

行政院及所屬各機關出國報告
(出國類別：進修)

攝護腺癌放射治療

服務機關：台北榮民總醫院
出國人職稱：主治醫師
姓名：劉裕明

出國地區：美國
出國期間：90. 7. 23. — 91. 7. 11.
報告日期：91. 年 8. 月 16. 日

J3/ c09003848

系統識別號:C09003848

公 務 出 國 報 告 提 要

頁數: 18 含附件: 是

報告名稱:

攝護腺癌放射治療

主辦機關:

行政院輔導會臺北榮民總醫院

聯絡人/電話:

/

出國人員:

劉裕明 行政院輔導會臺北榮民總醫院 癌病中心 主治醫師

出國類別: 進修

出國地區: 美國

出國期間: 民國 90 年 07 月 23 日 -民國 91 年 07 月 11 日

報告日期: 民國 91 年 08 月 16 日

分類號/目: J3/醫療 J3/醫療

關鍵詞: 攝護腺癌放射治療

內容摘要: 隨著國民平均壽命的逐漸升高，攝護腺癌的治療已成為國內癌病治療的重要課題，又本院於年相繼引進三度空間立體隨型放射治療及調強放射治療，此次赴美國加大學舊金山分院之目的在於研習包括體外放射治療及插種放射治療在攝護腺癌上之應用，此外論文纂寫及癌病資料庫之分析整理亦為學習的重點。

本文電子檔已上傳至出國報告資訊網

摘要

由於國人平均壽命提高，生活飲食漸趨西化，診斷技術進步，攝護腺癌發生率有增加的趨勢，攝護腺癌治療也成為癌症治療的重要課題之一。本院於 1996 引進三度空間立體隨形放射治療，可提供器官立體解剖學位置資料，並藉由影像重整之助，從各個不同的方位來設計照射照野。精準度高，副作用小，故可給與腫瘤更高的劑量，以達成更好的腫瘤控制率。

職此次赴美研習近日成功發展，能利用電腦作出近乎完美的治療計畫的調強放射治療及整合超音波與電腦影像針對早期癌症，提供有效又方便的局部治療的組織插種治療，並針對攝護腺癌治療相關的診斷、追蹤及賀爾蒙治療皆有深入的研究。於論文撰寫方面，除有兩篇摘要分別為美國放射治療學會及北美放射醫學會接受為口頭發表；另有一篇壁報展示，並帶回許多合作計畫的建議。

目次

摘要	1
正文	3
目的	3
過程	5
心得	7
建議	10
附錄	11

正文

壹、目的：

攝護腺癌為男性年長者之癌症。因國內醫療水準之進步，國人之平均壽命大幅延長，再加上近年攝護腺癌篩檢技術進步；攝護腺癌已成國內癌症治療之重要課題之一。

傳統上，攝護腺癌之治療以開刀切除(radical prostatectomy)為主。但隨著病患逐漸高齡化，手術治療所伴隨的麻醉、傷口感染....等風險也變成不可忽略的考量因素。

早期放射治療亦是攝護腺治療的方法之一，但受限於當時放射物理計量運算不發達之故，無法給予腫瘤足夠的劑量，也無法避免因高輻射劑量所造成之副作用，故當時之放射治療多用於不適合開刀之病患，如年齡太大或較末期者。

近年由於電腦影像科技之進步，使得精確的物理運算變為可能，因此給予腫瘤高輻射劑量，以提高腫瘤控制率，並避開正常組織減少副作用，為目前放射治療之主要趨勢。

癌病中心於一九九六年引進三度空間隨形放射治療(Three-dimensional Conformal Radiotherapy)，此治療結合電腦斷層影像及電腦強大的運算能力，精確的將腫瘤及鄰近正常組織繪出，並設計出精準的治療計劃。由於此系統之精確度極高，並可降低副作用，如攝護腺癌之治療劑量已由以往之六十格雷(Gray)提高至七十二(Gray)。不但名顯的提高了攝護腺癌腫瘤控制率，且使副作用更低。放射治療也因此成為攝護腺癌主要治療選擇之一，對早期或晚期癌症都有很好的療效。

本中心自民國八十五年九月至九十年六月已治療近五百名攝護腺癌病患。雖然臨床追蹤結果良好，但統計結果仍有百

分之八的病患發生直腸出血副作用。此少量出血副作用並不會造成病患健康上的影響，但仍然給病患不少的壓力。

為了提昇本院的治療水準，服務廣大的病患，本中心於民國九十年再次引進目前最先進之調強放射治療技術(Intensity Modulated Radiotherapy)。此系統不但能作影像合成(MR, CT scan Infusion)，並能更精確的計算腫瘤區域輻射劑量之分佈。此技術是藉由不同的數學物理運算，精確的給予劑量，配合上多葉式直準儀(Multi-leaf Collimator)更能「雕塑」腫瘤的計算分佈。就攝護腺腫瘤之治療而言，不但可將治療劑量提高至八十至九十格雷，更將副作用發生之機率降至更低。調強放射治療的缺點是其複雜度高，需要醫師與物理師的充分合作方能發揮最好的效果。其中包括複雜的物理運算觀念及醫學上各組織器官之輻射劑量忍受度(Radiation tolerance)。

此次赴美進修之目的主要在學習攝護腺癌治療之新觀念，觀摩調強放射治療於其他癌症治療之應用，及論文之纂寫。

貳、過程

職於民國九十年七月啟程赴美。到達美國舊金山後隨即往加州大學舊金山分校錫安山分院放射腫瘤部報到(UCSF, Mt.Zion Hospital Department of Radiation Oncology)。馬克·若許教授(Mack Roach III)為美國西岸最富盛名之攝護腺癌專家，不但對攝護腺癌之放射治療及荷爾蒙治療有獨特的見解，且為美國數個國家型研究計劃之主持人。職先與馬克教授討論職在國內所作的研究與將來要研究的方向。因職於國內所作的研究多與攝護腺腫瘤病患治療之定位準確度有關，故安排我做攝護腺體體內運動之研究(Prostate, organ movement)，並觀摩

院內各種腫瘤之治療方式。

本人於進修期間層參加各項臨床討論會，觀摩各項插種放射治療手術並參與論文寫作分述如後

- 一、磁振光譜討論會(MRS/I)：磁振光譜可利用攝護腺內癌細胞對檸檬酸代謝之不同偵測癌細胞之分佈(有癌細胞之區域檸檬酸濃度較低)。因目前仍以整粒腺體治療為主，若能因此只需治療部分攝護腺體則可能將治療副作用降至零。然而此檢驗目前精確度尚有爭議，且攝護腺癌之癌細胞於腺體內之分佈並不完全是局部性的(Localized)，也可能平均分佈在整個腺體。故目前 MRS/I 在臨床上的應用於攝護腺插種局部治療上。
- 二、攝護腺器官於人體內之運動(organ motion)及放射治療精確度(setup error)：傳統上認為攝護腺為體內解剖位置較為固定的器官。經由攝護腺內植標記(implanted marker)及電子照野影像攝影(Electronic Portal Image)結果顯示，攝護腺不但不是固定的器官，而且其運動範圍不小約四至八公厘，這在精密放射治療上算是不小的差距。攝護腺不但朝各個方向運動，且會依放射治療的時間變化而有一定的運動趨勢。故在作精密放射治療時，攝護腺內植標記及每日的影像校正對位是有必要的。
- 三、攝護腺癌之插種放射治療(Brachytherapy)：攝護腺癌之插種治療並不是新創的技術，因早期精確的劑量計算不易，易有嚴重副作用，故較少使用。近日因電腦科技之進步，可精確的計算，並可自動作治療計劃設計。再加上目前之插種儀器多配合即時超音波攝影，精確度很

高，副作用極低。插種治療分為傳統的永久性低劑率插種(Permanent Low dose Rate Brachytherapy)及高劑率插種(High Dose Rate Brachytherapy)兩種。前者為將射源植入攝護腺內，不取出，再由其低輻射活性之射源慢慢殺死癌細胞，好處是已有較多的臨床經驗，操作方便一次完成，但在台灣射源取得不易且較昂貴；後者為於攝護腺插入治療軟管，再用遙控方式以高劑量射源給予劑量，好處是費用較低，可依舊有的系統添加電腦系統即可，無射源取得問題，亦可應用於其他癌症之插種治療，缺點是醫師的技術必需熟練。插種治療的好處是可以將輻射劑量，極正確的投射到局部地區，而完全不殃及鄰近組織，而其缺點亦在於其只能治療極早期腫瘤，必須配合體外放射治療，方能治療較大之腫瘤。

四、鼻咽癌之調強放射治療：鼻咽癌為華人的重大疾病，而此地又為美西華人之集中地，故職亦觀摩了此地之鼻咽癌治療。其特色是以調強放射治療作整個療程，並非如一般只用於後續的加強照射。調強治療是能提供精確的輻射劑量，但於各項參數之設計極為耗時。職於進修期間加入參數設定之研究小組，目前論文摘要已被美國放射腫瘤協會(ASTRO)接受。論文內容主要是提供一種適用的通用參數供初使用調強放射治療鼻咽癌的單位，以減少計劃時間。

五、參加美國放射腫瘤學會(ASTRO)於舊金山年會，開會期間參加許多研討會，增加不少疾病新觀念及學術新知。

參、心得

- 一、此次進修發現美國醫師對於各種臨床統計數字十分清楚，不但熟記而且用於各種討論。數字是會說話的這項觀念深植人心。對比於一般的所謂臨床經驗或臨床印象，有統計數字確實是較為精確客觀的。
- 二、美國的放射治療科醫師只負責評估治療計劃是否可用而不必親自參與計劃設計，治療計劃的設計與運算完全由物理師負責。醫師大部分的時間都花在治療策略的規劃、治療後病患追蹤評估、與臨床資料處理上。就此點而言，本院的醫師不但要負責上述所有事項，尚需親自設計治療計劃，甚至部門儀器系統的管理。也許手藝的精緻度，本院的醫師較勝一籌，涉略較廣；但美國的醫師則花較多的時間於資料的收集與分析上，研究上較深入，因此而建立起來資料庫的價值就更可觀了。
- 三、放射治療科所配備的都是非常昂貴精密的儀器，必須有專人負責維修管理，且負責人不單只做簡單的維修，必須具備醫學電子相關背景，對於整套「系統」必須熟悉，且能開發系統的應用，並且改寫軟體。此類人員在美國多為博士背景，富研發能力，相同設備可發揮較大的功效。
- 四、國內的醫療水準並不比美國差，為所缺者為研發能力。醫師發大部分時間於醫務工作，只能從事小型研究工作(病患數目少，追蹤期短)。對於需較長時間追蹤，如長達十數年時間收集整理或達數千名病患的大型研究執行上非常吃力。

五、就攝護腺癌之治療有下列心得

1. 美國的病患年齡分佈較為年輕，一般為六十歲左右，五十幾歲的病患也不在少數。反觀國內病患的年齡多為七十歲左右。這也許與美國人較早作攝護腺言之篩檢有關。美國患者病情惡化的情形較嚴重，有相當高比例的患者因而致命。然而國內患者多死於心肺功能衰竭。這也許與國內統計資料有關。故我們是否一味依尋國外的數據來治療我們的病患是否正確？若能利用本院龐大的檢驗資料作分析，建立詳儘而有計畫性的臨床資料庫，必可使本院長居教學醫院之領導地位。
2. 目前攝護腺癌患者之臨床追蹤是以檢測血液中的攝護腺特殊抗原值(Prostate specific antigen PSA)為主。PSA值升高意味著病情惡化，有復發或遠處轉移之可能。然而近日一篇七年追蹤的調查報告顯示，PSA值之追蹤仍有其一定的價值，但其高低卻與病患之存活(survival)率關係不那麼密切。當然這個研究仍然繼續進行中，但一味的追蹤低PSA值是否為良策，值得深思。
3. 目前在攝護腺癌之治療原則則依腫瘤期別、腫瘤病理分期及攝護腺特殊抗原值分為高危險群(High Risk)、中期(Intermittent Risk)及低危險群。對於低危險群者可以較單純之療法如開刀或放射治療即可。對於中危險群之患者則建議結合治療前(Neoadjuvant)及治療中(concurrent)荷爾蒙與放射治療。對於高危險群患者則建議追加治療後荷爾蒙治療兩年。治療前荷爾蒙治療現今普遍使用手術治療及放射治療之前處理。其目的在使攝護腺體積縮

小以便於後續之手術或放射治療。而治療後之荷爾蒙治療亦僅止於兩年，並不建議終生服用。對於服用荷爾蒙較易有肝副作用的國人而言，是值得注意的。

4. 目前初步的五年插種治療追蹤報告極為良好，再加上體腔外放射治療的精準度問題，近接插種放射治療的確值得重視。

這一年進修的機會確實有很多的收穫，除了增加許多的新知外，並有初步的研究成果：兩篇第一作者摘要(一篇為美國放射治療學會 ASTRO 接受，一篇為 RSNA 北美放射醫學會接受)及一篇第二作者論文(ASTRO 接受)。(附錄於後)

肆、建議

- 一、對於配備有許多高科技設備的科部，希望能允許聘用高科技背景之專才使放療設備能充分應用及發揮。
- 二、數字是會說話的，完整而又有計畫性的資料庫是任何教學研究中心的夢想。希望能推動全院基礎臨床資料庫中心之建立，此工作需較長時間的追蹤。研究人員最好有統計背景。雖然可能需用到一些人 力，但在電腦科技的協助下，必能事半功倍。利用本院廣大的病患群眾可建立起華人的資料庫。這在國際會議上是很重要的資料庫，也可避免一味以外國資料庫為依據所造成的謬論。
- 三、發展攝護腺腫瘤插種治療是一件刻不容緩的事，隨著國人年齡的高齡化及檢驗技術之進步，會有越來越多的病患需接受插種治療。如此不但能提高治癒率，並能縮短療程。
- 四、電子照野影像攝影及攝護腺內值標記為精進體腔外攝護腺腫瘤放射治療最簡單最便宜的方法。此需與泌尿外科作充分的配合。
- 五、希望院方除了實驗室外，也能支持大規模且耗時又耗人力作臨床研究。

此次進修，需感謝院方及科內同仁之鼎力相助。有許多的心得無法一次寫完，將藉部內會議逐一報告。

附錄一

Prostate Movement during Simulation due to Retrograde Urethrogram

Liu, Yu-Ming^{1,2}; Ling, Stella M^{1,4}; Langen¹, KM; Shinohara, Katsuto³; Weinberg, Vivian¹; Roach, Mack¹

Radiation Oncology, UCSF, San Francisco, CA, USA¹

Cancer Center, Taipei Veterans General Hospital, Taipei, Taiwan²

Urology, UCSF, San Francisco, CA, USA³

Bat Area Regional Cancer Center, Pinole, CA, USA⁴

Purpose/Objective : Retrograde urethrogram is commonly used to define the prostate apex at time of simulation. A study recently reported that the urethrogram itself introduces error by causing prostate displacement (Malone et al. IJROBP Vol. 46(1) pp. 89-93, 2000). This current work further investigates the movement caused by the urethrogram as compared to "natural" movement of prostate.

Materials/Methods : Daily portal images, simulation films with urethrogram, and digitally reconstruction radiographs (DRR) from twenty-four patients treated with conformal radiotherapy for adenocarcinoma of prostate were compared. Gold markers were placed in the apex and bilateral bases of the gland prior to simulation. The location of the markers at the time of simulation and on the portal images acquired just prior to the treatment were compared with the location of markers on DRR. Movement in the superior-inferior and anterior-posterior direction as seen on lateral images were measured from 398 portal images by off-line customized imaging software and statistically evaluated using analysis of variance methods for repeated measures.

Results : The prostate has a "natural" movement that is not random around the "origin" of markers on DRR, but tends to be in a superior ($p = 0.047$) and anterior ($p = 0.07$) direction, the average shift being 2.88 mm and 2.85 mm. The urethrogram also tends to

introduce movement of the prostate in the superior and anterior direction with an average shift of 4 mm (anterior 3.6 mm, ranging 0 to 11.6 mm; superior 4.1 mm, ranging 0 to 11.5 mm). There was no difference between the absolute distance from the isocenter to the mean portal imaging results as "natural" movement and to the urethrogram-induced results (5.40 mm verse 5.75mm, respectively).

Conclusions : Use of the urethrogram does not cause any displacement of the prostate that is clinically insignificant when "natural" movement is take into account.

Implantation of gold markers or use of other prostate localization devices may be helpful along with portal imaging to ensure optimal daily positioning of the prostate.

附錄二

Set-up verification using portal images of implanted prostate markers: an inter-observer study

Yu-Ming Liu^{1,2}, M Aubin¹, K M Langen¹, K. Shinohara³, C. Anezinos¹, M. I. Osofsky¹, V. Weinberg¹, J. Pouliot¹, and Mack Roach III^{1,3}

¹Department of Radiation Oncology, ³Department of Urology

University of California San Francisco, 1600 Divisadero Street, San Francisco, CA-94143

²Cancer Center, Taipei Veterans General Hospital, Taipei, Taiwan

Purpose: Radioopaque markers that are implanted in the prostate are visible on portal images. Their expected location can be extracted from the radiographs that are digitally reconstructed from the treatment planning CT. Hardcopies of these latter images are available. Comparing the seed locations on the portal images with their expected location allows the determination of patient movement to realign the prostate in the radiation field. On a daily basis the radiation therapists need to decide in real time how to move the patient based on the two sets of images. Often this decision needs to be made quickly and in a stressful environment.

The purpose of this study is to compare the actual patient moves performed by the therapists with those determined by two radiation oncologists in a retrospective analysis of the portal images. The true patient movement was calculated using image analysis software that allowed a precise measurement of the distance between the desired and actual seed location. These measurements were used as our reference values.

Methods and Materials: Lateral portal images were acquired using an a-Si flat panel electronic portal imaging device (EPID). In the planning software, the seeds were contoured and hardcopies of the digitally reconstructed images were used for comparison with the portal images. The therapists were not given specific guidelines regarding the magnitude of the differences for which a move should be made. The moves performed by the therapists were recorded each day. Two radiation oncologists retrospectively and independently compared the portal images with the hardcopies of the reconstructed images. This process was done off-line and without any time pressure. Finally a careful measurement of the seed displacement was made for reference purposes by digitally overlaying the image sets. There are image sets available for 472 cases. To date 167 reviews of those cases from 18 patients have been completed.

Results: The individual responses between every pair of evaluators were highly correlated ($p < 0.004$ for each comparison) for both, the ant/post and sup/inf direction. Compared with the measured reference ant/post seed movement, the mean of the absolute difference between the reference and the user determined values for the two radiation oncologists and the therapists were 2.4, 1.4, and 2.5 mm, respectively. In the sup/inf direction the mean of the absolute differences from the reference compared with the user determined values were 2.2 and 1.4 mm for the two radiation oncologists and 2.4 mm for the therapists. Even though, there is a statistically significant difference ($p < 0.001$) among the reviewers, this is solely due to one radiation oncologist's readings. The percent of cases requiring moves 3 mm according to the reference measurements were 54 and 47 % in the ant/post and sup/inf direction. Subtracting the moves determined by the radiation oncologists and therapists from these reference values allows us to calculate the remaining frequency of positioning errors 3 mm. These remaining

frequencies were 23, 10, and 34 % according to the assessment of the two radiation oncologists and therapists in the ant/post direction and 23, 11, and 27 % respectively in the sup/inf direction. New positioning displacements of 3 mm were introduced by the radiation oncologists and therapists in 6, 1, and 2 % of the case in the ant/post direction. In the sup/inf direction the respective values were 5, 1, and 2 %.

Conclusions: Implanted radioopaque markers can be used reliably for daily prostate repositioning by therapists. An off-line analysis of the portal images by two radiation oncologists does not necessarily improve upon the therapists' patient alignment. An on-line display of the expected seed location on the computer screen may be a useful tool to improve positioning accuracy.

附錄三

Class Solution of Dose Constraints in Inverse Treatment Planning for Nasopharyngeal Carcinoma

Ping Xia, Ph.D., Y-M Liu², M.D., I. Poon, M.D., J.M. Quivey, M.D., P. Akazawa, CMD,
L. J. Verhey, Ph.D., and Nancy Lee, M.D.

¹Department Radiation Oncology, University of California, San Francisco, San Francisco,
CA, USA

² Cancer Center, Taipei Veterans General Hospital, Taipei, Taiwan

Purpose/Objective: The purpose of this study is to develop and test a class solution of dose constraints in inverse treatment planning for nasopharyngeal carcinoma (NPC), based on the analysis of dose volume histograms of the tumor targets and the involved sensitive structures from a series of 25 patients treated with inverse-planned IMRT (IP-IMRT).

Materials and Methods: Treatment plans for 25 NPC patients consecutively treated at our institution with IP-IMRT were reviewed. Of these, 9 were stage T1/T2 and 16 were stage T3/T4. The prescribed doses were 70 Gy to at least 95% of the gross tumor volume (GTV) and 59.4 Gy to at least 95% of the clinical tumor volume (CTV). From these treatment plans, dose volume histograms (DVHs) of sensitive structures were characterized through defined multiple endpoints, whether they were functional subunits (SFU) organized in series or in parallel. Using the mean values of these defined endpoints for subgroups of T1-2 and T3-4 patients, two sets of planning dose constraints were obtained for T1-2, T3-4 patients, separately. Using these two sets of dose constraints, 10 patients (five patients with stage T1/T2 and five patients with stage T3/T4

were subsequently re-planned without iterations. The qualities of the plans were evaluated by comparing the defined endpoints between the regenerated plans and the original clinically approved plans.

Results: The overall quality of the regenerated plans for the five T1-2 patients were better than the original plans when comparing the mean values of the endpoints. Sixty-seven percent of the mean endpoint doses from the regenerated plans were lower than that from the original plans. For T3-4 patients, the overall quality of the regenerated plans was comparable to that of the original plans. The planning time for these 10 patients using the standard dose constraints were significantly reduced from an average of five to ten iterations to one per patient.

Conclusions: Establishing a standard set of dose constraints for each specific cancer can significantly improve planning efficiency while keeping the high quality of each treatment plan.

Keywords: Intensity-modulated radiotherapy, head and neck cancer, inverse planning, optimization