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Real-World Outcomes and Molecular Profiling for Patients with Metastatic Castration-resistant Prostate Cancer with Lung Metastases: A Long-term Multicenter Experience

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Abstract

Background and objective: The prognostic impact of lung metastases (LuMs) in metastatic castration-resistant prostate cancer (mCRPC) remains poorly defined. Our aim was to evaluate the clinical and molecular characteristics of patients with mCRPC with LuMs and their outcomes.

Methods: This retrospective multicenter study included 930 patients with mCRPC across 13 centers in Italy. The primary endpoint was the impact of LuMs on overall survival (OS), progression-free survival (PFS), and prostate-specific antigen (PSA) response. As a secondary endpoint, next-generation sequencing for a subgroup with LuMs was used to identify molecular characteristics that might be useful in guiding personalized therapy.

Key findings and limitations: Among mCRPC patients treated with an androgen receptor signaling inhibitor, we observed no significant differences in median OS or PFS and PSA response between the LuMs group and the group with bone ± lymph node metastases. Multivariable analyses revealed that only Eastern Cooperative Oncology Group

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Androgen receptor signaling
inhibitors
Survival

performance status, PSA level, prior docetaxel treatment, and number of metastatic lesions were significant independent factors for both OS and PFS. Comparison of the groups with LuMs only versus liver metastases revealed a significant association between LuMs and a longer OS (15 vs 10 mo; $p = 0.002$) and PFS (9 vs 5 mo; $p = 0.002$). The proportion of patients with a $\geq 50\%$ PSA decline was higher in the LuMs group (odds ratio 3.57, 95% confidence interval 1.37–9.45; $p = 0.004$). Molecular profile results showed that *TP53* mutations accounted for a lower proportion of the pathogenic variants in LuMs than in liver metastases (15% vs 89%). Limitations include the retrospective design and clinical heterogeneity of the population, in addition to unavailability of metastatic biopsies for more in-depth analyses.

Conclusions and clinical implications: Our findings suggest that patients with LuMs in mCRPC exhibit clinical and molecular features more similar to those with bone $\pm$ lymph nodal metastases than to patients with liver metastases. Further prospective studies are warranted.

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ADVANCING PRACTICE

What does this study add?

This multicenter study shows that patients with metastatic castration-resistant prostate cancer with lung metastases could represent a clinical and biological subgroup more comparable to patients with bone and/or lymph node metastases than to patients with liver metastases. Our analyses highlight the importance of stratification of visceral metastatic status in clinical trial design to optimize patient outcomes. Molecular profiling of lung metastases is essential to identify genetic alterations that could inform personalized treatment decisions.

Clinical Relevance

In this study, the authors have analysed the clinical outcomes of patients with lung metastases compared to those with lymph nodes or bone metastasis only and with those with liver metastasis. Their results confirm prior results suggesting that patients with lung mets have better outcomes and should be considered a different clinical entity from those with liver mets. To support this, the authors compared the genomic profiles of lung and liver metastases, describing the differences in this manuscript. Associate Editor: Elena Castro, MD PhD.

Patient Summary

Our study looked at outcomes and molecular profile results (tests to identify genes or proteins linked to cancer outcomes) for men with metastatic prostate cancer that no longer responds to hormone therapy. Outcomes and molecular profiles for the group with metastases in the lung were more similar to the group with metastases in bone and/or lymph nodes than to the group with metastases in the liver. Our results show that the exact location of metastasis is important when recommending personalized treatment for individual patients.

1. Introduction

Prostate cancer (PC) is one of the most common malignancies among men worldwide and imposes a significant burden on health care systems because of its high incidence and mortality rates. Globally, PC accounts for approximately 30% of all cancer cases among men and remains the second leading cause of cancer-related deaths in the male population [1].

While most PC cases are diagnosed at a localized stage, ~ 10 – 20% of patients eventually develop metastatic disease, either at diagnosis or on progression of localized disease. Among metastatic PCs, visceral metastasis is a less common

but clinically significant subset that is associated with aggressive disease and poor prognosis [2]. The rate of visceral metastasis is significantly higher in castration-resistant PC (CRPC), with an incidence of ~ 20 – 30% among CRPC cases [3], while hormone-sensitive PC (HSPC) is characterized by lower incidence (10 – 15% of cases, depending on the study population and imaging modalities) [4,5].

Visceral metastases in PC most commonly involve the liver, lungs, and, less frequently, other organs such as the adrenal glands and brain. These patterns of spread are distinct from the typical skeletal tropism of PC metastases and may reflect underlying biological differences between metastatic sites. Patients with visceral metastases often

exhibit more rapid disease progression, a higher tumor burden, and resistance to standard therapies, including androgen deprivation therapy (ADT) and novel hormonal agents [6,7].

The heterogeneity of metastatic PC is partly driven by its molecular underpinnings. Variations in genetic and epigenetic alterations, such as mutations in *TP53*, *RB1*, and *PTEN*, may influence both metastatic potential and the organotropism of tumor cells [8,9]. In addition, differences in the tumor microenvironment at various metastatic sites, including the immune microenvironment, stromal factors, and vascularization, probably contribute to the distinct clinical behavior of visceral in comparison to bone metastases [10].

The incidence of lung metastases (LuMs) in metastatic PC varies across studies, with prevalence estimates ranging between 10% and 12.5% [3,11]. Although LuMs belong to the visceral metastasis category, some studies showed that patients with LuMs could have a more favorable clinical course than those with liver metastases (LVMs), with prognosis more akin to that for lymph node (LN) or bone metastases [12,13].

We conducted a retrospective study to evaluate the clinical and molecular characteristics of patients with metastatic CRPC (mCRPC) with LuMs and their outcomes with the aim of contributing to optimization of treatment strategies and improvements in outcomes for this underrepresented subgroup of patients.

2. Patients and methods

2.1. Study design and patients

This retrospective observational study included 930 patients with mCRPC treated across 13 centers in Italy. All patients had histologically confirmed adenocarcinoma without neuroendocrine differentiation. They were treated with an androgen receptor signaling inhibitor (ARSI; abiraterone 1000 mg daily + prednisone 5 mg twice daily; or enzalutamide 160 mg daily) until disease progression or unacceptable toxicity. Treatment was administered either before or after chemotherapy. Concurrent therapy with a luteinizing hormone–releasing hormone agonist or antagonist was maintained in all patients.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the independent review board at each participating site, and written informed consent was obtained from patients. Clinical and demographic data were collected via review of medical records.

2.2. Outcomes

In the overall study population, the primary endpoint was the impact of LuMs on overall survival (OS), progression-free survival (PFS) (biochemical and/or radiographic and/or clinical) and prostate-specific antigen (PSA) response. The secondary endpoint was molecular profiling of patients by site of metastasis in a selected cohort of men followed at Policlinico Riuniti, University of Foggia, Foggia, Italy.

2.3. Statistical analysis

OS was defined as either the time from diagnosis of cancer or the time from initiation of abiraterone or enzalutamide therapy until death from any cause or last follow-up. PFS was defined as the time from ARSI initiation until disease progression or death from any cause or last tumor evaluation. Survival curves were estimated using the Kaplan-Meier method. The Wilcoxon-Breslow test for equality of survivor functions was performed to compare survival curves between groups of patients by metastatic site. The median test (Wilcoxon) was applied to compare survival between patient groups with and without LuM. Cox regression models were used to evaluate independent effects on OS and PFS. PSA declines were evaluated according to the Prostate Cancer Clinical Trials Working Group 3 [14] guidelines, and waterfall plots were used to visualize the percentage PSA decline by metastatic site.

All statistical analyses were carried out using Stata version 14 (Stata Corp, College Station, TX, USA). For all analyses, a two-sided *p* value <0.05 was considered statistically significant.

2.4. Molecular assays

Somatic DNA was isolated from primary PC tissues using a QIAamp DNA FFPE tissue kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. MagCoreHF16 (Diatech Pharmacogenetics, Jesi, Italy) was used for automated extraction of germline DNA from peripheral blood lymphocytes from PC patients.

Genomic libraries for next-generation sequencing (NGS) were prepared using the 38-gene Hereditary Cancer Solution HCSO_v1 kit and 20-gene Custom Homologous Recombination Deficiency Solution CHRS_v1 kit (Sophia Genetics, Rolle, Switzerland). The genes included in these NGS panels are listed in [Supplementary Tables 1 and 2](#).

NGS was conducted on a MiSeq platform (Illumina, San Diego, CA, USA) with target region coverage of >1000× for germline and >50× for somatic DNA analysis. The Sophia Genetics DDMv.5.9.2 platform (ISO 13485 and ISO 27001 certifications) was used for bioinformatics analysis of variants (single-nucleotide variants, insertion/deletions, copy-number variation). Annotated variants were classified according to Human Genome Variation Society (HGVS) criteria [15].

Multiplex droplet digital polymerase chain reaction (ddPCR) assays to detect copy-number variations and mutations in the androgen receptor gene (*AR*) were performed as previously described [16]. Assays were carried out for detection of the *AR* mutations 210T→A (p.L702H), 236A→G (p.T878A), 2629T→C (p.F877L), and 1424C→T (p.A475V).

3. Results

3.1. Patient characteristics

We included 930 patients diagnosed with mCRPC from July 2011 to April 2024 in the study. Baseline characteristics of the patients stratified by site of metastasis at the time of ARSI treatment initiation are shown in [Table 1](#). For our

comparative analysis of LuMs versus no-LuMs, we excluded patients with visceral metastases (liver and other sites, including brain metastases), as these are associated with worse prognosis and could potentially skew interpretation of the data.

The median age of our population was 77 yr (interquartile range [IQR] 71–82). In the overall cohort, the most frequent sites of metastasis were bone only ($n = 316$, 34%), LN only ($n = 155$, 17%), and bone + LN ($n = 327$, 35%). In the group of 132 patients with visceral metastases, 61 (6.5%) had LuMs and 71 (7.5%) had liver-only ($n = 41$) or liver and/or other metastases (2 peritoneal, 8 adrenal, 5 brain, 15 soft tissue). A total of 270 patients (29%) with mCRPC had de novo metastatic disease at diagnosis, of whom 107 (39.6%) had “high-volume” disease according to the CHAARTED criteria.

In the visceral metastasis group, 79 patients (59.1%) had ≥ 8 metastases (median number in our cohort, range 1–22) and 41 (31.1%) had metastatic disease at the HSPC stage.

Comparison of the LuMs group of 61 patients and the group of 798 no-LuMs mCRPC patients (Table 1), showed no statistically significant differences in baseline patient and tumor characteristics were observed, except for higher Eastern Cooperative Oncology Group performance status (ECOG PS) and lower number of comorbidities in men with lung sites compared to those with no lung sites.

3.2. Survival outcomes by metastatic sites and predictors of survival

Comparison of OS by site of metastasis in our mCRPC cohort revealed median OS of 99 mo for the LuMs group, 89 mo for

the bone-only group, 109 mo for the LN-only group, 85 mo for the bone + LN group, and 64 mo for the liver + other group. The difference between the LuMs and bone $\pm$ LN group was not significant; however, OS was significantly shorter for the liver + other group than for the LuMs group ($p = 0.028$; Fig. 1).

All patients with mCRPC received ARSI therapy (548 abiraterone, 382 enzalutamide). In the overall population, median survival outcomes from initiation of ARSI therapy were 22 (range 11–36) mo for OS, and 9 (range 4–18) mo for PFS (Supplementary Fig. 1). There was no difference in the distribution of ARSI agents between the LuMs and no-LuMs groups (Table 1). Analysis of survival outcomes from ARSI initiation for the LuMs group versus no-LuMs group (excluding liver and other sites such as brain and soft tissue) revealed no significant difference in median OS (18 mo, IQR 11–42 vs 25 mo, IQR 13–50; $p = 0.126$; Fig. 2A) or median PFS (9 mo, IQR 5–15 vs 10 mo, IQR 5–19; $p = 0.717$; Fig. 2B).

Separate analyses of radiographic, clinical, and biochemical PFS revealed that LuMs presence had no impact on the response to either abiraterone or enzalutamide (Supplementary Table 3). In addition, there was no significant difference in the proportion of patients in the LuMs versus no-LuMs groups with a PSA decline of either ≥ 50 (odds ratio [OR] 1.61, 95% confidence interval [CI] 0.91–2.91; $p = 0.08$) or $\geq 90\%$ (OR 1.05, 95% CI 0.51–2.04; $p = 0.87$; Fig. 2C).

We used Cox regression models to identify potential predictors of OS and PFS among age, Gleason score, prior docetaxel therapy, number of previous therapies for mCRPC, serum lactate dehydrogenase (LDH) and PSA levels, ECOG

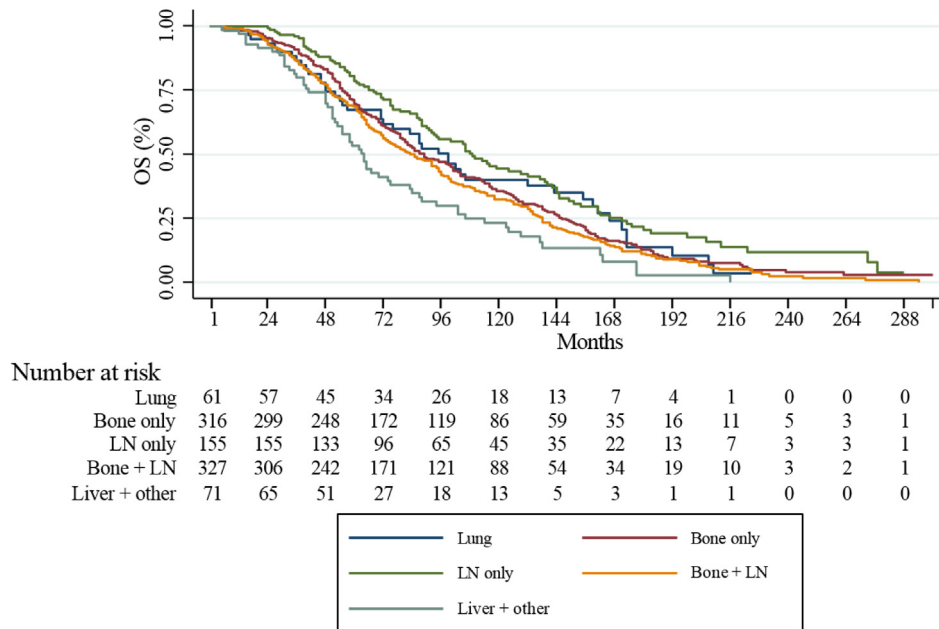
Table 1 – Patient characteristics by metastatic site

Parameter	Overall cohort	LuMs group	no-LuMs ^a	p value
Patients (n)	930	61	798	
Median age (yr)	77	75	77	0.235
Prostatectomy, n (%)				0.786
No	540 (58.1)	34 (55.7)	459 (57.5)	
Yes	390 (41.9)	27 (44.3)	339 (42.5)	
Radical radiotherapy, n (%)				0.627
No	654 (70.3)	41 (67.2)	560 (70.2)	
Yes	276 (29.7)	20 (32.8)	238 (29.8)	
Gleason score, n (%)				0.808
6–8	497 (53.4)	35 (57.4)	437 (54.8)	
9–10	329 (35.4)	21 (34.4)	275 (34.5)	
Unknown/missing	104 (11.2)	5 (8.2)	86 (10.8)	
ECOG performance score, n (%)				0.014
0–1	832 (92.7)	52 (85.2)	747 (93.6)	
2	68 (7.3)	9 (14.8)	51 (6.4)	
De novo metastatic disease, n (%)				0.757
Yes	270 (29)	16 (26.2)	224 (28.1)	
No	660 (71)	45 (73.8)	574 (71.9)	
Presence of comorbidity, n (%)				0.021
Yes	659 (70.9)	51 (83.6)	556 (69.7)	
No	271 (29.1)	10 (16.4)	242 (30.3)	
ARSI agent, n (%)				0.671
Abiraterone	548 (58.9)	34 (55.7)	467 (58.5)	
Enzalutamide	382 (41.1)	27 (44.3)	331 (41.5)	
Prior docetaxel, n (%) ^b				0.215
No	398 (42.8)	22 (36.1)	353 (44.2)	
Yes	532 (57.2)	39 (63.9)	445 (55.8)	
Median PSA before ARSI (ng/dl)	34.03	26	34.345	0.171

ARSI = androgen receptor signaling inhibitor; ECOG = Eastern Cooperative Oncology Group; IQR, interquartile range; LuMs = lung metastasis; PSA = prostate-specific antigen.

^a Excluded patients with metastasis in the liver and other sites, including brain and soft tissue.

^b Docetaxel for metastatic hormone-sensitive or castration-resistant prostate cancer.



Metastatic site	Patients	Median OS, mo (95% CI)	p-value
Lung	61	99 (48-166)	-
Bone only	316	89 (55-146)	0.891
LN only	155	109 (68-171)	0.106
Bone + LN	327	85 (50-138)	0.354
Liver + other	71	64 (41-106)	0.028

Fig. 1 – Kaplan-Meier survival curves for OS from diagnosis of prostate tumor, divided according to metastatic site. The table summarizes median OS for each group, with *p* values for comparison to the group with LuMs. CI = confidence interval; LN = lymph node; OS = overall survival.

PS, number of metastatic lesions, and LuMs presence. ECOG PS (OS: hazard ratio [HR] 1.46, 95% CI 1.08–1.97; *p* = 0.01; PFS: HR 1.51, 95% CI 1.13–2.03; *p* < 0.01), pretreatment PSA as a continuous variable (OS: HR 1.00, 95% CI 1.00–1.00; *p* < 0.01; PFS: HR 1.00, 95% CI 1.00–1.00; *p* < 0.01), prior docetaxel therapy (OS: HR 1.16, 95% CI 1.19–1.67; *p* < 0.01; PFS: HR 1.16, 95% CI 1.00–1.35; *p* = 0.04), and number of metastatic lesions (OS: HR 1.55, 95% CI 1.32–1.83; *p* < 0.01; PFS: HR 1.30, 95% CI 1.11–1.51; *p* < 0.01) were significant risk factors for both OS and PFS. In addition, age (HR 0.81, 95% CI 0.69–0.95; *p* = 0.01) and number of previous therapies for mCRPC (HR 1.21, 95% CI 1.01–1.47; *p* = 0.04) were independent factors for OS, and pretreatment LDH was significantly associated with PFS (HR 0.85, 95% CI 0.73–0.98; *p* = 0.03; [Supplementary Table 4](#)).

Of the patients in our cohort, 598 (64.3%) progressed to second-line therapy for mCRPC, which was docetaxel in 354 (59.2%), cabazitaxel in 184 (30.7%), an ARSI in 49 (8.2%), radioligand therapy (RLT) in 8 (1.4%), and olaparib in 3 (0.5%). Moreover, 369 (39.7%) received third-line therapy, which was docetaxel in 75 (20.3%), cabazitaxel in 197 (53.4%), an ARSI in 26 (7.0%), RLT in 8 (2.2%), olaparib in 5

(1.4%), and another chemotherapeutic drug in 58 (15.7%; carboplatin, vinorelbine, or cyclophosphamide). Lastly, 198 patients (21.3%) received fourth-line and 68 (7.3%) received fifth-line therapy.

3.3. Outcomes for the LuMs versus LVMs groups

For the visceral metastasis cohort, we compared outcomes between the LuMs and LVMs-only groups, excluding four patients with both metastatic localizations. LuMs versus LVMs were significantly associated with longer median OS (15 mo, IQR 9–29 vs 10 mo, IQR 3–18; *p* = 0.002; [Fig. 3A](#)) and longer median PFS (9 mo, IQR: 5–15 vs 5 mo, IQR 3–9; *p* = 0.002; [Fig. 3B](#)). Moreover, a higher proportion of patients with a PSA decline $\geq 50\%$ was observed in the LuMs group (OR 3.57, 95% CI 1.37–9.45; *p* = 0.004; [Fig. 3C](#)).

3.4. Molecular profile by metastatic site

The secondary endpoint of our study was molecular profiling of a selected cohort of patients with mCRPC enrolled at Policlinico Riuniti. Among the 428 patients profiled via NGS for germline or somatic DNA (from primary prostate tumor)

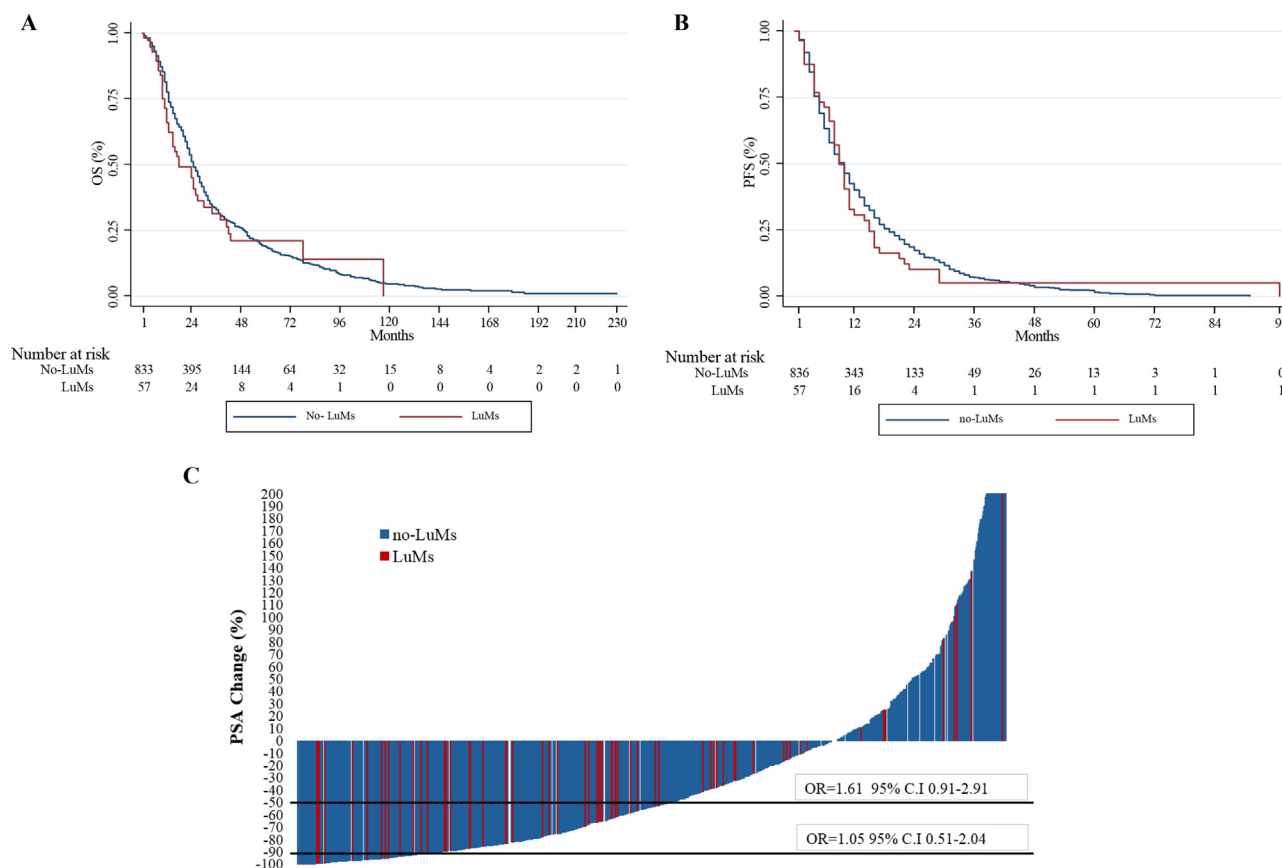


Fig. 2 – Association between LuMs and outcomes. Kaplan-Meier estimates of (A) OS and (B) PFS rates in the subgroups with and without LuMs before starting ARSI treatment. (C) Waterfall plot of the percentage PSA declines in the subgroups with and without LuMs. Patients with liver, brain, and soft-tissue metastases were excluded from this analysis. CI = confidence interval; OR = odds ratio; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen.

alterations, 109 (25.5%) harbored at least one pathogenic variant (PV) in a target gene according to the HGVS classification. Of these, 18 patients also had one variant of uncertain (or unknown) significance (VUS) in a target gene.

For analysis, we stratified this selected group of 109 patients with PVs according to sites of metastases: LuMs, bone and/or LN metastases (BM/LNMs), and LVMs (Fig. 4 and Supplementary Table 5).

In the subgroup of 13/109 patients (12.0%) with LuMs but no LVMs (9 of 13 also had BM + LNMs), the prevalence of germline or somatic PVs was 23.1% for *BRCA2*, 15.4% for *CDK12*, *PI3KCA*, and *TP53*, and 7.7% for *BRCA1*, *ATM*, *PALB2*, *PTEN*, *CHEK2*, and *MUTYH* (Fig. 4 and Supplementary Table 5).

In the subgroup of 68/109 patients (62.4%) with BM/LNMs only (no LuMs, no LVMs), the prevalence of germline or somatic PVs was 23.53% for *BRCA2*, 26.47% for *TP53* genes, 10.29% for *ATM*, 8.82% for *CHEK2*, 7.35% for *PTEN*, 5.88% for *PIK3CA*, and 5.88% for *PALB2*. PVs with a prevalence minor of 3% were also identified for *BRCA1*, *MUTYH*, *CDK12*, *POLE*, *PMS2*, and *BRIP1* in the BN/LNMs subgroup (Fig. 4 and Supplementary Table 5).

In the subgroup of 28/109 patients (25.7%) with LVMs and no LuMs (21/28 had also BMs + LNMs), the high prevalence of somatic PVs in *TP53* (89.29%) and *PTEN* (17.86%;

Fig. 4 and Supplementary Table 5) suggests more aggressive (and neuroendocrine-like) genomic features [7,16] limited to their molecular profile in comparison to the LuMs and BM/LNMs subgroups, in which PVs mainly affected genes related to DNA damage repair (DDR). In the LVMs subgroup, the prevalence of PVs was 10.71% for *BRCA2* and just 3.57% for *PALB2* and *PIK3CA*.

In relation to the AR-independent cellular state as a marker of the neuroendocrine phenotype [17], the LVMs subgroup had lower prevalence of AR PVs gene (3.57%) in comparison to the LuMs (7.7%) and BM/LNMs (11.76%) subgroups (Fig. 4 and Supplementary Table 5).

Interestingly, we identified a long-term response to ARSI therapy in a chemotherapy-naïve patient with mCRPC LuMs. Radiographic, biochemical, and molecular characteristics of this selected case are shown in Fig. 5. This patient, who had progression on ADT for localized HSPC, experienced a long-term radiographic and PSA response during first-line enzalutamide treatment for mCRPC. We detected a germline PV in *MUTYH*, a gene involved in DNA base-excision repair implicated in the activation of nuclear and mitochondrial apoptosis pathways, and a germline VUS in *BARD1*, a critical factor in *BRCA1*-mediated tumor suppression. No somatic alterations were detected in this patient.

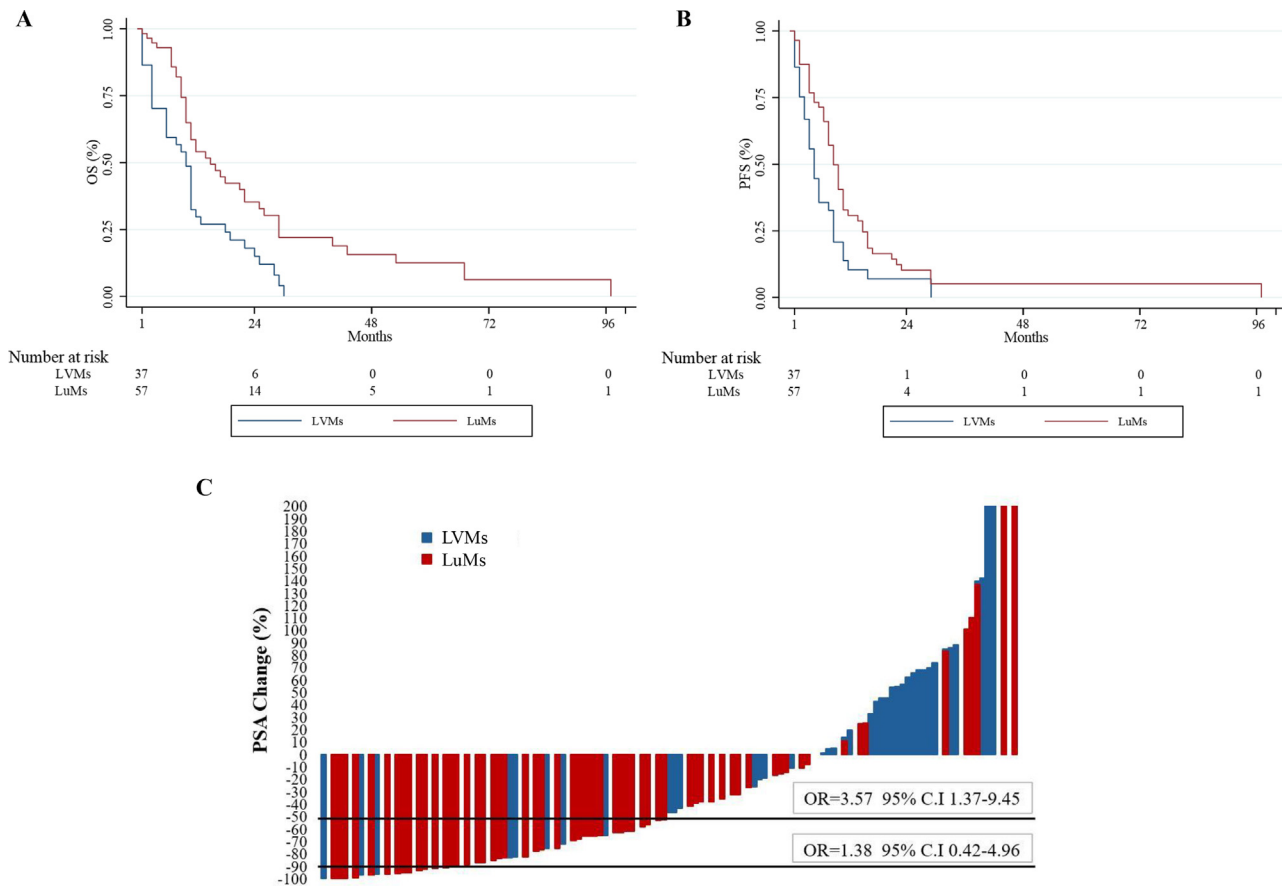


Fig. 3 – Comparison of outcomes between patient subgroups with LuMs and LVMs. Kaplan-Meier estimates of (A) OS and (B) PFS rates in the subgroups with LuMs versus LVMs. (C) Waterfall plot of the percentage PSA decline in the subgroups with LuMs versus LVMs. Patients with both metastatic sites were excluded from this analysis. CI = confidence interval; OR = odds ratio; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen.

4. Discussion

We performed a retrospective analysis to compare the impact of the site of metastasis on survival in patients with mCRPC in a real-world setting. Patients with LuMs experienced clinical outcomes more similar to those with BM/LNMs than to men with LVMs.

In our large multicenter study that included more than 900 patients with mCRPC with median follow-up exceeding 6 yr, the incidence of visceral metastases was 14%, which is comparable to previous reports, confirming the prognostic importance of visceral disease in mCRPC [18–21]. Patients with LuMs treated with abiraterone or enzalutamide had good clinical outcomes, including OS, PFS, and biochemical response rates, independent of ARSI agent.

Our results align with previous data demonstrating worse prognosis for LVMs in comparison to LuMs. Clinical trials such as COU-AA-301, CALGB 90401, and TAX 327 have shown that visceral disease, particularly LVMs, is an adverse prognostic factor in mCRPC regardless of treatment [22–24].

We found that among visceral metastases, LuMs represent a unique subset with distinct clinical and biological implications. Patients with isolated LuMs often experience longer OS than those with LVMs, as highlighted in subgroup

analyses from pivotal trials such as COU-AA-302 and PREVAIL [25,26].

In PREVAIL, which evaluated enzalutamide in chemotherapy-naïve mCRPC, patients with LuMs had better survival outcomes than patients with LVMs, but worse outcomes than patients with nonvisceral metastases [26]. Similarly, COU-AA-302 revealed that patients with LuMs benefited from abiraterone therapy, although OS and PFS were shorter in this group than in the group without visceral metastases [25].

Therapeutic responses among patients with LuMs vary by treatment modality. ARSI agents have shown efficacy in patients with LuMs; however, the magnitude of the benefit is generally lower than for patients with nonvisceral disease. Chemotherapy, particularly with cabazitaxel, has shown promise in this subgroup, as evidenced by the CARD trial, which included patients with visceral metastases, including LuMs [27]. The cytotoxic effects of chemotherapy may overcome resistance mechanisms more prevalent in LuMs.

Our study highlights the potential to optimize therapeutic strategies for patients with LuMs. Given the relatively favorable prognosis and apparent responsiveness of LuMs to ARSIs, routine use of chemotherapy in this subgroup

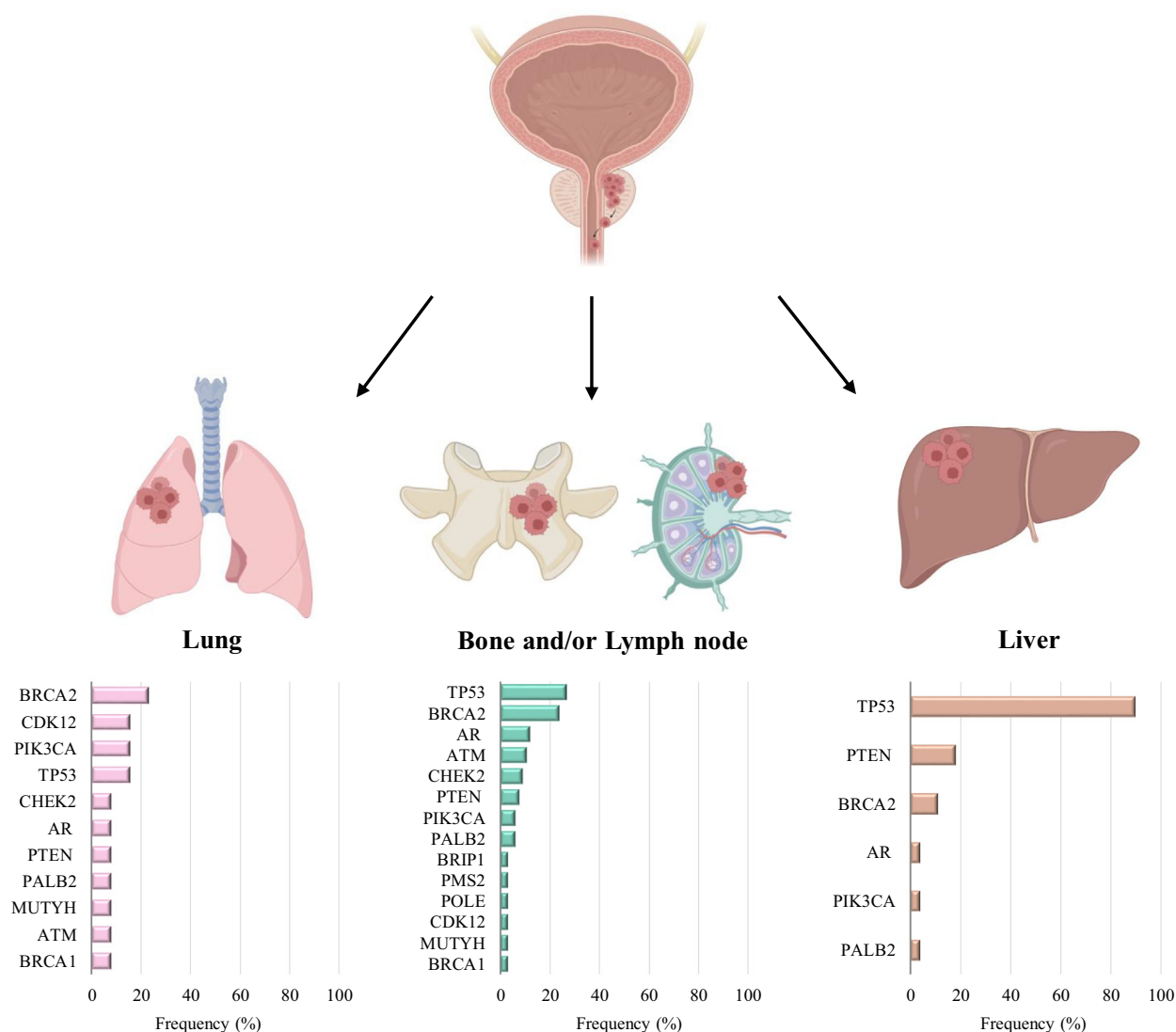
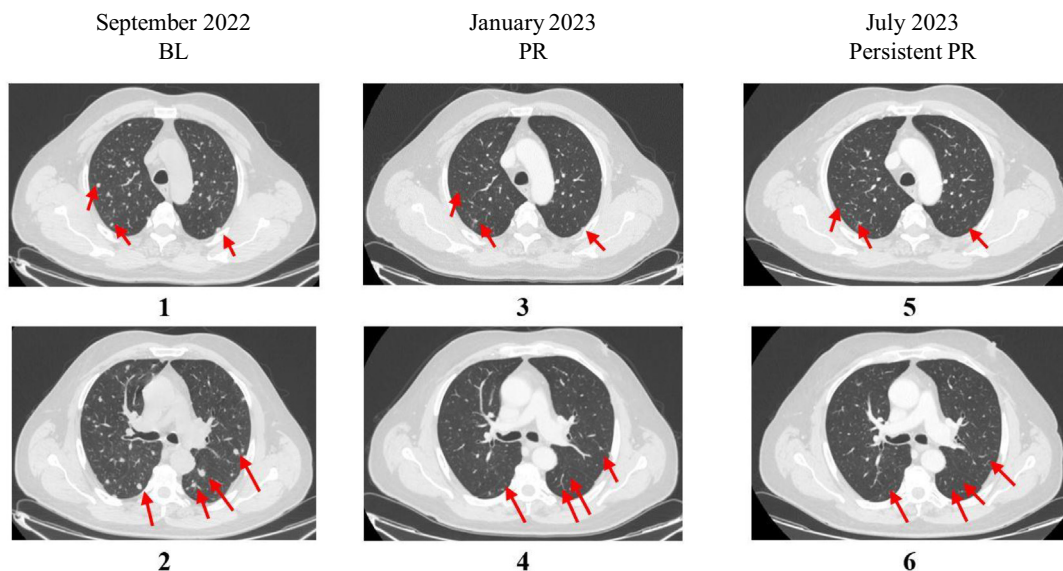
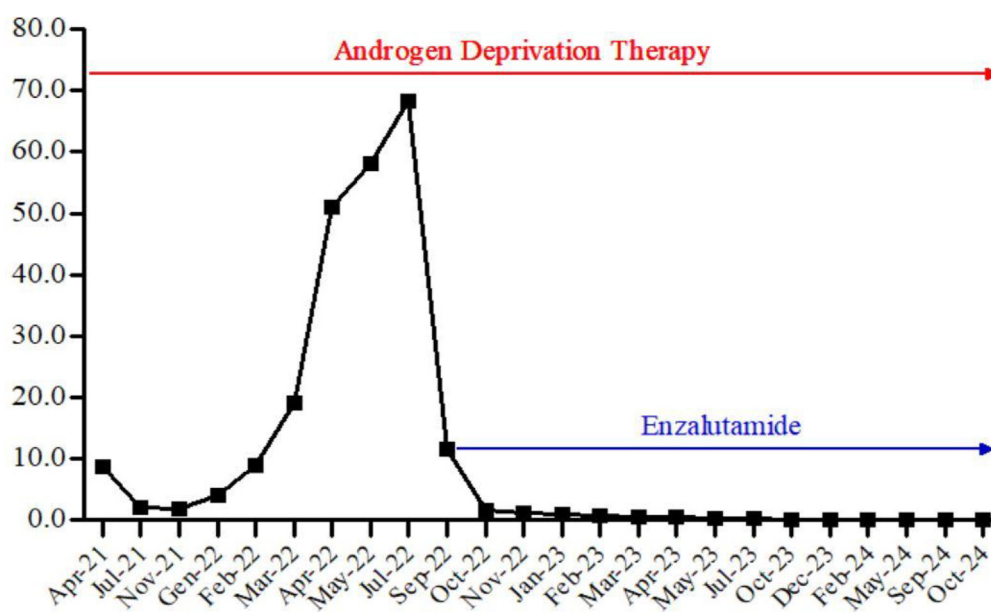


Fig. 4 – Distribution of germline or somatic pathogenic variants in the study population stratified by anatomic site of metastases. The denominator used to determine the percentage frequency for each gene was the total number of patients with metastases in the respective anatomic site. Images created with BioRender.com.

may not be essential. Disease volume remains one of the key criteria for treatment intensification in this context, as demonstrated by our multivariable analyses. This observation is particularly relevant in mHSPC setting, in which the role of combination treatments, such as doublet [28–30] versus triplet [31,32] regimens, should be carefully evaluated to avoid overtreatment. While chemotherapy remains a cornerstone for aggressive disease, its use in patients with LuMs warrants further investigation, especially considering the absence of molecular features typically associated with high-grade disease.

Tumor molecular profiling has emerged as a promising tool for identification of more aggressive phenotypes and correlation between driver mutations and high-risk clinical features, which can be used to stratify metastatic disease. It has been shown that tumor mutational profiles can provide a biological definition of oligometastatic CRPC beyond simple enumeration of lesions [33].

Tumor biology differs between LuMs and metastases in other visceral sites, reflecting heterogeneity in the tumor microenvironment and in metastatic potential. Although pulmonary involvement is uncommon in mHSPC, a genomic study of multiple foci of primary tumor and LuM sites in mHSPC demonstrated that patients lacked alterations in driver genes associated with more aggressive disease (*TP53*, *RB1*, or *DDR*-related genes) [34]. Our study showed that in comparison to LVMs, LuMs in mCRPC are often associated with a lower number of clinical and molecular features associated with aggressive PC variants. In line with this evidence, we observed lower incidence of genomic loss of the tumor suppressors *TP53* and *PTEN*, and higher incidence of *AR* alterations in our LuMs cohort [7,17]. A recent transcriptomic study in PC LuMs showed upregulation of genes associated with immunogenic responses and down-regulation of genes associated with epithelial-mesenchymal transition [35].

A**B****C**

Gene	Exon	Variant types	Molecular consequence	Mutation (DNA)	Mutation (AA)	Clinical significance
MUTYH	13	SNP	Missense	c.1187G>A	p.(Gly396Asp)	Pathogenic mutation
BARD1	6	SNP	Missense	c.15355T>C	p.(Leu 512 Pro)	VUS

Fig. 5 – Representative case with a long-term response to ARSI treatment in a patient with LuMs-only mCRPC . (A) Radiographic response to ARSI treatment. Computed tomography scans 1 and 2 were at baseline (BL). Scans 3 and 4 show a partial response (PR) after treatment with enzalutamide plus androgen deprivation treatment. Scans 5 and 6 show persistent PR. (B) Prostate-specific antigen (PSA) response during treatment. (C) Molecular profile for the patient. AA = amino acid; ARSI = androgen receptor signaling inhibitor; SNP = single-nucleotide polymorphism; VUS = variant of uncertain significance.

5. Conclusions

Despite the limitations of our study, including the retrospective design, the clinical heterogeneity of the population, the lack of knowledge of the exact date of the appearance of LuMs in the natural history of the disease, and the absence of biopsies from metastatic sites for sequencing, our results provide strong evidence supporting the hypothesis that LuMs in mCRPC could represent a clinical and biological subgroup more similar to the BM/LNMs group than the LVMs group. Future studies should focus on tailored therapeutic strategies for LuMs in mCRPC, including novel agents and combination approaches. Stratification by LuMs status in clinical trial design is crucial to optimize outcomes and address the unmet needs for this population. In addition, molecular characterization of LuMs in mCRPC is essential to identify distinct genetic alterations that could inform personalized treatment decisions.

Author contributions: Vincenza Conteduca had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Conteduca, Rosano.

Drafting of the manuscript: Conteduca, Bruno.

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Data sharing statement: The anonymized data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2025.05.002>.

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