作者篇數），含口頭與海報發表。

本次年會議程包含年會正式開始前的Physician/Scientist Categorical Seminars，內容涵蓋Translational Molecular Cardiovascular Imaging、Challenges of Regulatory and Reimbursement Approval for Molecular Imaging Agents、Radiolabeled Peptides/Proteins for PET imaging、A journey from PET/CT to PET/MRI、Molecular Imaging in Neurodegenerative Diseases、Hybrid Imaging in Pediatric Nuclear Medicine、Image and Dosimetry Guided Management of Neuroendocrine Tumors及Update on Tumor Imaging and Therapy等主題；而年會主要的主題則包含Plenary Sessions、Continuing Education Sessions、Scientific Sessions及Annual Meeting Highlight等，提供來自世界各國核子醫學領域之研究人員相互交流的機會，並可在此搜集各國在核子醫學領域研究之最新進度及趨勢。

會場展示區參與展示廠商約有百餘家，主要涵蓋臨床用醫療儀器、藥物、迴旋加速器、Dose Calibrator 和屏蔽、放射性同位素、發生器及自動合成盒等，GE、Siemens 及 Philips 等醫療儀器大廠仍爲主要展示者，而 BIOSCAN、Mediso 及 MILabs 等公司皆在會場展示其動物用 PET、SPECT、CT 等造影儀器。藥物方面，除了去年 FDA 通過 F-18-AV-45 藥物上市的藥廠 Lilly 外，今年度拜耳（Bayer）公司宣佈 FDA 已經批准 α 粒子放療藥物 Xofigo 使用於治療特定攝護腺癌患者，其仿單可參考附錄二，其展覽場地就位於整個展場的正中央，十足吸引來賓目光以及前往詢問，如圖一。

圖一　拜耳公司放療藥物 Xofigo 會場攤位。

本次會議內容，將按 Cardiology、General Clinical Specialties、Neuroscience、Oncology 等四個領域分別將本次國際核醫學會年會過去一年發展的主要重點詳述如下，並介紹 2013 SNMMI 年度影像（Image of the Year）。

(一) 心臟學領域（Cardiology）

在心臟學領域方面，從投稿的摘要數量及比例來看，和前幾年相比，臨床研究數量無增減，但是基礎研究佔整體比例則有增加趨勢。去年心臟學領域傳達的主要資訊包括：絕對定量應用於臨床使用上扮演主流、固態偵檢器是 SPECT 的發展主流、分子影像（發炎-梗塞-血栓影像）則獲得全面發展及並作路徑導引（pathway-driven）使用。

今年海報投稿共有 137 篇，基礎科學 42 篇，臨床醫學 61 篇，心臟學分子藥物 25 篇，教育展示海報 9 篇，口頭報告方面（每天的報告時段）共有 65 篇。發表主題的演變上，心臟灌注研究（Perfusion）、分子影像和全新技術（含軟、硬體）等三個主題上，從 2007、2009 到 2013 年以來，分子影像和全新技術的比例不斷上升，分子影像攻佔一半（49%），全新技術則上升到 32%，而心臟灌注研究則從 2007 年的 45%下降至 19%。這些主題常用的儀器如 SPECT 和 PET，自 2007、2009 到 2013 年以來，PET 的比例逐漸上升（2007 和 2013 年分別爲 44% 和 61%），而其中 PET-MR 和 CZT（碲鋅鎘偵檢器）在 2013 年則各佔了 6%。以下介紹幾篇本次會議中重要的論文。

荷蘭的 Stefan de Haan 及其團隊，研究 PET/CT 用在評估心肌支配及灌注的不匹配情形和心臟灌注造影（cardiac perfusion scan, CMR）評估之異源疤大小的相關性。從結果可以看出有良好的相關性。

加拿大的 JT Thackeray 和其研究團隊研究兒茶酚胺（Catecholamine）導致心臟衰竭之基因轉殖小鼠模式其心肌代謝之臨床表現型態（phenyotyping）。從軸向面、冠狀面及橫斷面影像上，可觀察到基因轉殖小鼠心臟對核醫藥物的攝取與正常小鼠相比較低；轉殖小鼠給予腎上腺素性乙型受體作用劑（Isoproterenol）後，其藥物攝取情形則明顯上升。轉殖小鼠取出的心臟及切片影像可看到明顯變異。

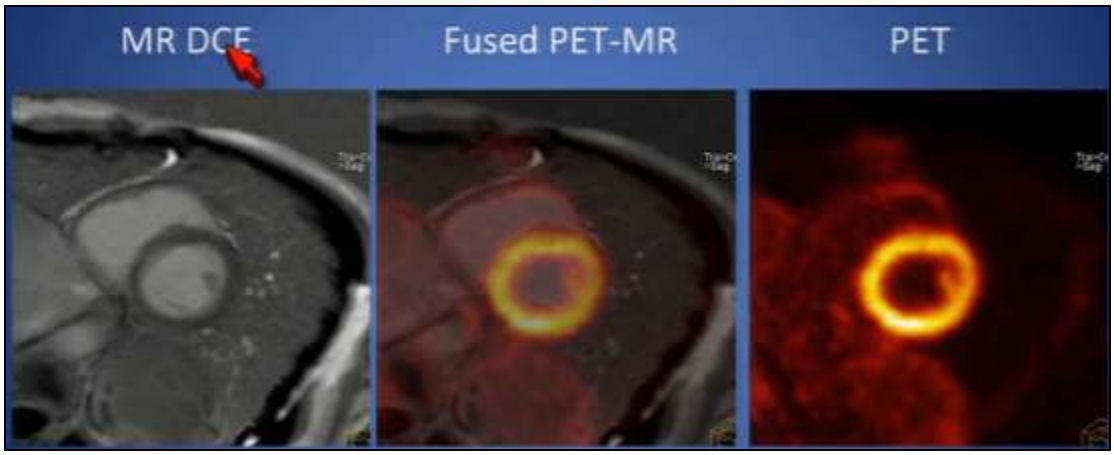
今年的 Herrmann Blumgart Award 演講，介紹心臟領域前五大（Big Five）研究，包括心臟灌注及定量研究、發炎定性（血管及心肌）研究、臨床研究之分子影像轉譯研究、重視高價值影像 – 高品質的證據及多重設備（Multimodality）的架構。

日本的 Miyagawa M 及其研究團隊，透過 CZT SPECT 對具有多重冠狀動脈疾病的病人，進行心肌血流保留（Myocardial Flow Reserve）評估研究。藉由動態 ^{99m}Tc-MIBI 造影及動態牛

眼圖形來觀察血流保流情形，並畫出時間活性曲線。

來自法國的 F. Rouzet 及其研究團隊則透過病人同時注射 ^{123}I-MIBG 及 ^{201}Tl，並利用 CZT 造影儀器於臨床上應用研究。研究對象有 32 個病人，年齡 55 ± 14 歲，男性有 22 位，其中 20 位有家族性類澱粉神經病變（Amyloid Neuropathy），而 12 位有心臟衰竭的情形。與傳統造影方式相比，同時注射能減少整體造影時間，而透過使用 ^{201}Tl 將能減少病人劑量，並避開 ^{123}I 能窗。

華盛頓 St. Louis 大學的 Jeffrey M.C. Lau 及其研究團隊，研究心肌 FDG-PET 造影中利用 MR 作爲衰減校正的可行性。結果顯示 PET/CT 和 PET/MR 獲得的相關性高達 0.9675，影像結果看到結合延遲對比提昇（Delayed Contrast Enhancement, DCE）的 PET/MR 影像可用來準確評估心肌存活情形（如圖二）。



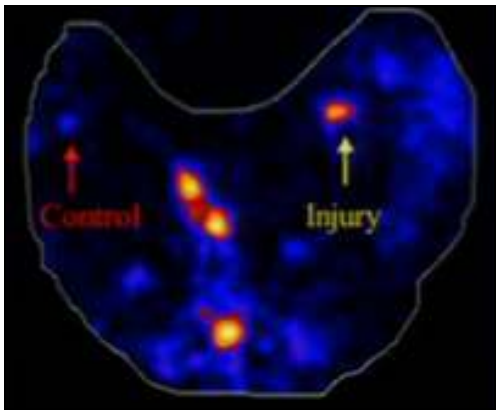
圖二　Fused PET-MR 的影像結果。其中 MR DCE 可提供解剖資訊，同時心肌無存活的部份顯示低對比。

來自丹麥的 Rasmus S. Ripa 及其研究團隊，研究頸動脈 PET/MR 造影的可行性：包括首次臨床實驗及與 PET/CT 之比較。影像上可以看到病人在注射核醫藥物後，PET 和 MR 影像結合後的藥物分佈情形。比較 PET/MR 和 PET/CT 在 6 位 HIV 陽性的病人不同切面影像 SUV_{max} 的結果，其相關性約爲 0.4。

來自德國的 T. Higuchi 及其研究團隊，進行 F-18 交感神經示蹤藥物 LMI1195 在兔子心臟的心肌動力學研究。結果可以看到第一次穿流式心臟檢查（first pass study）中注射去甲丙咪嗪（Desipramine，一種抗憂鬱藥）的組別其血液動力學活性下降情形較控制組明顯。

華盛頓 St. Louis 大學的 Yongjian Liu 及其研究團隊，開發放射性標靶奈米粒子，針對心房利鈉肽清除受器（natriuretic peptide clearance receptor, NRPC）進行動脈粥狀硬化

（atherosclerosis）PET 造影。針對 NRPC 的 polymeric 奈米粒子，接上 C-心房利鈉肽因子（C-atrial natriuretic factor, CANF）作爲標靶 ligand，接著標誌 ^{64}Cu 得到 ^{64}Cu-CANF-Comb nanoparticle，並進行血液動力學實驗；與 ^{64}Cu-DOTA-CANF 比較，血液動力學可以看到前者的停留在血液中較久，而後者於 30 分鐘內快速清除的情形，在生物分布結果中可以看到血液停留時間長及低肝、脾攝取情形。患動脈粥狀硬化兔子的 PET 影像上，可看到患部明顯的藥物積聚效果（如圖三）。此藥物正在進行 eIND 的試驗。

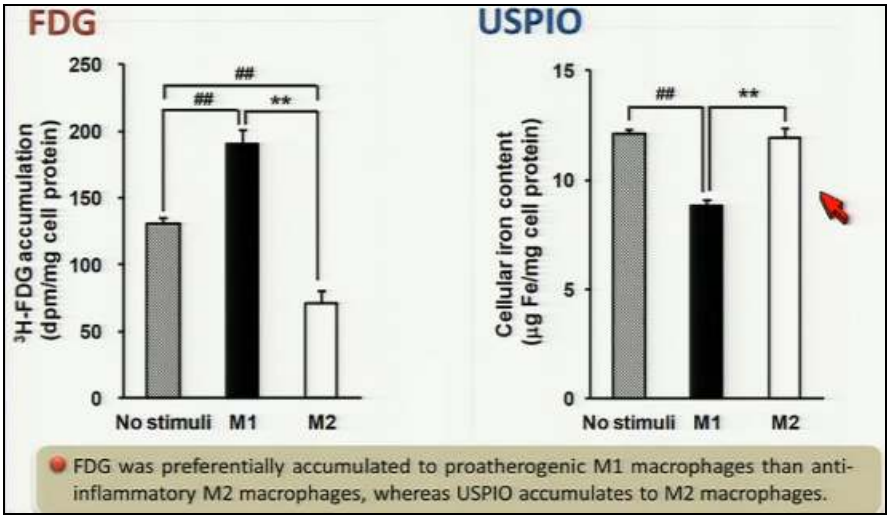


圖三　^{64}Cu-CANF-Comb nanoparticle 專一性積聚於病灶（黃色箭頭）的情形。

在心臟核醫學領域的主要趨勢有下列幾項：PET 續占鰲頭、固態偵檢器改變了 SPECT 領域的發展、定量上亟需提昇準確度、PET-MR 在心臟血管上的應用逐漸出現以及新的正子藥物正推向臨床。演講者 Frank M. Bengel 列出了他對 2013 年 SNM 的觀察與預期：包括了多儀器融合影像的重視、轉譯科學困境的解決及超越傳統器官邊緣（包括細胞軌跡、免疫訊息路徑、代謝）的思考與行動。傳統觀念中，心臟血管疾病是一種退化性（degenerative）疾病，著重於動脈粥狀硬化、灌注缺乏、梗塞傷疤及幫浦失效等現象，然而，近期出現的全新觀念指出，心臟血管疾病是一種“發炎性（inflammatory）”疾病，反而應該要著重在免疫訊息傳遞、細胞追蹤、組織重塑（remodeling）、組織再生等現象。

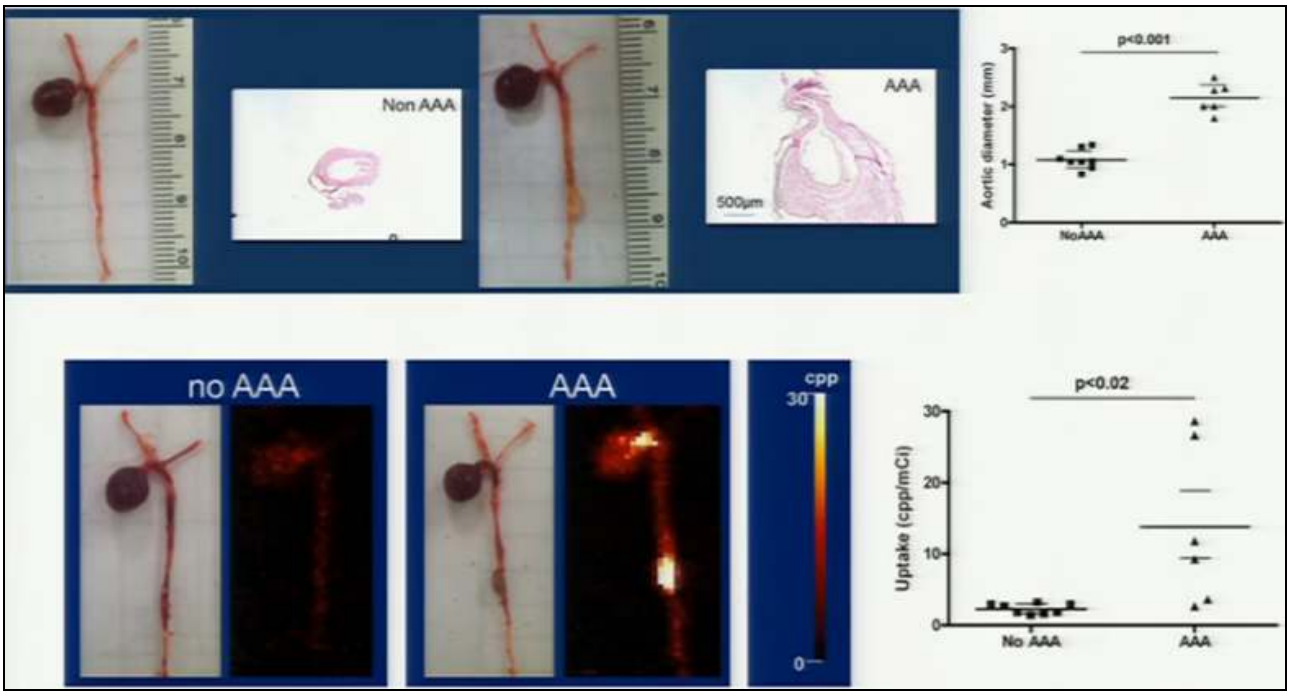
日本的 Mikako Ogawa 團隊研究動脈粥狀硬化的血塊中，巨噬細胞（macrophage）的極化（polarization）現象將影響 FDG 及 USPIO 攝取。在硬化部位浸潤的巨噬細胞，接受不同細胞激素刺激會進一步極化成不同功能的族群包括 M1 及 M2 型，M1 與導致粥狀硬化血塊去穩定與發炎有關，而 M2 與血塊穩定與抗發炎有關。定量結果可看到極化巨噬細胞的攝取：^{3}H-FDG 在 M1 巨噬細胞的積聚較高，而 USPIO 則主要積聚在 M2。未來可應用此方法進行診

斷。（如圖四）



圖四　M1 及 M2 巨噬細胞的極化現象將影響 FDG 及 USPIO 攝取。

來自 Yale 大學的 Razavianm Mahmoud 和其研究團隊，觀察腹部血管瘤活化基質金屬蛋白酶（matrix metalloproteinases, MMP）的分子影像。過去文獻指出，主動脈弓粥狀硬化（Aortic Arch Atherosclerosis，AAA）的形成牽涉到血管平滑肌細胞的老化、氧化壓力、產生促發炎細胞激素以及 MMP 的活性。注射 ^{99m}Tc-RP805（對活化 MMP 具專一性）藥物後，將 AAA 取出進行切片及活性定量，切片結果可看到 AAA 血管直徑較控制組爲高，活性測量結果可看到 AAA 的活性較控制組爲高，而影像上也可以觀察到明顯的積聚。（如圖五）



圖五　MMP 專一性藥物 ^{99m}Tc-RP805 於 AAA 的影像積聚表現、切片及定量結果。

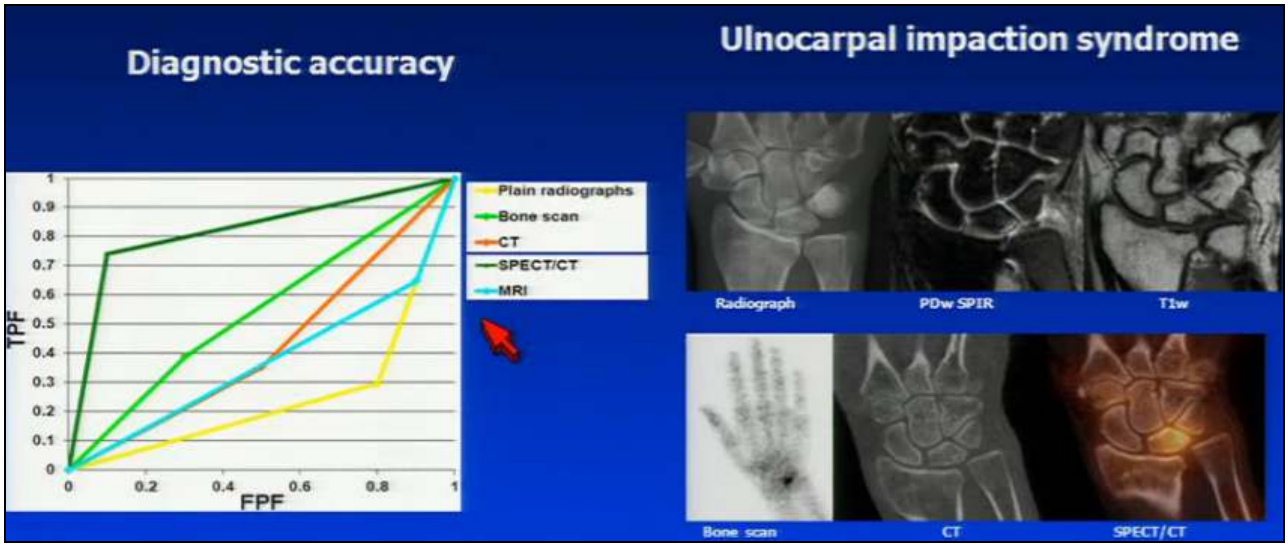
這次會議中提供的看法，大部分的心臟血管疾病都是發炎疾病，包括了動脈粥狀硬化、冠狀動脈疾病、心肌梗塞及心衰竭等疾病都與發炎有關。發炎是一種跨多層面的關鍵機制，如神經退化性疾病中神經發炎現象、癌症轉移及治療中免疫系統的角色、發炎在其他器官（如肺、腎）疾病扮演的角色等。今年度 SNMMI 心臟學影像領域揭示了，相關技術正在快速發展，分子影像也影響了我們觀察疾病的角度，並超越傳統器官界線的發展，未來以分子路徑爲基礎的造影及治療方式將持續發展。

核醫學會研討會是一重要之研發成果發表舞台，大會有許多臨床研究報告發表研究成果，除了新藥測試外，如果是已上市藥品，藥廠大都會繼續支持臨床應用研究，以擴大其適應症種類，GE 公司雖在 2009 年即取得 ^{123}I-MIBG 藥品許可證，但因主要臨床應用市場在心臟病患之診斷，因此 GE 公司續推動臨床應用研究，並利用學會之研討會介紹產品之研究成品，吸引更多臨床醫師之注意與興趣，終於在今年三月獲得 FDA 通過 ^{123}I-MIBG 可應用於心衰竭疾病之診斷。

(二) 一般臨床醫學領域（General Clinical Specialties）

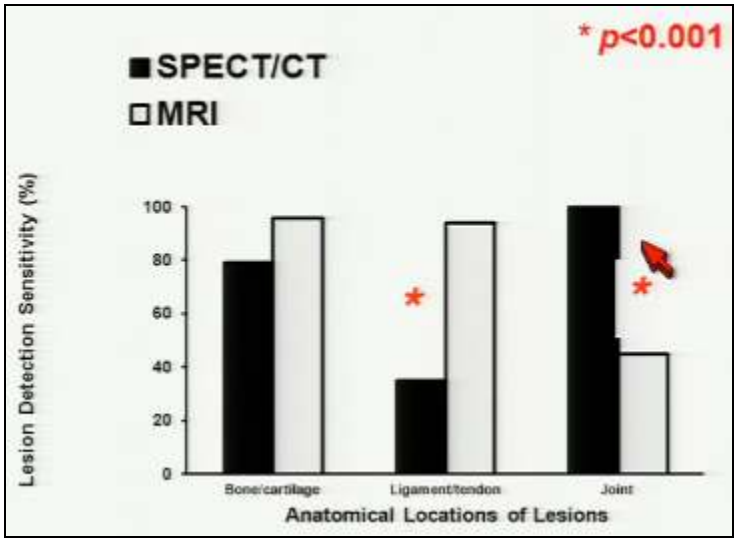
在一般臨床核醫學領域方面，2013 年是 *SPECT/CT* 的一年，單光子造影成爲了全新的標準。在這個領域中的許多研究都顯示，SPECT/CT 增加了敏感度/專一性/準確度，也增加了使用者的信心，同時減少不同使用者間出現的差異，此外也有許多創新出現。今年海報投稿共有 185 篇，內容主題可分爲內分泌（80 篇）、胃腸道（17 篇）、感染疾病/血液學（14 篇）、肌肉骨骼（27 篇）、小兒（4 篇）、肺部（21 篇）、腎臟/高血壓（10 篇）、產出/療效比較研究（12 篇），教育展示海報有 37 篇，口頭報告方面有 83 篇。以下介紹幾篇重要文摘。

來自瑞士的 Martin W. Huellner 和其研究團隊，研究非專一性手腕疼痛的病人 SPECT/CT、MRI、CT、平面骨造影及一般 X 光影像等診斷方式的準確度。32 位病人的結果分別由 2 位有經驗的和 2 位無經驗的判讀者來進行疾病判讀，SPECT/CT 對前者來說無論在準確度（如圖六，可看到 SPECT/CT 之真陽性（TPF）高、僞陽性（FPF）低）、專一性和靈敏度都較佳於 MRI 和平面骨造影；CT 和一般 X 光影像的判讀對於 4 人來說皆顯得較差。此研究的結論是，SPECT/CT 相較於其他診斷方式將能對手部及手腕有慢性疾病的病人提供幫助。



圖六　非專一性手腕疼痛的病人於 SPECT/CT、MRI、CT、核醫骨造影及一般 X 光影像等儀器獲得診斷影像及準確度比較。

來自韓國的 Seunggyun Ha 和其研究團隊，研究 SPECT/CT 與 MRI 兩者在腳踝和足部外傷的診斷表現。47 個病人中，針對 137 個病灶（含骨頭、軟骨、韌帶、肌腱、關節等部位）進行評估。影像定量結果顯示，診斷關節損傷之靈敏度，SPECT/CT（100%）較 MRI（45%）爲佳；而韌帶/肌腱病灶的結果，MRI（94%）> SPECT/CT（35%）；對於骨頭損傷之診斷 MRI 亦較 SPECT 爲佳（如圖七）。



圖七　關節、韌帶/肌腱及骨頭損傷在 SPECT/CT 與 MRI 診斷之靈敏度比較。

來自丹麥的 Sine Hvid Rasmussen 和其研究團隊，比較 SPECT 和三段 SPECT/CT（Triple-SPECT/CT，掃描範圍從頭到大腿）在骨轉移診斷上的功效。在研究的 68 位病人中，54%有攝護腺癌，38%有乳癌，而 8%則爲其他腫瘤病人，結果顯示在診斷上的改變只有 5/68

（7%），但是在診斷的信心有增加（46/67 即 69%），減少了病灶模糊診斷（equivocal study）的次數。

	Reference Standard										
	Bone metastases (n = 14)			No Metastases (n=53)			Interpretation*				
Modality	M	E	B/N	M	E	B/N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NVP (95% CI)	Accuracy (95% CI)
Planar	11	3	0	3	15	35	100.0 (78.5-100.0)	66.4 (52.6-77.3)	43.8 (28.1-60.1)	100.0 (90.1-100.0)	73.1 (61.5-82.3)
SPECT	13	0	1	6	18	29	92.9 (68.5-98.7)	54.7 (41.5-67.3)	35.1 (21,8-51,2)	96.7 (83,3-99,4)	62.7 (50.7-73.3)
Standard	14	0	0	9	1	43	100.0 (78.5-100.0)	81.1 (68.6-89.4)	58.3 (38.8-75.5)	100.0 (91.8-100.0)	85.1 (74.7-91.7)
Triple-SPECT/CT	14	0	0	10	1	42	100.0 (78.5-100.0)	79.3 (66.5-88.0)	56.0 (37.1-73.3)	100.0 (91.6-100.0)	83.6 (72.9-90.6)

M = Malignant, E = Equivocal, B/N = Benign or Normal
*Analysis categorizing equivocal interpretations as malignant.

圖八　Planar、SPECT w/wo CT 及 Triple-SPECT/CT 等儀器作爲骨轉移診斷之功效比較。

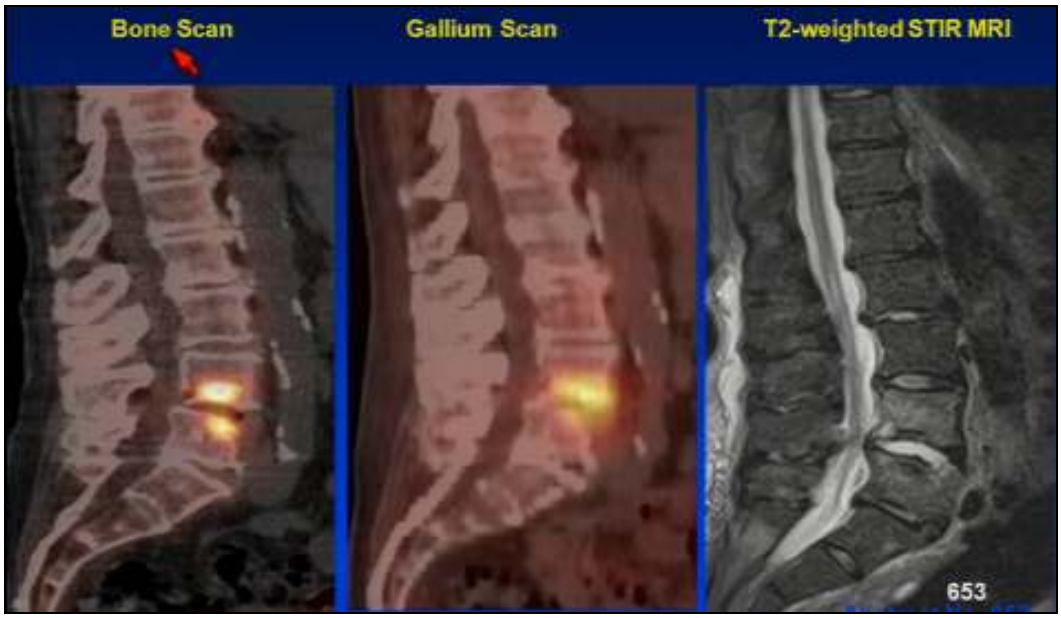
由圖八可知，無論是單一或是三段 SPECT/CT 與單獨 SPECT 和平面造影（Planar）相比，都可以減少模糊診斷的需求。前兩者和後兩者相比無論是在靈敏度、專一性、PPV（positive predictive value）、NVP(negative predictive value)及準確度方面都較佳。而 SPECT 和 SPECT/CT 應用於骨外病灶病人，如單個脊髓病灶的分期，可以看到同樣地 SPECT/CT 能減少模糊診斷的需求，並增加診斷準確率。

來自中國的 Lei Jiang 及其研究團隊，將 SPECT/CT 用在評估不定脊髓單個損傷的病人，病人無疾病史。48 個病人中，有 18 位病人爲良性病灶，30 位病人爲惡性，共比較了他們平面造影、SPECT 和 SPECT/CT 等儀器診斷之準確度、專一性、PPV 和 NVP 等因素，可以發現 SPECT/CT 都較高。

來自紐約 Sherif Heiba 及其研究團隊，透過初期白血球（WBC）和骨掃描等雙重同位素（Dual Isotope, DI）SPECT/CT 造影，進行糖尿病患足部骨髓炎（osteomyelitis, OM）和夏兒哥足（Charcot joint）的早期診斷。雙重同位素造影（第 1 個 DI）對 OM 和軟組織感染和感染部位的定位具有準確性，然而檢查還包括第 2 個 DI，用來判讀真的 OM 和在夏兒哥足病中骨髓增生（bone marrow hyperplasia, BMH）及 WBC 攝取的狀況。結果顯示 22 個病人當中，10 個檢查出爲骨髓炎，而 9/10 的病人可用 SPECT/CT 來定位。

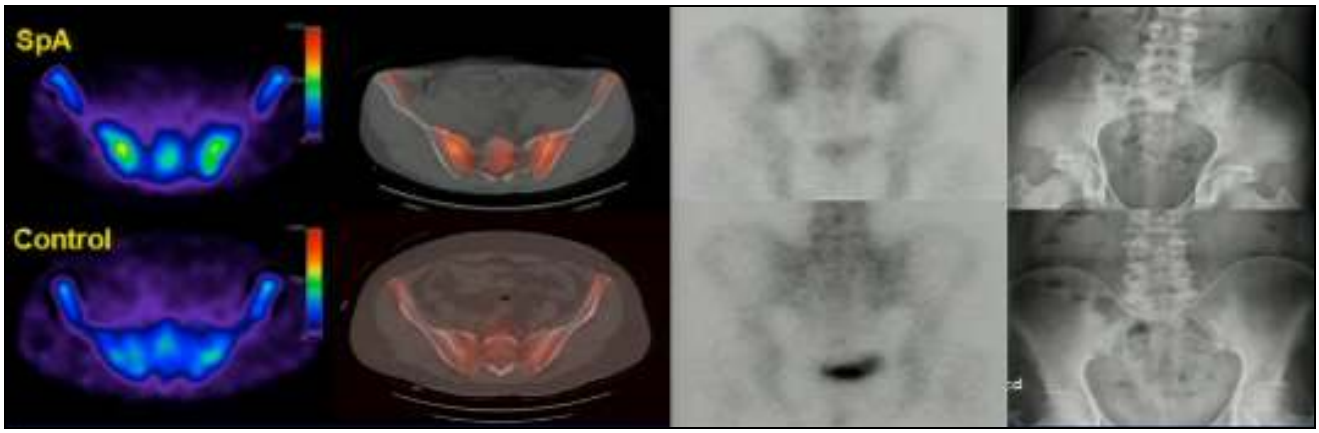
來自加拿大的 Alexander Tamm 和其研究團隊，進行骨掃描、鎵 SPECT/CT（^{67}Ga）和對比劑增強 MRI 在感染性脊椎裂（spondylodiscitis）疾病診斷的回溯性研究。34 個懷疑有感染

性脊椎裂的病人，進行骨掃描、鎵 SPECT/CT 和 T2-weighted STIR MRI 造影，影像結果可發現前兩種檢查方式不管是在靈敏度、專一性、PPV、NVP 或是準確度都與 MRI 非常相近（如圖九）。



圖九　骨掃描、鎵 SPECT/CT 和及 T2-weighted STIR MRI 在感染性脊椎裂的影像結果。

來自韓國的 Yong-il Kim 和其研究團隊，研究骨 SPECT/CT 配合 VOI 分析的使用，可進行早期軸向感染性脊椎裂（SpA）分析，並和平面骨掃描結果進行比較。具背痛症狀的 15 個病人，進行 SPECT/CT 和平面骨造影（如圖十），可看到 SpA 病灶有活性積聚的表現，定量結果上看到兩者 AUC 上明顯的差異（SPECT/CT：0.873 > Planar：0.560）。SPECT/CT 造影的靈敏度約 83%，專一性約 77%。

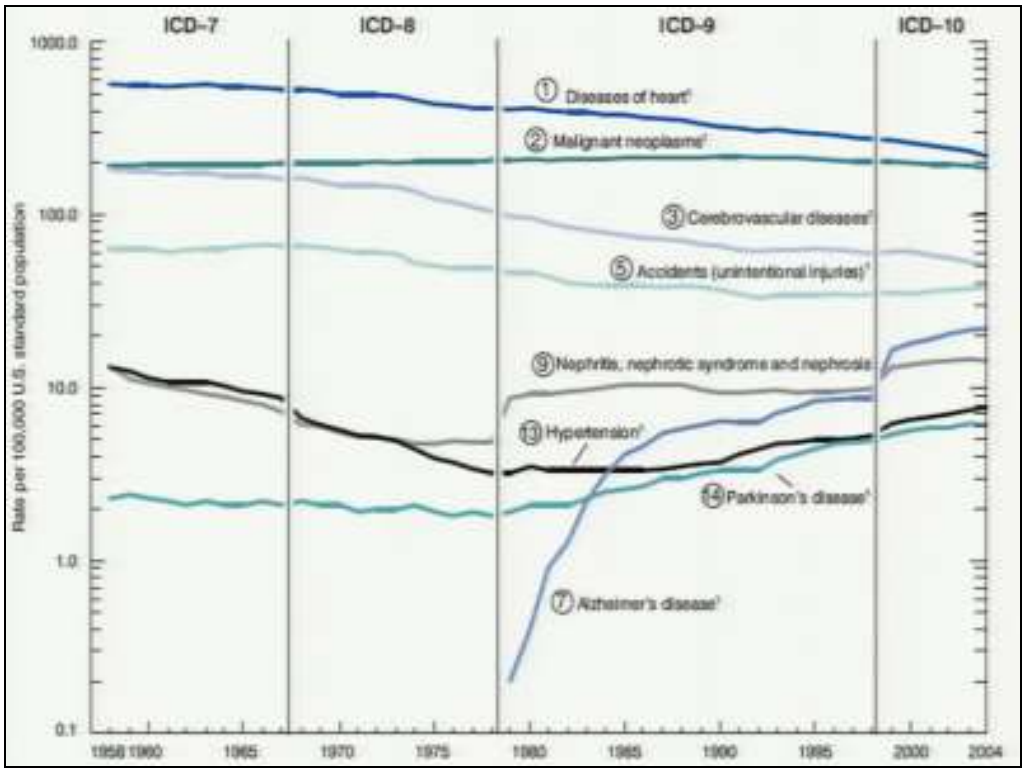


圖十　早期軸向感染性脊椎裂病人造影。圖中上列爲 SpA 病人造影結果，下列爲正常病人造影結果。由左而右分別爲 SPECT、SPECT CT fusion、平面骨掃描、X 光影像。

(三) 神經學領域（Neuroscience）

今年是 SNMMI 年會的 60 週年，30 年前 Wagner 教授和他的研究團隊取得人類大腦 dopamine 系統的第一張分子影像。而今年 Kuhl-Lassen 榮譽獎，由腦神經分子影像領域有相當成就的賓州大學孔繁淵（Dr. Hank F. Kung）教授獲得，孔教授過去與本所有密切合作，他這次帶來的演講題目是：Amyloid Plaque Imaging Probes: From Bench to Clinic。

今年神經學領域的海報投稿共有 183 篇，基礎科學 34 篇，神經學 75 篇，精神病學 8 篇，神經分子藥物 59 篇，教育展示海報 7 篇，口頭報告方面共有 69 篇。我們從一張統計圖中可以看到，過去幾年與年齡相關的死亡率，神經疾病包括帕金森氏症（Parkinson's disease）及阿茲海默症（Alzheimer's disease, AD）的比例有不斷增加的趨勢，是值得投入研究的 2 種疾病（如圖十一）。以下介紹幾篇本次會議重要的論文。

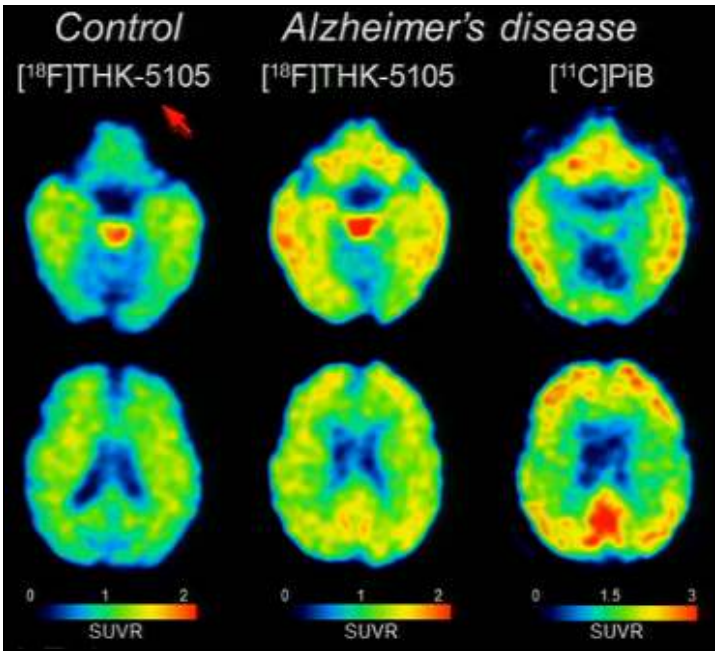


圖十一　與年齡相關的死亡率，神經疾病包括帕金森氏症及阿茲海默症有增加趨勢。

首先，從孔教授的演講中可以瞭解阿茲海默症形成的致病機轉主要有二：大腦內類澱粉斑塊（β-Amyloid Plaques）的沉積，以及神經細胞內神經纖維纏結（Neurofibrils tangles）的產生，也就是說若透過對斑塊或 Tau 蛋白的專一性結合將可早期診斷阿茲海默症。孔教授現階段已開發兩個針對斑塊結合的重要藥物：^{18}F-AV-1 及 ^{18}F-AV-45（Amyvid，已上市）；在神經退化性疾病的未來造影劑方面，他也預期若針對 Tau 蛋白進行專一性結合，結合位更多，

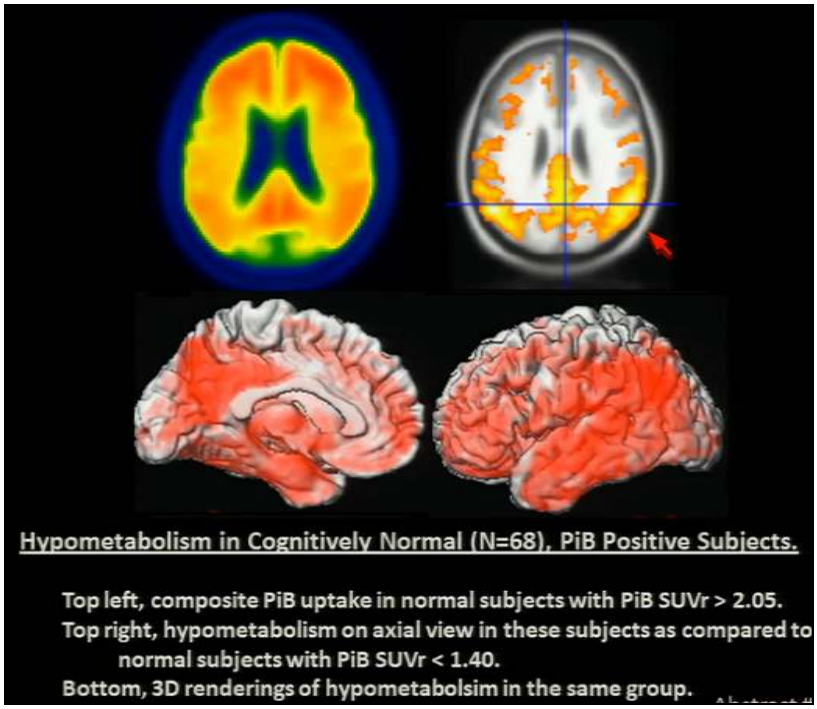
將更靈敏。

來自加拿大的 Victor L. Villemagne 和其研究團隊，進行阿茲海默症的 Tau 造影研究，使用的藥物包括 ^{18}F-THK523 及 ^{11}C-PiB（Pittsburgh compound B）等，預期阿茲海默症的病人其攝取 ^{18}F-THK523 會相當明顯，而 ^{11}C-PiB 於本研究中作爲比較標準。從 SUV 的定量結果看來，海馬迴中 ^{18}F-THK523 或是 ^{11}C-PiB 的攝取，與簡易智能量表（mini-mental state examination, MMSE）、臨床失智評估量表之總合分數（CDR SOB）、情節記憶系統（episodic memory system）及非記憶（non-memery）等病患認知測試結果，分別呈正相關或負相關，而與正常人之腦內攝取有明顯不同。影像結果顯示，阿茲海默病患與正常人相比，不管是 ^{18}F-THK523 或是 ^{11}C-PiB 都較高（如圖十二）。



圖十二　^{18}F-THK523 或 ^{11}C-PiB 在 AD 患者的腦部攝取皆較高，其中前者在正常腦部亦無升高。

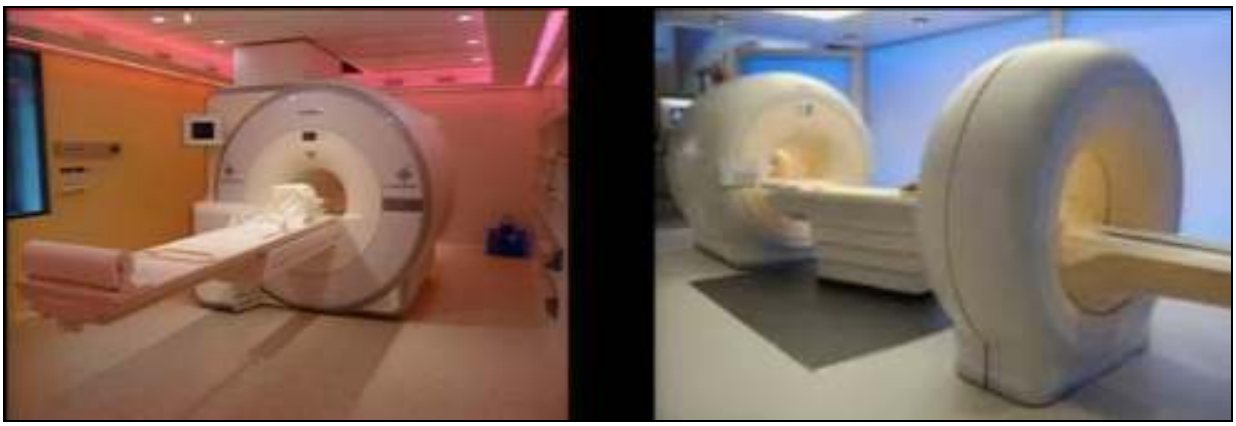
來自Rochester大學的Val J Lowe和其研究團隊，研究FDG攝取在PiB陽性、認知正常的個案中的改變。在過去的研究中，^{11}C-PiB作爲第一個廣泛使用的β-Amyloid造影劑，可用來評估類澱粉斑塊在認知功能障礙之前的分佈狀態，這些廣泛分佈的類澱粉蛋白沉積區域是與認知能力下降相對應的高風險區域，即PiB的攝取代表具有阿茲海默症高風險，而FDG的攝取則與腦內血糖代謝有關。研究結果顯示，PiB攝取較高、認知正常的個案中，在AD區域的影像，顯示有代謝低下（hypometabolism）的情形（如圖十三），而這種情形可能跟腦神經的退化有關。



圖十三　上圖左爲PiB影像，上圖右爲代謝低下（hypometabolism）之影像結果。

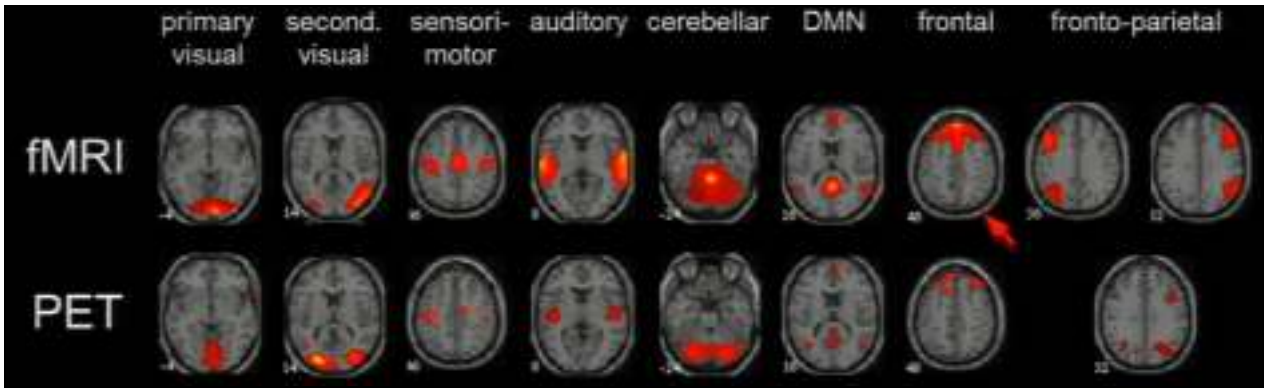
對於阿茲海默症之研究，除了 β-Amyloid 持續應用研究外，有許多研究團隊認爲 the deposition of tau is more closely related neuronal loss than that of Aβ，日本仙台之 Tohoku 大學設計一系列 2-phenyl quinoline 衍生物用於 Tau imaging agents，本次大會他們介紹 ^{18}F-THK523、^{18}F-THK-5105、^{18}F-THK-5117 等藥，先以 *in vitro* 確認其對 Tau 之高親和力後，再進行臨床應用研究，並與 ^{11}C-PiB 做比較，發現 ^{18}F-THK-5117 在 AD 大腦海馬迴有分佈，但相對 ^{11}C-PiB，目前仍待更多臨床試驗來驗證其診斷效用，未來值得注意其發展。

本次年會，PET/MRI 是今年大會之重點，臨床 PET/MRI（如圖十四）的出現帶動了腦科學全新的研究領域發展。有許多報告指出乳癌、心臟及許多疾病之診斷，PET/MRI 皆可有 PET/CT 相同之效果。



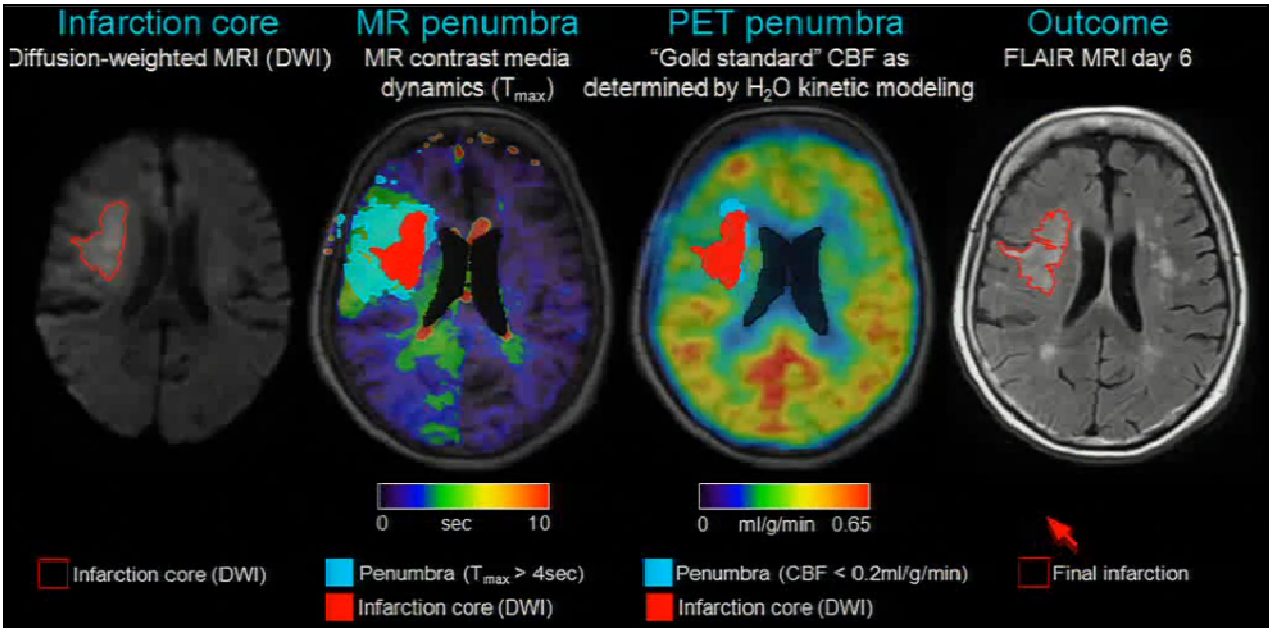
圖十四　PET/MRI 領域今年有顯著發展。

來自德國的 Igor Yakushev 和其研究團隊，利用 PET/MRI 觀察腦神經功能性和代謝靜止時的影像。fMRI（functional MRI）利用血氧濃度相依性（Blood Oxygenation Level Dependent, BOLD）對比能決定大腦內受神經活動刺激的區域。研究結果顯示，休息狀態時 BOLD 影像及糖代謝（FDG）的 PET 影像有類似的表現（如圖十五）。



圖十五　利用 MRI/PET 觀察休息狀態時 BOLD 影像及糖代謝的 PET 影像有類似的表現。

來自德國 Leipzig 大學的 Peter Werner 和其研究團隊，評估急性中風病人 ^{15}O-H_2O PET/MRI 影像。利用 MR 對比劑影像得到 MR 半影（penumbra）結果（Tmax > 4 sec）。缺血半影區是一個低灌流、低血氧的情況下，組織本身結構仍完整，但神經元功能受限，在梗塞的危險邊緣；接著利用 ^{15}O-H_2O PET 觀察腦血流量（CBF）的分佈，得到 PET 半影結果（CBF < 0.2 ml/g/min），並與腦梗塞核心處擴散權重影像（DWI）作比較（紅色部份）。六天後的液體衰減反轉恢復(FLAIR)影像，用來觀察最終梗塞情形，與其他影像作比較。結果可發現與 ^{15}O-H_2O CBF PET 範圍相比，MR 對比劑動態影像有高估的半影面積（如圖十六）。



圖十六　比較 DWI、MR 半影、PET 半影及 FLAIR 對腦梗塞範圍的評估。

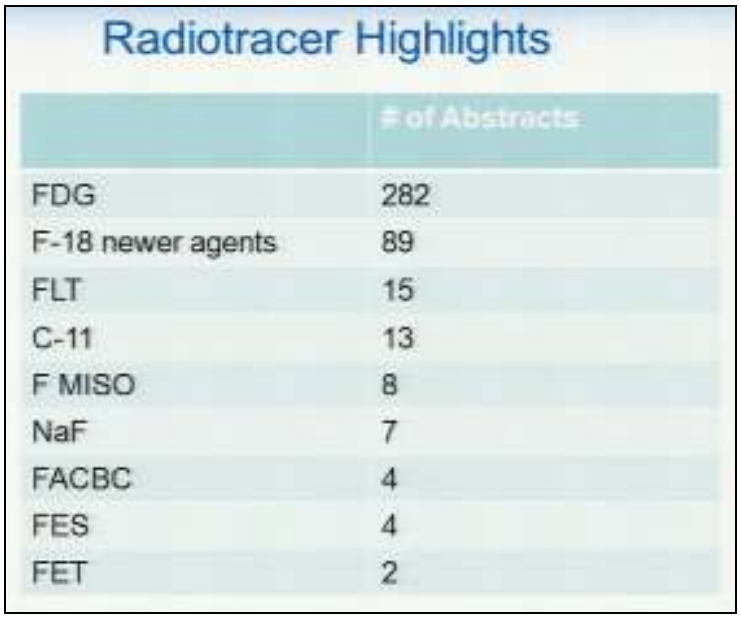
除了腦退化的疾病之外，另外，multi-modality imaging agent 之應用研究亦佔相當篇幅，例如 PET/NIRF 之開發，ZnO 奈米粒子結合 ^{64}Cu 再結合單株抗體（TRC105），形成 ^{64}Cu-NOTA-PEG-NP-TRC105 之複合物，可應用於 PET/NIRF（即 near-infrared fluorescence）。亦有人開發 ^{68}Ga-labeled superparamagnetic nanoparticle（^{68}Ga-SPIO），並應用 ^{68}Ga 之能量，形成 PET/MRI/Cherenkov luminescence imaging of sentinel nodes。有關於 Cherenkov luminescence imaging 之研究在今年大會之持續教育上亦安排有討論，目前除了 positron-emitting radionuclide 可以形成 Cherenkov luminescence 外，β emitter 是否具有此一能力？經實驗顯示，^{90}Y 及 ^{177}Lu 皆可有 Cherenkov luminescence 之產生，但 ^{90}Y 有較高之 β energy，可導致較佳之對比。

有關神經內分泌腫瘤（neuroendocrine tumor, NET）之診斷，^{68}Ga-DOTANOC 及 ^{68}Ga-DOTATATE 依然是大會討論之重點，頭頸部腫瘤之診斷，臨床數據顯示 ^{68}Ga-DOTANOC 較 ^{131}I-MIBG 有較佳之靈敏度。德國研究團隊分析 ^{68}Ga-DOTANOC 對於 primary NET 及 distant metastasis 之診斷靈敏度，結果顯示對 primary NET 之 sensitivity 及 accuracy 均爲 87%，對於 distant metastases 之 sensitivity 爲 94%，specificity 達 100%，accuracy 則有 98%。瑞典 Uppsula 大學，以同一組病患比較 ^{68}Ga-DOTANOC 及 ^{68}Ga-DOTATATE 之 Biodistribution radiation dosimetry，發現 ^{68}Ga-DOTATATE 對肝及膽有較高之劑量，分析兩種藥之體內輻射吸收劑量值皆爲 0.021 ± 0.003 mSv/MBq。另外，也有研究報告探討 ^{90}Y-DOTATOC 及 ^{177}Lu-DOTATOC 對於 metastases gastrinoma 之療效，發現 ^{90}Y-DOTATOC 及 ^{177}Lu-DOTATOC 合併給藥之療效較單獨投與 ^{90}Y-DOTATOC 有較長之病患存活率。

(四) 癌症領域（Oncology）

癌症領域是 2013 SNMMI 最主要的領域之一，今年此領域的投稿論文包含臨床及基礎共有 532 篇，會議期間週一（6/10）的儀器及成果總結課程有 245 篇，而週日（6/9）的分子標靶探針/分子影像/放射性藥物科學課程有 332 篇，因此總共有 532+577 篇癌症領域相關的摘要。此領域共有來自 38 個國家的投稿，排名最多的是美國 144 篇，其次是韓國及中國分別是 61 及 57 篇，台灣位居第 10 名投稿篇數爲 15 篇。此領域又分爲多種研究類別包括 PET、SPECT、診斷、監控治療（monitoring therapy）及治療等，最多的是以 PET 進行研究的類別

的摘要共有 310 篇，SPECT 有 33 篇（人類 20 篇、動物研究 12 篇）；診斷研究方面共有 211 篇（人類 199 篇，動物研究 12 篇），監控治療方面有 101 篇（人類 83 篇，動物研究 18 篇）；最後是治療研究的類別有 80 篇，除了人類 28 篇、動物研究 46 篇外，另有細胞層次的研究 6 篇。針對今年度在癌症領域使用的藥物及核種相關的摘要數目整理之後（如圖十七），可以看到本次最多的是 FDG 相關的摘要（282 篇），其次是 F-18 新型藥劑（89 篇）及 FLT 研究（15 篇），C-11 研究也佔了 13 篇在影像探針研究方面，涵括各種分子影像類別，包含放射性、光學、MRI 及多功能探針等。以下也將介紹幾篇本次會議相當重要的論文。



圖十七　今年度癌症領域的藥物及核種相關摘要數目統計整理。

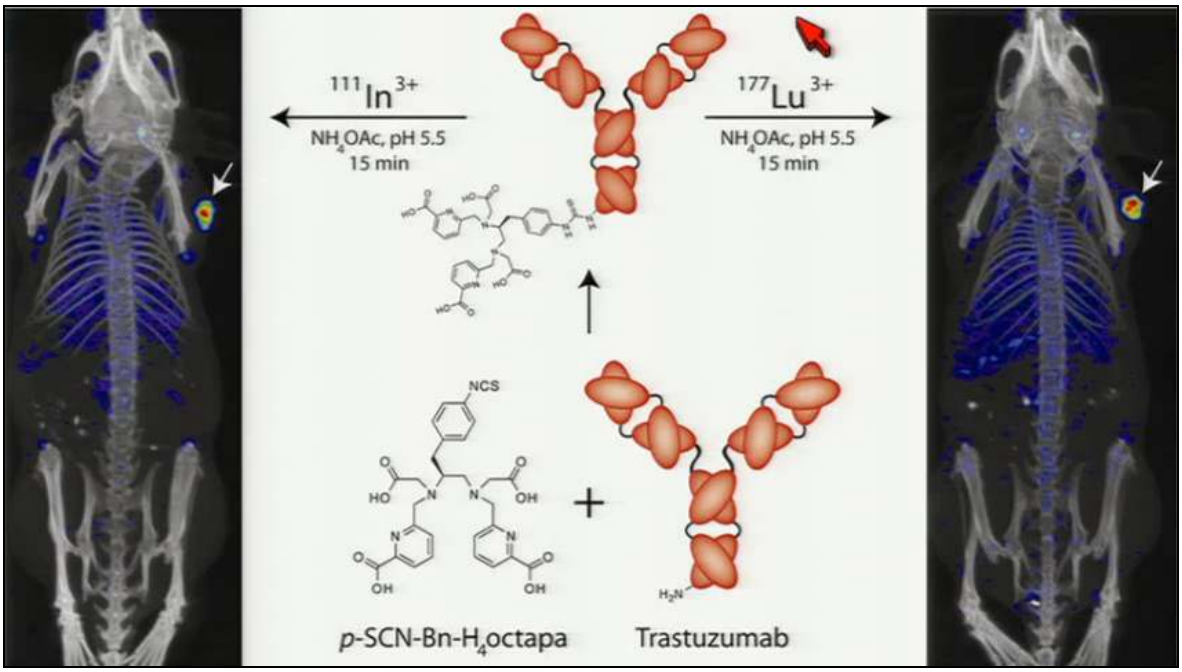
McMaster University 的 James P.K. Dzandzi 及其團隊發展了液-固態綜合劑型之放射性碘化及純化平台，用來產生高產率之碘放射性藥物，純化方式不採取 HPLC 相對較方便，純度 > 98%。

在 ^{68}Ga-PET 方面，來自英國的 Frank Rösch 及其研究團隊發展了具類似 AAZTA 結構的多種新型敖合基（chelator）如 DATA，與常見的 DOTA 等敖合基相比，發展此種敖合基可在室溫下與 ^{68}Ga 標幟且可將反應時間縮短（< 3 分鐘）（如圖十八）。使用此敖合基標幟的藥物穩定度已經測試，其他相關生物研究正在進行中。

Chelator	pH	Temp (°C)	Time (min)
DATA	3.7 - 7	25	< 3
NOTA	~ 4	25	10
TRAP	1 – 5	95	5
H_2DEDPA	~ 4.5	25	< 10
HBED	~ 4.5	25	5
CP256	5.5 – 6.5	25	< 5
DOTA	2.3 – 4.6	95	10

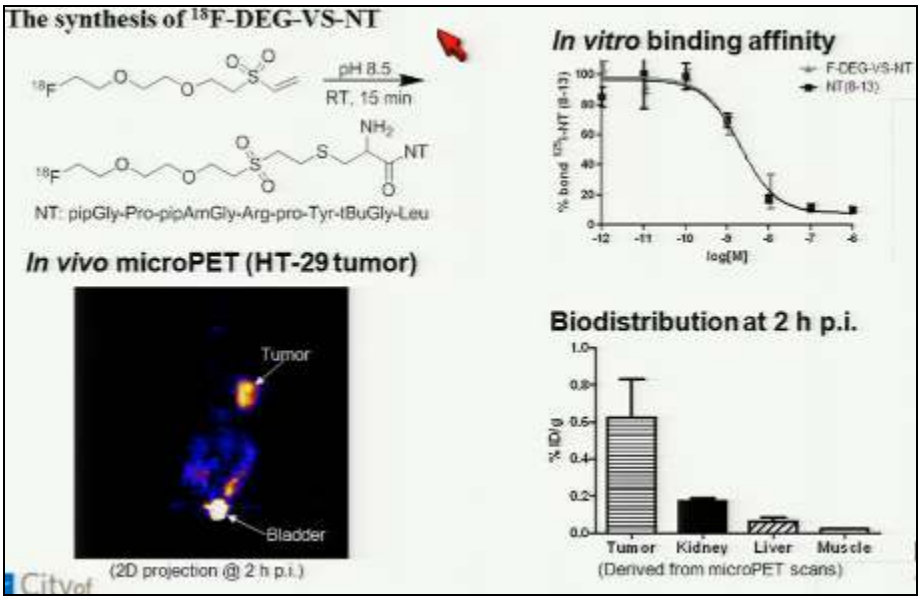
圖十八　DATA 與 DOTA 相比可在室溫下與 ^{68}Ga 標幟且可縮短反應時間。

來自加拿大的 Eric W. Price 及其研究團隊，發展 H_4octapa 敖合基結合賀癌平（Trastuzumab）藥物，可用來結合 ^{111}In 及 ^{177}Lu 提供 HER2 腫瘤造影及治療使用。與常見的敖合基 DOTA 相比，此藥劑在室溫下可進行快速放射性標誌，也有較高產率。^{111}In 及 ^{177}Lu 影像上可看到荷腫瘤小鼠皮下腫瘤內明顯積聚表現（如圖十九）。



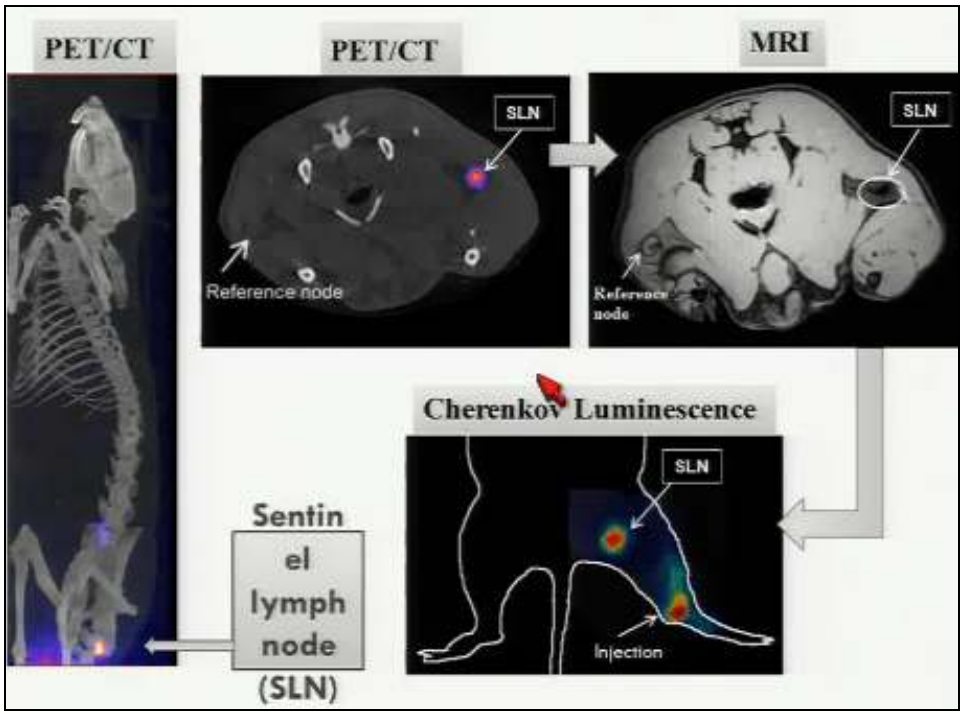
圖十九　H4octapa-Trastuzumab 結合 ^{111}In 及 ^{177}Lu，在小鼠影像上腫瘤專一性積聚的表現。

來自加拿大的 Zhanhong Wu 及其研究團隊，針對神經調壓素（neurotensin）受體 NTR1 發展正子標靶造影藥物 ^{18}F-DEG-VS-NT。結果 ^{18}F-DEG-VS-NT 在細胞中，具有受體專一性結合表現（透過與 ^{125}I-neurotensin（^{125}I-NT）的競爭實驗）；打入荷人類大腸癌腫瘤（HT-29）小鼠 2 小時後進行造影及生物分佈實驗，也可看到腫瘤專一性積聚的情形（如圖二十）。



圖二十　^{18}F-DEG-VS-NT 對 NTR1 受體及 HT-29 腫瘤專一性積聚表現。

來自瑞典的 Renata Madru 發展 ^{68}Ga 超順磁性奈米粒子（superparamagnetic nanoparticle），將藥物打入體內之後，可用來進行前哨淋巴腺（sentinel node, SLN）PET/MR/Cherenkov 螢光等多種儀器造影，其結果顯示不管是哪種方式都有明顯的積聚效果（如圖二十一）。



圖二十一　發展 ^{68}Ga 多功能超順磁性奈米粒子可用於 SLN 的 PET/MR/Cherenkov 螢光等造影。

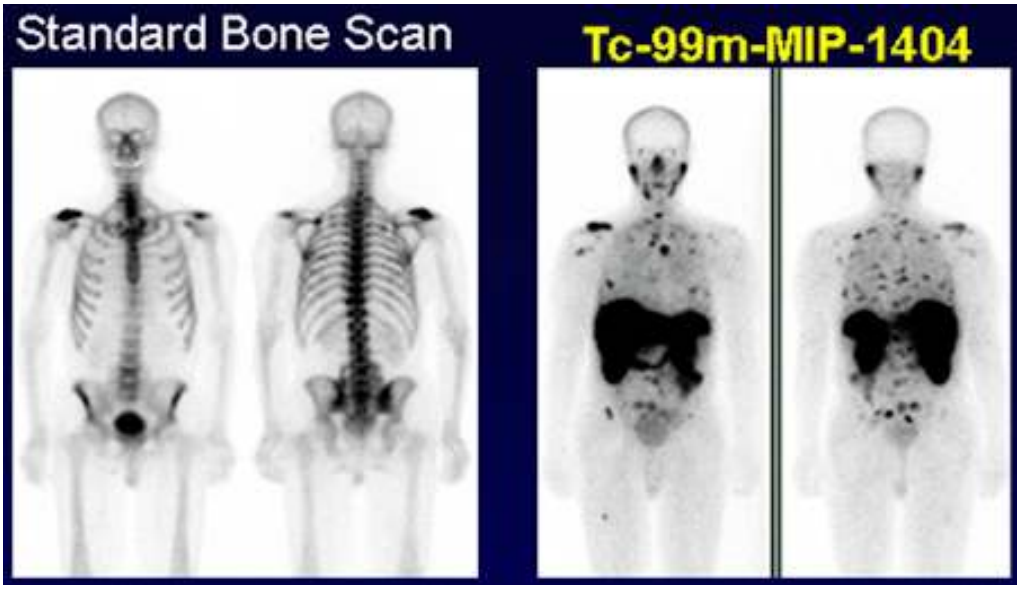
對於 gastrin releasing peptide receptor（GRPR）之應用研究，以往有 ^{99m}Tc-Demobesin1 之開發，近年德國及荷蘭之研究團隊持續研究，設計其新之衍生物，並將其 N4-chelator 取代爲 DOTA 後，即可用於標幟 ^{68}Ga 形成 ^{68}Ga-Sarabesin 3，經 SCID mice bearing PC-3 xenograft 之

prostate cancer model 測試，注射四小時後，tumor 之分佈達 40.0 ± 6.9 %ID/g，相同之模式但先投與 GRPR-blockade 後再注射 ^{68}Ga-Sarabesin 3，發現腫瘤之分佈僅有 7.4 ± 1.6 %ID/g，顯見其對腫瘤之專一性，未來值得注意其發展。

來自 Molecular Insight Pharmaceuticals Inc 與紐約康乃爾醫學院放射科研究人員發展的攝護腺癌診斷試劑，不管轉移性癌細胞藏在哪裡，這些癌細胞與正常細胞仍然表達的同一信號；在某些情況下更是如此，例如攝護腺專一性膜抗原（prostate-specific membrane antigen, PSMA）的表現，可作爲一全新的癌症發展、分期、治療中及治療後的判斷工具。

Vallabhajosula 博士說明，目前尚無理想的影像分析技術可應用在診斷特定攝護腺癌，可定期使用骨掃描分析轉移性攝護腺癌，但骨掃描對這些腫瘤並不具有專一性。因此針對 PSMA 研究的重點，可作爲攝護腺上皮細胞表現的一種抗原的新型造影劑。雖然 PSMA 在攝護腺癌是什麼作用尚未盡知，但使用抗攝護腺抗體特異性結合到 PSMA 的小分子造影劑，將能夠檢測原發性攝護腺癌和二次轉移至其他器官之癌症。

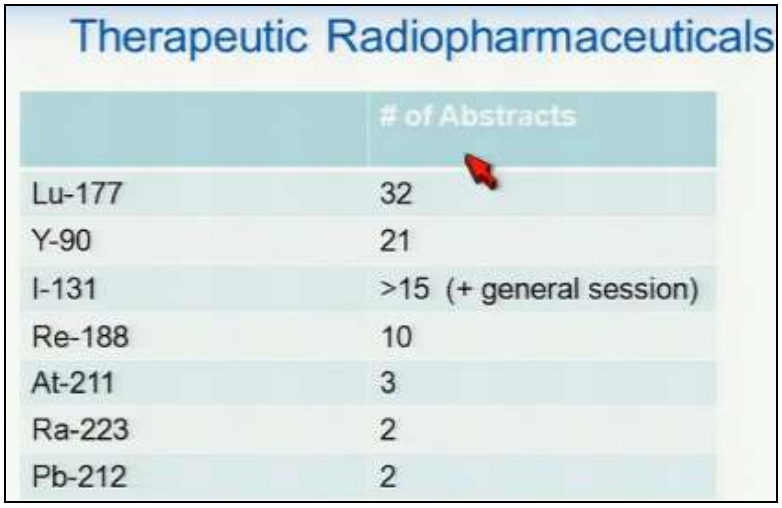
針對兩個涉及 PSMA 初步階段，稱爲谷氨酸羧胜肽酶 II（glutamate carboxypeptidase II, GCPII）或 NAAG 胜肽酶，開發出新型胺基酸造影劑 MIP-1404（glutamate-urea-glutamate pharmacophore），此爲谷氨酸-尿素-谷氨酸之組合，可與 $^{99\,m}$Tc 進行標誌得到 ^{99m}Tc-MIP-1404，提供放射性攝護腺癌檢測之功能性 SPECT 研究，結果如圖二十二。^{99m}Tc-MIP-1404 可與全身轉移性攝護腺腫瘤 PSMA 結合，同時在全身分佈的速率亦相當快，未來將進行更多臨床研究。



圖二十二　^{99m}Tc-MIP-1404 注射一小時後，比標準骨顯像法有更顯著的特異性影像。

根據美國癌症協會 2013 年資料，一年大約有 238,600 例新的攝護腺癌診斷報告。^{99m}Tc-MIP-1404 現在正進行第二期跨國臨床研究，目標將申請美國食品和藥物管理局（FDA）核准上市。

常見的治療核種包括 ^{177}Lu、^{90}Y、^{188}Re 等，今年度摘要使用的治療核種，以 ^{177}Lu 最多（32 篇），其次是 ^{90}Y 及 ^{131}I（21 及 15 篇）；本所使用的 ^{188}Re 則有 10 篇。目前國際上新發展的阿伐治療核種 ^{223}Ra 及 ^{211}At 方面的研究，則僅有較精緻的 2 及 3 篇。



圖二十三　本年度所有發表的摘要中使用的放射性治療核種種類及次數統計。

今年有關肝癌之研究，仍以 ^{90}Y-SIR-sphere 及 ^{90}Y-Therasphere 之臨床應用爲主，美國紐約西奈山醫學院（Mount Sinai School of Medicine）發表一篇論文，比較 ^{90}Y-SIR-sphere 及 ^{90}Y-Therasphere 之臨床療效，分析 79 位病患（26 位使用 SIR-sphere，53 位使用 Therasphere），經統計，發現兩者之療效相當，其 complete response（0-3%）、partial response（32-35%）、stable disease（23.1-39.6%）及 progress disease（30-38%）之結果並無統計上差異，但作者指示 SIR-sphere 會因 macroembolization effect 而有鬱血（stasis）現象產生。

由於現有體內劑量之軟體皆以標準健康人之模型建立，而臨床面臨皆是體型不一之病患，且治療劑量使用之活度相當高，如何能爲每一位病患設計其治療劑量（personal medicine）是臨床與基礎研究者努力之目標，長年致力於體內劑量研究之 Dr. Michael G. Stabin 今年即榮獲大會頒發 Hal Anger Lectureship。在本次年會發表之研究論文中，利用 voxel based Monte Carlo methods 以建立 patient-specific dose calculation for targeted radionuclide therapy 有多篇論文被提出，結合 OLINDA 之特點，利用 deformable anthromorphic model 以建立 patient-specific

anatomical model，以期提昇劑量計算之瓶頸。美國印第安那大學介紹他們建立 ^{90}Y-therasphere PET/CT dosimetric mapping 技術的研發，希望可以利用 PET 收集 ^{90}Y 之少量 gamma ray 建立病患之個人劑量，目前已有初步成果，但技術仍有待突破。

另外，在持續教育課程中，本次大會安排在 Novel Targeted Radionuclide 議題，邀請新加坡之 Dr. Aijt Kumar Padhy 介紹"A prospective on ^{188}Re-Lipiodol Therapy of Hepatocellular Carcinoma"，Dr. Padhy 參與 IAEA 之 ^{188}Re-HDD/Lipiodol 肝癌治療計畫，並發表有多篇重要 ^{188}Re-HDD/Lipiodol 臨床應用論文在 Journal of Nuclear Medicine、Seminars Nuclear Medicine 及 Radiology 等期刊，本次他則以回顧之方法有系統介紹 ^{188}Re-HDD/Lipiodol 研究成果，他認爲 ^{188}Re-Lipiodol 療效不錯，且價格便宜，十分值得推廣。由於 HDD 有製劑不穩定的問題，韓國學者已將其改良爲 AD-HDD 型式，他希望能吸引藥廠之投資興趣，一起來參與這項藥物（^{188}Re-AD-HDD/Lipiodol）之開發，或者，如果醫院有興趣來參與這項研究，他們可協助訓練並提供藥品，但必須依照其臨床試驗計畫，成果送回 Dr. Padhy 彙整，Dr. Padhy 表示今年八月將在印度舉行第一次訓練課程，歡迎大家一起來參加。

本次年會，本所發表一篇 ^{188}Re-MN-16ET/Lipiodol 應用研究，介紹應用肝癌動物模式，比較 ^{188}Re-MN-16ET/Lipiodol 與臨床常用之化學栓塞劑型（Lipiodol + anti-cancer drug）之療效，實驗結果顯示動物存活期差異不大，但 ^{188}Re-MN-16ET/Lipiodols 能致明顯較佳之腫瘤縮小效果。

本年度新加坡 Dr. Padhy 再次推動 ^{188}Re-Lipiodol 之研究，以往此一多國臨床試驗是由 IAEA 主導，隨著每年之推動主題不同，此一支持力量暫停後，參與本項研究之韓國及新加坡學者有感以往臨床效果不錯且價格十分具競爭力（相較於 ^{90}Y-microsphere），因此，希望能吸引者支持此一項臨床研究，或邀請有興趣之醫院或者國家自費參加，本所近年亦得政府補助推動 ^{188}Re-MN-16ET/Lipiodol 臨床試驗，顯見 ^{188}Re-Lipiodol 之肝癌治療應用未來將扮演重要角色。

今年度重要的新聞還包括，放療藥物 Xofigo 已獲准使用於治療特定攝護腺癌患者。今年 5 月 15 日，拜耳公司宣佈 FDA 已經批准 Xofigo（二氯化鐳-223）用於治療患去勢抵抗型攝護腺癌（castration-resistant prostate cancer）、伴有骨轉移症狀且無已知內臟轉移性疾病的患

者。Xofigo 是一種發射 α 粒子的放療藥物，而 FDA 批准 Xofigo 是基於一項關鍵性第Ⅲ期臨床試驗的資料，該研究的中期分析報告顯示，使用 Xofigo 顯著改善了患者的總存活時間（OS）[危險比（HR）0.695；95%信賴區間（CI）0.552 ~ 0.875；P = 0.00185]，Xofigo + 最佳標準治療方案組的中位 OS 爲 14.0 個月，而安慰劑 + 最佳標準治療方案組則爲 11.2 個月。另外報告也說，Xofigo 治療組與對照組相比，首次看到症狀性骨骼轉移事件的時間的延後出現，之後進行的一項非盲分析說明了 OS 有顯著改善，Xofigo 治療組與安慰劑對照組的中位 OS 分別爲 14.9 個月和 11.3 個月。

在這項第Ⅲ期試驗中，接受 Xofigo 治療者的最常見的不良反應是噁心、腹瀉、嘔吐及周圍水腫。最常見的血液學異常指標爲貧血、淋巴細胞減少、白細胞減少、血小板減少以及中性球（Neutrophil）減少。在隨機試驗中，與安慰劑對照組相比，Xofigo 治療組有 2%的患者曾發生骨髓衰竭或進行性全血細胞減少。死亡有 2 例歸因於骨髓衰竭，13 例接受 Xofigo 治療的患者中有 7 例在死亡時仍存在進行性骨髓衰竭。目前僅允許由授權醫師在特定臨床條件下接受病人使用 Xofigo；使用 Xifigo 亦可能會帶給他人潛在危險，如患者的尿液等體液、糞便或嘔吐物外泄可能給他人造成輻射或污染，因此採取放射防護措施。然而化療合併 Xofigo 的安全性和有效性尚未證實，因此考慮到累加性的骨髓抑制作用，在臨床試驗之外不推薦化療患者合併使用 Xofigo。

來自比利時的 Patrick Flamen 和其研究團隊的研究成果指出，80%的轉移性乳腺癌患者會發生骨轉移，往往引起的骨骼併發症進行預後不良和顯著的發病率。鐳-223 爲 α 粒子衰變的治療藥物，能發射短範圍高能 α 粒子治療成骨性的轉移（Osteoblastic metastasis）並不傷害健康組織和骨髓，使用在攝護腺癌骨轉移患者能延長存活時間，並顯著降低骨相關的副作用，證明其療效。在研究中，^{18}F-FDG PET 用來評估乳腺癌患者骨轉移。鐳-223 對骨顯性疾病 23 個轉移性乳腺癌患者治療，並獲得 ^{18}F-FDG PET/CT 造影，在進行第二次治療後即停止治療，並評估骨骼病變的代謝變化。待測病變（targeted lesions）指骨掃描影像增強（顯示高吸收在骨掃描）及代謝影像增強（強烈 FDG PET/CT 吸收）之區域。PET/CT 影像結果顯示，原本有 155 處待測病變，經兩次鐳-223 治療後，三分之一（32.3%）的待測病變呈現明顯的代謝下降。使用鐳-223 進行四次治療的病人，可看到 41.5%的待測病變有治療反應。研究人員指

出，透過臨床前期動物模式證明，鐳-223 能用來防止乳腺癌骨轉移、增加生存率，而 ^{18}F-FDG PET/CT 的反應清楚地呈現此療法治療轉移性乳腺癌的好處，大於 25%癌症患者骨病變減少。此種療法具有應用於所有類型的癌症患者潛力，並值得進一步研究。此研究被 SNMMI 大會高度重視，並獲選爲 *2013 年度影像（Image of the Year）*。

德國的胜肽受體放射性核種治療（Peptide-receptor radionuclide therapy, PRRT）研究，目前全國性研究證明 PRRT 治療不只安全，並能有效延長生命。PRRT 是治療神經內分泌腫瘤尚未批准之新療法，仍在進行臨床研究。神經內分泌腫瘤對於其他器官的激素能作出反應，當正常的神經內分泌細胞進入胰或胃腸道等其他激素敏感器官時（異位瘤），可利用放射性核種進行治療。此篇報告利用 octreotide 衍生物胜肽標誌 ^{177}Lu 或 ^{90}Y 來殺死癌細胞，進行包括轉移胰腫瘤和困難手術個案的第一次跨中心研究，目前結果令人滿意。德國波恩大學的資深內科醫生 Ezziddin 表示，化療和 multi-kinase 抑制劑能平均延長一年生存率，而 PRRT 即使在胰腫瘤，亦可平均延長三年以上存活時間，根據 Ezziddin 的說法，PRRT 爲神經內分泌腫瘤患者帶來了極大新希望。

本回顧性研究包括來自幾個德國癌症中心的 450 位病人，研究條件訂爲存活中位數爲 18 個月以內，具有一系列神經內分泌腫瘤。此研究胰腺腫瘤占 38%的病人數，小腸腫瘤爲 30%，其餘的腫瘤是大腸癌、肺癌或不明。73%的病人，其腫瘤之前有用 PRRT 以外的方式進行治療。

這項研究的結果顯示只有輕微的副作用，整體病人的存活中位數大於五年。病人在最後的治療後病程無進一步進展，其存活中位數爲 41 個月。胰神經內分泌腫瘤往往難以治療，在困難手術的病人中，PRRT 存活中位數亦有 39 個月，小腸腫瘤患者存活中位數爲 51 個月。Ezziddin 表示，如果美國提供這種治療，比大多數當前可用的療法病人會有較少副作用。這是一個非常寶貴和有效的治療選擇，其進一步研究將使 PRRT 作爲真正有針對性治療神經內分泌腫瘤的放射療法。Ezziddin 也估計，PRRT 治療神經內分泌腫瘤將可以在三年之內獲得歐盟核准。

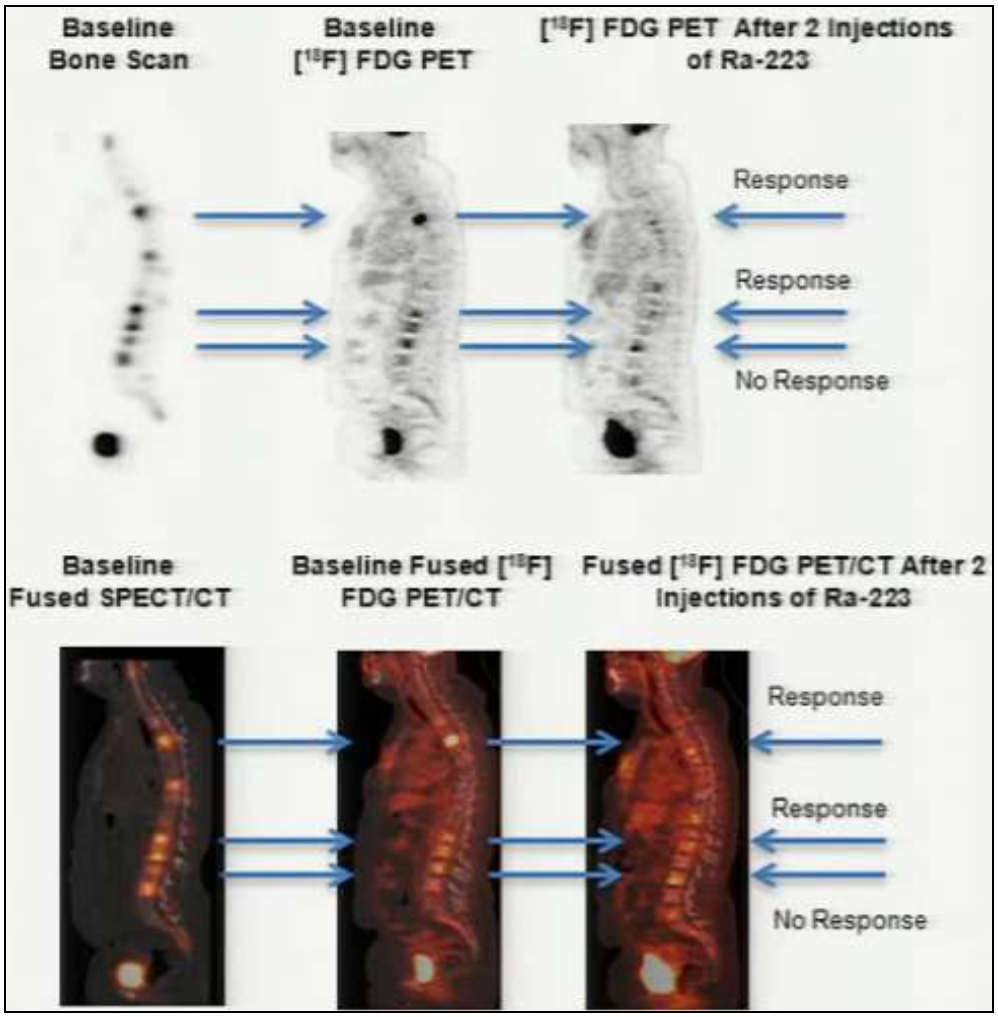
癌症領域是本年度會議內容中最大的領域，而其中 PET 方面的研究多於 SPECT 的研究；FDG 仍是主要放射性示蹤劑，而體內表顯性（*in vivo* phenotyping）的個人化、標準化的定量

已成爲趨勢。癌症治療領域的研究相當重要，而如何提昇病人的療效亦爲本會議焦點。

(五) 2013 SNMMI 亮點回顧（Highlight）及年度影像（Image of the Year）

大會最後一日的亮點回顧（Highlight）演講，分別請到四位專家回顧（review）今年四個重要領域的傑出論文：Frank M. Bengel 回顧 Cardiology，Alan H. Maurer 回顧 General Clinical Specialtie，Dr. Satoshi Minoshima 回顧 Neurosciences，Richard L. Wahl 回顧 Oncology。

每年 SNMMI 都會選擇一個年度影像（Image of the Year），展現一年來最先進的核子醫學與分子影像的研究，今年也不例外；獲得此殊榮的是：鐳-223 治療乳癌病人骨轉移並利用 ^{18}F-FDG 進行治療反應的影像追蹤研究（Radium-223 Dichloride Response in Bone Metastases in Breast Cancer Patients）。^{18}F-FDG PET/CT 斷層掃描提供鐳-223 治療骨轉移性乳癌患者的正子影像，足以顯示鐳-223 治療的有效性，此研究結合了核子醫學之放射治療與分子影像追蹤療效評估，因此被選爲 2013 SNMMI 的年度影像（如圖二十四）。



圖二十四　2013 年 SNMMI 的年度影像（Image of the Year）。

四、建 議 事 項

本次公差參加第 60 屆美國核醫學會年會（2013 Annual Meeting of Society of Nuclear Medicine and Molecular Imaging，SNMMI），對新知獲取、國際發展方向及合作研究，拓展國際關係皆有豐富收獲，依此次公差結果，對國內核醫發展有如下之建議：

(一) 國際會議論文發表之數量和內容代表該國之研發能力與產業受重視之程度，建議本所未來可以加強人才培訓，鼓勵青年學子參加國際研討會，發表論文，積極與國際科學研究接軌，與國內外研究人員互相交流，在本所知能技術和經驗傳承方面會有所助益。

(二) 癌症治療目前將走向標靶治療，建議所內可發展治療性放射性同位素鍵結專一性標靶藥物（抗體等），增進癌症治療效果。

(三) 多功能組合（multifunctional）藥物設計爲國外研發之重要方向，結合 PET、Fluorescence、NIR 及 MRI 等儀器之優點，開發診斷與治療兼具之藥物，除了本所內部之資源整合外，亦應擴大與國內學研單位合作，增強本所之競爭力。

(四) 臨床用藥如何擴大適應症或者增加臨床對它的興趣或認識，是藥物推廣者應多予深思之問題。本次出國期間，羅彩月博士與臨床醫師（包括台大醫院曾凱元主任、秀傳醫院洪光威主任、亞東醫院吳彥雯主任等等）有較多機會進行討論，充分了解臨床對 I-123 MIBG 之需求，對於研發藥物臨床應用與推廣策略多所啓發，建議未來研究人員應採主動與臨床醫師連繫與討論，以使藥物開發能獲得更多臨床之重視與應用。

(五) 美國核醫學會年會（SNMMI）今年有來自 40 餘國的科學家共同參與，此類大型國際重要會議，議題及展示繁多，建議維持每次至少 2 人前往與會，可從不同領域、不同觀點多方面收集國際新知及趨勢，獲取更全面的效益。

(六) 隨著核能研究所未來將隸屬經濟能源部，輻應與核醫領域的同仁在出國開會時，更應著重於產業化與應用研究之考量，以及業界對於新藥開發之趨勢，以跟上本所未來之研發目標與方向。

五、附　錄

附錄一、第 60 屆美國核醫學會年會（2013 Annual Meeting of Society of Nuclear Medicine and Molecular Imaging）議程。

PHYSICIAN/SCIENTIST CATEGORICAL SEMINARS

Saturday, June 8, 2013

TIME	TITLE	ROOM
8:00 AM - 4:15 PM	PC1: Translational Molecular Cardiovascular Imaging: From Bench to Bedside: Part I - Advances in Technology, Myocardial Receptors, and Metabolism:, Part II - Advances in Translational Imaging, Heart Failure, and Clinical Practice* SNMMI Cardiovascular Council	West - 202/204
8:00 AM - 4:15 PM	PC2: Challenges of Regulatory and Reimbursement Approval for Molecular Imaging Agents * SNMMI Clinical Trials Network	West - 212
8:00 AM - 4:15 PM	PC3: Radiolabeled Peptides/Proteins for PET Imaging * SNMMI Radiopharmaceutical Sciences Council	West - 215/216
8:00 AM - 4:15 PM	PC4: A Journey from PET/CT to PET/MRI: The Need for Introducing PET/MRI * SNMMI PET Center of Excellence and the Correlative Imaging Council	West - 205/207
8:00 AM - 4:00 PM	PC5: Molecular Imaging in Neurodegenerative Diseases: State of the Art and Future Trends * SNMMI Center for Molecular Imaging Innovation and Translation and Brain Imaging Council	West - 208/209
8:00 AM - 3:00 PM	PC6: Hybrid Imaging in Pediatric Nuclear Medicine * SNMMI Pediatric Imaging Council	West - 210
7:45 AM - 4:00 PM	PC7: Image and Dosimetry Guided Management of Neuroendocrine Tumors * SNMMI Computer and Instrumentation Council and the Young Professionals Committee	West - 217/219
9:00 AM - 4:00 PM	PC8: Update on Tumor Imaging and Therapy * SNMMI Nuclear Oncology Council	West - 201

6 月 8 日核醫教育課程之議程。

SNMMI Continuing Education Sessions

Saturday, June 8, 2013

	W. 213/214	W. 201	W. Ballroom A RWE	W. Ballroom B RWE	W. 205/207	W. 202/204	
4:00PM - 6:00PM	Calibration, Absolute Quantification, and Contrast Recovery in PET/CT	Technical Trouble-Shooting in Pediatric Nuclear Medicine	Multimodality Breast Imaging *	Quantification of Myocardial Viability Imaging: Who, When, and Which Protocol? *	Carbon - 11 Radiopharma-ceuticals	Use of Contrast in Hybrid Imaging - How Often and Why?	NO SCIENTIFIC (ABSTRACTS) SESSIONS HELD ON SATURDAY
6:00PM - 8:00PM	Welcome Reception & Exhibit/Poster Hall Preview						

Sunday, June 9, 2013

8:00AM - 9:45AM	Plenary Session and Formal Opening (East Building - Exhibit Hall A)
9:45AM - 12:30PM	Visit the Exhibits/Lunch

	Continuing Education Sessions						Scientific Sessions (Abstracts)							
	W. 213/214	W. 201	W. Ballroom A RWE	W. Ballroom B RWE	W. 205/207	W. 202/204	W. 220	W. 224	W. 221/222	W. 217/219	W. 215/216	W. 212	W. 208/209	W. 210
							Mol Targ Probes	Onc-Basic	Onc-Clinical	Cardio	Neuro	GCS	Inst & DA	Extra
12:30PM - 2:00PM	Technical Advances in Cardiac SPECT and PET	Item Writing and Developing SAMS (Self-Assessment Modules) - How to Do It Well	Emerging PET Radiotracers *	Radionuclide Imaging of Inflammation and Infection: State of the Art *	Multimodality Neuroendocrine Tumor Imaging	Translational Optical Imaging Modalities: Part I	Session 1: CMIIT Young Investigator Award Symposium	Session 2: Kinetic Analysis	Session 3: Molecular Imaging of Breast Cancer I	Session 4: Cardiovascular Council Young Investigator Award Symposium	Session 5: Neurotransmission in Psychiatric Disorders	Session 6: Benign Thyroid Diseases	Session 7: Computer & Instrumentation Young Investigator Award Symposium	Session 8: Dosimetry (Molecular Targeting Probes track)
2:00PM - 2:45PM	Visit the Exhibits													
2:45PM - 4:15PM	Challenging PET/CT Cases in the Chest with CT and Pathology Correlation	History Tribute for Henry Wagner, MD	Gastric Motility 2013 *	Epilepsy Diagnosis and Treatment *	Correlative Imaging in Response Assessment (From RECIST to PERCIST)	Prostate Cancer Imaging	Radiopharmaceutical Sciences/Molecular Imaging/CMIIT Basic Science Summary Session West Building 109/110							
4:30PM - 6:00PM	PET Quantification for Dosimetry in Radiopharma-ceutical Therapy	Translational Optical Imaging Modalities: Part II	Gynecologic Tumors and Metastases: MRI, Multiphasic Spiral CT, and PET/CT *	Cardiology Boot Camp for Nuclear Medicine Physicians *	Healthcare Reform: Impact on Nuclear Medicine and Molecular Imaging	The Role of the Urologist in the Screening and Imaging Evaluation of the Patient with Prostate Cancer	Session 9: RPSC Young Investigator Award Symposium	Session 10: Nuclear Oncology Young Investigator Award Symposium	Session 11: Molecular Imaging of Breast Cancer II	Session 12: Hermann Blumgart Lecture & Award Session	Session 13: Brain Imaging Council Young Investigator Award Symposium	Session 14: Outcomes/ Comparative Effectiveness Research	Session 15: Image Generation: PET	Session 16: Neuroendocrine Tumors (General Clinical Specialties track)
6:30PM - 8:00PM	RPSC/CMIIT Poster Hall Mixer (West Building - Exhibit Hall A)						SPECIAL "MEET THE AUTHOR" SESSION, featuring MOLECULAR TARGETING PROBES POSTERS (West Building - Exhibit Hall A)							

Exhibit Hall Hours for Sunday: 9:30AM to 4:30PM

West Building - Ballroom A & B use interactive "Read With the Experts" technology. Audience members may respond to speaker questions by submitting their answers via a keypad.

CONTINUING EDUCATION SESSION TRACKS (color-coded)	SCIENTIFIC SESSION TRACKS (color-coded in GOLD)
Cardiovascular Track	
Brain Imaging Track	Cardio (Room West 217/219) = Cardiovascular
Oncology & Therapy Track	Neuro (Room West 215/216) = Neurosciences
Molecular Imaging Track	GCS (Room West 212) = General Clinical Specialities
General Nuclear Medicine Track	Onc-Basic (Room West 224) = Oncology: Basic, Translational & Therapy
Basic Science Track	Onc-Clinical (Room West 221/222) = Oncology: Clinical Diagnosis
Pediatrics Track	Inst & DA (Room West 208/209) = Instrumentation & Data Analysis
PET/CT Track	Mol Targ Probes (Room West 220) = Molecular Targeting Probes
CTN Track	Extra (Room West 210) = Extra room for ALL tracks (overflow sessions)
Radiopharmaceutical Sciences Track	
Anatomical Imaging Track	

* These sessions have been submitted to the American Board of Nuclear Medicine (ABNM) for SAM qualification and are pending approval. The final approved list is located at the CE booth.

Monday, June 10, 2013

8:00AM - 9:30AM	Plenary Session - Anger Lecture (East Building - Exhibit Hall A)												
9:30AM - 10:00AM	Visit the Exhibits												
	Continuing Education Sessions						Scientific Sessions (Abstracts)						
	W. 213/214	W. 201	W. Ballroom A KWE	W. Ballroom B KWE	W. 205/207	W. 203/204	W. 220	W. 224	W. 221/222	W. 217/219	W. 215/216	W. 212	W. 208/209	W. 210
							Mol Targ Probes	Onc-Basic	Onc-Clinical	Cardio	Neuro	GCS	Instr & DA	Extra
10:00AM - 11:30AM	Cardiac PET Versus SPECT in Assessing CAD: Objective Evidence or Publication Bias Towards Cardiac MRI?	New Molecular Imaging Agent Validation for Research and Clinical Applications	KWE: Dementia Brain PET and SPECT	Sodium Fluoride - 18 Bone Scanning *	Neuroendocrine Tumors and Personalized Medicine	PET/CT and Molecular Imaging in the Management of Malignant Melanoma	Session 17: INTEGRATED Session: Tumor Angiogenesis - Biology and Imaging	Session 18: Radio-immunotherapy	Session 19: Molecular Imaging of Breast Cancer III	Session 20: INTEGRATED Session: Novel Cardiovascular Molecular Imaging Probes	Session 21: INTEGRATED Session: Inflammation Imaging and Neurological Disease	Session 22: Parathyroid Imaging	Session 23: INTEGRATED Session: Simultaneous PET/MR Imaging	Session 24: Miscellaneous (Neuroscience track)
11:30AM - 12:30PM	Visit the Exhibits													
12:30PM - 2:00PM	PET/MRI - How What? - Part I	Updates on Cardiac PET Perfusion Tracers	Imaging for Pulmonary Embolism: A Current Status Report *	Nuclear Medicine, Archiving, and PACS *	CT and PET/CT Anatomy and Pathology - Abdomen and Pelvis	Challenges and Opportunities for Hybrid Imaging in Developing Countries	Session 25: Radiopharmacy	Session 26: Quantitative Assessment of Therapy Response	Session 27: INTEGRATED Session: Lymphoma	Session 28: Atherosclerosis and Inflammation	Session 29: Movement Disorders	Session 30: INTEGRATED Session: Endocrine/ Neuroendocrine	Session 31: Brain	Session 32: Oncology (Instr & Data Analysis track)
2:00PM - 2:30PM	Visit the Exhibits													
2:30PM - 4:00PM	Certificate Presentations or Poster Award Winners for the Following Tracks in West Exhibit Hall A: Educational Exhibits, Oncology-Basic, Oncology-Clinical, Molecular Targeting Probes (2:30PM - 2:45PM)						"Meet the Author" Poster Session I, featuring poster presenters from the following scientific tracks: EDUCATIONAL EXHIBITS, ONCOLOGY: BASIC, TRANSLATIONAL & THERAPY, ONCOLOGY: CLINICAL DIAGNOSIS, TECHNOLOGIST						
3:30PM - 4:00PM	PET/MRI - How What? - Part II	Radiotherapy	Coronary CTA - A Primer *	Optimal Reporting of Oncologic PET/CT Studies *	Lung Imaging - From Planar to SPECT and PET with CT	Fukushima Nuclear Power Plant Accident: Medical Emergency, Radiation Exposure, & Food Contamination	Computer and Instrumentation Basic Science Summary Session West Building 109/110							
4:00PM - 4:30PM	Visit the Exhibits													
4:30PM - 6:00PM	Multimodality Imaging	PET/MRI - The Advent of New Applications	KWE: Pediatric Nuclear Medicine	SPECT/CT in Thyroid and Parathyroid Disease *	Future of PET Drug Monographs in USP: Responding to the Sunset of the FDA Modernization Act	Novel Targeted Radionuclide Therapy	Session 33: I-18 Labeled Probes for Oncology	Session 34: SIRT, Miscellaneous	Session 35: Other Tumors	Session 36: Electrophysiology and Heart Failure	Session 37: It's a Small World: Rodent Models for Imaging Neurological & Psychiatric Disorders	Session 38: Musculoskeletal PET & Experimental Imaging	Session 39: Modeling Methods	Session 40: Image Generation: SPECT & CT (Instr & Data Analysis track)

Exhibit Hall Hours for Monday: 9:30AM to 4:30PM

West Building - Ballroom A & B use interactive "Read With the Experts" technology. Audience members may respond to speaker questions by submitting their answers via a keypad.

CONTINUING EDUCATION SESSION TRACKS (color-coded)	SCIENTIFIC SESSION TRACKS (color-coded in GOLD)
Cardiovascular Track	Cardio (Room West 217/219) = Cardiovascular
Brain Imaging Track	Neuro (Room West 215/216) = Neurosciences
Oncology & Therapy Track	GCS (Room West 212) = General Clinical Specialties
Molecular Imaging Track	Onc-Basic (Room West 224) = Oncology: Basic, Translational & Therapy
General Nuclear Medicine Track	Onc-Clinical (Room West 221/222) = Oncology: Clinical Diagnosis
Basic Science Track	Instr & DA (Room West 208/209) = Instrumentation & Data Analysis
Pediatrics Track	Mol Targ Probes (Room West 220) = Molecular Targeting Probes
PET/CT Track	Extra (Room West 210) = Extra room for ALL tracks (overflow sessions)
CTN Track	
Radiopharmaceutical Sciences Track	
Anatomical Imaging Track	

* These sessions have been submitted to the American Board of Nuclear Medicine (ABNM) for SAM qualification and are pending approval. The final approved list is located at the CE booth.

Tuesday, June 11, 2013

	Continuing Education Sessions						Scientific Sessions (Abstracts)							
	W. 213/214	W. 301	W. Ballroom A RWE	W. Ballroom B RWE	W. 303/307	W. 302/304	W. 220	W. 224	W. 221/222	W. 217/219	W. 215/216	W. 212	W. 208/209	W. 210
							Mol Targ Probes	Onc-Basic	Onc-Clinical	Cardio	Neuro	GCS	Inst & DA	Extra
8:00AM - 9:30AM	Assessment of Ventricular Function and Synchrony	Intraoperative Imaging	Bone Scintigraphy *	CT Case Review for Nuclear Medicine Physicians 7:30AM - 9:30AM Head & Neck (Cases 1-12) *	Quantitative SPECT for Dosimetry in Radionuclide Therapy	FDA and NIH: Critical Concepts for Diagnostic Radiopharmaceutical Research	Session 41: Multimodality Probes for Oncological Imaging	Session 42: Clinical Pilot Studies	Session 43: Prostate/GU I	Session 44: PET/MR and PET/CT Hybrid Imaging	Session 45: Tau and Amyloid Imaging	Session 46: Thyroid Cancer Update I	Session 47: Organ Imaging	Session 48: Preclinical Probes for Neuroimaging: Oral I (Molecular Targeting Probes track)
9:45AM - 11:15AM	Ultra-Low Dose CT in PET/CT	The DOTA Debate: Approaches to Imaging Neuroendocrine Tumors	Diuretic Renography *	9:45AM - 11:45AM Head & Neck (Cases 13-25) *	Vulnerable Plaque Imaging	Amyloid PET: SNMMI-AA Appropriate Use Criteria	Session 49: Probes for Oncology: Monitoring Therapy	Session 50: Technical Advances	Session 51: Prostate/GU II	Session 52: Myocardial PET: Perfusion and Function	Session 53: Brain Tumors	Session 54: Thyroid Cancer Update II	Session 55: Quantification	Session 56: Preclinical Probes for Neuroimaging: Oral II (Molecular Targeting Probes track)
11:15AM - 12:30PM	Visit the Exhibits													
12:30PM - 2:00PM	Tom Miller Memorial Lecture: Optimized Nuclear Medicine Training in the Era of Hybrid Imaging	90 Yttrium - Microsphere Radio-embolization for Treatment of Hepatocarcinoma	Dopamine Transporter Imaging in Parkinson Syndromes: Difficult Case Studies *	CT Case Review for Nuclear Medicine Physicians 1:00PM - 3:00PM Chest (Cases 26-37) *	Preclinical Molecular Tracers and Techniques in Cardiovascular Imaging: What is on the Horizon?	Robert Lull Memorial Lecture: Growing into Mentorship	Session 57: Preclinical Probes: Cardiovascular, Endocrine, and Other	Session 58: Molecular Characterization	Session 59: Molecular Imaging of Gynecological Malignancies	Session 60: New Techniques	Session 61: Evaluation of Tracers for CNS Targets	Session 62: Musculoskeletal SPECT & SPECT/CT Imaging	Session 63: Detector Instrumentation	Session 64: Leukemia/ Lymphoma/ Myeloma (Onc, Clinical Diagnosis track)
2:00PM - 2:45PM	Visit the Exhibits													
2:45PM - 4:15PM	Certificate Presentations or Poster Award Winners for the Following Tracks in West Building Exhibit Hall A: Cardiovascular, Neurosciences, General Clinical Specialties, Instrumentation & Data Analysis (2:45PM - 3:00PM)						"Meet the Author" Poster Session II, featuring poster presenters from CARDIOVASCULAR, NEUROSCIENCES, GENERAL CLINICAL SPECIALTIES, INSTRUMENTATION & DATA ANALYSIS							
2:45PM - 4:15PM	Pediatric Functional/Metabolic Brain Imaging	Coronary Update	Non-coronary Artery Disease Applications of Nuclear Cardiology *	CT Case Review for Nuclear Medicine Physicians 3:15PM - 5:15PM Chest (Cases 38-50) *	Practical Issues and Calculations in Nuclear Medicine Dosimetry	Management of Thyroid Cancer	Session 65: Multimodality & Non-Radioactive Molecular Imaging Probes	Session 66: New Imaging Approaches	Session 67: Head & Neck I	Session 68: Flow Tracers	Session 69: Prediction of Cognitive Dysfunction & Multimodal Imaging	Session 70: Pediatric Oncology/PET I	Session 71: Human Imaging Instrumentation	Session 72: Image Generation: Motion (Inst & Data Analysis track)
4:15PM - 4:30PM	Break													
4:30PM - 5:00PM	Imaging Cardiac Innervation	Kuhl-Lassen Award Lecture	Hepatobiliary Imaging: The State of the Art *	CT Case Review for Nuclear Medicine Physicians 3:15PM - 5:15PM Chest (Cases 38-50) *	Update on Gallium-68 Generators and Radio-pharmaceuticals	Progress Toward Non-Reactor Based Tc-99m Production Alternatives	Session 73: Advances in Radioiodination & Chelation of Radiometals	Session 74: Response Assessment	Session 75: Head & Neck II	Session 76: Myocardial SPECT: Perfusion and Function	Session 77: New Paradigms & Methods in CNS Imaging	Session 78: Pediatric Oncology/ General II	Session 79: Data Management & Instrumentation: Motion	Session 80: GI: Non-Colorectal (Onc, Clinical Diagnosis track)

Exhibit Hall Hours for Tuesday: 9:30AM to 3:00PM

West Building - Ballroom A & B use interactive "Read With the Experts" technology. Audience members may respond to speaker questions by submitting their answers via a keypad.

CT Workshop Sessions will offer Category A+ Credits

CONTINUING EDUCATION SESSION TRACKS (color-coded)

- Cardiovascular Track
- Brain Imaging Track
- Oncology & Therapy Track
- Molecular Imaging Track
- General Nuclear Medicine Track
- Basic Science Track
- Pediatrics Track
- PET/CT Track
- CTN Track
- Radiopharmaceutical Sciences Track
- Anatomical Imaging Track

SCIENTIFIC SESSION TRACKS (color-coded in GOLD)

Cardio (Room West 217/219) = Cardiovascular

Neuro (Room West 215/216) = Neurosciences

GCS (Room West 212) = General Clinical Specialties

Onc-Basic (Room West 224) = Oncology: Basic, Translational & Therapy

Onc-Clinical (Room West 221/222) = Oncology: Clinical Diagnosis

Inst & DA (Room West 208/209) = Instrumentation & Data Analysis

Mol Targ Probes (Room West 220) = Molecular Targeting Probes

Extra (Room West 210) = Extra room for ALL tracks (overflow sessions)

* These sessions have been submitted to the American Board of Nuclear Medicine (ABNM) for SAM qualification and are pending approval. The final approved list is located at the CE booth.

Wednesday, June 12, 2013

	Continuing Education Sessions				Scientific Sessions (Abstracts)								
	W. Ballroom A RWE	W. Ballroom B RWE	W. 202/204	W. 205/207	W. 220	W. 224	W. 221/222	W. 217/219	W. 215/216	W. 212	W. 208/209	W. 210	W. 213/214
					Mol Targ Probes	GCS I	Onc-Clinical	Onc-Clinical II	Onc-Basic	GCS II	Inst & DA	Onc-Clinical III	Extra
8:00AM - 9:30AM	RWE: SPECT and PET Myocardial Perfusion Imaging	CT Case Review for Nuclear Medicine Physicians 7:30AM - 9:30AM Abdomen & Pelvis (Cases 51-62) *	Road to Translation - Addressing the Challenges		Session 81: Novel Oncology Probes and Chemistry	Session 82: Nephrourology	Session 83: Lung Cancer I	Session 84: GI: Colorectal & Liver I	Session 85: Peptide Receptor Radionuclide Therapy	Session 86: Advances in GI Imaging: PET, SPECT, & Gen Nuclear Scintigraphy	Session 87: Small Animal Imaging Instrumentation	Session 88: Sarcoma/ Melanoma I	Session 89: Automation & Development (Molecular Targeting Probes track)
9:45AM - 11:15AM	Optimizing SPECT Myocardial Perfusion Imaging and Stress Protocols for Your Laboratory *	9:45AM - 11:45AM Abdomen & Pelvis (Cases 63-75) *	Integrating PET/CT Into Radiation Therapy	Imaging for PET Probe Development From Idea to IND	Session 90: Advances in Carbon-11 & Fluorine-18 Radiochemistry	Session 91: Pulmonary Embolism, Hypertension, Segmental Perfusion, Inflammation, & More	Session 92: Lung Cancer II	Session 93: GI: Colorectal & Liver II	Session 94: Image-Guided Therapy	Session 95: Infectious Disease/ Hematology	Session 96: Image Generation: Luminescence & PET/MR	Session 97: Sarcoma/ Melanoma II	
11:30AM - 1:15PM	Presentation of Annual Meeting Highlights (West Building - Ballroom A)												
12:30PM - 2:30PM		CT Case Review for Nuclear Medicine Physicians 1:00PM - 3:00PM Musculoskeletal (Cases 76-87) *											
2:45PM - 4:45PM		3:15PM - 5:15PM Musculoskeletal (Cases 88-100) *											

CT Workshop Sessions will offer Category A+ Credits

CONTINUING EDUCATION SESSION TRACKS (color-coded)	SCIENTIFIC SESSION TRACKS (color-coded in GOLD)
Cardiovascular Track	
Brain Imaging Track	Onc-Clinical (Room West 217/219) = Oncology: Clinical Diagnosis
Oncology & Therapy Track	Onc-Basic (Room West 215/216) = Oncology: Basic, Translational & Therapy
Molecular Imaging Track	GCS (Room West 212) = General Clinical Specialities
General Nuclear Medicine Track	GCS (Room West 224) = General Clinical Specialities
Basic Science Track	Onc-Clinical (Room West 221/222) = Oncology: Clinical Diagnosis
Pediatrics Track	Inst & DA (Room West 208/209) = Instrumentation & Data Analysis
PET/CT Track	Mol Targ Probes (Room West 220) = Molecular Targeting Probes
CTN Track	Onc-Clinical (Room West 210) = Oncology: Clinical Diagnosis
Radiopharmaceutical Sciences Track	Extra (Room West 213/214) = Extra room for ALL tracks (overflow sessions)
Anatomical Imaging Track	

* These sessions have been submitted to the American Board of Nuclear Medicine (ABNM) for SAM qualification and are pending approval. The final approved list is located at the CE booth.

附錄二、拜耳公司已獲 FDA 批准之新藥 Xofigo（二氯化鐳-223）仿單資訊。

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOFIGO™ safely and effectively. See full prescribing information for XOFIGO.

Xofigo (radium Ra 223 dichloride) Injection, for intravenous use

Initial U.S. Approval: 2013

INDICATIONS AND USAGE

Xofigo is an alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. (1)

DOSAGE AND ADMINISTRATION

The dose regimen of Xofigo is 50 kBq (1.35 microcurie) per kg body weight, given at 4 week intervals for 6 injections. (2.1)

DOSAGE FORMS AND STRENGTHS

Single-use vial at a concentration of 1,000 kBq/mL (27 microcurie/mL) at the reference date with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date (3)

CONTRAINDICATIONS

Pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression: Measure blood counts prior to treatment initiation and before every dose of Xofigo. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after treatment. Monitor patients with compromised bone marrow reserve closely. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care measures. (5.1)

ADVERSE REACTIONS

The most common adverse drug reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema.

The most common hematologic laboratory abnormalities (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

SEE 17 FOR PATIENT COUNSELING INFORMATION

Revised: 05/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Xofigo is not approved for sale in Canada

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The dose regimen of Xofigo is 50 kBq (1.35 microcurie) per kg body weight, given at 4 week intervals for 6 injections. Safety and efficacy beyond 6 injections with Xofigo have not been studied.

The volume to be administered to a given patient should be calculated using the:

- Patient's body weight (kg)
- Dosage level 50 kBq/kg body weight or 1.35 microcurie/kg body weight
- Radioactivity concentration of the product (1,000 kBq/mL; 27 microcurie/mL) at the reference date
- Decay correction factor to correct for physical decay of radium-223.

The total volume to be administered to a patient is calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 50\ \text{kBq/kg body weight}}{\text{Decay factor} \times 1{,}000\ \text{kBq/mL}}$$

or

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 1.35\ \text{microcurie/kg body weight}}{\text{Decay factor} \times 27\ \text{microcurie/mL}}$$

Table 1: Decay Correction Factor Table

Days from Reference Date	Decay Factor	Days from Reference Date	Decay Factor
-14	2.296	0	0.982
-13	2.161	1	0.925
-12	2.034	2	0.870
-11	1.914	3	0.819
-10	1.802	4	0.771
-9	1.696	5	0.725
-8	1.596	6	0.683
-7	1.502	7	0.643
-6	1.414	8	0.605
-5	1.330	9	0.569
-4	1.252	10	0.536
-3	1.178	11	0.504
-2	1.109	12	0.475
-1	1.044	13	0.447
		14	0.420

The Decay Correction Factor Table is corrected to 12 noon Central Standard Time (CST). To determine the decay correction factor, count the number of days before or after the reference date. The Decay Correction Factor Table includes a correction to account for the 7 hour time difference between 12 noon Central European Time (CET) at the site of manufacture and 12 noon US CST, which is 7 hours earlier than CET.

Immediately before and after administration, the net patient dose of administered Xofigo should be determined by measurement in an appropriate radioisotope dose calibrator that has been calibrated with a National Institute of Standards and Technology (NIST) traceable radium-223 standard (available upon request from Bayer) and corrected for decay using the date and time of calibration. The dose calibrator must be calibrated with nationally recognized standards, carried out at the time of commissioning, after any maintenance procedure that could affect the dosimetry and at intervals not to exceed one year.

2.2 Administration

Administer Xofigo by slow intravenous injection over 1 minute.

Flush the intravenous access line or cannula with isotonic saline before and after injection of Xofigo.

2.3 Instructions for Use/Handling

General warning

Xofigo (an alpha particle-emitting pharmaceutical) should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal Xofigo are subject to the regulations and/or appropriate licenses of the competent official organization.

Xofigo should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Radiation protection

The administration of Xofigo is associated with potential risks to other persons (e.g., medical staff, caregivers and patient's household members) from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

For drug handling

Follow the normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns when handling blood and bodily fluids to avoid contamination. In case of contact with skin or eyes, the affected area should be flushed immediately with water. In the event of spillage of Xofigo, the local radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. A complexing agent such as 0.01 M ethylene-diamine-tetraacetic acid (EDTA) solution is recommended to remove contamination.

For patient care

Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. When handling bodily fluids, simply wearing gloves and hand washing will protect caregivers. Clothing soiled with Xofigo or patient fecal matter or urine should be washed promptly and separately from other clothing.

Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is expected to be low, because the typical treatment activity will be below 8,000 kBq (216 microcurie). In keeping with the **A**s **L**ow **A**s **R**easonably **A**chievable (ALARA) principle for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

The gamma radiation associated with the decay of radium-223 and its daughters allows for the radioactivity measurement of Xofigo and the detection of contamination with standard instruments.

Instructions for preparation

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Xofigo is a ready-to-use solution and should not be diluted or mixed with any solutions. Each vial is for single use only.

Dosimetry

The absorbed radiation doses in major organs were calculated based on clinical biodistribution data in five patients with castration-resistant prostate cancer. Calculations of absorbed radiation doses were performed using OLINDA/EXM (**O**rgan **L**evel **IN**ternal **D**ose **A**ssessment/**EX**ponential **M**odeling), a software program based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For radium-223, which is primarily an alpha particle-emitter, assumptions were made for intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed radiation dose calculations for Xofigo, considering its observed biodistribution and specific characteristics.

The calculated absorbed radiation doses to different organs are listed in Table 2. The organs with highest absorbed radiation doses were bone (osteogenic cells), red marrow, upper large intestine wall, and lower large intestine wall. The calculated absorbed doses to other organs are lower.

Table 2: Calculated Absorbed Radiation Doses to Organs

Target Organ	Mean (Gy/MBq)	Mean (rad/mCi)	Coefficient of Variation (%)
Adrenals	0.00012	0.44	56
Brain	0.00010	0.37	80
Breasts	0.00005	0.18	120
Gallbladder wall	0.00023	0.85	14
LLI[1] Wall	0.04645	171.88	83
Small intestine wall	0.00726	26.87	45
Stomach wall	0.00014	0.51	22
ULI[2] wall	0.03232	119.58	50
Heart wall	0.00173	6.40	42
Kidneys	0.00320	11.86	36
Liver	0.00298	11.01	36
Lungs	0.00007	0.27	90
Muscle	0.00012	0.44	41
Ovaries	0.00049	1.80	40
Pancreas	0.00011	0.41	43
Red marrow	0.13879	513.51	41
Osteogenic cells	1.15206	4262.60	41
Skin	0.00007	0.27	79
Spleen	0.00009	0.33	54
Testes	0.00008	0.31	59
Thymus	0.00006	0.21	109
Thyroid	0.00007	0.26	96
Urinary bladder wall	0.00403	14.90	63
Uterus	0.00026	0.94	28
Whole body	0.02311	85.50	16

[1]LLI: lower large intestine
[2]ULI: upper large intestine

3 DOSAGE FORMS AND STRENGTHS

Xofigo (radium Ra 223 dichloride injection) is available in single-use vials containing 6 mL of solution at a concentration of 1,000 kBq/mL (27 microcurie/mL) at the reference date with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date.

4 CONTRAINDICATIONS

Xofigo is contraindicated in pregnancy.

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Xofigo is not indicated for use in women. Xofigo is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

In the randomized trial, 2% of patients on the Xofigo arm experienced bone marrow failure or ongoing pancytopenia compared to no patients treated with placebo. There were two deaths due to bone marrow failure and for 7 of 13 patients treated with Xofigo, bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients on the Xofigo arm and 2% on the placebo arm permanently discontinued therapy due to bone marrow suppression.

In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) were similar for patients treated with Xofigo and placebo. Myelosuppression; notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia; has been reported in patients treated with Xofigo. In the randomized trial, complete blood counts (CBCs) were obtained every 4 weeks prior to each dose and the nadir CBCs and times of recovery were not well characterized. In a separate single-dose phase 1 study of Xofigo, neutrophil and platelet count nadirs occurred 2 to 3 weeks after Xofigo administration at doses that were up to 1 to 5 times the recommended dose, and most patients recovered approximately 6 to 8 weeks after administration *[see Adverse Reactions (6)]*.

Hematologic evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration of Xofigo, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L and hemoglobin ≥ 10 g/dL. Before subsequent administrations of Xofigo, the ANC should be $\geq 1 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L. If there is no recovery to these values within 6 to 8 weeks after the last administration of Xofigo, despite receiving supportive care, further treatment with Xofigo should be discontinued. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

The safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use with chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer with bone metastases, 600 patients received intravenous injections of 50 kBq/kg (1.35 microcurie/kg) of Xofigo and best standard of care and 301 patients received placebo and best standard of care once every 4 weeks for up to 6 injections. Prior to randomization, 58% and 57% of patients had received docetaxel in the Xofigo and placebo arms, respectively. The median duration of treatment was 20 weeks (6 cycles) for Xofigo and 18 weeks (5 cycles) for placebo.

The most common adverse reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema (Table 3). Grade 3 and 4 adverse events were reported among 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in Xofigo-treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (Table 4).

Treatment discontinuations due to adverse events occurred in 17% of patients who received Xofigo and 21% of patients who received placebo. The most common hematologic laboratory abnormalities leading to discontinuation for Xofigo were anemia (2%) and thrombocytopenia (2%).

Table 3 shows adverse reactions occurring in ≥ 2% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 3: Adverse Reactions in the Randomized Trial

System/Organ Class Preferred Term	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and lymphatic system disorders				
Pancytopenia	2	1	0	0
Gastrointestinal disorders				
Nausea	36	2	35	2
Diarrhea	25	2	15	2
Vomiting	19	2	14	2
General disorders and administration site conditions				
Peripheral edema	13	2	10	1
Renal and urinary disorders				
Renal failure and impairment	3	1	1	1

Laboratory Abnormalities

Table 4 shows hematologic laboratory abnormalities occurring in ≥ 10% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 4: Hematologic Laboratory Abnormalities

Hematologic Laboratory Abnormalities	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Anemia	93	6	88	6
Lymphocytopenia	72	20	53	7
Leukopenia	35	3	10	<1
Thrombocytopenia	31	3	22	<1
Neutropenia	18	2	5	<1

Laboratory values were obtained at baseline and prior to each 4-week cycle.

As an adverse reaction, grade 3-4 thrombocytopenia was reported in 6% of patients on Xofigo and in 2% of patients on placebo. Among patients who received Xofigo, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel naïve patients and in 3% of patients who have received prior docetaxel.

Fluid Status

Dehydration occurred in 3% of patients on Xofigo and 1% of patients on placebo. Xofigo increases adverse reactions such as diarrhea, nausea, and vomiting which may result in dehydration. Monitor patients' oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia.

Injection Site Reactions

Erythema, pain, and edema at the injection site were reported in 1% of patients on Xofigo.

Secondary Malignant Neoplasms

Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Due to its mechanism of action and neoplastic changes, including osteosarcomas, in rats following administration of radium-223 dichloride, Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms *[see Nonclinical Toxicology (13.1)]*. However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs. 2%; respectively), but the expected latency period for the development of secondary malignancies exceeds the duration of follow up for patients on the trial.

Subsequent Treatment with Cytotoxic Chemotherapy

In the randomized clinical trial, 16% patients in the Xofigo group and 18% patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy.

7 DRUG INTERACTIONS

No formal clinical drug interaction studies have been performed.

Subgroup analyses indicated that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of Xofigo in the randomized clinical trial.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category X *[see Contraindications (4)]*

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of Xofigo in pregnancy and Xofigo is not indicated for use in women, maternal use of a radioactive therapeutic agent could affect development of a fetus. Xofigo is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with Xofigo.

8.3 Nursing Mothers

Xofigo is not indicated for use in women. It is not known whether radium-223 dichloride is excreted in human milk. Because many drugs are excreted in human milk, and because of potential for serious adverse reactions in nursing infants from Xofigo, a decision should be made whether to discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Xofigo in pediatric patients have not been established.

In single- and repeat-dose toxicity studies in rats, findings in the bones (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganization of the physis/growth line) and teeth (missing, irregular growth, fibro-osseous lesions in bone socket) correlated with a reduction of osteogenesis that occurred at clinically relevant doses beginning in the range of 20 – 80 kBq (0.541 - 2.16 microcurie) per kg body weight.

8.5 Geriatric Use

Of the 600 patients treated with Xofigo in the randomized trial, 75% were 65 years of age and over and while 33% were 75 years of age and over. No dosage adjustment is considered necessary in elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

No dedicated hepatic impairment trial for Xofigo has been conducted. Since radium-223 is neither metabolized by the liver nor eliminated via the bile, hepatic impairment is unlikely to affect the pharmacokinetics of radium-223 dichloride *[see Clinical Pharmacology (12.3)]*. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with mild hepatic impairment. No dose adjustments can be recommended for patients with moderate or severe hepatic impairment due to lack of clinical data.

8.7 Patients with Renal Impairment

No dedicated renal impairment trial for Xofigo has been conducted. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with existing mild (creatinine clearance [CrCl] 60 to 89 mL/min) or moderate (CrCl 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CrCl less than 30 mL/min) due to limited data available (n = 2) *[see Clinical Pharmacology (12.3)]*.

8.8 Males of Reproductive Potential

Contraception

Because of potential effects on spermatogenesis associated with radiation, advise men who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective contraceptive method during and for 6 months after completing treatment with Xofigo.

Infertility

There are no data on the effects of Xofigo on human fertility. There is a potential risk that radiation by Xofigo could impair human fertility *[see Nonclinical Toxicology (13.1)]*.

10 OVERDOSAGE

There have been no reports of inadvertent overdosing of Xofigo during clinical studies.

There is no specific antidote. In the event of an inadvertent overdose of Xofigo, utilize general supportive measures, including monitoring for potential hematological and gastrointestinal toxicity, and consider using medical countermeasures such as aluminum hydroxide, barium sulfate, calcium carbonate, calcium gluconate, calcium phosphate, or sodium alginate.[1]

Single Xofigo doses up to 250 kBq (6.76 microcurie) per kg body weight were evaluated in a phase 1 clinical trial and no dose-limiting toxicities were observed.

11 DESCRIPTION

Radium Ra 223 dichloride, an alpha particle-emitting pharmaceutical, is a radiotherapeutic drug.

Xofigo is supplied as a clear, colorless, isotonic, and sterile solution to be administered intravenously with pH between 6 and 8.

Each milliliter of solution contains 1,000 kBq radium-223 dichloride (27 microcurie), corresponding to 0.53 ng radium-223, at the reference date. Radium is present in the solution as a free divalent cation.

Each vial contains 6 mL of solution (6,000 kBq (162 microcurie) radium-223 dichloride at the reference date). The inactive ingredients are 6.3 mg/mL sodium chloride USP (tonicity agent), 7.2 mg/mL sodium citrate USP (for pH adjustment), 0.2 mg/mL hydrochloric acid USP (for pH adjustment), and water for injection USP.

The molecular weight of radium-223 dichloride, $^{223}RaCl_2$ is 293.9 g/mol.

Radium-223 has a half-life of 11.4 days. The specific activity of radium-223 is 1.9 MBq (51.4 microcurie)/ng.

The six-stage-decay of radium-223 to stable lead-207 occurs via short-lived daughters, and is accompanied predominantly by alpha emissions. There are also beta and gamma emissions with different energies and emission probabilities. The fraction of energy emitted from radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5 - 7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01 - 1.27 MeV).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active moiety of Xofigo is the alpha particle-emitting isotope radium-223 (as radium Ra 223 dichloride), which mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases (see Table 2). The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from radium-223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.

12.2 Pharmacodynamics

Compared with placebo, there was a significant difference in favor of Xofigo for all five serum biomarkers for bone turnover studied in a phase 2 randomized study (bone formation markers: bone alkaline phosphatase [ALP], total ALP and procollagen I N propeptide [PINP], bone resorption markers: C-terminal crosslinking telopeptide of type I collagen [S-CTX-I] and type I collagen crosslinked C-telopeptide [ICTP]).

12.3 Pharmacokinetics

The pharmacokinetics of radium-223 dichloride in blood was linear in terms of dose proportionality and time independence in the dose range investigated (46 to 250 kBq [1.24 to 6.76 microcurie] per kg body weight).

Distribution

After intravenous injection, radium-223 is rapidly cleared from the blood and is distributed primarily into bone or is excreted into intestine. Fifteen minutes post-injection, about 20% of the injected radioactivity remained in blood. At 4 hours, about 4% of the injected radioactivity remained in blood, decreasing to less than 1% at 24 hours after the injection. At 10 minutes post-injection, radioactivity was observed in bone and in intestine. At 4 hours post-injection, the percentage of the radioactive dose present in bone and intestine was approximately 61% and 49%, respectively. No significant uptake was seen in other organs such as heart, liver, kidneys, urinary bladder, and spleen at 4 hours post-injection *[see Dosage and Administration (2.3)]*.

Metabolism

Radium-223 is an isotope that decays and is not metabolized.

Elimination

The whole body measurements indicated that approximately 63% of the administered radioactivity was excreted from the body within 7 days after injection (after correcting for decay). Fecal excretion is the major route of elimination from the body. At 48 hours after injection, the cumulative fecal excretion was 13% (range 0 - 34%), and the cumulative urine excretion was 2% (range 1 - 5%). There was no evidence of hepato-biliary excretion based on imaging data.

The rate of elimination of radium-223 dichloride from the gastrointestinal tract is influenced by the high variability in intestinal transit rates across the population. Patients with a slower intestinal transit rate could potentially receive a higher intestinal radiation exposure. It is not known whether this will result in increased gastrointestinal toxicity.

Special Populations

Pediatric patients

Safety and effectiveness of Xofigo have not been established in children and adolescents below 18 years of age.

Patients with hepatic impairment

No dedicated pharmacokinetic study in patients with hepatic impairment has been conducted. However, since radium-223 is not metabolized and there is no evidence of

hepato-biliary excretion based on imaging data, hepatic impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

Patients with renal impairment

No dedicated pharmacokinetic study in patients with renal impairment has been conducted. However, since excretion in urine is minimal and the major route of elimination is via the feces, renal impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

12.6 Cardiac Electrophysiology

The effect of a single dose of 50 kBq/kg of radium-223 dichloride on the QTc interval was evaluated in a subgroup of 29 patients (21 received Xofigo and 8 received placebo) in the randomized clinical trial. No large changes in the mean QTc interval (i.e., greater than 20 ms) were detected up to 6 hours post-dose. The potential for delayed effects on the QT interval after 6 hours was not evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic potential of radium-223 dichloride. However, in repeat-dose toxicity studies in rats, osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses 7 to 12 months after the start of treatment. The presence of other neoplastic changes, including lymphoma and mammary gland carcinoma, was also reported in 12- to 15-month repeat-dose toxicity studies in rats.

Genetic toxicology studies have not been conducted with radium-223 dichloride. However, the mechanism of action of radium-223 dichloride involves induction of double-strand DNA breaks, which is a known effect of radiation.

Animal studies have not been conducted to evaluate the effects of radium-223 dichloride on male or female fertility or reproductive function. Xofigo may impair fertility and reproductive function in humans based on its mechanism of action.

14 CLINICAL STUDIES

The efficacy and safety of Xofigo were evaluated in a double-blind, randomized, placebo-controlled phase 3 clinical trial of patients with castration-resistant prostate cancer with symptomatic bone metastases. Patients with visceral metastases and malignant lymphadenopathy exceeding 3 cm were excluded. The primary efficacy endpoint was overall survival. A key secondary efficacy endpoint was time to first symptomatic skeletal event (SSE) defined as external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention. There were no scheduled radiographic assessments performed on study. All patients were to continue androgen deprivation therapy. At the cut-off date of the pre-planned interim analysis, a total of 809 patients had been randomized 2:1 to receive Xofigo 50 kBq (1.35 microcurie)/kg intravenously every 4 weeks for 6 cycles (n = 541) plus best standard of care or matching placebo plus best standard of care (n = 268). Best standard of care included local EBRT, corticosteroids, antiandrogens, estrogens, estramustine or ketoconazole. Therapy was continued until unacceptable toxicity or initiation of cytotoxic chemotherapy, other systemic radioisotope, hemi-body EBRT or other investigational drug. Patients with Crohn's disease, ulcerative colitis, prior hemibody radiation or untreated imminent spinal cord compression were excluded from the study. In patients with bone fractures, orthopedic stabilization was performed before starting or resuming treatment with Xofigo.

The following patient demographics and baseline disease characteristics were balanced between the arms. The median age was 71 (range 44-94) with a racial distribution of 94% Caucasian, 4% Asian, 2% Black and <1% Other. Patients were enrolled predominantly from Europe (85%) with 4% of patients enrolled from North America. ECOG performance status was 0-1 in 86% of patients. Eighty-five percent of patients had 6 or more bone scan lesions and of those 40% had > 20 lesions or a superscan. Opiate pain medications were used for cancer-related pain in 54% of patients, non-opiate pain medications in 44% of patients and no pain medications in 2% of patients. Patients were stratified by baseline ALP, bisphosphonate use, and prior docetaxel exposure. Prior bisphosphonates were used by 41% of patients and 58% had received prior docetaxel. During the treatment period, 83% of Xofigo patients and 82% of placebo patients received gonadotropin-releasing hormone agonists and 21% of Xofigo patients and 34% of placebo patients received concomitant antiandrogens. Use of systemic steroids (41%) and bisphosphonates (40%) was balanced between the arms.

The pre-specified interim analysis of overall survival revealed a statistically significant improvement in patients receiving XOFIGO plus best standard of care compared with patients receiving placebo plus best standard of care. An exploratory updated overall survival analysis performed before patient crossover with an additional 214 events resulted in findings consistent with the interim analysis (Table 5).

Table 5: Overall Survival Results from the Phase 3 Clinical Trial

	Xofigo	Placebo
Interim Analysis		
Subjects randomized	541	268
Number of deaths	191 (35.3%)	123 (45.9%)
Censored	350 (64.7%)	145 (54.1%)
Median survival (months) [a]	14.0	11.2
(95% CI)	(12.1, 15.8)	(9.0, 13.2)
p-value [b]	0.00185	
Hazard ratio (95% CI) [c]	0.695 (0.552, 0.875)	
Updated Analysis		
Subjects randomized	614	307
Number of deaths	333 (54.2%)	195 (63.5%)
Censored	281 (45.8%)	112 (36.5%)
Median survival (months) [a]	14.9	11.3
(95% CI)	(13.9, 16.1)	(10.4, 12.8)
Hazard ratio (95% CI) [c]	0.695 (0.581, 0.832)	

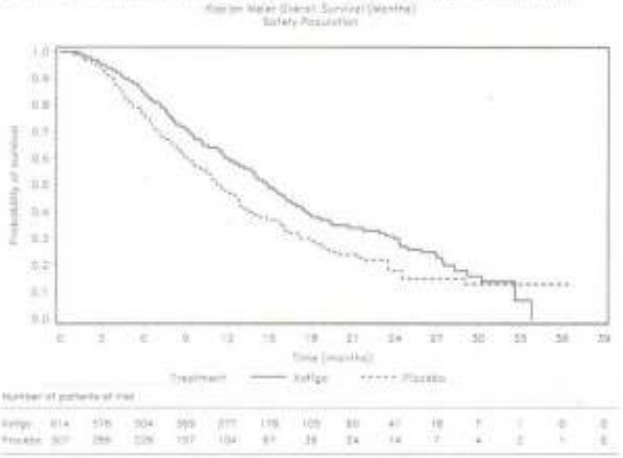
[a] Survival time is calculated as months from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.

[b] p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior use of docetaxel.

[c] Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel. Hazard ratio < 1 favors radium-223 dichloride.

The Kaplan-Meier curves for overall survival based on the updated survival results are shown in Figure 1.

Figure 1: Kaplan-Meier Overall Survival Curves from the Phase 3 Clinical Trial



The survival results were supported by a delay in the time to first SSE favoring the Xofigo arm. The majority of events consisted of external beam radiotherapy to bone metastases.

15 REFERENCES

1. Radiation Emergency Medical Management. [REMM/National Library of Medicine Website.] http://www.remm.nlm.gov/int_contamination.htm#blockingagents

16 HOW SUPPLIED/STORAGE AND HANDLING

Xofigo (radium Ra 223 dichloride injection) is supplied in single-use vials containing 6 mL of solution at a concentration of 1,000 kBq/mL (27 microcurie/mL) with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date (NDC 50419-208-01).

Store at room temperature, below 40° C (104° F). Store Xofigo in the original container or equivalent radiation shielding.

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

Follow procedures for proper handling and disposal of radioactive pharmaceuticals *[see Dosage and Administration (2.3)]*.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To be compliant with blood cell count monitoring appointments while receiving Xofigo. Explain the importance of routine blood cell counts. Instruct patients to report signs of bleeding or infections.
- To stay well hydrated and to monitor oral intake, fluid status, and urine output while being treated with Xofigo. Instruct patients to report signs of dehydration, hypovolemia, urinary retention, or renal failure / insufficiency.
- There are no restrictions regarding contact with other people after receiving Xofigo. Follow good hygiene practices while receiving Xofigo and for at least 1 week after the last injection in order to minimize radiation exposure from bodily fluids to household members and caregivers. Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing. Caregivers should use universal precautions for patient care such as gloves and barrier gowns when handling bodily fluids to avoid contamination. When handling bodily fluids, wearing gloves and hand washing will protect caregivers.
- Who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective method of birth control during treatment and for 6 months following completion of Xofigo treatment.

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Bayer HealthCare
Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470
Manufactured in Norway

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