Decision Analysis for Treatment of Early Stage Prostate Cancer

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We performed a decision analysis to evaluate the usefulness of pretreatment prediction of clinically significant or insignificant tumor in patients with prostate-specific antigen (PSA)-detected stage T1c prostate cancer nonpalpable on rectal examination. Analysis was done for otherwise healthy subjects with 20 years of life expectancy. The prevalence of insignificant tumor among those with T1c prostate cancer was initially assumed to be 0.2. Quality-adjusted life expectancy was calculated and compared between 2 strategies; one with prediction-based selection of either radical prostatectomy or watchful waiting and the other with unselective assignment of one of the treatments. The selection strategy was superior when the sensitivity and specificity for detecting clinically significant tumor were 0.92 and 0.73, respectively, as reported by Epstein et al. (1994) using criteria of PSA density and Gleason score in a needle biopsy specimen. Sensitivity analysis revealed that the prediction-based selection strategy is preferred, with sensitivity and specificity constant, when the prevalence of insignificant tumor exceeds 0.16. On the other hand, when the prevalence of insignificant tumor is kept constant at 0.2, sensitivity should be 0.85 or higher for the prediction strategy to be preferred. As the prevalence of insignificant tumor among those with T1c prostate cancer increased, the prediction-based selection strategy is preferred with lower values of sensitivity and specificity for detecting significant tumor. These results suggest that a selective treatment strategy of either radical or conservative treatment based on pretreatment prediction for significant tumor is a beneficial alternative to radical prostatectomy unselectively assigned to all patients at the T1c stage, if a reasonable accuracy in prediction is attained.

Key words: Decision analysis — Prostate cancer — Watchful waiting — Radical prostatectomy — Insignificant tumor

It has been reported that the mortality of clinically detected prostate cancer in the United States or in Europe is the second highest next to lung cancer. In fact, it is projected that 39,200 men will die of prostate cancer in 1998 in the United States.¹⁾ In Japan, although the incidence of clinically detected prostate cancer is still low, with approximately 4,700 deaths due to prostate cancer in 1995, its incidence has recently been exponentially increasing and the death rate is projected to reach 3 times the current level by the year 2015.2) In this context, various efforts towards early detection have been made in order to reduce the death rate from prostate cancer in western countries,^{3, 4)} as well as in Japan.⁵⁾ The combination of such diagnostic techniques as digital rectal examination (DRE), prostate specific antigen (PSA) assay and transrectal ultrasound examination has substantially increased the efficacy of detecting early stage prostate cancer. In fact, 90% of prostate cancers detected in screening programs were reported to be of early stage or

organ-confined.6) However, it is also well known that some prostate cancers grow slowly and often do not contribute to the cause of death. In fact, prostate adenocarcinoma was found at autopsy in more than 30% of men over 50 years old who had had no clinical evidence of cancer.7,8) These "latent" or clinically insignificant cancers, which are usually small in size and well-differentiated, have an excellent prognosis regardless of treatment.⁹⁻¹¹⁾ Recent studies have shown that the proportion of insignificant cancer was higher among nonpalpable stage T1c cancer detected on the basis of elevated PSA¹²⁾ than among palpable T2 cancers.¹³⁻¹⁶ It is therefore plausible to reason that the patient with prostate cancer detected early and clinically judged to be insignificant does not require aggressive and definitive treatments such as radical prostatectomy and rediation at the onset. Thus, selecting conservative treatment, i.e., watchful waiting, might be a reasonable strategy in patients with clinically detected localized tumors. However, this type of selective treatment carries with it a risk of possible delay in implementing appropriate treatment for significant tumors

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which would grow and metastasize if left untreated. Thus, previous decision analyses which have been used to examine the benefits of treatment strategies for localized prostate cancer^{17, 18)} suggested that an application of watchful observation may be appropriate only for men with well- or moderately differentiated tumor and a life expectancy of less than 10 years.¹⁹⁾ However, if the presence of clinically insignificant tumors which do not require aggressive treatments can be reasonably well predicted prior to treatment, conservative treatment might be extended to a population of patients who have a life expectancy of more than 10 years.¹⁹⁾ It has recently been shown that positive and negative predictive values for significant tumor in stage T1c prostate cancers were 86 to 95% and 63 to 66%, respectively, based on the combined use of PSA density and Gleason score in needle biopsy specimens.^{20, 21)} However, it is unknown whether selective treatment based on these prediction values is truly applicable to patients with early stage prostate cancer whose life expectancy is more than 10 years. Therefore, in the present study, we evaluated the potential consequences of selecting conservative treatment for T1c prostate cancer patients judged to have insignificant tumor using a decision analysis technique.

MATERIALS AND METHODS

A standard decision analysis was performed using a commercially available software package (Decision Analysis by Tree Age; DATA). We considered 60-year-old sexually active men with stage T1c prostate cancer who are otherwise healthy and have an anticipated life expectancy of 20 years, as shown in the Abridged Life Table for Japan 1990. Fig. 1 depicts the decision tree, in which the first decision node has two branches. The upper branch shows the strategy of selecting patients based on pretreatment prediction for significant and insignificant cancers. In this branch, patients judged to have insignificant cancer (presumably insignificant) were subjected to watchful waiting, while those judged to have significant tumor (presumably significant) were assigned to undergo radical prostatectomy. These two branches from the branch of selection were then divided into "true significant" and "true insignificant" tumor according to positive and negative predictive values which were calculated from a combination of prevalence of these true states and test characteristics (sensitivity and specificity) of the selection method.

We initially assumed that the prevalence of true significant tumor in T1c prostate cancer is 0.8 according to the data reported by pathological examination following radical prostatectomy for T1c prostate cancer.^{13–16)} Test characteristics of the selection method for detecting significant cancer (i.e., PSA density of more than 0.1, or any adverse pathological variable on needle biopsy such as 4 or 5 Gleason pattern and more than 50% cancer involvement in any biopsy core) were derived from the data of Epstein *et al.*²⁰ Based on their data, the sensitivity and specificity were calculated to be 0.92 and 0.73, respectively.

The lower branch from the first decision node shows the strategy leading to unselective application of either radical prostatectomy or watchful waiting. Two branches emanate from radical prostatectomy: "perioperative death" and "operative survival." The likelihood of perioperative mortality is estimated to be 0.01.22) Life expectancy for patients who had either radical prostatectomy or watchful waiting differs by tumor stage. Since life expectancy in patients with T1c cancer is not yet known, life expectancy in the present study was estimated by using the data obtained from T1-2 and T3 cancer patients. Patients with true insignificant cancer are expected to have a normal life expectancy (=20 years) regardless of the treatment chosen. Life expectancy for patients with true significant tumors was calculated by using the DEALE method²³⁾ based on the data in the literature for survival rate for stage B or lower (T1-2), and stage C (T3) cancer following either radical or conservative treatment.

Health-related quality of life adjustments were made in this analysis by assigning a relative worth (utility) to each branch of the decision tree. Utility value is a subjective health rating scale of each possible outcome. The worst possible outcome is operative death which is assigned a utility value of zero, while the asymptomatic state in patients with true insignificant tumor under watchful observation was assigned the best utility value of 1.0. The other outcomes such as operative morbidity or metastatic progression are then evaluated on a scale of zero to 1.0, since the patients with operative morbidity or complications due to metastatic spread are expected to have a much lower health-related quality of life. Utility values for impotence, incontinence and metastatic spread have been reported to be 0.85-0.95, 0.80-0.85 and 0.50-0.60, respectively, in the literature.^{17, 18, 24)} The likelihood of operative morbidity, such as urinary incontinence or impotence, has been reported to be 10-30% and 60%, respectively, in the literature.^{25, 26)} Also documented was the proportion of the patients with true significant cancer who had metastatic progression, which occurred following radical prostatectomy and watchful observation in 10 to 15% and 20 to 30%, respectively.²⁷⁾ Thus, it was estimated that the overall loss of utility following radical prostatectomy or watchful waiting was approximately 10-20% (i.e., 0.8–0.9 utility values) when each reported utility value for impotence, incontinence and/or metastatic progression was multiplied by the incidence rate of each complication, and then added according to each corresponding treatment modality (i.e., watchful waiting or radical prostatectomy). Therefore, in the present decision

model, utility values were initially set to be 0.9 for both radical prostatectomy and watchful observation in patients with significant cancer, i.e., 10% permanent loss in utility.

Finally, sensitivity analyses were conducted with respect to sensitivity and specificity for detecting significant cancers, as well as for the prevalence of significant tumor among stage T1c cancer, patient's life expectancy and utility values.

RESULTS

It has been reported that organ-confined and advanced tumors were almost equally found in specimens of clinically significant tumor among T1c cancers obtained by radical prostatectomy.^{20, 21} Life expectancy for patients with organ-confined and advanced tumors was estimated using life expectancy previously reported in patients with T1-2 and T3 tumors, respectively. With radical prostatectomy, the patients with T2 or lower stage tumors were expected to be cured and to have a normal life expectancy of 20 years, while life expectancy for those with T3 cancer was calculated to be 10 years based on the 10-year survival rate (36%) reported by Schroeder and Belt.²⁸⁾

Table I. Relationship among Sensitivity, Selectivity and Predictive Values

T1c prostate cancer	Presumably significant	Presumably insignificant	
True significant	0.736 (a)	0.064 (b)	0.8 (a+b)
True insignificant	0.054 (c)	0.146 (d)	0.2 (c+d)
	0.79 (a+c)	0.21 (b+d)	1.0 (a+b+c+d)

The cell "a+b" indicates prevalence of significant cancer (0.8). Sensitivity and selectivity were set to be 0.92 (a/a+b) and 0.73 (d/c+d), respectively.

Positive and negative predictive values were then calculated to be 0.93 (a/a+c) and 0.70 (d/b+d), respectively.



Fig. 1. Decision trees of treatment modalities for patients with stage T1c prostate cancer. WW, watchful waiting; RP, radical prostatectomy; LE, life expectancy (years); QALE, quality-adjusted life expectancy (years). Final QALE of the decision trees are indicated by arrows at the corresponding decision nodes.

Thus, on the assumption that T1-2 and T3 tumors are equally distributed in true significant tumors among T1c cancers, overall life expectancy for patients with true significant prostate cancers who were treated by radical prostatectomy was calculated to be 15 years (Fig. 1). Life expectancy following watchful observation was estimated to be 15 and 8 years for T1-2 and T3 tumors, respectively, based mainly on the data of Adolfsson et al.29) Thus, overall life expectancy in the case of watchful waiting for the patients with true significant tumors was calculated to be 11.5 years (Fig. 1). Then, if radical prostatectomy is chosen, quality-adjusted life expectancy in the patients with true insignificant and true significant prostate cancer was expected to be 18 and 13.5 years, respectively, as calculated by multiplying by the utility value of 0.9. In the same way, the patients with watchful waiting for true significant prostate cancer had 10.4 years of quality-adjusted life expectancy, as calculated by multiplying by the utility value of 0.9 (Fig. 1). The positive and negative predictive values were calculated to be 0.93 and 0.70, respectively, based on pretreatment prevalence of significant tumor (0.8), and sensitivity (0.92) and specificity (0.73) for detecting a significant tumor (Table I and Fig. 1).



Fig. 2. Sensitivity analysis of prevalence of significant tumor among T1c prostate cancer in relation to quality-adjusted life years in association with the selection strategy based on pretreatment prediction (radical prostatectomy and watchful waiting, RP+WW) and unselective radical prostatectomy (RP alone). Quality-adjusted life years was plotted against prevalence of significant tumor changing from 0 to 1.0. Note that the selection strategy afforded longer quality-adjusted life expectancy than unselective radical prostatectomy when prevalence was lower than 0.84.

Folding back of the decision tree yielded 14.25 and 12.28 quality-adjusted life years for radical prostatectomy and watchful waiting, respectively, in the branch of no selection. On the other hand, the branch of selection yielded 14.40 quality-adjusted life years (Fig. 1). Thus, in this decision model, the selection strategy is the best for treating T1c prostate cancer.

Sensitivity analysis was then performed to determine the threshold of prevalence of significant tumor under the assumption of sensitivity and specificity of 0.92 and 0.73, respectively. Quality-adjusted life years was plotted against prevalence of significant tumor for either prediction-based selective treatment strategy or radical prostatectomy unselectively assigned to all patients (Fig. 2). Radical prostatectomy offers a gain in quality-adjusted life years only when the prevalence of significant tumor is higher than 0.84. With a prevalence of significant tumor



Fig. 3. Sensitivity analysis of sensitivity and specificity for detecting significant tumor with different values of prevalence of significant tumor among T1c prostate cancer. Lines show the combination of threshold values of sensitivity and selectivity which determine the preference of either the selection strategy or unselective radical prostatectomy. Above the threshold line, the selection strategy is preferred (selection preferred) and, below the line, unselective radical prostatectomy is preferred (no selection preferred). The prevalence of significant tumor is indicated on each threshold line. The minimal sensitivity value for the selection strategy to be preferred is indicated on the right of each threshold line. Note that, when the prevalence of significant tumor was varied from 0.9 to 0.5, the minimal sensitivity value for which the selection strategy is to be preferred was reduced from 0.93 to 0.41.

of less than 0.84, the prediction-based selection strategy was preferred and the gain in quality-adjusted life years increased as the prevalence of significant tumor decreased, i.e., for higher prevalence of insignificant tumor.

Fig. 3 shows the result of sensitivity analysis in which the estimates for sensitivity and specificity in detecting significant cancers were varied on the longitudinal and horizontal axes, respectively, from zero to one under the assumption of a prevalence of significant tumor from 0.5 to 0.9. The threshold line sloped down to the right with an intersection at sensitivity 0.85 and specificity 1.0 when the prevalence of significant tumor was set to 0.8. The area below this line reflects the combinations of sensitivity and specificity for which unselective radical prostatectomy affords longer quality-adjusted life expectancy than the selection strategy. Conversely, in the area above this line, the selection strategy is preferable to unselective radical prostatectomy. As the prevalence of significant cancer is decreased from 0.9 to 0.5, the threshold lines became steeper to the right with the minimal threshold value of sensitivity decreasing from 0.93 to 0.41 (Fig. 3). This means that the selection strategy remains preferable even with a combination of low sensitivity and specificity as



Fig. 4. Sensitivity analysis of life expectancy in relation to quality-adjusted life years in association with the selection strategy (radical prostatectomy and watchful waiting, RP+WW), unselective watchful waiting (WW alone) and unselective radical prostatectomy (RP alone). Quality-adjusted life years was plotted against life expectancy changing from 10 to 14 years. Note that if life expectancy exceeds 11.7 years, the selection strategy shows more quality-adjusted life years than the other treatment options, whereas unselective watchful waiting was the most favorable when life expectancy is less than 11.7 years.

the prevalence of insignificant tumor among total prostate cancers increases.

The effect of changes in patient's life expectancy on quality-adjusted life years obtained with different treatment options such as selection strategy, unselective prostatectomy and unselective watchful waiting was then examined. In all ages examined (5 to 20 years of life expectancy), the selection strategy afforded more qualityadjusted life years than unselective radical prostatectomy. Fig. 4, in which quality-adjusted life years is plotted against change in life expectancy from 10 to 14 years, shows that, if life expectancy exceeds 11.7 years, the selection strategy gives more quality-adjusted life years than the other two treatment modalities. However, if life expectancy is decreased to less than 11.7 years, unselective watchful waiting is the best approach for treating patients with T1c prostate cancer, suggesting that conservative treatment could be the best option as patient's life expectancy decreases.

Finally, Fig. 5 demonstrates the results of sensitivity analysis in which the estimates for utility values following watchful waiting for significant tumors and radical prostatectomy were varied on the longitudinal and horizontal axes, respectively, from zero to one on the assumption of a prevalence of significant tumor of 0.8. The area to the left of the line reflects the combinations of utility values for which the selection strategy is preferable to unselec-



Fig. 5. Sensitivity analysis of utilities following watchful waiting in patients with significant tumor and radical prostatectomy. The line indicates the combination of threshold values of utilities which determines the preference for either the selection strategy or unselective radical prostatectomy. In the area to the left of the threshold line, the selection strategy is to be preferred (selection preferred), while in the area to the right of the line, unselective radical prostatectomy is to be preferred (no selection preferred).

tive radical prostatectomy. On the other hand, in the area to the right of the line, unselective radical prostatectomy affords a longer quality-adjusted life expectancy than the selection strategy. If the utility value after radical prostatectomy is less than 0.76, the selection strategy based on pretreatment prediction is always preferred regardless of values of utility following watchful waiting for significant tumors, whereas unselective radical prostatectomy is always favorable when the utility value following prostatectomy is over 0.95.

DISCUSSION

The present study shows that the decision analysis technique is a useful tool in determining treatment strategy for early stage prostate cancer. It is also suggested that, based on the probability values used in the present study, selecting watchful waiting for the patients with T1c prostate cancer who are judged to have insignificant cancer (presumably insignificant) might have a benefit when compared with unselective application of radical prostatectomy. In addition, as shown in this study, a sensitivity analysis can provide useful information by assessing the importance of each parameter in the decision analysis when particular parameters possibly vary over a range of values.

The optimal management of early stage organ-confined prostate cancer has already been the subject of decision analysis by several investigators. In 1992, Fleming et al. reported that aggressive treatment such as radical prostatectomy or irradiation offered only a marginal benefit over watchful waiting in many men with localized prostatic carcinoma, suggesting that watchful waiting is a reasonable alternative to invasive treatment for these patients.¹⁷⁾ However, Beck *et al.*¹⁸⁾ concluded that radical operation is preferable for all grades of localized prostate cancer based on reevaluation of the decision analytical researches using the data of Chodak et al. on conservative management for localized prostate cancer.³⁰⁾ At present, it is generally admitted that watchful waiting may be applied with the least risk for patients who have low-grade tumors and a life expectancy of less than 10 years.¹⁹⁾ This assumption is in line with our findings in the sensitivity analysis regarding patient's life expectancy, i.e., that the unselective watchful waiting strategy was the most favorable option in treating T1c prostate cancer patients with a life expectancy of less than 11 years. However, the present study also suggests that if preoperative selection of patients can be achieved with a reasonable accuracy, the watchful waiting strategy with patient selection could be applicable for patients with a life expectancy of more than 10 years.

In the present study, quality-adjusted life expectancy calculated for unselective radical prostatectomy (14.2 years) was similar to that reported previously,^{17,30)} and the

gain in quality-adjusted years as compared with unselective watchful waiting (2 years) was comparable to that found by Beck *et al.*¹⁸⁾ However, since the true life expectancy for patients with T1c cancer is not known, and the present study, as well as previous reports, mainly utilized data obtained before the widespread use of the PSA test, it should be further evaluated whether these data can reasonably be used for estimating life expectancy for patients with PSA-detected early stage prostate cancer. An ongoing randomized prospective trial (PIVOT), designed to determine whether radical prostatectomy or expectant management is to be preferred in managing clinically localized prostate cancer in the United States, should provide a more precise natural history of early stage prostate cancer.³¹

Recent, widespread use of PSA measurement has reportedly increased the accuracy of diagnosing prostate cancer by approximately 75% over screening with DRE alone.32) Further, 90% of prostate cancers found in PSAbased mass screening were organ-confined (T1-2), suggesting that this early detection of prostate cancer might substantially increase the proportion of possibly curable early stage prostate cancer.^{4,6)} However, it is uncertain whether the early detection of prostate cancer will eventually lead to a reduction in the cancer-related death rate, since prostate cancer has a variable natural history and often does not progress to cause morbidity or mortality. In fact, the detection rates of malignant cells in the prostate at autopsy are approximately 9,000 and 8,000 per 100,000 population, while those of clinical cancer are only 6.5 and 40 in Japanese and US white men, respectively. Lethal prostatic cancers are even rarer, with rates of 3.3 and 14 per 100,000 Japanese and US white men, respectively.³³⁾ Thus, it is likely that many of prostate cancers are latent and asymptomatic throughout life. In addition, these incidentally found "latent" prostate cancers are usually small, well-differentiated and confined to the prostate.^{7,8)} Thus, prostate cancers which are found in PSA-based screening might include insignificant tumors which do not require aggressive treatment. Although a perfect method to discriminate insignificant cancer from significant cancer is not yet available, Stamey et al. have demonstrated using specimens obtained cystoprostatectomy for patients with bladder cancer that prostate cancers smaller than 0.5 ml were clinically insignificant and not likely to reach a clinically significant size due to the long doubling time.³⁴⁾ According to this criterion, 13-26% of PSA-detected nonpalpable T1c prostatic cancers were clinically insignificant compared to 2–9% of the palpable T2 cancers.^{13–16, 21)} A recent study using decision analysis has suggested that PSA-based screening may result in poorer health outcomes, i.e., shorter quality-adjusted life expectancy, if all patients once detected are subjected to radical prostatectomy.²⁷⁾ Thus, as presented in our study, selecting either radical or conservative treatment based on prediction of biological potential for progression might be a favorable alternative strategy in treating early stage prostate cancer. In the present study, sensitivity analysis has also shown that the selection strategy offers a gain in quality-adjusted life expectancy when the prevalence of insignificant tumor is higher than 16%, using the sensitivity and specificity values derived from Epstein *et al.*²⁰⁾ Thus, it seems likely that the selection strategy would be more favorable in a population of patients with PSA-detected T1c cancers, approximately 20% of which are clinically insignificant, rather than in a population of patients with T2 prostate cancers, of whom less than 10% have insignificant tumors.¹³⁻¹⁶⁾

A recent study by Albertsen et al. has shown that patients with conservatively treated low-grade (Gleason scores 2 to 4) prostate cancer incurred no loss of life expectancy compared with the general population.³⁵⁾ Thus, tumor grade, in addition to tumor size, is likely to be a good indicator of biological potential for tumor progression. Epstein et al. reported that insignificant cancers, defined as those with a tumor volume less than 0.2 cm³ and Gleason scores less than 7, were preoperatively estimated with rather high sensitivity (0.92) and specificity (0.73) based on a combination of low PSA density and low Gleason scores in specimens obtained by needle biopsies.²⁰⁾ However, it has not yet been determined whether selection of treatment based on pretreatment prediction of significant and insignificant cancers in such a way actually leads to a beneficial outcome. Sensitivity analysis in the present study indicated that such a strategy with sensitivity and specificity values derived from Epstein et al.²⁰⁾ would lead to a gain of quality-adjusted life expectancy. In addition, it was also shown that the value of sensitivity for preference of the selection strategy should be higher than 0.85, given the prevalence of significant tumor as 0.8. It is therefore concluded that if a reasonable accuracy in prediction can be attained, the selection strategy is a favorable treatment strategy. However, in other words, this conclusion clearly indicates that highly sensitive diagnostic methods which increase the accuracy of pretreatment prediction are required if the selection strategy is to be chosen for treating sexually active patients with T1c prostate cancer whose life expectancy is anticipated to be 20 years. Thus, further efforts should be made to achieve more precise preoperative staging in patients with early stage prostate cancer.36)

Albertsen *et al.* has also reported that a half of patients with low grade prostate cancer had large tumors, but that they had good prognoses with conservative treatment.³⁵⁾ Thus, it seems that the definition of insignificant cancer could be less strict than that advocated by Stamey *et al.*,³⁴⁾

so as to include larger prostate cancers, resulting in an increase of the prevalence of insignificant prostate cancers. Also, as shown in the present study, the sensitivity and specificity for detecting significant tumors could be low, if the prevalence of insignificant cancer is high. In addition, there remains a possibility that biological markers other than tumor size, pathological grade and PSA may more accurately predict insignificant tumors and/or slowly growing tumors, and indicate the existence of subgroups of patients who do not require aggressive treatment.³⁶⁾ Thus, it is plausible that, in the future, the prediction-based selection of treatment modality might provide a larger benefit to patients with early stage prostate cancer than that found in the present study.

Finally, utility values following radical prostatectomy or watchful waiting were roughly estimated in this study. Few investigations have been reported concerning utilities associated with morbidity caused by tumor progression or metastasis, as well as aggressive treatment such as radical prostatectomy or radiation,^{17, 18, 24)} and none has been published on the patient's evaluation of utility values in the treatment of early stage prostate cancer. Since the results in decision analysis are sensitive to changes in utility values, as shown in our sensitivity analysis as well as others,^{17, 18, 24)} a more detailed assessment of utility values is definitely needed in further evaluating the outcome of each treatment decision.37-39) Moreover, since quality of life is very subjective,³⁷⁾ these utility values should be evaluated by each patient, and then be incorporated into a decision making process when counseling each patient with early stage prostate cancer about optimal treatment modalities.

In summary, our decision analysis in terms of qualityadjusted life expectancy of patients with PSA-detected early stage prostate cancers showed that the predictionbased selection of conservative treatment for patients judged to have insignificant cancer could be an alternative strategy to conventional treatment, in which radical treatment is usually applied to all patients. The present study also demonstrated that a decision analytical approach provides useful information to compare the possible outcome of different treatment strategies for prostate cancer patients.

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