2005 肿瘤精确放疗进展

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于金明 李建彬 黎 功 范廷勇 主编

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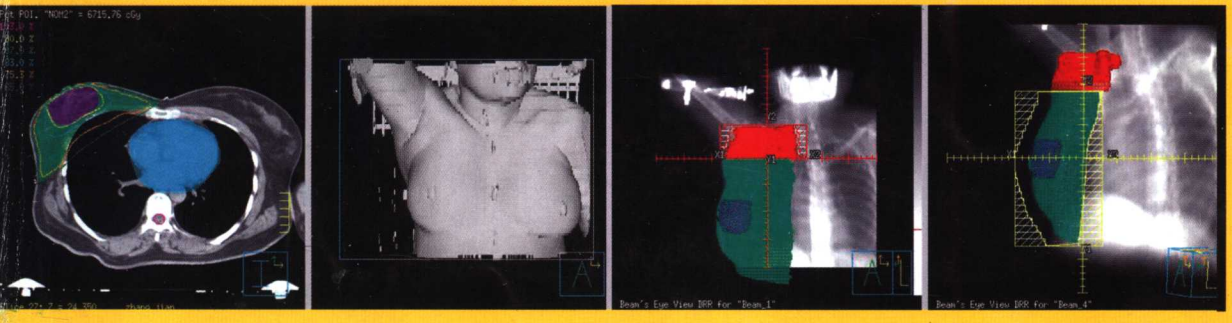

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前　言

随着放疗设备和相关学科的发展，肿瘤放射治疗发展迅速，特别是近五年来，肿瘤放射治疗技术的许多方面都发生了飞跃性的变化，以三维适形放疗和调强放疗为核心内容的精确放疗技术在国内得到了较为广泛的推广普及，影像引导放射治疗即将成为肿瘤放射治疗技术的主流。为构建肿瘤放疗技术进展的学术交流平台，展现近几年来肿瘤放射治疗研究成果，经中华医学会放射肿瘤治疗学分会批准，由山东省肿瘤医院主办的第三届济南国际肿瘤放射治疗新进展暨第二届全国中青年放射肿瘤学术研讨会在济南召开。本次会议得到了国内外专家同行的广泛支持，邀请到国内外近二十位知名肿瘤放疗界专家进行专题讲座，并收到多篇反映肿瘤放射治疗基础和临床研究进展的文稿，为了便于大家获得完整的资料，现结集出版。

本次会议的召开和本书的出版得到了肿瘤放疗届老前辈殷蔚伯教授、刘泰福教授、陈延条教授的关心与支持，得到了中华医学会放射肿瘤治疗学分会主任委员余子豪教授、副主任委员蒋国梁教授、何少琴教授的支持与帮助，得到了中华医学会放射肿瘤治疗学分会各位委员和中青年委员的支持，得到了国内外同行的支持。山东省肿瘤医院放疗科、设备科和药剂科的各位同志为本次会议做了大量的工作。在此一并表示感谢。

于金明　李建彬

2005 年 9 月

目　录

[Ⅰ. 专题讲座]

[Ⅱ. 综　述]

[Ⅲ. 基础研究]

[Ⅳ. 临床研究]

[Ⅴ. 放疗技术]

[Ⅵ. 短篇报道]

Ⅰ 专题讲座

4D CT (Computed Tomography) Improves Tumor Control Probability (TCP) When Compared With Helical CT Planning In 3D Conformal Radiation Therapy (CRT) For Patients With Lung Cancer

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Purpose: Tumor motion associated with respiration can cause geographic miss in 3D RT planned with helical CT scan. With the advent of 4D CT, it is feasible to determine internal target volume (ITV) representing the boundary of a volume in which GTV moves with respiration. The goals of this study were (1) to measure the extent of tumor motion associated with respiration in patients with lung cancer, and (2) to estimate detrimental impact in tumor control probability (TCP) relative to the magnitude of tumor motion when 3D RT is planned using conventional helical CT scan, and (3) to compare 3D RT planned with 4D CT vs. helical CT for normal tissue complication probability (NTCP) of lung.

Methods and Materials: Instrumentation used in this study includes a GE Lightspeed CT - scanner (4slice, 0.8s) and a Varian RPM respiratory monitoring system. The imaging protocol was approved by institutional IRB. Eligibility included: (1) medically inoperable stage I and II, and stage III lung cancer (T1 -4, N0 -3, M0) by the staging criteria of American Joint Committee on Cancer (AJCC); (2) a performance score 0 - 1 by the Eastern Cooperative Oncology Group (ECOG) scale; (3) candidate for definitive RT, RT plus chemotherapy or RT plus chemotherapy and surgery, and (4) ability to follow instructions for 4D CT scanning.

4D CT scans were acquired in axial cine mode, with timing signals relating scan acquisition with the motion of the anterior abdominal wall during shallow respiration. Briefly, scan data were acquired at a given table position over an entire respiratory cycle, x - rays were turned off, and the table was advanced to the next position with an interval of 2.5 mm. For each couch position typically 10 - 15 images were reconstructed, each at a different phase of the patient's respiratory cycle. In general as many as 1500 slices were acquired, after which the data were sorted according to small intervals of respiratory phase to generate up to 10 complete volumetric CT data sets over a respiratory cycle.

To determine the dosimetric implications of respiratory motion for standard 3D RT planning, a standard, static treatment plan was recalculated upon a 4D CT data set. For this study, a 4D CT study was obtained along with the normal helical CT scan. From the helical scan, a 3D RT plan using the CMS/Xio treatment - planning system was created based on the target volume contoured on the helical CT. The CTV was defined by a 10 mm expansion from the contoured GTV, and the planning volume included an additional 5 mm expansion for patient setup uncertainty and 5mm for beam penumbrae.

To obtain the actual dose delivered to the target volume, the standard 3D treatment plan was recalculated on the inhale, exhale and a mid - respiratory phase of the 4D CT study. Assuming no deformation of the target volume during respiration, the contoured target volume was shifted according to the centroid of the volume observed in the 4D CT scans. Dose to each voxel of the contoured target volume was calculated for each of the inhale, exhale and mid - respiratory breathing phases. Once the 3D dose was determined in each breathing phase, the dose to each corresponding voxel from the three breathing phases could be added

and weighed to construct a composite 3D dose distribution to the target volume, reflecting the actual dose the target received during treatment. From this 3D volume a true motion corrected DVH could be made and used for biological analysis.

Results: We have entered 90 patients with lung cancer who were judged candidate for 4D CT scan for RT planning. Age ranged from 40 to 88 years (median 71), and gender ratio consisted of male 48 to female 42. Tumor stages included stage IA (n = 17), IB (n = 4), IIA (n = 2), IIB (n = 11), IIIA (n = 36), and IIIB (n = 20).

The motion of the primary tumor (peak - to - peak) of these 90 patients varied from (5 mm to 54 mm with the following ranges: (10 mm (n = 17), 11 - 14 mm (n = 9), and (15 mm (n = 8) for stage IA - IIB (n = 34), and (10 mm (n = 23), 11 - 14 mm (n = 14), and (15 mm (n = 19) for stage IIIA and II-IB lesions (n = 56).

We chose a sample case with a peak - to - peak tumor motion of 40 mm for an illustration of negative impact in TCP when helical CT scan is used for RT planning. The impact of tumor motion on equivalent uniform dose (EUD) was calculated using generalized EUD model for free breathing plan with assumed no tumor motion, free breathing plan with assumed tumor motion, and ITV plan (4D CT data) at different levels of prescribed doses respectively (Table - 1).

Tumor control probability (TCP) at 3 years for stage I - II and III tumors was estimated using EUD for GTV and logistic dose - response model with slope ? 50 ?? of 1.5 (Table 2).

Table 1. EUD analysis (based on generalized EUD model with parameter a = - 10)

		Prescribed dose (Gy)			
		45	63	72	81
		Estimated EUD dose (Gy)			
Free breathing plan (Assumes no movement)	GTV	46	64	73	82
	CTV	45	63	72	82
Free breathing plan (Analysis with 4D CT data)	GTV	27	30	32	33
	CTV	5	7	8	9
ITV plan (Analysis with 4D CT data)	GTV	46	64	73	83

Table 2. Predicted TCP Relative To Tumor Motion

	Plan A[No Motion]			Plan B[No Correction for motion]			Plan C [Correction for motion with 4DCT]		
* Prescribed doses(Gy)	63	72	81	63	72	81	63	72	81
EUDdoses:GTV	64	73	82	30	32	33	64	73	83
(Gy) CTV	63	72	82	7	8	9			
TCP for stage I - II NSCLC at 3 years@	54	72	84	1.3	1.7	2.2	55	73	85
TCP for stage III NSCLC at 3 years@	37	56	73	~0	~0	~0	39	59	74

Plan A: GTV from helical CT (Assumes no motion)

Plan B: GTV from helical CT (Analysis with 4D CT data)

* Plan C: ITV from 4D CT data

@ : It is assumed that TCPs at 3 yrs with 60 Gy/30 F is 45% for Stage I – II and 30% for stage III NSCLC (calculations based on EUD for GTV and logistic dose – response model with slope ? 50 ?? of 1.5).

4D CT scan led us to change the management plan for this sample case from RT plus chemotherapy to preoperative RT and chemotherapy followed by surgery.

Conclusions: An initial experience with 4D CT scan for 90 consecutive patients with lung cancer is presented in terms of the prevalence of the range of tumor motion associated with respiration in the lung cancer patient population, and the deleterious impact in clinical outcome of RT is estimated when 3D CRT is planned with conventional helical CT scan in the presence of significant degree of tumor motion (a worst scenario).

Further analysis is underway for the assessment of the deleterious impact in TCP for tumors with a peak – to – peak movement of 30 mm, 20 mm, and 15 mm when planned with helical CT scan. The threshold of tumor motion, above which respiratory gating is beneficial by NTCP of lung will also be determined.

Physically and Biologically Targeted Radiation Therapy for Lung Cancer

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Standard treatment for patients with locally advanced non – small cell lung cancer (NSCL C), good performance status and minimal weight loss is now chemotherapy and radiation therapy. Concurrent chemo-radiotherapy is superior to sequential treatment for NSCLC and limited small cell lung cancer (LSCLC). Further improvement in survival was made by continuos hyperfractionated and accelerated Radiotherapy with concurrent chemotherapy for Lung Cancer However the therapeutic ratio seemed to have reached to a plateau due to increased normal tissue toxicity due to combined treatment modality. The toxicity compromised survival or quality of life among patients with common cancer such as cancer of the lung, esophagus, GI, Head/Neck, prostate, breast etc. Neither surgery, radiation, nor chemotherapeutic drugs are particularly selective against tumors. To enhance therapeutic ratio, reducing the toxicity of normal tissue is essential in addition to more efficacious cancer cell kill.

I will discuss mainly three ways to reduce normal tissue toxicity in combined cancer treatment Based on our clinical trials and investigational studies.

One way is to reduce physical damage to the normal tissue by applying three – dimensional conformal treatment (3DCRT); intensity modulated radiotherapy (IMRT), brachytherapy, proton or other high LET treatment and limited operation. 3DCRT is based on sum of gross target volume (GTV), clinical target volume (CTV) and planning target volume (PTV).

Tumor delineation by PET/CT and/or MRI is essential to determine GTV and CTV which also requires Radiation Oncologist's knowledge of pathological findings, such as microscopic tumor extension and frequency of nodal involvement to particular nodal stations depending primary tumor histology, differentiation, size and site. Planning target volume (PTV) needs to be more precisely delineated based on tumor motion, which can be reduced by respiration gating technique for lung cancer and adequate immobilization technique.

Acute severe esophagitis was significantly reduced by application of 3DCRT when patients with NSCLC treated with hyperfractionated RT and concurrent chemotherapy compared to conventional RT with same chemotherapy (10, Komaki et al IJROBP Vol 58, April1, 2004).

The second way to reduce normal tissue toxicity is biological protection by cytoprotective agents, such as Ethyol or KGF etc. or biologically targeted treatment to kill specific cancer cells, which can be done by more molecular targeted treatment such as C225, Iressa, Cox – 2 inhibitor, FTI, etc. To reduce normal tissue toxicity by applying molecular targeted treatment is that we can target antibodies and also block the signal transudation, which is a new molecular target. This could be at the cell membrane level or at the DNA level of the nucleus. Also, we can target genes, which have been investigated by many researchers for the past decade by Gene therapy. Now we are trying to investigate angiogenetic therapy and radiation therapy with or without chemotherapy. These treatments are supposed to increase local control as well as preventing micrometastasis for locally advanced lung cancer.

Ethyol is also known as Amifostine or WR 2721, which is an organic thyophosphate cytoprotective agent. Ethyol will protect all organs except for brain. The mechanism of protection of normal cells but not to the malignant cells by Ethyol is due to the high concentration of Alkaline Phosphates which exists in normal cells and activates Ethyol (WR 27 -21) to pro - drug WR 1065 which behaves as a scavenger for free radical produced by radiation or cisplatin before free radicals damage normal nucleus. Prospective randomized studied have shown that Ethyol will protect salivary gland from radiation for Head/Neck patients without tumor protection. Also several randomized study have shown that Ethyol protected esophagus when chemoradiation was used for lung cancer. Ethyol also prevented renal and neurotoxicity from cisplatin based chemotherapy for patients with advanced ovarian cancer.

The third way to reduce toxicity is modulation of timing of combined treatment to allow normal tissue recovery without recovering clonogens to proliferate. Hyperfractionated radiation therapy (HFXRT) was hoped for more cell kill of rapidly proliferating cells such as malignant cells without damaging normal cells, which usually have much slower proliferation rate. However, when accelerated HFXRT was combined with concurrent chemotherapy as a radiosentizer, normal tissue toxicity such as acute mucositis and esophagitis became major dose limiting toxicity. Therefore when and how combine chemotherapy and altered fractionation of RT is major task for oncologists. Especially when three cancer treatment modality e. g. chemoradiotherapy followed by surgery is utilized, timing of surgery, RT timing relative to chemotherapy, RT volume and dose, chemotherapeutic agents all important factors to be considered for normal tissue toxicities.

In summary, oncologists have been criticized because of slow progress of improvement in survival among cancer patients, which might be contributed death due to complication caused by too aggressive combined cancer treatment without normal tissue protection. We need to consider more individualized, genetically and molecular targeted treatment with application of sophisticated Radiation Planning, Equipment, Radioprotector and optimal agent and timing of Radiosensitizer relative to Radiation.

Current Status and Perspectives of Stereotactic Radiation Therapy for Early - Stage Lung Cancers in Japan

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Stereotactic irradiation (STI) for intracranial tumors has been widely available since 1990. The technique was expanded for extracranial tumors, especially tumors in the lung. We herein present the current status and perspectives of stereotactic radiation therapy (SRT) for lung cancers.

The critical issues concerning application of the stereotactic technique for lung tumors are the patient's setup reproducibility & the patient's movement. Several techniques are being developed to overcome these problems, which include the use of respiratory gating system, absolute breathing control, the use of body frame, and the development of the tracking system.

In this treatment modality, hypofractionated regimen is usually employed. The advantages of it are a shortend treatment course that requires far less trips to the clinic than a conventional program, and the adoption of a smaller irradiated volume allowed by greater setup precision. The disadvantages are the uncertain effects of altered fractionation and the theoretic risk of worsening the ratio of normal tissue to tumor tissue through the use of a high dose per treatment session.

At our department, we initiated three - dimensional (3 - D) conformal hypofractionated single high dose radiotherapy for lung tumors using a stereotactic body frame In 1998. This study was performed to evaluate the clinical outcomes of three - dimensional (3 - D) stereotactic radiotherapy of 48Gy in 4 fractions for Stage I lung cancer using a stereotactic body frame. Forty - five patients with Stage I non - small cell lung cancer has been treated between September 1998 and July 2003 at our department. Thirty - one patients had Stage IA lung cancer(T1N0M0), and the other 14 had Stage IB lung cancer(T2N0M0) whose tumor size was less than 4 cm in diameter. Three - dimensional treatment planning using 6 to 10 non - coplanar beams was performed to maintain the target dose homogeneity, and to decrease the irradiated lung volume > 20 Gy. All patients were irradiated using a stereotactic body frame and received 4 times 12 Gy single high dose radiation at the isocenter over a period of 5 - 13 (median = 12) days. Seven tumors (16%) disappeared completely after treatment (CR). Thirty - eight tumors (84%) decreased in size by 30% or more (PR) after treatment. Therefore, all tumors showed local response. During the follow - up of 5 - 63 (median = 23) months, no pulmonary complications greater than an NCI - CTC criteria of grade 3 were noted. Ninety - eight % (44/45) of the tumors were locally controlled without apparent evidence of local failure during the follow - up period. Regional nodal recurrences and distant metastases were in two and five of T1 patients, zero and four of T2 patients, respectively. Retrospective analysis for 281 patients with T1, 2 NSCLC treated at 13 institutes in Japan revealed excellent local control and survival outcomes. A multi - institutional study to evaluate the clinical benefits of SRT for T1N0M0 is underway with the support from Ministry of Health and Welfare in order to demonstrate that SRT is a standard treatment for inoperable cases and may be an alternative to surgical treatment for operable cases.

The treatment planning and respiratory gating to adopt respiratory motion of the tumor in proton beam therapy for hepatocellular carcinoma

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Recent advances of radiotherapy can be attributed from the development of technologies delivering higher doses to the target without deterioration of normal organ functions. Proton beam irradiation featured by Bragg – Peak is one of the revolutionized techniques with conformal dose distribution to include the target. However, the practical advantage of proton beam treatment can not be achieved unless the uncertainty of the target was regulated proficiently. Shizuoka Cancer Center has launched proton beam therapy in July, 2003 as the newest particle beam treatment institute in Japan. The indication of our institute was determined by the experience of preceding proton therapy institute in the world. However, because of difference in etiology of these cancers, the proportion of the disease is different from those of western proton treatment institutes. Of two hundred patients treated at our institute, the patients with truncal tumor account for more than ninety percent. Hepatocellular carcinoma is the second leading disease treated at our institute (first being prostate cancer) and is increasing cause of cancer death throughout East Asia. There are two specific problems to be resolved in order to utilize proton beam for treatment of hepatocellular carcinoma. First, the patients with liver cancer are also suffering from liver cirrhosis which might raise the mortality rate even after the treatment of hepatocellular carcinoma is performed successfully. In order to preclude severe liver function failure by irradiation of the patients with unfavorable liver function, we need to provide less toxic treatment for these patients. Several papers of dose – volume histogram analysis reported relationships with the morbidity of liver and deposited dose and irradiated volume, which means that precise definition of the target and less margins are required for the treatment. Second, the liver with which the cancer originated has been reported to be an organ showing remarkable movement by respiration. Therefore the deposited dose calculated by static CT dataset and giving to the target and normal tissues can not be applicable unless the respiratory motion was managed effectively. The motion of the targets measured in our cases ranged from 3mm to 40mm. The direction of the excursion of the target also varied with each patient. Therefore the tumor motion in the liver cannot be compensated by application of standardized robust margins added to the target. In our institute, three techniques, respiratory gating system, fiducial marker and individualized margins for internal motion have been introduced to deal with these issues. Respiratory gating treatment has been introduced for all patients with liver cancer in our institute. The proton beam is regulated by a signal reflecting abdominal wall motion through this system. In our protocol, the gating window during which the target is irradiated by proton beam was established five to ten percent of total respiratory motion. In this setting, the motion of the target during proton beam irradiation was estimated to be 4mm. The fiducial marker placed near the tumor allows us to define the tumor position during entire treatment by fluoroscopy. Less than 1mm of displacement of the marker can be detected by this method. The measuring motions of the marker provide the dynamic and quantitative information to predict the motion of the tumor during respiration, which helps us to define adequate margins for the target. The reduction of setting – up error by referring fiducial marker focuses on the issue of margin for internal motion. The direction and length of internal motion varies with each patient. Although respiratory gating system can reduce the margins for this displacementcation of the tumor, it is still