RESEARCH ARTICLE

Intensity-modulated Radiotherapy Combined with Endocrine Therapy for Intermediate and Advanced Prostate Cancer: Long-term Outcome of Chinese Patients

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Abstract

Aim: The aim of this study was to evaluate acute adverse events and efficacy of three-dimensional intensity-modulated radiotherapy (IMRT) combined with endocrine therapy for intermediate and advanced prostate cancer. Methods: Sixty-seven patients were treated with three-dimensional IMRT combined with maximum androgen blockade. The correlation between radiation-induced rectal injury and clinical factors was further analyzed. Results: After treatment, 21 patients had complete remission (CR), 37 had partial remission (PR), and nine had stable disease (SD), with an overall response rate of 86.5%. The follow-up period ranged from 12.5 to 99.6 months. Thirty-nine patients had a follow-up time of ≥ five years. In this group, three-year and five-year overall survival rates were 89% and 89.5%, respectively; three-year and five-year progression-free survival rates were 72% and 63%. In univariate analyses, gross tumor volume was found to be prognostic for survival (χ^2 = 5.70, P = 0.037). Rates of leucopenia and anemia were 91.1% and 89.5%, respectively. Two patients developed acute liver injury, and a majority of patients developed acute radiation proctitis and cystitis, mainly grade 1/2. Tumor volume before treatment was the only prognostic factor influencing the severity of acute radiation proctitis (P < 0.05). Conclusions: IMRT combined with endocrine therapy demonstrated promising efficacy and was well tolerated in patients with intermediate and advanced prostate cancer.

Keywords: Prostate cancer - radiotherapy - endocrine therapy - prognosis

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Introduction

Worldwide, prostate cancer is the second-most common malignancy in men. In contrast to the trends observed in Western countries, incidence and mortality rates are rising in China (Siegel et al., 2013). Previous studies have demonstrated that radiotherapy could have an impact on survival rate and biochemical control for localized prostate cancer (Wong et al., 2011). Using this technique, a proportion of patients will experience gastrointestinal toxicity. The use of neoadjuvant hormonal therapy (NHT) and adjuvant therapy (AT) was shown to decrease the risk of recurrence after radical prostatectomy (RP), and improve prognosis (Kumar et al., 2006). However, no systematic research has been reported by Chinese scholars on the clinical efficacy and safety of intensity-modulated radiotherapy (IMRT) combined with endocrine therapy for the treatment of patients with intermediate and advanced prostate cancer, thus the clinical benefit of this type of therapy remains unclear. To this end, the data from 67 patients with intermediate and advanced prostate cancer were analyzed to investigate the efficacy and safety of IMRT combined with endocrine therapy, as well as factors prognostic for specific outcomes and adverse events.

Materials and Methods

Inclusion criteria

Patients were required to have pathologically confirmed prostate cancer, a Karnofsky score ≥ 70, no distant metastases (revealed by clinical examination), no history of cancer or disease that may affect the completion of treatment, and must have met any one of the following three criteria: a. a Gleason score of 8 to 10; b. serum prostate specific antigen (PSA) ≥ 20 ng/ml; c. a magnetic resonance imaging (MRI)-predicted T stage of T3 or T4 (tumor penetration of the prostatic capsule or tumor invasion of other adjacent structures outside the seminal vesicle, such as the bladder neck, external sphincter, rectum, levator ani, and pelvic wall), with or without regional lymph node metastases.

Patients

Sixty-seven eligible patients with prostate cancer treated from February 2003 to December 2010 were

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included. The median age was 67 years (range 47 to 81 years). The median lever of PSA was 38.2±21.57 ng/ml Tumors were staged according to the 2010 American Joint Committee on Cancer (AJCC)/TNM staging system for prostate cancer: stage III, 45 cases; stage IV, 22 cases (T4N0M0, 18 cases; T4N1M0, 4 cases). The ECOG scores as follows:0 scores, 49 cases; 1 scores 16 cases; 2 scores,2 cases.The characteristics of these 67 patients are outlined in Table 1. The median follow-up was 76.8 months (range, 12.5-99)

Treatment

First, computed tomography (CT) simulation from L2 to 10 cm below the lower margin of the ischium was performed. CT images were transferred to the treatment planning system (varian CMS4.0 planning system). Based on the CT images and pelvic MRI results, clinical target volume (CTV) was outlined for the prostate, seminal vesicles, and pelvic lymph node drainage area in the planning system. For the prostate, the CTV was outlined for all tissues and the capsule. For the pelvic lymph node drainage area, the CTV was outlined according to the recommendations of the Radiation Therapy Oncology Group (RTOG) on outlining the prophylactic pelvic lymphatic drainage area in localized high-risk prostate cancer. The following organs at risk (OAR) were also outlined: rectum, bladder, femoral head, and enteric cavity and penile bulb outside the planning target volume (PTV). The PTV was defined by uniformly expanding the CTV by 0.5 cm anteriorly and by 0.3 cm posteriorly. The gross tumor volume (GTV) was outlined for the metastatic pelvic lymph nodes according to a standard short diameter of ≥ 1.0 cm. The medical Physicist developed a treatment plan for each patient as required. Tissue inhomogeneity correction was implemented for all plans. The prescribed radiation dose ranged from 70 to 75 Gy, with a median dose of 70.69 Gy: 2.2 - 2.4 Gy/time, once/day, 5 times/week, and 31 times in total. The prescribed dose of prophylactic irradiation to the pelvic lymph node drainage area was 1.8 Gy/f, with a total of 31 times and a total dose of 55.8 Gy. It was required that 95% of the PTV received more than 100% of the prescribed irradiation dose: V70 ≤ 25% for the rectum and bladder, V50 ≤ 5% for both femoral heads, and V70 ≤ 25% for the pubis. All patients successfully completed their treatment plan. Endocrine therapy was administered in combination with IMRT on the first day of radiotherapy. Patients received 50 mg of oral Casodex (AstraZeneca) once daily and a subcutaneous injection of 3.6 mg of Zoladex (AstraZeneca) once every 28 days, until biochemical recurrence (i.e., three consecutive increases in PSA level following the lowest value after radiotherapy).

Outcome measures

Short-term effects, PSA level, acute radiation proctitis, acute radiation cystitis, survival rate, local control rate, overall survival (OS), and progression-free survival (PFS) were observed.

Evaluation criteria of short-term efficacy and acute adverse events

The Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria revised by the American Society of Clinical Oncology (ASCO) and Radiological Society of North America (RSNA) in 2009 were applied (Eisenhauer et al., 2009; Schwartz et al., 2009). Acute adverse events were evaluated according to the early response evaluation criteria of the World Health Organization and the acute radiation injury grading criteria of RTOG.

Statistical analysis

SPSS 13.0 was employed in statistical analysis. The Kaplan-Meier method was used to calculate survival rates, the log-rank method to test for significant differences, and the Cox proportional hazards model to analyze the relationship between radiation-induced rectal injury and related prognostic factors.

Results

Follow-up results

The follow-up period ranged from 12.5 to 99.6 months. Six patients were lost to follow-up, with a follow-up rate of 91.0%. Thirty-nine patients had a follow-up time of at least five years.

Treatment completion and efficacy

All patients completed IMRT combined with endocrine therapy. Prostate MRI and PSA were reexamined after IMRT. Twenty-one patients had complete remission (CR), 37 had partial remission (PR), and nine had stable disease (SD), with an overall response rate (PR + CR) of 86.5%. In 59 patients, PSA levels dropped to normal; however, the PSA was still > normal after a decline of > 50% in seven patients. In patients with a follow-up time of at least five years, three-year and five-year OS rates were 89% and 89.5%, respectively, and three-year and five-year PFS rates were 72% and 63%, respectively. During follow-up, secondary bone metastases were observed in three patients (two to lumbar, and one to atlas) and biochemical recurrence was observed in three patients. One patient died of systemic bone metastasis progression and one patient died of cardiovascular and cerebrovascular diseases. The relationship of the rate of survival with tumor GTV and lymph node metastasis was further analyzed. A GTV ≥ 141 cm^3 was measured in 33 patients and one < 141 cm^3 in 34 patients; the difference in survival was statistically significant (χ^2 = 5.70, P = 0.037). Pelvic lymph node metastases were observed in four patients and no pelvic lymph node metastases were observed in 63 patients; however, the differences were not statistically significant (χ^2 = 12.67, P = 0.85). Survival curves are shown in Figure 1 and Figure 2.

Radiation dose to tumor target volume and OAR

With regard to GTV, CTV, and PTV, in all patients, bladder mean dose was 1473.25 cGy, rectum mean dose was 434.73 cGy, and small intestine mean dose was 797 cGy (Table 1).

Acute adverse events

In the entire group, the most common acute adverse events were leucopenia and anemia, with incidences of

Table 1. Analysis of Radiation Dose to GTV, CTV, and PTV

Target volume	Volume/cm^3	D100[a]/cGy	D95[b]/cGy	D_{mean}/cGy	D_{max}/cGy
GTV	130.20±59.24	5875.75±719.79	6347.44±664.49	6663.75±691.097	7182.75±750.20
CTV	765.75±250.50	4750.07±843.50	5550.44±604.59	4395.50±2508.717	7341.25±1141.41
PTV	171.14±103.77	5529.20±485.56	6179.30±498.10	6539.833±540.235	7038.50±597.97

[a]D100, radiation dose to 100% tumor volume; [b]D95, radiation dose to 95% tumor volume

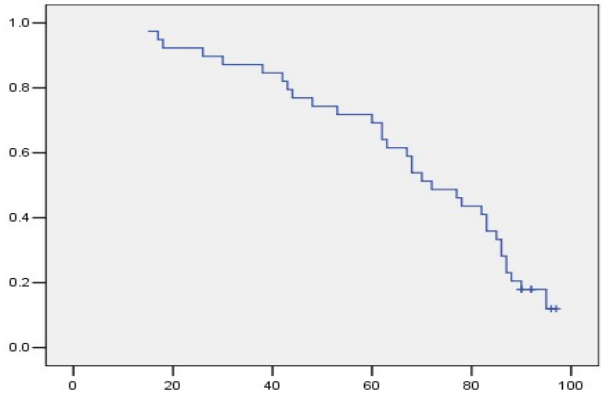

Figure 1. Survival Curves of 67 Patients with Intermediate and Advanced Prostate Cancer

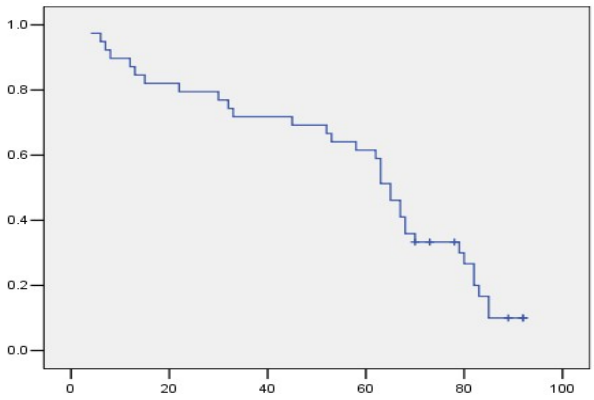

Figure 2. Progression-free Survival Curves of 67 Patients with Intermediate and Advanced Prostate Cancer

Table 3. Cox Multivariate Analysis of Acute Radiation Proctitis-related Factors

Influencing factor	*HR*	*Wald* χ^2	*P*
Age			
≥67 y			
<67 y	0.607 (0.079-4.640)	0.232	0.630
GTV			
≥141 cm^3			
<141 cm^3	2.132 (1.118-4.083)	5.180	0.023
Pelvic lymph node metastasis			
Yes			
No	1.219 (0.539-2.034)	0.008	0.946

91.1% (61/67) and 89.5% (60/67), respectively. Liver toxicity was also observed in two patients. Night sweats were reported by 29 patients (43.2%). See Table 2 for the incidence of acute radiation injury.

Acute radiation proctitis and cystitis

The incidence of acute radiation proctitis and cystitis was evaluated after the start of the radiotherapy. The incidence of acute radiation proctitis was 100%, but no grade 4 proctitis was observed in any patient. The incidence of grade 1, grade 2, and grade 3 proctitis was 55.2% (37/67), 40.2% (27/67), and 4.4% (3/67), respectively. The incidence of acute radiation cystitis was 95.5%, including one case of grade 4 cystitis. The incidence of grade 1, 2, and 3 cystitis was 43.2%, 47.7%, and 2.9%, respectively. In the one patient with grade 4 acute radiation cystitis, bleeding was controlled with oral iron therapy, hemostasis, and cystoscopic electrocautery. Acute urinary tract reactions that developed after radiotherapy included frequent urination (the most common), urgent urination, urodynia, urinary incontinence, and dysuria. See Table 2 for the incidence of acute radiation injury.

Correlation between clinical factors and acute radiation proctitis

Cox analysis of related variables revealed that the risk of acute radiation proctitis-related events at a GTV volume ≥ 141 cm^3 was only 42.3% of that at a GTV volume < 141 cm^3 (P = 0.023). Age and pelvic lymph node metastases did not increase the risk of acute radiation proctitis-related events (P > 0.05). See Table 3 for analysis of acute radiation proctitis-related factors.

Discussion

Treatment options for intermediate and advanced prostate cancer include surgical resection, radiotherapy, endocrine therapy, and combination therapy (Aus et al., 2001). However, the ideal treatment model is still being explored. A series of large-scale randomized clinical trials previously confirmed that radiotherapy improved PFS in patients with locally advanced prostate cancer (Bolla et al., 2005; Thompson et al., 2006; Wiegel et al., 2009). A retrospective study conducted by Dillman et al (2011) on the treatment of 1474 patients with locally advanced

Table 2. Incidence of Acute Radiation Injury

Indicator	Grade				
	0	1	2	3	4
Leucopenia, n (%)	8.9 (6/67)	47.8 (32/67)	38.8 (26/67)	3.0 (2/67)	1.5 (1/67)
Thrombocytopenia, n (%)	56.7 (38/67)	35.8 (24/67)	7.5 (5/67)	0	0
Anemia, n (%)	10.4 (7/67)	86.6 (58/67)	3.0 (2/67)	0	0
Acute radiation proctitis, n (%)	0	55.2 (37/67)	40.3 (27/67)	4.5 (3/67)	0
Acute radiation cystitis, n (%)	4.5 (3/67)	43.2 (29/67)	47.8 (32/67)	3.0 (2/67)	1.5 (1/67)

prostate cancer demonstrated that radiotherapy could increase long-term survival. The five-year survival was 80.5% in the present study, which was lower than that reported by Dillman et al. (2011). The small number of included cases and late stage may explain this difference.

With the increase in the dose of external radiation, an improved local control rate and long-term survival can be achieved in patients with prostate cancer (Chan et al., 2008; Zelefsky et al., 2008). However, conventional radiotherapy with a dose > 70 Gy has been demonstrated to cause more severe rectal and bladder toxicity (Hanks et al., 1997). High-dose three-dimensional conformal radiotherapy can also cause gastrointestinal and urinary adverse events (Peeters et al., 2005). IMRT has gradually become a standard radiotherapy technique, replacing other treatment techniques, because of its ability to reduce the acute adverse events induced by radiotherapy (Zelefsky et al., 2008; Al-Mamgani et al., 2009). The median radiation dose of IMRT combined with endocrine therapy was 70.69 Gy in the present study, which was lower than the 75.6 Gy reported by Housri et al. (2011). The incidence of grade 1, 2, and 3 rectal injuries was 55.2%, 40.2%, and 4.4%, respectively, with no grade 4 injury. These findings are similar to those of Aizer et al. (2011). The dose tolerated by the bladder was significantly lower than the 86.4 Gy reported by Cahlon et al. (2008). In this study, the incidence of leucopenia and anemia was 91.1% and 89.5%, respectively. Liver toxicity and night sweats were associated with endocrine therapy. Even image-guided radiotherapy (IGRT) is associated with an improvement in biochemical tumor control in a lower rate of late urinary toxicity compared with high-dose IMRT (Zelefsky et al., 2012). Because the present study began in 2003 (IGRT) was not employed. Moreover, no consensus has emerged on the appropriate radiation dose in China. Physical optimization of the target volumes was conducted while protecting the vital organs. Therefore, the radiation dose may be lower than those reported outside of China.

Factors affecting the acute adverse events of radiotherapy in prostate cancer include radiation dose, target volume, and radiotherapy technique (Ashman et al., 2005). Bladder filling appeared to be the dominaant foctor which predicted for acute toxicity, followed by the use of IMRT (Jain et al., 2012). For locally advanced prostate cancer, acute urinary tract adverse events of surgery, external radiation, and endocrine therapy had similar probabilities and occurred two to six months after treatment (Cozzarini et al., 2007). The follow-up observation after treatment found that the major urinary tract reaction was frequent urination, which occurred within three to six months. This was not consistent with the findings of Sanda et al. (2008). The small sample size may account for this difference. Aizer et al. (2011) confirmed that the greater the volume, the greater the probability of grade 3 urinary system toxicity. In the present study, 64 patients developed urinary toxicity, with an incidence of 95.5%, and six patients developed urinary toxicity of grade 3 or higher, with an incidence of 8.9%. These incidences were higher than those reported in previous studies. The fact that all enrolled patients had intermediate and advanced stages of disease may account for this difference. Intermediate and advanced stages resulted in an increased GTV, and most of the local lesions invaded the bladder or rectum, causing increased radiation dose to vital organs. Therefore, in consideration of oriental constitution and combination with endocrine therapy, a tumor dose of 70.69 is acceptable, and clinical adverse reactions can be tolerated.

Many clinical factors affect radiation-induced rectal injury. Some studies have suggested that the level of rectal injury could be observed by the introduction of a dose volume histogram (DVH) into the treatment plan (Cozzarini et al., 2003; Vargas et al., 2005). Storey et al. (2000) confirmed that the probability of grade 2 acute radiation injury with rectum V70 > 25% was significantly higher than that with V70 < 25%. In the long-term follow-up of patients with prostate cancer after radiotherapy, Nguyen et al. (2010) found that the main factor affecting rectal injury was the dose to the anterior rectal wall, rather than the overall dose to the entire rectum. The present study found that rectal injury was not significantly associated with the patient's age or PSA level. GTV was related with the occurrence of grade 2 and 3 rectal injuries ($P < 0.05$), but not with the occurrence of grade 0 or 1 rectal injuries ($P > 0.05$). This finding was similar to those obtained in the previous studies, demonstrating that the GTV of prostate lesions was correlated with rectal injury.

In conclusion, IMRT combined with endocrine therapy achieves good results in patients with intermediate and advanced prostate cancer. A radiotherapy dose of 70 -75 Gy is safe and feasible in Chinese patients. The acute adverse events of this type of therapy were well tolerated.

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