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Koichiro AKAKURA, and Kazuyuki AIHARA

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DEPARTMENT OF MATHEMATICAL INFORMATICS
GRADUATE SCHOOL OF INFORMATION SCIENCE AND TECHNOLOGY
THE UNIVERSITY OF TOKYO
BUNKYO-KU, TOKYO 113-8656, JAPAN

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Castration Resistance Implies the Existence of Metastasis in Prostate Cancer

Yoshito Hirata[1-4*], Kai Morino[1,3], Chris J. O'Callaghan[5], S. Larry Goldenberg[6], Celestia S. Higano[7], Keyue Ding[5], Koichiro Akakura[8], and Kazuyuki Aihara[1,3,4**]

[1]Institute of Industrial Science, The University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan; [2]Mathematics and Informatics Center, [3]Graduate School of Information Science and Technology, and [4]International Research Center for Neuro-intelligence (IRCN), The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan; [5]Canadian Cancer Trials Group (CCTG), Queen's Univeristy, Kingston, ON, Canada; [6]The Department of Urologic Sciences, University of British Columbia and Vancouver Prostate Centre, Vancouver, BC, Canada; [7]Department of Medicine, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington, USA; [8]Department of Urology, JCHO Tokyo Shinjuku Medical Center, Japan Community Health Care Organization Tokyo, Japan.

[*]hirata@mist.i.u-tokyo.ac.jp
[**]aihara@sat.t.u-tokyo.ac.jp

Prostate cancer is initially sensitive to androgen deprivation therapy, which lowers the testosterone in the body to castrate levels. However, cancer acquires the ability to survive despite the castrate levels of testosterone[1]. This phenomenon is called castration resistance, and its prognosis is poor because a relapse often follows. Another problem is metastasis[2], where the cancer cells spread to another organ. Currently under question is whether there exist nonmetastatic castration-resistant cancer cells[3]. However, a solid answer for this question has not been provided. Here, we approach this question by using mathematical models of prostate cancer[4,5] and clinical datasets[6–9] including a phase-3 study of intermittent androgen suppression[9]. A multinomial logistic regression analysis[10] shows that events of metastasis are related to a higher growth rate for castration-resistant cells, while metastasis and castration resistance are not significantly different in the set of estimated parameters from a series of tumor markers called prostate-specific antigens. When we predict an event of metastasis or castration resistance by the above logistic regression models, the prediction accuracy is improved compared with cases

where an event of metastasis or castration resistance is predicted separately. Further, if we use a two-compartment model to explicitly consider metastasis, then the predictability for a relapse is ameliorated. The above results imply that metastasis and castration resistance are different aspects of the same phenomenon, and that castration-resistant prostate cancer should be treated in a similar way to metastatic prostate cancer, as empirically demonstrated in refs. 11 and 12.

Prostate cancer is an ideal disease for formulating a mathematical model quantitatively because of the following two facts related to observation and control: (i) there is a good quantitative tumor marker called prostate-specific antigen[13] (PSA), which is considered to be proportional to the tumor volume and (ii) androgen deprivation therapy reduces the tumor volume only temporarily[1]. By observing the PSA values with time, androgen deprivation therapy is stopped and resumed repeatedly in intermittent androgen suppression[14,9,15] so that we can prolong the time to a relapse. A number of papers have been published that discuss mathematical modeling for the intermittent androgen suppression of prostate cancer[16,17,4,18–20]. Based on comparison studies[21,22], we use one of the models[4] to study the relationship between castration resistance[1] and metastasis[2], two of the main reasons that prostate cancer is deadly (see Methods section for details about the model of ref. 4).

A simple comparison between the events of castration resistance and metastasis in the phase-3 study of ref. 9 is given in Table 1. These events agreed in (474 + 117) / 690 ~ 86% of the cases. Thus, the relationship between the castration resistance and metastasis does not seem to be random coincidence. This is the first evidence that castration resistance is related to metastasis.

Multinomial logistic regression analysis[10] that connects the end-of-study status with the fitted parameters from PSA measurements obtained by the Bayesian method[5] shows that the growth rate of $w_{3,3}^{1}$ for castration-resistant cancer cells mainly contributes to the prediction of metastasis detection (see the second column of Supplementary Table 1). This is the second piece of evidence that the castration resistance is directly related to the metastasis.

In addition, there are no significant differences in the fitted parameters when the end state is metastasis or castration resistance (observe this point again in the third column of Supplementary Table 1). Thus, at least, the mathematical model of ref. 4 cannot distinguish the metastasis from castration resistance. This yields the third piece of evidence that the castration resistance and metastasis are strongly related.

If we combine the events of metastasis and castration resistance, then the probabilistic predictability for the events is improved (Fig. 1 and Supplementary Tables 2 and 3). Because the Brier scores[23] are inferior to the cases where we supply a constant probability for all of the patients (Supplementary Table 2), the score values themselves do not have much meaning. However, the results compared with cases where patient outcomes (metastasis, castration resistance, or both) for each patient are randomly paired with the estimated probabilities for some patient (Fig. 1 and Supplementary Table 3) mean that it is difficult to distinguish the events of metastasis from those of castration resistance. This is the fourth piece of evidence.

In addition, we constructed an index for progression. Here, using the datasets of refs. 6, 7, and 8 as training data, we checked the direction in which the mean for each estimated parameter moves when we narrow the population of patients to a subpopulation where all patients are classified as lacking castration resistance or metastasis. Then, for each patient of the test datasets of ref. 9, we counted the number of estimated parameters that are in the same sides with the parameters for the subpopulation of "without relapse" when the overall mean for each parameter is used as the dividing point. Therefore, if the index number is smaller, then the condition for the patient seems to be more severe. The results are presented in Supplementary Tables 4–7 and Extended Data Fig. 1. The areas under the receiver operative characteristic (ROC) curves[24] for the castration resistance, metastasis, or either of them are not much different, implying that there is no clear distinction between the castration resistance and metastasis.

When we conducted similar analyses by counting the number of estimated

parameters that move in the directions of the subpopulation of the castration resistance or metastasis in the training data, the area under the ROC curves did not show much difference among the characterizations of the castration resistance, metastasis, or either of them (Supplementary Tables 8 and 9, respectively). Hence, using the above proposed indexes, we conclude that there is not much difference between the events of castration resistance and metastasis.

Moreover, we constructed a two-compartment model to explicitly express the states of metastasis (see Methods section for details about the mathematical model). We found that the two-compartment model ameliorated the predictability for castration resistance but not for metastasis (Supplementary Table 3 and Fig. 1). Moreover, the two-compartment model did not improve the time-series prediction of PSA (Fig. 2 and Extended Data Fig. 2). In addition, the proposed indexes using this two-compartment model improved the areas under the ROC curves (AUC) for both the castration resistance and metastasis (Supplementary Table 7). These counterintuitive results mean that castration resistance and metastasis are not separable.

Even when we modified the original model from the viewpoint of evolutionary game theory[23] (see Methods section), we could not improve the overall results (Supplementary Table 3 and Fig. 1). In particular, although this model improved the prediction of PSA (Fig. 2 and Extended Data Fig. 2), the model itself did not improve the AUC when we used the proposed indexes for scoring the progression (Supplementary Table 7). These results mean that the original model of ref. 4 is Pareto-optimal. Therefore, if we combine all three models to produce the proposed indexes with the subpopulation of "without relapse," then the AUCs show the most improvement (Supplementary Table 7 and Fig. 3).

Even when we combined all three models to produce the AUCs in Supplementary Table 7, the AUCs were about 0.67, which was far from 1 (the perfect case). These results probably occurred because the end state for the phase-3 study was a snapshot for the ongoing process of the progression for each patient.

Based on the current research, the next question is, "How can metastasis appear?" It is widely known that metastasis may exist before hormone therapy is begun. We think that metastasis might appear naturally because prostate cancer can grow through mutations, for example. In fact, the estimated initial volume $\sum_{i=4}^{6} y_i(0)$ for metastasized cancer cells in the two-compartment model for all of the patients in this study was positive and different from 0 (see the Methods section for the mathematical definition of y_i). Therefore, metastasis could be a natural consequence of the progression of prostate cancer.

Summarizing the above results, we reached the conclusion that metastasis and castration resistance are two different consequences of the same process. Although the detailed process should be investigated more from a genomic perspective, this conclusion tentatively means that we should treat castration-resistant prostate cancer in a similar way to metastatic prostate cancer even if the metastasis is not of a detectable size.

Methods

Patient data. All patients provided written informed consent for their participation in the PR.7 trial and ethics committees of participating institutions approved the use of their data. The analysis of these patients' datasets was approved by the ethics committee of the University of Tokyo.

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Original mathematical model of ref. 4. Suppose that x_1 corresponds to the androgen-dependent prostate cancer cells, x_2 corresponds to the castration-resistant prostate cancer cells generated via reversible changes, and x_3 corresponds to the castration-resistant cancer cells generated via irreversible changes. In addition, assume that x_1, x_2, and x_3 are scaled so that $\sum_{i=1}^{3} x_i(t)$ becomes the value of the prostate-specific antigen (PSA) in ng/mol. Then, the underlying dynamics are supposed to follow these equations:

$$\frac{d}{dt}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} {w_{1,1}}^1 & 0 & 0 \\ {w_{2,1}}^1 & {w_{2,2}}^1 & 0 \\ {w_{3,1}}^1 & {w_{3,2}}^1 & {w_{3,3}}^1 \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix},$$

for on-treatment periods, and

$$\frac{d}{dt}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} {w_{1,1}}^0 & {w_{1,2}}^0 & 0 \\ 0 & {w_{2,2}}^0 & 0 \\ 0 & 0 & {w_{3,3}}^0 \end{pmatrix}\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix},$$

for off-treatment periods. The parameters for the models are fitted using Bayes' formula in the same way as ref. 5 using the first 1.5 cycles of intermittent androgen suppression (the code in C is provided in the Supplementary Information of ref. 5). The prior distribution is set to that used in ref. 5 exactly.

We constructed a two-compartment model by extending the model of ref. 4. A compartment corresponds to the prostate, and the other compartment, corresponding to another organ. The assumption here is that in the other organ, the concentration of the androgen level is always low. Then, we can extend the model in the following way:

$$\frac{d}{dt}\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \end{pmatrix} = \begin{pmatrix} {w_{1,1}}^1 & 0 & 0 & \mu_o & 0 & 0 \\ {w_{2,1}}^1 & {w_{2,2}}^1 & 0 & 0 & \mu_o & 0 \\ {w_{3,1}}^1 & {w_{3,2}}^1 & {w_{3,3}}^1 & 0 & 0 & \mu_o \\ \mu_p & 0 & 0 & {w_{1,1}}^1 & 0 & 0 \\ 0 & \mu_p & 0 & {w_{2,1}}^1 & {w_{2,2}}^1 & 0 \\ 0 & 0 & \mu_p & {w_{3,1}}^1 & {w_{3,2}}^1 & {w_{3,3}}^1 \end{pmatrix}\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \end{pmatrix},$$

for on-treatment periods, and

$$\frac{d}{dt}\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \end{pmatrix} = \begin{pmatrix} {w_{1,1}}^0 & {w_{1,2}}^0 & 0 & \mu_o & 0 & 0 \\ 0 & {w_{2,2}}^0 & 0 & 0 & \mu_o & 0 \\ 0 & 0 & {w_{3,3}}^0 & 0 & 0 & \mu_o \\ \mu_p & 0 & 0 & {w_{1,1}}^1 & 0 & 0 \\ 0 & \mu_p & 0 & {w_{2,1}}^1 & {w_{2,2}}^1 & 0 \\ 0 & 0 & \mu_p & {w_{3,1}}^1 & {w_{3,2}}^1 & {w_{3,3}}^1 \end{pmatrix}\begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \end{pmatrix}.$$

for off-treatment periods. Here y_1, y_2, and y_3 correspond to the variables of the prostate, and y_4, y_5, and y_6 correspond to the variables of the other organ. Now, we assume that the PSA is described as $\sum_{i=1}^{6} y_i(t)$, while the number of metastasized cancer cells at time t is proportional to $\sum_{i=4}^{6} y_i(t)$.

We fitted this mathematical model in a similar way as ref. 5 with the same prior distribution for the model of ref. 4 as above. This fitting procedure means that $y_4(0)$, $y_5(0)$, $y_6(0)$, μ_p, and μ_o are not constrained except that they are nonnegative. We used the first 1.5 cycles of the PSA values to fit the patients.

Evolutionary-game theoretical model. We further extended the model of ref. 4 by taking into account the evolutionary dynamics[25], especially the replicator dynamics[26], and introducing interactions with normal cells at the prostate. Let z_0 correspond to the

variable related to the normal prostate cells. The other interpretations are similar to those in the model of ref. 4. Then, we derived the following equations:

$$\frac{d}{dt}\begin{pmatrix} z_0 \\ z_1 \\ z_2 \\ z_3 \end{pmatrix} = \begin{pmatrix} z_0 \\ z_1 \\ z_2 \\ z_3 \end{pmatrix} .* \left\{ \begin{pmatrix} 0 & -\gamma_1 & 0 & 0 \\ \gamma_1 & {w_{1,1}}^1 & 0 & 0 \\ 0 & {w_{2,1}}^1 & {w_{2,2}}^1 & 0 \\ 0 & {w_{3,1}}^1 & {w_{3,2}}^1 & {w_{3,3}}^1 \end{pmatrix} \begin{pmatrix} z_0 \\ z_1 \\ z_2 \\ z_3 \end{pmatrix} \right\},$$

for on-treatment periods, and

$$\frac{d}{dt}\begin{pmatrix} z_0 \\ z_1 \\ z_2 \\ z_3 \end{pmatrix} = \begin{pmatrix} z_0 \\ z_1 \\ z_2 \\ z_3 \end{pmatrix} .* \left\{ \begin{pmatrix} 0 & -\gamma_0 & 0 & 0 \\ \gamma_0 & {w_{1,1}}^0 & {w_{1,2}}^0 & 0 \\ 0 & 0 & {w_{2,2}}^0 & 0 \\ 0 & 0 & 0 & {w_{3,3}}^0 \end{pmatrix} \begin{pmatrix} z_0 \\ z_1 \\ z_2 \\ z_3 \end{pmatrix} \right\},$$

for off-treatment periods. Now, the PSA value at time t is assumed to be $\sum_{i=1}^{3} z_i(t)$.

We obtained the prior distribution using the first 36 patients from the phase-2 study of intermittent androgen suppression published in ref. 6. Then, we estimated the parameters and initial conditions for the other patients in a similar way to ref. 5. We used the first 1.5 cycles to fit the rest of the patients.

Multinomial logistic regression. We used MATLAB's mnrfit function to conduct multinomial logistic regression (The MATLAB version was 2018a). For each combination of the models, we obtained the following two logarithmic likelihood ratios given the sets of the fitted parameters $\{q_j(i)\}$ for patient i:

$$\log \frac{P_{wo}(i)}{P_m(i)} \sim \sum_{j=1}^{J} a_j q_j(i)$$

for the ratio between "without relapse" ($P_{wo}(i)$) and "with metastasis" $\left(P_m(i)\right)$, and

$$\log \frac{P_m(i)}{P_c(i)} \sim \sum_{j=1}^{J} b_j q_j(i)$$

for the ratio between "with metastasis" ($P_m(i)$) and "with castration resistance" ($P_c(i)$). For the model of ref. 4, the parameters for $\{a_j\}$ and $\{b_j\}$ are listed in Supplementary Table 1. We used the datasets of refs. 6–8 as the database, and predicted the events of the metastasis and castration resistance in the datasets of ref. 9 probabilistically with the values $P_m(i)$ and $P_c(\mathrm{i})$, which were between 0 and 1 because we assumed that $P_{wo}(i) + P_m(i) + P_c(i) = 1$. When we combined the events of the metastasis and the castration resistance, we defined a single logarithmic likelihood ratio

$\log P_{wo}(i)/\left(P_m(i)+P_c(i)\right)$ and conducted a similar analysis.

Time series prediction. After fitting the PSA time course using the first 1.5 cycles as described above, we ran the model forward and predicted the next PSA value for each patient for each model. The obtained prediction errors are summarized in Fig. 2.

Table 1 | Simple comparison between castration resistance and metastasis in phase-3 study of ref. 9. Castration resistance and metastasis agreed in 86% of cases (Fisher's exact test: $P < 2.2 \times 10^{-16}$, obtained by R).

Cast. resist.＼met.	Without	With	Total
Without	474	14	488
With	85	117	202
Total	559	131	690

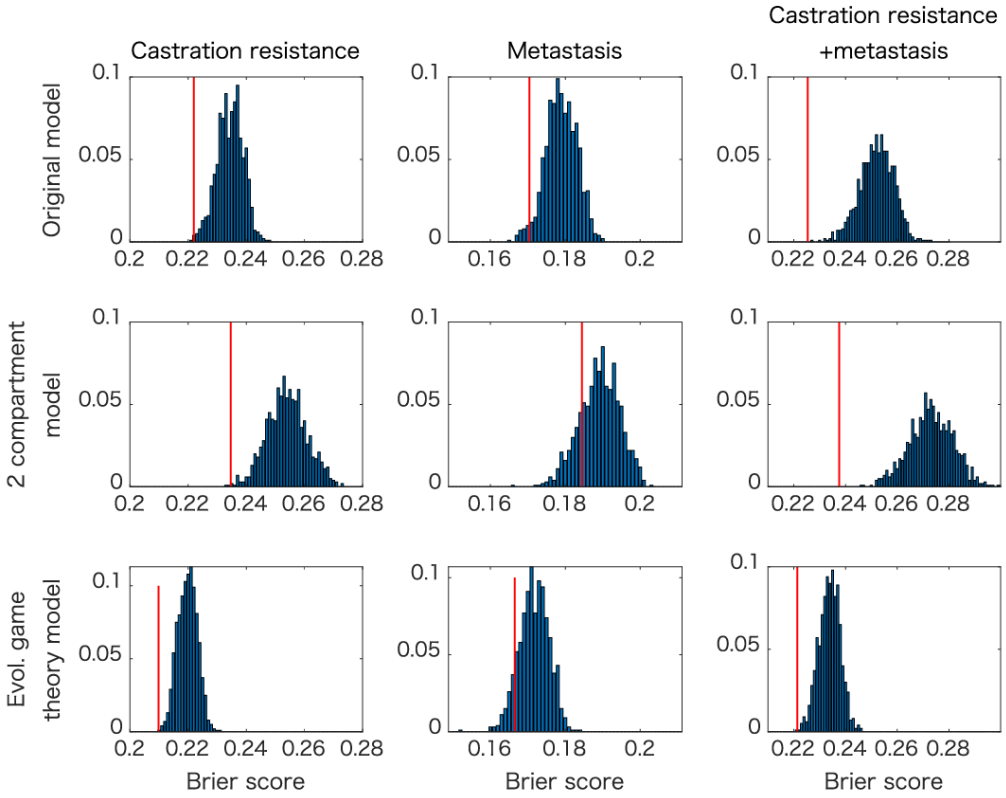

Figure 1 | Probabilistic prediction errors (Brier scores) for castration resistance, metastasis, or one of them, depending on three models. Top three panels correspond to results obtained from original model of ref. 4. Middle three panels correspond to the results obtained from two-compartment model. Bottom three panels correspond to results obtained from evolutionary-game theoretical model. Left column shows predictions of castration resistance, middle column shows predictions of metastasis, and right column shows predictions for either castration resistance or metastasis. In each panel, solid red line corresponds to value obtained from corresponding prediction and histogram as obtained from random patient assignments. In general, predictions for either castration resistance or metastasis are more statistically significant than predicting one of them separately. See Supplementary Table 2 for corresponding p-values.

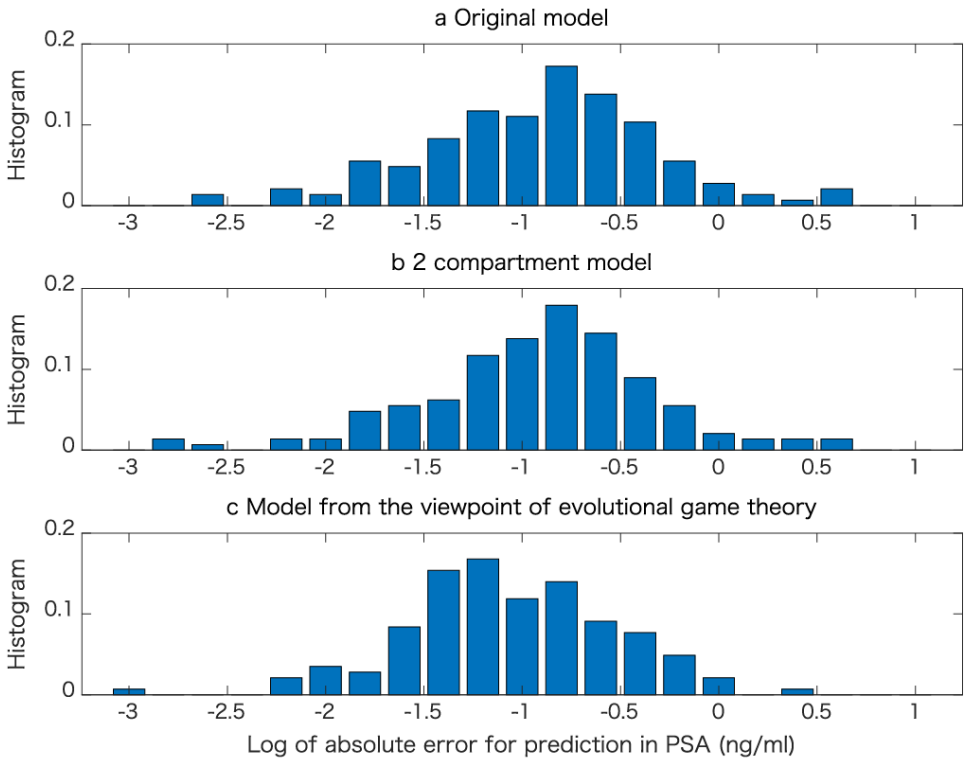

Figure 2 | One-step prediction errors for three models of prostate cancer used in this letter. Panel a corresponds to original model of ref. 4, panel b corresponds to two-compartment model, and panel c corresponds to revised model from viewpoint of evolutionary game theory.

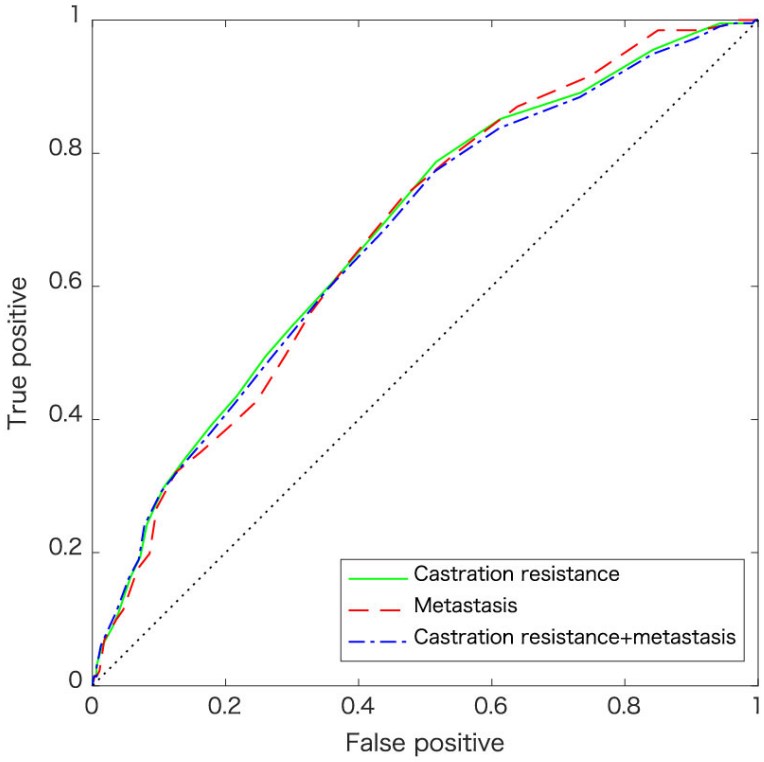

Figure 3 | Receiver operative characteristic curves by proposed indexes when all three mathematical models compared in this letter are combined.

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