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Abstract

In spite of clinical practice guidelines such as NCI-PDQ in which primary androgen deprivation therapy (PADT) is not recommended as the primary treatment for localized prostate cancer, many patients have been treated with PADT. One of the reasons is that urologists themselves permit patients' desire because they knew the effectiveness of PADT for some patients in their experiences.

In this review we demonstrated basic mechanisms and clinical efficacy of primary combined androgen blockade (PCAB) for localized or locally advanced prostate cancer. Then, we discussed what patients are candidates for PCAB, and showed that more than 30 % of low- or intermediate-risk localized prostate cancer could be controlled for long-term with only PCAB. Short-term or intermittent PADT could not be recommended because of the possibilities of the character change of cancer cells by incomplete androgen ablation. We proposed algorithms for the treatment of localized prostate cancer not only in low- and intermediate-risk group, but also in high-risk group.

Key words: localized and locally advanced prostate cancer, primary androgen deprivation, primary cambined androgen blockade, D' Amico risk grouping

Introduction

When Huggins and Hodges first reported the hormonal therapy for prostate cancer [1], it was mainly used for advanced disease. Therefore, most prostate cancer relapsed at a later time. Since then, a kind of misunderstanding that usefulness of the hormonal therapy is temporary became common knowledge among urologists like a magic formula. However, this thinking should be changed in cases of localized prostate cancer. Labrie et al. showed that localized or locally advanced prostate cancer could be controlled for long-term and possibly cured in some cases by primary androgen deprivation therapy (PADT) [2]. Labrie pointed out inappropriate use of hormonal therapy as followings: ① short-term ADT, ② intermittent ADT, ③ incomplete ADT (castration monotherapy, antiandrogen monotherapy) [3]. By the inappropriate ADT cancer cells which could be controlled for long-term may progress to cancer cells with more malignant potential. Furthermore, it is worried that clinical trials using incomplete ADT would deny the usefulness of PADT.

We would like to describe about appropriate implications of primary combined androgen blockade in localized and locally advanced prostate cancer in basis of our data.

Expression and activation of androgen receptor (AR) in prostate cancer cells

AR is a member of a steroid hormone receptor superfamily, and it is a nuclear receptor performing transcriptional regulation of target genes (for example, PSA). It is thought that GC box, a GGGA repetitive sequence of promoter, and CpG domain of transcriptional initiation site surroundings are important in basis transcription and for the transcriptional regulation of AR mRNA [4]. AR mRNA is composed of eight exons with 1.1 kb long 5'-untranslated regions (5'-UTR), and it is the area that is essential to translation of AR protein (Fig. 1) [5]. AR protein consists of about 918 amino acids: N-terminal exon A is the important region in activity of AR (AF-1). In

addition, a glutamine repetitive sequence (CAG repeat) and a glycine repetitive sequence (GCC repeat) exist in this domain, and a difference exists in the length with an each one person. Activity of AR decreases so that length of CAG repeat becomes long [6]. It is reported that the number of CAG repeat of AR is shorter in race of Orient origin than in an African-American [7]. There are racial differences in a reactive difference for hormonal therapy, and a difference of CAG repeat may be reflected. In addition, in combination of hormonal therapy and radiotherapy, it is reported that few men of the number of CAG repeat had local control by hormonal therapy [8]. However, there are negative reports for relations with the number of CAG repeat and reactivity of carcinogenesis and hormonal therapy [9, 10].

Exon B, C code DNA binding domain having two Zn finger motif. Motif of exon B is thought in particular to be important in a specific binding of DNA. Two Zn finger binds to specific sequence, androgen response element (ARE), for AR existing in promoter of target gene mainly and induce expression of target gene. Exon D is hinge domain and includes necessary important sequence when it translocates to nucleus from cytoplasm. Furthermore, area from exon D to H is a ligand-binding domain, and ligand specifically binds to it, and androgen dependence induces receptor activation (AF-2). AR exists in cytoplasm with heat shock protein under an androgen absence and does not have activity. However, when the androgen binds to AR, AR translocates to nucleus, and coactivators bind in AF-1 and AF-2 domains, AR interacts more and binds to target gene and promotes transcription.

Combined androgen blockade therapy in prostate cancer

Although the detailed relations between AR and androgen in prostate cancer cells were not known, androgen deprivation therapy (ADT) has been playing as important role in the treatment of prostate cancer since it was first reported more than 60 years ago by Huggins and Hodges [1]. At present, ADT is still used as the primary

treatment for advanced prostate cancer. Combined androgen blockade (CAB), that is ADT with LH-RH analogue and anti-androgen agents, now replaces surgical castration and estrogen agents.

In prostate cancer cells dihydrotestosterone (DHT) is converted from testosterone produced from the testis. DHT combining AR in the nucleus of prostate cancer cell activates androgen responsive genes, and finally plays main role for proliferation of prostate cancer cells (Fig. 2). Androgen deprivation by LH-RH analogue or surgical castration induces apoptosis of prostate cancer cells, and the treatment effect for prostate cancer is put out clinically.

On the other hand, testosterone and DHT are also converted from dehydroepiandrosterone (DHEA) and androstenedione secreted from the adrenal gland, and it is reported that approximately 40% of androgen in prostate tissue is derived from the adrenal gland [11]. Moreover, we demonstrated that approximately 25% of testosterone in prostate cancer tissue remained after castration [12]. These result suggested that ADT for prostate cancer requires not only surgical or medical castration using LH-RH analogue but also 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 of CAB treatment are shown by various kinds of anti-androgen agents.

Histopathological changes of prostate cancer by ADT

Histopathological changes induced by ADT have been reported [14-17]. These studies demonstrated the occurrence of pathological changes in prostate cancer 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 are evaluated by correlations between these 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 of prostate cancer [18]. Assessment of effect of ADT was based on the presence of nuclear pyknosis, nuclear karyolysis and cytoplasmic vacuolisation, and grading of the pathological was judged by these features. Pathological effect grade 3 was assigned to cases with almost all cancer cells having 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, that is histologically cured or nearly cured patients, accounted for more than 40 % of the total number. In addition, the recurrence-free survival rate of the patients with complete apoptosis (pathological effect grade 3) was 100 %. These results support that some cases of localized prostate cancer could be cured by PADT alone. Schulman et al. also performed neoadjuvant hormonal treatment for 3 months before radical prostatectomy in patients with localized prostate cancer, and reported good histological effects [20]. Labrie also demonstrated that about 80 % of Stage B prostate cancer could be controlled for long-term or cured with PADT [2].

Efficacy of PADT for localized or locally advanced prostate cancer

PADT is not recommended at all as the primary treatment for localized prostate cancer according to representative guidelines such as NCI-PDQ. In Japan, however, many patients with localize prostate cancer have been actually treated with PADT according to the cancer registration statistics of 2000 by Japanese Urological Association (Fig. 3)[21]. Despite urologist's explanation as to treatments for localized prostate cancer, many patients tend to select PADT [22]. Why do so many patients with localized prostate cancer select PADT? The reasons are probably that medical treatment like PADT is more acceptable compared with more invasive treatments such

as surgery for many Japanese patients, and that urologists themselves also permit patients' desire because they knew the effectiveness of PADT in their experiences. Sensitivity to hormonal therapy is possibly higher in Japanese patients. Fukagai et al. compared the effectiveness of hormonal therapy for patients with prostate cancer between 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 prostate cancer treated with PADT was equal to life expectancy of the same age [23]. Before Akaza'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 prostate cancer [24]. In their report disease-specific survival rate at 10 years of 56 patients with well-differentiated prostate cancer treated with PADT was 100 % (Fig. 4).

What patients are candidates of PADT ?

We performed a retrospective review of the efficacy of PADT in 628 patients with localized or locally advanced prostate cancer treated with PADT at 7 institutions in Japan, and attempted to predict patients in whom the disease could be controlled for long periods by PADT [25]. Disease-specific and overall survival rate at 8 years in all patients were 89.1 % and 75.0 %, respectively. In addition, disease-specific survival rate at 8 years of patients given CAB treatment was 95.3 %, which was significantly higher than that of patients treated with castration monotherapy. Among the patients given CAB treatment, disease-specific and progression-free survival rates at 8 years of those administered non-steroidal anti-androgen drugs were 95.4 % and 85.6 %, respectively, which were significantly higher than those of patients treated with steroidal anti-androgen drugs.

We classified the patients into three risk groups based on pretreatment PSA level

and Gleason score according to a modification of the D'Amico risk grouping [26]. Disease-specific survival rates at 8 years of low-, intermediate-, and high-risk groups were 97.6 %, 95.4 %, and 78.3 %, respectively (Fig. 5). Next, we divided low- and intermediate-risk patients into two groups based on the time to nadir PSA level after hormonal therapy. We defined <0.2 ng/mL as the nadir PSA level in this study for convenience. The time to nadir was within 6 months in 192 patients (good response group, Group G). These patients accounted for 30.6 % of the whole 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 of 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 in this study (Fig. 7).

Although a randomized controlled trial may be necessary for utilization of hormonal therapy in patients for whom such treatment is considered more effective, based on the results of our study T1c-T3 patients with PSA level≦20 ng/mL and Gleason score≦7 may be good candidates for hormonal therapy. These patients accounted for 52.7 % of the total number of the 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 combination therapy with radiotherapy or radical prostatectomy should be considered, if the PSA values does not decrease to <0.2ng/mL after 6 months of hormonal therapy. On the other hand, in patients in whom the PSA value drops to <0.2ng/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 prostate cancer 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 natural

history of early stage prostate cancer patients and reported an accumulated progression-free survival rate of 45 % and non-metastasis survival rate of 76.9 % with 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 follow-up (Fig. 9) [28]. In addition, most patients are anxious about the status of their disease, and few are willing to rely solely on watchful waiting (Fig. 10) [29].

How long should PADT be continued ?

Another possible problem is the period over which hormonal therapy should be continued. Labrie et al. performed long-term hormonal therapy in stage B and C patients and discontinued the treatment in patients who did not show PSA recurrence. Among 33 patients with stage B and C prostate cancer who stopped treatment after continuous CAB for more than 6.5 years, an increase in PSA occurred in only two patients. In addition, seven of eight patients with localized prostate cancer who received CAB treatment continuously 6.5-9.0 years before stopping treatment showed no PSA failure at least 5 years after cessation of CAB. CAB treatment was restarted in patients in patients showing PSA recurrence 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 the treatment. They concluded that relatively shorter period, e.g. 3 years, may be enough in cases which nadir PSA dropped to <0.01 ng/mL [30]. Although usefulness of intermittent hormonal therapy was reported for the treatment of advanced prostate cancer to maintain sensitivity to androgen [31], application of this treatment to localized

prostate cancer should be very careful. Because cancer cells which could be controlled for long-term or possibly cured by appropriate hormonal therapy may progress to cancer cells with more malignant potential by incomplete androgen ablation.

Issues of QOL and medical cost

Long-term hormonal therapy is sometimes criticized for reducing patients quality of life (QOL). In our institution the QOL of prostate cancer patients treated with PADT was investigated using the questionnaire of Androgen Deficiency in Aging Male (ADAM) 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 prostate cancer 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 the healthy control, except for sexual function in men aged 50-59 years (Table 1) [32]. Actually, most prostate cancer 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 prostate cancer using SF-36 and USLA-PCI [33]. They concluded that general HRQOL was mostly unaffected by ADT and that most patients did not report sexual bother in spite of deterioration of sexual function. Although Koffage et al. also reported that side effects such as erectile dysfunction are caused by PADT, this impact on the healthy status of prostate cancer patients may be not serious [34]. These reports suggest that QOL of prostatic cancer patients 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 regular injection of zoledronate [35].

Medical cost can also be a significant issue. The medical cost of hormonal therapy is higher than those of other treatments, but there are costs that are calculated directly, such as medical costs or transportation for hospital visits, and costs that cannot be calculated, such as loss of employment for disease treatment or psychological burden. Therefore, estimation of cost is very difficult, and further studies are required for comparison of costs with those of other types of treatment.

Role of hormonal therapy for high-risk localized prostate cancer

According to the modified D'Amico classification previously shown [26] disease-specific and progression-free survival rates of 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 results of the high-risk group is not necessarily pessimistic in cases whose PSA nadir was < 0.2 ng/mL [32]. They proposed that prostate cancer patients with high-risk should be at first treated with neoadjuvant CAB. Then, once PSA nadir of < 0.2 has been reached, patients with favorable parameters (Gleason score ≦ 6, pretreatment PSA ≦ 20, time to nadir ≦ 6 months) are likely to have less possibility (< 25 %)of relapse at even 10 years after commencement of CAB. Therefore, such patients could select any treatment option, e.g. surgery, radiotherapy, or PADT, with their wills. In contrast, they recommend that poor responders to neoadjuvant CAB should be treated with more intensive therapy using CAB combined with HDR-brachytherapy, intensity-moderated radiotherapy, EBRT or some forms of chemotherapy.

Summary

In this review we demonstrated basic mechanisms and clinical efficacy of PADT for localized or locally advanced prostate cancer. Although clinical practice guidelines such as NCI-PDQ does not recommended PADT as the primary treatment for localized prostate cancer, PADT may be effective for some cases by appropriate treatment.

We discussed what patients are candidates of PADT, and showed that more than 30 % of low- or intermediate-risk localized prostate cancer could be controlled for long-term with PADT. Short-term or intermittent PADT may not be recommended in the treatment of localized or locally advanced prostate cancer, because cancer cells which could be controlled for long-term or possibly cured by appropriate PADT may progress to cancer cells with more malignant potential by incomplete androgen ablation. We proposed algorithms for the treatment of localized prostate cancer not only in low- and intermediate-risk group, but also in high-risk group.

Although side effects of PADT affecting the healthy status of prostate cancer patients may be not serious by several reports, detriments of physical and mental conditions such as osteoporosis, anemia, and so on caused by ADT should be overcome by adequate treatments.

Practice Points

✶PADT is useful for selected patients with localized and locally advanced prostate cancer by appropriate CAB.

✶CAB is more effective and suitable as PADT than anti-androgen monotherapy.

✶The time to nadir PSA level after CAB should be an important selective marker for the selection of candidate of PADT.

Research Agenda

✶Improvements of quality of life for the patients treated with ADT are needed.

✶Large-scale trials of PADT for localized prostate cancer are needed.

✶The developments of new drugs suppressing intracrinological androgen synthesis in the prostate cancer tissues are needed.

✶The molecular targeting therapy for androgen receptor interacting protein are needed.

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Figure and Table Legends

Fig. 1.

Structures of messenger RNA of angrogen receptor.

Fig. 2.

The mechanism of combined androgen blockade. CMA: chlormadinone acetate.

Fig. 3.

New prostate cancer patients of Japan registered in 2000 according to Japanese Urological Association.

w/w: watchful waiting, RRP: radical retropubic prostatectomy, Rx: radiotherapy, Hx: hormonal therapy.

(modified from reference 21)

Fig. 4.

Disease-specific survival rates treated with primary androgen deprivation therapy (Hormone) or radical prostatectomy.

Well, Moderate, Poor: well-, moderately-, poorly-differentiated adenocarcinoma

(modified from reference 24)

Fig. 5.

Disease-specific survival rates of low-, intermediate-, high-risk groups treated with primary androgen deprivation therapy.

(cited from reference 25)

Fig. 6.

Classification of good response group (Group G) and poor response group (Group P) among low-, intermediate-risk groups according to time to nadir PSA.

(cited from reference 25)

Fig. 7.

Disease-specific survival rate of Group G patients receiving CAB treatment or castration monotherapy.

(cited from reference 25)

Fig. 8.

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

Fig. 9.

A supposed process of progression of prostate cancer.

(modified from “Labrie F. Androgen Blockade in prostate cancer in 2002: major benefits on survival in localized disease. Mol Cell Endcri 2002; **198:** 77-87.”)

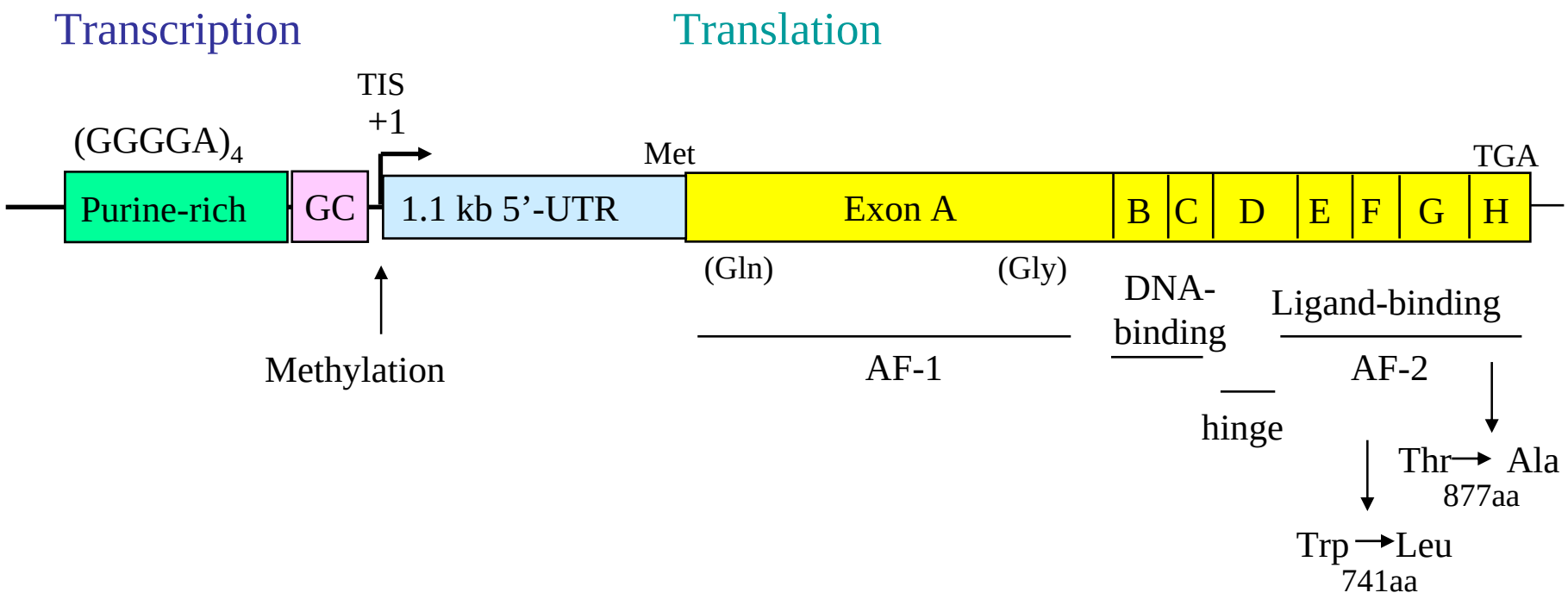
Fig. 10.

Continuation of watchful waiting in each risk group.

(cited from reference 29)

Table 1.

Comparison of physical, mental and sexual subgroup scores of ADAM questionnaire between prostate cancer patients receiving hormonal therapy and healthy men.


Transcription
Translation
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Met
TGA
Purine-rich
GC
1.1 kb 5'-UTR
Exon A
B
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E
F
G
H
(Gln)
(Gly)
DNA-
binding
Ligand-binding
Methylation
AF-1
AF-2
hinge
Thr→Ala
877aa
Trp→Leu
741aa

Figure 1

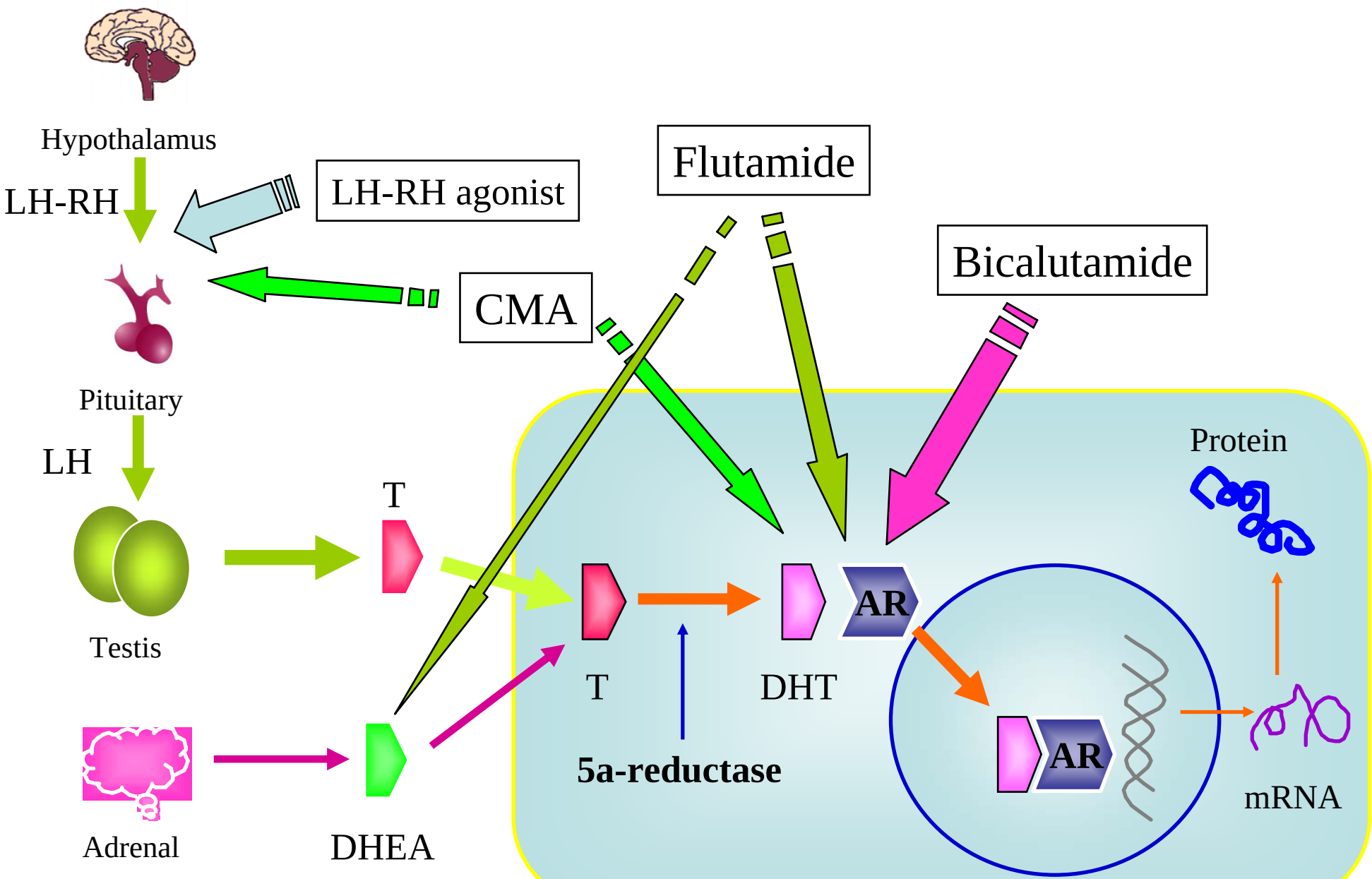
Hypothalamus
LH-RH
LH-RH agonist
Flutamide
Bicalutamide
CMA
Pituitary
LH
T
Testis
Protein
T
DHT
AR
5a-reductase
AR
mRNA
Adrenal
DHEA

Figure 2

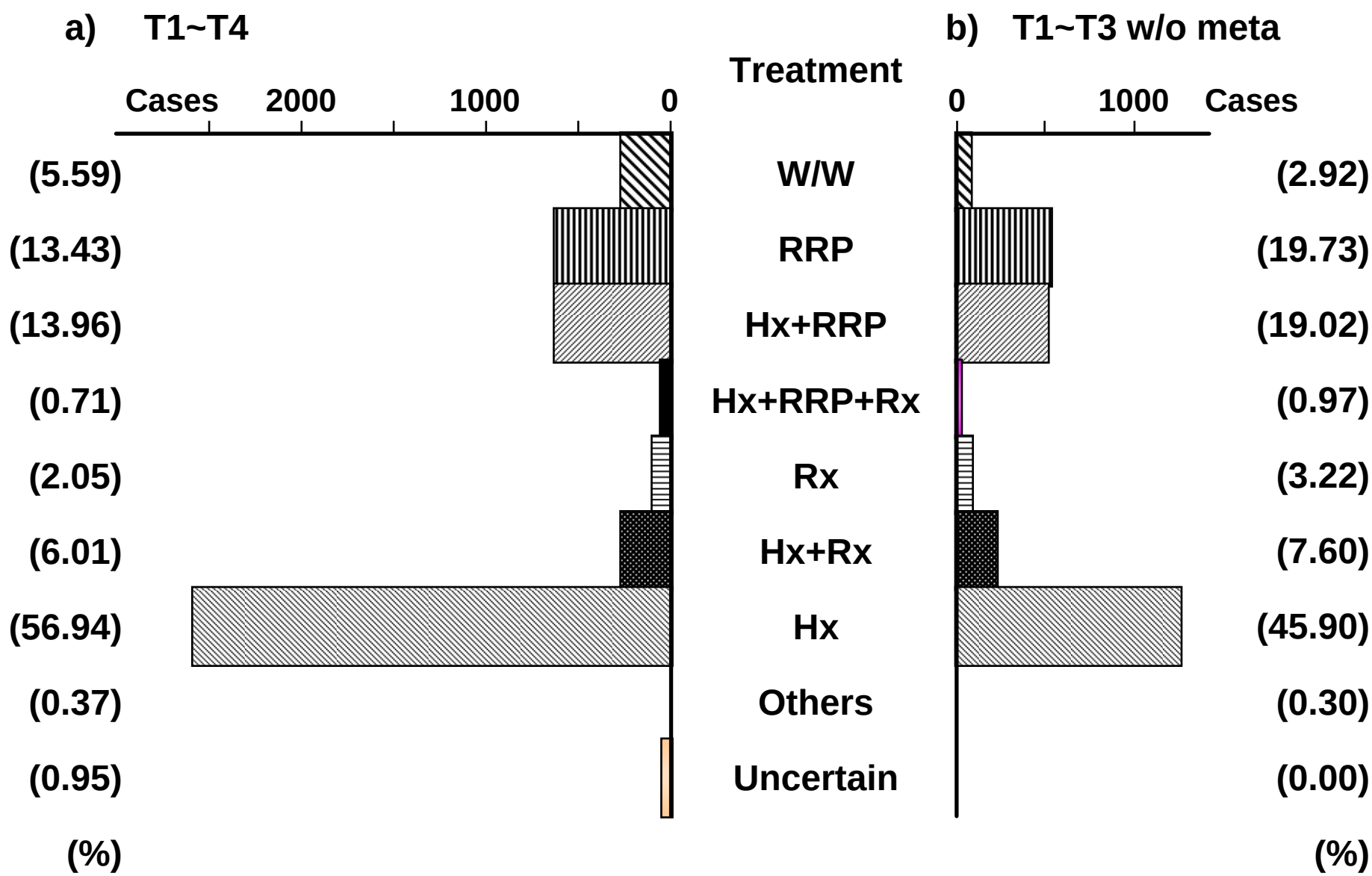
a) T1~T4
b) T1~T3 w/o meta
Treatment
Cases
2000
1000
0
0
1000
Cases
(5.59)
(13.43)
(13.96)
(0.71)
(2.05)
(6.01)
(56.94)
(0.37)
(0.95)
(%)
W/W
RRP
Hx+RRP
Hx+RRP+Rx
Rx
Hx+Rx
Hx
Others
Uncertain
(2.92)
(19.73)
(19.02)
(0.97)
(3.22)
(7.60)
(45.90)
(0.30)
(0.00)
(%)

Figure 3

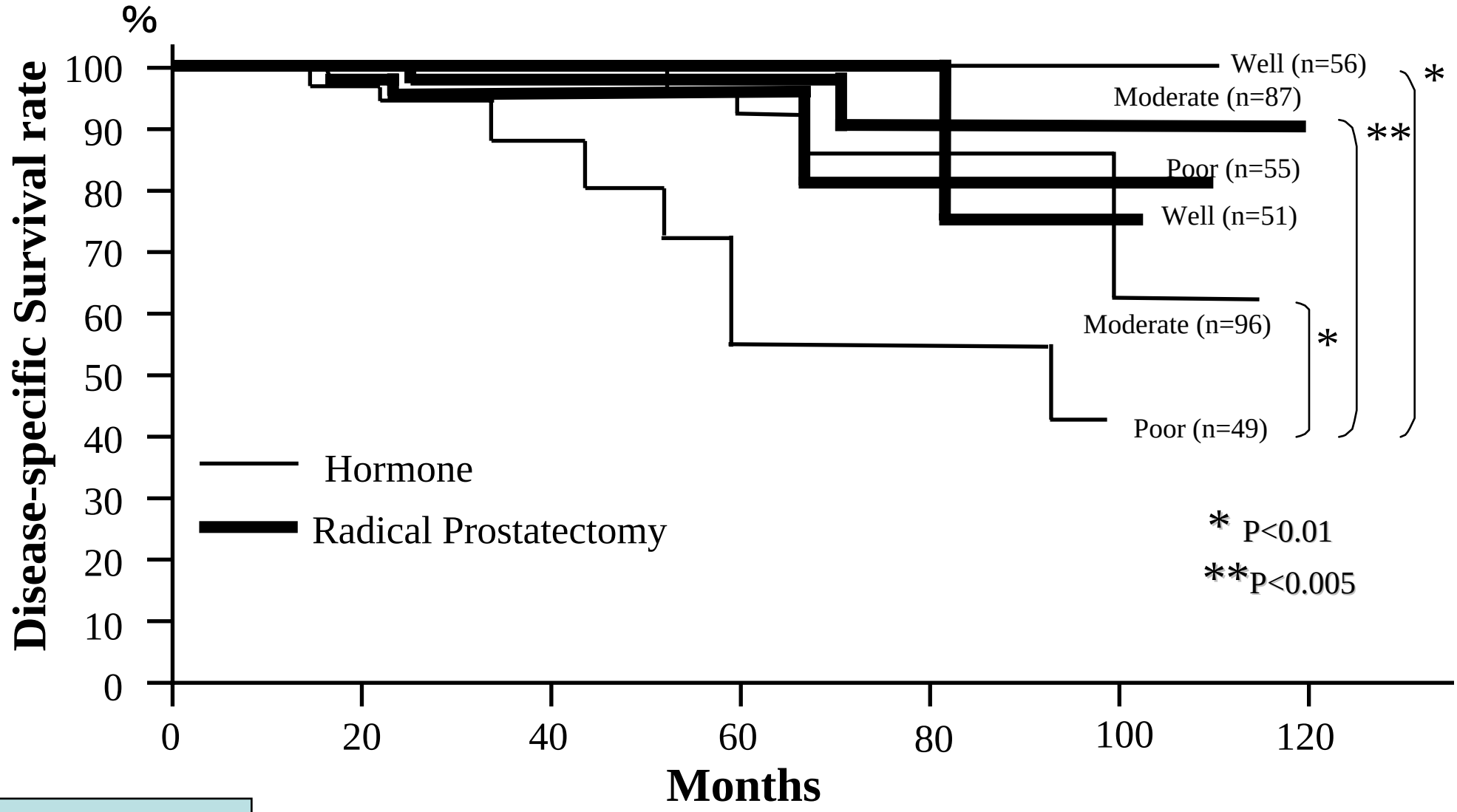
%
Disease-specific Survival rate
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
Months
Well (n=56)
Moderate (n=87)
Poor (n=55)
Well (n=51)
Moderate (n=96)
Poor (n=49)
*
**
*
Hormone
Radical Prostatectomy
* P<0.01
**P<0.005

Figure 4

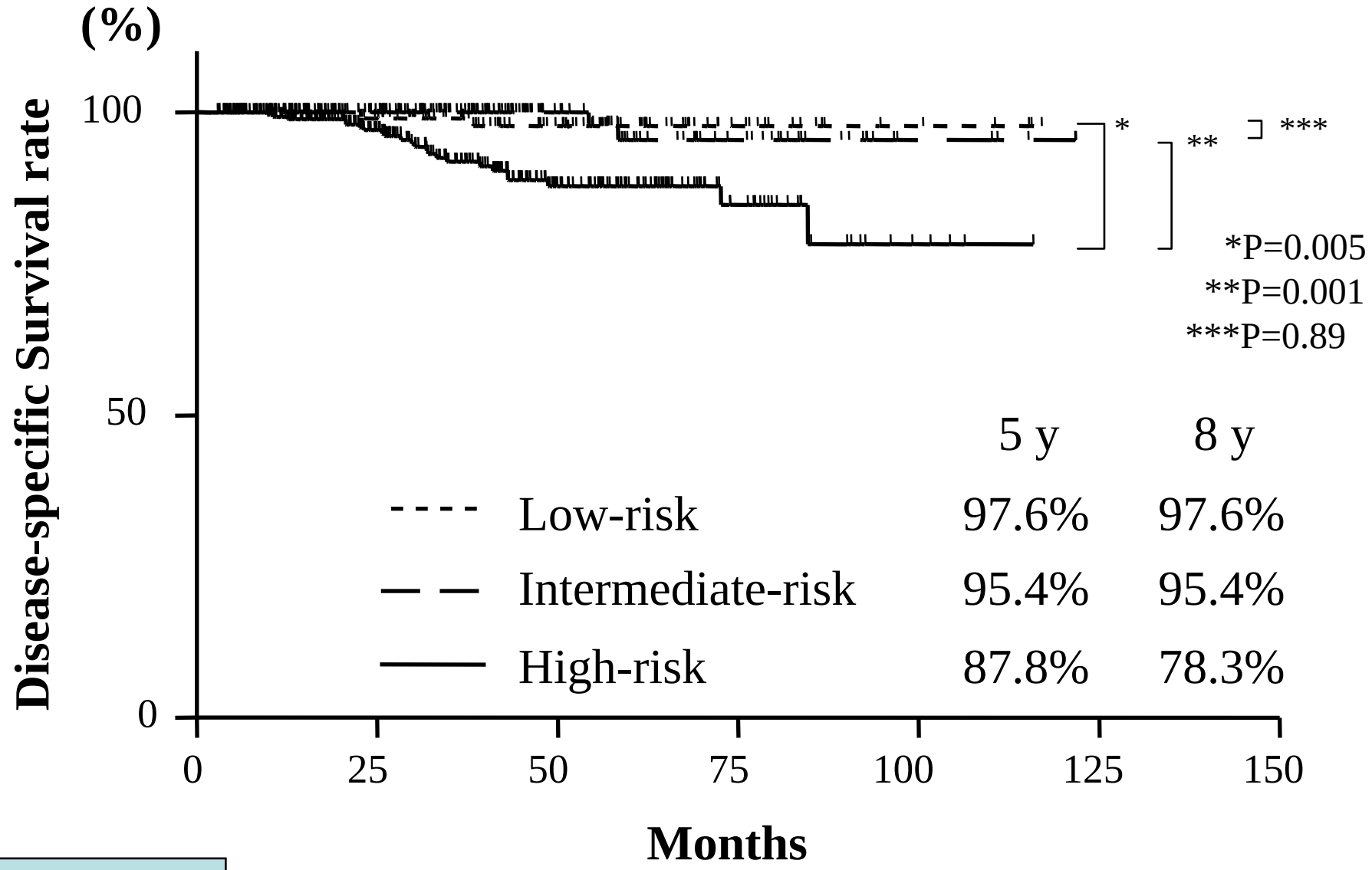
(%)
Disease-specific Survival rate
100
50
0
0
25
50
75
100
125
150
Months
*
**
***
*P=0.005
**P=0.001
***P=0.89
5 y
8 y
Low-risk
97.6%
97.6%
Intermediate-risk
95.4%
95.4%
High-risk
87.8%
78.3%

Figure 5

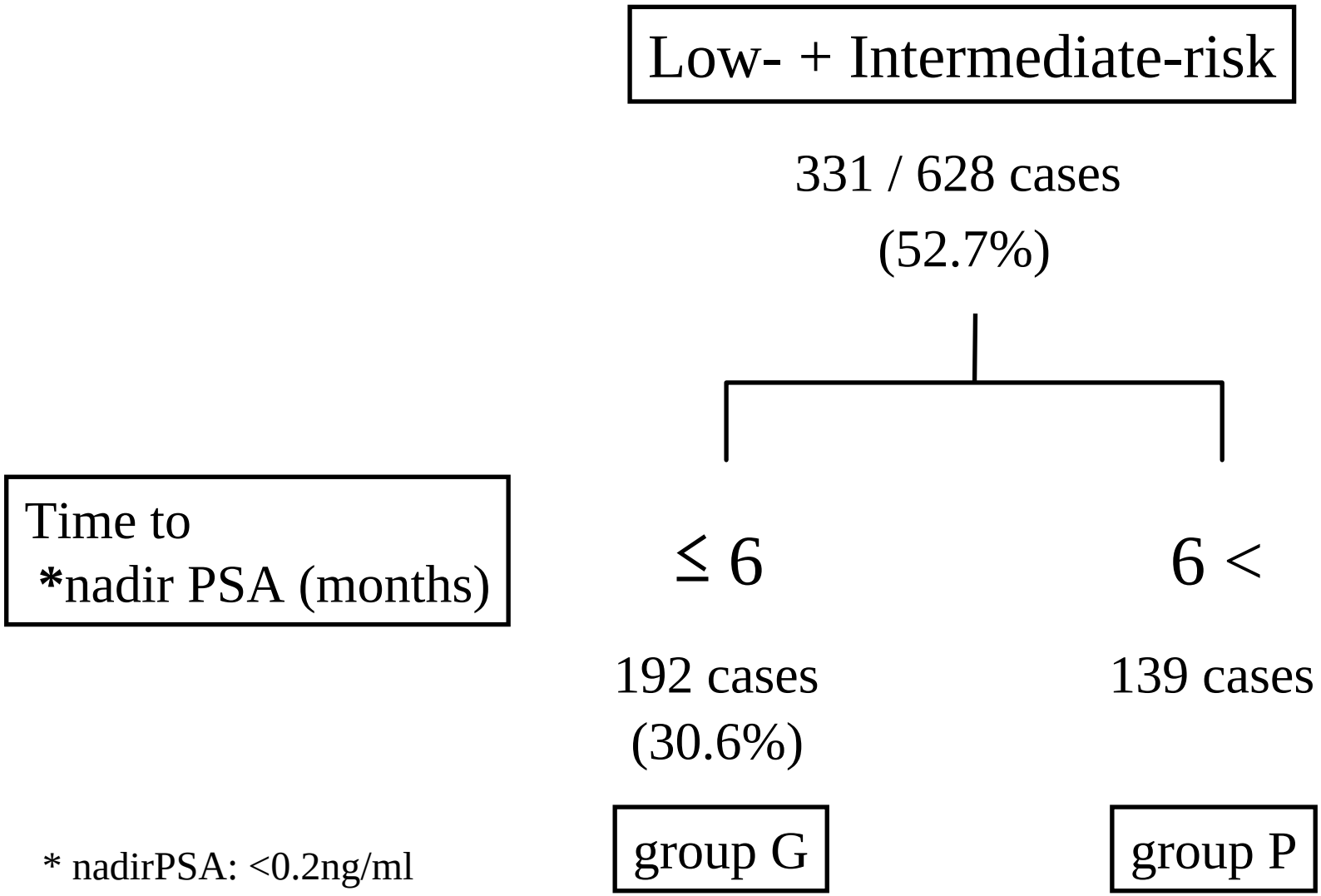
Low- + Intermediate-risk
331 / 628 cases
(52.7%)
Time to
*nadir PSA (months)
≤ 6
6 <
192 cases
(30.6%)
139 cases
group G
group P
* nadirPSA: <0.2ng/ml

Figure 6

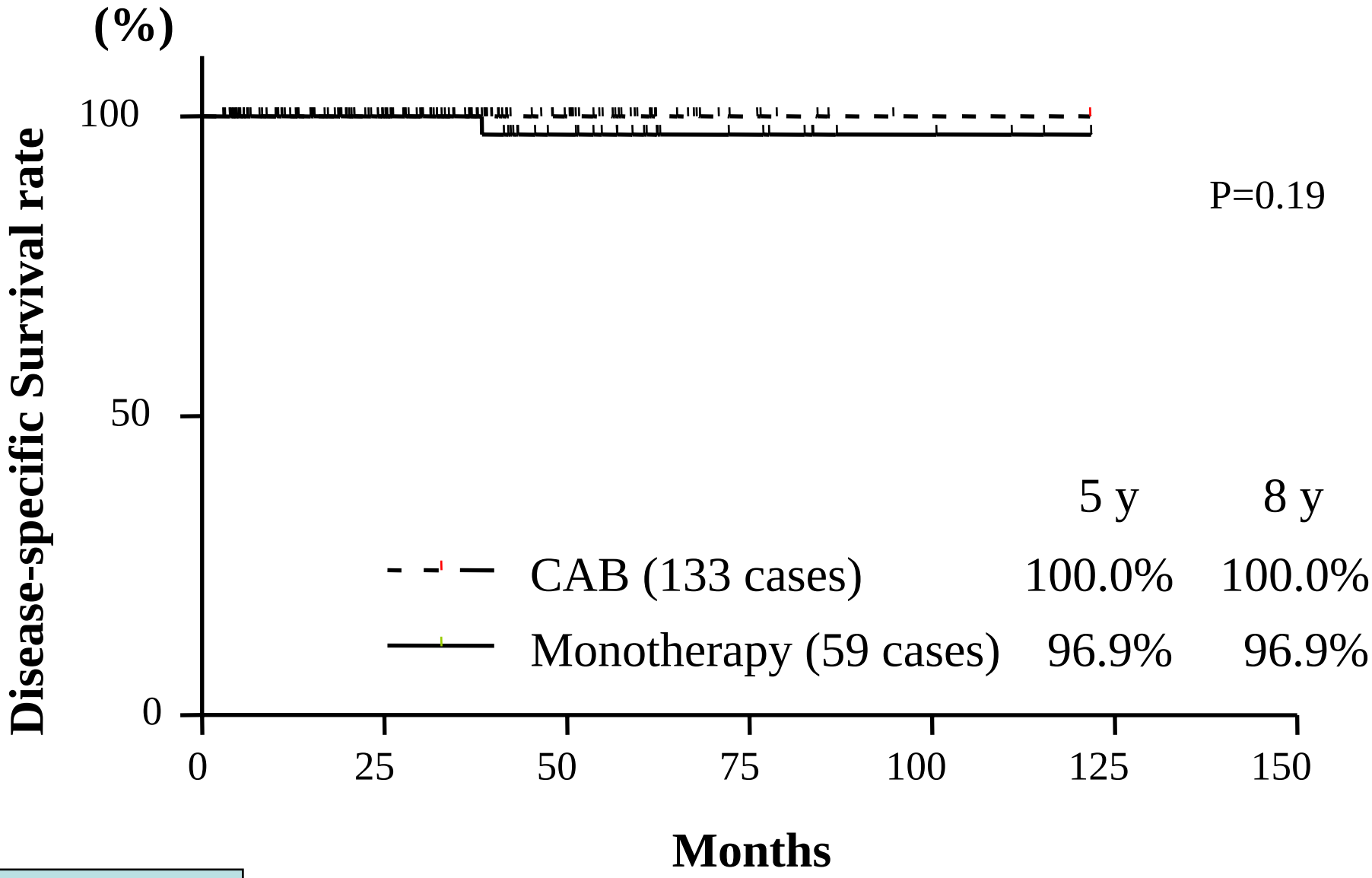
(%)
100
50
0
Disease-specific Survival rate
P=0.19
5 y
8 y
CAB (133 cases)
100.0%
100.0%
Monotherapy (59 cases)
96.9%
96.9%
0
25
50
75
100
125
150
Months

Figure 7

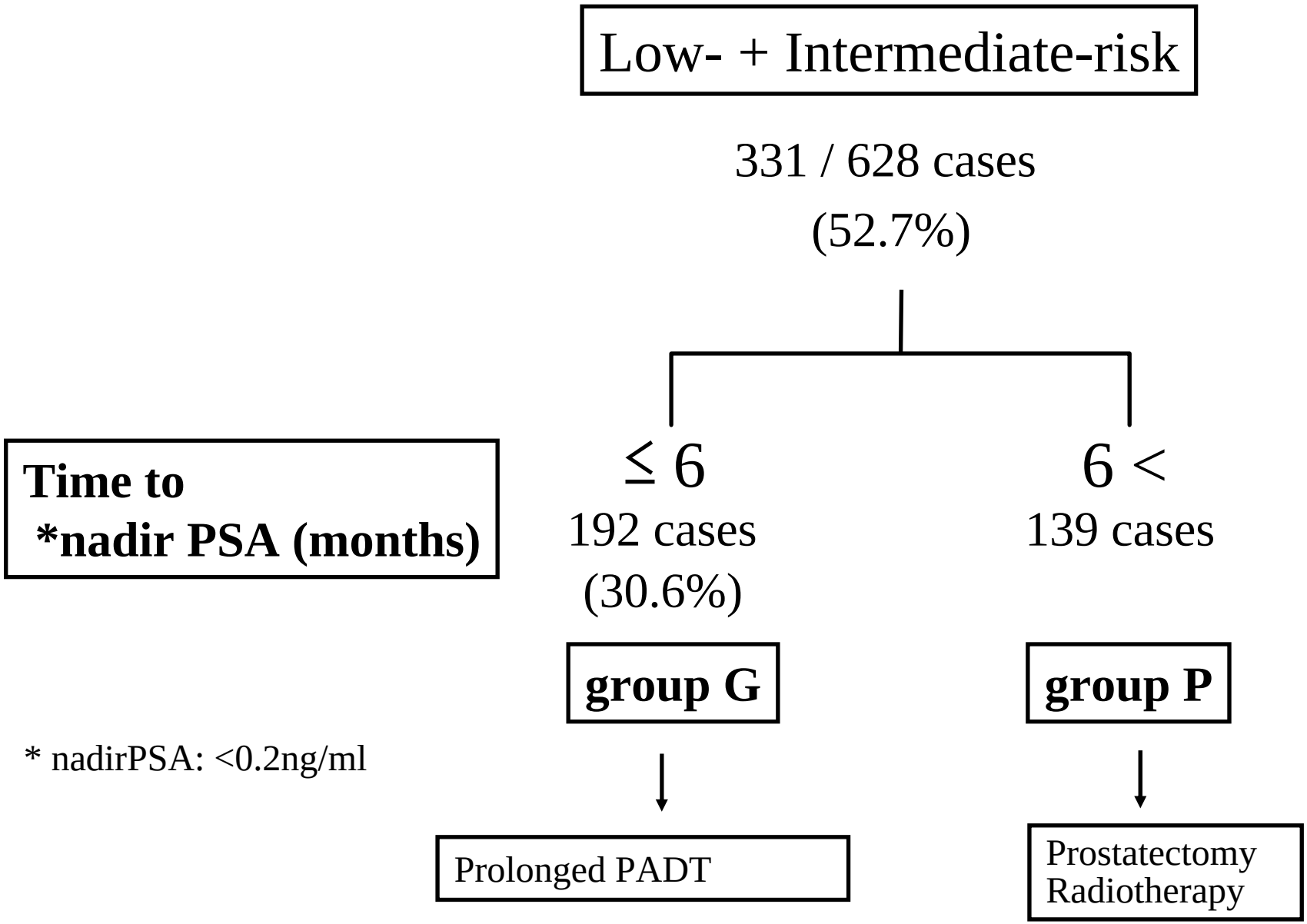
Low- + Intermediate-risk
331 / 628 cases
(52.7%)
Time to
*nadir PSA (months)
≤ 6
192 cases
(30.6%)
6 <
139 cases
group G
group P
* nadirPSA: <0.2ng/ml
Prolonged PADT
Prostatectomy
Radiotherapy

Figure 8

Evolution of Prostate Ca

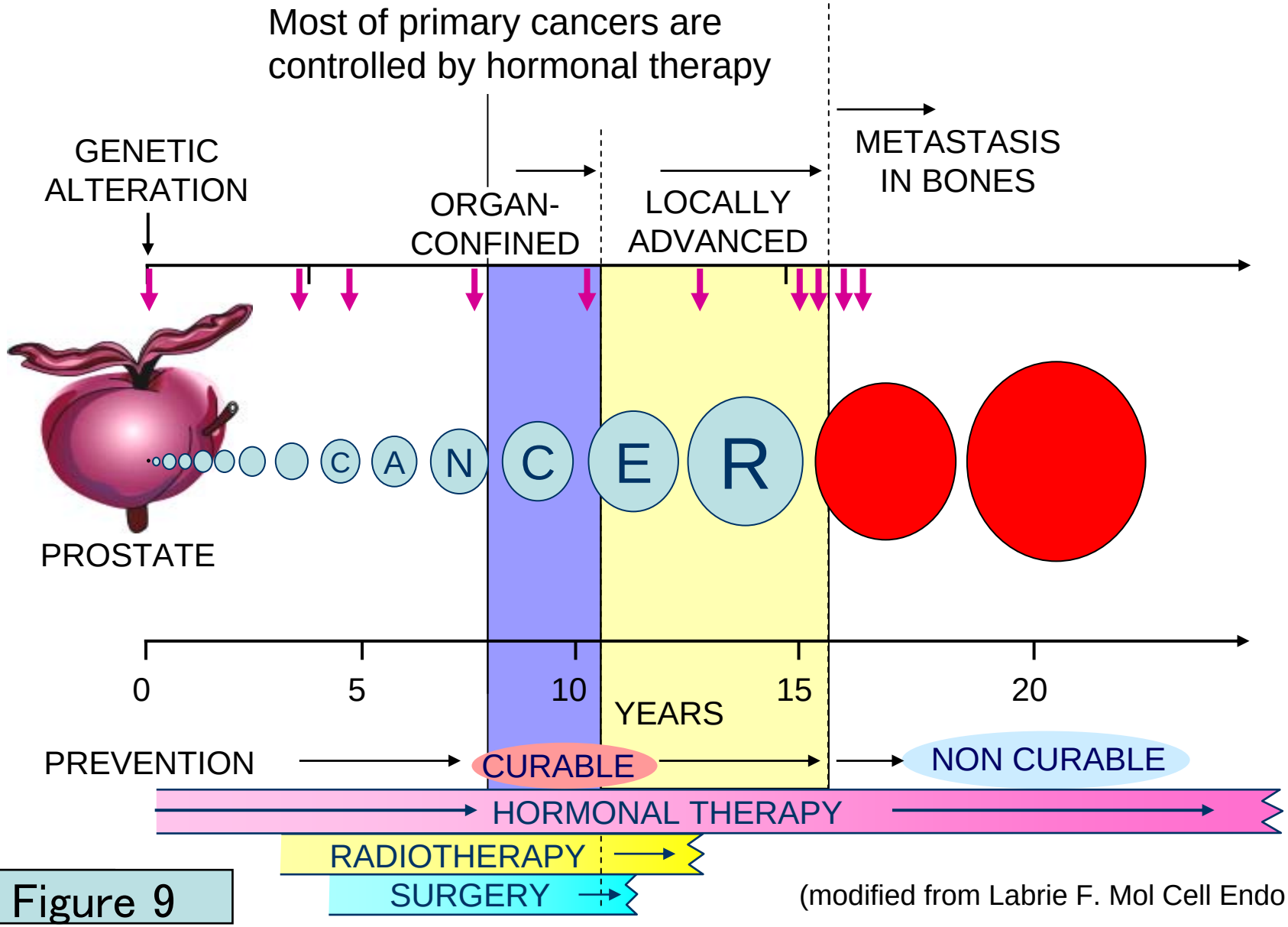

Figure 9

(modified from Labrie F. Mol Cell Endo 198:77-87, 2002)

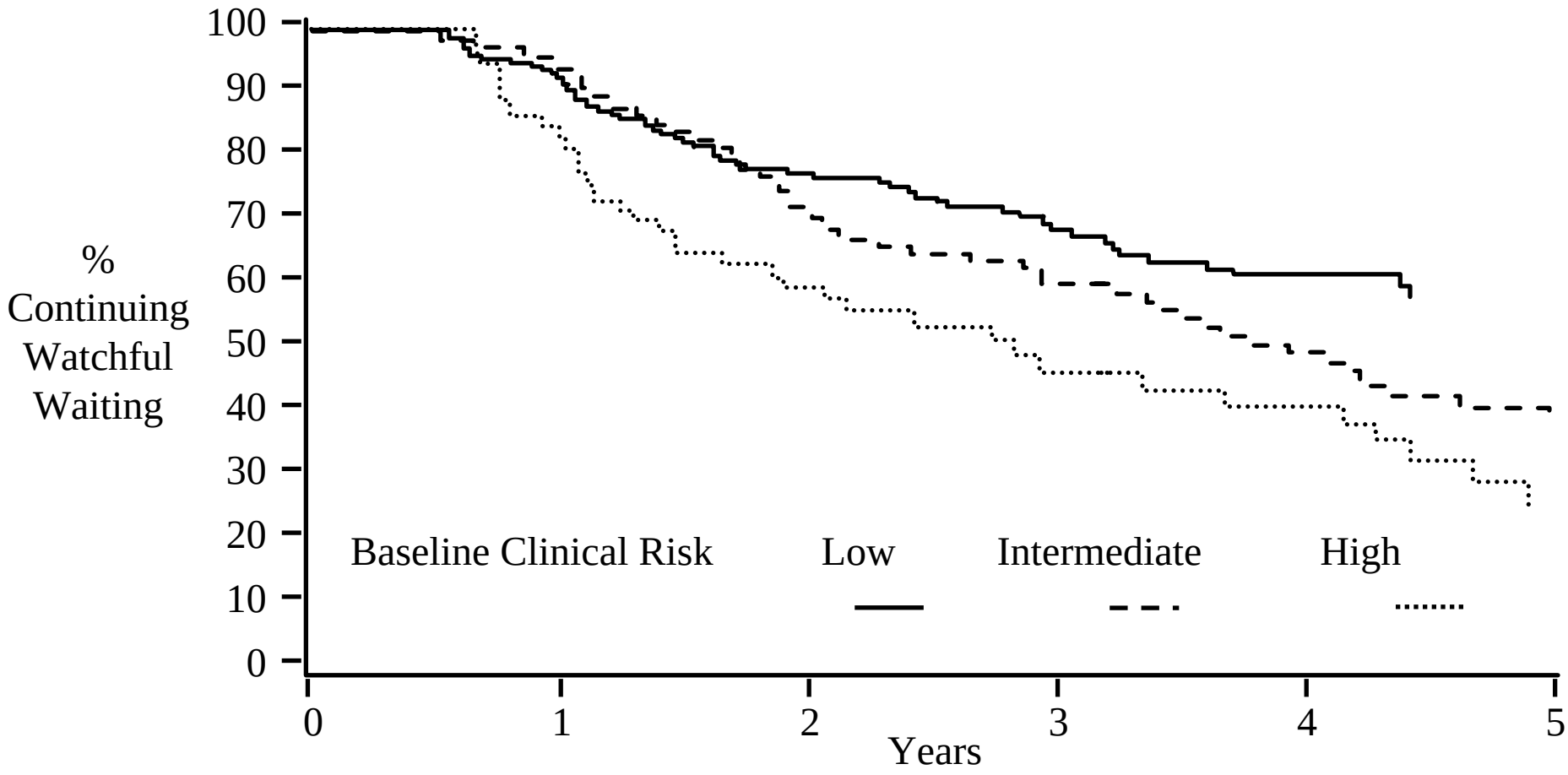
100
90
80
70
60
50
40
30
20
10
0
% Continuing Watchful Waiting
Baseline Clinical Risk
Low
Intermediate
High
0
1
2
3
4
5
Years

Figure 10

	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**

* : $P<0.05$

Table 1