Chapter 1

Prostate-Specific Antigen-Based Prostate Cancer Screening

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Abstract

Serum prostate-specific antigen (PSA) testing is a simple and effective method for diagnosing prostate cancer. The widespread PSA screening resulted in increased diagnosis of early-staged, localized prostate cancer and marked reduction in advanced, metastatic cancer, which contributed to subsequent reduction in prostate cancer mortality. Most patients with localized prostate cancer, especially low-grade cancer, have an indolent clinical course. In addition, the rate of death from prostate cancer itself is very low. Therefore, early diagnosis of prostate cancer can lead to overdiagnosis and overtreatment. There has been a controversy regarding the effect of PSA screening on prostate cancer mortality. Results of the two largest randomized trials concerning PSA screening were totally contrary. European countries-based trial showed a significant prostate cancer mortality reduction, whereas the USA-based trial showed no benefit in reducing prostate cancer mortality. In 2013, based on these arguments, the American Urological Association updated a guideline regarding PSA screening, which did not recommend routine PSA screening but a selective screening, according to patient's age, coexisting medical condition, and risks, such as family history. The guideline also emphasized shared decision making.

However, older patients have been shown to be more likely to have high-risk prostate cancer at diagnosis. Older patients more often have other medical conditions and are more likely to die from causes other than prostate cancer. Prostate cancer is more often diagnosed with older patients. These facts bring PSA-based screening for prostate cancer more and more complex. In this chapter, problems concerning PSA screening are presented.

Keywords: prostate-specific antigen, prostate cancer, screening, mortality, evidence

1. Introduction

Prostate cancer is the most common cancer, accounting for up to 29% of all incident cases and is the second most common cause of cancer death among men in the United States in 2012 [1]. The lifetime probability of being diagnosed as prostate cancer is approximately 16% [1]. Serum prostate-specific antigen (PSA) measurement is an extremely effective tool for identifying men with prostate cancer. Today, almost all prostate cancer patients are being diagnosed with an elevated PSA. It is well known that PSA screening has increased the incidence of prostate cancer but decreased a rate of advanced, metastatic prostate cancer and resulted in a subsequent drastic reduction in prostate cancer mortality.

In the United States, following the introduction of widespread PSA screening in the late 1980s, there was a 70% increase in prostate cancer incidence. In 1992, there was a peak of incidence, as if it can be called the prostate cancer incidence surge. Several years after the introduction of PSA testing, from around 1994, mortality rate began to fall [1].

In European countries, PSA screening decreased the absolute risk of being diagnosed with advanced prostate cancer [2]. A population-based, prospective, randomized, controlled screening study for prostate cancer, with biennial PSA testing group and control group, showed that after a follow-up of 10 year, the diagnosis of prostate cancer increased by 1.8-fold; however, the risk of being diagnosed with metastatic prostate cancer was reduced by 48.9% ($p = 0.0084$) [2].

The incidence of prostate cancer in Japan rapidly increased between 2000 and 2003, while the mortality rate started to decrease in 2004, immediately after the increase in incidence [3]. The proportion of localized prostate cancer rapidly increased between 1997 and 2003, from 40 to 60% or higher. These facts are explained by early diagnosis using serum PSA measurement [3].

The primary aim of PSA-based prostate cancer screening should be the early detection of asymptomatic patients with potentially fatal cancers resulting in reduction of cancer-specific mortality [4]. However, early diagnosis of the prostate cancer due to widespread PSA screening has also led to increased diagnosis of clinically indolent cancers. Almost all localized cancers, especially low-grade disease, rarely progress to advanced disease and even fewer have a fatal clinical course [5, 6]. Prostate biopsy as well as any treatment has some adverse events and harms. Thus, PSA screening itself is associated with overdiagnosis and overtreatment. PSA screening in asymptomatic individuals involves a trade-off of benefit and harm.

Randomized trial is the most valuable study design for making evidence in medical fields. To address whether there is a mortality benefit in PSA screening, several randomized trials were performed. However, results of the two largest randomized trials were extremely confusing. The USA-based, the prostate component of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) showed no benefit in reducing mortality rate [7]; however, the European-based, the European Randomized study of Screening for Prostate Cancer (ERSPC trial) showed a significant mortality reduction [8].

The United States Preventive Health Services Task Force (USPSTF) has regarded harms associated PSA screening more important and has recommended against PSA screening in

asymptomatic men regardless of age [9]. The USPSTF stated that current empiric evidence is insufficient to assess the risks and benefits of prostate cancer screening. Potential harms from screening and treatment are much more significant and clinicians should recommend against PSA screening for prostate cancer [9].

In 2013, based on these arguments, the American Urological Association (AUA) updated clinical guideline for PSA screening, "Early detection of Prostate cancer", which recommended against an organized PSA screening but for a selective PSA screening according to age, comorbidities, and risks such as family history [10]. In addition, the AUA strongly recommended shared decision making, a thorough discussion between physician and patient regarding the risks and benefits of PSA-based screening [10].

In general, the rate of prostate cancer incidence increases with age [1, 11]. Compared with younger men, older men are more frequently diagnosed with high grade and high risk prostate cancer [12]. In addition, coexisting medical conditions are also more prevalent in older patients. These facts bring PSA screening much more confusing.

As an alternative data source, a population level data, cohort study, concerning PSA screening is presented. Although cohort study is considered a lower level of evidence compared to the randomized study, it has some merit in reflecting "real world" clinical data.

2. Conflicting two large randomized trials concerning PSA screening

In 2009, totally conflicting two large randomized trials addressing the effect of PSA screening on the prostate cancer-specific mortality rate were published at the same time in the same journal, and consecutively [7, 8]. The USA-based, the prostate component of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (the PLCO trial), showed no benefit in reducing mortality rate, after 7–10 years of follow-up (rate ratio (RR) 1.13; 95% confidence interval (CI) 0.75–1.70) [7]. In contrast, European countries-based trial, the European Randomized study of Screening for Prostate Cancer (the ERSPC trial), showed a benefit of PSA screening in reducing prostate cancer mortality [8]. The ERSPC trial reported that during a median follow-up of 9 years, the rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% CI, 0.65–0.98; adjusted $p = 0.04$) [8].

The prostate component of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) is a multicenter, randomized trial designed to evaluate the effect of PSA screening for prostate cancer-specific mortality. A total of 76,685 men, aged 55–74 years, were randomly assigned to the intervention arm (offered annual PSA testing for 6 years and annual digital rectal examination for 4 years) and to the control arm (usual, opportunistic PSA examination) at 10 centers in the United States between 1993 and 2001. A PSA cutoff 4.0 ng/ml was used for prostate biopsy. The PLCO trial extended follow-up period to 13 years and concluded that there was also no evidence of a mortality benefit for organized annual screening compared with opportunistic screening (RR, 1.09; 95% CI, 0.87–1.36) [13].

On the other hand, the European Randomized study of Screening for Prostate Cancer (ERSPC trial) is also a randomized multicenter trial with core age group (55–69 years) evaluating the benefit of screening for prostate cancer with serum PSA in eight European countries, including the Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland, and France. Briefly, a total of 162,388 aged 55–69 men were randomly assigned as an intervention arm (invited to PSA screening once every 4 years in seven countries and once every 2 years in Sweden) or a control arm with no PSA testing offered. A PSA cutoff 3.0 ng/ml was used for prostate biopsy. The ERSPC group also extended follow-up to 11–13 years and reported that the rate ratio (RR) of prostate cancer incidence between the intervention and control arms was 1.91, 1.66, and 1.57 after 9, 11, and 13 years, respectively, and the RR of prostate cancer mortality was 0.85, 0.78, and 0.79 at 9, 11, and 13 years, respectively (95% confidence interval 13 years 0.69–0.91, p = 0.001), corresponding to a relative risk reduction of 21% at 13 years [14, 15]. The updated ERSPC study concluded a substantial prostate cancer mortality reduction due to PSA testing. In the ERSPC trial, a significant decrease in metastatic disease at diagnosis was demonstrated. The rate of advanced group (M1 and/or PSA > 100 ng/ml) was 3.4 and 9.6%, in the intervention and control arm, respectively.

The reasons why the results of these two trials were totally different might be due to differences in study design: screening protocol and PSA cutoff value. For example, the ERSPC trial compared screening group to no screening group, while the PLCO trial compared annual PSA screening to opportunistic PSA testing in the control arm [16].

Randomized trial has some unavoidable limitations: compliance in the intervention arm, nonparticipation in the screening arm, and PSA contamination, opportunistic PSA testing in the control arm. Because investigated individuals have the will, PSA contamination cannot be excluded completely. The contamination rates were 20–25% in the ERSPC trial and 40% in the first year and increased to 52% in the sixth years in the PLCO trial [7, 8]. Increased exposure to opportunistic PSA testing in the control arm reduces the reliability of the randomized study. The Rotterdam section of the ERSPC trial demonstrated that after correction for both nonattendance in the screening arm and PSA contamination in the control arm, PSA-based screening conducted in the Dutch center reduced the risk of dying from prostate cancer up to 51% (RR of 0.49; 95% CI, 0.27–0.87) in men who undergo organized screening at a median follow-up of 13 years [17].

In addition, randomized trial has another limitation. The primary end point of the trial is prostate cancer-specific mortality. Therefore, randomized trials would require a considerably long time to withdraw some conclusions. These trials randomly registered asymptomatic, healthy men and had followed until assigned men developed prostatic cancer and, further, died from prostate cancer or other causes. When a result is provided, the diagnostic method that is prostate biopsy method as well as treatment methods usually have progressed.

In addition, the rate of the death from prostate cancer is very low and there is a difficulty in assessing the effect of PSA screening on the prostate cancer-specific mortality. For example, the PLCO trial reported that after 7–10 years of follow-up, the incidence of death per 10,000 person-years was only 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI, 0.75–1.70) [7].

3. Localized, low-grade prostate cancer most often has an indolent character

The majority of prostate cancer patients with early, localized, low-grade cancer with proper treatments most often have an indolent clinical course. An analysis of 828 case records of men treated conservatively (with observation and delayed hormone therapy) for clinically localized prostate cancer showed that 10 years after diagnosis, disease-specific survival was 87% for men with grade 1 or 2 tumors and 34% for those with grade 3 tumors [5]. Most early-stage (T0-T2 NX M0 classification), initially untreated prostate cancer, had an indolent course during the first 10–15 years [6].

4. Patients with some coexisting conditions are more likely to die from causes other than prostate cancer

Patients with some comorbidities were more likely to die from causes other than prostate cancer [18]. The Surveillance, Epidemiology, and End Results (SEER) group conducted a 10-year competing risk analysis of men 66 years age and older with localized prostate cancer and received no surgery and radiation within 180 days of diagnosis and found that relatively few men died as a result of prostate cancer within 10 years of diagnosis [19]. Patients were more likely to die from comorbid causes other than prostate cancer during the first 10 years after diagnosis. Depending on patient age, Gleason score, and number of coexisting conditions, 10-year overall mortality rates increased from 28.8% (95% CI, 25.3–32.6%) to 94.3% (95% CI, 87.4–100%), in contrast, prostate cancer-specific mortality rates varied from 2.0% (95% CI, 0.0–5.3%) to 27.5% (95% CI, 21.5–36.5%). The group reported that most patients with localized prostate cancer older than 65 years would not die from prostate cancer within 10 years of diagnosis. Most prostate cancer patients with either no or one comorbidity would survive at least 10 years; in contrast, those with two or more comorbid conditions would have a substantial risk of dying from a coexisting disease within this time period [19]. Another randomized study demonstrated a similar result. After 10-year follow-up of 76,693 men with prostate cancer, a significant decrease in the risk of prostate cancer-specific mortality was observed in patients with no or minimal comorbidity (adjusted hazard ratio (HR), 0.56; 95% CI, 0.33–0.95; $p = 0.03$); however, no reduction of that was observed in patients with at least one significant comorbidity (adjusted hazard ratio, 1.43; 95% CI, 0.96–2.11; $p = 0.08$). The group concluded that selective use of PSA screening for men in good health appeared to reduce the risk of prostate cancer-specific mortality [20].

5. The AUA updated a guideline concerning early detection of prostate cancer

In 2013, the American Urological Association (AUA) updated clinical guideline regarding PSA screening, "Early detection of Prostate cancer", which recommended a selective PSA screening,

for example, according to age, coexisting medical conditions, or risks such as family history [10]. In addition, the AUA guideline strongly recommended "shared-decision making", which is a thorough discussion between clinicians and patients concerning the risks and benefits of PSA screening and treatment.

Above-mentioned arguments were the main reasons why the AUA recommended against routine PSA screening but for a selected screening and emphasized "shared-decision making". For example, the AUA guideline did not recommend routine PSA screening in 70 years of age or older men.

However, we must pay attention to the fact that the AUA guideline does not address diagnosis of symptomatic patients, where symptoms imply those that could be related to locally advanced or metastatic disease, but detection of disease at an early, pre-symptomatic stage when a man would have no reason to seek medical care.

6. Prostate cancer incidence increases with age

The rate of prostate cancer incidence increases with age. The incidence rate of prostate cancer increases, especially older than 70 years. In the United States, probability of developing prostate cancer for 60–69 years of age, 70 and older, and birth to death were 6.84, 12.54, and 16.48%, respectively [1]. As for in Japan, the Japan Cancer Surveillance Research Group reported that the prostate cancer incidence rate of all ages, crude rate, was 63.1 per 100,000 population in 2004; however, age-adjusted incidence rate increased from 32.2 in the 55- to 59-year-old group to 401.2 in the 80- to 84-year-old group [11].

7. Older men are more likely to be presented with high-risk prostate cancer

Older men are more likely to be presented with high-risk prostate cancer and to have lower cancer-specific survival [12]. A study from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) demonstrated that 26% of men above 75 years of age presented with high-risk prostate cancer and older men were less likely to receive curative treatment, partially explaining the higher prostate cancer-specific mortality rate [12]. Furthermore, post PSA screening follow-up study showed that compared with cancers detected during the screening period for men up to 69 year of age, cancers diagnosed after screening for men beyond 69 year of age were shifted toward more advanced, high-risk cancers with a low rate of low-risk cancers [21]. In addition, an extended follow-up study revealed that even patients with initially low risk tumors showed local progression and distant metastasis and eventually resulted in lethal outcome. A comparative study of early-staged prostate cancer patients between the first 15 years and the next 15–20 years demonstrated a substantial decrease in progression-free survival, from 45.0 to 36.0%; survival without metastases, from 76.9 to 51.2%; and prostate cancer-specific survival, from 78.7 to 54.4% [6]. In addition, the prostate cancer-specific mortality rate increased from 15 per 1000 person-years (95% CI, 10–21) during the first

15 years to 44 per 1000 person-years (95% CI, 22–88) following the first 15 years ($p = 0.01$) [6]. After 32 years of follow-up of this series, 90 (41.4%) cases showed local progression and 41 (18.4%) exhibited progression to distant metastasis [22]. These facts imply that localized prostate cancer most often has an indolent course; however, local progression and distant metastasis could develop over the long term, even among patients considered as low-risk disease at diagnosis.

8. Population-based cohort study reflects the real -world clinical outcome

Population-based cohort study is the second best study design for evidenced-based decision making in medicine. Randomized study searches for an idealized world data, while cohort study uses a real-world clinical data. Different from the randomized trials, the cohort study targets the patients with prostate cancer from the beginning.

Authors conducted a population-based cohort study of pathologically diagnosed prostate cancer patients in Yokosuka City, Japan, between 2001 and 2010 and compared their clinical outcomes until 2013. Prostate cancer patients were divided into two groups: 524 detected by PSA-based screening in Yokosuka City (screening, S group) versus 1044 those detected by opportunistic PSA examinations (non-screening, NS group) [23]. Median age at diagnosis in the S group was significantly lower than that in the NS group: 71 and 73 years of age, respectively ($p < 0.001$). The rate of Gleason score (GS) 8–10 in the S group was significantly lower than that in the NS group: 9.7 and 16.7%, respectively ($p < 0.001$). The rate of patients with metastasis or PSA 100 ng/ml or more in the S group was also significantly lower than that in the NS group: 7.8 and 23.0%, respectively ($p < 0.001$). The group reported 8 (1.5%) prostate cancer deaths in the S group, whereas 70 (6.7 %) deaths in the NS group during the follow-up period. There were 42 (8.0%) deaths from other causes in the S group and 119 (11.4%) such deaths in the NS group. In the study, the group found a significantly higher 10-year cancer-specific survival rate in the S group than in the NS group: 97 and 86%, respectively ($p < 0.001$). The 10-year overall survival rate in the S group was also significantly higher than the NS group, 77 and 64%, respectively ($p < 0.001$). Multivariate Cox regression analysis showed that GS 8–10 was significantly associated with cancer-specific survival rate (HR, 4.808; 95% CI, 1.044–22.14; $p = 0.044$). The significantly lower prevalence of advanced prostate cancer, especially lower prevalence of GS 8–10 in the S group, was considered to be associated with higher cancer-specific survival. Older patients are more likely to have high-risk prostate cancer at diagnosis [12, 21]. The difference in the median age between the two groups was only 2 years; however, this difference might be responsible for the significantly lower prevalence of GS 8–10 prostate cancer in the S group.

Prostate cancer patients are in general more likely to die from coexisting diseases other than prostate cancer [18–20]. This study also demonstrated that overall 5.0% of patients died from prostate cancer, whereas 10.3% died from other causes. However, we must pay attention to the fact that in patients with advanced disease group, metastasis positive, or PSA 100 ng/ml or more, especially in the NS group, the incidence of death from prostate cancer was higher than those from other causes, 22.5 and 13.8%, respectively.

The ERSPC trial demonstrated similar overall survival rates between the intervention and the control arms [8]. In contrast, this real-world analysis revealed a significantly higher 10-year overall survival rate in the S group. The higher cancer-specific survival rate in the S group and the 2 years difference in median age between the two groups might be partly responsible for the higher overall survival rate. In addition, a plausible reason for this difference is considered as follows: the S group might consist of health-conscious men, who are willing to seek PSA screening at their own will, in other words, who are eager to be in good health. PSA screening itself is not a national duty. In fact, the group noticed a significantly lower Charlson comorbidity score in the S group than in the NS group, 0.5 and 1.3, respectively ($p < 0.001$). These factors might be associated with a higher overall survival rate in the S group [23]. PSA-based population screening in Yokosuka City could contribute to reduce the rate of advanced prostate cancer and might help to reduce prostate cancer mortality rate.

Cancer statistical analysis reported that among men, prostate cancer was the most common cancer, accounting for up to 29% of all incident cases and was the second most common (9%) cause of cancer death in the United States in 2012 [1]. While lung and bronchus cancer was the second most common (14%) estimated new cases and the most common (29%) cause of cancer death among men in the United States in 2012 [1]. These figures suggest that at least prostate cancer, totally, is less aggressive than lung and bronchus cancer. In this statistical analysis, disease duration was not clearly shown; however, prostate cancer patients would seem to survive much longer than lung and bronchus patients. Prostate cancer is a highly heterogeneous cancer, ranging from low-grade, slow-growing, and indolent tumors to high grade, rapidly growing, and fatal carcinomas associated with significant morbidity [24].

An ideal tumor marker should be such that it could mainly detect asymptomatic patients with potentially fatal cancers; however, in fact, this would be rather impossible for PSA screening. Because PSA screening is an extremely sensitive examination, it inevitably detects indolent tumors as well as fatal carcinomas. Rather, if PSA screening could not detect a variety of prostate cancers, PSA would have no value as a screening marker for prostate cancer.

Prostate cancer is an extremely heterogeneous cancer, from low-grade, slow-growing, and indolent tumors to high-grade, rapidly growing, and fatal carcinomas. Prostate cancer incidence increases with age. Older men are more likely to be presented with high-grade prostate cancer. Older men are more likely to have comorbid medical conditions, such as diabetes, cardiovascular diseases, and cerebrovascular diseases. Health-conscious men would seek PSA screening. According to these facts, prostate cancer management should be tailored based on an individual patient's health status, coexisting medical conditions, life expectancy, and tumor characteristics [25]. One man argued as follows: the time has come from a "one size fits all" approach to a tailored approach based on an individual patient's health condition [26]. Physicians should be aware of these facts and should use PSA screening to offer the most appropriate approach to prostate cancer management for each patient.

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