

出國報告（出國類別：會議）

主題：第 17 屆國際中子捕獲治療學會
(17th International Congress on Neutron
Capture Therapy, ICNCT)

[將電子檔傳送至 yenli0509@ym.edu.tw](mailto:yenli0509@ym.edu.tw)

服務機關：臺北榮民總醫院腫瘤醫學部放射腫瘤科

姓名職稱：吳元宏研究醫師

派赴國家：美國密蘇里州哥倫比亞市

出國期間：2016/10/2-2016/10/9

報告日期：2016/10/9

摘要（含關鍵字）

本次參加 ICNCT-17，進行口頭報告，關於瀰漫性橋腦神經膠質瘤(Diffuse intrinsic pontine glioma, DIPG)的硼中子捕獲治療(Boron neutron capture therapy, BNCT)劑量模擬計算結果。DIPG 由於腫瘤細胞分散浸潤在腦幹中，手術不可能進行，而放療也因投鼠忌器，無法給到充足的劑量。BNCT 因可透過分子特性，達到腫瘤細胞集中劑量的效果，在 1960-1980 年間，在日本曾有 6 例 BNCT 治療 DIPG 的報告。但因為中子射束劑量無法穿透腦部深處，需要先將頭骨打開進行照射。但最近二十年因為技術進步，已有更高能量的中子束，或許不用打開頭骨，就可進行治療。這次研究，模擬本院過去曾使用傳統放療治療的 DIPG 病人，使用 BNCT 的劑量分布。透過四個不同方向的射束集中劑量，驗證 BNCT 治療 DIPG 不用打開頭骨就可進行。「加速器型 BNCT 設施發展」，去年已經議定為本院中長程發展目標。

本院兩年後將與清大在台北合辦下一屆 ICNCT-18。這次參與會議能與世界各地 BNCT 的大師共同討論學習，並有機會宣傳下一屆大會，收穫豐碩。

關鍵字: BNCT, DIPG

一、目的

BNCT 在醫學應用上已經有約 50 年以上的歷史。能透過腫瘤細胞對於特定分子的過度攝取，在細胞層次的距離內，對腫瘤細胞達到倍數的放射劑量差異。在膠質母細胞瘤(glioblastoma multiforme, GBM)，目前證據顯示，可達到與標準的手術+放療+化療類似的治療效果。但治療時間可大幅縮短。在復發頭頸癌上，本院最近完成的臨床試驗，也展現不錯的治療結果。ICNCT 大會從 1980 年代開始舉辦，是目前世界 BNCT 界的最大型國際會議。這次投稿 DIPG 劑量計算的模擬結果，被安排在會議第三天下午 plenary session，對所有與會者，進行 20 分鐘的口頭報告。因此規劃本次行程，希望能與世界各地 BNCT 的大師共同討論學習，並有機會宣傳下一屆在台北舉辦的大會。

二、過程

大會議程是從 10/2 到 10/7。我們搭乘 10/2 的班機，從台北到 Columbia，結束後由於班機無法銜接，搭乘 10/8 清晨的班機回台。我的口頭報告是在第三天下午對全體人員進行。第三天理事的選舉，本院顏上惠顧問，也順利當選，並被指定為副理事長。

<p>Sunday, October 2, 2016</p> <p>3:00 pm - 4:00 pm Executive Board Meeting</p> <p>4:00 pm - 4:30 pm Board of Councilors Meeting</p> <p>4:30 pm - 6:00 pm Registration & Check-in</p> <p>4:30 pm - 7:00 pm Exhibits</p> <p>4:30 pm - 7:00 pm Networking Reception</p> <p>Monday, October 3, 2016</p> <p>8:00 am - 9:00 am Registration & Check-in</p> <p>8:00 am - 6:15 pm Exhibits</p> <p>9:00 am - 9:30 am Opening Ceremony</p> <p>9:30 am - 10:15 am Hatanaka Lecture</p> <p>10:15 am - 10:35 am Break</p> <p>10:40 am - 12:10 pm Plenary Session 1</p> <p>12:15 pm - 1:15 pm Lunch</p> <p>1:30 pm - 3:05 pm Plenary Session 2</p> <p>3:05 pm - 3:25 pm Break</p> <p>3:30 pm - 5:00 pm Plenary Session 3</p> <p>5:15 pm - 6:15 pm Small Committee Meetings</p> <p>5:15 pm - 6:15 pm Poster Session 1</p> <p>Tuesday, October 4, 2016</p> <p>8:30 am - 6:00 pm Exhibits</p> <p>8:30 am - 9:45 am Breakout Session 1</p> <p>9:45 am - 10:15 am Break</p> <p>10:15 am - 11:50 am Plenary Session 4</p> <p>11:50 am - 2:00 pm Lunch & Exhibits</p> <p>2:00 pm - 3:10 pm Plenary Session 5</p>	<p>3:15 pm - 4:15 pm Poster Session 2</p> <p>4:30 pm - 6:05 pm Breakout Session 2</p> <p>Wednesday, October 5, 2016</p> <p>8:00 am - 4:00 pm Exhibits</p> <p>8:30 am - 10:05 am Plenary Session 6</p> <p>10:10 am - 10:50 am General Assembly Meeting</p> <p>10:55 am - 11:55 am Poster Session 3</p> <p>11:55 am - 12:55 pm Lunch</p> <p>1:00 pm - 2:35 pm Plenary Session 7</p> <p>2:35 pm - 3:00 pm Break</p> <p>3:00 pm - 4:15 pm Breakout Session 3</p> <p>5:45 pm - 6:00 pm Group Photo</p> <p>6:00 pm - 9:00 pm Banquet & Reception</p> <p>Thursday, October 6, 2016</p> <p>8:30 am - 1:30 pm Exhibits</p> <p>8:30 am - 9:00 am Executive Board Meeting</p> <p>9:00 am - 10:15 am Breakout Session 4</p> <p>10:15 am - 10:40 am Break</p> <p>10:45 am - 12:20 pm Plenary Session 8</p> <p>12:20 pm - 1:15 pm Lunch</p> <p>1:15 pm - 9:00 pm Pre-paid Excursion</p> <p>Friday, October 7, 2016</p> <p>9:00 am - 10:35 am Plenary Session 9</p> <p>10:35 am - 11:00 am Break</p> <p>11:00 am - 12:00 pm Closing Session</p> <p>12:30 pm - 1:30 pm Executive Board Meeting & Lunch</p>
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班機行程

2016-10-02 9:50 UA872 TPE-SFO

2016-10-02 10:45 UA606 SFO- STL

2016-10-08 8:00 UA4542 STL-ORD

2016-10-08 12:00 UA881 ORD-NRT

2016-10-08 17:40 UA7943 NRT-TPE



口頭報告之後，得到聽眾廣泛的迴響。過去 BNCT 界普遍存在深處腫瘤不合適使用 BNCT 治療的想法。然而這次的研究，驗證其實只要多用幾個角度從不同地方入射，即使頭頸部最深處的腦幹腫瘤，也可能有治療效益。

各方回應整理如下：

現場:

---Dr. Rolf F. Barth, MD, professor of pathology(Emeritus), University distinguished scholar, The Ohio State University

“Nice talk. Have you heard about convection enhanced drug delivery? This technique developed by Dr. Steven Gill from Bristol University should be of use.”

---Dr. Shin-Ichi Miyatake(宮武伸一), Department of Neurosurgery, Osaka Medical College, Japan

“Wonderful job. To treat DIPG is also my dream. I have two questions: should you treat fresh case or recurrent case? Will you do BPA-PET before first course of radiotherapy?”

“I have one suggestion: to use bevacizumab before BNCT” .

Session 結束後:

---Dr. Kaiger, Harvard medical school, author of the treatment planning system NCTPlan:

“There might be problem of the eye shielding” .

---Dr. David Yue-Wei Lee, Associate professor, department of psychiatry, Harvard Medical School

“吳醫師，您好，精彩的演講，請問您那邊可以安排做一些新藥的人體試驗嗎?我這

邊有一些新的含硼藥物(NPI-BNCT-001B)，可以寄些給您做實驗。”

---Dr. Daniel Quah, Associated consultant, radiation oncology, Department of Radiation Oncology, National Cancer Centre, Singapore:

“吳醫師，請問你們可以治療外國病人嗎？我想轉介病人過去。”

---Dr. Takushi Takata(高田卓志), Assistant professor, department of radiation life science and radiation medical science, division of radiation life science, radiation medical physics laboratory

“Inspiring ideas. Did you also calculate heterogeneous index?”

---不知名的女士，來自 Organizing committee，

“very interesting work.”

---Dr. Melvin Piestrup, Adelphi technology incorporation

“I am happy that somebody presented BNCT with multiple portals. Our accelerator could generate multiple beams at the same time.”

---Dr. Satish S. Jalisatgi, President of International Society for Neutron Capture Therapy

“We could provide you MAC-TAC liposomes. But the size of 200nm might not penetrate BBB.”

---Dr. Koji Ono, KURRI, Japan

“The paper of Nagasawa restricting dose to the major vessel to 12 Gy(W) or less because they used BSH. The regime mostly stay in the vessel without penetrating it. The scenario of BPA is different. Also, you have to pay attention to the CBE factors.”

三、心得

這次出發之前，我準備了三個學習重點，希望能得到解答。

- 1) 與美國方面專家，討論請教 2000 年以前，在美國進行 glioblastoma 的 BNCT 臨床試驗，為何效果不彰的各種可能原因。
- 2) 多照野的 BNCT 設計，對腦部的安全劑量應該如何評估？
- 3) 日本方面，對復發 glioblastoma 的 BNCT 成功經驗，如何應用在 DIPG 疾病的治療？

會議當中，把握各種機會，得到的初步方向是：

- 1)目前的各種證據顯示，BNCT 用在 GBM 治療上，能夠達到的治療效果，類似於傳統的手術+放療+化療(temozolomide)，但治療時間可以縮短到一次至兩次。美國 Harvard-Brookhaven trial 的設計，採用多角度照射已進行劑量加強試驗，發現

劑量越高時，病人的存活反而越差。看起來，試圖增加照射計量的嘗試，在當時並沒有帶來顯著存活的好處。可能原因在於 BNCT 利用腫瘤對於 phenylalanine 這個胺基酸增加攝取的特性，使腫瘤內部 boron-phenylalanine(BPA)濃度增加，在照射中子時，腫瘤處捕獲更多中子，增加吸收的放射劑量。然而，實際 GBM 在接受中子照射時，可能有一些並沒有真的增加吸收 BPA，導致照射劑量不足。

2) 目前研究參考 Harvard-Brookhaven trial 的 ED50% somnolence 劑量，限制腦部平均劑量不超過 14.1 Gy(W)，而全腦平均劑量不超過 6.3 Gy(W)。對於 Circle of Willis 的劑量限制，過去為 12 Gy(W)，是參考 BSH 的狀況。目前使用 BPA，應按照 CBE factor 的精神修正。

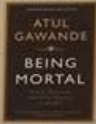
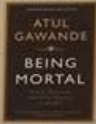
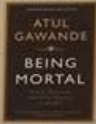



3) 日本目前看似較佳的 GBM 治療結果，可能只是慎選病人造成，也可能部分來自於日本醫師固定使用 bevacizumab (Avastin)預防 radiation necrosis 的緣故。Dr. Miyatake 甚至建議，未來若我們要進行 recurrent DIPG 照射 BNCT 的臨床試驗，他會建議預先注射 bevacizumab。

除了預先想的問題，這次與會有許多其他的感受收穫。最強烈的是這張 poster。這是新加坡國立癌症中心的放射腫瘤科同行醫師，Dr. Daniel Quah 所提出。他提醒大家一個重要的事情。歷史上，大家首先進行 BNCT，目的是希望克服 GBM 這樣惡性的疾病。因為 GBM 在解剖上發現它會 infiltrate 到正常腦部組織到兩公分以上的距離。即使做了 grossly total removal，但周圍的正常腦部，仍有相當多的癌細胞。卻又投鼠忌器，無法將其他腦組織都切除以達到足夠的手術邊緣，否則對於神經功能將造成悲劇影響。原本放腫前輩們，滿心期待，希望藉由癌細胞對 phenylalanine 的渴求，增加攝取，能夠達成殺掉癌細胞同時保留正常腦細胞的結果。然而即使劑量高到將近 100Gy(W)，多數病人仍然死於腫瘤復發。除了美國的試驗，瑞典、芬蘭、日本等國，也陸續對 GBM 的 BNCT 效果做出嘗試。除了日本有稍微好一些的試驗結果外，其他國家的治療效果只能說差強人意，跟標準治療類似。

National Cancer Centre Singapore
 SingHealth

How Boron Neutron Capture Therapy and other Innovative Therapies can be Game Changers in Palliative Care

D.S.C. Quah, D.S.H. Lim
 National Cancer Centre Singapore, Department of Radiation Oncology, Department of Palliative Medicine, Singapore
 Email: Daniel.Quah.S.C@singhealth.com.sg

INTRODUCTION					
Known Fact	Patients with advanced disease have limited lifespan				
Two Different Aims	<table border="1"> <tr> <td> Disease Modification : Aim - Attempt to slow or halt disease progression, and thus attempt to increase their lifespan. </td> <td> Palliative Care : Aim - Increase Quality of Life to remaining lifespan </td> </tr> </table>	Disease Modification : Aim - Attempt to slow or halt disease progression, and thus attempt to increase their lifespan.	Palliative Care : Aim - Increase Quality of Life to remaining lifespan		
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CONCLUSION					
<p>The BNCT community has come a long way, and the next biggest obstacle will be "Economics", not just in the traditional financial sense but more so in terms of the limited "Lifespan Currency" of patients with advanced cancer. Medical Tourism is a creative and ingenious solution to overcome this obstacle. It not only allows BNCT to be more widespread without incurring extra infrastructure costs, but may also result in economical advantage in terms of tourism revenue. In doing so, patients deemed incurable may suddenly get a second lease of life as BNCT controls their tumour or even eradicates it, while enjoying what may be an unforgettable vacation in more ways than one.</p>					

Patients. At the Heart of All We Do.

然而，最近幾年，大家開始將注意力放到頭頸癌復發上。發現對於 GBM 以外的疾病，BNCT 可能具有相當好的局部控制症狀緩解的效果。本院最近發表的結果也是類似。假如我們將條件放寬，不要再執著於要一次高劑量照射讓腫瘤永遠根治，而是將 BNCT 應用在癌症症狀的緩解上，這個治療將可以達到藥物、手術、或是傳統放療，無法達成的高度治療效益。BNCT 最適合的狀況，是局部的巨大腫瘤，與正常組織交纏在一起，已經接受過多次放療化療時，當看到腫瘤產生壓迫效應，甚至爛在外面流血流膿時，BNCT 只需要一到兩次照射，就可以看到明顯的腫瘤縮小甚至消失。就算病人幾個月或幾年後終究死亡，這段時間因為症狀減輕而改善的生活品質，仍然很有意義。

過去因為 BNCT 僅限於在原子反應爐才能產生足夠的中子射束，想照 BNCT，必須將病人從病房，帶到原子爐照射，而醫療人員必須隨侍在側。早期 GBM 的臨床試驗，甚至是外科醫師直接在原子爐開刀，做開顱手術，術中進行 BNCT，種種不便造成前輩同業，對於將 BNCT 應用在 palliative treatment 上，保守踟躕。然而最近全世界對於「加速器型 BNCT 設施發展」熱潮勢不可擋，機器已經在治療病人，許多處都正在進行或著手規劃臨床試驗。BNCT 融入癌症治療，成為標準治療的一部分，可以說是倒數計時，預期幾個月或幾季後，將會成真。除了緩解治療的療效已經看到明顯作用外，各種新型含硼藥物的發展，也預期將會把 BNCT 帶到新的水平。目前最常用的 BPA，只能期待最高有 2-4 倍於正常組織的劑量。而已經動物實驗的許多種含硼藥物，已經看到高達百倍的腫瘤吸收劑量。

這次會議主席，Dr. Satish S. Jalisatgi, 在 Missouri University 發展的 MAC-TAC 微脂體，已經在頭頸癌動物模型上，驗證可以達到十倍以上的腫瘤劑量，正預備申請 FDA 認證。BNCT 的另一特色，在於治療之前，可以透過 PET/CT，預測腫瘤的吸收劑量。假如未來有更多的含硼藥物，可預先檢查腫瘤吸收，合併使用，達到個人化精準治療的效果。

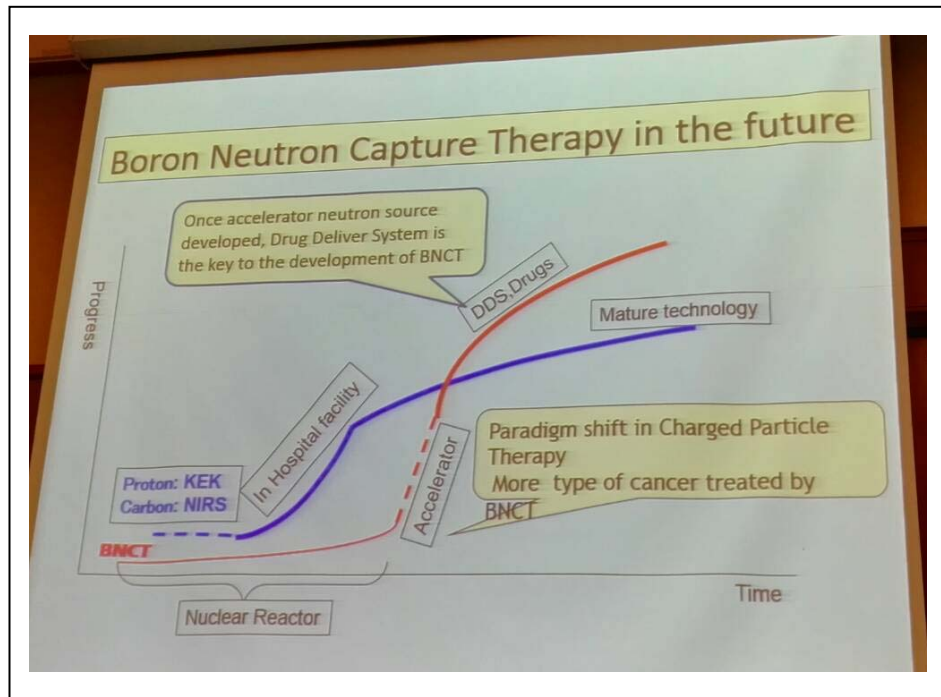
除了腦癌、頭頸癌外，BNCT 目前已經看到在皮膚癌、骨肉癌、mesothelioma、melanoma、breast cancer、Paget's disease、等等疾病上，有不錯的治療效果。其他許多疾病的臨床試驗，也在進行中。這次 National Cancer Institute 的 radiation oncology chair 有上台傳達 FDA 的政策。他說他知道 BNCT 想要做到 phase 3 trial 與既有治療一較高下的難度。但他說 NCI 與 FDA 其實一直有在關注這項技術的進展。他的建議，是可以找一個目前沒有其他有效治療的疾病，進行 prospective trial。不必有對照組也沒關係。Endpoint 未必要是 overall survival，單純 quality of life 的顯著改善也可以。FDA 現在對於沒有其他療效的疾病，有 accelerated pathway，先核准，讓保險能給付，之後再逐漸補做 phase 3 trial。他建議 BNCT 可以走這條路。

從現在臨床上看到的療效，我想 BNCT 很有機會短期內透過這個方式通過 FDA 認證。

四、 建議事項（包括改進作法）

本院目前積極爭取發展重粒子治療。然而，BNCT 具有特定優勢，是其他粒子治療無法取代的。主要在於它有機會達成細胞大小($\sim 1\mu\text{m}$)等級的劑量調控。當腫瘤與正常組織混雜再一起的時候，BNCT 仍有機會達到讓腫瘤接受數倍劑量同時保存正常組織的效果。目前 BNCT 界風起雲動，可以預期不久將來會非常火熱。這次會議接近尾

聲的一個 talk 也提到這個預測。



藍線是質子與重粒子治療的發展程度，紅線是 BNCT。講者預期，當加速器 BNCT 進入醫院後，將可造成放療的典範轉移，吸引更多含硼藥物研發，BNCT 發展將超越質子與重粒子治療。

個人建議，雖然我們積極爭取重粒子設備，對於 BNCT 的關注仍然不可減少。北榮目前與清大以及京都大學合作，在國內於 BNCT 領域達到領先，相當難得。宜持續精進，並投入足夠資源，不要放掉加速器進入醫院這一波發展的機會。

附錄

Abstract of the presentation

Preliminary study on feasibility of boron neutron capture therapy in patients of diffuse intrinsic pontine glioma without craniotomy

Yuan-Hung Wu¹, Yi-Wei Chen¹, Jia-Cheng Lee¹, Fang-Yuh Hsu²

¹*Department Oncology, Taipei Veterans General Hospital, Taiwan*

²*Nuclear Science and Technology Development Center, National Tsing Hua University,
Taiwan*

Email: yuanhung@gmail.com

Introduction

Diffuse intrinsic pontine glioma (DIPG) has been a very frustrating disease for patients, family, and doctors. Boron neutron capture therapy (BNCT), as a targeted radiotherapy, might carry potential to project adequate radiation dose to the tumor cells while sparing normal brain stem.

Materials and methods

In this study, simulation computerized tomography (CT) of consecutive 12 patients with DIPG treated with external beam photon radiotherapy in our institute during 2008 and 2016 was used with NCTplan v.1.1 to estimate the radiation dose to the pontine tumor and surrounding normal tissues irradiating from 4 portals with equal weighting. The ages of patients were between 4 and 53 year-old, with median of 10 year-old. The default neutron energy and flux was 1.2 MW and $9.4E+08(n \cdot cm^{-2} \cdot sec^{-1})$, respectively. RBE of photon dose, ¹⁰B dose, thermal neutron dose and fast neutron dose were 1, 1.35, 3.2, 3.2, respectively, in normal tissue, and 1, 3.8, 3.2, 3.2, respectively, in tumor. Prescribed dose was 20 Gy(w) received in 80% volume. Tumor/normal tissue (T/N) ratio between boron concentrations was assumed to be 3.5.

Results

The ratio of minimal dose to the tumor and maximal dose to normal tissue was between 1.81 and 2.62, with an average of 2.26. Ten of the 12 patients achieved a ratio greater than 2. The mean dose to whole brain was between 4.03 Gy(w) and 5.22 Gy(w), with an average of 4.59 Gy(w). The maximal dose to normal brain was between 7.26 Gy(w) and 9.36 Gy(w), with an average of 7.71 Gy(w).

Conclusion

Therapeutic benefits might be achieved using four-ports BNCT in patients with DIPG.