

Journal Pre-proof

Human
PATHOLOGY

Metastatic solid tumors to the testis: a clinicopathologic evaluation of 157 cases from an international collaboration

Luiz M. Nova-Camacho, MD, Andres M. Acosta, MD, Kiril Trpkov, MD, Ankur R. Sangui, MD, Allaume Pierre, MD, Angela Chou, FRCPA, PhD, Asli Yilmaz, MD, Aurélien Morini, MD, Ângelo Rodrigues, MD, Christopher DM. Fletcher, MD, FRCPath, Delia Perez-Montiel, MD, Fiona Maclean, MBBS, FRCPA, Félix Contreras, MD, PhD, Francisco Javier Queipo, MD, Gorka Muñiz Unamunzaga, MD, Hector Mesa, MD, PhD, Inés de Torres, MD, PhD, Irune Ruiz, MD, Isabel Alvarado-Cabrero, MD, PhD, João Lobo, MD, PhD, Lauren Schwartz, MD, Liang Cheng, MD, Mahmut Akgul, MD, María García-Martos, MD, PhD, Matthew B. Palmer, MD, Manju Aron, MD, Maria Rosaria Raspollini, MD, Manuel Manrique Celada, MD, Michael Hwang, MD, Muhammad T. Idrees, MD, Nathalie Rioux-Leclercq, MD, Nicole Zalles, MD, PhD, Norge Vergara, MD, Priti Lal, MD, Sara Wobker, MD, Solène-Florence Kammerer-Jacquet, MD, Susan Prendeville, MD, Théau Tilmant, MD, Thomas M. Ulbright, MD, Virginie Verkarre, MD, PhD, Katrina Collins, MD, Sean R. Williamson, MD, Angel Panizo, MD, PhD

PII: S0046-8177(23)00135-1

DOI: <https://doi.org/10.1016/j.humpath.2023.06.002>

Reference: YHUPA 5475

To appear in: *Human Pathology*

Received Date: 28 March 2023

Revised Date: 31 May 2023

Accepted Date: 13 June 2023

Please cite this article as: Nova-Camacho LM, Acosta AM, Trpkov K, Sangui AR, Pierre A, Chou A, Yilmaz A, Morini A, Rodrigues Â, Fletcher CD, Perez-Montiel D, Maclean F, Contreras F, Queipo FJ, Unamunzaga GM, Mesa H, de Torres I, Ruiz I, Alvarado-Cabrero I, Lobo J, Schwartz L, Cheng L, Akgul M, García-Martos M, Palmer MB, Aron M, Raspollini MR, Celada MM, Hwang M, Idrees MT, Rioux-Leclercq N, Zalles N, Vergara N, Lal P, Wobker S, Kammerer-Jacquet S-F, Prendeville S, Tilmant T, Ulbright TM, Verkarre V, Collins K, Williamson SR, Panizo A, Metastatic solid tumors to the testis: a clinicopathologic evaluation of 157 cases from an international collaboration, *Human Pathology*, <https://doi.org/10.1016/j.humpath.2023.06.002>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Elsevier Inc. All rights reserved.

Metastatic solid tumors to the testis: a clinicopathologic evaluation of 157 cases from an international collaboration

Luiz M. Nova-Camacho MD ^{a,*}, Andres M. Acosta MD ^{b,c}, Kiril Trpkov MD ^d, Ankur R. Sangoi MD ^e, Allaume Pierre MD ^f, Angela Chou FRCPA, PhD ^g, Asli Yilmaz MD ^d, Aurélien Morini MD ^h, Ângelo Rodrigues MD ⁱ, Christopher DM Fletcher MD, FRCPath ^b, Delia Perez-Montiel MD ^j, Fiona Maclean MBBS, FRCPA ^k, Félix Contreras MD, PhD ^l, Francisco Javier Queipo MD ^m, Gorka Muñiz Unamunzaga MD ^m, Hector Mesa MD, PhD ⁿ, Inés de Torres MD, PhD ^o, Irune Ruiz MD ^a, Isabel Alvarado-Cabrero MD, PhD ^p, João Lobo MD, PhD^{i,q,r}, Lauren Schwartz MD ^s, Liang Cheng MD ^t, Mahmut Akgul MD ^u, María García-Martos MD, PhD ^v, Matthew B. Palmer MD ^s, Manju Aron MD ^w, Maria Rosaria Raspollini MD ^x, Manuel Manrique Celada MD ^a, Michael Hwang MD ⁿ, Muhammad T. Idrees MD ⁿ, Nathalie Rioux-Leclercq MD ^f, Nicole Zalles MD, PhD ^y, Norge Vergara MD ^s, Priti Lal MD ^s, Sara Wobker MD ^z, Solène-Florence Kammerer-Jacquet MD ^f, Susan Prendeville MD ^{aa}, Théau Tilmant MD ^{ab}, Thomas M. Ulbright MD ⁿ, Virginie Verkarre MD, PhD ^{ab}, Katrina Collins MD ⁿ, Sean R. Williamson MD ^y, Angel Panizo MD, PhD ^{ac}

Affiliations

- ^a Department of Pathology, Donostia University Hospital, San Sebastian, 20014, Spain
- ^b Department of Pathology, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, 02115, USA
- ^c Department of Pathology, Faulkner Hospital, Boston, MA, 02130, USA
- ^d Department of Pathology and Laboratory Medicine, University of Calgary, Calgary, T2V 1P9, Canada
- ^e Department of Pathology, El Camino Hospital, Mountain View, CA, 94040, USA
- ^f Department of Pathology, CHU Rennes - Hôpital Pontchaillou, Rennes, 35000, France
- ^g Department of Anatomical Pathology, Royal North Shore Hospital and University of Sydney, Sydney, 2065, Australia
- ^h Department of Pathology, Grand Hôpital de l'Est Francilien, Jossigny, Ile-de-France, 77600, France
- ⁱ Department of Pathology, Portuguese Oncology Institute of Porto, Porto, 4200-072, Portugal
- ^j Department of Pathology, Instituto Nacional de Cancerología, Mexico City, 14080, Mexico
- ^k Department of Pathology and Laboratory Medicine, Douglass Hanly Moir Pathology, Sonic Healthcare, Sydney, 2000, Australia
- ^l Laboratorio de Patología, Clínica Universitaria Unión Médica, PUCMM, Santiago, 51000, Dominican Republic
- ^m Department of Pathology, San Jorge University Hospital, Huesca, 22004, Spain
- ⁿ Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, 46202, USA
- ^o Department of Pathology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, 08035, Spain
- ^p Department of Pathology Oncology, Star Medica Hospital, Oncology Hospital, IMSS, Mexico City, 03810, Mexico
- ^q Cancer Biology and Epigenetics Group, IPO Porto Research Center (GEBC CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto) & Porto Comprehensive Cancer Center (P.CCC), Porto, 4200-072, Portugal

^r Department of Pathology and Molecular Immunology, Institute of Biomedical Sciences Abel Salazar, University of Porto (ICBAS-UP), Porto, 4050-313, Portugal

^s Department of Pathology, University of Pennsylvania, Philadelphia, PA, 19104, USA

^t Department of Pathology and Laboratory Medicine, Brown University Warren Alpert Medical School, Providence, RI, 02903, USA

^u Department of Pathology and Laboratory Medicine, Albany Medical Center, Albany, NY, 12208, USA

^v Department of Pathology, Gregorio Marañón University Hospital, Madrid, 28007, Spain

^w Department of Pathology and Laboratory Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, 90033, USA

^x Histopathology and Molecular Diagnostics, Careggi University Hospital, Florence, 50134, Italy

^y Department of Pathology and Laboratory Medicine, Cleveland Clinic, Cleveland, OH, 44106, USA

^z Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA

^{aa} Laboratory Medicine and Pathobiology, University of Toronto, Toronto, M5S 1A1, Canada

^{ab} Department of Pathology, European Georges Pompidou Hospital, Université Paris-Cité, Paris, 75015, France

^{ac} Department of Pathology, University Hospital of Navarra, Pamplona, 31008, Spain

*** Corresponding Author:**

Luiz M. Nova-Camacho, M.D.

Department of Pathology, Donostia University Hospital,
Begiristain Doktorea Pasealekua, s/n, 20014 San Sebastian, Spain

E-mail: luismi_15_16@hotmail.com

Phone: +1 (352) 436-3345

Twitter: @LuizMiguelN

Running title: Metastatic solid tumors to the testis

Word count: 2807

Conflict of interest statement: The authors have no conflicts of interest to disclose.

Data availability statement: The data generated in this study are available from the corresponding author upon request.

Funding statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Approval/Consent to Participate: Retrospective study not interfering with diagnosis and patient management.

Clinical trial registration: No

This work has been presented as a poster during the United States & Canadian Academy of Pathology's 112th Annual Meeting, March 11-16, 2023, in New Orleans, Louisiana. (Poster Session on Wednesday, March 15, 2023, from 9:30 AM - 12:00 PM at the New Orleans Ernest N. Morial Convention Center in Exhibit Hall B).

Abstract

Aims: To elucidate the spectrum of metastatic solid tumors to the testis and their clinicopathologic features.

Methods: The databases and files of 26 pathology departments from 9 countries on 3 continents were surveyed to identify metastatic solid tumors to the testis and to characterize their clinicopathologic features in detail.

Results: We compiled a series of 157 cases of metastatic solid tumors that secondarily involved the testis. The mean patient age at diagnosis was 64 years (range, 12 to 93 years). Most patients (127/144; 88%) had clinical manifestation of the disease, with testicular mass/nodule (89/127; 70%) being the most common finding. The main mechanism of testicular involvement was metastasis in 154/157 (98%) cases. Bilateral testicular involvement was present in 12/157 (8%) patients. Concurrent or prior extratesticular metastases were present in 78/101 (77%) patients. The diagnosis was made mainly in orchectomy specimens (150/157; 95%). Different types of carcinomas (138/157; 87%), most commonly adenocarcinoma (72/157; 46%), were the most common malignancies. The most common primary carcinomas included prostatic (51/149; 34%), renal (29/149; 20%), and colorectal (13/149; 9%). Intratubular growth was identified in 13/124 (11%) cases and paratesticular involvement was found in 73/152 (48%) cases. In patients with available follow-up (110/157; 70%), more than half (58/110; 53%) died of disease.

Conclusion: In this largest series compiled to date, we found that most secondary tumors of the testis represent metastases from the genitourinary and gastrointestinal tract carcinomas and typically occur in the setting of disseminated disease.

Keywords: testis, testicular, metastasis, secondary tumors

1. Introduction

Testicular neoplasms are rare and account for approximately 1% of all malignancies affecting male patients worldwide. However, testicular cancer is the most common solid malignancy affecting young post-pubertal men, peaking at 30-40 years of age, and showing the highest incidence in developed countries. Most primary neoplasms arising in the testicular parenchyma are of germ cell origin (about 95%) and, much less frequently, of sex-cord stromal derivation [1,2].

Unlike other sites such as liver and lungs, metastases to the testes are rare and often found in patients with an established history of malignancy [1-3]. In prior studies, the most frequent sites of origin of metastatic solid tumors to the testes were prostate, stomach, lung, skin (melanoma), colon/rectum, kidney, and urinary bladder [2]. There have been approximately 500 examples documented in the English language literature, mostly as case reports and small case series [1,3-9]. Thus far, the largest cohorts of secondary solid malignancies of the testis were compiled by Dutt et al. [10] and Price et al. [11], which included 31 and 38 cases, respectively. In this study, we evaluated a large, multi-institutional, contemporary series of secondary solid tumors of the testis and evaluate the clinicopathologic features and outcomes of patients with secondary malignant involvement of the testis. Although hematological cancer can also form a testicular mass, in this work the term “solid tumor” refers exclusively to tumors forming solid testicular metastatic tumors that do not include hematological neoplasms.

2. Material and Methods

2.1. Cohort selection

The databases and files of 26 pathology departments from 9 countries on 3 continents, which included several large tertiary and quaternary referral centers, were surveyed to identify metastases of solid tumors to the testis (excluding hematological neoplasms).

2.2. Clinical and histopathological features

Medical records and pathology reports were reviewed to obtain clinical data that included: age, clinical presentation, prior history of cancer, type of spread (direct invasion or metastatic spread), concurrent metastatic disease to other sites, time from primary diagnosis to testicular metastasis, time from testicular metastasis to last follow-up, and status at last follow-up.

Pathology reports and/or available slides of the testicular metastases were reviewed to collect the following information: specimen type, laterality, gross appearance, tumor size, histologic type, primary site, lymphovascular invasion, paratesticular involvement, presence of an intratubular component, results of the diagnostic immunohistochemical workup and results of molecular studies (when available). Representative macroscopic and microscopic images of selected cases were obtained from the corresponding pathologists.

All data were compiled in a Microsoft Excel (2019) (Microsoft Corporation, Redmond, Washington, United States) and analyzed using both the Microsoft Excel (2019) and the IBM SPSS statistic for macOS software version 29.0 (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Cohort demographics

One hundred and fifty-seven (157) patients were included in the study (4 cases were reported previously and 2 are currently in press) [3,12,13]. The mean and median age at

diagnosis was 64 and 65 years, respectively (range 12-93 years). Of note, only 4/157 (2.5%) patients were under the age of 30 years, including a 24-year-old with von Hippel-Lindau syndrome-associated clear cell renal cell carcinoma, a 28-year-old with a neuroendocrine carcinoma of the lung, a 29-year-old with a poorly differentiated adenocarcinoma of the lung, and a 12-year-old with alveolar rhabdomyosarcoma of the right zygomatic arch.

3.2. Clinicopathologic Findings

A detailed oncologic history was available for 141/157 (89%) patients. Of those with available history 123 (87%) had a known prior or concurrent malignancy, while testicular involvement was the initial clinical manifestation of disease in the remaining 18 (13%) patients. Detailed information about the clinical presentation was available for 144/157 (91%) patients, of which the great majority (127/144; 88%) had a clinical manifestation of disease. The most common clinical presentations were testicular mass/nodule (89/127; 70%), and testicular pain (13/127; 10%). In 17/144 (12%) patients, testicular involvement was discovered incidentally on imaging studies or in orchectomy specimens, the latter of which comprised 14/144 (10%) cases identified after bilateral orchectomy for surgical castration in patients with advanced prostate cancer (Table 1).

The diagnosis was made on a variety of specimen types, including orchectomy (149/157; 95%), biopsy (4/157; 3%), autopsy (3/157; 2%), and epididymectomy (1/157; 1%).

Testicular involvement was unilateral in 145/157 (92%) patients, with almost equal distribution: left side in 72 (49%) patients and right side in 69 (48%) patients. In 4 (3%) patients there was no information on laterality. Involvement was bilateral in 12/157 (8%) patients and included 6 prostatic adenocarcinomas, and one each, clear cell renal cell carcinoma, well-differentiated neuroendocrine tumor of the small intestine, colorectal

adenocarcinoma, melanoma of the skin, Kaposi sarcoma, and an alveolar rhabdomyosarcoma.

Information regarding the macroscopic appearance was available in 121/157 cases. The mean tumor size was 3.5 cm (range 0.1-13.5 cm), and gross appearances varied, with most cases exhibiting white-colored, well to poorly defined nodules/masses. A single lesion was found in 112/121 (93%) patients, while multiple lesions were found in 9/121 (7%) patients (Figure 1).

Data on the primary site of origin was available in 148/157 (94%) patients. The genitourinary tract was the most common primary site (93/148, 63%), followed by the gastrointestinal/pancreatobiliary tract (27/148, 18%), respiratory tract (12/148, 8%), skin (8/148, 5%), skeletal system (3/148, 2%), retroperitoneum (2/148, 1%), liver (1/148, 1%), pleura (1/148; 1%), and eye (1/148, 1%).

Within the genitourinary system, the most frequent primary sites were the prostate (51/148; 34%), and the kidney (29/148; 20%); rare genitourinary tract sites included Müllerian remnants (1/148; 1%), and the upper urinary tract (1/148; 1%). Within the gastrointestinal/pancreatobiliary tract, the most frequent sites were the colon/rectum (13/148; 9%), and the small intestine (4/148; 3%). Within the respiratory tract, the lungs were the most common primary site (11/148; 7%) (Table 2).

The most frequent histologic type was carcinoma (138/157; 88%), including adenocarcinoma [mucinous, signet ring cell, and not otherwise specified (NOS)] (72/157; 46%), renal cell carcinoma (RCC) (29/157; 18%) [clear cell (27 cases) and RCC NOS (2 cases)], and urothelial carcinoma (11/157; 7%) [conventional (9 cases), poorly differentiated (1 case), and with trophoblastic differentiation (1 case)], among others. Other histologic types included sarcoma (7/157; 4%), well-differentiated neuroendocrine tumor (6/157; 4%), melanoma (5/157; 3%), and mesothelioma (1/157; 1%) (Table 3). Of

note, there were no other recorded types of renal cell carcinoma that metastasized to the testis. Representative microscopic images are shown in Figures 2 and 3.

Among the metastatic prostate carcinomas, information regarding the specific histologic type was available for 22/51 (43%) cases. The great majority were acinar prostatic adenocarcinomas (19 cases), followed by ductal prostatic adenocarcinoma (1 case), poorly differentiated adenocarcinoma (1 case), and small cell carcinoma (1 case). In the remaining 29 cases, there was no available information on the histological type of the tumor from the medical records or pathology reports. Among the metastatic colorectal carcinomas, the most frequent histologic type was adenocarcinoma NOS (11 cases), followed by mucinous adenocarcinoma (1 case), and large cell neuroendocrine carcinoma (1 case). Among the metastatic pulmonary carcinomas, the histologic types included acinar adenocarcinoma (3 cases), poorly differentiated adenocarcinoma (4 cases), small cell carcinoma (2 cases), mucinous adenocarcinoma (1 case), and neuroendocrine carcinoma (1 case).

Ancillary studies (immunohistochemistry and/or molecular tests) were performed as part of the original diagnostic workup in 108/127 (85%) cases with available data. In the remaining 19 (15%) cases, the diagnosis of testicular metastasis was made based on morphology and the relevant clinical information.

In cases with available data, the mechanism of testicular involvement was by metastatic spread in nearly all the cases (154/155, 99%) and by direct spread in 1/155 (1%) case.

Lymphovascular invasion (LVI) was identified in 88/131 (67%) cases, including 7 with extensive LVI and intratubular tumor components, consistent with colonization of seminiferous tubules was demonstrated in 13/124 (10%) cases.

Seventy-three of 152 (48%) cases with available data demonstrated involvement of one or more paratesticular structures, including the epididymis (29/152, 19%), spermatic cord

(23/152, 15%), tunica vaginalis (13/152; 9%), and tunica albuginea (7/152; 5%). In 14/152 (9%) cases, the involved paratesticular structures were not specified. Involvement of the rete testis was present in 21/152 (13%) cases.

Data on metastases to other sites were available for 101/157 (64%) patients, of whom 78/101 (77%) had concurrent or prior extratesticular metastases and among those, 32/78 (41%) had metastasis to one extratesticular site, and 46/78 (59%) had metastases involving two or more extratesticular sites. In the remaining 23/101 (23%) cases, the testis was the only organ involved by the metastatic malignancy.

Information regarding the time from the primary diagnosis to the diagnosis of testicular metastasis was available for 105/157 (66%) patients. The mean and median time intervals between the primary diagnosis and testicular metastasis were 44 months and 22 months, respectively (range 0-288 months). In 12/105 (11%) patients, testicular metastasis was synchronous with the primary tumor and in 51/105 (49%) patients the testicular metastasis developed subsequently, within the first three years of the primary diagnosis. (Table 4).

Follow-up data were available for 110/157 (70%) patients. Of these, 58/110 (53%) died of the disease, 38/110 (35%) were alive with disease, 4/110 (4%) died of other causes, and 6/110 (5%) were alive without evidence of disease. Detailed information on the cause of death was unavailable for 4/110 (4%) patients. The mean and median time intervals between the diagnosis of the testicular metastasis and patient death of the disease were 22 months and 13 months, respectively (range 0 to 144 months).

4. Discussion

To our knowledge, the current study of 157 patients represents the largest and most comprehensive series reported to date on metastatic solid tumors to the testis. The novel

aspect of this study is that it represents a real-life practice evidence, generated by aggregating a broad multi-institutional and international experience on this topic. In this large series, we found that most secondary solid tumors to the testis represent metastasis from genitourinary and gastrointestinal tract primaries that typically occur in the setting of disseminated disease. Over the past decades, various aspects of this topic have been previously studied, largely in smaller and single institution studies [5,10,11]. An early study performed in 1956 by Price and Mostofi [11] found the ratio of secondary to primary testicular tumors was 0.02:1 (38/1600) over the time period analyzed. In their series, 6 cases were recognized clinically, 5 were diagnosed incidentally in orchectomy specimens for surgical castration, and 20 were found at time of autopsy. The most common primary site was the lung, followed by the prostate. In a study of 24,000 autopsies performed over the course of 49 years, 15 cases of metastatic carcinoma to the testis were identified (incidence of 0.6%) [5]. In this study, the most common primary site was also the lung. More recently, a retrospective study carried out at the Royal London Hospital by Dutt et al. [10] reported 31 secondary neoplasms involving the testis. Fourteen (4.6%) were discovered at autopsy and 10 (1.6%) were diagnosed in orchectomy specimens for testicular mass (4), testicular pain (1), hydrocele (1), and as incidental findings in orchectomies for the treatment of prostatic carcinoma (4). The most common primary sites were prostate, stomach, and lung. Ulbright and Young [3] reported 26 metastatic carcinomas to the testis, all of which showed clinical manifestation of disease and diagnosed in orchectomy specimens. The most common primary site was prostate, followed by the kidney, colon, urinary tract, lung, and esophagus. Several additional reports of individual cases and small case series have documented metastases of diverse tumor types including hepatocellular carcinoma, Merkel cell carcinoma, small cell carcinoma of the lung, prostate adenocarcinoma, gastric signet ring cell carcinoma,

urothelial carcinoma, medullary thyroid carcinoma, carcinoma of the bile duct, pancreatic adenocarcinoma, RCC, and neuroblastoma [8,12,13,14-25].

Metastases of solid tumors to the testis are rare and may be discovered incidentally, with a reported incidence that ranged from 0.06% to 4.6% [3-6,10,26,27]. In our study, based on the 7 cases (1 autopsy and 6 orchietomies) contributed from one of the main participating institutions, Donostia University Hospital (San Sebastian, Spain) over a 22-year period, we estimate the incidence at 3.6% of all orchietomy specimens, which is within the range of the previously reported data.

In accordance with the published literature [2,10,11], the mean and median age at presentation in our study was 64 and 65 years, respectively. However, 4 patients were younger than 30 years. Of these, two died of disease and one was alive with disease at the last follow-up (1 month). This highlights that metastases to the testis, albeit rare, do occur in younger patients warranting a critical evaluation of the histologic findings, especially when there is a history of prior malignancy [2].

Testicular metastases are commonly identified in patients with an established oncologic history [1-3]. In this series, 87% of the patients had a known malignancy, whereas testicular metastasis was the initial clinical manifestation of disease in the remaining 13% of the patients. Most patients (88%) in this study were symptomatic at presentation, with testicular mass/nodule and pain being the most common symptom(s).

Secondary testicular involvement is most often unilateral, with bilateral involvement seen in a relatively minor subset (about 15-20%) [17,21,28-31]. Consistently, most (92%) patients in our study demonstrated unilateral involvement (right: 45%, left: 47%), and the remaining 8% of the patients had bilateral testicular involvement.

Secondary testicular involvement may occur either by direct spread or via lymphatic or blood-borne routes [5, 7, 27]. In our study, most secondary testicular tumors (98%) were

metastases, with only 1 case (colorectal adenocarcinoma) spreading by contiguous invasion. Metastatic disease was associated with histologic evidence of lymphovascular invasion in most cases (67%).

In line with the results of prior studies, the most common primary site of testicular metastasis was prostate (34%), followed by the kidney (19%), colon/rectum (9%), lung (8%), and urinary bladder (7%) [2, 3, 6]. Dutt et al. [10] found that the most frequent histologic type was adenocarcinoma, followed by small round blue cell tumors. In the present series, the most common types were carcinoma (88%) including adenocarcinoma, NOS (46%), renal cell carcinoma (18%), and urothelial carcinoma (7%), followed by sarcoma (4%), well-differentiated neuroendocrine tumor (4%), melanoma (skin and uveal) (3%), and mesothelioma (1%).

Interestingly, where histological information was available, we observed that the great majority of metastatic prostate carcinomas to the testis were acinar adenocarcinoma. This differs from previously published studies where most cases of metastatic prostate carcinoma to the testicle and penis were ductal adenocarcinoma. [3,32] However, one of the previous studies included only three cases of testicular metastasis and another study only reported the histology details of two prostatic carcinoma cases. It should also be noted that most of the studies published on this topic do not offer detailed information on the histological type of prostate carcinoma. [5,10]

Generally, metastatic solid tumors to the testis infiltrate the testicular interstitium, sparing the seminiferous tubules [3,5,11]. However, Ulbright and Young [3] found that 27% of 26 metastatic carcinomas to the testis had at least focal (and sometimes prominent) intratubular growth (5 prostatic adenocarcinomas, 1 RCC, and 1 urothelial carcinoma). Cases with secondary colonization of the seminiferous tubules can be problematic, because the intratubular components may mimic intratubular germ cell neoplasia [3, 33].

In our study, secondary colonization of the seminiferous tubules was observed in 13 (10%) cases that included 7 prostatic adenocarcinomas, and one each of squamous cell carcinoma of the anus, small cell carcinoma of the lung, poorly differentiated carcinoma of the upper gastrointestinal tract, retroperitoneal sarcoma, carcinoma NOS of the urinary tract, and melanoma (of unknown primary or occult).

In a review of metastatic colorectal carcinoma to the testis, Hatoum et al. [7] found that 19/31 (61.3%) patients had extratesticular metastases at the presentation of the disease. In our series, 77% of the patients had concurrent or prior extratesticular metastases, with 59% demonstrating widespread disease involving two or more sites. In patients with available follow-up data, 53% died of disease, which highlights that testicular metastases typically occurs in the setting of widespread and advanced metastatic disease.

The main limitation of this study is its multi-institutional, retrospective, and descriptive design. In addition, because participating institutions had different laboratory information systems, obtaining detailed and comprehensive information from individual patient records was somewhat limited. However, despite these limitations, this represents by far the largest and most detailed multi-institutional series of metastatic solid tumors to the testis, which captures the broad spectrum of testicular secondary tumors across different countries and reflecting various clinical settings.

In conclusion, because of the broad multi-institutional nature of this study, which resulted in the largest and most detailed cohort compiled to date on this subject, this study extends our understanding of the secondary testicular tumors. The current study also strongly validates the prior published data, based on limited and mostly single institution series on this topic. We found that most patients presented with symptomatic testicular involvement in the context of a known oncologic history and/or disseminated disease.

Testicular metastasis should also be always considered in patients with testicular tumors and a history of a prior malignancy.

Author Contribution Statement: Concept, design, and coordination: LMNC, AP; contribution of cases: all authors; histopathological evaluation: all authors; analysis of clinical and histopathologic data: LMNC, AMA; manuscript draft: LMNC, AMA, KT; intellectual contributions: all authors; manuscript editing: all authors.

References

- [1] WHO. WHO classification of tumours: urinary and male genital tumours, ed. 5. Vol. 8. International Agency for Research on Cancer; 2022.
- [2] Robert E. Emerson and Thomas M. Ulbright. Neoplasms of the Testis. In: Liang Cheng, Gregory T. MacLennan, David G. Bostwick. Urologic Surgical Pathology. 4th ed. Elsevier; 2020, p. 731-833.
- [3] Ulbright TM, Young RH. Metastatic carcinoma to the testis: a clinicopathologic analysis of 26 nonincidental cases with emphasis on deceptive features. Am J Surg Pathol. 2008;32:1683-93. <https://doi.org/10.1097/PAS.0b013e3181788516>.
- [4] Nistal M, González-Peramato P, Paniagua R. Secondary testicular tumors. Eur Urol. 1989;16:185-8. <https://doi.org/10.1159/000471566>.
- [5] Pienkos EJ, Jablokow VR. Secondary testicular tumors. Cancer. 1972;30:481-5. [https://doi.org/10.1002/1097-0142\(197208\)30:2<481::aid-cncr2820300228>3.0.co;2-x](https://doi.org/10.1002/1097-0142(197208)30:2<481::aid-cncr2820300228>3.0.co;2-x).
- [6] Patel SR, Richardson RL, Kvols L. Metastatic cancer to the testes: a report of 20 cases and review of the literature. J Urol. 1989;142:1003-5. [https://doi.org/10.1016/s0022-5347\(17\)38969-3](https://doi.org/10.1016/s0022-5347(17)38969-3).
- [7] Hatoum HA, Abi Saad GS, Otrock ZK, Barada KA, Shamseddine AI. Metastasis of colorectal carcinoma to the testes: clinical presentation and possible pathways. Int J Clin Oncol. 2011;16:203-9. <https://doi.org/10.1007/s10147-010-0140-z>.
- [8] Datta MW, Ulbright TM, Young RH. Renal cell carcinoma metastatic to the testis and its adnexa: a report of five cases including three that accounted for the initial clinical presentation. Int J Surg Pathol. 2001;9:49-56. <https://doi.org/10.1177/106689690100900108>.

[9] Morichetti D, Mazzucchelli R, Lopez-Beltran A, et al. Secondary neoplasms of the urinary system and male genital organs. *BJU Int.* 2009;104:770-6.

<https://doi.org/10.1111/j.1464-410X.2009.08746.x>.

[10] Dutt N, Bates AW, Baithun SI. Secondary neoplasms of the male genital tract with different patterns of involvement in adults and children. *Histopathology*. 2000;37:323-31. <https://doi.org/10.1046/j.1365-2559.2000.00983.x>.

[11] Price Eb Jr, Mostofi Fk. Secondary carcinoma of the testis. *Cancer*. 1957;10:592-5. [https://doi.org/10.1002/1097-0142\(195705/06\)10:3<592::aid-cncr2820100326>3.0.co;2-3](https://doi.org/10.1002/1097-0142(195705/06)10:3<592::aid-cncr2820100326>3.0.co;2-3).

[12] Gigliano D, Lobo J, Lopes P, et al. Merkel cell carcinoma metastatic to the testis: report of a rare diagnosis and review of the literature. *Autops Case Rep*. 2020;11:e2020198. <https://doi.org/10.4322/acr.2020.198>.

[13] Santos-Lopes S, Lobo J, Henrique R, Oliveira J. Epididymal metastasis from prostate adenocarcinoma: An unusual and challenging diagnosis suspected in gallium-68 prostate-specific membrane antigen-positron emission tomography/computed tomography and histologically confirmed. *Urol Ann*. 2017;9:89-91. <https://doi.org/10.4103/0974-7796.198886>.

[14] Young RH, Van Patter HT, Scully RE. Hepatocellular carcinoma metastatic to the testis. *Am J Clin Pathol*. 1987;87:117-20. <https://doi.org/10.1093/ajcp/87.1.117>.

[15] Ro JY, Ayala AG, Tetu B, et al. Merkel cell carcinoma metastatic to the testis. *Am J Clin Pathol*. 1990;94:384-9. <https://doi.org/10.1093/ajcp/94.4.384>.

[16] Rosser CJ, Gerrard E. Metastatic small cell carcinoma to the testis. *South Med J*. 2000;93:72-3.

[17] Olorunsola IS, Etonyeaku AC, Lekwa BO, Ojo OS. Bilateral secondary testicular, epididymal and spermatic cords carcinoma of prostatic origin: a case report and review

of the literature. J Med Case Rep. 2021;15:222. [https://doi.org/10.1186/s13256-021-02807-4.](https://doi.org/10.1186/s13256-021-02807-4)

[18] Schaefer IM, Sauer U, Liwocha M, Schorn H, Loertzer H, Füzesi L. Occult gastric signet ring cell carcinoma presenting as spermatic cord and testicular metastases: "Krukenberg tumor" in a male patient. Pathol Res Pract. 2010;206:519-21. <https://doi.org/10.1016/j.prp.2010.02.006>.

[19] Morgan K, Srinivas S, Freiha F. Synchronous solitary metastasis of transitional cell carcinoma of the bladder to the testis. Urology. 2004;64:808-9.

<https://doi.org/10.1016/j.urology.2004.05.022>.

[20] Fukagawa E, Endo F, Kyono Y, Hashimoto J, Hattori K. Testicular metastasis from urothelial carcinoma of the bladder. IJU Case Rep. 2021;5:79-83.

<https://doi.org/10.1002/iju5.12398>.

[21] Orsolini F, Prete A, Falcetta P, et al. Bilateral testicular metastases of medullary thyroid carcinoma in an adult male with multiple endocrine neoplasia 2A syndrome: case report and review of literature. Eur Thyroid J. 2022;11:e210016.

<https://doi.org/10.1530/ETJ-21-0016>.

[22] Appeteccchia M, Barnabei A, Pompeo V, et al. Testicular and inguinal lymph node metastases of medullary thyroid cancer: a case report and review of the literature. BMC Endocr Disord. 2014;14:84. <https://doi.org/10.1186/1472-6823-14-84>.

[23] Tozawa K, Akita H, Kusada S, et al. Testicular metastases from carcinoma of the bile duct: a case report. Int J Urol. 1998;5:106-7. <https://doi.org/10.1111/j.1442-2042.1998.tb00253.x>.

[24] Cormio L, Sanguedolce F, Massenio P, Di Fino G, Bruno M, Carrieri G. Testicular metastasis as the first clinical manifestation of pancreatic adenocarcinoma: a case report. J Med Case Rep. 2015;9:139. <https://doi.org/10.1186/s13256-015-0626-4>.

- [25] Simon T, Hero B, Berthold F. Testicular and paratesticular involvement by metastatic neuroblastoma. *Cancer*. 2000;88:2636-41. [https://doi.org/10.1002/1097-0142\(20000601\)88:11<2636::aid-cncr28>3.0.co;2-k](https://doi.org/10.1002/1097-0142(20000601)88:11<2636::aid-cncr28>3.0.co;2-k).
- [26] García-González R, Pinto J, Val-Bernal JF. Testicular metastases from solid tumors: an autopsy study. *Ann Diagn Pathol*. 2000;4:59-64. [https://doi.org/10.1016/s1092-9134\(00\)90012-1](https://doi.org/10.1016/s1092-9134(00)90012-1).
- [27] Hanash KA, Carney JA, Kelalis PP. Metastatic tumors to testicles: routes of metastasis. *J Urol*. 1969;102:465-8. [https://doi.org/10.1016/s0022-5347\(17\)62174-8](https://doi.org/10.1016/s0022-5347(17)62174-8).
- [28] Moriyama S, Takeshita H, Adachi A, et al. Simultaneous bilateral testicular metastases from renal clear cell carcinoma: A case report and review of the literature. *Oncol Lett*. 2014;7:1273-5. <https://doi.org/10.3892/ol.2014.1830>.
- [29] Kamble VR, Agrawal PM. Bilateral Testicular Metastases from Occult Primary Prostate Cancer in a Young Adult: A Rare Case Report. *J Clin Diagn Res*. 2017;11:TD03-5. <https://doi.org/10.7860/JCDR/2017/25292.9783>.
- [30] Ozeki T, Fujiwara K, Shimonishi A, et al. Bilateral Testicular Metastases from Lung Adenocarcinoma Showing an Objective Response to Nivolumab: A Case Report and Review of the Literature. *Intern Med*. 2019;58:3277-82.
<https://doi.org/10.2169/internalmedicine.2927-19>.
- [31] Blumberg JM, Sedberry S, Kazmi SO. Bilateral asynchronous metastatic carcinoid tumor of the testis. *Urology*. 2005;65:174. <https://doi.org/10.1016/j.urology.2004.07.003>.
- [32] Tu SM, Reyes A, Maa A, et al. Prostate carcinoma with testicular or penile metastases. Clinical, pathologic, and immunohistochemical features. *Cancer*. 2002;94(10):2610-2617. doi:10.1002/cncr.10546

[33] Henley JD, Young RH, Wade CL, Ulbright TM. Seminomas with exclusive intertubular growth: a report of 12 clinically and grossly inconspicuous tumors. Am J Surg Pathol. 2004;28:1163-8. <https://doi.org/10.1097/01.pas.0000132742.12221.82>.

Tables

Table 1. Summary of demographics and clinical presentations.

Characteristic	n (%)
Number of patients	157
Mean/median age, years	64/65
Prior history of cancer	141
Yes	123 (87)
No	18 (13)
Clinically manifested disease	144
Yes	127 (88)
No	17 (12)
Symptoms and presentations	127
<i>Testicular mass/nodule</i>	89 (70)
<i>Testicular pain</i>	13 (10)
<i>Testicular swelling</i>	5 (5)
<i>Cyst</i>	2 (2)
<i>Other</i> ¹	18 (14)

¹Other symptoms/presentations include paratesticular lesion, enlarged testis, inguinal hernia, hydrocele, scrotal ulceration, varicocele, epididymitis, and dysuria.

Table 2. Primary sites of metastatic solid tumors to the testis (n=148).

Primary site	n (%)
Prostate	51 (34)
Kidney	29 (19)
Colon/rectum	13 (9)
Lung	11 (7)
Bladder	10 (7)
Skin (back, leg, left wrist, and right buttock)	8 (5)
Small intestine (jejunum and ileum)	4 (3)
Upper GI tract (probable pancreas/biliary tract/stomach)	3 (2)
Head & Neck	3 (2)
Appendix	2 (1)
Anus	2 (1)
Retroperitoneum	2 (1)
Mullerian remnant/Kidney	1 (1)
Urinary tract (site not specified)	1 (1)
Renal pelvis	1 (1)
Stomach	1 (1)
Pancreas	1 (1)
Gastrointestinal (site not specified)	1 (1)
Bronchus	1 (1)
Liver	1 (1)
Pleura	1 (1)
Eye (uvea)	1 (1)

Abbreviations: GI, gastrointestinal.

Note: numbers are rounded up to the integer value.

Table 3. Histologic types of metastatic solid tumors to the testis (n=157).

Histologic type	n (%)
Carcinoma	138 (88)
Adenocarcinoma (mucinous, signet ring cell, and NOS)	72 (46)
Renal cell carcinoma (clear cell and RCC NOS)	29 (18)
Urothelial carcinoma (conventional, poorly differentiated, and with trophoblastic differentiation)	11 (7)
Poorly differentiated carcinoma	10 (6)
Neuroendocrine carcinoma (small cell and large cell)	6 (4)
Merkel cell carcinoma	4 (3)
Squamous cell carcinoma	4 (3)
Hepatocellular carcinoma	1 (1)
Carcinoma	1 (1)
Sarcoma	7 (4)
Alveolar rhabdomyosarcoma	2 (1)
Rhabdomyosarcoma	1 (1)
Sarcoma (not specified)	1 (1)
Epithelioid angiosarcoma	1 (1)
GIST spindle cell type	1 (1)
Kaposi's Sarcoma	1 (1)
Well-differentiated neuroendocrine tumor	6 (4)
Melanoma (skin, uveal)	5 (3)
Mesothelioma	1 (1)

Abbreviations: NOS, not otherwise specified, GIST, gastrointestinal stromal tumor.

Note: numbers are rounded up to the integer value.

Table 4. Time interval between the primary tumor and testicular metastasis (n=105).

Months (years)	n (%)
0 / synchronous	12 (11)
1 to 12 (≤ 1)	24 (23)
13 to 36 (1 to 3)	27 (26)
37 to 60 (3 to 5)	17 (16)
61 to 120 (5 to 10)	15 (14)
> 121 (> 10)	10 (10)

Figure legends

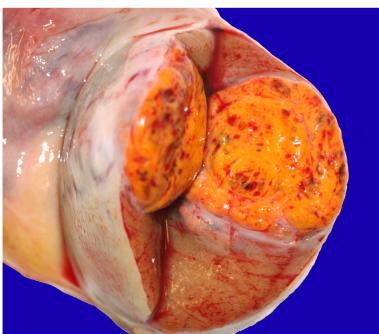
Figure 1. Representative macroscopic images of metastatic solid tumors to the testis. **A**, a case of metastasis of urothelial carcinoma from the urinary bladder. **B**, a case of metastasis of a clear cell renal cell carcinoma. **C**, a case of metastasis of a prostatic adenocarcinoma. **D**, one case of a well-differentiated neuroendocrine tumor from the ileum. **E**, a case of a large cell neuroendocrine carcinoma from the rectum. **F**, a case of a Merkel cell carcinoma from the left wrist.

Figure 2. Microscopic pictures of metastatic solid tumors to the testis. **A-C**, one case of well-differentiated neuroendocrine tumor from the ileum showing positivity for CDX2 and synaptophysin immunostain. **D-E**, one case of prostatic adenocarcinoma showing positivity for NKX3.1 immunostain. **F-G**, one case of poorly differentiated adenocarcinoma from the lung showing positivity for TTF-1 immunostain. **H-I**, one case of urothelial carcinoma with trophoblastic differentiation from the renal pelvis showing positivity for beta hCG immunostain. (A, x200 magnification; B, x200 magnification; C, x200 magnification; D, x400 magnification; E, x400 magnification; F, x200 magnification; G, x200 magnification; H, x200 magnification; I, x200 magnification).

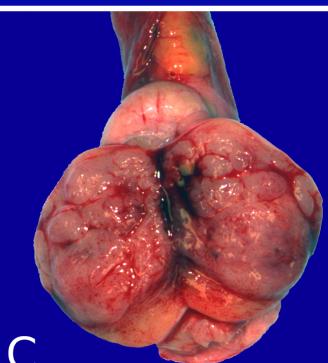
Figure 3. Microscopic pictures of metastatic solid tumors to the testis. **A-B**, one case of epithelioid angiosarcoma. **C-D**, one case of malignant melanoma from the back. **E-F**, one case of alveolar rhabdomyosarcoma from the right palate. (A, x20 magnification; B, x200 magnification; C, x20 magnification; D, x200 magnification; E, x20 magnification; F, x200 magnification).



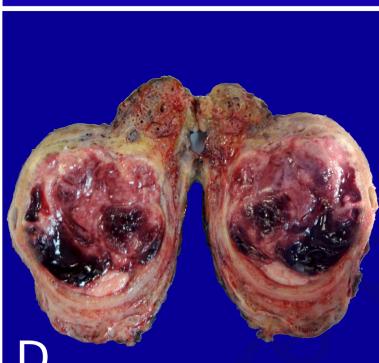
A



B



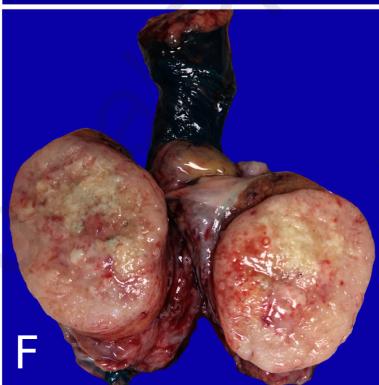
C



D



E



F

