Adjuvant Androgen Deprivation Therapy Loses Its Therapeutic Benefit after Premature Termination: An Experience of Combined Modality Treatment on Prostate Cancer

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Background: To investigate the effect of the premature termination of recommended androgen deprivation therapy (ADT) as an adjunct to radiotherapy.

Methods: Between December 2001 and March 2004, 92 patients with non-metastatic prostate cancer underwent primary, curative radiotherapy via an intensity-modulated technique. Four patients (5%) were treated with a dosage of 70.2 Gy, while 74 (80%) and 14 patients (15%) were treated to 72 and 75.6 Gy. Thirty patients (33%) received pelvic irradiation to 45 Gy as a part of their treatment. Seventy-nine patients (86%) also received variable ADT, but only 35 patients (38%) followed a strict protocol when on ADT. Biochemical failure was defined as nadir plus 2 ng/mL or if there was any clinical evidence of tumor recurrence.

Results: The median follow-up time was 37.5 months (20.4 – 57.8 months). The 3-year overall survival rate was 91.8%. The estimated 3 year recurrence-free survival rates were 100%, 88.9%, and 69.7% for the low, intermediate, and high risk groups, respectively. High risk group patients receiving ADT of an inappropriate length was the only significant risk factor correlated to disease recurrence. The 3-year recurrence-free survival rate was extremely poor (28.6%) in high risk group patients who received adjuvant ADT for less than 2 years. This was significantly worse than patients with the same risk who received long-term ADT (88.1%) or no adjuvant ADT (76.4%, $p < 0.001$).

Conclusions: Long-term adjuvant ADT after radiotherapy on high risk prostate cancer has no benefit if the duration is less than 2 years. Premature termination should be avoided.

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Key words: prostate neoplasms, intensity-modulated radiotherapy, hormone therapy

During the past decade, the efficacy of combining radiotherapy (RT) and androgen deprivation in the treatment of prostate cancer has been proven effective in many randomized studies. Two random-

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ized trials have shown the benefit of long-term adjuvant androgen deprivation therapy (ADT) post radiotherapy, with disease-free or overall survival rate increases.[1,2] Short-term ADT has also proven effective for reducing disease recurrence.[3,4] Another Radiation Therapy Oncology Group (RTOG) trial has demonstrated that long-term ADT is superior to the short-term variant for treatment of locally advanced prostate cancer in terms of every efficacy endpoint except overall survival.[5] Gradually, ADT has become an important adjunct to radiotherapy for prostate cancer, with the degree of androgen ablation proportional to disease advancement.

Unfortunately, following treatment guidelines without deviation is usually impossible and, prior to 2003, some of our prostate cancer patients did not receive ADT as our institutional treatment guidelines. There were two reasons for this deviation from the standard treatment: insurance and financial problems, and a lack of supervision by an uro-oncology specialist. These ADT treatments were often considered unnecessary, and resulted in treatments of an inappropriate length, or of suboptimal intensity. At the time of this writing, there has been no study demonstrating the treatment outcomes associated with the above conditions, therefore, the objectives of this retrospective investigation were to review our past treatment results and to clarify the relevance of our ADT guidelines.

METHODS

Between December 2001 and March 2004, 92 patients with non-metastatic prostate adenocarcinoma underwent primary curative intensity modulated radiotherapy (IMRT) at our hospital. Patients who underwent IMRT for other indications, such as postoperative radiotherapy (RT) or salvage treatment, were not included in the current study.

Preparations for RT included customization of an immobilization device, computed tomography simulation, target and organ-at-risk delineation by the attending physician, and RT plan optimization by a medical physicist. Defecation was requested before treatment. The patient was also asked to drink 300 ml of water after emptying their bladder; then wait for 30 minutes before RT. However, strict rules such as routine colon preparation and emptying of the bladder via catheter were not applied. Organ delineation was based on the magnetic resonance image acquired before treatment. Initially, the prostate, gross tumor extension, and seminal vesicles were included in the clinical target volume (CTV). The planning target volume (PTV) was created by 1-cm expansion of CTV in all directions except at the prostate-rectum junction, where the margin was reduced to 7 mm. After the initial dose of 63 Gy, a second CTV was plotted containing only the involved regions (such as the prostate or seminal vesicles in the T3b stage of the disease). The margins of expansion from CTV to PTV were also reduced to 7 mm at the prostate-rectum and prostate-bladder junctions, and in the cranial direction. Parameters given for the IMRT were as follows: (1) 100% prescribed dose < CTV dose < 110% prescribed dose; (2) 95% prescribed dose < PTV dose < 110% prescribed dose; (3) maximal dose to the rectum < 105% prescribed dose and < 15% rectal volume receiving > 72 Gy; and, (4) maximal bladder dose < 105% prescribed dose and less than 25% bladder volume receiving > 72 Gy. Given the problematic IMRT planning, < 25% of the rectal volume receiving > 70 Gy was considered acceptable if the original constraints were unachievable.

The daily radiation fraction was 1.8 Gy, with a total prescribed dose of 70.2-75.6 Gy depending on the duration of RT and achievement of dose constraints. Radiation was given as one fraction per day, 5 fractions per week. Forty-five Gy was delivered to the mid-pelvis using the conventional four-field technique where patient risk for pelvic node metastasis was > 15%, as calculated by the Roach formula (pelvic nodal metastasis rate = 2/3 prostatic specific antigen (PSA) level + (Gleason score [GS] – 6) x 10 x %). However, if the patient's age was > 75 years, Eastern Cooperative Oncology Group (ECOG) performance status ≥ grade 2, or a diagnosis included a multiple systemic disease, then pelvic irradiation was not arranged.

Generally, ADT was not administered if the cases were classified as low risk recurrence with no risk factors (T1-2a, and GS 2-6, and PSA < 10). If the patients had any of the factors related to high recurrence risk (T3-4, N1, GS 8-10, or PSA ≥ 20), they were assigned to the high risk group, and 2-year or permanent ADT, either by Luteinizing Hormone-Releasing Hormone (LHRH) analogue or orchiectomy, was started. An oral antiandrogen was also pre-

scribed for the first 4 months. Other patients were assigned to the intermediate-risk group and received short-term neoadjuvant and concurrent ADT for 4 months using an LHRH analogue combined with an oral antiandrogen. All ADT was started 2 months before RT.

PSA was checked the same day that RT was completed and a follow-up was scheduled every 3-4 months in the first 2 years, and 4-6 months thereafter, depending on the recurrence risk estimated for each patient. PSA testing and digital rectal examination (DRE) was performed at each visit. Biochemical failure was defined using the nadir + 2 ng/mL criterion[6] or from the start of ADT after PSA elevation. No elective prostate biopsy was arranged after radiotherapy. Examinations other than a regular PSA check and DRE were arranged only if disease relapse was suspected through PSA monitoring, DRE or appearance of other suspicious symptoms/signs.

The main study endpoints were disease relapse in any form. Survival was measured from the last day of RT, while Kaplan-Meier survival calculations were based on the actual RT completion date. The log-rank test was used to determine differences in univariate analysis. Cox proportional hazards regression analysis was employed to confirm the treatment independence and risk stratification in multiple covariate analysis of recurrence-free survival and complication rates. SPSS for Windows (version 11.0; SPSS Inc, Chicago, IL) was used for all data analysis.

RESULTS

Patient population

Median follow-up was 37.5 months (20.4 – 57.8); median age was 73 years (range 55-83). There were 60 (65%), 22 (24%) and 10 (11%) patients in the high, intermediate and low-risk groups, respectively. Salient patient characteristics are listed in Table 1. A total of 30 (33%) patients underwent pelvic RT receiving 72 Gy (n = 74; 80%) or 75.6 Gy (n = 14; 15%). Only four patients (5%) received 70.2 Gy because the dose constraints were unachievable after many optimization attempts. Thirty-nine (42%) and 40 (44%) patients received long and short-term ADT, respectively. Treatment parameters are listed in Table 2. ADT did not follow our treatment guidelines in 57 (62%) cases. The details of guideline deviations are listed in Table 3.

Overall and recurrence-free survival

At the time of analysis, patient status was as follows: 57 (62%) were alive without disease; 17 (18%) were alive with disease recurrence; only three (3%) had expired from the disease; six (7%) had died from other causes; eight (9%) were alive but of unknown status; and, one was lost to follow-up. The 3-year overall survival rate was 91.8%.

Prostate cancer relapse occurred in 21 patients. Types of failure, in descending order of prevalence were biochemical (n = 19), local (n = 6), and distant metastasis (n = 4). Two patients suffered distant

Table 1. Characteristics of Patients

Characteristics	Frequency (percentage)
Age	Median: 73 (55-84) years old
Any systemic disease	
No	30 (33%)
Yes	62 (67%)
Pretreatment PSA level	
< 10 ng/ml	23 (25%)
≥ 10 but < 20 ng/ml	39 (43%)
≥ 20 ng/ml	3 (3%)
Unknown	27 (29%)
Gleason score	
2-6	43 (47%)
7	21 (23%)
8-10	25 (27%)
Not available	3 (3%)
Tumor state (AJCC 1997)	
T1	11 (13%)
T2	44 (47%)
T3	34 (37%)
T4	1 (1%)
Unknown	2 (2%)
Node stage	
N0	85 (92%)
N1	7 (8%)
Risk classification	
Low	10 (11%)
Intermediate	22 (24%)
High	60 (65%)

Table 2. Treatment Parameters of the Patients

Parameters	Frequency (percentage)
Androgen deprivation therapy	
No	13 (14%)
Neoadjuvant	40 (44%)
Adjuvant	39 (42%)
Transurethral resection of prostate before radiotherapy	
No	52 (56%)
Yes	40 (44%)
Whole pelvic irradiation	
No	62 (67%)
Yes	30 (33%)
Total dose	
70.2 Gy	4 (5%)
72 Gy	74 (80%)
75.6 Gy	14 (15%)

Table 3. Detail of Androgen Deprivation Therapy in Each Group

	Conditions	Frequency (percentage)
Low-risk group		
	No violation	6 (60%)
	Unnecessary ADT before IMRT	4 (40%)
	Unnecessary adjuvant ADT	0 (0)
Intermediate-risk group		
	No violation	7 (32%)
	No ADT	7 (32%)
	Inappropriate intensity of ADT before IMRT	5 (23%)
	Unnecessary adjuvant ADT	3 (13%)
High risk group		
	No violation	22 (37%)
	No ADT after IMRT	26 (43%)
	Inappropriate ADT	12 (20%)
	(range: 1-12 months, median: 5.5 months)	

Abbreviations: ADT: androgen deprivation therapy; IMRT: intensity-modulated radiotherapy.

metastasis without preceding biochemical failure. The estimated 3-year recurrence-free survivals were 100%, 88.9% and 69.7%, for the low, intermediate and high risk groups, respectively. Data processing revealed that numerous treatment failures developed in high risk patients who had received adjuvant ADT for less than 1 year. Other conditions, such as non-castration neoadjuvant ADT or unnecessary ADT did not affect the tumor recurrence rate in the low and intermediate-risk groups. Therefore, the patients were assigned to four groups based on risk and ADT form: low or intermediate risk receiving any ADT type (HR0); high risk receiving adjuvant ADT $\geqq 2$ years (HR1); no adjuvant ADT (HR2); and, adjuvant ADT < 2 year (HR3). ADT pattern was the only significant factor for recurrence-free survival from univariate analysis. The 3-year recurrence-free survivals were 92.3%, 88.1%, 76.4% and 28.6% for the HR0, HR1, HR2 and HR3 groups, respectively. ADT pattern was also the only significant factor from multivariate analysis. HR3 group membership incurred the highest risk of recurrence (relative risk 9.77; 95% CI 2.549-35.448). The recurrence-free survival curves for each risk group and ADT pattern are depicted in Figs. 1 and 2. All analyzed factors and its survival are listed in Table 4.

DISCUSSION

Androgen deprivation therapy has been proven

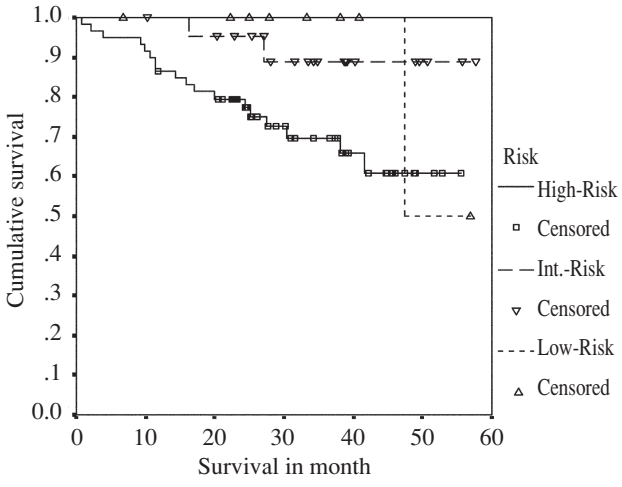

Fig. 1 The recurrence-free survival of different risk groups. ($p = 0.09$).

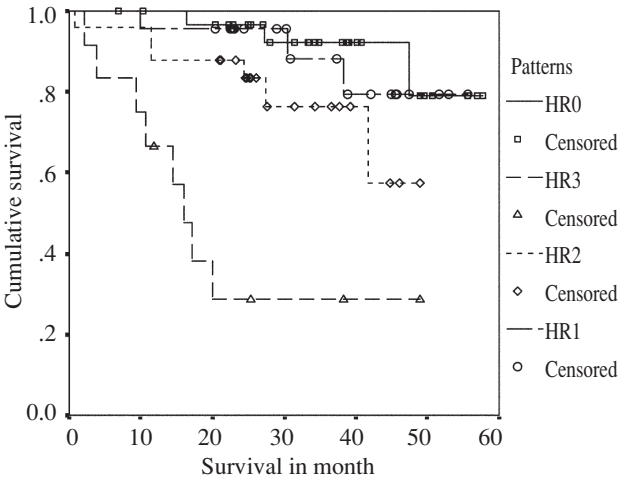

Fig. 2 The recurrence-free survival of different patterns of androgen deprivation therapy. ($p < 0.001$). Only the HR3 group was significantly different from other groups. There was no significant difference ($p = 0.19$) after excluding the HR3 Group. Abbreviations used: HR0: low or intermediate risk group with any kind of ADT; HR1: high risk group with ADT duration more than 2 years; HR2: high risk group but no adjuvant ADT applied; HR3: high risk group with adjuvant ADT duration less than 1 year.

to be an effective adjuvant treatment to radiotherapy for advanced non-metastatic prostate cancer[1-3] and our study hypothesized that it might lose its benefit if terminated earlier than 2 years. Unexpectedly, inappropriate adjuvant ADT appears to be even worse than no ADT therapy in high risk patients and so we re-examined the medical histories and clinical data. As a result, we confirmed that ADT termination was not a subsequent event of developing hormone refractory disease. However, we found that the mean pretreatment PSA in HR3 (63.8 ng/ml, 95% CI 30-97.5 ng/ml) was significantly higher than HR2 (31.4 ng/ml, 95% CI 17.2-45.5 ng/ml) but not HR1 (94.7 ng/ml, 95% CI 47.7-141.7 ng/ml). The unexpected result could be caused by bias in our data but one previous study reported that high-risk prostate cancer patients with pretreatment PSA > 50 ng/ml and no evidence of metastatic disease still have survival characteristics similar to other high-risk prostate cancer patients.[7] So, the possibility of premature termination of adjuvant ADT resulting in high biochemical failure rate in HR3 group cannot be completely excluded. Certainly, there is no doubt that premature ADT termination is inferior to long-term ADT, since the selection bias we mentioned above did not exist between the HR3 group and the HR1 treatment group.

To the best of our knowledge, no detrimental effects of ADT have been reported. There is no study that addresses the topic of premature termination of adjuvant ADT, and studies referring to the stopping of ADT a short period of time after RT are uncommon. A randomized study using short-term ADT that stopped 2 months after completion of RT provided some benefit to the patients. However, we feel that this evidence does not rule out our suspicions since their research included mostly patients with intermediate risk prostate cancer.[4] Another report presented results of 2 randomized trials which compared 3 different treatment arms: RT alone, neoadjuvant and concurrent ADT with RT, and neoadjuvant, concurrent, and adjuvant ADT (total 10 months) ADT with RT. Ten months of ADT with RT was superior to RT alone but equal to short-term ADT that stopped with RT. However, these 2 trials also included some patients with intermediate risk prostate cancer.[8]

If this detrimental effect is authentic, rapid occurrence of biochemical failure may result from the rapid progression of microscopic distant metastasis. We already know that irradiating primary tumors may trigger tumor growth at a distant site[9] and an animal study has proven the role of angiogenesis in this event. The endogenous antiangiogenetic factor may be suppressed after irradiation of the main tumor, since administration of angiostatin could reverse the risk of distant lesion progression.[10] While the anti-tumor effect of ADT was also assisted by antiangiogenesis, androgen deprivation, on the other hand, resulted in a decrease of microvessel density in the prostate.[11,12] Another study found that the antiangiogenetic effect was a result of expression of thombospondin, but it would also stimulate the expression of vascular endothelial growth factor.[13] If these effects are combined, microscopic metastatic lesions may progress faster after cessation of ADT because treatment had not achieved its maximal effect. Since high-risk prostate cancer has more chance to develop micrometastases before treatment, we observed this effect only in the patients with high-risk prostate cancer. This is only a hypothesis, and we need more evidence to prove it. Animal studies seem to be the only way to confirm this since

Table 4. Recurrence-free Survival vis-à-vis Clinical Variables in 92 Patients with Prostate Cancer

Risk factors	3-year recurrence-free survival	Univariate analysis	Multivariate analysis
Age			
< 73 y/o	78.7%	$p = 0.827$	$p = 0.511$
≧ 73 y/o	76.6%		HR = 0.646 (0.176-2.372)
Other systemic disease			
Yes	74.4%	$p = 0.258$	$p = 0.593$
No	82.8%		HR = 1.366 (0.436-4.285)
Risk classification			$p = 0.385$
Low	100%	$p = 0.069$	HR = 1
Intermediate	88.9%		HR = 1.29 (0.112-14.925)
High	69.7%		HR = 3.817 (0.185-78.584)
Clinical T-stage			
1-2	86.1%	$p = 0.065$	$p = 0.144$
3-4	63%		HR = 2.466 (0.735-8.271)
Gleason score			
2-7	81.9%	$p = 0.257$	$p = 0.951$
8-10	68.4%		HR = 1.036 (0.334-3.217)
PSA level			
< 20 ng/ml	83.2%	$p = 0.205$	$p = 0.746$
≧ 20 ng/ml	71.7%		HR = 0.799 (0.206-3.105)
Neoadjuvant ADT			
Yes	75.6%	$p = 0.394$	$p = 0.731$
No	88.9%		HR = 0.647 (0.054-7.733)
TURP			
Yes	77.5%§	$p = 0.962$	$p = 0.264$
No	77.5%		HR = 0.564 (0.206-1.542)
Pelvic irradiation			
Yes	76.1%§	$p = 0.865$	$p = 0.675$
No	78.5%		HR = 0.782 (0.248-2.47)
Radiation dose			
≦ 72 Gy	76.5%	$p = 0.377$	$p = 0.182$
> 72 Gy	75%		HR = 0.996 (0.990-1.002)
Adjuvant ADT			$p = < 0.001$
HR0	92.3%	$p < 0.001$	HR = 0.718 (0.145-3.562)
HR1	88.1%		HR = 1
HR2	76.4%		HR = 2.227 (0.553-8.974)
HR3	28.6%		HR = 9.77 (2.549-37.448)

Abbreviations: HR0: low or intermediate risk group with any kind of ADT; HR1: high risk group with ADT duration more than 2 years; HR2: high risk group but no adjuvant ADT applied; HR3: high risk group with adjuvant ADT duration less than 1 year.

conducting any short-term adjuvant ADT with RT to patients with high risk prostate cancer is not ethical.

At the time of this analysis, there was only 1 cancer-specific death and 2 hormone- refractory disease occurrences. Therefore, the impact of premature termination of adjuvant ADT on other clinical observation end points in the current study is unknown. A review of the past clinical trials and studies has shown that short-term ADT may not affect the therapeutic effect of later salvage hormone treatment. The following analysis of RTOG 86-10 showed that short-term ADT will not compromise the beneficial effect of salvage ADT.[14] Also, salvage ADT still has a durable effect on recurrence after radiotherapy; some intermittent androgen ablation trials have already shown acceptable results. A phase II trial of intermittent ADT for recurrence after radiotherapy, conducted by Curry and colleagues, showed a 5-year survival at 92.3%. The distant metastasis rate was only 6.8%.[15] In another phase II trial of intermittent ADT, with a median follow-up of 4.2 years, the cancer-specific death was only 2%.[16] According to these studies, the overall survival of patients who received prematurely terminated adjuvant ADT may be comparable to patients who received no adjuvant ADT after salvage treatment. However, continuous long-term ADT has demonstrated overall survival benefits for high risk patients, compared to RT alone.[5,17] Based on these studies, the overall survival of premature terminated adjuvant ADT is comparable to no adjuvant ADT, and is inferior to adjuvant long-term ADT. So stopping adjuvant ADT for high-risk patients for any reason is dangerous and should be avoided.

Conclusions

Long-term adjuvant ADT after RT in high risk prostate cancer patients has no benefit if the duration is less than 2 years and so premature termination should be avoided. The mechanism detrimental effect is not revealed of the, and animal studies should be carried out to further investigate our unexpected finding.

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攝護腺癌整合治療經驗：追加男性荷爾蒙阻斷治療因提早終止失去效用

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背 景： 研究放射治療後追加荷爾蒙治療若提早終止後的治療結果。

方 法： 在 2001 年 12 月到 2004 年 3 月間，有 92 位尚未擴散之攝護腺癌病患，接受治癒性的放射治療並採用強度調控技術。其中 4 位病患 (5%) 接受劑量 70.2 格雷，74 (80%) 位病患接受 72 格雷，另外 14 (15%) 位病患接受 75.6 格雷的放射線照射。這些病患中有 30 位接受骨盆腔照射 45 格雷。有 79 位病患 (86%) 接受任一形式的荷爾蒙阻斷，但其中只有 35 位病患接受的荷爾蒙阻斷有依照現行的治療指引。在治療後，若攝護腺特異抗原增加超過最低值 2 ng/mL 以上，或發現任何臨床上顯見的證據，定義爲治療失敗。

結 果： 追蹤期中位數爲 37.5 個月 (範圍爲 20.4 到 57.8 個月)。三年的存活率爲 91.8%。三年的無復發存活率對低危險度，中危險度，及高危險度的病患，分別爲 100%，88.9%，以及 69.7%。高復發危險分組且接受追加荷爾蒙阻斷時間太短爲對疾病復發唯一顯著相關的因子。當高復發危險病患的追加荷爾蒙阻斷治療不到兩年便停止時，三年的無復發存活率爲 28.6%。此結果明顯低於接受治療超過兩年的病患 (88.1%)，甚至明顯低於沒有接受追加荷爾蒙阻斷治療的病患 (76.4%，$p < 0.001$)。

結 論： 高復發危險之攝護腺癌病患若其追加荷爾蒙阻斷提早於兩年內停止，將喪失追加治療的療效，所以需盡量避免提前終止此治療。

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關鍵詞： 攝護腺腫瘤，強度調控放射治療，荷爾蒙治療

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