Preliminary Treatment Results of Intensity-Modulated Radiotherapy for Prostate Cancer

Kang-Hsing Fan[1], MD; Yen-Chao Chen[1], MD; Cheng-Keng Chuang[2], MD, PhD; Min-Li Hsieh[2], MD; Ji-Hong Hong[1,3], MD, PhD

Background: To review the initial treatment results of intensity-modulated radiotherapy (IMRT) for prostate cancer.

Methods: Ninety-two patients treated with IMRT before July 2003 were included in this study. The median follow-up was 32 months. The indications for IMRT included primary, adjuvant, and salvage treatment. Combined treatment with androgen suppression therapy was variable. The primary study endpoints were chronic adverse events which were subjectively reported. Only patients with an adenocarcinoma and who had been treated by primary radiotherapy were included in the analysis of disease relapse.

Results: At the time of analysis, 89 patients were still alive, and only 2 patients had died of prostate cancer. In the survival analysis, the 30-month failure-free survival rates were 100%, 89.2%, and 67.3% for the low-, intermediate-, and high-risk groups of patients, respectively. Pretreatment PSA level, Gleason score, risk classification, and adjuvant hormone therapy were significantly associated with relapse according to the univariate analysis, while only risk classification remained significant in the multivariate analysis. During follow-up, 5 (6%) patients developed grade 2 gastrointestinal (GI) adverse events (AE). Sixteen (18%) and 7 (8%) patients developed grade 2 and 3 urinary AE, respectively. Development of severe urinary adverse events was closely related to previous surgical treatment. No factor was identified as being correlated with the GI adverse events. The preservation rate of sexual function was 25.7%.

Conclusions: Seventy-two Grays of irradiation, administered by IMRT, is a safe method as the primary treatment for prostate cancer. However, severe urinary toxicity was related to previous surgical treatment. There is a need for longer follow-up periods to verity the benetit of this dosage level.

(Chang Gung Med J 2006;29:313-24)

Key words: prostate cancer, intensity-modulated radiotherapy (IMRT), adverse event, complications.

Prostate cancer (PC) is the leading male cancer in many Western countries, and its incidence also increased rapidly in Taiwan in the last decade.[1] Choices for curative treatment include surgery and

From the [1]Department of Radiation Oncology, [2]Division of Urology, Department of Surgery, Chang Gung Memorial Hospital, Taipei; [3]Department of Medical Imaging and Radiological Science, Chang Gung University, Taoyuan.

Received: Sep. 29, 2005; Accepted: Jan. 19, 2006

Correspondence to: Dr. Ji-Hong Hong, Department of Radiation Oncology, Chang Gung Memorial Hospital. 5, Fushing Street, Gueishan Shiang, Taoyuan, Taiwan 333, R.O.C. Tel.: 886-3-3281200 ext. 2601; Fax: 886-3-3280797; E-mail: jihong@cgmh.org.tw

radiotherapy (RT), which can be brachytherapy, external beam radiotherapy (EBRT), or a combination of both. As compared with EBRT alone, surgery and brachytherapy are more commonly applied to patients with early-stage PC. Several retrospective studies and a randomized trial have provided evidence of dose-dependence in the control of PC by RT.[2,3] However, the rectum and bladder are usually the dose-limiting organs, and dose escalation increases the risk of complications there. Dose escalation, even by 3-dimensional conformational radiotherapy, was shown to increase the complication rate in some studies.[3-5] Intensity-modulated radiotherapy (IMRT) is a new treatment technique invented in the early 1990s.[6,7] This novel technique provides the ability to conform the radiation dose to a tumor with an irregular shape, create a rapid dose fall-off surrounding the target, and decrease the volume of the high-radiation dose for adjacent normal organs.[8,9] When IMRT is applied to PC treatment, the upper limit of the dose prescription to the prostate can be increased, and complication rates for normal tissues remain the same or are even reduced.

In this study, we report our preliminary results of using IMRT for treating prostate cancer. Although the dose level we used for primary RT was relatively low as compared to many other studies, we still obtained useful information on disease control and toxicity. We believe that our results provide important references for the treatment of ethnic Chinese patients with prostate cancer.

METHODS

Patient characteristics

Ninety-two prostate cancer patients treated by IMRT between December 2000 and July 2003 were included in this study, and the minimal follow-up time was 2 years. The median age was 71 (range, 54~83) years. Fifty-nine patients (64%) had systemic diseases such as diabetes, hypertension, heart disease, or other cancers before RT. All patients had an adenocarcinoma except for 3 patients who respectively had a sarcoma, clear cell carcinoma, and transitional cell carcinoma. Indications for IMRT included primary curative treatment (73 patients, 2 of whom had received unsatisfactory high dose-rate brachytherapy before IMRT), postoperative radiotherapy (10 patients), and salvage of biochemical failure following surgery (9 patients).

Preparation for RT included customization of an immobilization device, computed tomographic (TC) simulation, target and organ-at-risk delineation by a physician, and plan optimization by a medical physicist. The daily fraction size was 1.8 Gy. For patients receiving primary RT, the prescribed doses to the seminal vesicle and prostate were 63 and 72 Gy, respectively, if the seminal vesicles were not involved. If the seminal vesicles were involved by the cancer, they were irradiated with 72 Gy. Forty-five Grays to the mid-pelvis by box-field was given to patients whose risk for pelvic node metastasis was higher than 15%, as calculated using the Roach formula (pelvic nodal metastasis rate = 2/3 PSA + (Gleason score - 6) x 10%), and who were $\leqq$ 75 years old and in good general condition. For IMRT, the clinical target volume (CTV) was the prostate and seminal vesicles identified from the CT image, and the planning target volume (PTV) was the CTV plus a 1-cm margin in all directions except for the prostate-rectum junction where the margin was reduced to 7 mm. Parameters given for the IMRT plan were as following: (1) 100% of the prescribed dose < dose of the CTV < 110% of the prescribed dose; (2) 95% of the prescribed dose < dose of the PTV < 110% of the prescribed dose; (3) maximal dose to the rectum < 105% of the prescribed dose and < 15% of the volume of the rectum received a dose of > 72 Gy; and (4) maximal dose to the bladder < 105% of the prescribed dose and < 30% of the volume of the bladder received a dose of > 72 Gy. For patients receiving postoperative RT or salvage treatment following biochemical failure, the initial CTV was defined as the "prostate fossa" (the region occupied by the prostate gland before surgery). The expansion of the PTV from the CTV was similar to that for the primary RT. All cases received 63 Gy to the prostate fossa (CTV), and a 3.6-Gy boost dose was given to those with a positive margin in the anastomotic site or capsular region. For patients receiving salvage RT following biochemical failure, the dose to the prostate fossa was 66.6 Gy, and the dose to the gross tumor, if identified from magnetic resonance imaging (MRI), was 72 Gy.

Androgen suppression therapy (AST) was given with variable conditions and intensities during the initial period of our practice. Since combined AST proved to have survival benefits, prescriptions of

neoadjuvant and adjuvant AST were protocolized after the year 2003. Neoadjuvant (2 months before and during IMRT) AST was recommended for the intermediate-risk group of patients (risk classifications are listed below). Two years of or permanent AST luteinizing-hormone releasing hormone analogue or an orchiectomy) was recommended for the high-risk group of patients. The characteristics of all patients are listed in Table 1a and b.

Follow-up principle

Prostate-specific antigen (PSA) was checked on the last day of the radiotherapy course. The follow-up schedule was every 3 months within the first 2 years and every 4~6 months after 2 years, depending on the risk classification of the patient. The PSA test and a digital rectal examination (DRE) were performed at each visit. No elective prostate biopsy was arranged after radiotherapy. Examinations other than regular PSA checking and DRE were arranged only if disease-relapse was suspected through PSA monitoring, DRE, or the appearance of other suspicious symptoms and signs.

RT-related adverse events including urinary, gastrointestinal, and sexual events were evaluated at each visit. The appearance of adverse events was recorded mostly by patient's subjective observations, either voluntarily or upon being questioned. Objective examinations or interventions were arranged when bothersome events or those that interfered with daily activities appeared. Minimal or tran-

Table 1a. Patient Characteristics

Characteristic	Frequency (percentage)
Age (years)	Median: 71 (range, 54~83)
Any systemic disease	
No	32 (35%)
Yes	60 (65%)
Pretreatment PSA level	
< 10 ng/ml	24 (26%)
≥ 10 but < 20 ng/ml	26 (29%)
≥ 20 ng/ml	39 (42%)
Unknown	3 (3%)
Histology	
Adenocarcinoma	89 (97%)
Others	3 (3%)
Gleason score	
2~6	42 (46%)
7	25 (27%)
8~10	22 (24%)
Not available	3 (3%)
Tumor state	
T1	13 (14%)
T2	40 (44%)
T3	31 (34%)
T4	4 (4%)
Unknown	4 (4%)
Node stage	
N0	87 (95%)
N1	5 (5%)
Suspicious distant metastasis	
Negative	88 (96%)
Positive	4 (4%)

Table 1b. Distribution of Treatment Modalities

Characteristic	Frequency (percentage)
Androgen suppression therapy before radiotherapy	
No	29 (31%)
Yes	63 (69%)
Adjuvant androgen suppression therapy after radiotherapy	
No	61 (66%)
Yes	31 (34%)
Transurethral resection of the prostate (TURP) before radiotherapy	
No	50 (54%)
Yes	42 (46%)*
Radical prostatectomy before radiotherapy	
No	73 (79%)
Yes	19 (21%)
Indications for IMRT	
Primary treatment	71 (77%)
Failure of brachytherapy	2 (2%)
Postoperative radiotherapy	10 (11%)
Salvage treatment of biochemical failure	9 (10%)
Whole-pelvic irradiation	
No	63 (68%)
Yes	29 (32%)
Total dose of IMRT	
< 60 Gy	2 (2%)
60~69.99 Gy	21 (23%)
> 70 Gy	69 (75%)

Abbreviations: IMRT: intensity-modulated radiotherapy; Gy: Gray.

* Eight patients received a radical prostatectomy after TURP. In the following analysis, the factor "TURP" was not taken into consideration in these patients because the effect of TURP was masked by radical prostatectomy.

sient adverse events such as rectal bleeding and hematuria were not routinely confirmed by endoscopic examination.

Assessment of disease control

To prevent interference from other different modalities, the analysis of survival and tumor control only included patients who had an adenocarcinoma and who underwent primary RT. These patients were classified into 3 groups depending on the pretreatment PSA level, the sum of the Gleason score, and the clinical stage. The low-risk group included patients with T1-2aN0M0, PSA < 10 ng/ml, and the sum of the Gleason score of < 7. The high-risk group included patients with any of following risk factors: T3-4, nodal or distant metastasis, PSA ≧ 20 ng/ml, or the sum of the Gleason score ≧ 8. Characteristics of all patients included in the disease-control analysis are listed in Table 2.

Table 2. Characteristics of Patients with an Adenocarcinoma, Treated by Primary Radiotherapy, and Included in the Survival Analysis

Characteristics of prognostic and treatment factors	Frequency (percentage)
Gleason score	
2~6	33 (47%)
7	20 (28%)
8~10	18 (25%)
PSA level	
< 10 ng/ml	17 (24%)
≥ 10 but < 20 ng/ml	21 (30%)
≥ 20 ng/ml	33 (46%)
Tumor stage	
T1~2a	22 (31%)
T2b	21 (30%)
T3~4	28 (39%)
Risk classification	
Low-risk group	9 (12%)
Intermediate-risk group	19 (27%)
High-risk group	43 (61%)
Neoadjuvant androgen suppression therapy	
No	12 (17%)
Yes	59 (83%)
Adjuvant androgen suppression therapy	
No	42 (59%)
Yes	29 (41%)
Pelvic irradiation	
No	50 (70%)
Yes	21 (30%)

Assessment of radiotherapy-related toxicities

Acute and late adverse events were recorded at each outpatient department (OPD) visit, and these were mainly focused on the gastrointestinal (GI) and urinary systems. Adverse events appearing after 6 weeks or persisting for 6 weeks after completion of RT were defined as late events. The severity of the urinary and GI adverse events was recorded according to the Common Terminology Criteria for Adverse Events 3.0 (CTCAE 3.0) published by the Cancer Treatment Evaluation Program of the National Cancer Institute (CTEP/NCI, http://ctep.cancer.gov/reporting/ctcnew.html), Bethesda, MD, USA. To evaluate sexual function, we developed a simple 4-grade scoring system for subjective evaluation. Scores of 3, 2, 1, and 0 represent normal, unsatisfactory but able to complete intercourse, erection inadequate to completion intercourse, and totally impotent, respectively. The grade of toxicity was expressed as the pretreatment score - post-treatment score.

Data analysis

The primary events that we wanted to observe were disease relapse in any form and the occurrence of any RT-related adverse events. Kaplan-Meier survival calculations were dated from the completion of RT. The log-rank test was used to determine differences in survival curve comparisons. Cox proportional hazards regression analysis was used to confirm the independence of the treatment and risk stratification in the multiple covariate analysis of failure-free survival (FFS). Pearson's Chi-square test or Fisher's exact test was used (2-sided) to determine the correlation significance between adverse event development and patient's characteristics or treatment methods.

RESULTS

Dose profile

The dose-volume profile is given in Table 3. Overall, most of the IMRT plan achieved the requirements of the rectal and bladder dose constraints. Eighteen (20%) patients did not meet the requirement for the dose constraint for the urinary bladder, and their bladder volumes (mean ± SD, 65.3 ± 19.1 ml) shown on the CT simulation image were relatively smaller than those of other patients (mean

Table 3. Dose Profile for the Rectum and Bladder

	Bladder maxima dose (Gy)	Bladder mean dose (Gy)	Percentage of bladder volume receiving 64.80 Gy	Percentage of bladder volume receiving 72 Gy	Rectal maximum dose (Gy)	Rectal mean dose (Gy)	Percentage of rectal volume receiving 72 Gy
Mean value	74.5	53.95	37.6%	19.6%	73.5	52.98	14.5%
Maximum value	83.99	68.65	95%	52%	79.56	70.34	46%
80 percentile	77.28	62.41	52%	30.1%	77.1	62.35	21.2%
90 percentile	78.50	63.32	54%	41.4%	78.69	63.87	28.2%

Abbreviation: Gy: Gray.

$\pm$ SD, 112.8 $\pm$ 59.6 ml); the difference reached borderline significance (p = 0.077). No factor was found to be correlated with achieving the rectal dose constraint.

Overall survival

At the time of analysis (July 2005), 89 (97%) patients were alive, and 2 and 1 patients had died of prostate cancer and intercurrent disease (pneumonia), respectively. The median follow-up time of living patients was 32 months. The estimated 3-year overall survival rate was 96.4%. The 2 patients who died of prostate cancer were both in the high-risk group, and 1 of them had developed hormone-refractory disease before RT. The patient who died of intercurrent disease had had pneumonia which occurred soon after completion of IMRT and was not recognized as treatment-induced mortality because there was no sign for infection during RT.

Failure-free survival

Seventy-three patients received RT as the primary treatment for PC. For the remaining 19 patients, 10 had been treated with IMRT as adjuvant therapy to a radical prostatectomy, and 9 as salvage treatment for biochemical failure with or without obvious local recurrence. Two of the 73 patients who received primary IMRT had tumor histology other than an adenocarcinoma and were excluded from the recurrence and survival analysis.

According to our risk classification, 9 (13%), 19 (27%), and 43 (61%) patients were classified into the low-, intermediate-, and high-risk groups, respectively. Eighteen (25%) patients developed biochemical and/or clinical failure during follow-up; all but 2 patients developed biochemical failure before clinical failure. In 16 patients without clinical failure when biochemical failure was defined, 2 local, 2 distant, and 1 local combined with distant failure were subsequently identified. No regional nodal recurrence was observed. All 9 low-risk-group patients were failure-free at the time of analysis. Two of the 19 intermediate-risk-group patients had biochemical failure only. Among the 43 high-risk-group patients, 2 developed symptomatic bony metastasis without biochemical failure, and 14 patients developed biochemical failure. In these 14 patients, 3 local and 3 distant failures were subsequently observed. As shown in Figure 1, the 30-month FFS rates were 100%, 89%, and 67% for the low-, intermediate-, and high-risk-group patients, respectively. Pretreatment PSA level, Gleason score, risk classification, and whether receiving adjuvant hormone therapy were significantly associated with FFS in the univariate analysis. Only risk classification remained significant in the multivariate analysis. The results of the univariate and multivariate analyses are listed in Table 4.

Acute radiotherapy-related adverse events

Six patients (7%) developed grade 3 toxicities: 1 presented with severe diarrhea, 3 with urinary frequencies at intervals of < 1 h, and 2 with urinary tract infections requiring admission. The acute toxicities of the other patients were well managed by outpatient medications. Because severe acute events were uncommon, our data analysis combined patients with grades 2 and 3 acute adverse events into a single group. The factors analyzed included age, systemic disease, androgen suppression therapy, transurethral resection of the prostate (TUPR), radical prostatectomy, pelvic irradiation, the total, maximal, and mean doses to the rectum or bladder, and the specific dose volume percentage of the rectum

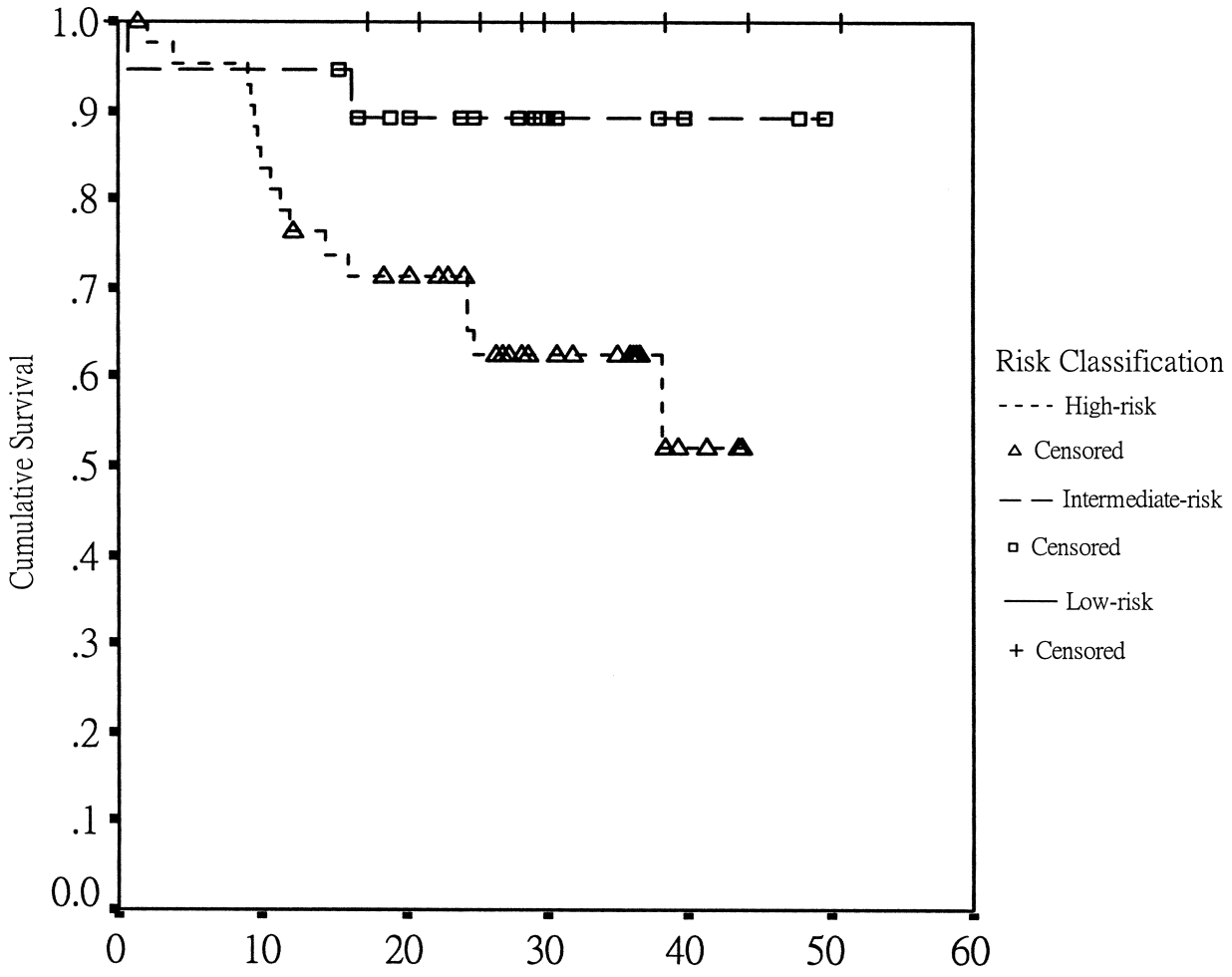

Fig. 1. Failure-free survival curve of different risk groups.

and bladder. The Chi-squared test revealed that acute grade 2 or 3 GI adverse events were only closely related to pelvic irradiation (p = 0.001), but not to the other factors. The odds ratio of pelvic irradiation was 5.1 (95% confidence interval (CI): 1.9~13.4). No factor was found to have a statistically significant correlation with grade 2 or higher acute urinary adverse events through Fisher's exact test. No obvious dose response with the acute adverse events was observed.

Late radiotherapy-related adverse events

Four patients did not receive regular follow-up in the clinics and were excluded from the analysis of late toxicity. The frequencies of late adverse events are listed in Table 5. Twenty-one (24%) patients developed late gastrointestinal adverse events; most of these events (18%) were grade 1, and no grade 3~5 late GI events were observed. The median time to first appearance of grade 1~2 adverse GI events was 9 (range, 2~39) months. Four (5%) cases of rectal bleeding occurred during follow-up. Only grade 2 or higher acute GI adverse events during RT and pelvic irradiation were found to be associated with late GI adverse events with borderline statistical significance, with the p values of Fisher's exact test being 0.058 and 0.071 (two-sided), respectively.

Thirty-five (41%) patients had grade 1~3 late urinary adverse events, and 7 of them (8%) were grade 3 events (requiring admission and/or interventional treatment). No grade 4~5 late urinary events were observed. The time to appearance of the late

Table 4. Results of the Univariate and Multivariate Analyses of Failure-free Survival

Factors	30-month failure-free survival	Univariate analysis *p* value	Multivariate analysis Hazard ratio (95% CI)	*p* value
Gleason score†		*0.047	†1.039 (0.958~1.127)	0.355
2~6	87.1%			
7	60.8%			
8~10	65.5%			
PSA level		*0.025	‡1.000 (1.000~1.000)	0.149
< 10 ng/ml	94.1%			
≥ 10 but < 20 ng/ml	83.8%			
≥ 20 ng/ml	57.7%			
Tumor stage		0.211	0.704 (0.408~1.213)	0.206
T1~2	83.3%			
T3~4	69.7%			
Risk classification		*0.042	§4.273 (1.126~16.208)	*0.033
Low-risk group	100%			
Intermediate-risk group	89.2%			
High-risk group	67.3%			
Neoadjuvant AST		0.228	0.208 (0.009~ 5.001)	0.334
No	91.7%			
Yes	71.4%			
Adjuvant AST		0.0245	2.38 (0.729~7.724)	0.151
No	86.6%			
Yes	65.2%			
Pelvic irradiation		0.533	1.243 (0.389~3.971)	0.713
No	78.1%			
Yes	75.3%			

Abbreviations: AST: androgen suppression therapy; HR: hazard ratio, CI: confidence interval.

* Statistically significant, $p < 0.05$.

Groups with similar survival were combined together:

† Gleason scores of 7 and 8~10.

‡ PSA < 10 ng/ml and PSA ≥ 10 but < 20 ng/ml.

§ Low- and intermediate-risk groups

Table 5. Frequencies of Chronic Adverse Events

	Grade 0	Grade 1	Grade 2	Grade 3	Grades 4~5
Gastrointestinal system	67 (76%)	16 (18%)	5 (6%)	0	0
Rectum	78 (88%)	6 (7%)	4 (5%)	0	0
Bowels	74 (84%)	13 (15%)	1 (1%)	0	0
Urinary system	52 (59%)	13 (15%)	16 (18%)	7 (8%)	0
Outlet obstruction	78 (89%)	2 (2%)	4 (5%)	4 (5%)	0
Incontinence	64 (73%)	11 (12%)	10 (11%)	3 (3%)	0
Cystitis	82 (93%)	1 (1%)	5 (6%)	0	0

urinary effects ranged from 0 (persistent symptoms) to 23 (median, 4) months. After excluding patients who developed urinary complications immediately after surgery or at the beginning of RT, the median time to onset was 13 (range, 3.5~23) months. For those with grade 3 adverse events, 4 patients developed a grade 3 obstruction requiring surgical intervention, and 3 had total urinary incontinence which was present before RT and had been caused by surgery. Two of the 4 patients with a grade 3 obstruction had had similar events several times before RT; another had had urinary tract obstructions twice

caused by bladder stones before RT. Therefore only 1 event of acute urinary retention with outlet fibrosis was truly ascribed as being an RT-induced late urinary event. Surgical management before RT was significantly correlated with development of grade 2 or higher urinary adverse events. The relationship between grade 2 or higher urinary adverse events and surgical treatment (TURP and a radical prostatectomy) is given in Table 6. Five (6%) patients developed mild and transient gross hematuria, but it spontaneously resolved in all patients within 1 month. Moderate or severe cystitis that required medical management was not observed in any patient. We tested the relationship between chronic urinary adverse events and the radiation dose profile. The volumes of bladders receiving 64.8 Gy (V64.8) and 70 Gy (V70) of patients having grade 2~3 adverse events were dispersed over a great range. The V64.8 ranged from 4% to 54%, with a median value of 36%. The V70 ranged from 0% to 27%, with a median value of 17%. No factor was found to be significantly related to the development of chronic urinary adverse events by the Chi-square test ($p > 0.05$), including the maximum bladder dose, the mean bladder dose, V64.8, V70, or whether the entire pelvis was irradiated. So, there was no obvious dose-response relationship for the development of urinary adverse events.

Sexual function was not evaluated, either before or after treatment in 16 patients. The reasons were either loss to follow-up, no records for sexual function, or patient refusal to be questioned. Sexual potency was lost before treatment in 41 patients, and only 35 patients who had a score of 2~3 for sexual function before any treatment (including surgery and hormone therapy) were eligible for analyzing the toxicity of treatment on sexual function. Nine of these 35 patients were treated by a radical prostatectomy and RT, and all became impotent (with a score of 0~1) after surgery; only 1 (11%) patient subsequently regained potency (with a score of 2). For 26 patients treated by primary RT, deterioration of sexual function developed in 20 (77%) patients, and 8 (31%) patients remained potent, 5 with a score of 3 and 3 with a score of 2. The median time to first appearance of impaired sexual function was 7 (range, 0~38) months. However, even in 10 patients who received primary RT without adjunct hormone therapy, only 1 patient retained a score of 3 for sexual function. In these 10 patients, only 4 of them had received TURP before RT, including the only patient who remained potent after RT. This result suggests that RT, not short-term hormone therapy, was the main reason inducing sexual dysfunction. No other factor was identified as being correlated with change in sexual function. Only 7 patients were willing to take Viagra® (sildenafil citrate, Pfizer) for erectile dysfunction. Sexual function was improved from a score of 0~1 to a score of 2 in 2 patients and from a score of 2 to 3 in 1 patient. All of them had had a score of 3 for sexual function before any treatment.

DISCUSSION

In the literature, there are many retrospective studies showing a strong dose-dependency of exter-

Table 6. Relationship between Chronic Urinary Adverse Events and Surgical Treatment

a. Grade 2 or Higher Chronic Urinary Adverse Events and Surgical Treatment			
Chronic urinary adverse events	Surgical treatment		Significance (2-sided) and odds ratio
	No	Yes	Significance: 0.049
Grades 0~1	30	35	OR: 3.068 (1.023~9.310)
Grades 2~5	5	18	
Total	35	53	(Total: 88 patients)
b. Severity of Urinary Incontinence and Surgical Treatment			
Urinary incontinence	Surgical Treatment		Significance (2-sided) and odds ratio
	No	Yes	Significance: 0.013
Grades 0~1	34	41	OR: 9.951 (1.231-80.458)
Grades 2~5	1	12	
Total	35	53	(Total: 88 patients)

Abbreviation: OR: odds ratio.

nal-beam RT for the control of intermediate- and high-risk prostate cancer.[10,11] This dose-dependency was confirmed by a randomized trial reported by Pollack *et al.*,[3,10,11] and this was the only one we found. However, the tolerance of the normal organs around the prostate gland is the major obstacle to dose escalation. Obvious increment of radiation-related toxicities was observed in some dose-escalation studies before the IMRT era.[3,12,13] Since our experience in the treatment of localized prostate cancer was limited when we first introduced the IMRT technique, we decided to begin the IMRT program for prostate cancer with a relatively low radiation dose and perform dose escalation in a step-by-step manner.

The 30-month failure-free survival rate was 70.5% for all patients, among which 87% were in the intermediate- and high-risk groups. This survival rate is comparable to the control arm of a randomized trial administered by Pollack and colleagues.[3] Our preliminary results showed a low complication rate following IMRT using 72 Gy. Although several factors were found to be significantly related to the failure-free survival, most of them are related to the risk classification. The Gleason score, PSA level, and staging are the main factors used for risk classification. Whether or not hormone therapy is applied depends on the risk classification of the patient. The indication for pelvic irradiation is also strongly related to the risk classification. So only the risk classification appearing to be significant in the multivariate analysis is very reasonable. To improve disease control, dose escalation should be applied to intermediate- or high-risk-group patients because prospective and randomized trials have proven its survival benefit in such patients. The necessity for dose escalation for low-risk patients is still controversial,[14,15] and as our results of 30-month failure-free survival indicate that the benefit of dose escalation might not be substantial within a short follow-up time. Longer follow-up times are needed to evaluate the benefits of dose-escalation for low-risk-group patients.

Complications caused by RT are another concern with dose escalation. Some dose escalation trials have reported a link between the complication rate and the dose-volume relation. Pollack et al. reported that a rectal volume exceeding 70 Gy (V70) was a critical factor in rectal complications,[3] and the risk of grade 2 or higher late rectal complication at 6 years was as high as 46% if the rectal V70 was more than 25%. The risk was 16% for those with a rectal V70 of < 25%. Grade 2 and 3 late bladder complication rates were 11% vs. 15% and 2% vs. 4%, respectively, for the 70-Gy and 78-Gy arms in that study. No statistical difference was detected between these 2 arms.

Another trial from Memorial Sloan Kettering Cancer Center, reported by Zelefsky *et al.*,[16] delivered 81 or 86.4 Gy through IMRT to the PTV. At the overlapping area of the PTV and the rectal/bladder wall, 88% and 98% of the prescription dose were the respective upper limits for the rectal and bladder walls. Grade 2 acute gastrointestinal and genitourinary (GU) complication rates were 4% and 28%, respectively. Only 1 grade 3 acute GU complication was observed. The late grade 2 and 3 rectal complication rates were 1.5% and 0.5%, respectively. Although the 3-year actuarial likelihood of a GU complication rate for higher than grade 2 was 15%, only 0.5% of patients developed grade 3 GU complications. This result confirms that IMRT is a useful technique for escalating the radiation dose without increasing complications.

Several toxicity reports were also published from an RTOG dose escalation trial. Late rectal complications were minimal if the rectal volume receiving the reference dose was < 20%. The late bladder complication rate was positively associated with the volume of the bladder irradiated with the reference dose, but a clear-cut discrimination point could not be found.[12,17]

In our study, the minimal dose to the GTV was only 72 Gy, while the maximal dose was < 79 Gy. Only 12% of patients had a rectal V70 of ≧ 25%, and only 1 patient had a rectal V70 of > 30%. This was the possible reason a dose response in developing adverse GI events was lacking. Furthermore all rectal bleeding spontaneously disappeared with no active management. This dose constraint to the rectum may be a safety guide to prevent rectal complications. However, some studies proposed that instead of delineating the entire rectum, it might be a more-specific and safer way to only delineate the rectal wall and compute its dose-volume histogram.[18]

The relationship between urinary bladder complications and the dose-volume relation has been discussed less. Organ preservation treatment for bladder cancer has provided some information on the radia-

tion tolerance. The complication rate is acceptable if the entire bladder receives 60~65 Gy,[19,20] but these data provided no clues as to the dose-volume-rate correlation. A systematic review showed that the complication rate would be acceptable if < 20% of the bladder volume received the total dose of 65~75 Gy.[21] Whether data from older treatment techniques can be transferred to novel treatments, such as IMRT, is still questionable. The RTOG 9406 trial proved overestimation of the complication rate using the old data from RTOG 7506 and 7706.[12,17] The risks of grade 3 late urinary adverse events in our study were higher than the control arms in those studies, even when urinary incontinence events related to a radical prostatectomy were excluded. However, 3 of 4 obstruction events might not have been caused by RT after reviewing the personal histories and cystoscopic findings. The real incidence of grade 3 RT-induced complications might be as low as 1.1%, suggesting that a bladder volume of 65~70 Gy to 25%~33% may be a safe interval for an IMRT dose constraint.

The presence of grade 2 or higher urinary adverse events was strongly correlated with previous surgery in our study. The incidence doubled if patients had received surgical management before RT, and 12 of 13 instances of ≧ grade 2 urinary incontinence occurred in patients who had received previous surgical management. A systematic review of radiation effects of RTOG/EORTC suggested that a prior TURP increased the risk of developing urethral strictures.[21] However, the urinary complication rate after adjuvant RT was not increased, or at least only temporarily increased, in some studies.[22-24] It cannot be definitively concluded that a combined modality increases the urinary complication rate, but our results after stratification further proved the safety of IMRT, especially in terms of the rarity of urinary incontinence.

The rate of maintenance of potency was only 31% in patients receiving primary RT. Even with higher doses delivered to the penile bulb, 52% patients maintained potency in the RTOG 9406 trial.[25] Other studies reported similar or better maintenance rates which were usually more than 50%.[26-28] The reason for the relatively low potency rate after RT in our patients is unknown. A troublesome shortcoming of this evaluation was patients' attitudes. A portion of patients were reluctant to participate in our simple survey. Many elderly ethinic Chinese patients do not consider erectile function an important concern, and requests for management of erectile dysfunction are not common from our patients. A prospective study with complete data recording and a subjective evaluation is the next step needed to clarify this problem.

According to our preliminary results, 72 Gy of irradiation given by IMRT with appropriate dose constraints for normal tissue protection is a very safe method for the treatment of prostate caner. Based on these results, dose escalation to the next level has begun. Since PC is a slowly progressing malignancy, there is a need for longer follow-up periods to be able to draw final conclusions about the treatment results with this dose level.

REFERENCES

1. Pu YS. Prostate cancer in Taiwan: epidemiology and risk factors. Int J Androl 2000;23(Suppl 2):34-6.
2. Zelefsky MJ, Marion C, Fuks Z, Leibel SA. Improved biochemical disease-free survival of men younger than 60 years with prostate cancer treated with high dose conformal external beam radiotherapy. J Urol 2003;170:1828-32.
3. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, von Eschenbach AC, Kuban DA, Rosen I. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002;53:1097-105.
4. Hanks GE, Hanlon AL, Schultheiss TE, Pinover WH, Movsas B, Epstein BE, Hunt MA. Dose escalation with 3D conformal treatment: five year outcomes, treatment optimization, and future directions. Int J Radiat Oncol Biol Phys 1998;41:501-10.
5. Lee CM, Lee RJ, Handrahan DL, Sause WT. Comparison of late rectal toxicity from conventional versus three-dimensional conformal radiotherapy for prostate cancer: analysis of clinical and dosimetric factors. Urology 2005;65:114-9.
6. Brahme A. Optimization of stationary and moving beam radiation therapy techniques. Radiother Oncol 1988;12:129-40.
7. Woo SY, Sanders M, Grant W, Butler EB. Does the "peacock" have anything to do with radiotherapy? Int J Radiat Oncol Biol Phys 1994;29:213-4.
8. Amer AM, Mott J, Mackay RI, Williams PC, Livsey J, Logue JP, Hendry JH. Prediction of the benefits from dose-escalated hypofractionated intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2003;56:199-207.
9. Nutting CM, Convery DJ, Cosgrove VP, Rowbottom C, Padhani AR, Webb S, Dearnaley DP. Reduction of small

and large bowel irradiation using an optimized intensity-modulated pelvic radiotherapy technique in patients with prostate cancer. Int J Radiat Oncol Biol Phys 2000;48:649-56.
10. Zelefsky MJ, Leibel SA, Gaudin PB, Kutcher GJ, Fleshner NE, Venkatramen ES, Reuter VE, Fair WR, Ling CC, Fuks Z. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998;41:491-500.
11. Cheung R, Tucker SL, Dong L, Kuban D. Dose-response for biochemical control among high-risk prostate cancer patients after external beam radiotherapy. Int J Radiat Oncol Biol Phys 2003;56:1234-40.
12. Michalski JM, Purdy JA, Winter K, Roach M 3rd, Vijayakumar S, Sandler HM, Markoe AM, Ritter MA, Russell KJ, Sailer S, Harms WB, Perez CA, Wilder RB, Hanks GE, Cox JD. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. Int J Radiat Oncol Biol Phys 2000;46:391-402.
13. Roach M 3rd, Pickett B, Weil M, Verhey L. The "critical volume tolerance method" for estimating the limits of dose escalation during three-dimensional conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 1996;35:1019-25.
14. Hurwitz MD, Schnieder L, Manola J, Beard CJ, Kaplan ID, D'Amico AV. Lack of radiation dose response for patients with low-risk clinically localized prostate cancer: a retrospective analysis. Int J Radiat Oncol Biol Phys 2002;53:1106-10.
15. Kupelian PA, Buchsbaum JC, Reddy CA, Klein EA. Radiation dose response in patients with favorable localized prostate cancer (stage T1-T2, biopsy Gleason < 6, and pretreatment prostate-specific antigen < 10). Int J Radiat Oncol Biol Phys 2001;50:621-5.
16. Zelefsky MJ, Fuks Z, Hunt M, Yamada Y, Marion C, Ling CC, Amols H, Venkatraman ES, Leibel SA. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002;53:1111-6.
17. Michalski JM, Winter K, Purdy JA, Parliament M, Wong H, Perez CA, Roach M, Bosch W, Cox JD. Toxicity after three-dimensional radiotherapy for prostate cancer on RTOG 9406 dose level V. Int J Radiat Oncol Biol Phys 2005;62:706-13.
18. Tucker SL, Dong L, Cheung R, Johnson J, Mohan R, Huang EH, Liu HH, Thames HD, Kuban D. Comparison of rectal dose-wall histogram versus dose-volume histogram for modeling the incidence of late rectal bleeding after radiotherapy. Int J Radiat Oncol Biol Phys 2004;60:1589-601.
19. Chen WC, Liaw CC, Chuang CK, Chen MF, Chen CS, Lin PY, Chang PL, Chu SH, Wu CT, Hong JH. Concurrent cisplatin, 5-fluorouracil, leucovorin, and radiotherapy for invasive bladder cancer. Int J Radiat Oncol Biol Phys 2003;56:726-33.
20. Shipley WU, Kaufman DS, Zehr E, Heney NM, Lane SC, Thakral HK, Althausen AF, Zietman AL. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology 2002;60:62-8.
21. Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. Int J Radiat Oncol Biol Phys 1995;31:1257-80.
22. Fontaine E, Ben Mouelli S, Thomas L, Otmezguine Y, Beurton D. Urinary continence after salvage radiation therapy following radical prostatectomy, assessed by a self-administered questionnaire: a prospective study. BJU Int 2004;94:521-3.
23. Hofmann T, Gaensheimer S, Buchner A, Rohloff R, Schilling A. An unrandomized prospective comparison of urinary continence, bowel symptoms and the need for further procedures in patients with and with no adjuvant radiation after radical prostatectomy. BJU Int 2003;92:360-4.
24. Chawla AK, Thakral HK, Zietman AL, Shipley WU. Salvage radiotherapy after radical prostatectomy for prostate adenocarcinoma: analysis of efficacy and prognostic factors. Urology 2002;59:726-31.
25. Roach M, Winter K, Michalski JM, Cox JD, Purdy JA, Bosch W, Lin X, Shipley WS. Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys 2004;60:1351-6.
26. Incrocci L, Slob AK, Levendag PC. Sexual function after radiotherapy for prostate cancer: a review. Int J Radiat Oncol Biol Phys 2002;52:681-93.
27. Selek U, Cheung R, Lii M, Allen P, Steadham RE, Vantreese TR Jr, Little DJ, Rosen, II, Kuban D. Erectile dysfunction and radiation dose to penile base structures: a lack of correlation. Int J Radiat Oncol Biol Phys 2004;59:1039-46.
28. Chen CT, Valicenti RK, Lu J, Derose T, Dicker AP, Strup SE, Mulholland SG, Hirsch IH, McGinnis DE, Gomella LG. Does hormonal therapy influence sexual function in men receiving 3D conformal radiation therapy for prostate cancer? Int J Radiat Oncol Biol Phys 2001;50:591-5.

強度調控放射治療對攝護腺癌的初期治療結果

范綱行[1] 陳彥超[1] 莊正鏗[2] 謝明里[2] 洪志宏[1,3]

背 景： 本回溯性研究在回顧過去以強度調控放射治療 (IMRT) 對攝護腺癌治療的成果。

方 法： 總共 92 名於 2003 年 7 月前完成 IMRT 治療的攝護腺癌病人納入本次研究。對仍存活的病人追蹤期中位數爲 32 個月。接受 IMRT 的適應症包括對攝護腺癌的主要治療，因應其他治療後的追加治療，或是因治療失敗安排的救贖性治療。放射治療總計量，從 63 格雷到 72 格雷不等，並配合不同的荷爾蒙治療。主要的觀察終點在因治療引起的副作用，副作用主要依據病人主觀的回報。另外，病人的存活及疾病的控制結果也在觀察之列，但侷限在診斷病理組織爲腺癌，且以 IMRT 爲主要治療法的病人。

結 果： 在分析結果的時間點時，有 89 名病人仍存活，只有兩名病人死於攝護腺癌。三年的總存活率爲 96.4%。存活分析中，低復發危險度，中復發危險度，及高復發危險度的病人，30 個月的無復發存活率爲 100%，89.2%，及 67.3%。在單變數分析中，治療前的 PSA 數值，病理分化程度 (Gleason score)，復發危險度分級，以及是否接受追加荷爾蒙治療，是對疾病復發有影響的因子。但在多變數分析中，僅有復發危險度的分級有統計上的顯著意義。有 7 名病人 (8%) 在治療中產生了超過第三級的急性副作用。而在治療後追蹤的過程中，有 5 名病人 (6%) 發生了第二級的慢性腸胃道副作用，並沒有更嚴重的腸胃道副作用發生。有 23 名病人 (26%) 發生了第二或第三級的泌尿道副作用。其中有第三級副作用的病人有七位，只有一位病人被認爲是因爲放射治療所引起。在放射治療前接受過手術治療和發生泌尿道副作用有明顯相關的因子。對於發生腸胃道副作用與否，則沒有發現任何相關顯著因子。另外，並沒有任何病人發生第四或第五級的副作用。放射治療後性功能保留的機率爲 31%。

結 論： 在攝護腺癌的治療時，強度調控放射治療，配合 72 格雷的劑量是一個安全的治療方式。只有在放射治療前接受手術治療的病人會有較高的機率發生泌尿道的副作用。根據這些結果，我們已經開始將治療劑量增加。對於治療效果，則需要更長的時間來評估。

(長庚醫誌 2006;29:313-24)

關鍵字： 攝護腺癌，強度調控放射治療，副作用。

長庚紀念醫院 台北院區 [1]放射腫瘤科，[2]泌尿外科；[3]長庚大學 醫學影像暨放射科學系
受文日期：民國94年9月29日；接受刊載：民國95年1月19日
通訊作者：洪志宏醫師，長庚紀念醫院 放射腫瘤科。桃園縣333龜山鄉復興街五號。Tel.: (03) 3281200轉2601; Fax: (03) 3280797; E-mail: jihong@cgmh.org.tw