Cancer Treatment Reviews 39 (2013) 872–878

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Management of high-risk prostate cancer: Radiation therapy and hormonal therapy

Takuma Nomiya [a,*], Hiroshi Tsuji [a], Shingo Toyama [a], Katsuya Maruyama [a], Kenji Nemoto [b], Hirohiko Tsujii [a], Tadashi Kamada [a]

[a] National Institute for Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba 263-8555, Japan
[b] Yamagata University Hospital, Yamagata, Japan

ARTICLE INFO

Article history:
Received 24 February 2013
Received in revised form 4 April 2013
Accepted 8 April 2013

Keywords:
Prostatic neoplasms
Radiotherapy
Androgen antagonists
Clinical trial
Review

SUMMARY

The prognosis of high-risk prostate cancer is poor with a high mortality rate. The Radiation Therapy Oncology Group (RTOG) has performed dose-escalation studies of external beam radiation therapy (EBRT) and has developed high-precision radiation therapy (RT) methods such as intensity-modulated RT, carbon ion therapy, and proton beam therapy. High-dose rate brachytherapy (HDR-BT) is also studied as an option for high-risk prostate cancer treatment. Past clinical trials have suggested that the local control rate of high-risk prostate cancer improves with total EBRT dose, even for doses >70 Gy. Several randomized controlled trials, including RTOG 94-06, have shown significantly better prognoses with higher doses (>75 Gy) than with lower doses (<70 Gy). A proton beam therapy trial (PROG 95–09) also showed similar results. A phase II clinical trial (National Institute for Radiological Sciences, Japan; trial 9904) showed that carbon ion therapy resulted in very good biochemical recurrence-free survival rates among high-risk prostate cancer patients, demonstrating particle therapy to be a valid treatment option. RTOG 86-10 showed that short-term neo-adjuvant hormonal therapy (HT) was inadequate for high-risk prostate cancer but effective for intermediate-risk prostate cancer, whereas RTOG 92-02 and the European Organisation for Research and Treatment of Cancer (EORTC) 22863 showed significant improvements in the prognosis of high-risk groups receiving long-term (>2 years) HT combined with definitive RT. Further studies are warranted to elucidate optimal irradiation doses, HT treatment durations, and combination therapy schedules.

Introduction

Several risk classifications for prostate cancer are used to define the prognosis of the disease in routine medical practice, and the classifications proposed by D'Amico et al.[1] and the National Comprehensive Cancer Network (NCCN)[2] are particularly well known. The risk classification by D'Amico et al. defines high-risk prostate cancer as disease accompanied by a prostate specific antigen (PSA) level of >20 ng/mL, a Gleason score of $\geqslant$8, and/or T-factor $\geqslant$T2c. The NCCN guideline defines high-risk prostate cancer as disease accompanied by a PSA level of >20 ng/mL, a Gleason score of $\geqslant$8, and/or T-factor $\geqslant$T3a or disease accompanied by two or more intermediate risk factors. Although there are some differences between the risk classifications, the boundaries of each risk are generally consistent.

On the other hand, the consensus of definition of PSA failure after definitive radiation therapy (RT) has been changed several times. Fixed PSA cutoff values were used previously. While three consecutive increases in PSA have been defined as biochemical failure by the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus statement, a PSA increase of $\geqslant$2.0 ng/mL above the nadir PSA level has been defined as biochemical failure by the Radiation Therapy Oncology Group (RTOG)–ASTRO Phoenix consensus conference.[3,4] Of late, the latter consensus tends to be used more often in clinical practice.

Because the definition of PSA failure after RT differs according to treatment period, unconverted PSA recurrence rates and biochemical recurrence-free survival (bRFS) rates are presented in this paper.

Search strategy and selection criteria

A search of PubMed (Medline; http://www.ncbi.nlm.nih.gov/pubmed) was used to identify related English language papers using the following search terms: (1) "high-risk" [title] AND "prostate cancer" [All Fields] AND ("radiotherapy" [Subheading] OR "radiotherapy" [All Fields] OR "radiotherapy" [MeSH Terms]), and (2) "high-risk" [title] AND "prostate cancer" [All Fields] AND (("androgens" [MeSH Terms] OR "androgens" [All Fields] OR "androgen" [All Fields] OR "androgens" [Pharmacological Action])

* Corresponding author. Tel.: +81 43 206 3360; fax: +81 43 206 6506.
E-mail addresses: t_nomiya@nirs.go.jp, t.nomiya@med.id.yamagata-u.ac.jp (T. Nomiya).

0305-7372/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ctrv.2013.04.003

AND deprivation [All Fields] AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]). Studies with a publication date between 1980 and 2012 were included.

Studies regarding definitive surgery, RT for postoperative recurrence, and those that did not include clinical outcomes of RT and/or hormonal therapy (HT) were excluded. The websites of several major clinical trial groups (RTOG, European Organisation for Research and Treatment of Cancer (EORTC), SWOG (Southwest Oncology Group), etc.) were searched for clinical trials of radiation and HTs and publications that included clinical outcomes in high-risk prostate cancer cases were included.

External beam RT: photon beams

Although prophylactic pelvic irradiation has been routinely performed for prostate cancer treatment in the past, prophylactic irradiation to the pelvic lymph nodes (LNs) is rarely performed at present on the basis of the results of several clinical trials. A summary of clinical trials on definitive RT for prostate cancer is shown in Table 1.

In a randomized controlled trial (RCT) named RTOG 75-06, the outcomes of patients with LN metastasis-negative stage C (LN − stage C) cancer who received whole pelvic (WP) irradiation were compared with those of patients with pelvic LN metastasis who received WP and prophylactic periaortic LN (PALN) irradiation.[5] The results showed that 5-year disease-free survival (DFS) rate for the two groups (WP + PALN and WP alone) was 37% and 42%, respectively, and there were no significant differences in overall survival (OS), DFS, and metastasis-free survival between the two arms. The study also showed that extended prophylactic irradiation did not decrease the recurrence rate.

In RTOG 77-06, prostate cancer patients without LN metastasis (T1-2N0M0) were randomly assigned to a WP irradiation arm and a localized prostatic irradiation arm and outcomes were compared.[6] The 5-year DFS rate for the two groups was 64% and 67%, respectively, which were not significant (N.S.), and there were no significant differences in OS and local control rate (LCR) between the two groups. Following these results, the standard irradiation field for LN − prostate cancer began to shift toward a local irradiation field.

Kuban et al.[7] evaluated the treatment outcomes of 652 patients treated during the same period and reported that the 5-year bRFS rate was 47% for patients with stage C cancer, 49% for patients with a Gleason score of ⩾8, and 44% for patients with a PSA level of >20 ng/mL. However, these outcomes were worse than those recently reported for high-risk prostate cancer patients, which may be explained by the lower prescribed irradiation dose (approximately 65 Gy/7 weeks) and the lack of consensus regarding combination HT.

The MD Anderson Cancer Center (Houston, TX, USA) conducted a phase III RT dose-escalation study that involved a conventional dose group (70 Gy/35 fractions) and a high-dose group (78 Gy/39fr.). There was a significant difference in the 6-year bRFS rate between the two groups (64% vs. 70%, respectively, $p = 0.03$), whereas subgroup analyses showed a more significant difference in 6-year bRFS rates between the two arms (43% vs. 62%, $p = 0.01$) in patients

Table 1
Clinical trials of radiation therapy for high-risk prostate cancer.

Trials (authors)	Category of trials	No. of total patients	Treatment arms (subgroup)	Total dose/ fractions	Type of radiation	Treatment outcomes	References
RTOG75-06	Phase III (RT field)	523	Arms			5y-DFS	[5]
			WP + PALN	65 Gy/35fr.	Photon	37%	
			WP	65 Gy/35fr.	Photon	42%	
RTOG77-06	Phase III (RT field)	445	Arms			5y-DFS	[6]
			WP	65 Gy/35fr.	Photon	64%	
			Prostate bed	65 Gy/35fr.	Photon	67%	
MDACC Pollack et al.	Phase III (RT dose)	305	Arms			6y-FFF	[8]
			Low-dose	70 Gy/35fr.	Photon	24%	
			High-dose	78 Gy/39fr.	Photon	10%	
MSKCC Zelefesky et al.	Phase III (RT dose)	2047	Arms (High-risk)			5y-bRFS	[9]
			Low-dose	⩽70.2 Gy	Photon	45%	
			High-dose	75.6–86.4 Gy	Photon	65%	
RTOG94-06	Phase III (RT dose/fraction size)	1051	Arms (High-risk)			5y-bRFS	[10]
			Low-dose	68.4 Gy/38fr.	Photon	42%	
			Intermediate-dose	73.8 Gy/41fr.	Photon	62%	
			High-dose	79.2 Gy/44fr.	Photon	68%	
MSKCC Cahlon et al.	Prospective study	478	Arms (High-risk)			5y-bRFS	[11]
			Ultra-high-dose	86.4 Gy/48fr.	Photon	72%	
MGH Shipley et al.	Phase III (RT dose)	202	Arms (GS 4or5)			5y-LCR	[23]
			Low-dose	67.2 Gy/36fr.	Photon	64%	
			High-dose	75.6CGE/40fr.	Photon + Proton	94%	
LLUMC Slater et al.	Prospective study (Proton)	643	Arms (GS 8-10)			5y-bRFS	[24]
			Photon + Proton	75GyE/40fr.	Photon + Proton	50%	
			Proton	74GyE/37fr.	Proton		
PROG95-09	Phase III (RT dose)	392	Arms (Inter-High risk)			5y-bRFS	[25]
			Low-dose	70.2 Gy/39fr.	Photon + Proton	63.4%	
			High-dose	79.2 Gy/44fr.	Photon + Proton	79.5%	
NIRS 9904(1) Tsuji et al.	Phase II (Carbon ion)	201	Arms (High-risk)			5y-bRFS	[31]
			Single-arm	66GyE/20fr.	Carbon ion	80.5%	
NIRS 9904(3) (ongoing)	Phase II (Carbon ion)	986	Arms (High-risk)			5y-bRFS	[a]
			Single-arm	57.6GyE/16fr.	Carbon ion	88.5%	

RTOG: Radiation Therapy Oncology Group, PROG: Proton Radiation Oncology Group, MDACC: M.D. Anderson Cancer Center, MSKCC: Memorial Sloan-Kettering Cancer Center, MGH: Massachusetts General Hospital, LLUMC: Loma Linda University Medical Center, NIRS: National Institute for Radiological Sciences, WP: Whole Pelvic irradiation, PALN: ParaAortic Lymph Node irradiation, fr.: fractions, DFS: Disease-Free Survival, FFF: Freedom-From Failure, bRFS: biochemical Recurrence-Free Survival, GS: Gleason Score, CGE: Cobalt Gray Equivalent, GyE: Gray Equivalent.

[a] Unpublished.