Feasibility of Simultaneous Integrated Boost IMRT (SIB-IMRT) for Castration-Resistant Prostate Cancer

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Abstract. *Aim: We examined the feasibility of local intensity-modulated radiation therapy (IMRT) with pelvic irradiation using the simultaneous integrated boost (SIB) technique to treat patients with castration-resistant prostate cancer (CRPC) after several lines of hormonal therapy. Patients and Methods: Data from 10 consecutive patients with CRPC treated with SIB-IMRT between November 2001 and September 2009 were analyzed retrospectively. Results: A decline in prostate-specific antigen (PSA) level was observed in all cases after SIB-IMRT. Biochemical progression-free survival at 5 years was 70% with a median follow-up of 33.5 months after SIB-IMRT. All patients completed SIB-IMRT without delay due to acute toxicity. The PSA nadir after first-line hormonal therapy, the PSA before SIB-IMRT, the PSA doubling time before SIB-IMRT and the PSA nadir after SIB-IMRT were significant factors for biochemical progression after SIB-IMRT. Conclusion: SIB-IMRT for patients with CRPC is feasible and has a satisfactory effect in terms of disease control.*

Androgen-deprivation therapy (ADT) is the most common therapeutic option for locally advanced or metastatic prostate cancer (PCa) (1). Although initial ADT results in significant long-term remission for many patients, development of hormone ablation resistance is inevitable and is known as castration-resistant PCa (CRPC). The ideal therapeutic intervention for this disease stage has not been fully-established. At present, cytotoxic chemotherapy using docetaxel is the gold standard for treatment of CRPC. Although docetaxel is highly effective, decreased quality of life occurs due to side-effects. In addition, new therapeutic drugs -such as abiraterone acetate and enzalutamide- have been introduced; however, these do not cure the disease.

In general, the benefit of radiation therapy (RT) for CRPC is palliative; thus, the curative usefulness of RT for CRPC remains unclear. However, some reports have indicated the usefulness of increasing the therapeutic dose or widening the irradiation field for treating CRPC (2-3). The relationship between higher RT dose and better clinical prognosis for localized PCa has been widely accepted, particularly because the greatest advantage is in high-risk patients with PCa (4, 5).

Thus, we hypothesized that this relationship could be applied to some patients with CRPC and we retrospectively analyzed whether dose escalation to the prostate/seminal vesicles and pelvic lymph nodes would improve local control and reduce systemic progression. Modern RT techniques -such as intensity-modulated RT (IMRT) and helical tomotherapy- are applied as safe RT for a pelvic regimen. IMRT also allows for simultaneous differential dose delivery to multiple tumor targets [simultaneous integrated boost (SIB)], obviating sequential treatment of an initial volume with a subsequent boost.

This is the first report regarding treating patients with CRPC using local IMRT combined with pelvic irradiation and the SIB technique after various hormonal therapies.

Patients and methods

Patients and patients' characteristics. Data from 10 consecutive patients (median age, 68 years; range, 60-77 years) treated with SIB-IMRT for CRPC after several lines of hormonal therapy at a single institute between November 2001 and September 2009 were retrospectively analyzed. The patients' characteristics are shown in Table I. Nine (90%) patients had T3 or T4 disease at diagnosis. Gleason scores of 8-10 were obtained from nine (90%) patients at the initial biopsy. The median initial prostate specific antigen (PSA) value and PSA nadir after first-line therapy were 92.1 ng/ml (range, 22.4-1700 ng/ml) and 0.16 ng/ml (range, 0-4.49 ng/ml), respectively. The median follow-up after SIB-IMRT was 33.5 months (range=9-49 months). All patients showed

Abbreviations: PCa, prostate cancer; ADT, androgen deprivation therapy; CRPC, castration resistant prostate cancer; IMRT, intensity modulated radiation therapy; SIB, simultaneous integrated boost; PSA, prostate specific antigen; EBRT, external beam radiotherapy.

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Key Words: Castration-resistant prostate cancer, simultaneous integrated boost, intensity modulated radiation therapy.

Table I. *Patients' characteristics*.

Characteristic	Value
Patients (n)	10
Age (years)	
Median (range)	68 (60-77)
T stage (n)*	
T2	1
T3-4	9
N stage (n)*	
N1	4
M stage (n)*	
M1	2
Gleason score (n)	
7	1
8-10	9
Initial PSA value (ng/ml)	
Median (range)	92.1 (22.4-1700)
PSA nadir after first line therapy (ng/ml)	
Median (range)	0.16 (0-4.49)
Follow-up after SIB-IMRT (months)	
Median (range)	33.5 (9-49)

PSA, Prostate-specific antigen. *2009 Union for International Cancer Control 7th edition.

Table II. *Summary of SIB-IMRT*.

Variable	Value
Age on SIB-IMRT starting (years)	
Median	71
Range	64-83
PSA before SIB-IMRT (ng/ml)	
Median	2.5
Range	0.35-284.6
Dose of SIB-IMRT (Gy)	
(Prostate/Lymph node)	
Median	76/52
Range	72-76/52-58
PSA nadir after SIB-IMRT (ng/ml)	
Median	0.02
Range	0-218.6
PSA reduction rate (%)	
Median	97
Range	23.2-99.9
Biochemical progression-free rate	
All cases*	70%
N1 cases**	75%

*Median follow-up of 33.5 months; **Median follow-up of 20.0 months; PSA, prostate-specific antigen; SIB-IMRT, simultaneous integrated boost–intensity-modulated radiation therapy.

biochemical progression following combined androgen blockade as first-line therapy for locally advanced or metastatic PCa. Biochemical progression was defined as at least three consecutive increases in PSA at least 4 weeks apart (6).

Treatment protocols. PSA progression was observed in all patients after anti-androgen withdrawal. Seven patients were treated with alternative anti-androgen therapy and three patients were treated with estrogen as second-line therapies. Third-line therapy was performed for four patients (ethinyl estradiol in two and dexamethasone in two) when the second-line therapy failed. Gonadotropin releasing hormone (GnRH) agonists were continued during each step of therapy in all patients.

SIB-IMRT treatment. When the second- or third-line hormonal therapy failed, computed tomography and bone scintigraphy were performed to evaluate the progression of local or metastatic lesions. If there were no new detectable lesions, SIB-IMRT was started for these patients. Four patients had N1 or M1 disease at the initial diagnosis. In such cases, we carried out SIB-IMRT only after confirmation of undetectable metastatic disease following several hormone therapies. The most recent hormonal therapy was continued during SIB-IMRT treatment.

Our system of IMRT was as follows: linear accelerator (LINAC): Clinac2100C/D (10-MV photon, 60 pairs MLC, Varian medical systems, Chuo-ku, Tokyo, Japan), treatment planning system (TPS): Pinnacle^3 (step and shoot, convolution superposition, HITACHI medical corporation, Chiyoda-ku, Tokyo, Japan), computed tomography (CT): Dxi (General Electric Company, Hino-shi, Tokyo, Japan), QA system: 0.6 cm^3 Farmer-type ionization chamber (type 30006, PTW-Freiberg, Lörracher Strasse 7, 79115 Freiburg, Germany): 0.015-cm3 Pinpoint chamber (type 31006, PTW-Freiberg), Solid phantom (type 29672, PTW-Freiberg) and DD-System (+EDR2, R-TECH. INC. Itabashi-ku, Tokyo, Japan), Stabilize system: Vaclock (CIVCO Medical Solutions, Orange City, Iowa 51041, USA), image guided radiation therapy (IGRT) system: SonArray (Varian medical systems, Chuo-ku, Tokyo, Japan).

In general, the clinical target volume (CTV) was the prostate and two-thirds of the seminal vesicles. We expanded the irradiation field for cases of locally advanced disease such as T3a, T3b and T4 to include the prostate, seminal vesicles, and invasive portion (Figure 1). The planned target volume (PTV) was CTV + 5 mm (rectal projection was 3– 5 mm). The elective nodes contoured included those within approximately 7 mm of the internal iliac, external iliac, obturator and lower common iliac vessels. The nodal PTV was defined by a 5-mm expansion of the CTV nodes. We fixed the patient's body using Vaclock with an empty rectum and bladder 1 h before treatment and recognized position of the prostate and seminal vesicle contours directly with the SonArray system.

Statistical analysis. The statistical analysis was performed with the Mann–Whitney *U*-test. A $p<0.05$ was considered to indicate significance. Acute and late morbidities were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTC AE) ver. 4.0 and the Radiation Therapy Oncology Group (RTOG) toxicity scoring system; late morbidities occurring >3 months after SIB-IMRT are described.

Results

Table II is a summary of SIB-IMRT. The median (range) age and PSA before SIB-IMRT were 71 (64-83) years and 2.5 (0.35-284.6) ng/ml, respectively. The median (range) IMRT

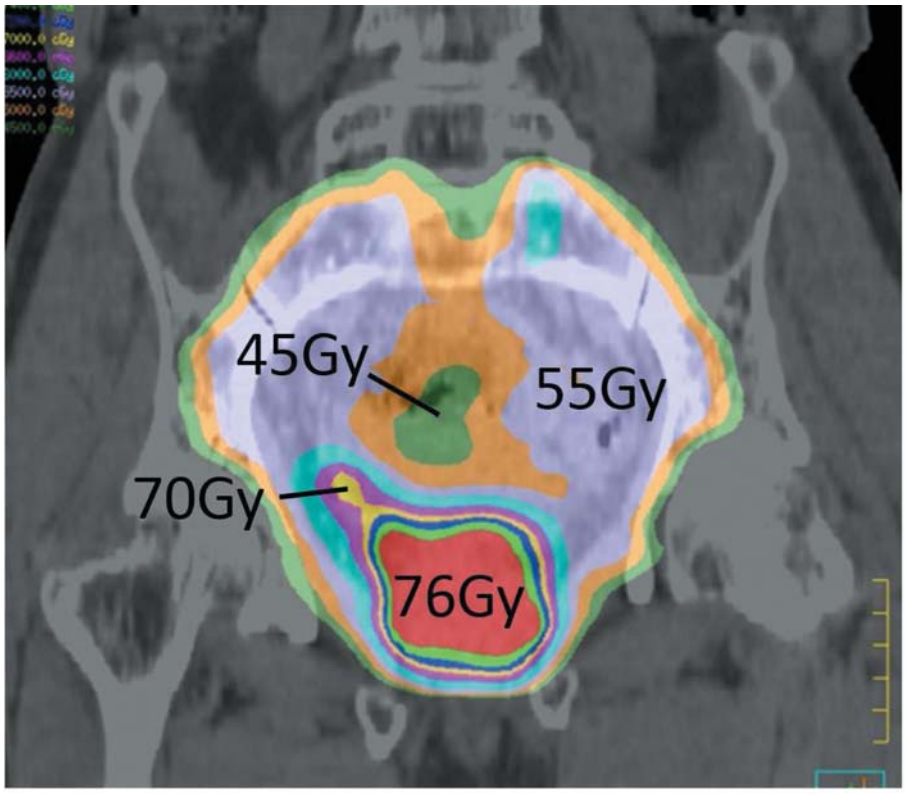

Figure 1. Dose distribution for patients with right seminal vesicle invasion treated with simultaneous integrated boost–intensity-modulated radiotherapy. Red, yellow and white areas indicate planning target volume for prostate, right seminal vesicle and elective nodes.

doses were 76 (72-76) Gy and 52 (52-58) Gy for the prostate and pelvic lymph nodes, respectively. A decline in PSA was observed in all cases after SIB-IMRT, including nine patients (90%) who achieved a PSA decline ≥50%. The median PSA reduction rate by SIB-IMRT was 97% (range=23.2-99.9%). With a median follow-up of 33.5 months (range=9-49 months) after SIB-IMRT, three patients had clinically progressed, including two who died of PCa. The remaining seven patients (70%) were free from biochemical progression with a median (range) PSA value of 0.01 (0-0.215) ng/ml, including one patient who died of pancreatic cancer. Biochemical progression-free survival was 75% after SIB-IMRT (median follow-up, 20.0 months) in four patients with N1 disease at diagnosis.

Statistical analysis showed that the PSA nadir after first-line therapy (p=0.01), PSA before SIB-IMRT (p=0.01), PSA doubling-time before SIB-IMRT (p=0.02) and PSA nadir after SIB-IMRT (p=0.01) were significant predictive factors for biochemical progression (Table III).

No patient had grade 3 or 4 toxicities according to NCI-CTC AE for acute adverse events and the RTOG toxicity scoring system for late adverse events after SIB-IMRT (Table IV). One patient required catheterization because of urinary retention. No rectal bleeding was detected throughout the follow-up period.

Discussion

The concept of CRPC includes a wide spectrum of conditions. We hypothesized that a curable patient group may exist after local radiation therapy in patients with CRPC without distant metastasis. Thus, we evaluated the efficacy and feasibility of local IMRT for the prostate with pelvic irradiation using the SIB technique to treat with curative intent CRPC patients after several lines of hormonal therapy.

In general, local IMRT is insufficient for treating patients with CRPC because microscopic lymph node metastasis potentially exists in the CRPC condition even though there is radiologically non-metastatic disease. Thus, we planned to irradiate pelvic lymph nodes simultaneously. Bolla *et al*. introduced external-beam radiation (EBRT) to pelvic lymph nodes in addition to local irradiation for locally advanced PCa (7). In their report, lymph node recurrence in the EBRT alone group was identified in 6 of 207 cases and was 0 of

Table III. *Prognostic factors*.

Variable	Relapse (n=3) median	Relapse-free (n=7) median	*p*-Value*
Initial age (years)	68	67.5	0.75
Initial PSA (ng/ml)	246.8	74.3	0.39
Gleason score	8	8.5	0.37
PSA nadir after first-line therapy (ng/ml)	2.39	0.01	0.01
Time-to-PSA relapse (months)	27.5	15	0.62
PSA before SIB-IMRT (ng/ml)	18.2	0.59	0.01
PSA doubling-time (year) before SIB-IMRT	0.64	0.73	0.02
Dose of SIB-IMRT (Gy)	74	76	0.52
PSA nadir after SIB-IMRT (ng/ml)	4.17	0.01	0.01
Follow-up (months)	24	31.9	0.46

*Mann–Whitney *U*-test. PSA, prostate-specific antigen; SIB-IMRT, simultaneous integrated boost–intensity-modulated radiation therapy.

Table IV. *Adverse events*.

	Adverse event	Cases
Acute phase*	Urinary retention	1 (Grade 2)
	Cystitis non infective	1 (Grade 1)
	Urinary tract obstruction	1 (Grade 1)
Late phase**	None	None

*Acute adverse events (NCI/CTCAE v4.0). **Late adverse events (RTOG toxicity scoring system).

208 in the hormone therapy combination group at a median of 65.7 months' follow-up in patients with locally advanced PCa (EORTC 22863 study). Their data suggest the usefulness of irradiating the pelvic lymph nodes with androgen ablation therapy only for cases with a high PSA and a high Gleason score.

Several authors have reported the toxicity of pelvic SIB-IMRT for patients with intermediate- to high-risk localized PCa (8, 9). The combination of SIB dose escalation and broad pelvic treatment with IMRT was generally well-tolerated in their series. However, no report has applied SIB-IMRT to treat CRPC. Several studies have reported an effect of EBRT on CRPC, but the results were limited (2, 3). Sasaki *et al*. concluded that EBRT for patients with localized CRPC is limited in terms of its effects on patient survival and has a role only in control of local symptoms (3). Akiyama *et al*. reported that EBRT for CRPC could achieve a 78% clinical relapse-free survival rate at 3 years (2). They treated patients with EBRT using the unblocked oblique four-field technique with a total dose of 69 Gy; however, some patients (19%) developed rectal bleeding due to radiation proctitis.

In the present study, 10 patients with CRPC were treated with SIB-IMRT after failure of several lines of hormone therapy. Although they were very high-risk cases, with a median follow-up of 33.5 months after SIB-IMRT, the biochemical relapse-free and overall survival rates at 5 years were 70% each and the median PSA nadir after SIB-IMRT was 0.02 ng/ml. In 2 of 10 cases, all hormone therapy was discontinued after SIB-IMRT due to undetectable PSA levels. These patients have been free from any hormone therapy for more than 1 year with no biochemical relapse. Another two cases stopped flutamide and estramustine, respectively, with no biochemical relapse, and the GnRH-agonist was continued by the physician's decision. It is thought that dose escalation and the extended irradiation field achieved by SIB-IMRT may have contributed to the curative effect.

As shown in Table III, the PSA nadir after initial hormonal therapy, the PSA value at initiation of SIB-IMRT, the PSA doubling-time before SIB-IMRT and the PSA nadir after SIB-IMRT were significantly related to biochemical progression after SIB-IMRT. It was interesting that a good response to initial hormonal treatment and earlier introduction of SIB-IMRT were related to disease control. However, there is no solid consensus on who becomes a good candidate for SIB-IMRT and when treatment should be started. Further prospective randomized trials will provide stronger confirmation.

All patients completed SIB-IMRT without treatment delay caused by acute toxicity. It was feasible to escalate the dose using the SIB technique and patients tolerated the treatment. It is thought that the SIB-IMRT technique greatly contributed to the reduction of RT-induced toxicity.

This study had several limitations. First, this was a retrospective study involving patients with various characteristics and treatments. Second, the sample size was very small and the observation period may not have been sufficient. In addition, a validated questionnaire for quality of life and morbidities was not provided. However, despite these limitations, the results provide valuable insight into CRPC treatment. Further studies are needed to clarify the role of SIB-IMRT for CRPC and randomized comparisons are required before definitive conclusions can be drawn.

Conclusion

We revealed the effects and safety of SIB-IMRT for patients with CRPC. The present study describes the first series of patients treated with SIB-IMRT for CRPC after several lines of hormone therapy. SIB-IMRT for patients with CRPC was feasible and seemed to have a satisfactory effect on disease control. Further well-designed studies are required to establish the appropriate role of SIB-IMRT for CRPC after hormone therapy.

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