A global approach to improving penile cancer care

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Abstract | Rare tumours such as penile carcinoma have been largely neglected by the urology scientific community in favour of more common — and, therefore, more easily fundable — diseases. Nevertheless, penile cancer represents a rising burden for health-care systems around the world, because a lack of widespread expertise, ineffective centralization of care and absence of research funds have hampered our ability to improve the global care of these patients. Moreover, a dichotomy has arisen in the field of penile cancer, further impeding care: the countries that are mainly supporting research on this topic through the development of epidemiological studies and design of clinical trials are not the countries that have the highest prevalence of the disease. This situation means that randomized controlled trials in developed countries often do not meet the minimum accrual and are intended to close before reaching their end points, whereas trials are almost completely absent in those areas with the highest disease prevalence and probability of successful recruitment, such as Africa, South America and South Asia. The scientific and organizational inaction that arises owing to this mismatch translates into a burdensome cost for our patients. A global effort to gather experts and pull together scientific data from around the world may be the best way to boost clinical research, to change clinical practice and, ultimately, to improve care for patients and their families.

The World Health Organization (WHO) has estimated 36,068 new cases of penile cancer in 2020, with an age-standardized incidence of 0.8 per 100,000 people worldwide[1]. Accordingly, penile cancer is the fourth-least common cancer type by incidence[1], and it is classified as a rare tumour according to the definition of the National Cancer Institute[2].

Despite its rarity, penile cancer is characterized by a heterogeneous geographical distribution, ranging from age-standardized incidence >2.0 per 100,000 inhabitants in Africa, South America and South Asia to an age-standardized incidence of <0.5 per 100,000 inhabitants in the Mediterranean countries, Middle East and East Asia[1]. This heterogeneous distribution has been linked to many factors, including socioeconomics, tobacco smoking, molecular and genetic predisposition, and rates of neonatal circumcision[3]. In this context, a Swedish population-based study investigated the effect of socioeconomic status on penile cancer risk[4], reporting that low educational level (OR 2.07, 95% CI 1.19–3.58), and being divorced (OR 1.84, 95% CI 1.17–2.90) or never married (OR 1.81, 95% CI 1.13–2.89) all increase the risk of advanced-stage penile cancer. Similarly, evaluation of the effect of socioeconomic variables on penile cancer stage, treatment delay and survival outcomes from a US study showed that lack of health insurance (OR 1.79, $P < 0.001$), Black race (OR 1.17, $P = 0.046$), Hispanic ethnicity (OR 1.66, $P < 0.001$) and living in nonmetropolitan areas (OR 1.46, $P = 0.008$) were identified as poor prognostic factors and associated with advanced stage, treatment delay and poor overall survival[5].

Thus, rarity and geographical heterogeneity are two factors that contrast with research efforts[6]: low-income countries are, in general, those with the highest prevalence of penile cancer, but obtaining the financial support and running the expensive randomized trials that are needed to advance our knowledge in these countries, is especially difficult. Thus, promoting research on penile cancer cannot be based on singular or isolated initiatives, but requires global efforts and structured collaborations, bringing together experts on several disciplines and from different countries to cooperate and advance research.

In this Perspective, we discuss the current situation in penile cancer research, exploring countries that are currently committed to promoting scientific research on penile cancer and how these countries are cooperating in this effort. We also discuss major issues surrounding the management of patients with penile cancer following the recommendations and claims of experts in the field from different geographical areas and discuss how the late presentation of penile cancer cases is pressurizing our health-care systems. Finally, we introduce the Global Society of Rare Genitourinary Tumors (GSRGT) as a unifying organization for addressing current shortcomings in penile cancer research and management.

The evolving state of research in penile cancer

Understanding the current status of penile cancer research around the world requires an appreciation of the available literature. Assessing the penile cancer literature over the past 5 years provides a snapshot of the state of research in penile cancer.

Primary literature versus incidence

A comparison of the author affiliations on research papers about penile cancer with worldwide incidence of the disease illustrates a profound discrepancy between the incidence of the disease and the number of published papers from different

Table 1 | **Per-nation publications, contributions to multi-institutional studies and ASR of penile cancer incidence in different countries**[1]

Region	ASR	Number of publications, *n* (%)	Multi-institution contributions, *n* (%)	Ratio[a] (%)
Africa	0.53	7 (1.6)	10 (1.2)	13.2
Egypt	0.03	3 (0.7)	3 (0.4)	100
Mozambique	1.8	1 (0.2)	1 (0.1)	0.6
Rwanda	3.4	1 (0.2)	5 (0.6)	0.3
South Africa	0.84	1 (0.2)	1 (0.1)	1.2
Tunisia	0.1	1 (0.2)	–	10
Asia	0.74	68 (15.4)	186 (22.5)	91.9
China	0.42	67 (15.2)	129 (15.6)	159.5
Hong Kong	–	1 (0.2)	–	–
India	1.6	12 (2.7)	13 (1.6)	7.5
Indonesia	0.74	3 (0.7)	2 (0.2)	4.1
Iran	0.11	3 (0.7)	5 (0.6)	27.3
Japan	0.25	8 (1.8)	22 (2.7)	32
Philippines	0.28	1 (0.2)	1 (0.1)	3.6
South Korea	0.20	5 (1.1)	3 (0.4)	25
Russia	0.71	1 (0.2)	1 (0.1)	1.4
Singapore	0.56	1 (0.2)	–	1.8
Thailand	1.3	1 (0.2)	–	0.8
Turkey	0.05	1 (0.2)	8 (1)	20
Vietnam	0.76	1 (0.2)	2 (0.2)	1.3
Europe	0.94	190 (43.1)	336 (40.7)	202.1
Austria	0.86	6 (1.4)	8 (1)	6.9
Belgium	1.0	5 (1.1)	6 (0.7)	5
Czech Republic	1.1	1 (0.2)	2 (0.2)	0.9
Denmark	1.2	11 (2.5)	16 (1.9)	9.2
Finland	0.68	1 (0.2)	1 (0.1)	1.5
France	0.76	9 (2)	21 (2.5)	11.8
Germany	1.1	35 (7.9)	65 (7.9)	31.8
Greece	0.77	3 (0.7)	3 (0.4)	3.9
Hungary	0.86	5 (1.1)	5 (0.6)	5.8
Ireland	0.92	3 (0.7)	7 (0.8)	3.3
Italy	0.79	27 (6.1)	64 (7.7)	34.2
Netherlands	0.97	20 (4.5)	28 (3.4)	20.6
Norway	1.3	1 (0.2)	3 (0.4)	0.8
Poland	1.3	6 (1.4)	8 (1)	4.6
Portugal	1.1	3 (0.7)	4 (0.5)	2.7
Romania	1.2	1 (0.2)	–	0.8
Spain	0.95	6 (1.4)	10 (1.2)	6.3
Sweden	0.91	10 (2.3)	23 (2.8)	10.9
Switzerland	0.79	2 (0.5)	2 (0.2)	2.5
United Kingdom	1.2	35 (7.9)	60 (7.3)	29.2
North America	0.51	108 (24.5)	139 (16.8)	211.8
Canada	0.57	11 (2.5)	9 (1.1)	19.3
United States	0.5	97 (22)	130 (15.7)	194
South America	1.3	63 (14.3)	144 (17.4)	48.5
Brazil	1.3	36 (8.2)	112 (13.6)	27.7

Table 1 (cont.) | **Per-nation publications, contributions to multi-institutional studies and ASR of penile cancer incidence in different countries**[1]

Region	ASR	Number of publications, *n* (%)	Multi-institution contributions, *n* (%)	Ratio[a] (%)
Chile	0.67	1 (0.2)	1 (0.1)	1.5
Colombia	1.9	5 (1.1)	6 (0.7)	2.6
Ecuador	1.2	1 (0.2)	1 (0.1)	0.8
Guatemala	0.29	1 (0.2)	1 (0.1)	3.4
Honduras	1.9	1 (0.2)	1 (0.1)	0.5
Mexico	1.0	5 (1.1)	6 (0.7)	5
Paraguay	3.4	11 (2.5)	15 (1.8)	3.2
Peru	1.4	1 (0.2)	–	0.7
Venezuela	1.8	1 (0.2)	1 (0.1)	0.5
Oceania	0.64	5 (1.1)	11 (1.3)	7.8
Australia	0.56	4 (0.9)	10 (1.2)	7.1
New Zealand	0.48	1 (0.2)	1 (0.1)	2.1

ASR, age-standardized rate per 100,000 population. [a]Ratio = number of publications/ASR; a higher ratio indicates a high concentration of publications relative to standardized incidence in that country or region.

geographical areas (TABLE 1). In particular, North America and Europe have made the highest contribution to the number of published studies in the past 5 years (24.5% and 43.1%, respectively), whereas, by contrast, studies by authors with affiliations from Asia (15.8%), South America (14.3%), Africa (1.6%) and Oceania (1.1%) are under-represented. Moreover, when considering multi-institutional involvement on penile cancer research, depicted as the age-standardized rate (ASR) of penile cancer incidence per 100,000 population, continents with the highest incidence of penile cancer, such as South America, Africa and Asia are minimally involved in multi-institutional projects, compared with North America and Europe (TABLE 1). Exceptions are China, which has an ASR of 0.42, and Brazil (ASR 1.3), which are examples of countries with a high incidence of penile cancer that are also among the most involved in multi-institutional initiatives, compared with the other countries of the continent to which they belong[3,7]. Notably, 69.3% and 77.8% of multi-institutional projects conducted in Asia and South America originated from China and Brazil, respectively (TABLE 1).

Registry data

Data from a registry-based source analysis are even more demonstrative of the gap between incidence of penile cancer and the sources of scientific data in developing countries (TABLE 2). Registries are a valuable source of data for studies that focus on epidemiology, risk factors and the natural history of diseases, especially when considering rare tumours[8]. Unfortunately, registries of patients with penile cancer are scant and, again, they are not properly located in those areas of the world where this type of tumour is most prevalent — North America and Europe have the highest rate of active registries that contribute the most to penile cancer research, despite the comparatively low rates of the disease in those areas (TABLE 2).

Clinical trials

A search of ClinicalTrials.gov including the keywords 'penile cancer' identifies 69 studies, 46 of which could be excluded from discussion because the trial was not focusing on penile cancer or because they were not recruiting patients. The final selection yields 23 ongoing randomized controlled trials (RCTs) from 11 countries (TABLE 3). Notably, all the ongoing clinical trials available worldwide are enrolling patients with node-positive or unresectable disease and 60.9% of these are treating patients with immune checkpoint inhibitors alone or combined with chemotherapy, radiotherapy or receptor tyrosine kinase inhibitors. Conversely, trials focusing on locally confined disease (cN0M0) are lacking. For other common neoplasms, clinical trials are enrolling patients with both advanced and localized disease, whereas the clinical research of penile cancer is focused only on advanced disease, which has a poor prognosis. Prevention and early treatment of localized penile cancer must be improved to reduce cancer mortality, especially in those countries with the highest incidence.

RCTs are the ideal setting for treating patients with the most appropriate and innovative treatment options for their tumour. For instance, two landmark clinical trials of systemic therapy conducted in penile cancer showed that chemotherapy using the TIP (paclitaxel, ifosfamide and cisplatin) or TPF (5-fluorouracil, cisplatin and docetaxel) regimens could be offered equally to patients with locally advanced penile cancer who are fit enough to tolerate them[9,10].

However, the overall number of active RCTs on penile cancer is low worldwide, and this becomes even more concerning when considering countries with the highest incidence of the disease. We note that Africa and Oceania, where the incidence of penile cancer is 5.7% and <1%[1], respectively, are entirely devoid of recruiting RCTs, whereas in South America ($n = 1$) and Asia ($n = 1$), where the incidence of penile cancer is 13.8% and 56.3%[1], respectively, only two trials are ongoing, preventing patients from receiving advanced or innovative treatments. Furthermore, only 34.8% ($n = 8$) of these 23 RCTs are exclusively enrolling patients with penile cancer; the remainder are focused on HPV-related tumours or advanced malignancies, and include penile cancer among others (TABLE 3).

Thus, availability of RCTs across continents or vast geographical areas would be ideal, enabling patients to access those trials even if their country of origin has none; referring patients to a trial in a neighbouring country where a suitable RCT is available could be a solution, without the obligation of long and expensive journeys. Of course, this brief analysis of clinical trials is limited by the fact that not all ongoing trials are registered on ClinicalTrials.gov, and ongoing studies that are recorded on different national registries are not included[11].

Table 2 | **Relative contribution of countries to penile cancer research according to publications based on national cancer registries**

Continent or country, total *n* (%)	Registry	Number of publications by registry, *n* (%)
Asia 4 (5.8)	–	–
China 1 (1.4)	China Cancer Registry	1 (1.4)
Japan 1 (1.4)	Nationwide hospital cancer registry database	1 (1.4)
South Korea 2 (2.9)	KNCIDB (National Cancer Incidence Database)	1 (1.4)
	NHI (National Health Insurance Claim Database)	1 (1.4)
Europe 17 (24.7)	–	–
Denmark 6 (8.8)	DaPeCa (Danish Penile Cancer Database)	6 (8.9)
France 1 (1.4)	FRANCIM (French Network Cancer Registries)	1 (1.4)
Germany 1 (1.4)	Common Cancer Registry	1 (1.4)
Netherlands 1 (1.4)	PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief)	1 (1.4)
Norway 1 (1.4)	CRN (Cancer Registry of Norway)	1 (1.4)
Spain 1 (1.4)	CMBD (Conjuncto Minimo Basico de Datos)	1 (1.4)
Sweden 5 (7.4)	PenCBaSe (Penile Cancer Database Sweden)	2 (2.9)
	NPECR (National Penile Cancer Register)	2 (2.9)
	Swedish Family Cancer Database	1 (1.4)
UK 1 (1.4)	UK National Cancer Registry	1 (1.4)
North America 45 (65.2)	–	–
Canada 2 (2.9)	Canadian Cancer Registry	2 (2.9)
USA 43 (62.5)	NCDB (National Cancer Database)	23 (33.4)
	SEER (Surveillance, Epidemiology, and End Results)	13 (18.9)
	SHRI (State Health Registry of Iowa)	1 (1.4)
	DLD (Iowa Driver License Database)	1 (1.4)
	Iowa Oncology Registry	1 (1.4)
	Florida Cancer Data System	1 (1.4)
	National Inpatient Sample Database	1 (1.4)
	American Board of Urology Case Logs	1 (1.4)
	ACS National Surgical Quality Improvement Program	1 (1.4)
Oceania 2 (2.9)	–	–
Australia 2 (2.9)	Central Cancer Registry	1 (1.4)
	South Australian Cancer Registry	1 (1.4)
South America 1 (1.4)	–	–
Brazil 1 (1.4)	Brazilian Public Health System Database	1 (1.4)
Worldwide 69 (100)	–	69

A need for collaboration and centralization

This overview of published studies and ongoing RCTs clearly illustrates a great gap of knowledge that is likely to be related to the difference between the geographical distribution of this disease and research funding, as the major contribution in terms of clinical research and innovative treatments is mainly reported by countries with a low incidence of penile cancer. Thus, international collaboration is needed, with the aim of limiting the effect of the lack of research funds and resources in countries with the highest rates of penile cancer incidence and the contrasting problem of trial accrual in resource-rich countries that arises owing to the small number of patients available. Global coordination and collaboration between countries under the umbrella of a dedicated scientific society could enable us to offer patients improved and precision management, as well as offering the opportunity to answer many of the unanswered questions in penile cancer pathogenesis and treatment.

To effectively improve and standardize the care of patients with penile cancer, the first step is to promote comprehensive and inclusive discussion of the main unmet needs faced by experts in the field all around the world. The management of penile cancer is affected by several obstacles that differ among developed and developing countries but are all equally challenging. For example, even though Europe is among the geographical areas with the lowest incidence of penile cancer, a relatively high number of clinical trials are available in which to enrol these patients. However, the variable distribution of these trials among European countries and the lack of centralization of patients suffering from penile cancer in tertiary centres inevitably translate into suboptimal management of these patients, making penile cancer a major European health-care problem. Thus, even in resource-rich countries, centralization of patients towards qualified and high-specialized centres is desirable.

Effects of centralization on surgical outcomes

The low incidence of penile cancer and the associated low operative volume limits the spread of advances in penile cancer management amongst urologists, especially if patients with penile cancer continue to be treated by unspecialized surgeons. In a population-level study that evaluated how centralization of cases towards high-volume hospital care changed over a 10-year period for the treatment of different cancers, the increase in centralization of rare tumour management was shown to lead to improvements in cancer outcomes, whereby in-hospital mortality for oesophageal, pancreatic and colon cancer surgery declined (all $P<0.05$)[12]. As such, the centralization of penile cancer management has been suggested to be likely to improve the outcomes of this rare disease. A population-based study based on the National Cancer Data Base (NCDB) and the American Board of Urology case log database reported discrepancies in management of penile cancer between academic centres and community centres. The authors reported greater rates of lymph node dissections (48.4% versus 26.6%, $P<0.001$) and higher lymph node yield (79.2% versus 56.2%, $P<0.001$) in academic centres than in community centres[13]. However, the study was not able to

determine the effect of these differences on patients' outcomes, as follow-up data were lacking. In this context, a study using data from the Surveillance, Epidemiology, and End Results (SEER) programme database demonstrated that inguinal lymph node dissection of ≥8 lymph nodes was associated with improved 5-year survival (HR 0.54; 95% CI 0.36–0.79). However, a substantial number of patients with pT2–T4 penile cancer at risk for metastases do not routinely receive inguinal lymphadenectomy[14].

Table 3 | **Ongoing clinical trials enrolling patients with penile cancer according to population, type of intervention and countries involved**

Identifier	Phase	Diagnosis (planned *n*)	Intervention	Study dates	Sites	Country
Studies enrolling only patients with penile cancer (n = 8)						
NCT03686332 (PERICLES)	II	Unresectable penile carcinoma (32)	Atezolizumab + radiotherapy	2018–2022	1	Netherlands
NCT04475016	II	Neoadjuvant locally advanced penile carcinoma (29)	Albumin-bound paclitaxel + ifosfamide + cisplatin + nimotuzumab + triprilimab	2020–2025	1	China
NCT04224740 (HERCULES)	II	Advanced penile carcinoma (33)	Pembrolizumab + standard-of-care chemotherapy	2020–2025	4	Brazil
NCT02817958 (AFU-GETUG 25 MEGACEP)	II	Node-positive penile carcinoma eligible to lymph-node dissection (37)	Paclitaxel + ifosfamide + cisplatin	2016–2022	17	France
NCT03391479	II	Unresectable/metastatic penile carcinoma (24)	Avelumab + best supportive care	2018–2022	1	Canada
NCT03774901 (PULSE)	II	Advanced penile carcinoma after PBT (32)	Avelumab	2019–2022	1	France
NCT04231981 (ORPHEUS)	II	Unresectable/metastatic penile carcinoma (18)	INCMGA0012	2020–2022	12	Italy, Spain
NCT02305654 (InPACT)	III	Node-positive penile carcinoma (400)	Multi-arm, two randomizations (chemotherapy, lymph-node dissection, radiotherapy)	2017–2022	17	UK, USA
Studies enrolling patients with HPV-associated or virus-associated malignancies, including penile cancer (n = 5)						
NCT03427411	II	HPV-associated cancers (120)	M7824	2018–2023	1	USA
NCT03439085	II	HPV-associated cancers (77)	INO-3312 + durvalumab	2018–2022	1	USA
NCT02379520 (HESTIA)	I	HPV-associated cancers (32)	HPV-specific LyT ± (cisplatin + 5-fluorouracil + nivolumab)	2015–2021	1	USA
NCT04180215	I–II	HPV-16-confirmed cancers (140)	TheraT HPV 16 + vectors	2019–2022	16	USA
NCT03357757 (LATENT)	II	Virus-associated cancers (39)	Valproic acid + avelumab	2018–2027	1	Canada
Studies enrolling patients with advanced malignancies including penile cancer (n = 10)						
NCT02496208	I	Metastatic genitourinary malignancies (152)	Cabozantinib + nivolumab ± ipilimumab	2015–2021	8	USA
NCT03866382	II	Rare genitourinary malignancies (224)	Cabozantinib + nivolumab ± ipilimumab	2019–2023	525	USA
NCT04357873 (PEVOsq)	II	Progressive advanced mucosal cancers (111)	Pembrolizumab + vorinostat	2020–2024	14	France
NCT02721732	II	Inoperable or metastatic rare tumours (225)	Pembrolizumab	2016–2020	1	USA
NCT03333616	II	Advanced rare genitourinary tumours (57)	Nivolumab + ipilimumab	2017–2025	6	USA
NCT02834013 (DART)	II	Rare tumours (818)	Nivolumab + ipilimumab	2017–2021	944	USA
NCT02012699 (iCaRe2)	–	50 different tumour types, including solid and haematological cancers	Longitudinal database (no intervention)	2013–2099	78	USA
NCT03517488 (DUET-2)	I	Advanced solid tumours (154)	XmAb20217	2018–2021	17	USA
NCT03221400	I–II	Advanced solid malignancies (290)	PEN-866 ± 5-fluorouracil	2017–2022	10	USA
NCT02571036	I	Advanced malignancies (320)	Ripertinib	2015–2022	28	USA, Austria, Canada, Germany, Italy, Netherlands, Spain, UK

HPV, human papilloma virus; PBT, proton beam therapy.

These data reflect the urgent need for centralization of penile cancer management to improve patient outcomes worldwide.

In line with this need, in the UK, the National Institute for Health and Care Excellence (NICE) has mandated the use of supraregional networks for management of penile cancer since 2002 (REFS[15,16]). Each supraregional network should be serving an area with a population of ≥4 million people and should see a minimum of 25 cases per year. The UK experience with centralization of penile cancer management has demonstrated considerable clinical benefits. In a study comparing the records of patients treated before and after the supraregional networks, a significant increase was reported in penis-preserving surgery and nodal surgery (58.3% versus 4.5%; $P < 0.01$) and a decrease in mortality rate (10.7% versus 20.5% after a mean follow-up of 27 ± 9 months and 65 ± 14 months, respectively; $P < 0.05$), especially in patients with poorly differentiated cancer[17]. Similarly, in a series of 220 men with penile cancer, a lower risk of death was observed at high-volume (≥4 cases per year) versus low-volume (<4 cases per year) centres (HR 0.40, 95% CI 0.19–0.85)[18]. Moreover, the benefits of centralization were not limited to the surgical techniques and outcomes only, but also extended to improved histopathological reviews and diagnostic accuracy. In a review of 155 penile cancer biopsy specimens referred from 15 health-care centres to a supraregional network, histological diagnosis changed in 31% of cases, 60% of which resulted in altered management plans[19].

In addition to poorer outcomes, the lack of centralization of penile cancer care, coupled with the low incidence of this disease among some countries, and the management of patients by urologists with little experience in managing penile cancer treatment, might also affect the spread of technical and surgical innovations, such as minimally invasive techniques for inguinal lymphadenectomy.

However, despite data showing that centralization improves penile cancer management[20], to date only four European nations — the UK, Norway, Sweden and Denmark[16,21,22] — have incentivized the centralization of care for patients with the disease. Instead, many European countries are still treating penile cancer in a decentralized fashion, with some centres treating <5 patients per year[18,20]. Importantly, this situation is not influenced by a lack of qualified centres in Europe, but rather by the absence of government regulation that would encourage the centralization of patients with penile cancer towards qualified institutions in European countries.

Effects of centralization on genomics and biomarker research

Advancing our knowledge on penile cancer depends on our ability to produce data on genomic biomarkers[23,24] and predictors[25] of cancer aggressiveness and prognosis. Unfortunately, genomic data on penile cancer are sparse and mainly derived from small cohorts of patients, potentially limiting the generalizability of those findings. Even so, genomic data are becoming useful in many aspects of penile cancer research, such as the relationship between HPV infection and clinical outcomes and the role of *TP53* mutation in penile cancer development and aggressiveness. For instance, in a cohort of 57 patients with high-risk HPV infection, $p16^{INK4A}$ protein expression was a surrogate marker for HPV infection, whereas *TP53* positivity was an independent predictor of nodal metastases in patients who were $p16^{INK4A}$-negative (OR 4.4, 95% CI 1.04–18.6)[26]. Similarly, in a separate study, *TP53* mutation positivity was independently associated with nodal metastatic disease, whereas patients with tumours negative for *TP53* mutation had significantly better 5-year and 10-year overall survival outcomes (65% versus 55%, and 30% versus 26%, respectively)[27]. A 2020 initiative from a multi-institutional collaboration of four referral centres in China explored the correlations between a methylation score and penile cancer-specific survival[28]. The study collected 92 frozen samples of primary penile cancer in order to develop and validate a methylomic signature that enabled improved stratification of patients, tailoring salvage therapies in selected groups at risk. Samples were divided into three groups: a discovery set, a development set and a validation set. In the discovery set, 17 CpG sites were significantly associated with cancer-specific survival. In the development set, the authors developed a 3-CpG based prognostic model, which was then validated in the validation group. Use of this molecular tool improved the pN-stage C-index from 0.69 to 0.78 ($P < 0.001$).

The expression of immune-checkpoint markers in locally advanced penile cancer has been investigated using immunohistochemical staining for PDL1[29]. In this study from North America, PDL1 expression did not correlate with patient age, tumour location, histological subtype, tumour stage or tumour grade (all $P > 0.05$).

These biomarkers could have valuable clinical applications in the near future, mainly as prognostic markers to guide the aggressiveness of initial treatment with increased usage of multimodal management. However, despite advances in our understanding of the biology, genomic and biomarker profile of penile cancer, such initiatives are of limited value if their findings cannot be confirmed in large and external cohorts of patients. This further illustrates the need for a global approach and implementation from governments worldwide: gathering large amounts of data and biospecimens from several centres could enable adequate powering of studies to understand the biological mechanisms that regulate the natural history of penile cancer[30] and help to determine actionable targets to improve our treatment armamentarium.

Challenges in developing countries

The issues that plague developing countries with a high prevalence of the disease — such as India, Africa and South America — are different from those of developed countries, but no less burdensome or important.

Penile cancer in India. In 2020, India reported the highest crude number of prevalent cases of penile cancer, reporting 6,901 diagnoses[1]. This number has increased over the previous 4 years[1], despite the diagnostic delay caused by the global COVID-19 pandemic[31,32]. Nevertheless, such a large volume of cases does not always translate into adequate management and guidelines compliance across the country. Indeed, treatment of patients with penile cancer in India is not centralized in referral centres, but mainly managed at local centres. Consequently, patient management is not always uniform across centres, in terms of both diagnostic and surgical practices. This discrepancy becomes even more important in patients with clinically negative lymph node disease, who could benefit the most from new diagnostic techniques, such as dynamic sentinel lymph node biopsy, which is used mostly in high-volume hospitals[33]. In addition, India has a lack of population-based registries and no recruiting RCTs available countrywide (TABLES 2,3).

Penile cancer in African countries. A similar situation is seen across numerous regions of Africa, where eight countries — Eswatini, Botswana, Uganda, Burundi, Zambia, Zimbabwe, Lesotho and Rwanda — are among the ten countries in the world most affected by penile cancer, according to the WHO[1], with an ASR of >1.3 for each

country. A major concern in those countries is the delayed consultation time, which often reaches 21 months[34] from the onset of the disease to physician evaluation, leading to alarming rates of locally invasive disease (T2–4)[35], whereby up to 50% of patients present with T3 disease and almost 20% with nodal involvement at diagnosis[33]. Moreover, a lack of the availability of appropriate chemotherapy and radiotherapy treatments further worsens the prognosis of penile cancer in these countries[36].

In Africa, the penile cancer burden is increased by socioeconomic issues, poor knowledge of the disease, poor access to health care, poor access to sanitation and hygiene[3], low rates of circumcision, and the reduced availability of physical contraceptive methods, such as the male condom, especially in rural areas[37]. The latter is a particular concern in Africa[38], where a lack of physical contraceptive methods contributes to the spread of both HIV and HPV infections in sub-Saharan Africa countries[37] — the interplay of HIV and HPV increases the incidence of HPV-related malignancies, including penile cancer, and its incidence is up to four times higher in HIV-infected men than in HIV-negative men[39,40].

In addition, penile cancer care in some African countries — especially those in sub-Saharan Africa — is hampered by a lack of trained urologists. For example, the ratio of urologists to inhabitants is 1:3,800,000 in Nigeria and 1:2,500,000 in Ghana, which is extremely low when compared to 1:16,000 in Japan, 1:27,000 in the USA, and 1:90,000 in the UK[41,42]. The lack of urologists is probably the most important limitation that must be overcome in order to improve inequalities and ensure adequate cures among patients with penile cancer in Africa, although this issue is also associated with other concerns, including limited resources and a lack of good-quality training programmes for penile cancer care in African countries.

Centralization of penile cancer management in Africa could help to address these problems, by developing supraregional heath networks of multidisciplinary teams. The increased exposure to penile cancer for clinicians and surgeons in these centres would improve diagnostic accuracy and optimize management plans.

An example of how improving networks between hospitals in Africa can improve the training of surgeons, nurses and health personnel and can optimize patient care is the early neonatal circumcision campaign in Uganda, which is supported by several global and local authorities including WHO, UNAIDS and PEPFAR[41,42]. The association between a lack of circumcision and penile cancer has been well established from several studies[3]. Notably, a meta-analysis showed a strong protective effect of childhood circumcision against invasive penile cancer (OR 0.33; 95% CI 0.13–0.83)[43]. Since a health-care campaign to encourage circumcision in Uganda was implemented in 2007, the rate of medical male circumcision increased from 28.5% to 52.0% in 2014 in all men and from 18.7% to 45.7% in non-Muslim men[44]. In this way, supraregional networks and campaigns supported by global health authorities could improve outcomes for the entire health-care system[45].

However, the status of penile cancer in Rwanda warrants particular focus. Despite the improvement in awareness of HPV-related cancers that has occurred since a national HPV vaccination programme was implemented in 2011 (REF.[46]), Rwanda still has the highest age-standardized incidence of penile cancer of all African countries. This disappointing outcome is mainly related to socioeconomic barriers, such as poor hygiene, lack of circumcision[47] and the low availability of physical contraceptive methods compared with richer, more developed African countries, such as Egypt, South Africa and Tunisia[48,49]. Furthermore, 47% of Rwandan patients with penile cancer have non-HPV-related disease, suggesting that penile cancer development in this country could occur via a different pathogenic mechanism to in other countries where HPV-related tumours are more frequent[47]. More research into the reason for this heterogeneity is needed in order to reduce penile cancer incidence in this developing country.

Penile cancer in South American countries. South America is one of the geographical areas most affected by penile cancer: 10.7% of new cases and 7.3% of deaths from penile cancer worldwide arise in South America[1].

HPV infection is a major factor in promoting and spreading the disease through the continent[50]; around 50% of patients with penile cancer present with a concomitant HPV infection[50]. In South America, the identified HPV serotypes linked to penile cancer are similar to those of the rest of the world (that is, serotypes 16 and 6), as well as several additional serotypes (52, 61 and 69) that are more commonly found in this area, probably owing to the high socioeconomic and cultural diversity observed across South American countries[51].

Brazil introduced an HPV immunization programme for children 9–14 years old using the quadrivalent vaccine in 2014 and is currently adopting a two-dose vaccination schedule[52]. Despite this programme, a considerable proportion of patients with penile cancer present with a concomitant infection from an HPV serotype that is not included in the common quadrivalent vaccine (which covers types 6, 11, 16 and 18). Data from the POP-Brazil study[51,53], in which 53.6% of samples were HPV-positive, reported that only 14.8% of patients harboured a type of HPV that was covered by the quadrivalent vaccine, whereas 27.7% had an infection with non-valent HPV types[53]. Between the most prevalent serotypes not covered by HPV vaccines, HPV 62 was recognized in 6.8% of patients included in the study, HPV 89 in 6.3%, and HPV 61 in 6.0%. Moreover, the POP-Brazil study showed that the pattern of HPV infection differed widely between sexes: although HPV 16 (8.9%) and 52 (8.8%) were the most prevalent high-risk HPV types in women, HPV 59 (6.5) and 52 (6.0%) were the most frequent in men[53].

Data from Brazil highlight another important problem that could affect many of the countries with high HPV-infection incidence. If the rapid spread of HPV infection cannot be stopped, controlling the increasing number of new cases of HPV-related penile cancer will be even more challenging. In this scenario, large vaccination campaigns should be promoted only after a careful cost-effectiveness evaluation. For example, where the quadrivalent vaccine fails to control the rising number of cases of penile cancer, the nine-valent vaccine (which covers HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58) should be considered as an alternative. Thus, international collaboration could enable implementation of a gender-neutral vaccination campaign using the nine-valent vaccine, which could have a considerable impact on public health. Such an effect was observed in France, where introduction of a nine-valent gender-neutral HPV vaccine was approved and dynamic modelling showed that the approach would be effective in reducing new HPV-related diseases, including HPV-linked cervical and anal cancers[54].

The initiation of a global society focusing on penile cancer could facilitate the spread of gender-neutral vaccination campaigns worldwide, potentially reducing the incidence of HPV-related penile tumours. Specifically, such a society can facilitate centralization of epidemiological data, which could also include the prevalence and distribution of different serotypes of

HPV across countries, and stimulate ad hoc campaigns to target the spread of HPV, thus increasing cost-effectiveness, particularly in developing countries.

Similar to Brazil, Paraguay reports the highest incidences of penile cancer in the whole of South America, and one of the highest worldwide (ASR 3.4 per 100.000)[1]. Epidemiological data suggest that the main factor responsible for this high ASR is the incidence of HPV infection among the young population. This hypothesis is supported by the concomitant high incidence of cervical cancer, in which Paraguay ranks second-highest among all South American countries[55].

As is the case in Africa, some cultural and socioeconomic factors are contributing to the rising incidence of penile cancer in South America. A 2020 study from Brazilian investigators identified some demographic profiles that recur in patients with diagnosed penile cancer — living in rural areas (57%) and working in farming (58%), low schooling (90%), multiple partners (74%), zoophilia (60%), poor hygiene (73%), and phimosis (66%) were the most prevalent characteristics in Brazilian patients with penile cancer[56]. Thus, as also proposed for African countries, promotion of neonatal circumcision, tobacco cessation, proper genital hygiene, early detection of precursor lesions, and educational campaigns to inform the public of preventive measures (such as vaccination and use of condoms) should be urgently initiated to control the rising cases of patients with penile cancer.

The rise of a global society

International cooperation is urgently needed to identify the major clinical gaps surrounding rare genitourinary malignancies, including penile cancer, to homogenize care and treatments across countries, and to improve the life expectancy of these patients. GSRGT aims to fulfill these goals[6].

The first aim of the GSRGT is to involve developing countries that have been previously ignored from registries and trials but that represent a large reservoir of rare tumours. For instance, tertiary care institutions located in South America, Africa, India and Asia should join European and North American academic centres, enabling fast and comprehensive recovery of data from all around the globe. GSRGT will promote collaboration between physicians from different countries to disseminate updated and accessible information on penile cancer, providing patients with the best available evidence-based treatments through collaboration with established medical societies.

The second aim of the GSRGT is to bring together experts in the field of rare genitourinary malignancies to identify the most urgent open controversies and, ultimately, to enable the design of guidelines that can be embraced by all involved centres and that can meet clinical needs across different countries.

The third goal of the GSRGT is to collaborate with established medical societies such as the American Society of Clinical Oncology (ASCO), the American Urological Association (AUA), the European Association of Urology (EAU), The European Society for Medical Oncology (ESMO), the Société Internationale d'Urologie (SIU), the International Rare Cancers Initiative and the World Urologic Oncology Federation to generate scientific collaborations to increase the discussion of rare genitourinary cancers during conferences, to provide common guidelines across scientific societies and to improve research protocols.

Finally, this global cooperation aims to advance the field of rare genitourinary malignancy by boosting clinical research, by changing clinical practice and, ultimately, by improving care for patients and their families. Among the several initiatives that will be promoted by the GSRGT, annual meetings will focus on rare diseases that are too frequently neglected by general urology conferences.

Another important initiative will be to develop an international data registry on penile cancer, which is actively being developed. This registry has the potential to improve patient care, education and research across the globe, through incidence and prevalence studies on the geographical variations of penile cancer to better appreciate potential environmental, socioeconomic and demographic risk factors, as well as a comprehensive classification of penile cancer based on molecular alterations, which could improve the diffusion of new treatments worldwide. Access to this registry will be granted to all academic and non-academic centres willing to collect data on penile cancer, regardless of their country of origin and connection with the academic community. The primary aim of the registry is to create the largest retrospective treated cohort of patients with penile cancer, which will provide an invaluable source of data on the disease and its impact across the globe.

Despite its rarity, penile cancer is a rising burden for health-care systems around the globe. One of the main barriers to improving clinical research on penile cancer and, consequently, developing both surgical and clinical innovations is the lack of consolidated results on the topic, given that the countries that are mainly supporting research on this topic are not the countries with the highest prevalence of the disease. Thus, international collaboration, such as that organized by the GSRGT, could provide an opportunity to make this disease more easily manageable.

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Competing interests

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