Rediscovering secondary tumors of the prostate in the molecular era

Rediscovering Secondary Tumors of the Prostate in the Molecular Era.

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Abstract

Metastatic involvement of the prostate from noncontiguous solid tumors is a rare event occurring by means of vascular dissemination. The reported cases of biopsy and surgical samples with metastatic involvement have increased; however, a comprehensive understanding of secondary tumors of the prostate is currently missing. Metastases to the prostate carry a dismal prognosis and may pose serious diagnostic challenges to both clinicians and pathologists, with crucial therapeutic implications. Secondary tumors of the prostate spread more frequently from the digestive tract, the lung, and the kidney. The integration of clinicoradiologic data with appropriate pathologic and immunohistochemical analyses is essential for the identification and the characterization of secondary tumors of the prostate, whereas molecular analyses could provide additional and complementary information, enabling precise diagnosis and appropriate clinical management. Patients with solitary metastases could benefit from prostatic resection and adjuvant therapy, whereas in cases of disseminated diseases, symptom control may be obtained with palliative procedures. The purpose of this review was to assess the current state of knowledge of secondary tumors involving the prostate gland and to discuss short-term future perspectives, while providing a practical approach to these uncommon conditions for pathologists and oncologists.

INTRODUCTION: DEFINITION AND OVERVIEW

Metastatic involvement of the prostate gland is an exceedingly rare event, occurring in <1% of all prostatic surgical specimens and in up to 3% of the postmortem examinations of patients with disseminated neoplasms.1–3 The condition of secondary tumors of the prostate is referred to as metastases from solid tumors accessing the prostate by means of vascular dissemination, excluding continuous spread from neighboring organs.1 This heterogeneous group of disorders embraces tumors from different primary sites often showing dissimilar responses to therapeutic interventions. However, clinical presentations and morphologic features of these uncommon conditions might overlap, providing significant diagnostic challenges and requiring ancillary studies as well as the integration of clinical and pathologic data. Despite the current lack of a comprehensive understanding, clinicians and pathologists must be aware of the possibility of prostatic secondaries to optimize patients' management. Secondary tumors of the prostate spread more frequently from the digestive tract,4–11 the lung,3,12–15 and the kidney,16–21 although prostatic metastases from the urinary bladder, malignant melanoma, and testicular, upper-respiratory tract, adrenal gland, and thyroid tumors have also been described.3,22–24 Albeit secondary tumors of the prostate have been historically described as incidental autopsy findings and/or manifestations of disseminated diseases,2 recent studies provided circumstantial evidences that the number of core biopsies or prostatic resections with metastatic involvement is increasing, in particular solitary metachronous epithelial secondaries (Table 1).5,12,16 This scenario may be due to the enhanced accuracy of patients' workup, the use of more sensitive imaging techniques, and the increasing rate of prostatic resection and biopsies.25 Accordingly, the initial histologic diagnosis of malignancy by a prostatic metastasis, although reported in the literature, is vanishingly rare nowadays.3 Up to 20% of the patients with secondary tumors of the prostate, either synchronous and metachronous, have a clinicopathologic diagnosis with no evidence of metastatic disease in other anatomic sites except the prostate.3 These patients could reasonably benefit from surgical prostatic resection and, possibly, tailored adjuvant treatments.26

In this review, we seek to outline the clinical and morphologic features of secondary tumors of the prostate, in particular focusing on the current armamentarium available for their pathologic characterization, with a glimpse at the state-of-the art molecular tools, and to discuss the therapeutic implications of these uncommon diagnoses.

CLINICAL FEATURES

Patients with secondary tumors of the prostate characteristically have a history of neoplastic disease; however, only rare reports contain well-documented clinical and imaging data as well as complete follow-up information.5,17 Taken together, the mean age at diagnosis is 53 years (range, 23 to 83 y), with the youngest reported individual with a secondary tumor of the prostate being affected by a metastatic small cell carcinoma of lung origin.15 Infections of the urinary tract refractory to antibiotic therapy in patients with a history of extraprostatic neoplasms might represent the first sign of secondary tumors of the prostate; however, prostatic metastases may also be asymptomatic.13,18 Other clinical signs, such as pelvic pain, obstructive symptoms, hematuria, and dysuria, are highly variable in solitary metachronous secondary tumors of the prostate, as summarized in Table 1. Generally, serum prostate-specific antigen (PSA) levels are normal, ranging from 0 to 4 ng/mL.13,17 This observation is consistent with the notion that the abnormal secretion of this serine protease is a specific indicator of intrinsic prostatic disorder, but not necessarily of prostatic involvement by other concurrent conditions, including tumors originating elsewhere.27 On digital rectal examination, the prostate gland may be enlarged and present abnormal nodules; however, cases with negative or nonrelevant physical features are more common.1,3 In the presence of persistent urinary symptoms and a history of neoplastic disease, it is recommended to perform an accurate physical examination, together with comprehensive imaging techniques such as ultrasound, computed tomography,

and magnetic resonance.3 After the initial diagnosis of primary extraprostatic malignancy, the relapse-free survival in metachronous secondary tumors of the prostate is variable, ranging from 5 months to 10 years, with the longest time to relapse reported in a case of colon cancer with distant solitary metastasis to the prostate gland.4 Of note, secondary tumors of the prostate may be discovered incidentally during diagnostic procedures for a concurrent primary prostate cancer, whereas cases of tumor-to-tumor metastases have also been described (Table 1).3,28

In this background, it appears that clinical signs and imaging findings in secondary tumors of the prostate are nonspecific, requiring histopathologic evaluation in the vast majority of the cases.1 However, pathologic identification and characterization of secondary tumors of the prostate is not trivial, with all challenges that their uncommonness poses.1 Morphologic and immunophenotypical resemblance to primary prostatic neoplasms and small specimen sizes, such as core biopsies, might even compound the task.10,15

MORPHOLOGY, MICROSCOPIC PATHOLOGY, AND DIAGNOSTIC ISSUES

On macroscopic examination, the prostate involved by metastatic deposits is frequently enlarged and stony hard, with well-demarcated, typically unencapsulated, spherical lobulated masses that can be variable in shape and size, measuring up to 7 cm, and may have a firm textured cut surface.13,17,23 However, given the spectrum of macroscopic features that primary prostate cancer may bear, these findings are not at all specific.1 Histologically, secondary tumors of the prostate have the propensity to reproduce the morphologic features of the tumor of origin.1 However, in the largest reported series of consecutive secondary tumors of the prostate, also encompassing cases of direct spread to the prostate as well as autopsy findings, the morphologic heterogeneity between primary tumors and secondary tumors of the prostate was observed.3 Meticulous morphologic analysis of the sample is required to identify and/or confirm the origin of the tumor, thus allowing tailored therapies. Whenever available, representative histologic slides of contingent previously diagnosed primary extraprostatic tumors should be retrieved to perform a direct comparison of the morphologic and immunohistochemical features of the two lesions.29 Secondary tumors of the prostate almost invariably present as neoplastic cells occurring widely through the prostate gland, often sparing normal/benign glandular elements with associated desmoplastic stromal response; tumor populations may be arranged in variable patterns, according to the primary histotype.2,16,23,30 Multifocal vascular invasion may often be detected, supporting the hematogenous spread of the primary tumor.1,8,12,30 However, the identification of secondary neoplasms involving the prostate may be extremely problematic in cases with missing or unavailable clinical information and/or unknown primary malignancies.2

Primary Prostate Adenocarcinoma

Primary prostate cancer may resemble a constellation of different intraprostatic and extraprostatic neoplasms, including tumors with squamous, mucinous, signet-ring, neuroendocrine, transitional (urothelial), and sarcomatoid features.1 In this setting, given the high prevalence of these malignancies in patients with other concurrent neoplasms, the exclusion of a prostatic primary tumor is a critical diagnostic step.29,30 Immunohistochemistry remains a cornerstone and helps pathologists tackling the complexity of this issue. According to the International Society of Urologic Pathology, PSA and prostate-specific acid phosphatase (PSAP) are the most specific immunohistochemical markers of prostatic origin, which are usually negative in extraprostatic malignancies and are expressed in the vast majority of the primary prostate adenocarcinomas (Fig. 1).31 Pathologists should take into account, however, that negative immunoreactivity for PSA and PSAP may be observed in a subset of high-grade prostate adenocarcinomas and in postradiation

primary prostate cancer (Fig. 1).1,32 Such a behavior contributes to the diagnostic challenges of secondary tumors of the prostate, particularly in the presence of a poorly differentiated morphology.31,32 Recently, the homeobox protein Nkx-3.1 (NKX3.1) emerged as an excellent biomarker in the prostate.31,33 Immunohistochemical nuclear expression of this androgen-regulated tumor-suppressor protein is also helpful for prostatic-derived tumors and the normal secretory epithelium, being present only in a small subset of extraprostatic malignancies, such as estrogen and androgen receptor–positive breast cancer.33,34 Other newer prostatic lineage–associated markers include prostate-specific membrane antigen and prostein (p501s). These newer markers frequently retain their positivity in poorly differentiated prostatic tumors and at metastatic sites.

Gastrointestinal Cancer

The digestive tract represents the most common site of origin of metachronous secondary tumors of the prostate. In the majority of the cases, tumors involving the prostate are moderately differentiated colorectal adenocarcinomas 4; however, metastatic poorly differentiated colon cancer and gastric cancer have also been described.5,25 Usually, neoplastic deposits are composed of variably sized glands lined by a pseudostratified columnar atypical epithelium, giving rise to a striking desmoplastic stromal response in the prostate.3,30 This resembles a ductal adenocarcinoma of prostate histology. On immunohistochemistry, cytokeratin (CK) 7 and CK20 patterns of expression may be helpful in defining secondary tumors of the prostate of colorectal origin, as their expression typically mirrors the primary site,30,35 as depicted in Figure 1. Specifically, CK7 is expressed in up to 85% of the upper gastrointestinal tract tumors, such as gastric cancer, whereas tumors originating from the lower gastrointestinal tract, including colon cancer, are characteristically CK7 negative and CK20 positive, with the exception of a submodal group of rectal adenocarcinomas (Fig. 1).5,32 These data suggest that CKs, albeit informative, should be interpreted with caution in secondary tumors of the prostate, as rectal cancer almost invariably involves the prostate by means of direct invasion.36 Recent studies have confirmed that the overexpression of caudal-type homeobox 2 (CDX2) is a retained immunophenotypical feature of secondary tumors of the prostate originating in the colorectal tract, as primary prostate adenocarcinoma is predominantly CDX2 negative (Fig. 1).31 It should be noted, however, that the specificity of this nuclear transcription factor in the diagnosis of secondary tumors of the prostate is debatable, as approximately 20% of the well-differentiated primary prostatic adenocarcinomas display CDX2 immunohistochemical overexpression (Fig. 1).29,30,37 Combining the above markers with prostatic lineage markers could facilitate resolving this differential diagnosis, as PSA, PSAP, prostate-specific membrane antigen, and NKX3.1 are not expressed by gastrointestinal tumors (Fig. 1).5,29,31

Lung Cancer

There are presently no documented cases of squamous cell carcinoma of the lung metastatic to the prostate; however, lung adenocarcinoma represents one of the neoplasms with the greatest proclivity to spread to the prostate.12 These tumors consistently overexpress CK7, but more specific protein markers should be used in the characterization of prostatic metastases from the lung adenocarcinoma, such as thyroid transcription factor 1 (TTF1) and aspartic peptidase Napsin A.32 A combination of these antibodies has shown utility in detecting prostatic metastasis from lung adenocarcinomas, as primary acinar and ductal adenocarcinomas of the prostate are typically negative for both TTF1 and Napsin A, as detailed in Figure 1. One extremely aggressive form of lung cancer with strong metastatic potential that could provide significant diagnostic challenges is small cell carcinoma.15,38 Prostatic metastases of this tumor are morphologically characterized by pure well-demarked foci of oat cell neoplastic populations within the prostate stroma.39 In these cases, the main differential diagnosis is primary small cell carcinoma of the prostate, a rare neoplasm related to

androgen deprivation therapies that can present in association with acinar adenocarcinoma.40 Direct extension from a bladder small cell carcinoma may be associated with urothelial carcinoma in situ papillary or invasive tumor and may be GATA 3 positive. Disappointingly, immunohistochemical stains have very limited diagnostic value in this setting, as TTF1 expression as well as neuroendocrine markers are retained in the vast majority of the metastatic small cell carcinomas of the lung and in over 50% of the primary small cell carcinomas of the prostate, whereas PSA and PSAP are overexpressed in only 17% to 25% of the primary tumors, often focally (Fig. 1).41 Furthermore, NKX3.1 is negative in small cell carcinoma of the lung as well as in 82% of the primary small cell carcinomas of the prostate.33 More specific biomarkers are needed to characterize this condition, as the incidence of prostatic small cell carcinomas is likely to increase in the near future due to the use of new potent hormonal agents for prostate adenocarcinoma.42 As a matter of fact, the ability to distinguish prostatic metastases of lung cancer reliably is presently based on provider-specific clinical and pathologic assumptions.3,12

Renal Cell Carcinoma

Patients with clear cell renal cell carcinoma may present with delayed recurrences in unusual sites, including the prostate gland,16 as exemplified in Figure 2. In the presence of a clear cell phenotype, the use of an immunohistochemical panel composed of paired box (PAX) 8, PSA, and possibly vimentin show utility in differentiating primary prostatic clear cell carcinoma, originating in the prostatic urethra, from metastatic clear cell renal cell carcinoma (Fig. 1).17,43 These tumors demonstrate an excellent prognosis after radical prostatectomy in cases of solitary metastases,19 whereas in multimetastatic settings, hypofractionated radiotherapy may be preferred to achieve symptom palliation and a longer locoregional control.44

Urothelial Carcinoma

Carcinoma of urothelial origin may be accepted as a secondary tumor of the prostate when a prostatic stromal invasion without dysplasia/in situ change of the prostatic urothelium is detected in patients with a documented history of primary bladder tumor (Fig. 3).3 Whereas the clinical context and the pattern of invasion (direct vs. noncontiguous) remains a cornerstone in the identification of urothelial secondary tumors of the prostate, the nuclear expression of GATA-binding protein 3 (GATA3), recently emerged as a highly sensitive and reproducible biomarker of urothelial differentiation, is helpful to prove urothelial histogenisis.45,46 However, primary urothelial carcinoma of the prostate cannot be entirely ruled out on the basis of a history of bladder cancer, as urothelial tumors can arise synchronously in the bladder and the prostate as a consequence of multicentric tumorigenesis.47 Furthermore, direct extension of bladder carcinoma to the prostate gland is a relatively common finding in advanced-stage diseases. At present, the prognostic significance of this distinction, particularly in metachronous cases, is still unexplored due to their rarity. Recent studies provide evidence to suggest that prostatic stromal involvement by urothelial carcinoma seems to determine the outcome in itself, regardless of the primary site; however, these data refer to direct prostatic extension in stage III-IV and stage II-III urothelial carcinomas of the bladder and the prostatic urethra, respectively, without taking into account secondary tumors of the prostate.47

Malignant Melanoma

Prostatic localization of malignant melanoma is currently considered as a rare event occurring in patients with disseminated disease.2,48 Interestingly, cases of melanoma metastatic to a concurrent primary prostate cancer and resulting in a dismal prognosis have been reported.23,28 The identification of prostatic foci of melanoma is therefore pivotal in assessing the prognosis and in defining the most appropriate treatment

regimen for these patients. Other intrinsic melanin-containing lesions of the prostate should also be considered in the differential diagnosis, such as primary malignant melanoma of the prostate, prostatic blue nevus, and melanosis.49 These lesions may also occur in association with prostate adenocarcinoma.50 Given the wide spectrum of morphologic appearances that melanoma may exhibit, immunohistochemistry could be very helpful in confirming the tumor origin. In the diagnosis of metastatic melanoma, the use of S100 protein and melanoma antigen recognized by T cells 1 (MART1) is generally recommended, as combinations of these 2 immunomarkers have shown the highest levels of specificity and sensitivity in metastatic settings, including secondary tumors of the prostate.51

Soft Tissue Tumors

Involvement of the prostate by metastatic sarcomas is an exceptionally rare event occurring almost exclusively in the setting of advanced-stage diseases with peritoneal and pelvic involvement.2,48,52 The uncommonness of this condition together with its striking clinical landscape have led, in practical terms, to the exclusion of metastatic sarcomas in the differential diagnosis of spindle cell and undifferentiated tumors of the prostate, such as primary prostatic sarcomatoid carcinoma.1 It should be noted, however, that most primary mesenchymal malignancies originating from the specialized stromal tissue of the prostate (eg, stromal sarcomas) are clinically characterized by poor prognosis,1,53 whereas a subset of rarer stromal tumors, including stromal tumors of uncertain malignant potential, extraintestinal gastrointestinal tumor, and solitary fibrous tumor, present an unpredictable behavior.1 In contrast, prostatic inflammatory myofibroblastic tumors and nerve sheath tumors are reported to behave almost indolently.1 In this scenario, the recognition of secondary sarcomas of the prostate appear to be critical, given the possible unique clinical management of these conditions, as reported in a single case of solitary metachronous prostatic metastasis from a fibromyxoid sarcoma, in which, after pelvic radiotherapy, the patient had an excellent outcome.52

IMPLEMENTATION OF PRECISION MEDICINE IN SECONDARY TUMORS OF THE PROSTATE

This multifaceted scenario exemplifies the diagnostic challenges of secondary tumors of the prostate, confirming that multidisciplinary approaches are warranted to address the clinical implications of this issue. Unfortunately, the rarity of this heterogeneous group of conditions, together with the complexity of their medical ramifications, has questioned our ability to treat these patients successfully, with a conspicuous absence of focused studies aiming to improve our diagnostic potential and subsequent effective tailored therapies for secondary tumors of the prostate.

Combining Pathology With Avant-garde Molecular Tools

Recently, De Mattos-Arruda et al 54 provided direct evidence that massively targeted parallel-sequencing analysis can be of clinical value to determine the relationship between primary tumors and their metastatic deposits. Moreover, additional molecular techniques, including loss of heterozygosity analysis, array comparative genomic hybridization, and chromosomal breakpoint analysis, revealed a high level of concordance for recurrent somatic alterations between primary and metastatic cancer.55 Results of these studies highlight the potential of integrating conventional pathology with state-of-the-art molecular tools in establishing the clonal origin of neoplastic lesions, even in small biopsies. These approaches are emerging as pivotal tools to characterize metastatic neoplasms precisely; however, further studies are required to delineate clinical, biological, and specific diagnostic objectives in secondary tumors of the prostate. Recent advances in the biology of prostate cancer revealed that the RNA expression of prostate cancer antigen 3 (PCA3) is restricted to primary prostate tumors.56 So far, PCA3 has been shown to represent a promising

cancer-specific biomarker for differentiating primary prostate tumors from other malignancies, particularly in metastatic samples with possible overlapping PSA immunohistochemical overexpression, such as urothelial carcinoma. Wide multicentric studies are needed to unravel the clinical utility of PCA3 RNA testing in secondary tumors of the prostate, specifically in terms of its sensitivity. Intriguingly, a novel gene related to colon cancer invasion, namely the metastasis-associated in colon cancer 1 (MACC1), has been identified recently and characterized in a considerable number of primary and matched secondary colon carcinomas.57 These results highlight the role of molecular aberrations involving this transcriptional factor as driver genetic events in the multistep metastatic process of colon neoplasms. Further molecular studies focusing on the role of MACC1 as an additional tool in the diagnostic workup of secondary tumors of the prostate are warranted to improve our understanding of this critical issue. Massive parallel-sequencing analyses have recently provided insights in the characterization of metastatic small cell carcinoma of the lung, particularly in terms of differential diagnosis. There are several lines of evidence that prostatic adenocarcinoma and primary small cell carcinoma of the prostate harbor both a recurrent translocation involving transmembrane protease serine (TMPRSS) and an erythroblast transformation-specific related gene (ERG) as an early oncogenic event, suggesting a clonal relationship between different primary prostatic histotypes.58 Furthermore, TMPRSS and ERG genes are wild type in small cell carcinomas from other anatomic sites, implying the clinical utility of TMPRSS-ERG fusion as a reliable molecular biomarker in detecting the origin of small cell carcinomas.58,59 These data suggest that genomic profiles of primary lung tumor could reflect, to a certain degree, the genomic spectrum of patients' metastatic disease and may isolate key somatic alterations present in the various metastatic sites, including the prostate. However, the clinicoradiologic context (eg, positron emission tomography) remains a cornerstone in clarifying the behavior of these tumors with poor prognosis.1,15 At present, there are no validated molecular biomarkers in routine clinical use for metastatic clear cell renal cell carcinoma, and the identification of secondary tumors of the prostate originating from the kidney continues to be morphology-based with support from PAX 8 immunohistochemistry.16,17,20 However, it has recently been observed that the majority of the sporadic carcinomas of the kidney, both primary and metastases, present the involvement of the von Hippel-Lindau (VHL) gene.1,60,61 Specifically, the clear cell renal cell carcinoma samples included in the Cancer Genome Atlas and other published datasets available on cBioPortal 61 display recurrent somatic mutations in this tumor-suppressor gene in up to 53% of the cases, confirming that these alterations might be promising tools for the identification of metastatic deposits (Fig. 4).60 Clinicopathologic and molecular key features suggestive of tumor origin in secondary tumors of prostate are outlined in Figure 5.

Building Up Individual Therapeutic Gears

To date, no validated specific treatment protocols for secondary tumors of the prostate are available, and the prognosis of these patients is dogmatically considered poor.16,23 Radical prostatectomy may be recommended for patients with solitary synchronous and metachronous metastasis, whereas symptom control in patients with disseminated disease may be obtained with palliative procedures, such as urinary catheterization and surgical or transurethral resection of the prostate.13,16 Considerable progress has been made in the management of patients with advanced-stage tumors over the last decades, with the realization of substantial improvements in terms of the outcome and the life quality. Such advances have, at least in part, come from the development of polychemotherapy regimens, endocrine therapies, and targeted molecular therapies.62 For example, the reported case of a 77-year-old man with prostatic metastasis of renal cell carcinoma confirms the impressive antitumor activity of sunitinib, a multitargeted tyrosine kinase receptor inhibitor, even in metachronous secondary tumors of the prostate.17 Further improvements in survival, both in synchronous and metachronous metastatic settings, may be expected for solitary secondary tumors of the prostate, given the progress currently being made with targeted therapies for the corresponding primary tumors' histotypes, including pulmonary, colorectal, gastric, and renal cell

carcinomas. In contrast, the case reported two decades ago of a young male with small cell lung cancer metastatic to the prostate archetypes the subgroup of patients with disseminated disease harboring the worst outcome in the proto-personalized-medicine era.15 After the diagnosis was established by ultrasound-guided transrectal biopsies and bronchial lavage, this patient received 7 cycles of polychemotherapy. Regrettably, the primary pulmonary tumor responded with a remarkable remission, whereas the extent of the prostatic metastasis remained unchanged, even after massive radiotherapy regimens, confirming a substantial heterogeneity in terms of therapeutic responses between primary and secondary neoplasms.4,15 We are experiencing profound changes in the interpretation of the biology underpinning metastatic processes, with the extraordinary conception that the molecular heterogeneity between primary tumors and metastases, once defined, may potentially be translated and hence targeted in clinical practice, in particular, but not only, for rare and lethal conditions such as secondary tumors of the prostate.62 However, the natural question on why only a small subset of patients with specific tumor histotypes have the propensity to develop prostatic secondaries, compared with the vast majority of the population, is still open. This topic is not only of academic interest, but could have important clinical implications, given that the identification of a high-risk subgroup in secondary tumors of the prostate could help pathologists and oncologists to better characterize and treat each individual patients. At present, only mechanistic and speculative models involving the peculiar vascularization of the prostate, together with the characteristic immunologic environment of this exocrine gland, have been proposed to address this legitimate biological issue. These models, albeit trustable and convincing in their logical arrangement, appear to be insufficiently corroborated by functional studies and inadequately integrated by molecular insights. In particular, it should be taken into account that the epistasis between molecular alterations and between molecular alterations and the microenvironment in intraprostatic and extraprostatic neoplasms, together with the phenomenon of intragenic complementation, might play a fundamental role not only in tumorigenesis and disease progression, but also in terms of the response to specific therapeutic interventions.3,35,54,62 Currently, however, no prospective wide multicentric studies have been specifically designed to uncover the biology involving secondary tumors of the prostate, with a plethora of case reports and case series approaching this topic anecdotically, thus generating results not immediately translatable to specifically treat these patients.

CONCLUSIONS

The increasing frequency of secondary tumors of the prostate is bringing the variety of these conditions closer to clinical practice rather than to the status of oncologic oddities. However, the rarity of secondary tumors of the prostate together with their dismal prognosis has not led to a setup of studies aiming to characterize these entities comprehensively, from an integrated clinical, histopathologic, and molecular standpoint. It is unclear as to why some tumors metastasize to the prostate or why some metastases are unicentric and others multifocal when they involve the prostate. The prognosis, although poor, may also be highly variable between patients.

In this era of precision medicine, health care providers and research scientists should address the operational implications of the diagnosis of secondary tumors of the prostate. Multicenter studies are warranted to perform analyses on a larger scale of cases, and to start approaching the underlying biology of secondary tumors of the prostate. Furthermore, there is an opportunity to integrate into the available armamentarium for oncologists and pathologists, the combination of high-throughput sequencing, gene expression profiling, and bioinformatics technologies to define the biological landscape of cancers and to administer the most appropriate personalized treatment. Thus, a comprehensive clinical and pathogenomic approach may play a pivotal role in appropriately characterizing secondary tumors of prostate from a precision therapy and accurate prognostication point of view at an individualized level.

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TABLE

Table 1

Reference Number	Specimen	Primary Site	Occurrence	Histotype	Clinical Signs
22	Prostatectomy	Skin	Metachronous	Melanoma	Dysuria
22	Prostatectomy	Skin	Synchronous	Melanoma	Pelvic pain
24	Prostatectomy	Pancreas	Synchronous	Adenocarcinoma	Acute urinary retention, hematuria
18	Core biopsy	Kidney	Metachronous	Renal cell carcinoma	Acute urinary retention
23	Core biopsy	Skin	Synchronous	Melanoma	Acute urinary retention
9	Prostatectomy	Stomach	Metachronous	Adenocarcinoma	Acute urinary retention
6	Prostatectomy	Colon	Metachronous	Adenocarcinoma	Dysuria
15	Core biopsy	Lung	Synchronous	Small cell carcinoma	Asymptomatic
19	Core biopsy	Kidney	Synchronous	Renal cell carcinoma	Dysuria
19	Core biopsy	Kidney	Metachronous	Renal cell carcinoma	Dysuria, hematuria
3	Prostatectomy	Bladder	Synchronous	Urothelial carcinoma	Tumor-to-tumor metastasis
8	Core biopsy	Colon	Metachronous	Adenocarcinoma	Acute urinary retention
3	Core biopsy	Lung	Metachronous	Small cell carcinoma	Dysuria
7	Core biopsy	Colon	Metachronous	Adenocarcinoma	Dysuria
20	Core biopsy	Kidney	Metachronous	Renal cell carcinoma	Asymptomatic, nodule on digital rectal examination
10	Core biopsy	Stomach	Metachronous	Signet-ring cell	Acute urinary retention
16	Core biopsy	Kidney	Metachronous	Renal cell carcinoma	Acute urinary retention, hematuria, weight loss
17	Core biopsy	Kidney	Metachronous	Renal cell carcinoma	Dysuria, hematuria
12	Core biopsy	Lung	Metachronous	Squamous cell carcinoma	Complicated urinary tract infection
11	Core biopsy	Stomach	Metachronous	Adenocarcinoma	Acute urinary retention
8	Core biopsy	Colon	Metachronous	Adenocarcinoma	Dysuria
21	Core biopsy	Kidney	Metachronous	Renal cell carcinoma	Acute urinary retention
5	Core biopsy	Stomach	Synchronous	Adenocarcinoma	Diffuse abdominal pain
Present study	Core biopsy	Kidney	Metachronous	Renal cell carcinoma	Complicated urinary tract infection
Present study	Core biopsy	Bladder	Synchronous	Urothelial carcinoma	Acute urinary retention, concurrent primary prostate adenocarcinoma

TABLE 1 An Overview of Metastatic Tumors With Solitary Prostatic Secondarisms

FIGURES

Figure 1

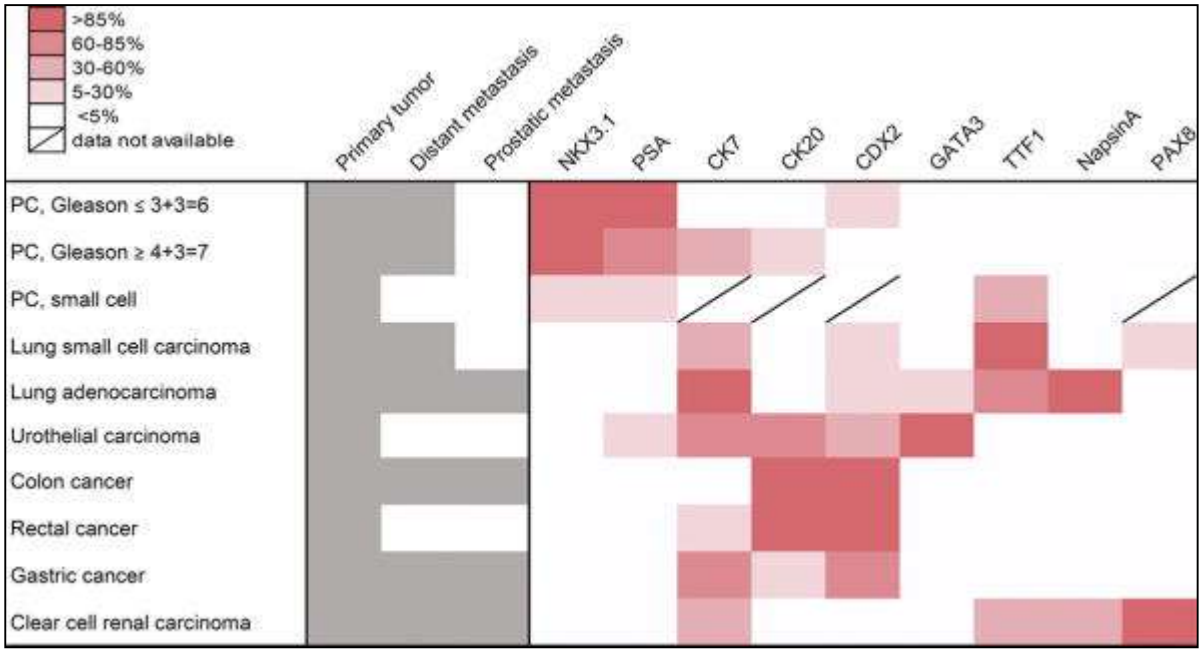

FIGURE 1 . A diagram illustrating the immunohistochemical expression of selected markers in epithelial neoplasms affecting the prostate gland. Tumor types are depicted in rows, as indicated on the left; protein markers are represented in columns. Tumor origins pertaining to each immunophenotype is depicted in gray, whereas the frequency of tumors with a positive immunohistochemistry is color-coded on the basis of the percentage of immunoreactive cases, as explained in the color key. PC indicates prostate cancer

Figure 2

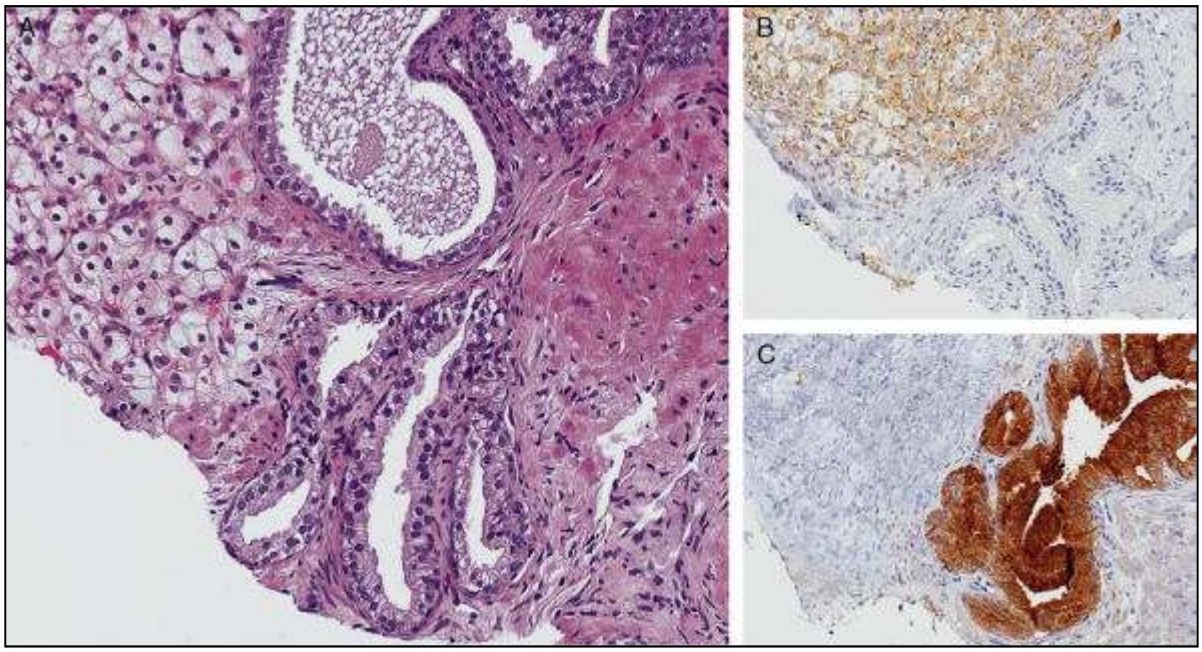

FIGURE 2 . Representative micrographs of a metachronous metastasis from renal cell carcinomas in a prostate core biopsy, 2 years after nephrectomy. The neoplastic deposit of malignant clear cells within the prostate stroma can be appreciated by hematoxylin and eosin (A) and vimentin immunostain (B), whereas non-neoplastic prostate ducts are highlighted by the expression of the prostate-specific antigen (C).

Figure 3

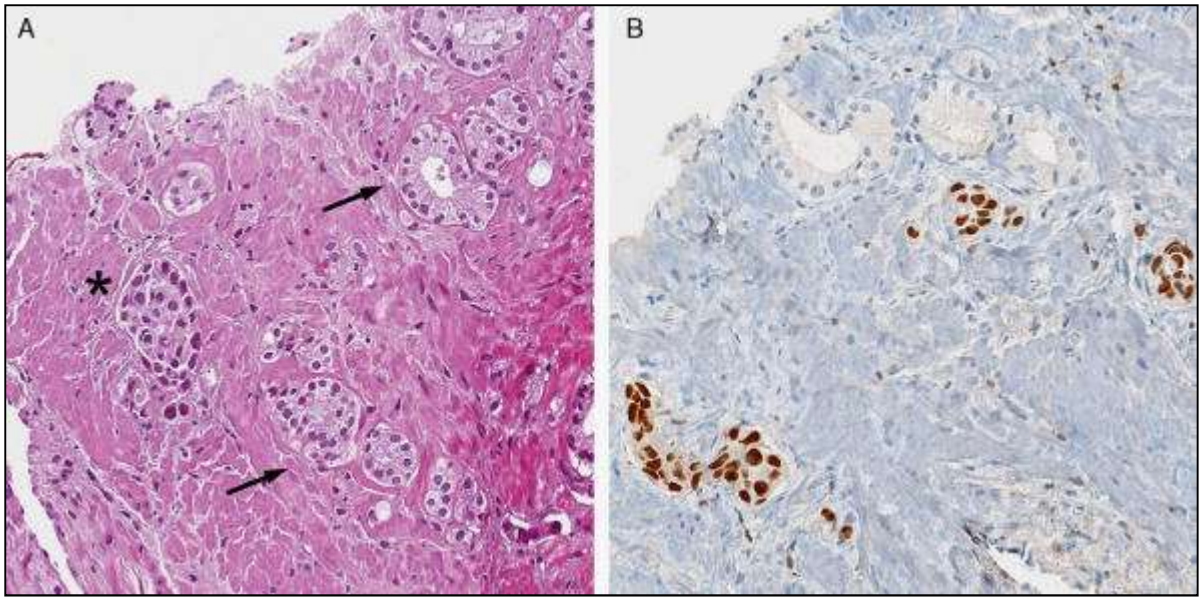

FIGURE 3 . Representative micrographs showing the coexistence of primary Gleason score 6 (3+3) acinar adenocarcinoma (arrows) and metastatic high-grade urothelial-cell carcinoma of the bladder (star) in a prostatic core biopsy. Given the morphologic resemblance of the double population of neoplastic cells on hematoxylin and eosin staining (A), the use of an immunohistochemical marker of urothelial origin, such as GATA3 (B), is requested to confirm the diagnosis. In this particular case, the histopathologic analysis allowed the identification of an unknown primary tumor of the bladder.

Figure 4

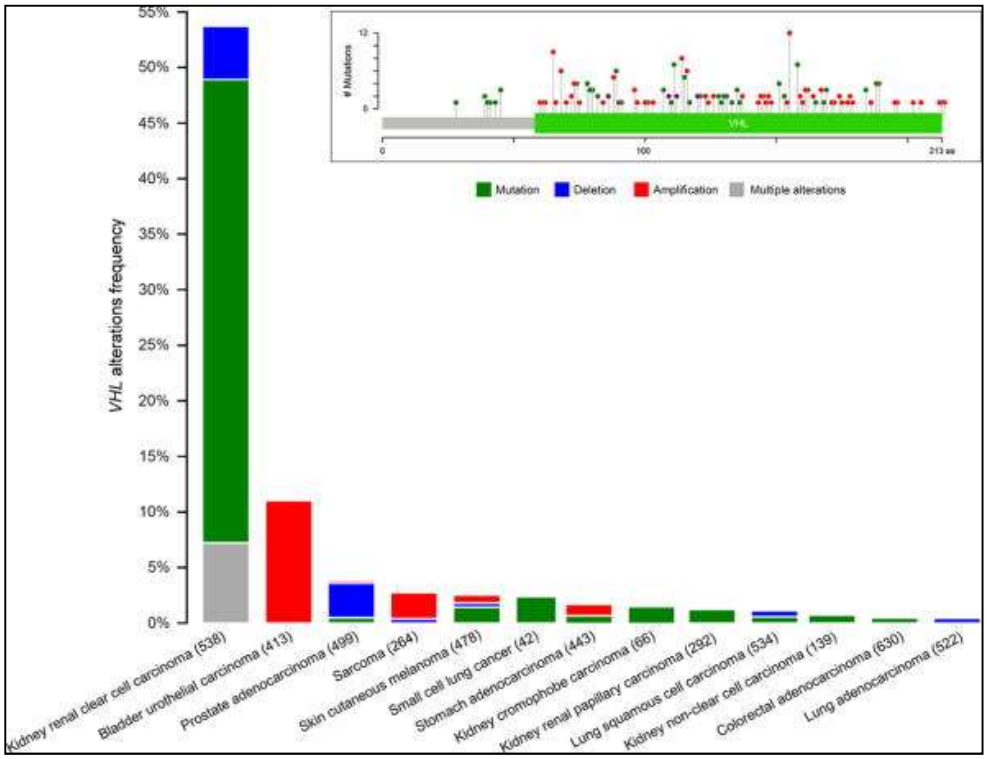

FIGURE 4 . VHL mutational frequencies from public datasets accessible from cBioPortal 61 in renal clear cell carcinomas and in other primary cancer types reported to metastasize to the prostate gland. The number of samples with available data are shown within parentheses. The domain structure of the VHL protein and

alterations identified in primary clear cell renal cell carcinoma of the kidney available from cBioPortal 60 (inset on the top right) show the absence of hotspot mutations. Mutation types are color-coded on the basis of the legend on the top.