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Preliminary Result of Using Intensity Modulated Radiation Therapy (IMRT) as a Primary Treatment for Prostate Cancer at Siriraj Hospital in Thailand: Toxicity and Biochemical Outcomes

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ABSTRACT

Objective: This study is a retrospective study of the outcome and the incidence of the toxicity of using intensity-modulated radiation therapy (IMRT) as the primary treatment for prostate cancer at Siriraj Hospital.

Methods: Hospital records and radiotherapy medical records of prostate cancer patients treated with IMRT as the primary treatment between July 2004 and May 2009 at Siriraj Hospital were all reviewed. Seventy-five prostate cancer patients were included in the study. Patient's biochemical failure was established at the time of prostatic specific antigen progression above the post-treatment nadir value +2 ng/ml according to the Phoenix definition. Acute and late toxicity were assessed and scored according to the Radiotherapy Oncology Group grading system.

Results: The median follow up time was 25 months (range 3 - 63 months). The two years overall survival (OS) and freedom from biochemical failure rate (FFBF) were 93.7 and 95.8%, respectively. Five patients (6.6%) developed prostatic specific antigen failure according to the Phoenix definition. The incidences of grade $\geq$ 2 of acute and late gastrointestinal to xicity were 12% and 2.7%, respectively. The incidences of grade $\geq$ 2 of acute and late genito-urinary toxicity were 61.3% a nd 41.3%, respectively.

Conclusion: This preliminary result of using IMRT as the primary treatment for prostate cancer provides good outcomes. The FFBF and OS are comparable with other studies. The incidences of acute and late gastrointestinal toxicity are acceptable, but the incidences of acute and late genito-urinary toxicity are higher than other studies.

Keywords: IMRT, prostate cancer, Thailand, freedom from biochemical failure

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The Siriraj Hospital tumor registry[1] in 2008 indicated that there were 564 (6.83% of all primary site) new prostate cancer patients from a total of 8,256 all new cancer patients treated in Siriraj Hospital. These account for the 5th most frequent incidence of all cancer patients. Also it is the 2nd most common malignancy in males (14.44%).

Nowadays, the practical guideline[2,3] of treatment of prostate cancer patients shows that prostate cancer could be treated with radiation therapy in all stages. Intensity Modulated Radiotherapy (IMRT) is a relatively recent refinement of three-dimensional conformal radiotherapy (3D-CRT) techniques. The results of a dose-escalating study at the MD Anderson Cancer Center[4] showed that a higher dose arm (78Gy) was superior to a lower dose arm (70Gy) in freedom from biochemical or clinical failure. Moreover, freedom from biochemical

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or clinical failure (FFBF) was superior for the 78 Gy arm, 78%, as compared with 59% for the 70 Gy arm (p = 0.004).

In March 2004, we installed a Varian CLINAC 23EX equipped with a 120 multileaf collimator and automatic beam sequencing software. However, we have never collected data about the outcome and toxicity of treatment for prostate cancer. On the other hand, other countries reported in many articles, the benefit of treatment with IMRT in prostate cancer. Thus, we would like to collect data to establish evidence in this matter as the first study in Thailand.

MATERIALS AND METHODS

This study is a retrospective review of the medical records of 75 consecutive patients with clinically localized prostate cancer treated with IMRT with or without androgen deprivation for a curative aim between July 2004 and May 2009 at the Division of Radiation Oncology, Siriraj Hospital. The inclusion criteria of this study were new prostate cancer patients who were completely treated by IMRT with or without androgen deprivation for a curative aim, whose pathologic reports were prostatic adenocarcinoma, and these patients with AJCC showed T1-3 lesion, any N, and M0. The exclusion criteria of this study were patients who received prostatectomy, patients with previous pelvic radiation, patients with synchronous cancer, patients with recurrent disease or rising PSA after other treatments, and patients who participated in other treatment study protocols.

The aim of this study was to report freedom from biochemical failure rate (FFBF), and overall survival rate (OS) of prostate cancer patients who were treated by IMRT and the relationship between biochemical failure and other factors. Moreover, we would like to analyze the incidence of acute and late radiation toxicity of the bladder and rectum with IMRT treatment.

The parameters used to characterize the risk groups included pre-treatment PSA, T stage and Gleason score (GS), (According to NCCN classification system).[3]

FFBF was analyzed with the American Society of Therapeutic Radiology and Oncology (ASTRO) consensus definition of the nadir plus 2 ng/mL definition (Phoenix definition).[5] The date of failure for the ASTRO analysis was the date of the first PSA rise. The date of failure for the nadir plus 2 ng/mL was the date at which this level was reached. All endpoints were calculated from the radiation start date.

Acute and late radiation gastro-urinary (GU) and gastro-intestinal (GI) toxicity were scored according to the Radiation Therapy Oncology Group (RTOG) morbidity grading scale.[6] We scored from the maximal grade of all treatment time and followed the time in each patient.

The Statistical Package for the Social Sciences (SPSS V17.0) was used for statistical analysis. Distributions of FFBF and OS were calculated by the Kaplan-Meier method. Univariate and multivariate analyses were performed to determine predictors of biochemical relapse. Statistical significance was achieved when the p value $\leq$ 0.05. Disease status was determined at the time of analysis in January 2010. Univariate analyses were carried out to examine the relationship between T staging, pre-treatment PSA, Gleason score, age, total prescribed dose and hormonal treatment versus OS and FFBF. Univariate analyses were analyzed using the Cox regression model.

Our study was certified by the Siriraj Institutional Review Board that is in full Compliance with International Guidelines for Human Research Protection.

RESULTS

From July 2004 until May 2009, 131 prostate cancer patients were treated with IMRT at the Division of Radiation Oncology, Siriraj Hospital. There were only 75 prostate cancer patients that were enrolled following the application of the inclusion criteria of this study. There were 56 patients who were excluded from this study. There were 42 patients who received radical prostatectomy. 8 patients had no available data and 4 patients were T4 lesion. One patient had recurrent disease and one patient refused treatment.

Patients' characteristics are shown in Table 1. Regarding radiotherapy, there were 49.3% (37 in 75 patients) in pelvic node irradiation, and the mean dose was 46 Gy (45-50Gy). The mean dose to the prostate gland was 77.5 Gy (72-79.2 Gy). With regard to hormonal therapy, there were 81.4% (61 in 75 patients) in long-term hormonal therapy (>2 years). There were 13.3% (10 in 75 patients) in short-term hormonal therapy. 4 patients (5.3%) were not treated by hormonal therapy. In addition, there were 66 patients who were treated by neoadjuvant hormonal therapy.

TABLE 1. Characteristics of the patients.

Characteristics	All patients (N=75)
Age (years)	
Median, (range)	72 (45-84)
Performance status (No, %)	N (%)
ECOG 0	52 (69.3%)
ECOG 1	21 (28.0%)
ECOG 2	2 (2.7%)
Risk Group (No, %) According to NCCN guidelines	N (%)
Low	3 (4.0%)
Intermediate	13 (17.3%)
High	59 (78.7%)
T stage (According to AJCC)	N (%)
T1	16 (21.3%)
T1a,T1b,T1c	1, 0, 15
T2	17 (22.7%)
T2a,T2b,T2c	6, 3, 8
T3	42 (56.0%)
T3a,T3b	21, 21
Pretreatment PSA (ng/ml)	N (%)
<10	18 (24.0%)
10-20	14 (18.7%)
>20	43 (57.3%)
Gleason score (No, %)	N (%)
2-6	14 (18.6%)
7	26 (34.7%)
8-10	35 (46.7%)
Pretreatment evaluation	N (%)
CXR	24/71 (32%)
Bone scan	64/71 (85.3%)
MRI prostate	64/71 (85.3%)
CT abdomen	10/71 (13.3%)
No documented	4

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At the time of analysis, the median follow up time was 25 months (range 3 - 63 months). There were 5 patients (66.6%) who had biochemical failure and were the only high-risk group patients. The 2 years FFBF was 95.8%. When we classified patients' risk groups, 2 years FFBF for the low-, intermediate- and high-risk group were 100, 100 and 94.7%, respectively. There were 2 patients in 5 patients who showed distant metastasis (bone and lung metastases). There was one patient who presented regional node recurrence. In addition, there were 2 patients who were not available to identify sites of failure.

Six patients in 75 patients (8%) died. One patient was in the intermediate risk group and the others were in the high-risk group. The two years overall survival rate was 93.7%. When we classified the patients' risk group, 2 years overall survival rates for the low-, intermediate- and high-risk group were 100, 90.9 and 93.7%, respectively.

According to univariate analysis using the Cox regression model, there was no significant prognostic factor for biochemical failure. However, stage > T3a, initial PSA level > 20 ng/ml, or Gleason score > 7 showed a trend to high biochemical failure rate (Table 2).

Toxicity

Acute GI toxicity was concentrated on the rectum, in which most patients had no GI toxicity. However, there were about 12% in grade ≥ 2 of acute GI toxicity. The incidence of acute GI toxicity showed that 68%, 20%, 10.7%, and 1.3% were in grade 0, 1, 2, and 3, respectively. Regarding pelvic lymph node irradiation, the incidence of grade ≥ 2 acute GI toxicity (9.3%) was more in concern with pelvic lymph node irradiation than in concern without pelvic lymph node irradiation (2.7%). The relative risk of this toxicity for receiving pelvic node irradiation was 3.41 (95% CI = 0.75-15.34).

Acute GU toxicity was concentrated on the bladder. The incidence of grade ≥ 2 of acute GU toxicity was about 61.3%. The incidence of acute GU toxicity showed that 20%, 18.7%, 40%, and 21.3% were in grade 0, 1, 2, and 3, respectively. The patients who were treated with pelvic lymph nodes irradiation showed that the incidence of grade ≥ 2 of acute GU toxicity (29.3%) was similar to those with no pelvic lymph node irradiation. The relative risk of receiving pelvic node irradiation was 0.89 (95% CI = 0.62-1.27).

Late GI toxicity was concentrated on the rectum. Most patients had no GI toxicity. However, there were only 2.7% in grade ≥ 2 of late GI toxicity. The incidence of late GI toxicity showed that 87.1%, 9.7%, 3.2%, and 0% were in grade 0, 1, 2, and 3, respectively.

Late GU toxicity was concentrated on the bladder. There were about 41.3% in grade ≥ 2 of late GU toxicity. The incidence of late GU toxicity showed that 37%, 19.7%, 38.3%, and 5% were in grade 0, 1, 2, and 3, respectively.

DISCUSSION

Our study is the first study of prostate cancer patients treated with IMRT in Thailand. We compared our outcome with three studies (Table 3), which used the same biochemical failure definition (Phoenix definition).[5]

The first study by Kupelian et al.,[7] had evaluated 770 localized prostate cancer patients, treated with radiation therapy to a total dose of 70 Gy delivered at 2.5 Gy/fraction within 5 weeks. The result of this study showed the 5 years FFBF was 83% (95% CI, 79-86%). For patients with low-risk, intermediate-risk, and high-risk disease, the 5-year FFBF rates were 94%, 83%, and 72%, respectively. We considered that the total dose to the prostate of this study was slightly lower than our study (76 Gy versus 78 Gy with BED Gy2, alpha/beta = 3). However, a minimal difference of total dose to prostate might not affect the outcome. In addition, there were 60% of all patients in Kupelian et al., that received hormonal therapy, which was lower than in our study (94.7% of all patients).

TABLE 2. Univariate analysis of biochemical failure.

Factor	Parameter	Hazard Ratio	P value	95%CI
Stage	T3b	3.864	0.139	0.644-23.204
Pretreatment PSA	> 20 ng/ml	4.124	0.196	0.481-35.370
Gleason score	> 7	4.433	0.183	0.495-39.689
Age	≥ 70 yr	0.509	0.460	0.085-3.052
Total prescribed dose	≥ 78 Gy	0.630	0.682	0.069-5.727
Hormonal treatment	Yes	24.325	0.640	Very wide CI

TABLE 3. Freedom from biochemical failure rate (FFBF) and overall survival rate (OS).

Study	Number of patient	Total radiation dose (Gy)	2 yr FFBF (%)	2 yr OS (%)
Our study	75	72-79.2 (2Gy/F)	Overall: 95.8% Low 100% Int 100% High 94.7%	Overall: 93.7% Low 100% Int 90.9% High 93.7%
Swiss trial[9]	408	67-78.4 (2Gy/F)	~85%	~95-98%
Cahlon O, et al[8]	478	86.4 (1.8Gy/F)	Low ~100% Int ~95% High ~90%	Not available
Kupelian P, et al[7]	770	70 (2.5Gy/F)	Low ~98% Int ~95% High ~85%	Not available

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The second study from Cahlon et al.,[8] had reported preliminary biochemical outcomes and toxicity with high-dose IMRT to a dose of 86.4 Gy (1.8Gy/F) using a 5- to 7- field IMRT technique for localized prostate cancer. The 2-year actuarial PSA relapse-free survival according to the Phoenix definition was 100%, 95% and 90% for the low, intermediate, and high-risk NCCN prognostic groups, which were comparable to our study, although the total dose in our study is smaller than in that study.

The last study from Miralbell et al.,[9] had retrospectively reviewed 408 prostate cancer patients treated with an external radiotherapy with or without androgen deprivation from 1991 to 2004. The result of this study presented that two-year OS and biochemical disease-free survival rate (bDFS) were 95-98% and 85%, respectively. The outcome of our study is superior to this study. We considered that the total dose to prostate in Miralbell et al.,[9] was lower than our study. However, the overall survivals were similar.

About prognostic factors, there are two studies that reported the affecting factors for freedom from biochemical failure. In a Swiss study,[9] the results showed that there were some factors, which correlated with biochemical disease free survival. The hazard ratios of initial PSA of 10-20 and > 20 ng/mL were 2.8 ($p < 0.001$, 95%CI 1-5), and 6.2 ($p < 0.001$, 95%CI 3.6-10.6), respectively, when compared with initial PSA < 10 ng/mL. The hazard ratio of Gleason 7 and 8-10 were 1.8 ($p = 0.015$, 95% CI = 1.1-2.8), and 2.3 ($p = 0.029$, 95%CI 1.1-4.9), respectively, when compared with Gleason < 7. The hazard ratio of radiotherapy with the androgen deprivation group was 0.3 ($p < 0.001$, 95% CI 0.2-0.5) when compared with radiotherapy alone. Kupelian et al.,[7] studied 770 localized prostate cancer patients treated with 70 Gy in 2.5 Gy/fraction within 5 weeks. This study showed that the T stage, pretreatment PSA level and Gleason score tended to be three significant independent factors for prediction of biochemical failure using either definition. Usage of hormonal therapy was an independent predictor of a worse outcome in the analysis with the Phoenix definition, but not with the ASTRO definition. Our study did not show any statistically significant factors enabling prediction of the biochemical failure.

GI toxicity

From Table 4, there were only three studies that reported acute GI toxicity by the RTOG scale. In our study, the incidence of grade ≥ 2 acute GI toxicity (12%) is comparable with the studies done by Zelefsky et al., (4%),[10] and Kupelian et al., (9%).[7] Our result was better than the study by Jani et al., (60%: ≥ grade 2 acute GI toxicity).[11] Concerning late GI toxicity, the incidence in our study was comparable with the other studies in the RTOG scale.

We analyzed the reason for a high incidence of acute GI toxicity in the Jani study[11] and concluded that the CTV margin of 1 cm in their study might be a possible cause of more GI toxicity, which differed from our study that used about a 0.5-0.8 cm margin for PTV.

GU toxicity

From Table 4, the incidence of grade ≥ 2 acute GU toxicity (61.3%) in our study is higher th an the incidence in the other three studies. The incidence of late GU toxicity in our study is more than the other studies in the RTOG scale. It is a consequence from the acute GU toxicity rate in which our study is higher than the other studies.

We analyzed the reasons for higher incidence of GU toxicity in our study and concluded there are three reasons for it. Inter-observer variation for giving a grade of incidence of GU toxicity is the first reason. We noticed that details of grade 2 and 3 of acute and late GU toxicity showed a moderate and severe frequency, but we did not recommend the exact number of frequency in each grade. Second, in our study, there are many high-risk group patients (78.7%) more than other studies (60% in Jani et al.[11], 22.6% in Zelefsky et al.[10], and 38% in Kupelian et al.[7]), and that, therefore, the GU toxicities might be somewhat higher as we had electively treated the pelvic lymph node in about 50.7% of the patients. On the other hand, the Zelefsky and Kupelian studies did not treat the pelvic lymph node. This might provide the reason for the higher GU toxicity rate. Finally, the internal organ motion of the bladder is a reason for higher incidence of GU toxicity. The set up in our institute used the time of full bladder control and Electronic Portal Image Device (EPID). On the other hand, the Kupelian study[7] used BAT trans-abdominal ultrasound.

However, this study was a retrospective study that had many limitations. For example, the sample size of this study was smaller than that recommended by calculation from formula. Thus, our results might not be definitely accurate. Finally, the median follow up time of our study was shorter than other studies, which had an effect on the outcomes.

CONCLUSION

This preliminary result of using IMRT as the primary treatment for prostate cancer provided good outcomes. The FFBF and OS were comparable with other studies. There are three factors (T stage, initial PSA and Gleason score) that tend to be the predictive factors for the biochemical failure rate. The incidences of acute and late gastro-intestinal toxicity were acceptable, but the incidences of acute and late genito-urinary toxicity were higher than in other studies. However, a longer follow up time and a greater number of patients may provide further information about outcomes and toxicities.

TABLE 4. Incidence of toxicity compared with other studies.

Grade ≥ 2	Our study	Jani, et al.[11]	Zelefsky, et al.[10]	Kupelian, et al.[7]
Acute GI toxicity	12%	60%	4%	9%
Late GI toxicity	2.7%	6%	2.5%	5%
Acute GU toxicity	61.3%	20%	29%	19%
Late GU toxicity	41.3%	23%	12%	6%

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