Androgen and prostate cancer: the role of primary androgen deprivation therapy in localized prostate cancer

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Abstract

Background: The basic mechanisms and clinical efficacy of primary androgen deprivation therapy (PADT), especially combined androgen blockade (CAB) for localized or locally advanced prostate cancer (PCa) have been outlined. An important point relates to which patients are suitable candidates for PADT.
Methods: A retrospective review of the efficacy of PADT in 628 patients with localized or locally advanced PCa treated with PADT at seven institutions in Japan was carried out.
Results: It was found that more than 30% of low- or intermediate-risk localized PCa patients could have their disease controlled over the long-term by PADT alone. Short-term or intermittent PADT could not be recommended because of the possibility of character change in the cancer cells as a result of incomplete androgen ablation.
Conclusion: Algorithms are proposed for the treatment of localized PCa not only in low- and intermediate-risk groups, but also in the high-risk group. Future research directions are indicated.

Introduction

Androgens play a crucial role in the development and growth of prostate cancer (PCa). Therefore, one of the main targets for the treatment of PCa is to reduce androgen levels in PCa cells. Androgen deprivation therapy (ADT), first reported by Huggins & Hodges in 1941 [1], dramatically reduced the mortality caused by PCa. Dr Huggins was later awarded the Nobel Prize for this achievement. When Huggins & Hodges first reported ADT for PCa, it was mainly used for advanced disease and, therefore, most PCa relapsed at a later date. Since then, a kind of misunderstanding arose, in that it became common knowledge among urologists that the usefulness of this hormonal therapy was, like a magic formula, only temporary. However, this thinking should be changed in cases of localized PCa. Labrie et al. showed that localized or locally advanced PCa could be controlled over the long-term and, possibly, cured in some cases by primary androgen deprivation therapy (PADT) [2]. However, the following were identified as an inappropriate use of hormonal therapy: (1) short-term ADT, (2) intermittent ADT, (3) incomplete ADT (castration monotherapy, antiandrogen monotherapy) [3]. By the inappropriate use of ADT, cancer cells which could be controlled over long-term might progress to cancer cells with a more malignant potential. Furthermore, a concern is that clinical trials using incomplete ADT would deny the usefulness of PADT.

In this review we will describe appropriate applications for PADT in localized and locally advanced PCa on the basis of our data.

Role of androgen receptor in the proliferation of PCa cells

The androgen receptor (AR) is a member of a steroid hormone receptor superfamily. It is a nuclear receptor performing transcriptional regulation of target genes (e.g. prostate-specific antigen (PSA)). It is thought that a GC box, a GGGA repetitive promoter sequence, and a CpG domain surrounding the transcription initiation site are important in basic transcription and for the transcriptional regulation of AR mRNA [4]. AR mRNA is composed of eight exons with a 1.1 kilo-base (kb) long 5'-untranslated regions (5'-UTR), and it is this area that is essential for translation of the AR protein (Fig. 1) [5]. The AR protein consists of about 918 amino acids and the N-terminal exon A (AF-1) is the important region for AR activity. In addition, there is a glutamine repetitive sequence (CAG repeat) and a glycine repetitive sequence (GCC repeat) in this domain, and their lengths differ between individuals. AR activity decreases with increasing length of the CAG repeat [6]. It is reported that the number of CAG repeats in AR is shorter in those of Oriental origin compared to African Americans [7]. There are racial differences in the response to hormonal therapy, and this may reflect a difference in the number of CAG repeats. In addition, in cases where hormonal therapy and radiotherapy are combined, it has been reported that men with a low number of CAG repeats had good local control by hormonal therapy [8]. However, there are negative reports for the relationship between the number of CAG repeats and the reactivity of carcinogenesis and hormonal therapy [9,10].

Exons B and C code for a DNA binding domain with a two Zn finger motif. The exon B motif, in particular, is thought to be important for the specific binding of DNA. Two Zn fingers bind to a specific sequence, the androgen response element (ARE), on the promoter of the target genes, thus inducing the expression of those target genes. Exon D is the hinge domain and includes an important sequence that is necessary for translocation to the nucleus from the cytoplasm. Furthermore, the area from exon D to exon H is a ligand-binding domain, where the specific ligand binds, thus causing receptor activation (AF-2). AR exists in the cytoplasm with heat shock proteins and in the absence of androgens it is not active. However, when androgen binds to the AR, the receptor translocates to the nucleus, and the coactivators bind at the AF-1 and AF-2 domains, the AR then binds to target genes and promotes transcription.

Role of combined androgen blockade therapy in the treatment of PCa

Although the detailed relationship between the AR and androgen in PCa cells was not known, ADT has been playing an important role in the treatment of PCa since it was first reported more than 60 years ago by Huggins & Hodges [1]. At present, ADT is still used as the primary treatment for advanced PCa. Combined androgen blockade (CAB), which is ADT using a luteinizing hormone-receptor hormone (LH-RH) analog and anti-androgen agents, now replaces surgical castration and estrogen agents.

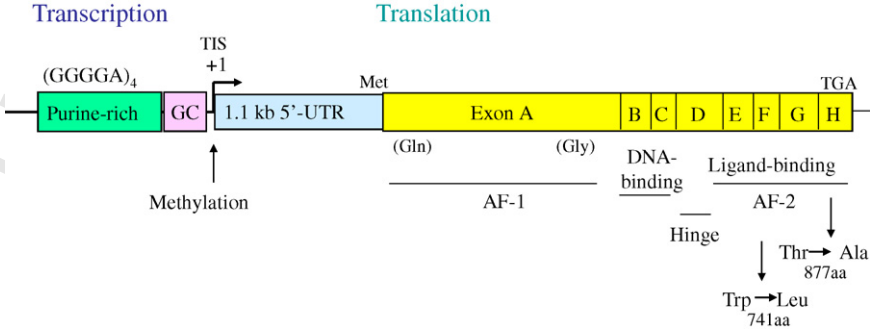

Figure 1 Androgen receptor messenger RNA structure.

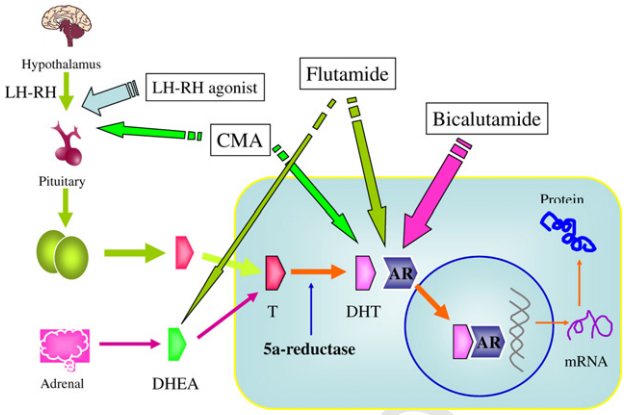

Figure 2 The mechanism of action for combined androgen blockade. CMA, chlormadinone acetate; LH, luteinizing hormone; RH, receptor hormone; T, testosterone; DHT, dihydrotestosterone; DHEA, dehydroepiandrosterone; AR, androgen receptor.

In PCa cells, the testosterone produced in the testis is converted into dihydrotestosterone (DHT). DHT combines with the AR in the nucleus of the PCa cell and activates androgen responsive genes, which play a main role in the proliferation of PCa cells (Fig. 2). Androgen deprivation using an LH-RH analog or by surgical castration induces apoptosis of the PCa cells, resulting in a clinically observed treatment effect for PCa.

However, dehydroepiandrosterone (DHEA) and androstenedione, which are secreted by the adrenal gland, are also converted into testosterone and DHT. It is reported that approximately 40% of the androgen in prostate tissue is derived from the adrenal gland [11]. Moreover, we have demonstrated that approximately 25% of the testosterone present in PCa tissue remained after castration [12]. These results suggest that ADT for PCa requires not only surgical or medical castration using LH-RH analog but also the use of anti-androgen agents [13]. Anti-androgen agents have various mechanisms for blocking the activities of androgen (Fig. 2). There is a possibility that the different clinical outcomes seen after CAB treatment could be due to the different kinds of anti-androgen agents used.

Histopathological changes of PCa after ADT

The histopathological changes induced by ADT have been reported [14–17]. Those studies demonstrated the occurrence of pathological changes in PCa tissues subsequent to ADT, and especially emphasized that the cancer tissues showed higher grade changes than normal tissues. However, there are few reports in which the effects of ADT have been evaluated by correlations between the histological changes and the risk of clinical progression. In Japan, pathological changes after ADT were determined in accordance with the Japanese *General Rule for Clinical and Pathological Studies on Prostate Cancer* [18]. The assessment of the effect of ADT was based on the presence of nuclear pyknosis, nuclear karyolysis, and cytoplasmic vacuolization, and the pathological grade of the effects was judged using these features. Pathological effect grade 3 was assigned to cases where almost all cancer cells had these features, and grade 0 to cases with none of these features. We retrospectively investigated the clinical and pathological effects of ADT on specimens from patients treated with radical prostatectomy after neoadjuvant ADT using the Japanese General Rule as the criterion [19]. The patients with pathological effect grade 2 and 3 after neoadjuvant ADT, i.e. histologically cured or nearly cured patients, accounted for more than 40% of the total number. In addition, the recurrence-free survival rate of those patients with complete apoptosis (pathological effect grade 3) was 100%. These results support the idea that some cases of localized PCa could be cured by PADT alone. Schulman et al. also performed neoadjuvant hormonal treatment for 3 months before radical prostatectomy in patients with localized PCa, and reported good histological effects [20]. Labrie et al also demonstrated that about 80% of Stage B PCa

could be controlled over the long-term, or cured, using PADT [2].

Efficacy of PADT for localized or locally advanced PCa

PADT is not recommended at all as the primary treatment for localized PCa according to representative guidelines such as the National Cancer Institute Physician data Query (NCI-PDQ) database. In Japan, however, according to the cancer registration statistics from the Japanese Urological Association in 2000, many patients with localized PCa have actually been treated using PADT (Fig. 3) [21]. Despite explanations by urologists of the various treatments for localized PCa, many patients tend to select PADT [22]. Why do so many patients with localized PCa select PADT? The reasons are probably that medical treatment, such as PADT, is more acceptable in comparison to more invasive treatments, such as surgery, for many Japanese patients, and urologists themselves are happy to comply with the patient's wishes because they have experience of the effectiveness of PADT. Sensitivity to hormonal therapy is possibly higher in Japanese patients. Fukagai et al. compared the effectiveness of hormonal therapy for PCa patients in both Caucasian and Japanese-American men and reported that the latter had a better outcome than the former with regard to both overall and cause-specific survival rates [7]. Recently Akaza et al. demonstrated that overall survival of patients with localized or locally advanced PCa treated with PADT was equal to normal life expectancy at that same age [23]. Before Akaza et al's report, Egawa et al. had already reported that PADT was as effective as radical prostatectomy with regard to disease-specific survival rate in localized PCa [24]. In their report, disease-specific survival rate at 10 years for 56 patients with well-differentiated PCa treated with PADT was 100 % (Fig. 4). These results show that PADT may be promising for the treatment of localized PCa in Asian people. But, this does not necessarily mean that PADT is not promising for Caucasians.

Which patients are candidates for PADT ?

We performed a retrospective review of the efficacy of PADT in 628 patients with localized or locally advanced PCa treated with PADT at seven institutions in Japan, and attempted to predict in which patients the disease could be controlled for long periods using PADT [25]. Disease-specific and overall survival rate at 8 years in all patients was 89.1% and 75%, respectively. In addition, disease-specific survival rate

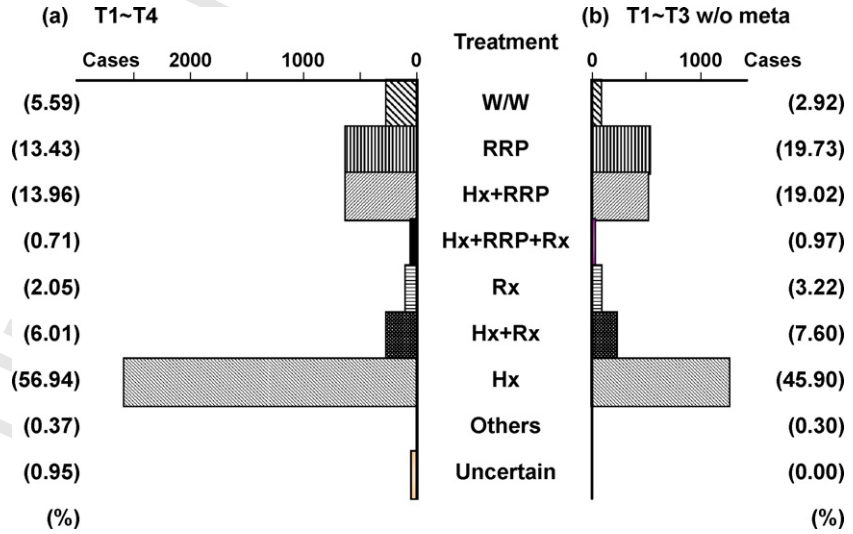

Figure 3 Numbers of new prostate cancer patients registered in Japan in 2000 (from the Japanese Urological Association). W/W, watchful waiting; RRP, radical retropubic prostatectomy; Rx: radiotherapy; Hx, hormonal therapy. (Modified from [21]).

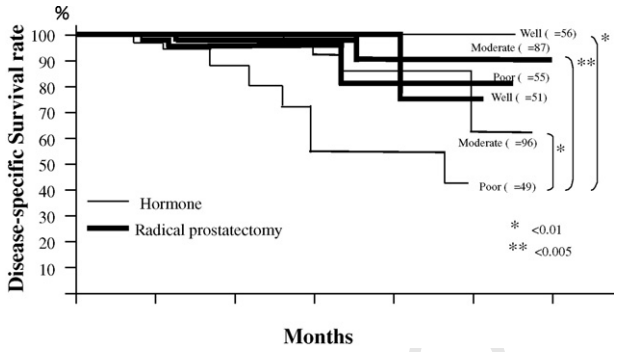

Figure 4 Disease-specific survival rates in those treated with primary androgen deprivation therapy (Hormone) or radical prostatectomy**.** Well, Moderate, Poor, well-, moderately-, poorly-differentiated adenocarcinoma. (Modified from [24]).

at 8 years for patients given CAB treatment was 95.3%, which was significantly higher than that for patients treated using castration monotherapy. Among the patients given CAB treatment, disease-specific and progression-free survival rates at 8 years for those administered non-steroidal anti-androgen drugs were 95.4% and 85.6%, respectively, which were significantly higher than of the rates for patients treated with steroidal anti-androgen drugs.

We classified the patients into three risk groups based on pretreatment PSA level and Gleason score using a modification of the D'Amico risk grouping [26]. The disease-specific survival rates at 8 years for the low-, intermediate-, and high-risk groups were 97.6%, 95.4%, and 78.3 %, respectively (Fig. 5). Next, we divided the low- and intermediate-risk patients into two groups based on the time to nadir PSA level after hormonal therapy. For convenience, we defined the nadir PSA level as <0.2 ng/ml. The time to nadir was within 6 months in 192 patients (good response group, Group G). These patients accounted for 30.6% of the total number of patients. We classified the 139 patients in whom the PSA level did not fall below 0.2 ng/ml within 6 months as the poor response group (Group P) (Fig. 6). The disease-specific survival rates at 8 years for Group G and Group P were 98.9% and 94.0%, respectively. Notably, there were no cancer-related deaths during the observation period among the 133 patients in Group G receiving CAB treatment (Fig. 7).

Although a randomized controlled trial may be necessary to investigate the utility of hormonal therapy in patients for whom such treatment is considered more effective, based on the results of our study, T1c–T3 patients with a PSA level ≤20 ng/ml and a Gleason score of ≤7 may be good candidates for hormonal therapy. These patients accounted for 52.7% of the total number of T1c–T3 patients in our study. It may be possible to choose hormonal therapy as the initial treatment for such patients, but changing to another curative regimen or to combination therapy with radiotherapy or radical prostatectomy should be considered if the

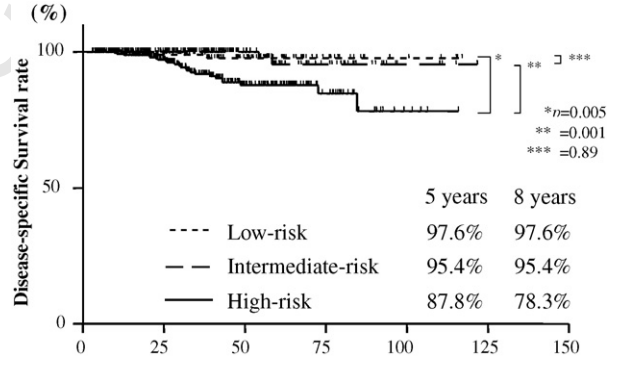

Figure 5 Disease-specific survival rates for low-, intermediate-, and high-risk groups treated with primary androgen deprivation therapy**.** (Reproduced, with permission from [25]).

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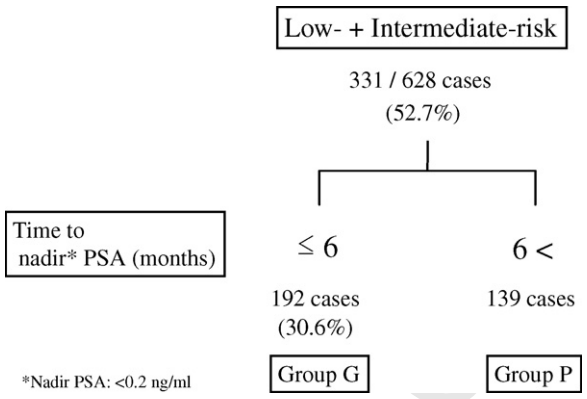

Figure 6 Classification algorithm for the good response group (Group G) and the poor response group (Group P) from the low- and intermediate-risk groups according to time to nadir PSA level. (Reproduced, with permission from [25]).

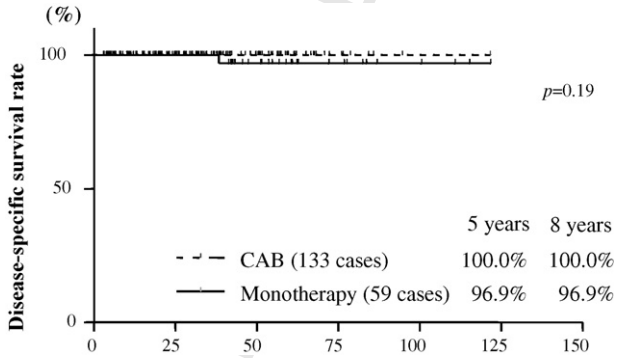

Figure 7 Disease-specific survival rate of Group G (good response) patients receiving CAB (combined androgen blockade) treatment or castration monotherapy. (Reproduced, with permission from [25]).

PSA value does not decrease to <0.2 ng/ml after 6 months of hormonal therapy. However, in patients in whom the PSA value drops to <0.2 ng/ml within 6 months of the commencement of hormonal therapy, continuation of the same regimen may be reasonable with careful observation (Fig. 8).

Another preference for early stage PCa patients involves watchful waiting. So, we feel that further investigations are necessary to compare the disease-specific or progression-free survival rates of a low risk group, such as Group G, with those of watchful waiting. Johansson et al. investigated the long-term

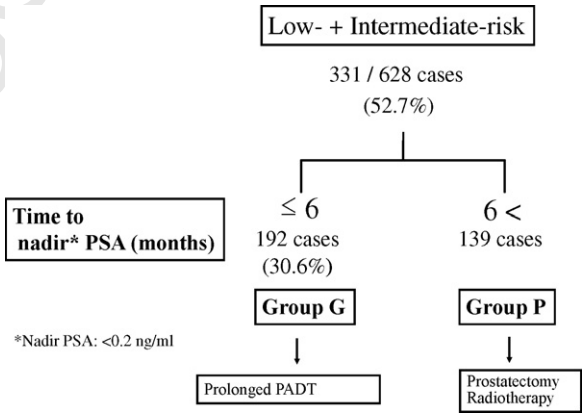

Figure 8 Treatment algorithm for patients with low- and intermediate-risk localized prostate cancer.

natural history of early stage PCa patients and reported an accumulated progression-free survival rate of 45% and a non-metastasis survival rate of 76.9% over a 15-year follow-up. In addition, cancer progressed and metastatic cancer developed when the observation period was increased to more than 15 years [27]. Thus, even cancer cells for which observation alone without treatment was at first thought to be sufficient are not always inactive after long periods. These cancer cells may become impossible to control due to malignant transformation by gene mutation during the follow-up period [28]. In addition, most patients are anxious about the status of their disease, and few are willing to rely solely on watchful waiting [29].

How long should PADT be continued ?

Another possible problem is the period over which hormonal therapy should be carried out. Labrie and colleagues performed long-term hormonal therapy in stage B and C patients, and discontinued the treatment in patients who did not show a recurrence of a rise in PSA levels. Among 33 patients with stage B and C PCa who stopped treatment after continuous CAB for more than 6.5 years, an increase in PSA level occurred in only two patients. In addition, seven out of eight patients with localized PCa who received CAB treatment continuously for 6.5–9.0 years before stopping treatment showed no PSA failure for at least 5 years after cessation of CAB. CAB treatment was restarted in patients showing a recurrence in PSA levels rising after cancellation of the initial hormonal treatment, and control was achieved again in most patients. Thus, they concluded that CAB treatment for 7 years may be suitable. Recently, Tanaka et al. also investigated when hormonal therapy could be discontinued based on nadir PSA levels after treatment. They concluded that a relatively shorter period, e.g. 3 years, might be enough in cases in which the nadir PSA dropped to <0.01 ng/ml [30]. Although the usefulness of intermittent hormonal therapy, in order to maintain sensitivity to androgen, has been reported for the treatment of advanced PCa [31], the application of this treatment to localized PCa should be done with care. This is because cancer cells that could be controlled over the long-term, or possibly cured, by appropriate hormonal therapy may progress to cancer cells with a greater malignant potential by incomplete androgen ablation.

Issues of quality of life and medical cost

Long-term hormonal therapy is sometimes criticized for reducing patients' quality of life (QOL). In our institution, the QOL of PCa patients treated with PADT was investigated using the Androgen Deficiency in the Aging Male (ADAM) questionnaire to allow comparison with healthy aged men who visited the institution to receive a medical examination. The healthy group consisted of 150 subjects with a mean age of 66.4 years. The PCa group included 49 subjects with a mean age of 73.7 years who had been receiving PADT for an average of 3.5 years. Surprisingly, the QOL of men receiving PADT was rather better than that of the healthy controls, except for sexual function in men aged 50–59 years (Table 1) [32]. In fact most PCa patients reported no anxiety regarding their primary disease or side effects of the treatment. Kato et al. evaluated health-related QOL (HRQOL) in Japanese men receiving ADT for PCa using the Short Form-36 (SF-36) and UCLA Prostate Cancer Index (UCLA-PCI) questionnaires [33]. They concluded that general HRQOL was mostly unaffected by ADT and that most patients did not report sexual problems in spite of a deterioration in sexual function. Although Koffage et al. also reported that side effects such as erectile dysfunction are caused by PADT, the impact of this on the health status of PCa patients may be not serious [34]. These reports suggest that QOL of PCa receiving hormonal therapy is rather better than previously thought.

Although osteoporosis and pathological fracture have been reported as side-effects of hormonal therapy, Smith et al. reported that the bone salt density of patients undergoing hormonal therapy was increased compared to pretreatment levels by the regular injection of zoledronate [35]. A recent study has suggested that the metabolic syndrome was present in more than 50% of the men undergoing long-term ADT [36]. Research is needed to delineate this association.

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Table 1 Comparison of physical, mental and sexual subgroup scores from the ADAM questionnaire for PCa patients receiving hormonal therapy and healthy men

	Physical (0–5)		Mental (0–3)		Sexual (0–2)	
	HTx	Healthy	HTx	Healthy	HTx	Healthy
50 years	0	2.3	0	0.8	2	1.3
60 years	2.3	2.8	1.0	1.0	1.2	1.7
70 years	2.1*	3.1	0.6*	1.4	1.0*	1.6
80 years	3.1	3.3	1.0	1.6	0.6*	1.8

PCa, prostate cancer; HTx, hormone therapy.
* $p < 0.05$.

Cost can also be a significant issue. The medical cost of hormonal therapy is higher than that of other treatments, but there are some costs that can be calculated directly, such as medical fees or transportation for hospital visits, and costs that cannot be calculated so easily, such as loss of employment for disease treatment or psychological burden. Therefore, an estimation of the costs involved is very difficult, and further studies are required to compare these costs with those for other types of treatment.

Role of hormonal therapy for high-risk localized PCa

According to the modified D'Amico classification mentioned above [26], disease-specific and progression-free survival rates for the high-risk group treated with PADT at 5 years were 87.8% and 58.8 %, respectively. From these results, long-term control by PADT seems to be difficult in the high-risk group. However, Mizokami et al. re-analyzed the previous data and showed that the result from the high-risk group was not necessarily pessimistic in those cases whose PSA nadir was <0.2 ng/ml [32]. They proposed that PCa patients with high-risk should first be treated with neoadjuvant CAB. Then, once a PSA nadir of <0.2 ng/ml had been reached, patients with favorable parameters (Gleason score ≤6, pretreatment PSA value ≤20 ng/ml, time to nadir ≤6 months) are likely to have a lower possibility (<25%) of relapse, even 10 years after commencement of CAB. Therefore, such patients could select any treatment option, e.g. surgery, radiotherapy, or PADT, as they preferred. In contrast, Mizokami et al. recommend that poor responders to neoadjuvant CAB should be treated with more intensive therapy using CAB combined with high dose rate (HDR)-brachytherapy, intensity-moderated radiotherapy, external beam radiation therapy (EBRT) or some form of chemotherapy.

Conclusion

We have discussed which patients are suitable candidates for PADT, and shown that more than 30% of low- or intermediate-risk localized PCa could be controlled over the long-term with PADT. Short-term or intermittent PADT is not recommended for the treatment of localized or locally advanced PCa, because cancer cells which could be controlled over the long-term, or possibly cured, by appropriate PADT may progress to cancer cells with a greater malignant potential as a result of incomplete androgen ablation. We have proposed algorithms for the treatment of localized PCa, not only in low- and intermediate-risk groups, but also for high-risk groups.

Although, according to several reports, the side effects of PADT do not have a serious effect on the health status of PCa patients, any decline in physical and mental condition, such as osteoporosis, anemia, and so on, that is caused by ADT should be overcome by adequate treatments.

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