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# Genomic characterization of metastatic patterns in prostate cancer using circulating tumor DNA data from the SCRUM-Japan MONSTAR SCREEN project

Masaki Shiota [a,*], Nobuaki Matsubara [b], Taigo Kato [c], Masatoshi Eto [a], Takahiro Osawa [d], Takashige Abe [d], Nobuo Shinohara [d], Koshiro Nishimoto [e], Yota Yasumizu [f], Nobuyuki Tanaka [f], Mototsugu Oya [f], Takao Fujisawa [g], Satoshi Horasawa [h], Yoshiaki Nakamura [i], Takayuki Yoshino [i], Norio Nonomura [c]

[a] Department of Urology, Graduate School of Medical Sciences, Kyushu University, Japan
[b] Department of Medical Oncology, National Cancer Center Hospital East, Japan
[c] Department of Urology, Osaka University Graduate School of Medicine, Japan
[d] Department of Urology, Graduate School of Medicine Hokkaido University, Japan
[e] Department of Uro-Oncology, Saitama Medical University International Medical Center, Japan
[f] Department of Urology, Keio University School of Medicine, Japan
[g] Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Japan
[h] Translational Research Support Office, National Cancer Center Hospital East, Japan
[i] Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Japan

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ABSTRACT

*Purpose:* Genomic characterization of the predisposition of tumors to metastasize to specific sites has been performed in a few studies using mainly tissue-derived genomes. This nationwide prospective observational study investigated the association between genomic characteristics using circulating tumor DNA (ctDNA), and the synchronous and metachronous metastasis of tumors to specific target organs in advanced prostate cancer.
*Methods:* Patients with advanced prostate cancer undergoing systemic treatment were included. ctDNA was analyzed using the FoundationOne®Liquid CDx assay at enrollment. Associations between genomic characteristics and metastatic status were examined.
*Results:* Alterations in the genes *MYC*, *APC*, and *BRCA2* and the DNA repair, MYC, and WNT pathways were associated with lung and liver metastasis. *PTEN* gene alterations and PI3K pathway alteration were associated with synchronous lung metastasis. *RB1* gene alteration and RAS/RAF/MAPK pathway alteration were associated with synchronous liver metastasis. *RB1* and *BRCA2* gene alterations predicted metachronous lung metastasis, while *TP53* and *MYC* gene alterations predicted metachronous liver metastasis.
*Conclusions:* This study identifies genomic alterations in ctDNA associated with synchronous and metachronous metastases. These findings may be clinically helpful for treating, managing, and monitoring cancer.

## 1. Introduction

Cancer progression from a localized disease to a metastatic disease is often a critical step affecting disease outcome [1]. Interestingly, prostate cancer frequently spreads to bone but rarely to the viscera, such as the lung and the liver, suggesting that metastasis is not random but coordinated through an interaction between the tumor and the whole body [2]. The presence of visceral metastasis in prostate cancer is associated with aggressive tumors and poor prognosis, and the development of effective treatment for patients with visceral metastasis is an unmet need [3,4]. Currently, metastatic prostate cancer is treated with androgen deprivation therapy sequentially combined with androgen receptor (AR) signaling inhibitor, taxanes, and radiopharmaceuticals [5,6]. Among them, radiopharmaceutical radium-223 can be used for bone-metastasized castration-resistant prostate cancer without visceral metastasis [7]. Then, metastatic sites are key factors to choose

* Corresponding author.
*E-mail address:* shiota.masaki.101@m.kyushu-u.ac.jp (M. Shiota).

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treatment.

Genomic alterations have been suggested to be one of the critical regulators of a tumor's predisposition to metastasize to a specific organ. Recently, genomic characterization of metastatic patterns across 50 cancer types, including prostate cancer, demonstrated that genomic alteration patterns in tumor tissue from the primary or the metastatic site differed by metastatic organ [8]. However, genomic characteristics at the primary site can vary from the genomic characteristics in tumors at metastatic sites, where clonal evolution may occur. In addition to potential spatial divergence, attention must be paid to the timing of primary tumor establishment and metastasis establishment because spatiotemporal divergence hinders accurate evaluation of the association between genomic characteristics and metastasis to a specific target organ.

Next-generation tumor tissue sequencing from metastatic sites is an optimal method with little spatiotemporal divergence; however, tissue sampling of metastatic sites is sometimes challenging. In addition, tumor tissue from only one region may not be sufficient to capture intra-patient tumor heterogeneity. Recently, circulating tumor DNA (ctDNA) analysis has emerged as a novel tool that could facilitate the development of precision cancer medicine. CtDNA can be obtained less invasively and repeatedly, capturing the tumor's genomic profile, including its heterogeneity [9–11]. Evidence for the utility of ctDNA analysis of advanced prostate cancer in clinical settings is accumulating [12–14]. However, evidence is limited for the association between genomic characteristics obtained using ctDNA and the predisposition of tumors to metastasize to specific organs. As yet, no association has been reported between genomic characteristics and synchronous presentation or metachronous presentation of metastasis. This study used data from the prospective observational study of the SCRUM-Japan MONSTAR SCREEN project to investigate the association between genomic characteristics as determined by ctDNA analysis and the predisposition of tumors for synchronous and metachronous metastasis to specific target organs in advanced prostate cancer.

## 2. Methods

### 2.1. Patient enrollment

The SCRUM-Japan MONSTAR SCREEN is a nationwide study conducted at core cancer institutions in Japan that incorporates ctDNA genomic profiling and gut microbiome analysis. The institutions involved in the MONSTAR-Urology subgroup are the National Cancer Center Hospital East, Osaka University Hospital, Kyushu University Hospital, Hokkaido University Hospital, Keio University Hospital, and Saitama Medical University International Medical Center.

The main inclusion criteria were: (1) histopathologically confirmed unresectable or metastatic solid cancer; (2) receipt of or planned systemic therapy: cohort A 1st line treatment, cohort B treatment after predefined genomic alterations were identified, cohort C immune checkpoint inhibitors, and cohort D pre-defined AR signaling inhibitors, including abiraterone and enzalutamide; (3) patient age $\geq$16 years; (4) an Eastern Cooperative Oncology Group performance status of 0–1; (5) adequate organ function, and (6) receipt of or planned cancer genomic profiling test using tumor tissue. Patients diagnosed with prostate cancer and enrolled at institutions in the MONSTAR-Urology subgroup were the subjects in this study. Patients whose ctDNA at enrollment was undetectable were excluded.

This study was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. Eligible patients provided written informed consent. The study protocol was approved by the institutional review board of each participating institution and registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol nos. UMIN000036749). This study was initiated in August 2019, and enrollment was completed in February 2022.

### 2.2. ctDNA genotyping

Next-generation sequencing analysis of ctDNA was performed using FoundationOne®Liquid CDx (F1LCDx®) at a Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists (CAP)-accredited laboratory designated by Foundation Medicine Inc., as described previously [15–18]. Sequencing data using tumor tissues was not used in this study. The 324 cancer related gene panel assay uses hybrid capture technology and deep sequencing to detect single nucleotide variants, indels, genomic rearrangements, copy number variations (amplifications and losses), and genomic signatures, including blood tumor mutational burden (bTMB) and tumor fraction (TF) [15]. The bTMB, microsatellite instability (MSI), and TF were assessed as described previously [17]. A high bTMB (bTMB-high) was defined as $\geq$14 mutations/Mb, and TF $\geq$ 10 % was considered elevated when estimated using aneuploidy [16,18]. The result of bTMB was not available for clinical use.

Oncogenic alterations were grouped by major signaling pathways from pan-cancer analyses [16,17], excluding the HIPPO, NRF2, and TGFβ pathways, which were altered in <1 % of samples within clinical subgroups. *TP53* was not grouped with DNA repair genes and considered separately, as were two genes (*AR* and *SPOP*) relevant in prostate cancer [17].

### 2.3. Clinical data

The clinicopathological information was collected using an electronic data capture system, including metastatic status by organ and systemic therapy type. These clinical data and genotyping results were stored in a clinical-grade database and used for integrated clinico-genomic analysis. A physician performed the imaging exams, and radiographic evaluation was conducted according to RECIST ver1.1 [19]. For the analysis of time to specific target organ metastasis, the emergence of *de novo* metastasis to particular target organs was defined as an event in patients without metastasis to specific target organs. Patients who did not experience any of these events were censored at the last follow-up visit. The number of months from the enrollment date to the earliest event or censoring date was calculated for the survival analysis.

### 2.4. Statistical analyses

All statistical analyses were performed using JMP16 software (SAS Institute, Cary, NC, USA). Continuous and categorical data were presented as median with interquartile range (IQR) and number with percentage, respectively. Comparisons between groups of categorical data were analyzed using Fisher's exact test. Survival analysis was performed using the Kaplan–Meier method and log-rank test. Univariate analyses were performed using the Cox hazard proportional model to estimate hazard ratios (HRs) with 95 % confidence intervals (CIs). All P-values were two-sided. P-values <0.05 were considered significant.

## 3. Results

### 3.1. Genomic features associated with synchronous metastasis to specific target organs

In total, 192 patients were enrolled from six institutions to participate in the MONSTAR-Urology subgroup, and 174 patients were analyzed after exclusion of patients whose clinical data were unavailable (n = 3), those with no metastatic status data at enrollment (n = 2), and those with undetectable ctDNA (n = 13) (Fig. 1). Patients' characteristics are listed in Table 1. Bone, lung, and liver metastases were observed in 136 (78.2 %), 25 (14.4 %), and 6 (3.4 %) patients at enrollment, respectively. Treatments performed after enrollment for castration-sensitive prostate cancer and castration-resistant prostate

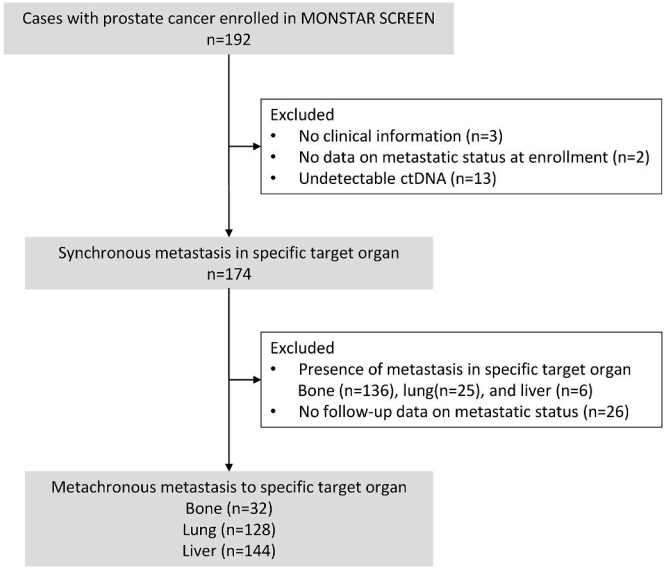


**Fig. 1.** CONSORT flow diagram illustrating the allocation of patients.

**Table 1**
Patients' characteristics.

| Variables | n = 174 |
|---|---|
| Median age at enrollement, years (IQR) | 73 (69–77) |
| Median PSA level at enrollement, ng/ml (IQR) | 42.9 (6.9–282) |
| ISUP grade group, n (%) | |
| ≤3 | 21 (12.3 %) |
| 4 | 51 (29.8 %) |
| 5 | 99 (57.9 %) |
| NA | 3 |
| Metastasis at initial diagnosis, n (%) | |
| Synchronous | 120 (69.0 %) |
| Metachronous | 54 (31.0 %) |
| Prior local treatment, n (%) | |
| Absence | 114 (65.9 %) |
| Curative radiation | 59 (34.1 %) |
| NA | 1 |
| Lymph node metastasis at enrollment, n (%) | |
| Absence | 89 (51.1 %) |
| Presence | 85 (48.9 %) |
| Bone metastasis at enrollment, n (%) | |
| Absence | 38 (21.8 %) |
| 1 | 23 (13.2 %) |
| 2 or 3 | 23 (13.2 %) |
| ≥4 | 90 (51.7 %) |
| Lung metastasis at enrollment, n (%) | |
| Absence | 149 (85.6 %) |
| Presence | 25 (14.4 %) |
| Liver metastasis at enrollment, n (%) | |
| Absence | 168 (96.6 %) |
| Presence | 6 (3.4 %) |
| Treatment line, n (%) | |
| CSPC | 73 (42.0 %) |
| 1st line for CRPC | 67 (38.5 %) |
| 2nd line for CRPC | 13 (7.5 %) |
| ≥3rd line for CRPC | 21 (12.1 %) |

IQR, interquartile range; ISUP, International Sciety of Urological Pathology; NA, not available; PSA, prostate-specific antigen.

cancer were categorized as 1st line, 2nd line, and 3rd line, or later in 73 (42.0 %), 67 (38.5 %), 13 (7.5 %), and 21 (12.1 %) patients, respectively.

We first examined the associations of genomic alteration signatures, altered genes, and altered pathways with synchronous metastasis to specific target organs. Bone metastasis was observed more frequently in patients with TF ≥ 10 % (33.1 % vs. 7.9 %, P = 0.018) (Fig. 2A, Supplementary Table 1). Similarly, lung (60.0 % vs. 22.1 %, P = 0.0004) and the liver (100 % vs. 25.0 %, P = 0.0003) metastases were observed more frequently in patients with TF ≥ 10 % (Fig. 2B and C, Supplementary Table 1). In addition, *MYC* (12.0 % vs. 2.0 %, P = 0.039), *PTEN* (28.0 % vs. 8.1 %, P = 0.0085), *APC* (16.0 % vs. 4.0 %, P = 0.048), and *BRCA2* (24.0 % vs. 8.1 %, P = 0.039) gene alterations and DNA repair (44.0 % vs. 23.5 %, P = 0.048), MYC (12.0 % vs. 2.0 %, P = 0.039), PI3K (40.0 % vs. 14.8 %, P = 0.0092), and WNT (28.0 % vs. 7.4 %, P = 0.0059) pathway alterations were associated with simultaneous presence of lung metastasis (Fig. 2B–Supplementary Table 2). Furthermore, *RB1* (33.3 % vs. 4.8 %, P = 0.040), *MYC* (33.3 % vs. 2.4 %, P = 0.014), *APC* (33.3 % vs. 4.8 %, P = 0.040), and *BRCA2* (50.0 % vs. 8.9 %, P = 0.015) gene alterations and DNA repair (83.3 % vs. 24.4 %, P = 0.0052), MYC (33.3 % vs. 2.4 %, P = 0.014), RAS/RAF/MAPK (66.7 % vs. 21.4 %, P = 0.026), and WNT (66.7 % vs. 8.3 %, P = 0.0011) pathway alterations were associated with presence of liver metastasis (Fig. 2C–Supplementary Table 1).

### 3.2. Genomic features associated with the emergence of metachronous metastasis to specific target organs

Next, we examined the association between genomic alterations and the emergence of metachronous metastasis to specific target organs. Since most patients exhibited bone metastasis at enrollment, the time to emergence of metachronous bone metastasis was not examined because of limited statistical power. Data on the emergence of metachronous lung and liver metastasis after enrollment were available in 128 and 144 patients, respectively (Fig. 1). *RB1* and *BRCA2* alterations were associated with a shorter time to the emergence of metachronous lung metastasis in patients without lung metastasis at enrollment (P = 0.0021 for *RB1*, P = 0.035 for *BRCA2*, Fig. 3A, Supplementary Table 2). Also, *TP53* and *MYC* alterations were associated with a shorter time to the emergence of metachronous liver metastasis in patients without liver metastasis at enrollment (P = 0.0001 for *TP53*, P < 0.0001 for *MYC*, Fig. 3B–Supplementary Table 2).

## 4. Discussion

This study demonstrates that a high level of TF is associated with a higher prevalence of synchronous bone, lung, and liver metastasis, suggesting that a high tumor burden results in a high level of TF in patients with advanced prostate cancer. More specifically, *MYC*, *APC*, and *BRCA2* gene alterations and DNA repair, MYC, and WNT pathway alterations are associated with the presence of lung and liver metastasis (as summarized in Fig. 4). In addition, *PTEN* gene alteration and PI3K pathway alteration are associated with synchronous lung metastasis (Fig. 4). Furthermore, *RB1* gene alteration and RAS/RAF/MAPK pathway alteration were associated with synchronous liver metastasis (Fig. 4). Consistent with these data, Nguyen et al. reported that WNT pathway alteration including *APC* and *CTNNB1* mutations in tissues from primary and metastatic regions were associated with lung metastasis [8]. Additionally, *RB1* deletion and *APC* mutation were associated with liver metastasis [8]. Similarly, WNT pathway alteration in primary/metastatic tissue was more common in patients with metachronous visceral metastatic castration-sensitive prostate cancer [20], and Alshalalfa et al. showed that *MYC* amplification, *PTEN* deletion, and *PIK3CB* amplification were observed in tissues from liver metastasis using publicly available sequencing data [21]. Dall'Era et al. reported that DNA repair gene alterations were more frequently observed in visceral metastases than in the primary tumor site [22]. Moreover, higher rates of *RB1* gene alterations in ctDNA or tissue were observed among patients with metastatic castration-resistant prostate cancer and metastasis to the viscera, including the lung and the liver [23]. These studies and the present study demonstrate that the genomic alterations in genes such as *RB1*, *PTEN*, and *MYC* that are known to be associated with aggressive tumor phenotype and poor prognosis in various studies are associated with visceral metastases [24]. Therefore, genomic

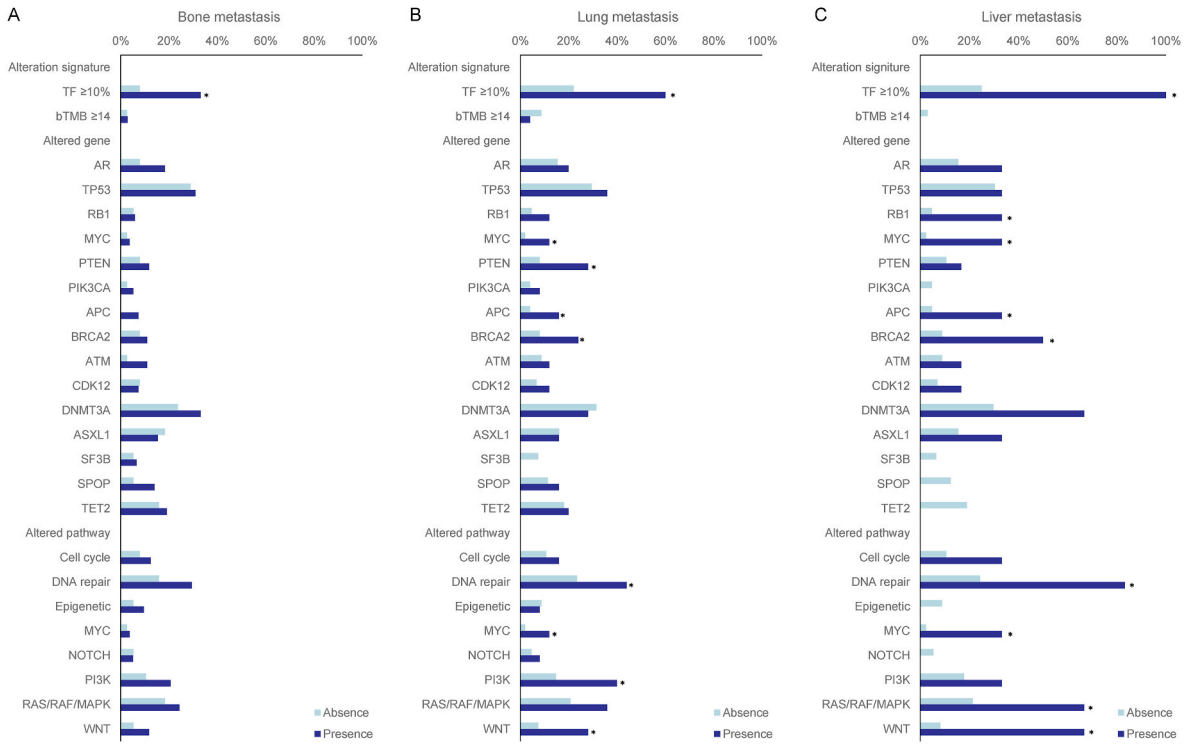


**Fig. 2.** Genomic features associated with synchronous metastasis to specific target organs. The frequency of alteration signatures, gene alterations, and pathway alterations according to the presence and absence of bone (A), lung (B), and liver (C) metastases are indicated. The alterations with statistical significance are marked with an asterisk.

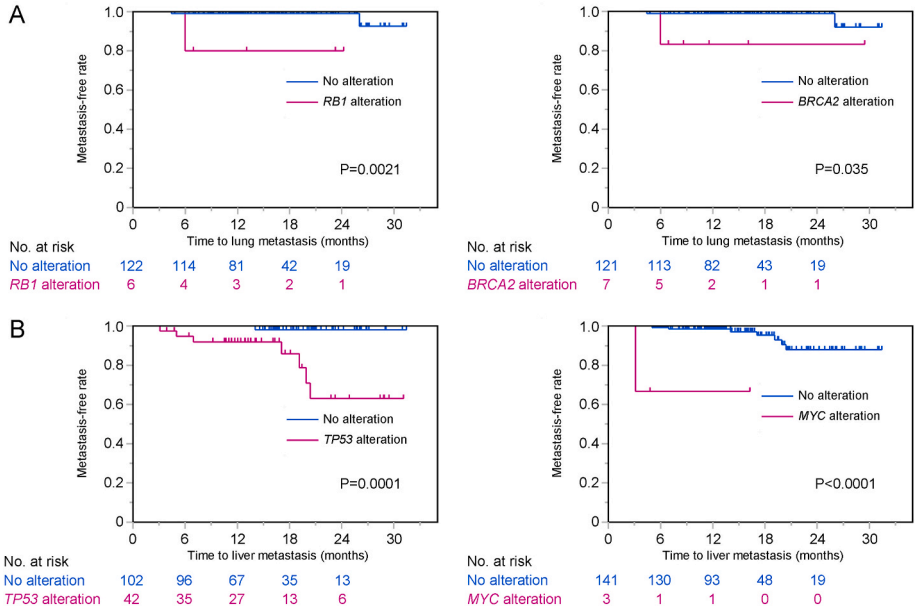


**Fig. 3.** Analyses of genomic alterations associated with metachronous metastasis to specific target organs. (A) Time to lung metastasis stratified by *RB1* alteration (left) and *BRCA2* alteration (right). (B) Time to liver metastasis stratified by *TP53* alteration (left) and *MYC* alteration (right).

characteristics associated with visceral metastasis may account for the poor prognosis among patients with metastasis to the viscera, especially to the liver. Notably, this study identified five gene alterations and five pathway alterations associated with visceral metastasis, demonstrating the advantage of using ctDNA to detect genomic alterations simultaneously and comprehensively.

In addition, this study highlights the ability of genomic alterations to predict the emergence of metachronous lung and liver metastasis. Specifically, *RB1* and *BRCA2* gene alterations were predictive of metachronous lung metastasis, while *TP53* and *MYC* gene alterations were predictive of metachronous liver metastasis (Fig. 4). Although *RB1*, *BRCA2*, and *MYC* alterations are common with gene alterations associated with synchronous visceral metastasis, *TP53* alteration was unique to metachronous liver metastasis. To our knowledge, the present study is the first to identify genomic characteristics associated with the metachronous emergence of visceral metastasis. These findings are clinically

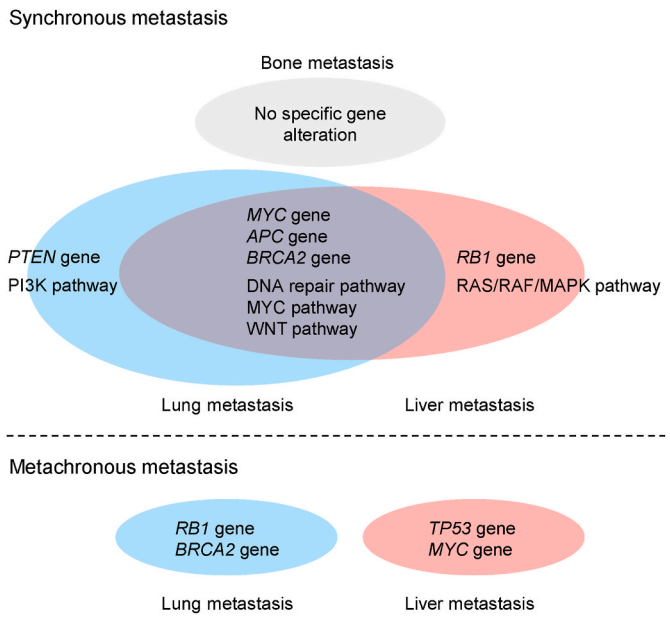


**Fig. 4.** Schematic of altered genes and altered pathways associated with synchronous and metachronous metastases to specific target organs.

valuable because they could be used to identify patients with a higher risk of metachronous visceral metastasis who would benefit from more careful monitoring, including frequent imaging examinations. These results may also help treatment choices, such as radium-223, because radium-223 treatment effectively treats bone metastasis but not visceral metastases.

In the study by Nguyen et al., *AR* amplification, *PTEN* deletion, and negative *ERG* fusion in tissues were associated with bone metastasis [8]. However, this study did not identify a genomic signature associated with bone metastasis. This discrepancy may be because the poor ability of ctDNA analysis to detect copy number alterations and fusion genes. *AR* alterations are a key driver of resistance to the therapeutics targeting the AR pathway in prostate cancer [25]. Interestingly, the study by Gong et al. reported that *AR* alterations in ctDNA or tissue were observed among patients with liver metastasis, but no alterations were detected in lung metastasis [23]. However, the present study and Nguyen et al. [8] observed no significant association of *AR* alteration with visceral metastasis.

There are several limitations to this study. First, radiographic evaluation of metastasis was not in the protocol, which might affect the analysis of time to metastasis emergence. Second, the imaging modality used for metastasis detection was not pre-defined. Although computed tomography and bone scans were estimated to be mainly used, next-generation imaging, such as positron emission tomography using prostate-specific membrane antigen, can evaluate metastasis status more accurately [26]. Lastly, the number of prostate cancer patients enrolled in this study is not large, and the case number of some subgroups is small. Nevertheless, this study, using commercially available ctDNA testing technology, demonstrated the ability to capture genomic characteristics associated with metastasis to specific target organs in a clinical setting.

## 5. Conclusions

This study characterized genomic alterations in ctDNA associated with synchronous and metachronous metastases. Identifying genomic characteristics associated with synchronous and metachronous metastases to the viscera is clinically useful information.

## Consent to participate

All participants provided written informed consent.

## Authors contributions

Study conception and design: M. Shiota, N Matsubara.

Acquisition of data: M. Shiota, N. Matsubara, T. Kato, M. Eto, T. Osawa, T. Abe, N. Shinohara, K. Nishimoto, Y. Yasumizu, N. Tanaka, M. Oya, N. Nonomura.

Analysis and interpretation of data: M. Shiota.

Drafting of the manuscript: M. Shiota.

Critical revision of the manuscript for important intellectual content: N. Matsubara, T. Kato, M. Eto, T. Osawa, T. Abe, N. Shinohara, K. Nishimoto, Y. Yasumizu, N. Tanaka, M. Oya, T. Fujisawa, S. Horasawa, Y. Nakamura, T. Yoshino, N. Nonomura.

Statistical analysis: M. Shiota.

Obtaining funding: T. Yoshino.

Administrative, technical, or material support: T. Fujisawa, S. Horasawa, Y. Nakamura.

Supervision: T. Yoshino, N. Nonomura.

## Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval

The SCRUM-Japan MONSTAR SCREEN study was approved by the Institutional Review Board of each participating institution and registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol nos. UMIN000036749).

## Funding

This work was supported by SCRUM-Japan funds, which had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Takayuki Yoshino reports a relationship with Chugai Pharmaceutical Co Ltd that includes: funding grants and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jlb.2024.100282.

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