Searching for potential surrogate endpoints of overall survival in clinical trials for patients with prostate cancer

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Abstract

Background: The purpose of this study was to investigate the correlation between overall survival (OS) and other clinical outcomes in patients with prostate cancer. Further, we conducted subgroup analysis in the correlation of OS.

Aim: This study intended to investigate potential surrogate endpoints of OS for prostate cancer by examining the correlation between OS and the other endpoints.

Methods: We performed a systematic review through a literature search by computer-based searches of the Medline database (January 1965 and May 2014).

Results: The contents of 115 studies with endpoint as OS were analyzed in our study. Our results showed that 47.8% (55/115) of the studies used progression-free survival as an endpoint besides OS, followed by time to progression (43.5% [50/115]) and PSA response (40.9% [47/115]). Also, the relationship between OS and each surrogate endpoint was examined using the hazard ratio (HR) by a Bayesian hybrid model for random effect multivariate meta-analysis. Our results showed that the endpoint that had the highest correlation with OS was progression-free survival (PFS) with an estimated marginal correlation of 0.939 (95%CI: 0.900, 0.967). Furthermore, our stratified analysis identified PFS in castration-resistant prostate cancer patients (0.937), in sensitive patients (0.932), in none of chemotherapy patients (0.929), in first line of the chemotherapy (0.948), in patients who received no Doce-taxel previously (0.942), in both symptomatic and asymptomatic patients (0.950), in patients who received only chemotherapy (0.956), and in phase III (0.960), time to progression (TTP) in castration-resistant prostate cancer (CRPC) patients (0.942), in metastasis patients (0.948), in both symptomatic and asymptomatic patients (0.953), in patients who received only chemotherapy (0.938), and in Phase III (0.927) as endpoints, which showed a lower limit for 95% CI of estimated marginal correlation ≥0.850 with overall survival.

Conclusions: Our study suggests that PFS is a potential surrogate endpoint of OS in clinical trials for patients with prostate cancer. It also suggests potential surrogate endpoints for CRPC and locally advanced prostate cancer.

KEYWORDS
clinical trial, prostate cancer, surrogate endpoint, survival
INTRODUCTION

Overall survival (OS) is undoubtedly a gold standard endpoint or “hard endpoint” in clinical trials of cancer treatment and intervention. Regulatory authorities in developed countries such as the U.S. Food and Drug Administration (FDA), the European Medical Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA) require OS as an endpoint for a pivotal clinical study included in clinical data package for application for anticancer drugs (New Drug Application [NDA]).

On the other hand, a surrogate endpoint as well as OS might be approved for accelerated oncology approvals. In fact, surrogate endpoints of OS have been studied for breast cancer, colorectal cancer, stomach cancer, lung cancer, kidney cancer, brain tumor, and so on. Also, the Prentice criteria among others have been evaluated as a method to study such surrogate endpoints. A valid surrogate endpoint must satisfy three statistical conditions: the surrogate must be associated with the cancer; the treatment must be associated with the surrogate endpoint; and the surrogate must mediate the association between the treatment and the cancer. Also, drugs can be harmful to patients if results of clinical trials where a surrogate endpoint is used are adopted without validation.

Prostate cancer is a major cause of cancer morbidity and mortality globally, as it is the second most common cancer and the sixth leading cause of cancer death in men. The 2008 global age-standardized incidence and mortality rates for prostate cancer were 27.9 and 7.4 per 100,000 total population, respectively, and the incidence among Asian population has increased in recent years. Also, among the various cancers, prostate cancer is characterized by a much longer life expectancy after diagnosis of the disease. However, regulatory agencies such as the FDA basically require survival as an endpoint leading to approval of drugs for prostate cancer, and surrogate endpoints are not acceptable. Also, it is insufficient for a putative surrogate endpoint only to be strongly correlated with a clinical outcome. For example, prostate-specific antigen (PSA) is a strong prognostic factor for prostate cancer, but PSA endpoints have been found to be inadequate as surrogates of OS. Therefore, it is challenging and very important in prostate cancer to evaluate and explore surrogate endpoints required for approval.

This study is intended to investigate the surrogate endpoints of survival for prostate cancer by examining the correlation between OS and the other endpoints for prostate cancer.

MATERIALS AND METHODS

Search for studies

We performed a systematic review through a literature search by computer-based searches of the Medline (ProQuest) database (January 1965–May 2014). We abstracted studies by including the search keywords of “prostate cancer or prostatic carcinoma” and “randomized” and then abstracted those by including “overall survival” and “other endpoints” in the title, keywords, or abstract. Then, we read full papers and reviewed them one by one to see whether they met the objective of this study. This was conducted by two independent reviewers. To avoid publication bias, unpublished papers (e.g., presentation) were not identified as a full paper. No limitation based on language was defined. We included web information if sufficient information on study design, characteristics of participants, interventions, and outcomes was available. We abstracted the data in accordance with the Preferred Reporting Items for Systemic Review and Meta-analysis Protocols (PRISMA-P).

We investigated package inserts and obtained regulatory information of the United States, EU, and Japan from the FDA (.http://www.fda.gov), the European Medicines Agency (http://www.ema.europa.eu), and the Pharmaceutical and Medical Devices Agency (http://www.pmda.go.jp/english/index.html) websites, respectively.

Procedure

Randomized trials of drug therapy (hormonal drugs, chemotherapeutic drugs, molecular-targeting drugs, vaccine therapy, etc.), radiotherapy, surgery, and their combination for patients with histologically confirmed prostate cancer (locally advanced or metastatic disease) were included in the analysis. Eligibility for the study was limited to trials that included data on OS and data of at least one other endpoint. The other endpoints included the following: progression-free survival (PFS), time to progression (TTP), time to progression or death (TTDP), time to treatment failure (TTTF), and prostate-specific antigen (PSA) response. Exclusion criteria included trials designed to evaluate risk reduction with treatment for OS or other endpoints, and those that did not report either hazard ratios (HRs) or Kaplan-Meier survival curves. For each trial, the following information was extracted: information on the paper (first author’s name, title, issues, pages and year of publication), characteristics of patients (hormone status [hormone-sensitive, castration-resistant], symptoms, status of metastasis, line of chemotherapy, use of Docetaxel), trial design (phase, blinded or not), treatment regimens and number of enrolled patients, and name of trial (if the trial had a name). The following were also extracted if reported: hazard ratio (HR) for clinical endpoints (OS, PFS, TTP, TTTF, ET C.). All data were checked for internal consistency.

Definition of endpoints

OS is defined as the time from randomization until death from any cause, the most commonly used endpoint in Phase III trials. It requires randomized trial with lengthy follow-up and can be affected by subsequent therapies.

PFS is defined as time from randomization to objective tumor progression or death. PFS includes death from any cause as well as progression.

TTP is the time from randomization until objective tumor progression. Unlike PFS, it does not include deaths, but if most deaths are not cancer-related, TTP can be an acceptable endpoint. Like PFS, it is unaffected by subsequent therapies.
TTPP is the time from randomization until PSA progression.

TTTF is a composite endpoint measuring the time from randomization to treatment discontinuation for any reason (disease progression, treatment toxicity, death).

PSA response is defined as the proportion of patients with reduction in PSA by a predefined amount.

### 2.4 Statistical methods

For each trial, the hazard ratios with 95% confidence intervals (CI), median survival times, and survival rates at time points were abstracted. If HRs were not provided, they were estimated as relevant effect measures from the given median survival times or survival rates at time points. The Bayesian hybrid model for random effect multivariate meta-analysis\(^\text{17}\) was used to evaluate surrogacy between the HRs for OS and each endpoint. A frequentist hybrid model for random-effects multivariate meta-analysis was used for sensitivity analysis. No covariates were used in the hybrid models for random effect multivariate meta-analysis. A random effects meta-regression model was used to quantify the association between the natural logarithm of the HRs for OS and each endpoint.\(^\text{18,19}\) All statistical analyses were performed using SAS ver. 9.3 and R ver. 3.6.2 software.

### 3 RESULTS

#### 3.1 Selection of eligible studies

From January 1, 1965 to April 30, 2014, 1974 papers were hit as those including “prostate cancer or prostatic carcinoma” and “randomized” in titles. Then we read the title, abstract, and keywords of the 1974 papers, picked up the ones including “overall survival” and “other endpoints”, and identified 233 papers after the primary selection. The final selection was performed among the 233 papers after reading full papers. In the final selection, 118 papers were excluded because of the absence of control arms (not a comparative study), lacking OS data, including only OS data (no data on endpoints other than OS), a study on screening, a duplicated paper of sub-group analysis/full analysis, or a paper of systematic review. Eventually, 115 papers were identified as eligible for this study (Figure 1). The number of patients involved in the trials of the 115 papers added up to 57,948.

#### 3.2 Endpoints other than OS in eligible studies

We stratified the contents of the eligible 115 studies and analyzed the number of studies and the proportion of the number of studies. We also analyzed what endpoints other than OS were frequently used in the studies (Table 1). Our analysis showed that 47.8% (55/115) of the studies used PFS besides OS as an endpoint, followed by TTP (43.5% [50/115]), and PSA response (40.9% [47/115]). We also analyzed what endpoints other than OS were frequently used in the studies by castration, metastasis, intervention type, and study phase (Table 1). An endpoint in more than two-thirds of the studies used and the number of studies \(\geq 10\) was considered an endpoint frequently used as a trial this time. As a result, the endpoints relatively frequently used in each stratum were PFS in patients who received second- or more-line chemotherapy (81.8% [9/11]), PFS in patients who previously used Docetaxel (90.0% [9/10]), PSA response in castration-resistant prostate cancer (CRPC) (78.2% [43/55]), PSA response in patients who received first-line chemotherapy (71.9%, [23/32]) and...
| Study details         | OS     | PFS    | TTP    | TTPP   | TTTF   | PSA response |
|----------------------|--------|--------|--------|--------|--------|--------------|
| **Castration**       |        |        |        |        |        |              |
| Sensitive            | 60     | 21     | 25     | 15     | 11     | 4            |
| (100.0%)             | (35.0%)| (41.7%)| (25.0%)| (18.3%)| (6.7%)  |              |
| Resistant (CRPC)     | 55     | 34     | 24     | 21     | 3      | 43           |
| (100.0%)             | (61.8%)| (43.6%)| (38.2%)| (5.5%)  | (78.2%) |              |
| **Metastasis**       |        |        |        |        |        |              |
| Locally advanced     | 38     | 12     | 17     | 15     | 8      | 1            |
| (100.0%)             | (31.6%)| (44.7%)| (39.5%)| (21.1%)| (2.6%)  |              |
| Metastasis           | 59     | 39     | 23     | 17     | 4      | 38           |
| (100.0%)             | (66.1%)| (39.0%)| (28.8%)| (6.8%)  | (64.4%) |              |
| Both                 | 18     | 4      | 9      | 4      | 2      | 8            |
| (100.0%)             | (22.2%)| (50.0%)| (22.2%)| (11.1%)| (44.4%) |              |
| **Number of line**   |        |        |        |        |        |              |
| First                | 32     | 19     | 13     | 11     | 2      | 23           |
| (100.0%)             | (59.4%)| (40.6%)| (34.4%)| (6.3%)  | (71.9%) |
| Second or more       | 11     | 9      | 6      | 6      | 0      | 10           |
| (100.0%)             | (81.8%)| (54.5%)| (54.5%)| (0.0%)  | (90.9%) |
| None                 | 72     | 27     | 30     | 19     | 12     | 14           |
| (100.0%)             | (37.5%)| (41.7%)| (26.4%)| (16.7%)| (19.4%) |
| **Docetaxel**        |        |        |        |        |        |              |
| +                    | 10     | 9      | 6      | 5      | 0      | 9            |
| (100.0%)             | (90.0%)| (60.0%)| (50.0%)| (0.0%)  | (90.0%) |
| −                    | 104    | 45     | 42     | 31     | 14     | 38           |
| (100.0%)             | (43.3%)| (40.4%)| (29.8%)| (13.5%)| (36.5%) |
| Unknown              | 1      | 1      | 1      | 0      | 0      |              |
| (100.0%)             | (100.0%)| (100.0%)| (0.0%)  | (0.0%)  | (0.0%)  |
| **Symptom**          |        |        |        |        |        |              |
| Asymptomatic         | 40     | 12     | 20     | 15     | 9      | 1            |
| (100.0%)             | (30.0%)| (50.0%)| (37.5%)| (22.5%)| (2.5%)  |
| Symptomatic          | 5      | 2      | 3      | 3      | 0      | 3            |
| (100.0%)             | (40.0%)| (60.0%)| (60.0%)| (0.0%)  | (60.0%) |
| Both                 | 61     | 36     | 24     | 18     | 4      | 39           |
| (100.0%)             | (59.0%)| (39.3%)| (29.5%)| (6.6%)  | (63.9%) |
| Unknown              | 9      | 5      | 2      | 0      | 1      | 4            |
| (100.0%)             | (55.6%)| (22.2%)| (0.0%)  | (11.1%)| (44.4%) |
| **Intervention**     |        |        |        |        |        |              |
| Hormone therapy      | 31     | 12     | 13     | 8      | 6      | 5            |
| (100.0%)             | (38.7%)| (41.9%)| (25.8%)| (19.4%)| (16.1%) |
| Chemotherapy         | 57     | 33     | 22     | 16     | 2      | 41           |
| (100.0%)             | (57.9%)| (38.6%)| (28.1%)| (3.5%)  | (71.9%) |
| Radiotherapy         | 18     | 5      | 8      | 10     | 5      | 1            |
| (100.0%)             | (27.8%)| (44.4%)| (55.6%)| (27.8%)| (5.6%)  |
| Surgery              | 3      | 0      | 3      | 0      | 0      |              |
| (100.0%)             | (0.0%)  | (100.0%)| (0.0%)  | (0.0%)  | (0.0%)  |
| Combination          | 1      | 1      | 0      | 1      | 0      |              |
| (100.0%)             | (100.0%)| (100.0%)| (100.0%)| (100.0%)| (100.0%)|
| Others*              | 5      | 4      | 3      | 1      | 1      | 0            |
| (100.0%)             | (80.0%)| (60.0%)| (20.0%)| (20.0%)| (0.0%)  |
| **Phase**            |        |        |        |        |        |              |
| 2                    | 21     | 12     | 5      | 5      | 2      | 17           |
| (100.0%)             | (57.1%)| (23.8%)| (23.8%)| (9.5%)  | (81.0%) |
| 3                    | 60     | 33     | 28     | 23     | 4      | 26           |
| (100.0%)             | (55.0%)| (46.7%)| (38.3%)| (6.7%)  | (43.3%) |
second- or more-line chemotherapy (90.9% [10/11]), PSA response in patients who previously used Docetaxel (90.0% [9/10]), PSA response in clinical studies of chemotherapy (71.9% [41/57]), and PSA response in Phase II studies (81.0% [17/21]).

### 3.3 Examination of the correlation between OS and each endpoint in terms of HR

We examined the correlation between OS and the following endpoints in terms of HR: progression-free survival (PFS), time to progression (TTP), time to prostate-specific antigen progression (TTPP), and time to treatment failure (TTTF). As a result, PFS had the highest correlation with OS in all prostate cancer patients with an estimated marginal correlation of 0.930 (95%CI: 0.889, 0.958) by the Bayesian hybrid model for random effect multivariate meta-analysis (Table 2). The sensitivity frequentist analysis also showed similar results (Table 2).

We also examined the correlation between OS and HR for either PFS, TTP, TTPP, or TTTF by stratum. The results are shown in Table 2. As a reference for a high estimated marginal correlation, a lower limit for 95%CI of the estimated marginal correlation ≥0.850 are shown in italic type and underlined in Table 2. High estimated marginal correlation between OS and PFS were seen in all prostate cancer patients (0.930, 95%CI: 0.889, 0.958), in CRPC patients (0.937, 95%CI: 0.873, 0.973), in sensitive patients (0.932, 95%CI: 0.865, 0.968), in none of the chemotherapy patients (0.929, 95%CI: 0.863, 0.967), in first line of chemotherapy (0.948, 95%CI: 0.863, 0.984), in patients who received no previous Docetaxel (0.942, 95%CI: 0.895, 0.970), in both symptomatic and asymptomatic patients (0.950, 95%CI: 0.902, 0.976), in patients who received only chemotherapy (0.956, 95%CI: 0.904, 0.981), and in phase III (0.960, 95%CI: 0.922, 0.981). Also, high estimated marginal correlations between OS and TTP were seen in CRPC patients (0.942, 95%CI: 0.893, 0.970), in metastasis patients (0.948, 95%CI: 0.902, 0.973), in both symptomatic and asymptomatic patients (0.953, 95%CI: 0.908, 0.977), in patients who received only chemotherapy (0.938, 95%CI: 0.879, 0.969), and in phase III (0.927, 95%CI: 0.864, 0.964).

In addition, we examined the association between the natural logarithm of HR for OS and each endpoint using a random effect meta-regression model. In the case of OS and PFS, the random effects meta-regression model adjusted for estimation errors was as follows:

\[
\log(\text{HR of OS}) = 0.011 + 0.545 \times \log(\text{HR of PFS}).
\]

The 95% CIs were (−0.040, 0.061) and (0.397, 0.693) for the intercept and slope, respectively. The 95% prediction interval was (0.361, 0.731) for slope. The equation predicted a 54.5% increase in the log HR of OS for every unit increase in the log HR of PFS. The surrogate threshold effect (STE) was 0.512 (Figure 2). The association between the natural logarithm of HR for OS and TTP/TTPP/TTTF is given in Figures 3–5.

### 4 DISCUSSION

The endpoint supported by almost all drug approvals by the FDA to date is survival. The exceptions are Estramustine approved in 1981 itself; Degarelix, a drug for androgen deprivation therapy; Zoledronic acid; and Denosumab, an inhibitor of bone resorption for prostate cancer bone metastases. No other drug than the four drugs listed above has been approved based on an overall survival endpoint by the FDA.

For Leuprolide acetate and Goserelin acetate, drugs for androgen deprivation therapy for patients with hormone-sensitive prostate cancer, clinical trials were conducted using OS as an endpoint, while the subsequent drug, Degarelix, was submitted for approval with a surrogate endpoint of suppressing serum testosterone levels to castrate levels and maintaining castrate levels in patients with hormone-dependent prostate cancer. Clinical symptomatic improvement and antitumor effects were observed by suppressing serum testosterone levels to castrate levels, which shows clinical benefits comparable to orchietomy. Zoledronate and Denosumab for prostate cancer bone metastases were approved based on skeletal-related events. Surrogate endpoints in prostate cancer were frequently debated within the FDA and NCI around 2004. Also, several studies on surrogates for OS in prostate cancer have been conducted to date and the following have been reported: 30% PSA decrease is a surrogate of OS in CRPC patients in first-line chemotherapy and it meets the Prentice criteria, but 30% PSA decrease cannot be a surrogate endpoint as it does not meet the Prentice criteria in second-line chemotherapy (Cabazitaxel). While surrogate endpoints for mCRPC are needed and various surrogate endpoints have been studied, it is still challenging, and there is no particular surrogate endpoint. For example, PFS is not a good surrogate marker of OS for mCRPC. PSA is not a good surrogate marker for HSPC. TTP (time to PSA progression) could
### TABLE 2  Relationship between overall survival (OS) and potential factors in hazard ratio (HR)

|                      | PFS         | TTP         | TTPP        | TTTF        |
|----------------------|-------------|-------------|-------------|-------------|
| All prostate cancer  | Estimated marginal correlation 0.939 (0.900, 0.967) | 0.896 (0.839, 0.935) | 0.652 (0.338, 0.847) | 0.857 (0.687, 0.948) |
|                      | Estimated marginal correlation (Frequentist) 0.952 (0.911, 0.979) | 0.901 (0.844, 0.939) | 0.737 (0.460, 0.910) | 0.849 (0.677, 0.941) |
|                      | Number of papers 55 | 50 | 36 | 14 |
|                      | Number of patients 33 781 | 30 059 | 25 406 | 6870 |
| Castration Resistant (CRPC) | Estimated marginal correlation 0.937 (0.873, 0.973) | 0.942 (0.893, 0.970) | 0.530 (−0.450, 0.853) | 0.027 (−0.968, 0.958) |
|                      | Number of papers 34 25 | 21 3 | 15 | 11 |
|                      | Number of patients 21 089 | 16 729 | 13 836 | 1257 |
| Sensitive           | Estimated marginal correlation 0.932 (0.865, 0.968) | 0.847 (0.692, 0.933) | 0.725 (0.301, 0.920) | 0.905 (0.757, 0.970) |
|                      | Number of papers 21 | 25 | 15 | 11 |
|                      | Number of patients 12 692 | 13 300 | 11 570 | 5613 |
| Metastasis Locally advanced | Estimated marginal correlation 0.935 (0.838, 0.975) | 0.773 (0.334, 0.922) | 0.675 (0.201, 0.913) | 0.897 (0.612, 0.982) |
|                      | Number of papers 12 | 17 | 15 | 8 |
|                      | Number of patients 10 649 | 11 087 | 12 086 | 4702 |
| Metastasis          | Estimated marginal correlation 0.903 (0.840, 0.946) | 0.948 (0.902, 0.973) | 0.717 (0.479, 0.861) | 0.415 (−0.881, 0.967) |
|                      | Number of papers 39 | 24 | 17 | 4 |
|                      | Number of patients 22 299 | 15 945 | 12 265 | 1540 |
| Both                | Estimated marginal correlation 0.864 (−0.499, 0.998) | 0.908 (0.084, 0.996) | 0.582 (−0.899, 0.998) | −0.110 (−1.000, 0.998) |
|                      | Number of papers 4 | 9 | 4 | 2 |
|                      | Number of patients 833 | 3027 | 1055 | 628 |
| Line of chemotherapy | None        | Estimated marginal correlation 0.929 (0.863, 0.967) | 0.882 (0.787, 0.941) | 0.500 (−0.135, 0.837) | 0.911 (0.746, 0.976) |
|                      | Number of papers 27 | 30 | 19 | 12 |
|                      | Number of patients 15 503 | 15 004 | 13 125 | 6701 |
|                    | Estimated marginal correlation 0.948 (0.863, 0.984) | 0.863 (0.588, 0.959) | 0.024 (−0.887, 0.919) | 0.144 (−0.957, 0.988) |
|                      | Number of papers 19 | 14 | 11 | 2 |
|                      | Number of patients 10 849 | 9920 | 6976 | 169 |
|                   | Estimated marginal correlation 0.838 (−0.462, 0.995) | −0.187 (−0.984, 0.973) | −0.079 (−0.989, 0.989) | 0.003 (−0.996, 0.996) |
|                      | Number of papers 9 | 6 | 6 | 0 |
|                      | Number of patients 7429 | 5135 | 5305 | 0 |
| PreviousDocetaxel Yes (+) | Estimated marginal correlation 0.917 (0.602, 0.986) | 0.812 (−0.533, 0.984) | 0.876 (−0.745, 0.997) | 0.006 (−0.996, 0.996) |
|                      | Number of papers 9 | 6 | 5 | 0 |
|                      | Number of patients 7429 | 5135 | 5265 | 0 |
|                    | Estimated marginal correlation 0.942 (0.895, 0.970) | 0.883 (0.810, 0.930) | 0.558 (0.080, 0.823) | 0.833 (0.620, 0.945) |
|                      | Number of papers 45 | 43 | 31 | 14 |
|                      | Number of patients 26 026 | 24 598 | 20 141 | 6870 |
| Unknown             | Estimated marginal correlation 0.029 (−0.995, 0.997) | 0.005 (−0.996, 0.996) | 0.000 (−0.996, 0.996) | 0.000 (−0.996, 0.996) |
| Intervention        | Estimated marginal correlation | Number of papers | Number of patients |
|---------------------|--------------------------------|------------------|-------------------|
| Hormone therapy     | 0.832 (0.459)                  | 12               | 7723              |
|                     | 0.758 (0.557)                  | 13               | 8887              |
|                     | 0.760 (0.002)                  | 8                | 611               |
|                     | 0.932 (0.583)                  | 6                | 242               |
| Chemotherapy        | 0.956 (0.904)                  | 33               | 24841             |
|                     | 0.938 (0.879)                  | 23               | 1558              |
|                     | 0.748 (0.123)                  | 10               | 11705             |
|                     | 0.149 (−0.959)                 | 5                | 21                |
| Radiotherapy        | 0.668 (−0.782)                 | 5                | 1615              |
|                     | 0.591 (−0.576)                 | 8                | 1287              |
|                     | −0.390 (−0.893)                | 16               | 9373              |
|                     | 0.398 (−0.877)                 | 6                | 919               |
| Surgery             | −0.001 (−0.996)                | 1                | 42                |
|                     | −0.646 (−1.000)                | 2                | 799               |
|                     | −0.001 (−0.996)                | 1                | 799               |
|                     | −0.003 (−0.996)                | 1                | 799               |
| Others              | 0.150 (−0.998)                 | 0                | 1940              |
|                     | 0.007 (−0.997)                 | 0                | 1940              |
|                     | −0.007 (−0.998)                | 0                | 1940              |
|                     | 0.001 (−0.996)                 | 0                | 1940              |
| Combination         | 0.016 (0.095)                  | 0                | 0                 |
|                     | 0.022 (0.096)                  | 0                | 0                 |
|                     | 0.010 (0.095)                  | 0                | 0                 |
|                     | 0.001 (0.096)                  | 0                | 0                 |
| Unknown             | 0.599 (−0.908)                 | 5201             | 452               |
|                     | 0.041 (−0.991)                 | 24               | 452               |
|                     | 0.012 (−0.996)                 | 36               | 452               |
|                     | −0.007 (−0.996)                | 1017             | 452               |
|                     | 0.993 (0.836)                  | 1017             | 452               |
|                     | 0.751 (0.407)                  | 1017             | 452               |
|                     | 0.722 (0.308)                  | 1017             | 452               |
|                     | 0.846 (0.522)                  | 1017             | 452               |

(Continued)
be a surrogate for HSPC, but the correlation coefficient is not high.26
PSA is not a good surrogate marker for CRPC or HRPC.27 Not many
patients with prostate cancer (CRPC) can be evaluated by RECIST.
PSA and tumor shrinkage cannot be a good surrogate marker.28
Patient-reported outcome (PRO) or circulating tumor cells (CTC) can-
not be a marker permitted by a regulatory authority for monitoring.29
In addition to the above reports, there is debate about surrogate end-
points for cancer within the FDA and NCI, but no particular conclu-
sions on surrogate endpoints for OS have been drawn so far.30

There are numerous advantages in using surrogate endpoint in
comparison to those in using OS: (1) It takes less time for completion
of trials; (2) Drug approval takes shorter time; (3) Patients can receive
novel therapies faster; (4) More frequent measurements can be made;
(5) It provides insights into clinical pharmacology and mechanisms of
action; (6) It provides guidance for dose selection; (7) More efficient
screening of promising drug candidates is possible; and (8) It costs less
to the manufacturer or sponsor.

This study analyzed, to our knowledge, most clinical trials of the
1974 papers identified by a comprehensive literature search for surro-
gate endpoints in prostate cancer.

We analyzed the contents of 115 studies and showed that 47.8%
(55/115) of the studies used PFS besides OS as an endpoint, followed
by TTP (43.5% [50/115]) and PSA response (40.9% [47/115]). Also, the
correlation between OS and each surrogate endpoint in terms of HR
was examined by the Bayesian hybrid model for random effect multi-
variate meta-analysis, and the endpoint with the highest correlation
with OS was PFS with an estimated marginal correlation of 0.930 (95%
CI: 0.908, 0.958). The sensitivity frequentist analysis also showed similar
results. The random effect meta-regression model predicted a 54.5%
increase in the log HR of OS for every unit increase in the log HR of
PFS. Furthermore, PFS in CRPC patients (0.937, 95%CI: 0.873, 0.973),
in sensitive patients (0.932, 95%CI: 0.865, 0.968), in none of chemo-
therapy patients (0.929, 95%CI: 0.863, 0.967), in first line of the chemo-
therapy (0.948, 95%CI: 0.863, 0.984), in patients who received no
Docetaxel previously (0.942, 95%CI: 0.895, 0.970), in both symptomatic
and asymptomatic patients (0.950, 95%CI: 0.902, 0.976), in patients
who received only chemotherapy (0.956, 95%CI: 0.904, 0.981), in phase
III (0.960, 95%CI: 0.922, 0.981), TTP in CRPC patients (0.942, 95%:
0.893, 0.970), in metastasis patients (0.948, 95%CI: 0.902, 0.973), in
both symptomatic and asymptomatic patients (0.953, 95%CI: 0.908, 0.977),
in patients who received only chemotherapy (0.938, 95%: 0.879, 0.969), and in phase III (0.927, 95%CI: 0.864, 0.964) showed a
high estimated marginal correlation with OS in our stratified analysis.

Our study showed how to interpret results of clinical trials where
a surrogate endpoint is used and the possibility and adequacy of sur-
grogate endpoints meeting the approval requirements in conducting
clinical trials for prostate cancer. We believe these findings will be
indicators when planning clinical trials that use surrogate endpoints
for conducting clinical trials for prostate cancer and may be used as
interpretation of results and as approval requirements. We strongly
hope that it would lead to conducting efficient and quick clinical trials
to deliver innovative drugs to patients even if a day sooner.

This study has several methodological limitations. First, this is not
a study based on data obtained from individual patients and is a post
hoc analysis of data contained in papers, which means that it is better
to compare individual-level data for comparing data of two endpoints.
We intend to study this additionally in the future. Second, not all stud-
ies report all secondary endpoints examined this time, and paper
selection bias might be present. Although we estimated HRs as rele-
vant effect measures from the given median survival times or survival
rates at time points if the HRs were not provided, this assumption
might be strong. Third, this study examined trial-level surrogacy in a
long-term (1965–2014) clinical trial. It did not take into account changes in standard treatment or disease status over time, and it did not examine individual-level surrogacy. Finally, since not all trials reported information on subset analysis, such as CRPC, lines, Docetaxel, and so on, our results, which were derived from or referred to these variables, are likely insufficient.

**FIGURE 2** Hazard ratio of overall survival (OS) and progression-free survival (PFS) in 55 prostate cancer trials. The random effects meta-regression model adjusted for estimation errors was as follows: log(HR of OS) = 0.011 + 0.545 × log(HR of PFS). The 95%CIs were (0.040, 0.061) and (0.397, 0.693) for the intercept and slope, respectively. The 95% prediction interval was (0.095, 0.520) for slope. The regression line is shown in solid line and the 95% prediction boundaries are in dotted line. The surrogate threshold effect (STE) was 0.144

**FIGURE 3** Hazard ratio of overall survival (OS) and time to progression (TTP) in 50 prostate cancer trials. The random effects meta-regression model adjusted for estimation errors was as follows: log(HR of OS) = −0.006 + 0.308 × log(HR of TTP). The 95%CIs were (−0.040, 0.016) and (0.099, 0.507) for the intercept and slope, respectively. The 95% prediction interval was (0.095, 0.520) for slope. The regression line is shown in solid line and the 95% prediction boundaries are in dotted line. The surrogate threshold effect (STE) was 0.011

**FIGURE 4** Hazard ratio of overall survival (OS) and time to prostatic specific antigen progression (TTPP) in 36 prostate cancer trials. The random effects meta-regression model adjusted for estimation errors was as follows: log(HR of OS) = −0.05 + 0.272 × log(HR of TTPP). The 95%CIs were (−0.144, 0.037) and (0.145, 0.398) for the intercept and slope, respectively. The 95% prediction interval was (0.119, 0.424) for slope. The regression line is shown in solid line and the 95% prediction boundaries are in dotted line. The surrogate threshold effect (STE) was 0.023

**FIGURE 5** Hazard ratio of overall survival (OS) and time to treatment failure (TTTF) in 14 prostate cancer trials. The random effects meta-regression model adjusted for estimation errors was as follows: log(HR of OS) = −0.063 + 0.301 × log(HR of TTTF). The 95%CIs were (−0.219, 0.093) and (0.071, 0.530) for the intercept and slope, respectively. The 95% prediction interval was (0.119, 0.424) for slope. The regression line is shown in solid line and the 95% prediction boundaries are in dotted line. The surrogate threshold effect (STE) was 0.135
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AUTHOR CONTRIBUTIONS
Hideki Maeda: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; visualization; writing-original draft; writing-review and editing. Kentaro Takeda: Conceptualization; data curation; formal analysis; investigation; methodology; resources; software; supervision; validation; visualization; writing-original draft; writing-review and editing. Hisashi Urushihara: Project administration; resources; supervision; validation; writing-original draft; writing-review and editing. Tatsuo Kurokawa: Conceptualization; funding acquisition; project administration; resources; supervision; validation; visualization; writing-original draft; writing-review and editing.

CONFLICT OF INTEREST
Kentaro Takeda is an employee of Astellas Pharma Global Development, Inc. Other authors have no conflict of interest.

ETHICAL STATEMENT
Institutional ethics approval and patient consent were not required for this study.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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