our clinical results and introduce the current status of stereotactic body radiotherapy (SBRT) for lung cancer.

Materials and Methods: More than 200 patients have been treated with SBRT. Forty-five patients who were treated between September 1998 and July 2003 were evaluated. Thirty-one patients had Stage IA lung cancer, and the other 14 had Stage IB lung cancer 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.

Results: 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. No other serious complications have not been encountered. All tumors except one were locally controlled without apparent evidence of local failure during the follow-up period. However, regional nodal recurrences and distant metastases were in three and four of T1 patients, zero and four of T2 patients respectively.

Discussion: The key issues for SBRT are fixing apparatus, respiratory regulation, treatment planning and verification. A few types of stereotactic body frames are available. For regulation of respiratory movement, abdominal wall compression, breath-holding, respiratory gating and tumor chasing methods were used. For irradiation technique, 6 to 10 non-coplanar beams or multiple arc beams were adopted. Daily verification is mandatory for SBRT. Portal films, EPID and CT on rails were used. Frequently used radiation regimens were 48 to 60 Gy in 3 to 5 fractions. Single dose radiosurgery technique is still pursued in a few institutes. The local control rates were almost always above 90 % for lung cancer, with few complications. Long term follow-up results have also been reported. Several unanswered questions and currently ongoing protocols will be also reviewed. The patient accrual for RTOG 0236, 60 Gy in 3 fractions was complete, and the operable patient accrual for JCOG 0403, 48 Gy in 4 fractions were also finished. The other multi-institutional studies are underway.

Conclusions: SBRT seems to be a promising method especially for the treatment of early stage lung cancer.

E14-03 State-of-the-Art Innovation in Radiation Therapy, Tue, Sept 4, 16:00 – 17:30

Image guided (4D) radiation therapy

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Improper knowledge of the patient's anatomy and position during the course of therapy has always been a major source of concern in radiation therapy potentially compromising the clinical results by insufficient dose coverage of the target volume and/or overdose of normal tissues. The management of target localization emanates in the concept of treatment margins to cope with the uncertainty of the true location of the target volume during irradiation (gross target volume or GTV; clinical target volume or CTV; set-up margin or SM; internal margin or IM; planning target volume or PTV; and planning risk volume or PRV). Concerning these so-called set-up uncertainties, it is generally accepted that 2 classes can be identified, systematic and random. Systematic errors exist because the imaging performed for treatment planning is typically a snapshot and the target position determined at that instant of time may differ from the average target position at treatment time, or if a certain procedure introduces an error that is repeated systematically in time. The random error is the day-to-day deviation from the average target position introduced with internal organ motion and the repeated treatment set-up that occurs in fractionated radiation therapy. The systematic error is generally considered more important, because if uncorrected it would propagate throughout the treatment course and lead to deleterious effect on local control. On the other hand day-to-day variations may be substantial requiring safety margins that limit the maximum dose administered to the tumour volume due to possible toxicity to surrounding healthy tissue. With the introduction of image-guided radiation therapy (IGRT) clinical confidence has grown and the opportunity is given to examine whether the traditional fractionated radiation therapy at 2 Gy per fraction is still the optimum strategy. This, in turn, introduces treatment schedules using less fractions (so-called hypo-fractionation), and the day-to-day variation in target localization may no longer be statistically random. And finally, motion management becomes an issue as tumour motion interacts with dose delivery causing a dose spread along the path of motion in some delivery techniques.

With the improved imaging modalities to define and delineate tumour volumes, identifying both morphologic as well as functional and biologic information, and the introduction of treatment modalities that allow for shaped dose distributions (e.g. intensity modulated radiation therapy or IMRT, stereotactic body radiotherapy or SBRT, and charged particle beams), the radiotherapy community is now capable to create dose distributions that match the tumour volume tightly. Conformal radiation therapy (CRT) aims at shaping the dose distribution to the delineated target volume, whereas conformal avoidance aims at avoiding critical structures. These advancements have been driven by the dual goals of maximizing radiation dose to tumour volume whilst minimizing dose to surrounding healthy tissue. It goes without saying that accurate knowledge of the patient's anatomy during the radiation process is of utmost importance and in fact it can be argued that these novel technologies such as IMRT and shaped beam radiosurgery are useless without proper image-guidance.

The concept of image-guidance as such is not new in radiotherapy. Aspects of image guidance have always existed, even with the first use of x-rays for cancer therapy, probably using the same radiation source for both imaging and treatment. The concept of IGRT however, has been introduced as to define the accomplishment of tumour and soft tissue imaging in real-time or near real-time for correction of both systematic and random errors on a daily basis. It was born out of the need for accurate target localization required for IMRT and SBRT, and allowing delivery of boost doses to sub-volumes identified with functional and biological imaging. IGRT will be mandatory to exploit the possible clinical benefits of these new treatment procedures. As the capabilities of IGRT improve, it will provide the tools to better understand treatment uncertainties and allow a re-examination of the present practice regarding treatment margins. Conceptually, IGRT refers to in-room image-guidance just before or during treatment and is based on the assumption that the tumour volume has been defined adequately. The imaging modalities applied for tumour identification and delineation, although they also help to ìguide the treatmentî, are not part of the IGRT concept in its current definition.

For simplicity, an ideal IGRT system should have 3 essential elements: (a) 3D and if possible motion (4D) assessment of the target volume (preferably 3D volumetric information of soft tissue including tumour volume), (b) efficient comparison of the image data with reference data,

and (c) an efficacious and fast process for clinical meaningful intervention (preferably fully automated). The clinical introduction of on-line electronic imaging devices (EPID) has led to the improved understanding of treatment uncertainties, and of the need for strategies to further reducing them. Already in the early 90ís strategies had been developed to use EPID for near real-time patient set-up, and although the first requirement (3D assessment) could be established by using multiple planar images, this procedure never became a mainstream solution as it was cumbersome for implementation into the daily workflow. Yet, this development did raise the awareness of the potential benefits of image guidance and the concept IGRT was born. IGRT solutions could be classified as follows: (1) megavolt (MV) imaging, (2) kilovolt (kV) imaging, and (3) solutions using non-ionising radiation. Some of these IGRT techniques are designed for interfraction target localization, some techniques will be able to perform intrafraction target motion management. In other words not limited to target observation only, but also offering the possibility of controlling the treatment beam based on that information for breathing synchronized irradiation. In principle 2 approaches exist: one uses the image guidance to align the target volume with respect to the treatment beam using a robotic couch control system in combination with a beam triggering system switching the beam on-and-off in synchronization with a breathing signal, the other in turn, uses the imaging information to guide the treatment beam using a robotic linac or computer control of the beam collimating system to actually follow the target during beam-on. The latter has the potential of true real-time tumor tracking, whereas the former can be used to gate the treatment in case of organ motion.

It will be shown, that the introduction of new technologies such as IGRT and 4D Radiation therapy significantly helped reducing complications and paved the way for more aggressive treatment schedules, (in)directly improving outcome. It is with the clinical introduction of IGRT that we start to understand the true concept of margins and organ motion. The adoption of new technologies in IGRT, not only allowed for more precise and aggressive therapies, but also influenced the indications of radiation therapy and initiated a revision of generally accepted fractionation schemes and concepts of radiobiology. New imaging modalities help avoiding inter-observer variation, and provide increased functional/biological information of the tumour to focus the treatment more efficiently. These developments will guide us to "paint dose by numbers" acknowledging the heterogeneous nature of tumours so far neglected by delivering homogeneous dose distributions. Finally, this review will demonstrate the necessity of a close collaboration and synergy between the different disciplines in combating cancer.

E14-04 State-of-the-Art Innovation in Radiation Therapy, Tue, Sept 4, 16:00 – 17:30

Particle beam therapy

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Background: Particle beams have a distinct physical advantage over conventional photon beams. Particle beams have a low entrance dose, a maximal dose at any prescribed depth, called the "Bragg peak", and no exit dose. The "Bragg peak" can be spread out and shaped to conform to the depth and volume of an irregular target. Particle beam therapy (PBT) can thus create an inherently three-dimensional conformal dose distribution without extra dose to the surrounding normal tissue compared with conformal photon treatment. At present, two particle beams are used for clinical purpose in the world. One is proton beam and the other is carbon-ion beam. The difference of these particle beams is its biological effect. Proton beam has a value of relative biological effectiveness (RBE) as 1.1, which would be considered to be almost identical biological effect with X-rays. In contrast, RBE of carbon-ion beam is estimated to be 3.0, and this high value is expected carbon-ion beam would be more effective for radio-resistant tumors. In Japan, PBT for lung cancer was performed under respiratory gating irradiation that means beam will turn on in only end expiration phase, and irradiated volume can be minimized. However, in western countries, respiratory gating system is rarely used.

Literature review: Most of the published articles employing PBT were focus on treating early stage no-small cell lung cancer (NSCLC), especially for Stage I disease. At University of Tsukuba, 51 NSCLC patients were treated with PBT with protons. Stage I, II, III, IV patients were 28, 9, 8, 5, respectively. The 5-year overall survival rate for Stage IA and IB were 70% and 16%, respectively (1). At Loma Linda University Medical Center, hypofractionated PBT with protons with 51 cobalt Gray equivalent (CGE) or 60 CGE in 10 fractions were delivered for 22 and 46 Stage I NSCLC patients, respectively. With a median follow-up period of 30 months, 3-year disease specific survival rates were 72% (2). At the National Institute of Radiological Sciences in Japan, hypofractionated PBT with carbon-ions has been conducted (3-5). Recently, results of 51 patients with Stage I NSCLC treated with 72 CGE in 9 fractions were reported. With a median follow-up period of 59.2 months, 5-year cause specific survival rates were 75.7% (IA: 89.4; IB: 55.1), and overall survival 50.0% (IA: 55.2%; IB: 42.9%). No severe acute and late toxicities were observed in all the published literatures.

NCC experiences: We already reported our initial experience of PBT with protons for Stage I NSCLC (6), and updated results were analyzed. Between December 1999 and September 2006, 77 patients with stage I NSCLC were treated by PBT with protons in our institution. The indication of PBT were 1) clinical stage I NSCLC, 2) $PaO2 > 60$ torr, 3) medically inoperable, or refusal of surgery, 4) performance status 0-2, 5) written informed consent. The target volume was defined as the gross tumor volume (GTV) plus appropriate margins for subclinical tumor extension. In general, 8 mm margin was added for all directions as the clinical target volume (CTV). Margins for set-up error and respiratory motion were added for planning target volume (PTV). Treatment was performed using respiratory gating with strain gauge. Based on the analysis of respiratory movement during gating irradiation, 5 mm internal margin for respiratory movement was added. A total dose of 70 - 94 CGE was delivered in 20 fractions over 4 to 5 weeks. Kaplan-Meier method and CTC-AE version 3.0 were used to assess survival and toxicity.

Patients characteristics were as follows: median age 75 years (range, 52 to 87); male/female, 54/23; Stage IA/IB, 43/34; squamous/ adenocarcinoma/ others, 28/23/26; total dose 70/80/88/94 CGE, 3/57/16/1. The initial response rate was 74% (95% confidence interval (CI), 63 to 83%). With a median follow-up period of 24 months (range, 3 to 82 months), the 2-year local progression-free and overall survivals were 94% (95%CI, 87 to 99%) and 91% (95% CI, 83 to 99%)(Fig.1), respectively. No severe acute toxicity was observed. Late grade 2 and grade 3 pulmonary toxicities were observed in 5 and 3 patients, respectively. Four patients experienced fractures of ribs within irradiated volume. The 2-year loco-regional progression-free survivals in stage IA and IB patients were 95% (95% CI, 88 to 100%) and 67% (95% CI, 50 to 84%)(Fig. 2), respectively. Six of 8 patients who suffered late grade 2 or greater pulmonary toxicities had stage IB disease.

Conclusions: Literature review and updated our data show that PBT with both protons and carbon-ions is a promising treatment modal-