報告人姓名 | 林育駿 | 系所及年級 | 電機所博士班三年級 |
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會議期間 | 99/09/08 – 99/09/11 | 檢定補助日期 | 年 月 日 |
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會議名稱 | (中文) 世界分子影像會議 |
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<td>(英文) World Molecular Imaging Congress</td>
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發表論文題目 (請附論文全文) | (中文) 以藥物動力學模型使用在動態磁振造影評估腦部轉移腫瘤在細微血管狀況。 |
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<td>(英文) Assessment of tumor microvasculature in brain metastasis by pharmacokinetic model using dynamic MRI.</td>
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Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was proposed to investigate the microvascular structure. The pharmacokinetics of injected contrast agents were tracked by MRI as they pass through the tumor vasculature. Quantitative parameters can be derived, which reflected the treatment responses in primary tumors. The purpose of the study was to explore the induced changes from metastatic tumors in patients with brain metastasis from breast cancer. Patients of breast cancer with brain metastasis underwent radiotherapy and/or chemotherapy. Imaging of the brain were performed before and one month after treatment using a 3 Tesla MRI scanner. Contiguous 3D volumes were obtained with a gradient echo sequence and a rapid intravenous bolus injection (0.1 mmol/kg) of Gadopentetate dimeglumine. 120 volumes were acquired with the temporal resolution of 2.6 seconds. Quantitative DCE parametric maps were reconstructed based on two-compartment model, including the vascular plasma volume (Vp), transcapillary contrast agent transfer constant (Ktrans) and extracellular extravascular volume (Ve). The derived parameters at regions of tumors as well as the tumor volumes were compared before and after treatment. The findings showed that the microenvironment from a metastatic...
tumor can be modified by radiotherapy and/or chemotherapy. The vascular permeability within the tumor could be decreased, as reflected in the reductions in Ktrans immediately after the treatment. It could suggest an early sign of the tumor response to the treatment, because of the disruption of vasculatures. The changes of Ve and Vp could be a reflection of the temporal evolutions from the therapeutic intervention. Decreased tumor volume was expected at a later stage. The findings obtained from the DCE derived indices are consistent with the expected biological effect. The underlying mechanism quarantines the worth of further investigation.

In summary, Dynamic MRI enables quantification of the tumor vascularity and permeability, hence could serve as a potential surrogating biomarker for treatment response for patients with brain metastasis.
參加 2010 世界分子影像會議報告

長庚大學電機所博士班 林育駿

2010/09/16

一、參加會議經過

世界分子影像會議 (World Molecular Imaging Congress, WMIC) 是由四個國際性學會 (SMI, AMI, FASMI, and ESMI) 所聯合舉辦的學術研討會，每年在世界不同國家舉辦。今年首次移至日本京都舉辦，格外吸引了許多亞洲各國人員前往參加。近年這個會議參加的人數愈來愈多，今年大會總共接受了 1150 篇論文發表，其中我們長庚大學與長庚醫院今年成果特別豐碩，共發表 10 篇論文。

會議是在京都的國際會議中心舉行，進行內容包括第一天的教育課程 Education workshop 及後三天進行各項研究口頭報告、壁報展示及特定議題的演講。主要探討的議題除了以往的各種動物影像的研究，今年有更多的轉譯型研究以及臨床研究也都納入這次的會議中。所有發表的論文摘要將會被刊登在 SMI, AMI 及 ESMI 的官方期刊 "Molecular Imaging and Biology" 的副刊上。

二、與會心得

這是我第一次參加此會議，跟以往所參加專門針對 MRI 議題的會議有很多不同的感受。這個會議強調的研究重心是從實驗動物到臨床試驗的一系列的轉譯研究，由於我本身的研究方向是以 MRI 探討腫瘤微環境的變化，在許多研究的議題需要探討到細胞層級的生物變化，而目前大部份在這個層級的功能性影像的研究主要是以核子醫學的的藥物製作標記各種不同的細胞進而達到細胞追蹤及反應偵測的效果。近幾年，愈來愈多研究人員也開始使用 MRI 的造影劑包埋各種藥物同時進行細胞追蹤以及疾病治療。所以對我本身而言此行最主要目的是想
進一步了解其他影像工具在分子影像的領域的最新進展，希望能激發自己本身研究的更多靈感，探討在MRI與其他影像工具的強弱及利用其他工具協助研究的進行。

針對幾個和MRI在腫瘤比較相關的題目，整理心得如下:

1. Prof. Robert Gillies, from Moffitt Cancer Center, Tampa, USA, was invited for a keynote speech entitled “Targeting the Hallmarks of Cancer: Survival of the Fittest”. He mentioned that cancers are complex ecosystems that are characterized by profound spatial and temporal heterogeneity. The conversions from genome to the anatome are non-linear processes that are affected by genetic and epigenetic events, and their interaction with the microenvironment. A fundamental problem in modern biology is how to directly link genetic data to cellular phenotypes. These complex interactions between intra- and extracellular processes leads to complex intra-tumoral heterogeneity due to cell-environment interactions. He emphasized that “Nature selects for phenotype, not genotype.” Phenotypic heterogeneity is the most significant factor underlying evolutionary rates.

   One targetable hallmark of cancer therapy is the angiogenesis, which results in a chaotic and inefficient vasculature. This leads to poor perfusion and tumor hypoxia and acidosis. Hypoxia in early cancers leads to selection of cells with a glycolytic phenotype. This phenotype is maintained in metastatic cancers because it produces acid, which provides a selective advantage of the tumor cells over stroma. Hypoxia and acidosis are therapeutic targets that may have application over a wide variety of solid tumors. He showed that inhibiting the acid with oral buffers can prevent experimental metastasis, and this is in clinical trials.

   The comprehensive talk gave me an inspiration that the issues of hypoxia
and angiogenesis should be considered together when I’m imaging the tumor therapy. Maybe I should target the hypoxia in my near future using the BOLD (blood oxygen level dependent) MRI technique and then combined my current DCE MRI approach for the angiogenesis. A more complete investigation can be conducted thereby.

2. Prof. Jan-Bernd Hovener, from University Hospital of Freiburg, Germany. was invited to give a speech for a review of the advanced Animal MRI from anatomy to function. Currently, modern high-field animal MR methods deliver anatomical maps using relaxivity contrast at the micrometer resolution. A new focus is being given to the assessment of physically functional parameters, such as diffusion (of liquids along structures), perfusion (of blood in organs), oxygen consumption (in the brain) and venous blood flow. Ideally, these “physical parameters” translate to “diagnostic parameters” such as the distribution of nervous fiber bundles or lipid-content of the liver. In this session, both present and future MR methodologies are presented, including diffusion tensor imaging, MR-spectroscopy, vessel-size imaging and hyperpolarization. He showed a lot of examples of current researches and discussed the potential of MR for molecular imaging. The speech was quite comprehensive.

3. A lot of researchers focused on various approaches and methods in MRI probe design. One of the most popular probes is the superparamagnetic iron oxide (SPIO) nanoparticles, which the physicochemical properties have been studied in detail for more than 60 years. Prof. Jeff W, from Johns Hopkins University School of Medicine, mentioned that many different methods exist that can produce particles under “the critical domain size” (required for superparamagnetism), i.e.,
iron oxides with a crystal core diameter no larger than about 50 nm. The particles have an additional coating that can take the total diameter to above 100 nm. There are many different coatings that can be used to prepare stable iron oxide colloid formulations, e.g., dextran, carboxydextran, silica, lipids, citrate, amino acids, peptides, and dendrimers et al. Initially, dextran-coated iron oxides were developed for clinical imaging of macrophages, with liver and lymph node imaging as the main application that was later extended to contrast-enhanced imaging of plaques occurring in multiple sclerosis and arteries. Methods for labeling for cell tracking include the use of transfection agents or cationic peptides/dendrimers as secondary coatings, or magneto-electroporation or -sonoporation based instant labeling techniques. Approaches for conjugating targeting ligands for molecular imaging vary and are dependent on the particle coating. As for clinical use and safety concerns, the human adult has about 4 grams of total iron in the body and any given iron oxide contrast formulation will be in the microgram dosing range. This natural abundance, together with the biocompatibility and the ability of the body to recycle the injected iron, makes iron oxide particles one of the safest contrast agents available for molecular and cellular imaging.

4. Hyperpolarized MR Spectroscopic Imaging is a hot topic in the meeting, although researches were only conducted in limited institutes. Nuclear spin hyperpolarization techniques can increase sensitivity in the MR experiment by >10,000 times, which offered us a new way to image tissue metabolism. Using this technique it is possible to image the location of an injected hyperpolarized $^{13}$C-labelled cell substrates and, more importantly, its metabolic conversion into other cell metabolites. A keynote speech delivered by Prof. Kevin
Brindle, from University of Cambridge, mentioned that treatment response is frequently assessed from measurements of decreases in tumour size, however imaging changes in tumour metabolism can give a much earlier indication of whether a tumour is responding to treatment. He reviewed the ways in which researchers have used to image various aspects of tumour metabolism, with a focus on detecting early evidence of response to treatment. Moses M. Darpolor, from Stanford University, also showed results of in Vivo metabolic imaging of $^{13}\text{C}$-Pyruvate in hepatocellular carcinoma and recommended that hyperpolarized $^{13}\text{C}$ 3D MRSI may be a diagnostic tool for detection of HCC and a potentially useful imaging tool as a surrogate marker or endpoint for drug activity targeting these specific enzymatic pathways.

5. Another interesting talk that impressed me very much was given by Niels J. Harlaar, from Technische Universität München and Helmholtz Zentrum München, Munich, Germany, entitled “Real-time Multispectral Near Infrared Fluorescence (NIRF) Intra-operative Imaging in Cancer by Using an $\alpha\nu\beta^3$ - Integrin Targeted Fluorescence Agent”. He showed a lot of movies of their novel real-time, in vivo, multi-spectral fluorescence imaging system in mice bearing xenograft human ovarian and breast cancer injected with an $\alpha\nu\beta^3$-integrin receptor targeted fluorescent probe. This approach that is based on real time feedback to the surgeon in the theatre, has potential of further clinical development to eventually accomplish clinical application in patients with ovarian cancer and breast cancer.

6. The Bruker company announced a MALDI (matrix-assisted laser desorption ionization) technique which allows the direct non-targeted imaging of tissue. The
distribution of hundreds of compounds, such as proteins, peptides, lipids, drugs and metabolites can be measured at once. The technique is in current use in oncology for the direct molecular analysis of tumors, in drug development for the analysis of drug and metabolite distributions and in model studies in small animals.

三、心得與建議

以往此會議大部份是以核子醫學影像議題為主軸，近幾年 MRI 的研究也漸漸朝向功能性分子影像發展，小動物的研究是臨床前期重要的工作，未來研究的趨勢是結合各個不同領域的專長而朝向特定目標。長庚大學與醫院擁有強大的師資及醫師陣容，加上一流的設備，希望學校和醫院能有更多更密切的合作，期望我們可以做出許多世界一流的研究成果。

四、攜回資料名稱與內容

2010 WMIC Proceeding, program book.