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REVIEW ARTICLE

Epidemiology

Prostate cancer in transgender women: considerations for screening, diagnosis and management

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Transgender individuals represent 0.55% of the US population, equivalent to 1.4 million transgender adults. In transgender women, feminisation can include a number of medical and surgical interventions. The main goal is to deprive the phenotypically masculine body of androgens and simultaneously provide oestrogen therapy for feminisation. In gender-confirming surgery (GCS) for transgender females, the prostate is usually not removed. Due to limitations of existing cohort studies, the true incidence of prostate cancer in transgender females is unknown but is thought to be less than the incidence among cis-gender males. It is unclear how prostate cancer develops in androgen-deprived conditions in these patients. Six out of eleven case reports in the literature presented with metastatic disease. It is thought that androgen receptor-mediated mechanisms or tumour-promoting effects of oestrogen may be responsible. Due to the low incidence of prostate cancer identified in transgender women, there is little evidence to drive specific screening recommendations in this patient subpopulation. The treatment of early and locally advanced prostate cancer in these patients warrants an individualised thoughtful approach with input from patients' reconstructive surgeons. Both surgical and radiation treatment for prostate cancer in these patients can profoundly impact the patient's quality of life. In this review, we discuss the evidence surrounding screening and treatment of prostate cancer in transgender women and consider the current gaps in our knowledge in providing evidence-based guidance at the molecular, genomic and epidemiological level, for clinical decision-making in the management of these patients.

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INTRODUCTION

Transgender is an umbrella term which describes individuals who have a gender identity which does not align with the gender assigned at birth [1]. As per the Center for Disease Control (CDC) Behavioral Risk Factor Surveillance System (BRFSS) survey, transgender individuals represent 0.55% (95% CI, 0.51–0.59%) of the US population, which is equivalent to 1.4 million transgender adults [2, 3]. Transgender individuals do not have equitable access to healthcare. The 2015 US Transgender survey found that transgender patients encountered high levels of mistreatment when seeking healthcare [4]. In the year prior to completing the survey, one-third (33%) of those who saw a healthcare provider had at least one negative experience related to being transgender, such as being refused treatment because of their gender identity. Nearly one-quarter (23%) of respondents reported that in the preceding year, they did not seek the healthcare needed due to fear of being mistreated as a transgender person [4]. Forty per cent of respondents from that survey had attempted suicide in their lifetime [4]. This is nearly nine times the attempted suicide rate in the U.S. population (4.6%) [4].

There are multiple contributing factors to this disparity in healthcare access, including financial and social issues. Transgender individuals are increasingly visible in both popular culture and in daily life but still face severe discrimination, stigma, violence and systemic inequality [4]. In 2019, Badgett et al. found that transgender people in the United States have especially high rates of poverty (29.4%) compared to 12% in the general U.S. population [5]. A major contributor to the high rate of poverty is their high unemployment rate (15%) [4]. Health insurance issues are also large contributors to healthcare disparity experienced by this population with 14% of transgender patients being uninsured [4]. In oncology care, transgender patients may be diagnosed at later stages, be less likely to receive treatment, and have worse survival for many cancer types [6].

Feminising gender-confirming surgery requires a number of medical and surgical interventions. The main goal is to deprive the

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Table 1. Studies estimating prostate cancer incidence in transgender women.

Data source	Date of data acquisition	*N*	Median age time of study	Median follow-up	Number of PCa cases	Median age starting GAHT	Estimated PCa incidence per 100,000	References
Transgender females Amsterdam Clinic*	1975–2006	2306	Unknown	21.4 years	1	29.3 years	43.37	Gooren et al. [22]
Insured transgender females at Three Kaiser sites	2006–2014	2791	39 years	4 years	8	Unknown	286.64	Silverberg et al. [23]
North American Association Central cancer registries	1995–2013	805	Unknown	Unknown	48	Unknown	5962.73	Nash et al. [24]
Amsterdam University Medical Center*	1972–2016	2281	50 years	14 years	6	31 years	263.04	Nie et al. [26]

*These studies are from the same medical centre and based on the same patient population.

phenotypically masculine body of androgens through the use of a testosterone antagonist, GnRH agonist, or bilateral orchiectomy. Simultaneously the individual is started on oestrogen therapy for feminisation. The gender-confirming surgery (GCS) performed depends on the patient's goals from surgery and the length of the phallus but usually includes a penile disassembly and creation of a vagina with a skin flap from the phallus combined with skin graft (penile inversion vaginoplasty, PIV), the use of a peritoneal flap with phallic skin flap (peritoneal flap vaginoplasty, PFV), or the use of a segment of colon typically the sigmoid (sigmoid vaginoplasty, SV). For most, there is no benefit to performing a prostatectomy during gender-confirming surgery and doing so may compromise sexual fulfilment and urinary function [7].

It is estimated that almost 250,000 cases of prostate cancer were diagnosed in the USA in 2021 [8, 9]. Well-established risk factors for prostate cancer are increasing age, African ancestry, a family history of the disease, and certain inherited genetic conditions [8–10]. Germline pathogenic variants in cancer predisposition genes are reported in 7.3–11.8% of aggressive prostate cancer cases, including genes associated with homologous repair deficiency (e.g., *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *CHEK2*, *NBN*, *BARD1*, *RAD51C*, *MRE11A* and *PALB2)*, and mismatch repair deficiency (e.g., *MLH1*, *MSH2*, *MSH6* and *PMS2)* [11]. Predictors of having a pathogenic variant include increasing Gleason score; personal history of breast, bladder or pancreatic cancer; family history of breast, bladder, ovarian or pancreatic cancer; and family history of Lynch syndrome-associated cancers [11]. The topic of prostate cancer in transgender females remains under-researched with just 11 case reports and a small number of cohort studies in the literature [12–26]. Prior reviews have identified the absence of guidelines, but a notable gap in the literature exists where experts specifically address the clinical conundrum which is screening and management of a hormonally regulated tumour (prostate cancer) in a population taking long-term hormonal therapies. This review aims to summarise what we currently know, important considerations surrounding screening and treatment of prostate cancer in transgender women as well as highlighting current research gaps, while providing an evidence base for clinical decision-making when direct clinical data is limited.

PROSTATE CANCER EPIDEMIOLOGY

In 2022, 268,490 people are expected to be diagnosed with prostate cancer in the United States. Age-adjusted incidence fluctuated from 155 per 100,000 in 2003 to 106.4 in 2019 [27, 28]. Incidence was highest for men aged 70–74 years (764) and Black men (202) [27]. As mentioned previously, the incidence of prostate cancer among transgender women is unclear. Small cohort studies have reported varying rates of incidence, but most reporting prostate cancer rates less than the general male population [21] (see Table 1). The interpretation of these results is generally limited by the fact transgender people experience various barriers to accessing care thus limiting accurate representation in national databases. In addition, prostate cancer is diagnosed most often in those over the age of 60, thus necessitating prolonged follow-up in longitudinal studies [10].

Gooren et al. included medical records from 2306 transgender females treated at the Amsterdam Gender Clinic between 1975 and 2006 [22]. A single case of prostate cancer was identified in this group giving an overall incidence of 0.04% in this population, but the rate was 0.13% when those who initiated treatment at ≥40 years [22]. The affected individual was 63 years old, started gender-affirming hormone treatment (GAHT) at the age of 53 years and underwent bilateral orchiectomy at age 55 [22]. This case was also reported separately by van Haast et al. and is listed in Table 2. There were a number of limitations to this study, chief amongst them is the relatively young median age and short follow-up, and so brought concerns that this study underestimates

Table 2. Reported cases of prostate cancer in transgender women.

#	Source	Age at dx	PSA at dx	Presenting sxs	Gleason	Dx post GAS	Mets on presentation	Years on hormones	Cancer treatment
1	Markland, 1975 [127]	54	–	–	–	Yes	–	6	–
2	Thurston [12]	64	27	LUTS	–	Yes	Yes	12	Radiation
3	van Haarst, 1998 [13]	63	1710	Weight loss, bone pain	–	Yes	Yes	10	ADT
4	[γ]Miksad et al. [14]	60	240	Haematuria	8	Yes	Yes	41	Radiation, ADT
5	Dorff et al. [15]	78	177	Haematuria	9	Yes	Yes	26	Radiation, chemotherapy
6	Turo et al. [16]	75	13.5	LUTS	7	Yes	Yes	30	Radiation
7	Ellent et al. [17]	65	19	LUTS	9	Yes	Yes	35	Orchiectomy, chemotherapy, prostatectomy
8	Sharif et al. [19]	56	5	Abnormal DRE	7	Yes	No	20	Prostatectomy
9	Ingham et al. [20]	60	3.3	Abnormal DRE	9	Yes	No	20	Prostatectomy
10	Deebel et al. [18]	65	7.5	Elevated PSA	7	Yes	No	20	Prostatectomy
11	Sada, 2021 [128]	~59	–	–	9	No	No	0	Prostatectomy + Radiation + ADT
12	+ Case 1*	62	7.5	Elevated PSA	8	No	No	0	NeoAdj ADT + Prostatectomy
13	+ Case 2*	50	1.4	Asymptomatic. Family history	6	Yes	No	3	Active surveillance

GAS gender-affirming surgery, *Dx* diagnosis, *PSA* prostate-specific antigen, *Sxs* symptoms, *Mets* metastases, *ADT* androgen-deprivation therapy.
It should be noted that others have reported an additional case as Molokwu et al. [129] BJUI; however, this is the same case previously reported by Miksad et al. [14]. [γ]This case is discussed in further detail in the manuscript. *Cases 12 and 13 describe patients that presented at our institution and are described in the text.

the actual incidence of prostate cancer in this population. Indeed this is the case, as a more recent publication by de Nie et al., consisting of 2281 trans-women from the same centre in the Netherlands, identified 6 prostate cancer cases [26]. While the study by De Nie et al. included patients from a longer time period, it appears more stringent inclusion criteria were used, and it included 13 more years of data. The study by De Nie et al. cross-referenced the database with the Nationwide Network and Registry of Histopathology and Cytopathology in the Netherlands (PALGA) to obtain data regarding prostate cancer histology and the date of prostate cancer diagnosis. Doing so lead to the discovery of more cases of prostate cancer who may have had treatment outside Amsterdam University Medical Center [22, 26]. The median age at starting GAHT was 31 years, and median duration of GAHT was 17 years in the entire cohort. This contrasts with the 6 trans-women who were diagnosed with prostate cancer who started GAHT at a median age of 47 years (range 38–58). Four of these individuals had undergone orchiectomy, at a median of 11 years (range 2–14) prior to their prostate cancer diagnosis [26]. Among the six patients with prostate cancer, five had histopathological reports showing a Gleason score of ≥7 [26]. The median age at the time of diagnosis was 64 years (range 53–77) [26], and median age for the entire cohort at the time of the study was 50 years (interquartile range of 37–59 years [26].

Silverberg et al. included 2791 insured transgender females from the United States and again found the incidence of prostate cancer (72 in 100,000) to be lower compared with reference males (HR = 0.4; 95% CI: 0.2, 0.9) but higher than the rate among transgender women reported in other studies [23]. The higher incidence of prostate cancer in this American cohort may be explained by the fact that 38% of their study population consisted of trans-women who had not undergone GAHT and were, therefore, not androgen-deprived [23, 26]. Another important consideration is that transgender patients have a 14% uninsured rate in the USA, with rates being as high as 20% in southern areas of the country where some of this data was collected [4]. In addition, the cohort analysed was again relatively young compared to cohorts who typically present with prostate cancer, with a mean age of 39 years and only 14% being aged >55 years [23].

Nash et al. examined the North American Association of Central Cancer Registries from 1995 to 2013, identifying 48 cases of prostate cancer in transgender women. When compared to cisgender males in the same database, the incidence of prostate cancer in transgender women was lower, with a proportional incidence ratio of 0.3 (95% CI 0.2–0.4) [24].

Through a targeted literature review using PubMed, Web of Science and Google Scholar, we identified eleven published case reports which are outlined as part of Table 2. These case reports generally describe advanced cases of prostatic cancer; of the ten cases that report M-stage, six patients had metastatic cancer at diagnosis. Of note, there was significant variance in exposure to gender-affirming hormone therapy prior to diagnosis of prostate cancer in these reports (6–41 years). Miksad et al. describes a transgender female, who started on gender-affirming hormone therapy at the age of nineteen, with orchiectomy at 34 years old but still developed metastatic prostate cancer over forty years later [14]. Her total serum testosterone level was 44 ng/dL (1.5 nmol/L) (expected castrate level <50 ng/dL [1.7 nmol/L]). Hormone levels were consistent with a feminised male with the detectable androgens presumed to be of adrenal origin [14]. We have also included two cases from our institution in Table 2. Case 1 was a 62-year-old patient with elevated PSA of 7.5 ng/mL at diagnosis, Gleason score 8 who had not yet started gender-affirming therapy. Case 2 was a 50-year-old patient, on gender-affirming therapy for 3 years, who presented for screening due to a family history of prostate cancer and was subsequently found to have a Gleason 6 tumour. These contemporary cases contrast with what has been previously published in the literature.

IMPACT OF GENDER-AFFIRMING HORMONAL TREATMENT (GAHT) ON THE PROSTATE GLAND

The usual aim of GAHT is to induce physical changes to match gender identity [29]. The treatment goal is to maintain hormone levels in the normal physiological range for that gender. For transgender females, dual therapy with one compound that suppresses androgen secretion (gonadotropin-releasing hormone (GnRH) agonist therapy) or action (spironolactone, cyproterone acetate) and a second compound that supplies oestrogen is generally recommended [30]. Anti-androgen therapy is stopped once orchiectomy is performed [21]. Transgender adults face a number of barriers to accessing GAHT and Stroumsa et al. found that 992 (9.17%) of their 12,037 transgender adults were using non-prescription hormones [31]. In cohort studies mentioned previously, the low rates of prostate cancer in transgender females relative to cis-gender cohorts has been attributed to the protective effect of oestrogen use [23] (see Fig. 1).

Anti-androgens

The discovery of the hormonal regulation of prostate cancer by Huggins in 1940 first demonstrated the androgen dependence of prostate cancer as the driving underlying mechanism as well as a point of treatment [32]. Androgen-deprivation therapy (ADT) has been found to inhibit the progression from latent prostate cancer to macroscopic disease [33]. Anti-androgen therapy is a mainstay treatment for metastatic disease and neoadjuvant therapy prior to treatment in locally advanced diseases [34, 35]. However, therapeutic resistance eventually emerges under conditions of ADT [36].

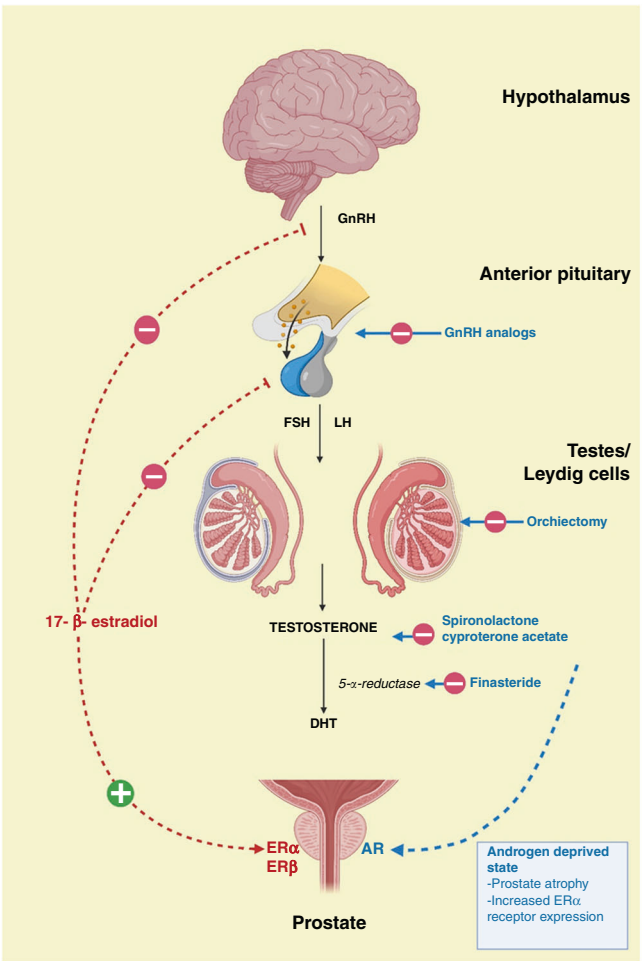

Fig. 1 Impact of feminising therapies on the prostate. Of note: both spironolactone and cryproterone acetate are contraindicated in active prostate cancer.

Oestrogens

The role of estrogens is less well defined. In early prostate cancer research, the role of oestrogen was primarily seen as an indirect anti-androgen action [37]. This effect was mediated through feedback inhibition of hypothalamic luteinizing hormone and pituitary luteinizing hormone release, resulting in decreased testicular androgen production and release [37] (see Fig. 1). Administration of exogenous estrogens such as the non-metabolised diethylstilbestrol was used to reduce circulating androgens to castrate levels in patients with advanced disease [37].

Paradoxically estrogens might also be involved in prostate carcinogenesis [38]. Changes in the oestrogen receptor (ER) signalling axis have been implicated in advanced prostate cancer, and evidence in pre-clinical models shows induction of prostate cancer using oestrogen plus androgens [38, 39]. Elegant studies by Bosland et al. demonstrated that rats developed a drastic increase in prostate cancer incidence when oestrogen was given in conjunction with testosterone [40]. Rats which received testosterone alone demonstrated a 35–40% incidence of prostate cancer, while those that received oestrogen in conjunction with testosterone had an incidence of 90–100% [40]. Oestrogen's direct effects on the prostate are primarily mediated through ER-α and ER-β; where ER-α is expressed in prostate stroma and ER-β is expressed in both stroma and luminal epithelial cells of the prostate. ER-α expression in prostate stroma has been reported to be significantly upregulated in prostate cancer and particularly in androgen-deprived states [41, 42]. This finding is further supported by a reported case of prostate cancer in a 56-year-old transgender female whom had received 20 years of androgen suppression via depot oestrogen injections: immunohistochemistry results demonstrated ER-α and progesterone receptor-positive staining in stromal cells, while androgen receptor-positive staining was found in malignant glands with weak scattered staining in the adjacent stroma [19]. ER-α expression also occurs in prostate cancer epithelium and is significantly associated with high Gleason score and poor patient survival [43, 44]. ER-β, on the other hand, is expressed in the epithelial compartment of the prostate, where it has anti-proliferative effects and acts as an 'onco-suppressor gene' in the prostate [45, 46]. Expression levels of ER-α and ER-β change over time and with disease progression [45].

ER modulation in prostate cancer has been investigated as a therapeutic strategy. High doses of oestrogen compete with androgens for androgen receptors and have in vitro cytotoxic effects on androgen-sensitive and androgen-insensitive prostate cancer cells [47]. Oestrogen has been used in patients with advanced prostate cancer to suppress androgens. Although offered by oral administration, first pass metabolism in the liver was associated with a ~35% increased risk of cardiovascular toxicity, and thromboembolic disease in particular. Since the development of LHRH analogues, oral oestrogen use to treat prostate cancer has declined. However, alternative routes of administration of estrogens were also assessed; transdermal in particular. The added benefit of oestrogen over LHRHa, is that it protects against the development of castration-associated osteoporosis. The Prostate Adenocarcinoma Trans-Cutaneous Hormones (PATCH) study examined the use of transdermal estradiol vs LHRHa in patients with locally advanced or metastatic prostate cancer, which was castration-sensitive. In a recent publication of interim data from this randomised study of 1694 patients, castration was achieved in 93% in both study arms by 3 months [48]. The study was also specifically powered to address cardiovascular morbidity; rates of cardiovascular adverse events were not significantly higher with transdermal estradiol than LHRHa nor was time to first cardiovascular event significantly earlier. Recruitment for this study is still ongoing (NCT00303784).

Patients as part of this study reported better quality of life over 6 months compared to LHRHa, and improved metabolic profile and bone mineral density were also observed [49]. Administration of oral Diethylstilbestrol (DES) is currently acknowledged by the National Comprehensive Cancer Network as second-line hormone therapy for individuals with metastatic prostate cancer, with studies showing inhibition of telomerase as well as direct apoptosis in cancer cells [50, 51]. DES is a synthetic oestrogen that blocks gonadotropin-releasing hormone secretion through negative feedback. A clinical trial of DES as a second-line agent for CRPC was evaluated in 58 men and compared to bicalutamide; median response duration and PSA response rate were similar (DES vs bicalutamide = 9 months vs 12 months, and 23% vs 31%) and there was a notable amount of cardiovascular toxicity in the DES group [52]. However, clinical data supporting its use largely comes from the setting of initial hormone therapy for castration-sensitive disease [37, 53, 54].

Selective ER modulators (SERMs) are synthetic oestrogen receptor ligands, examples include tamoxifen, toremifene and raloxifene. SERMs show both oestrogenic and/or antiestrogenic effects, depending on cell type and the different expression and/or activation of transcriptional co-regulators [55]. Clinical trials examining the use of these drugs in prostate cancer have failed to show significant benefits: Bergan et al. examined the use of high-dose tamoxifen in patients with castration-resistant prostate cancer, with a 3.3% objective response rate (ORR), a median progression-free survival (PFS) of 2.1 months and a median overall survival (OS) of 10.5 months [56]. A Phase 2 trial of toremifene in a similar population reported no response to treatment [57]. Fujimura et al., in a separate Phase 2 trial, demonstrated that toremifene with conventional ADT significantly improved the biochemical recurrence rate in treatment-naive bone metastatic prostate cancer [58]. A Phase 2 trial studying the combination of bicalutamide and raloxifene for patients with castration-resistant prostate cancer again failed to demonstrate clinical benefit with PFS of 1.8 months [59]. These clinical trials have not allowed for clear conclusions to be drawn, and it currently remains unclear if late initiation of oestrogen as GAHT in a transgender female, in the presence of already existing prostate cancer would impact prostate tumour growth. However, tamoxifen, toremifene and raloxifene are have been demonstrated to simultaneously exhibit oestrogen-like agonist activity, and oestrogen antagonist activity in different tissues [60]. As mentioned earlier, one of the reasons for these seemingly contradictory effects of SERMS, is that there is different expression of co-regulatory proteins and ER subtypes in different tissues [60, 61]. Perhaps of greater clinical utility in this context, would be a SERM which is specifically antagonistic for the ER-α subtype in prostate, and simultaneously is agonistic of the ER-β subtype, thereby inhibiting the oncogenic effects of ER-α, and promoting the anti-oncogenic effects mediated by ER-β.

Phytoestrogens; naturally occurring plant compounds such as isoflavones (from sources such as soy), flavonoids (ie from tea and red wine) and lignans (ie from cereals), have inherent oestrogenic properties and have been demonstrated to be beneficial in risk reduction following diagnosis with prostate cancer. Studies have shown that phytoestrogens have anti-androgenic effects and relatively greater interactions with the -β subtype of the ER in castration-resistant PCa [51]. A recently published study examining soy protein supplement versus casein-based placebo supplement in patients who had underwent surgery for Stage II PCa. After 2 years, those who received the soy supplement had reduced circulating testosterone and SHBG, but not free testosterone, and did not affect serum concentrations of estradiol [62]. While there is some evidence to suggest modulation of the oestrogen receptor in combination with ADT improves time to biochemical recurrence in a metastatic hormone-sensitive prostate cancer population, there are a number of studies which suggest it is not of any benefit in the context of castrate-resistant prostate cancer; such as that encountered in patients where prostate tumour growth is occurring in the absence of androgens (or in transgender women on GAHT or post orchiectomy).

Interaction of androgen and oestrogen signalling

Prostate tumour growth in transgender women may have initiated and go undetected prior to GAHT initiation [18]. This is supported by the fact in many of the reported cases, hormone therapy was initiated after the age of 45 [12, 13, 15, 16] (see Table 2). Of 11 reported cases, ten had M-stage reported, and six presented with metastatic disease [12–18]. The development of castrate-resistant prostate cancer entails both androgen-dependent and androgen-independent growth signalling pathways with oestrogen implicated in disease progression [36, 63]. Androgen receptor-dependent mechanisms include: androgen receptor (AR) amplification and overexpression, gain-of-function mutations in AR, AR splice variants, post-translation modification of AR and AR coactivators or corepressor modification [64, 65]. Prostate cancer also employs intracrine androgen biosynthesis, and commensal bacteria androgen biosynthesis is another method to allow growth in androgen-depleted conditions [66, 67]. These mechanisms of resistance may also play a role in the development of prostate cancer in androgen-deprived conditions in transgender females.

ERβ is the most prevalent oestrogen receptor in clinical specimens of prostate cancer. Hormone naive prostate cancer generally retains high levels of ERβ expression in cancer cells where the substantial loss of ERβ is encountered in castration-resistant prostate cancer [68]. In one study, reduced levels of ERβ were found in about 40% of castration-resistant cases and was undetectable in 10% of these tumours [68]. The presence of the ERα in prostate cancer cells is a late event in disease progression [69]. In one study, high-grade (Gleason Grade 4 and 5) tumours revealed ERα protein expression in 43% and 62% of cases, respectively [63]. The most significant ERα gene expression was observed in metastatic and castration-resistant prostate cancer with ERα expression in >25% of tumour cells in 45.5% and 55.5% of cases, respectively [63]. The authors concluded that approximately 50% of these tumours harbour a significant amount of oestrogen-responsive tumour cells [63, 69]. ERα detected in these tumours appears to be functionally active with other studies demonstrating evidence of transcriptional activity of ERα-regulated genes like progesterone receptor (PR), PS2, TMPRSS2-ERG fusion and NEAT1 in castration-resistant prostate cancer [63, 70]. Although ERα emerges typically in metastatic and castration-resistant disease, this receptor can be induced by androgen-deprivation therapy after a short period of treatment, demonstrated by Shaw et al. who reported upregulation of ERα expression in prostate cancer cells after just 7 days of anti-androgen therapy [71]. This upregulation was associated with differential expression of ERα-regulated genes, and sustained tumour cell proliferation in an androgen-deprived milieu [71]. Elevated functionally active ERs may potentially explain the high number of patients that present with advanced aggressive disease. Miksad et al. outline that in their case report of a 60-year-old TG woman who was diagnosed with Gleason 8 prostate cancer 41 years after commencing GAHT; that the lack of ERα/PR expression and the PSA response to anti-androgen treatment despite oestrogen supplementation suggests that oestrogen did not promote their patients cancer [14].

PROSTATE CANCER SCREENING IN THE TRANSGENDER FEMALE

Prostate-specific antigen (PSA) is an androgen-regulated serine protease produced by both prostate epithelial cells and prostate cancer and is the most commonly used serum marker for prostate cancer screening and assessing response to prostate cancer treatment [72]. PSA can be raised for a number of different

reasons, and PSA therefore has varying sensitivity and specificity in detecting prostate cancer with ranges from 61 to 100%, and from 5 to 74%, respectively [73, 74].

The most recent recommendation from the US preventative services task force (USPTF) published in 2018 recommends that patients who want to undergo PSA-based screening discuss the risks and benefits of screening with their doctor [75]. The American Urological Association (AUA) recommends shared decision-making for men aged 55–69 years that are considering PSA screening, while the European Association of Urology (EAU) recommends offering early PSA testing to well-informed men at elevated risk of having prostate cancer, such as men greater than 50 years of age, men from age 45 who have a family history of prostate cancer or who are of African descent, or men from age 40 who carry BRCA2 mutations [76, 77]. PSA-based screening programmes in men aged 55–69 years may prevent ~1.3 deaths from prostate cancer over ~13 years per 1000 men screened and may also prevent approximately three cases of metastatic prostate cancer per 1000 men screened [75]. The above-listed guidelines explore the potential harms of screening which include frequent false positives and subsequent harms from diagnosis and treatment. For example, of men who undergo radical prostatectomy, as many as 1 in 5 will develop long-term urinary incontinence, and 2 in 3 experience long-term erectile dysfunction [75]. USTPF and AUA do not recommend routine screening for patients over 70 years of age, while the EAU recommends stopping early diagnosis efforts based on life expectancy and performance status and does not provide an age-based cut-off [75–77].

The use of digital rectal examination (DRE) for screening is also debated with a 2018 systematic review reporting sensitivity of DRE performed by primary care clinicians as 0.51 (95% CI, 0.36–0.67; $I^2 = 98.4\%$) and pooled specificity as 0.59 (95% CI, 0.41–0.76; $I^2 = 99.4\%$) [78]. Pooled PPV was 0.41 (95% CI, 0.31–0.52; $I^2 = 97.2\%$), and pooled NPV was 0.64 (95% CI, 0.58–0.70; $I^2 = 95.0\%$) [78]. While the USPTF does not recommend DRE as a screening test, prior USPTF recommendations against screening for prostate cancer have also pre-empted a shift towards higher grade and stage of disease at presentation and an increased incidence of patients presenting with metastatic prostate cancer in the USA [75, 79, 80]. Similar to the limitations to the studies relied upon for the 2012 USPSTF recommendations against using PSA to screen for prostate cancer, there are significant limitations to the studies relied upon to have made this recommendation. In a prospective multicenter trial of 6630 volunteers, more than 1 in 6 patients who were diagnosed with prostate cancer, had a PSA <= 4, but an abnormal DRE as performed by an urologist [81, 82]. In studies where DRE was performed by urologists, an abnormal DRE was associated with an increased risk of higher ISUP grade prostate tumour [83, 84].

The World Professional Association for Transgender Health and the Endocrine Society both recommend that transgender females should follow the same prostate cancer screening recommendations as cis-gender males [85, 86]. A Belgian prospective, centre-based observational study, reported the PSA and testosterone levels of 50 transgender women. Median serum levels for testosterone (ng/dl) and prostatic-specific antigen (PSA, ng/ml) were 29.57 (IQ range 21.45–38.24) and 0.03 (IQ range 0.0300–0.0815), respectively, which is significantly less than in biological men of corresponding age and hence also well below the diagnostic cut-off values for prostatic disease [87]. Gooren et al. recommend that any PSA value greater than 1.0 ng ml^{-1} be regarded as concerning [22]. This value is slightly more liberal than the PSA threshold of 0.65 ng ml^{-1} that identifies cis-gendered men with substantial testosterone deficiency (total T < 230 ng/dL) [88]. Gooren et al. also recommended that all transgender females over the age of 50 years undergo annual prostate evaluations consisting of DRE and PSA measurement, considering that most prostate cancers occur in patients who initiate gender-affirming hormone therapy later in life. A later review suggested that DRE and measurement of PSA may be limited to candidates with a late start of hormone treatment or to those who have a family history of prostate cancer [89].

In transgender women after vaginoplasty, DRE will not necessarily allow examination of the prostate [21]. Weyer et al. found that vaginal palpation of the prostate was possible in merely half of the transgender women [87]. Palpability of the prostate was found to be explained by the length (0.332, $P = 0.018$) and the tissue rigidity of the neovagina (0.396, $P = 0.004$) and not prostate size which proved to be consistently small (<35 mL on ultrasound) and within or below the normal range for young men [87]. In transgender women who have undergone GCS and have a vaginal depth of at least 5 inches and supple vaginal skin, the prostate should be easily palpable.

SCREENING TRANSGENDER WOMEN PROSTATE CANCER: THE MOUNT SINAI EXPERIENCE

The Mount Sinai Center for Transgender Medicine and Surgery (CTMS) opened in 2016 and combines a multi-disciplinary team to deliver advanced care for transgender and non-binary people. The Mount Sinai CTMS has performed over 2000 transgender-specific surgeries. In the absence of data suggesting optimisation of screening, we individualise screening and begin with a thorough history. One important consideration in the history is a family history of high-risk prostate cancer. In addition, the age when hormones were instituted should be determined particularly in older patients who may have had pre-existing undiagnosed prostate cancer. DRE, if the prostate is palpable, typically demonstrates a small prostate and is of uncertain significance. In most cases, we have been able to evaluate the prostate through a vaginal exam if there is no vaginal stenosis. In patients who have not had GCS, a rectal exam is easily performed. PSA is anticipated to be lower than cis-gender counterparts but PSA change over time may be useful. Although there is no data on the utility of MRI in these patients, in patients who have an abnormal DRE, increased PSA or suspicious PSA kinetics, MRI will be ordered prior to prostate biopsy. There is no set algorithm for diagnosis, but screening is individualised (see Fig. 2). For example, we have had a positive biopsy in a patient with a family history of aggressive cancer and a palpable prostate abnormality but a low PSA and normal MRI.

THE ROLE OF MRI IN SCREENING TRANSGENDER WOMEN

Multiparametric, contrast-enhanced magnetic resonance imaging (MRI) is a diagnostic test with good accuracy for the detection of clinically significant cancer in men referred to the hospital with an elevated PSA level [90, 91]. A recent cohort study of 408 men found that a Prostate Imaging-Reporting and Data System (PIRADS) score of 4 or 5 was associated with improved detection of clinically significant prostate cancer without an increase in the number of men who underwent biopsy or were overdiagnosed with clinically insignificant prostate cancer, if prostate-specific antigen testing alone was used [92]. It is proposed that in transgender women, a similar process should exist in evaluating prostate MRIs for concerning lesions [21]. Imaging findings in transgender patients after GCS is discussed elsewhere [93] but there is limited data available assessing the use of MRI screening in transgender females after GCS. One study by Jin et al. showed mean prostate volume measured by transvaginal ultrasound in transgender women after GAS to be a mean of 1.19 cm^3 (SD 5.95 cm^3, range 5–35 cm^3) [94], which serves as a good basis for expectations of results in this population but a more thorough and updated investigation should be performed to better interpret mpMRI findings of transgender women. For patients who have had a vaginoplasty, an MRI scan will characterise the volume and length of the neovagina as well as assess the presence of a bowel

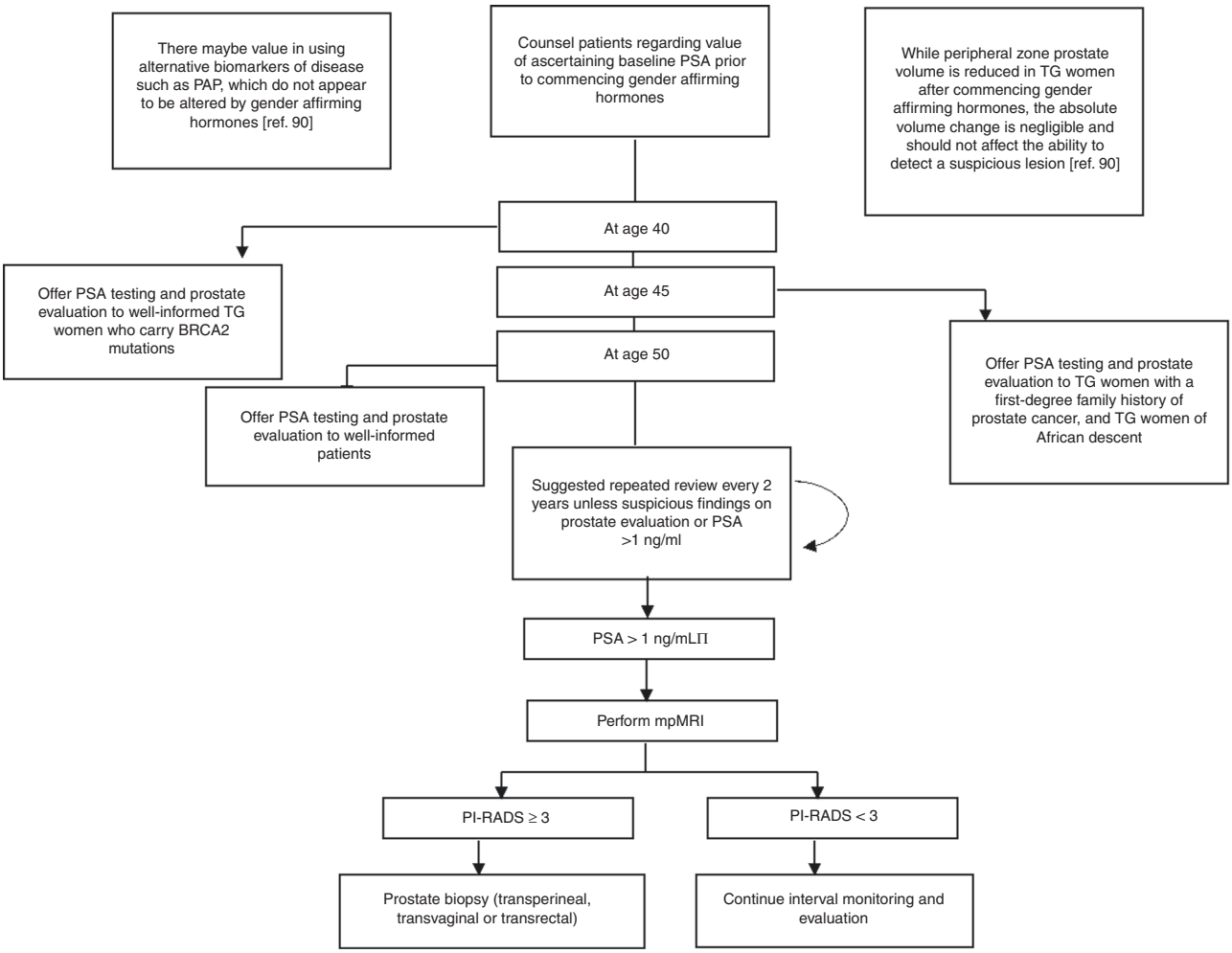

Fig. 2 Proposed approach to prostate cancer screening in transgender women. Π = the choice of a PSA threshold of 1.0 ng/ml is an arbitrary one widely in use, and should be revised as a broader evidence base is established. Establishing a baseline PSA in each individual and identifying deviations from baseline, is likely to be of greater utility than an absolute cut-off value applied to everybody.

graft or perineal flap. As discussed by Bertoncelli Tanaka et al., this will impact the position of the prostate and its relationship with the rectum and neovagina, thus influencing the decision of transvaginal, transrectal or transperineal prostatic biopsy [21].

The previous mentioned MRI studies were carried out on patients with castration-sensitive prostate cancer. While we are unaware of published data on the use of MRI to screen for prostate cancer in transgender women, imaging in patients on 5α reductase inhibitors (5-ARIs) is a useful surrogate. Since 5-ARIs impact the conversion of testosterone to its more bioactive form-DHT, and reduce prostate volume, the analysis of the impact of 5-ARI use on the performance of imaging studies of the prostate, is a useful surrogate. Starobinets et al. performed mpMRIs on 20 men with biopsy-proven prostate cancer of Gleason score 3 + 3; 10 of whom were receiving 5-ARI treatment for at least a year at the time of image acquisition, and 10 untreated patients matched to the treated cohort, in order to determine the effect of 5-ARI treatment on low-grade prostate cancer imaging [95]. The authors found there was a better separation between low-grade cancerous and benign regions of prostatic tissues and overall a reduction in variation of MR measurements for those treated with 5-ARIs when compared to the untreated group [95]. These findings are important to understand the benefit of 5-ARI pretreatment in screening for prostate cancer through mpMRI.

An earlier study discussed the impact of 5-ARI treatment on prostate-specific antigen density (PSAD) in evaluating prostate cancer with MRI imaging [96]. Data from 895 men with BPH in a placebo-controlled study found that treatment with finasteride for twelve months increased the positive predictive value of PSAD for identifying the presence of prostate cancer from 14 to 30% with MRI imaging [96]. As finasteride use induces similar prostate changes to GAHT, PSAD with MRI imaging may have a role in the transgender female population.

Recent development of PSMA as a diagnostic and therapeutic target

PSMA expression levels are inversely related to androgen levels and have been found to be useful in the setting of low androgen activity [97], and so maybe of particular relevance in the setting of prostate cancer in TG women. Several small compounds for labelling PSMA have been developed as imaging probes for positron emission tomography (PET) scans, with the (68)Ga-labelled PSMA inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC being the most widely studied agent [98].

The first PSMA imaging agent approved by the U.S. Food and Drug Administration (FDA) was in December 2020, and was granted to the University of California Los Angeles (UCLA) and the University of California San Francisco (UCSF). The approval was for the use of for 68Ga–prostate-specific membrane antigen–11 [99], and was followed by the approval of piflufolastat F-18 in May 2021, for the same indication: “PSMA positive lesions in men with prostate cancer: with suspected metastasis who are candidates for

initial definitive therapy…(or)…with suspected recurrence based on elevated serum PSA level".

Valuable insights into the utility of PSMA imaging to screen and diagnose clinically significant prostate cancer can be gained from the recently published Phase 2 PRIMARY trial [100]. The investigators examined PSMA-guided PET imaging in combination with mpMRI for the diagnosis of prostate cancer. In this prospective multi-centre Phase II imaging trial, 296 men with suspected prostate cancer underwent MRI, pelvic-only PSMA PET-CT, and systematic +/− targeted biopsy to evaluate the combination of MRI and PSMA as a diagnostic tool for prostate cancer [100]. Of the 163 (56%) men who had clinically significant prostate cancer, 81% were positive for combined PSMA + MRI. This combination improved negative predictive value and sensitivity compared to MRI alone (91% vs 72%, $P < 0.001$ and 97% vs 83%, $P < 0.001$, respectively). Despite a reduction in specificity (40% vs 53%, $P = 0.011$), the authors argue the combination of PSMA + MRI could be a diagnostic paradigm which eliminates biopsies in those patients with negative results (34465492). These findings also support the role for PSMA PET in the diagnosis of prostate cancer in TG women, where MRI alone may overestimate the conspicuity of a prostate lesion, as it does in patients treated with 5-ARIs [101].

Furthermore, the research into PSMA has led to the development of radionuclide therapeutic agents targeting these proteins in the treatment of prostate cancer. One such recent success is the development of lutetium-177-PSMA-617 (177Lu-PSMA-617) for the treatment of metastatic castration-resistant prostate cancer [102].

Though there is no specific research on the use of PSMA in detection or therapeutic treatment of prostate cancer in transgender women, its role in castrate-resistant prostate cancer (CRPC) may indicate some benefit to patients with GAS and GAHT, where in androgen deplete tumour microenvironments, there is abundant PSMA expression. However, while there may be some concern that the FDA approval and labels specifying "men", may affect access and reimbursement for the use of such agents in TG women, it is our view that such stakeholders will adopt a pragmatic approach and not obstruct the use of such agents in the diagnosis and treatment of TG women who may stand to benefit greatly from them.

EVALUATING GENETIC PREDISPOSITIONS IN TRANSGENDER WOMEN

Genetic predisposition is another important factor in assessing a patient's risk of developing prostate cancer, particularly the impact of hormonal therapy on a patient's inherit risk of cancer development. Two case studies highlighted transgender females with BRCA gene mutations, one with BRCA1 and one with BRCA2, and discussed the importance of genetic and cancer screening in these patients [103, 104] Men who are BRCA1 carriers have an absolute risk of prostate cancer of 21% by 75 years (95% CI 13–34%) and 29% by 85 years (95% CI 17–45%); those with BRCA2 have an absolute risk of 27% by 75 years (95% CI 17–41%) and 60% by 85 years (95% CI 43–78%) [105]. These authors argue transgender women with BRCA mutations should follow standard breast and prostate cancer screening guidelines and that any change in DRE or detectable PSA should trigger diagnostic prostate biopsy [103]. The American Cancer Society recommends that women who are at high for breast cancer (including those with BRCA mutations or those with first-degree relative with a known BRCA mutation) should get a breast MRI and a mammogram every year, typically starting at age 30. The national comprehensive cancer network recommends screening for high-risk patients every year starting at 25–40 depending on the gene mutation or youngest age of breast cancer in the family [106]. The guidelines for breast cancer screening in transgender women are discussed by Clarke et al. but for those with high-risk genetic mutations they recommend an individualised approach with consideration for earlier screening based on available family cancer history data [107].

Even without genetic mutations, male to female transgender patients are at higher risk of breast cancer due to hormonal supplementation and prophylactic mastectomy is recommended to minimise the risk of occurrence in the setting of ongoing oestrogen supplementation [103]. One study, though potentially controversial, found transgender women to exhibit significantly longer polymorphic CAG repeat sequences in the androgen receptor gene, though there is no knowledge on whether this predisposes one to prostate cancer development [108].

DIAGNOSTIC CONSIDERATIONS FOR THE TRANSGENDER WOMAN WITH PROSTATE CANCER

As previously discussed, in transgender females, interpretation of prostate MRI should take into account the smaller prostate volumes in patients post GAHT [87, 94]. There is no data on the role of pre-biopsy MRI in transgender females however detailed imaging of the pelvis, including the prostate, is needed for the surgical planning of GCS.

Prostate biopsy is not contraindicated post gender-affirming surgery. For a patient who has not had vaginoplasty (i.e., no surgery, bilateral orchiectomy only, or labiaplasty/zero-depth vaginoplasty), the conventional transrectal probe or transperineal approach could be used. Transneovaginal ultrasound probe placement allows for prostate visualisation and biopsy in a manner quite similar to standard transrectal ultrasound and biopsy [20]. Weyer et al. described that transvaginal scanning of the prostate was feasible among 94% of 50 transgender women, while in three patients the vagina was too short to allow the introduction of the tip of the probe but the prostate could adequately be visualised transperineally [87]. Proper imaging of the seminal vesicles through transvaginal ultrasound was obtained in 80% of the patients [87]. The transperineal route was used in the remaining cases where the neovagina was too short to allow introduction of the tip of the probe. While transvaginal ultrasound was successful in most patients, it is thought that with more recent advancement in surgical technique and ultrasonography practice, these numbers have potential to improve. This improvement will be significant because transperineal ultrasound is an effective alternative to transvaginal ultrasound in the visualisation of the prostate but may be impacted by distortion of the anatomy after vaginoplasty and biopsy may not be as feasible or successful through this method [21].

In terms of grading, Bostwick et al. discussed that all forms of androgen-deprivation therapy, including finasteride, induce distinctive histologic changes in benign and neoplastic prostatic epithelial cells, including cytoplasmic clearing, nuclear and nucleolar shrinkage, and chromatin condensation [109]. The authors recommend the Gleason grading system for cancer not be used after finasteride treatment as it is likely to overestimate the biologic potential of high-grade cancer [109]. It is unclear if GAHT may have the same effect, however, all published cases of prostate cancer in this population were ISUP grade > =2.

TREATMENT CONSIDERATIONS FOR LOCALISED PROSTATE CANCER

The treatment choice for localised prostate cancer is dependent on risk stratification which includes PSA, prostate biopsy results and imaging studies [110] Patients with clinically localised, very low-risk or low-risk prostate cancer can generally be treated with active surveillance. For patients with intermediate or higher-risk disease, surgery, RT and/or ADT are standard-of-care treatments. While these guidelines are the same for patients who are ADT

naive (patients considered to have CSPC), the concepts underpinning these guidelines is the same for localised disease, regardless of prior ADT. Analysis of the National Cancer Database in the USA revealed 2% of patients with PCa were treated with neoadjuvant ADT prior to radical prostatectomy, and demonstrated a decreased odds of positive surgical margins among low- and intermediate-risk patients [111]. A recent analysis of 128,062 patients with intermediate and high-risk prostate cancer treated with radical prostatectomy demonstrated no difference in adverse pathology, upgrading, node-positive disease or adjuvant treatments between those treated immediately and those who underwent radical prostatectomy delayed up to 12 months [112]. Combined, this suggests a basis for offering active surveillance to transgender women diagnosed with very low-risk or low-risk prostate cancer; as if their disease shows further evidence of progression, radical therapies may be offered.

The case reports documenting PCa in TG women provide some basis for the role of radical prostatectomy or radiotherapy treatments in patients with intermediate and high-risk disease (Table 2). The upfront treatment approach for localised prostate cancer in transgender females should also consider and discuss whether the patient has undergone GCS or if they plan to undergo GCS in the future. Whilst labiaplasty or minimal depth vaginoplasty is feasible after radical prostatectomy, brachytherapy or radiotherapy, neovagina formation may be surgically challenging, with a significantly greater risk of rectal injury and subsequent rectovaginal fistula and a greater risk of damage to the urinary sphincter [21]. If the patient has yet to undergo planned GCS, input from a gender-affirming surgeon should be sought. If a radical prostatectomy is planned in a patient who has undergone GCS, the surgeon will need to consider existing anatomy when planning the surgical approach [113] (see Fig. 3). Care must be taken during dissection to remain vigilant of the modified anatomy between the prostate, neovagina and rectum [20]. GAHT generally causes prostate atrophy so anatomical prostatic landmarks may be less clear, necessitating extra care and attention [20]. In addition, the skin flap or graft (if a PIV was performed) will have to be peeled off of the prostate.

Radiation therapy in patients who have had GCS again requires consideration of new anatomic relationships in the area of the prostate with the aim being to avoid excessive radiation dose to the neovagina [20]. Radiation leads to epithelial injury, decreased blood supply, hypoxia and telangiectasia, resulting in atrophy of mucosa, absent lubrication, loss of vaginal elasticity, formation of adherences and fibrosis in cis-gender females [114]. Transgender females should likewise be counselled on the risk of neovaginal stenosis from any dose of radiation which may later require neovaginal dilation as well as the risk of fistula formation. The atrophic prostate may also prove more technically challenging for more targeted radiation approaches like brachytherapy in the absence of a perineum [115]. Smaller prostates also have more post-implant oedema post brachytherapy which also needs to be accounted for in treatment planning [116, 117]. While any type of radiation therapy can cause damage to the vaginal wall, the clinician should also consider the type of vaginoplasty that was performed (PIV, PFV or SV), and the degree and type of vascular supply to the vaginal tissues. For example, in PIV, the distal portion of the vaginal canal is typically composed of a skin flap from the phallic skin while the apical portion is made of a split-thickness skin graft. The location of the junction between these two vaginal wall components should be assessed with respect to the prostate. Radiation to the prostate would be more likely to fistulize if an overlying skin graft is used, than if an overlying flap was used. If a segment of colon has been harvested to construct the vagina, for example, with SV, the thickness of the vascularises tissue would suggest a lower risk of fistulization or stenosis.

A descriptive study of men with clinically localised castration-resistant prostate cancer treated with "curative" radiotherapy reported the development of metastatic disease in 79% of patients at a median follow-up of 33 months [118]. The addition of ADT or brachytherapy boost are intensified treatments for patients with unfavourable intermediate and high-risk prostate cancer treated with external beam radiotherapy [119]. We have already discussed the difficulties with brachytherapy in this population. It is unclear if the use of androgen-deprivation therapy in conjunction with external beam radiation therapy for localised prostate cancer in transgender females with already castrate levels of testosterone provides any additional benefit. In cis-gender men with non-metastatic CRPC,

Considering the high risk of complications after GCS and potential impact on quality of life after prostate cancer treatment, clinicians should not apply a standard cis-gender algorithm in the treatment of the transgender population. There are some important misconceptions which should be clarified: Active surveillance is a valid treatment choice for all closely monitored transgender females with localised disease; vaginoplasty does not preclude surveillance options which include prostate biopsy, MRI and PSA screening. In addition, clinicians should not necessarily prioritise treatment of prostate cancer over alleviation of gender dysphoria in patients who have not yet had GCS performed. Patients with gender dysphoria have a significantly higher incidence of suicide than the cis-population [4]. GCS decreases the mental health distress caused by gender dysphoria in these patients [120]. Both gender dysphoria and prostate cancer are life-threatening conditions and treatment decisions should be individualised with patients wishes prioritised, with input from a reconstructive urologist.

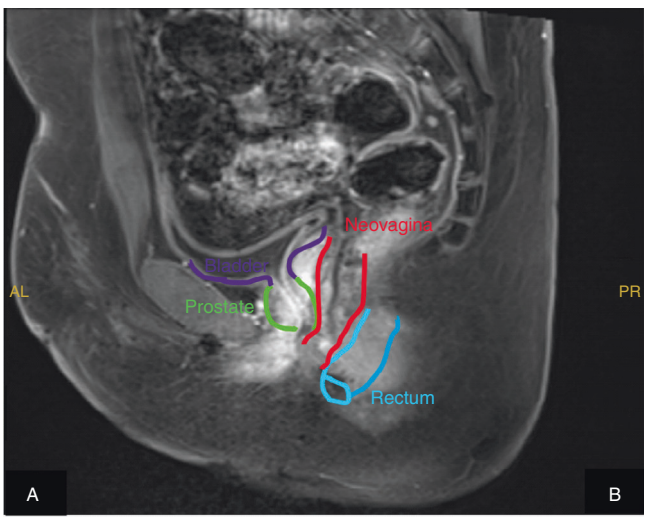

Fig. 3 MRI sagittal view from the pelvis of a transgender woman post gender-confirming surgery. Anatomical structures are annotated to highlight the relationship of between the perineum, the prostate (green), neovagina (red), bladder (purple) and rectum (blue).

URINARY COMPLICATIONS

Anecdotally, we have found that urinary complications after prostate cancer treatment in transgender women can be devastating although there is little data to help inform treatment. Although the treatment options for prostate cancer may be similar in transgender and cis-gender patients, the consequences of complications are very different and as such, should be considered differently and not be treated equivalently. For example, stress urinary incontinence after treatment of prostate cancer in the cis-gender population, can be effectively treated with surgical options such as the AdVance sling or the artificial urinary sphincter (AUS)

by an experienced surgeon [121]. Stress incontinence from sphincteric injury in transgender patients who have undergone GCS is more difficult to manage and may never be corrected. In transgender women who have undergone GCS the urethra is typically transected at the level of the mid to proximal bulbar urethra, leaving little room for placement of the cuff of the AUS or an AdVance sling. An alternative may be the placement of the AUS around the bladder neck but this is a technically challenging surgery, and has not yet been reported in this population. Minor incontinence may be theoretically treated with bulking agents and/or behavioural modification but data on efficacy is absent. One technique that has been reported is the use of an autologous rectus fascial sling in a patient post radical prostatectomy who developed total incontinence after attempted vaginoplasty. The intent was to create less bothersome retention managed by intermittent catheterisation [122].

The lack of good treatment options for incontinence in these patients warrants careful deliberation about the need for surgery for prostate cancer. Similarly, the management of stress incontinence after radiation therapy is complex. In transgender women with urge incontinence after prostate cancer treatment, an anatomic abnormality such as a fistula should be ruled out but treatment would otherwise be analogous to cis-gender counterparts. For those who develop a fistula communicating with the urinary tract, the severity of the fistula would dictate treatment options which range from simple repair, use of bowel for revision vaginoplasty, vaginectomy, and/or urinary diversion.

TREATMENT CONSIDERATIONS FOR ADVANCED METASTATIC PROSTATE CANCER

While the treatment of localised prostate cancer in this population has been discussed elsewhere, the unique implications for the treatment in metastatic disease in this population has not [21]. Most individuals with advanced prostate cancer eventually stop experiencing a response to traditional androgen-deprivation therapy and are categorised as castration-resistant. Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL) [123]. In oncology generally, transgender patients may be diagnosed at later stages, be less likely to receive treatment, and have worse survival for many cancer types [6]. Significantly, six out of the eleven reported cases of prostate cancer in transgender females that document M-stage, describe cases of metastatic prostate cancer. As illustrated in Table 1, treatments varied for these cases as guidelines for the treatment of metastatic prostate cancer evolved. Long-term outcomes for most of these patients is unknown. It is unclear if their presentation with metastatic disease is related to late presentation, a lack of screening in this population or if this population have the more aggressive disease due to cellular level changes secondary to GAHT use. As previously discussed, transgender patients with castrate testosterone levels may have castration-resistant prostate cancer when diagnosed. One patient with metastatic disease who had been on GAHT therapy for 41 years, had a testosterone level of 44 ng/dl but interestingly had a good response with androgen-deprivation therapy and radiation therapy with 56 months of follow-up [14]. NCCN outlines the treatment approach for metastatic prostate cancer based on exposure to prior docetaxel and prior novel hormone therapy [123]. Doublet and triplet chemohormonal therapy early in ADT therapy has been shown to significantly prolong survival in high-volume metastatic hormone-sensitive prostate cancer in cis-gender males [124–126]. In our transgender female population, initiation of non-AR targeting therapy early in treatment is important. Recent results from the ARASENs trial, investigating the impact of addition of darolutamide to standard-of-care doublet chemohormonal therapy (docetaxel and ADT) on survival in hormone-sensitive prostate cancer demonstrated a survival benefit: 86.1% of participants in this trial had metastatic disease at initial diagnosis, potentially a similar disease profile to that experienced by the transgender women who develop prostate cancer. In recent years, we have seen the approval of novel targeted agents in advanced prostate cancer. PARP inhibitors are approved for patients with DNA damage repair gene alterations and the PD-L1 inhibitor pembrolizumab is approved for patients with microsatellite instability–high (MSI-H)/deficient mismatch repair prostate cancer [123]. The limitations in the management of advanced disease in transgender females include the limited data on genetic alterations in this population and the use of estrogens affecting the eligibility for potential clinical trials.

FUTURE DIRECTIONS AND CURRENT UNMET NEEDS

The unique hormonal milieu to which the transgender woman is exposed may well deliver insights into prostate carcinogenesis, disease progression, and delineating indolent from aggressive disease. While the future directions for research in this field are myriad, in our view the single greatest unmet need in prostate cancer care for transgender women, is the provision of equitable access to healthcare. Important conversations around cancer screening and risk/benefits of treatment occur most often in primary care offices, outpatient clinics and hospitals. And important opportunities to reach vulnerable patient groups exist through patient and healthcare worker education, advocacy groups, and accurate communication through mass media, among other means.

A significant proportion of patients already commence their transition without medical supervision; initiating estrogens with intact androgen production, and in doing so possibly increase the future risk for developing prostate cancer; a disease which may not become clinically apparent for many years, but that can be life-altering and even life ending. It is imperative that these conversations about prostate cancer risk, screening and management occur, and this can only happen with equitable access.

CONCLUSION

It remains unclear how prevalent prostate cancer is among transgender women. Large longitudinal studies spanning over decades which capture patients over 65 years of age will be needed to answer this question. What is also unknown at the current time is how these women, many of whom have been on androgen depletion for their entire post-adolescent life, develop prostate cancer. It may be possible for those who began their transition late in life that they had pre-existing microscopic disease at the time of transition. For those on life-long GAHT, the answer may be related to AR-mediated mechanisms which we usually see in castrate-resistant disease or due to oestrogen-driven disease via ER upregulation. Data on screening for prostate cancer in the transgender population is limited and, in our opinion, decisions around screening should be individualised. The treatment of all stages of prostate cancer in transgender women should be individualised and take into account the morbidity and mortality associated with untreated gender dysphoria. The type of vaginoplasty that transgender women may have undergone alters the side effect profile from prostate cancer treatment; some side effects such as urinary incontinence are not amenable to cure in this population compared to cis-gender males. If it is in line with a patient's wishes, the fallback treatment option for localised prostate cancer treatment after GCS should be active surveillance. Reconstructive urologists should be involved in treatment planning when treatment decisions for transgender females with prostate cancer are being discussed, so the unique ramifications for each patient are understood upon making treatment recommendations.

DATA AVAILABILITY

Not applicable.

REFERENCES

1. Cooper K, Russell A, Mandy W, Butler C. The phenomenology of gender dysphoria in adults: a systematic review and meta-synthesis. Clin Psychol Rev. 2020;80:101875.
2. Baker KE. Findings from the behavioral risk factor surveillance system on health-related quality of life among US transgender adults, 2014-2017. JAMA Intern Med. 2019;179:1141–4.
3. Flores AR, Brown TN, Herman J. Race and ethnicity of adults who identify as transgender in the United States. CA: Williams Institute, UCLA School of Law Los Angeles; 2016.
4. James SE, Herman JL, Rankin S, Keisling M, Mottet L, Anafi, M. The Report of the 2015 U.S. Transgender Survey. National Center for Transgender Equality, Washington, DC. 2016.
5. Badgett MV, Choi SK, Wilson BDM. LGBT poverty in the United States: a study of differences between sexual orientation and gender identity groups (2019). https://williamsinstitute.law.ucla.edu/wp-content/uploads/National-LGBT-Poverty-Oct-2019.pdf.
6. Jackson SS, Han X, Mao Z, Nogueira L, Suneja G, Jemal A, et al. Cancer stage, treatment, and survival among transgender patients in the United States. J Natl Cancer Inst. 2021;113:1221–7.
7. Rosser BRS, Capistrant B, Torres B, Konety B, Merengwa E, Mitteldorf D, et al. The effects of radical prostatectomy on gay and bisexual men's mental health, sexual identity and relationships: qualitative results from the restore study. Sex Relatsh Ther. 2016;31:446–61.
8. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA: A Cancer J Clin. 2021;71:7–33.
9. Viale PH. The American Cancer Society's facts & figures: 2020 edition. J Adv Pr Oncol. 2020;11:135–6.
10. American Cancer Society. Cancer Facts & Figures 2021. Atlanta: American Cancer Society. 2021. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf.
11. Pritzlaff M, Tian Y, Reineke P, Stuenkel AJ, Allen K, Gutierrez S, et al. Diagnosing hereditary cancer predisposition in men with prostate cancer. Genet Med. 2020;22:1517–23.
12. Thurston AV. Carcinoma of the prostate in a transsexual. Br J Urol. 1994;73:217.
13. van Haarst EP, Newling DW, Gooren LJ, Asscheman H, Prenger DM. Metastatic prostatic carcinoma in a male-to-female transsexual. Br J Urol. 1998;81:776.
14. Miksad RA, Bubley G, Church P, Sanda M, Rofsky N, Kaplan I, et al. Prostate cancer in a transgender woman 41 years after initiation of feminization. J Am Med Assoc. 2006;296:2316–7.
15. Dorff TB, Shazer RL, Nepomuceno EM, Tucker SJ. Successful treatment of metastatic androgen-independent prostate carcinoma in a transsexual patient. Clin Genitourin Cancer. 2007;5:344–6.
16. Turo R, Jallad S, Prescott S, Cross WR. Metastatic prostate cancer in transsexual diagnosed after three decades of estrogen therapy. Can Urol Assoc J. 2013;7:E544–546.
17. Ellent E, Matrana MR. Metastatic prostate cancer 35 years after sex reassignment surgery. Clin Genitourin Cancer. 2016;14:e207–209.
18. Deebel NA, Morin JP, Autorino R, Vince R, Grob B, Hampton LJ. Prostate cancer in transgender women: incidence, etiopathogenesis, and management challenges. Urology. 2017;110:166–71.
19. Sharif A, Malhotra NR, Acosta AM, Kajdacsy-Balla AA, Bosland M, Guzman G, et al. The development of prostate adenocarcinoma in a transgender male to female patient: could estrogen therapy have played a role? Prostate. 2017;77:824–8.
20. Ingham MD, Lee RJ, MacDermed D, Olumi AF. Prostate cancer in transgender women. Urol Oncol. 2018;36:518–25.
21. Bertoncelli Tanaka M, Sahota K, Burn J, Falconer A, Winkler M, Ahmed HU, et al. Prostate cancer in transgender women: what does a urologist need to know? BJU Int. 2022;129:113–22.
22. Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. Andrologia. 2014;46:1156–60.
23. Silverberg MJ, Nash R, Becerra-Culqui TA, Cromwell L, Getahun D, Hunkeler E, et al. Cohort study of cancer risk among insured transgender people. Ann Epidemiol. 2017;27:499–501.
24. Nash R, Ward KC, Jemal A, Sandberg DE, Tangpricha V, Goodman M. Frequency and distribution of primary site among gender minority cancer patients: an analysis of U.S. national surveillance data. Cancer Epidemiol. 2018;54:1–6.
25. Braun H, Nash R, Tangpricha V, Brockman J, Ward K, Goodman M. Cancer in transgender people: evidence and methodological considerations. Epidemiol Rev. 2017;39:93–107.
26. de Nie I, de Blok CJM, van der Sluis TM, Barbé E, Pigot GLS, Wiepjes CM, et al. Prostate cancer incidence under androgen deprivation: nationwide cohort study in trans women receiving hormone treatment. J Clin Endocrinol Metab. 2020;105:e3293–e3299.
27. Siegel DA, O'Neil ME, Richards TB, Dowling NF, Weir HK. Prostate cancer incidence and survival, by stage and race/ethnicity—United States, 2001–2017. Morbidity Mortal Wkly Rep. 2020;69:1473.
28. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7–33.
29. Gooren L. Hormone treatment of the adult transsexual patient. Horm Res. 2005;64:31–36.
30. Moore E, Wisniewski A, Dobs A. Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. J Clin Endocrinol Metab. 2003;88:3467–73.
31. Stroumsa D, Crissman HP, Dalton VK, Kolenic G, Richardson CR. Insurance coverage and use of hormones among transgender respondents to a national survey. Ann Fam Med. 2020;18:528.
32. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol. 2002;168:9–12.
33. Tsukamoto S, Akaza H, Onozawa M, Shirai T, Ideyama Y. A five-alpha reductase inhibitor or an antiandrogen prevents the progression of microscopic prostate carcinoma to macroscopic carcinoma in rats. Cancer. 1998;82:531–7.
34. Wibowo E, Schellhammer P, Wassersug RJ. Role of estrogen in normal male function: clinical implications for patients with prostate cancer on androgen deprivation therapy. J Urol. 2011;185:17–23.
35. Dal Pra A, Cury F, Souhami L. Combining radiation therapy and androgen deprivation for localized prostate cancer—a critical review. Curr Oncol. 2010;17:28–38.
36. Crowley F, Sterpi M, Buckley C, Margetich L, Handa S, Dovey Z. A review of the pathophysiological mechanisms underlying castration-resistant prostate cancer. Res Rep. Urol. 2021;13:457–72.
37. Citrin DL, Resnick MI, Guinan P, al-Bussam N, Scott M, Gau TC, et al. A comparison of Zoladex and DES in the treatment of advanced prostate cancer: results of a randomized, multicenter trial. Prostate. 1991;18:139–46.
38. Bosland MC. The role of estrogens in prostate carcinogenesis: a rationale for chemoprevention. Rev Urol. 2005;7:S4–S10.
39. Nelles JL, Hu W-Y, Prins GS. Estrogen action and prostate cancer. Expert Rev Endocrinol Metab. 2011;6:437–51.
40. Bosland MC. A perspective on the role of estrogen in hormone-induced prostate carcinogenesis. Cancer Lett. 2013;334:28–33.
41. Kruithof-Dekker IG, Têtu B, Janssen PJ, Van der Kwast TH. Elevated estrogen receptor expression in human prostatic stromal cells by androgen ablation therapy. J Urol. 1996;156:1194–7.
42. Lundon DJ, Boland A, Prencipe M, Hurley G, O'Neill A, Kay E, et al. The prognostic utility of the transcription factor SRF in docetaxel-resistant prostate cancer: in-vitro discovery and in-vivo validation. BMC Cancer. 2017;17:1–13.
43. Takizawa I, Lawrence MG, Balanathan P, Rebello R, Pearson HB, Garg E, et al. Estrogen receptor alpha drives proliferation in PTEN-deficient prostate carcinoma by stimulating survival signaling, MYC expression and altering glucose sensitivity. Oncotarget. 2015;6:604–16.
44. Megas G, Chrisofos M, Anastasiou I, Tsitlidou A, Choreftaki T, Deliveliotis C. Estrogen receptor (alpha and beta) but not androgen receptor expression is correlated with recurrence, progression and survival in post prostatectomy T3N0M0 locally advanced prostate cancer in an urban Greek population. Asian J Androl. 2015;17:98–105.
45. Prins GS, Korach KS. The role of estrogens and estrogen receptors in normal prostate growth and disease. Steroids. 2008;73:233–44.
46. Di Zazzo E, Galasso G, Giovannelli P, Di Donato M, Bilancio A, Perillo B, et al. Estrogen receptors in epithelial-mesenchymal transition of prostate cancer. Cancers. 2019;11:1418.
47. Landstrom M, Damber JE, Bergh A. Estrogen treatment postpones the castration-induced dedifferentiation of Dunning R3327-PAP prostatic adenocarcinoma. Prostate. 1994;25:10–18.
48. Langley RE, Gilbert DC, Duong T, Clarke NW, Nankivell M, Rosen SD, et al. Transdermal oestradiol for androgen suppression in prostate cancer: long-term cardiovascular outcomes from the randomised prostate adenocarcinoma transcutaneous hormone (PATCH) trial programme. Lancet. 2021;397:581–91.
49. Langley RE, Kynaston HG, Alhasso AA, Duong T, Paez EM, Jovic G, et al. A randomised comparison evaluating changes in bone mineral density in advanced prostate cancer: luteinising hormone-releasing hormone agonists versus transdermal oestradiol. Eur Urol. 2016;69:1016–25.
50. Geier R, Adler S, Rashid G, Klein A. The synthetic estrogen diethylstilbestrol (DES) inhibits the telomerase activity and gene expression of prostate cancer cells. Prostate. 2010;70:1307–12.

51. Dobbs RW, Malhotra NR, Greenwald DT, Wang AY, Prins GS, Abern MR. Estrogens and prostate cancer. Prostate Cancer Prostatic Dis. 2019;22:185–94.
52. Manikandan R, Srirangam SJ, Pearson E, Brown SC, O'Reilly P, Collins GN. Diethylstilboestrol versus bicalutamide in hormone refractory prostate carcinoma: a prospective randomized trial. Urol Int. 2005;75:217–21.
53. Byar DP, Corle DK. Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urological Research Group studies. NCI Monogr. 1988;7:165–70.
54. Veterans Administration Co-operative Urological Research Group. Treatment and survival of patients with cancer of the prostate. Surg Gynecol Obstet. 1967;124:1011–7.
55. Di Zazzo E, Galasso G, Giovannelli P, Di Donato M, Castoria G. Estrogens and their receptors in prostate cancer: therapeutic implications. Front Oncol. 2018;8:2.
56. Bergan RC, Reed E, Myers CE, Headlee D, Brawley O, Cho H-K, et al. A Phase II study of high-dose tamoxifen in patients with hormone-refractory prostate cancer. Clin Cancer Res. 1999;5:2366–73.
57. Stein S, Zoltick B, Peacock T, Holroyde C, Haller D, Armstead B, et al. Phase II trial of toremifene in androgen-independent prostate cancer: a Penn cancer clinical trials group trial. Am J Clin Oncol. 2001;24:283–5.
58. Fujimura T, Takahashi S, Kume H, Urano T, Takayama K, Yamada Y, et al. Toremifene, a selective estrogen receptor modulator, significantly improved biochemical recurrence in bone metastatic prostate cancer: a randomized controlled phase II a trial. BMC Cancer. 2015;15:1–8.
59. Ho TH, Nunez-Nateras R, Hou Y-X, Bryce AH, Northfelt DW, Dueck AC, et al. A study of combination bicalutamide and raloxifene for patients with castration-resistant prostate cancer. Clin Genitourin Cancer. 2017;15:196–202. e191
60. Shang Y, Brown M. Molecular determinants for the tissue specificity of SERMs. Science. 2002;295:2465–8.
61. Martinkovich S, Shah D, Planey SL, Arnott JA. Selective estrogen receptor modulators: tissue specificity and clinical utility. Clin Inter Aging. 2014;9:1437–52.
62. Bosland MC, Huang J, Schlicht MJ, Enk E, Xie H, Kato I. Impact of 18-month soy protein supplementation on steroid hormones and serum biomarkers of angiogenesis, apoptosis, and the growth hormone/IGF-1 axis: results of a randomized, placebo-controlled trial in males following prostatectomy. Nutr Cancer. 2022;74:110–21.
63. Bonkhoff H. Estrogen receptor signaling in prostate cancer: implications for carcinogenesis and tumor progression. Prostate. 2018;78:2–10.
64. Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nat Clin Pract Urol. 2009;6:76–85.
65. Koochekpour S. Androgen receptor signaling and mutations in prostate cancer. Asian J Androl. 2010;12:639.
66. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res. 2008;68:4447.
67. Pernigoni N, Zagato E, Calcinotto A, Troiani M, Mestre RP, Calì B, et al. Commensal bacteria promote endocrine resistance in prostate cancer through androgen biosynthesis. Science. 2021;374:216–24.
68. Fixemer T, Remberger K, Bonkhoff H. Differential expression of the estrogen receptor beta (ERbeta) in human prostate tissue, premalignant changes, and in primary, metastatic, and recurrent prostatic adenocarcinoma. Prostate. 2003;54:79–87.
69. Bonkhoff H, Fixemer T, Hunsicker I, Remberger K. Estrogen receptor expression in prostate cancer and premalignant prostatic lesions. Am J Pathol. 1999;155:641–7.
70. Bonkhoff H, Fixemer T, Hunsicker I, Remberger K. Progesterone receptor expression in human prostate cancer: correlation with tumor progression. Prostate. 2001;48:285–91.
71. Shaw GL, Whitaker H, Corcoran M, Dunning MJ, Luxton H, Kay J, et al. The early effects of rapid androgen deprivation on human prostate cancer. Eur Urol. 2016;70:214–8.
72. Balk SP, Ko YJ, Bubley GJ. Biology of prostate-specific antigen. J Clin Oncol. 2003;21:383–91.
73. Schröder FH, Carter HB, Wolters T, van den Bergh RC, Gosselaar C, Bangma CH, et al. Early detection of prostate cancer in 2007. Part 1: PSA and PSA kinetics. Eur Urol. 2008;53:468–77.
74. Merriel SWD, Pocock L, Gilbert E, Creavin S, Walter FM, Spencer A, et al. Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. BMC Med. 2022;20:54.
75. Force USPST. Screening for prostate cancer: US preventive services task force recommendation statement. J Am Med Assoc. 2018;319:1901–13.
76. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, et al. Early detection of prostate cancer: AUA guideline. J Urol. 2013;190:419–26.
77. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017;71:618–29.
78. Naji L, Randhawa H, Sohani Z, Dennis B, Lautenbach D, Kavanagh O, et al. Digital rectal examination for prostate cancer screening in primary care: a systematic review and meta-analysis. Ann Fam Med. 2018;16:149–54.
79. Butler SS, Muralidhar V, Zhao SG, Sanford NN, Franco I, Fullerton ZH, et al. Prostate cancer incidence across stage, NCCN risk groups, and age before and after USPSTF Grade D recommendations against prostate-specific antigen screening in 2012. Cancer. 2020;126:717–24.
80. Fleshner K, Carlsson SV, Roobol MJ. The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat Rev Urol. 2017;14:26–37.
81. Catalona William J, Richie Jerome P, Ahmann Frederick R, Hudson M'Liss A, Scardino Peter T, Flanigan Robert C, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol. 1994;151:1283–90.
82. Richie JP, Catalona WJ, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. Urology. 1993;42:365–74.
83. Okotie OT, Roehl KA, Han M, Loeb S, Gashti SN, Catalona WJ. Characteristics of prostate cancer detected by digital rectal examination only. Urology. 2007;70:1117–20.
84. Gosselaar C, Roobol MJ, Roemeling S, Schröder FH. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol. 2008;54:581–8.
85. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society* clinical practice guideline. J Clin Endocrinol Metab. 2017;102:3869–903.
86. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgenderism. 2012;13:165–232.
87. Weyers S, De Sutter P, Hoebeke S, Monstrey G, G TS, Verstraelen H, et al. Gynaecological aspects of the treatment and follow-up of transsexual men and women. Facts Views Vis Obgyn. 2010;2:35–54.
88. Rastrelli G, Corona G, Vignozzi L, Maseroli E, Silverii A, Monami M, et al. Serum PSA as a predictor of testosterone deficiency. J Sex Med. 2013;10:2518–28.
89. Trum HW, Hoebeke P, Gooren LJ. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. Acta Obstet Gynecol Scand. 2015;94:563–7.
90. Ahmed HU, Bosaily AE-S, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389:815–22.
91. Drost FJH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019;4. https://doi.org/10.1002/14651858.CD012663.pub2.
92. Eldred-Evans D, Burak P, Connor MJ, Day E, Evans M, Fiorentino F, et al. Population-based prostate cancer screening with magnetic resonance imaging or ultrasonography: the IP1-PROSTAGRAM study. JAMA Oncol. 2021;7:395–402.
93. Stowell JT, Grimstad FW, Kirkpatrick DL, Brown ER, Santucci RA, Crane C, et al. Imaging findings in transgender patients after gender-affirming surgery. RadioGraphics. 2019;39:1368–92.
94. Jin B, Turner L, Walters WA, Handelsman DJ. The effects of chronic high dose androgen or estrogen treatment on the human prostate [corrected]. J Clin Endocrinol Metab. 1996;81:4290–5.
95. Starobinets O, Kurhanewicz J, Noworolski SM. Improved multiparametric MRI discrimination between low-risk prostate cancer and benign tissues in a small cohort of 5α-reductase inhibitor treated individuals as compared with an untreated cohort. NMR Biomed. 2017;30:e3696.
96. Gormley GJ, Ng J, Cook T, Stoner E, Guess H, Walsh P. Effect of finasteride on prostate-specific antigen density. Urology. 1994;43:53–58.
97. Parsi M, Desai MH, Desai D, Singhal S, Khandwala PM, Potdar RR. PSMA: a game changer in the diagnosis and treatment of advanced prostate cancer. Med Oncol. 2021;38:89.
98. Eder M, Schäfer M, Bauder-Wüst U, Hull WE, Wängler C, Mier W, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem. 2012;23:688–97.
99. FDA approves first PSMA-targeted PET drug. J Nucl Med. 2021;62:11N. https://jnm.snmjournals.org/content/62/2/11N.2.long.
100. Emmett L, Buteau J, Papa N, Moon D, Thompson J, Roberts MJ, et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic

resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol. 2021;80:682–9.
101. Starobinets O, Kurhanewicz J, Noworolski SM. Improved multiparametric MRI discrimination between low-risk prostate cancer and benign tissues in a small cohort of 5alpha-reductase inhibitor treated individuals as compared with an untreated cohort. NMR Biomed. 2017;30:e3696.
102. Diao W, Cai H, Chen L, Jin X, Liao X, Jia Z. Recent advances in prostate-specific membrane antigen-based radiopharmaceuticals. Curr Top Med Chem. 2019;19:33–56.
103. Li JZ, Tu HYV, Avram R, Pinthus J, Bordeleau L, Hodgson N. Cancer prevention and screening in a BRCA2-positive male to female transgender patient. Breast J. 2018;24:1112–3.
104. Colebunders B, T'Sjoen G, Weyers S, Monstrey S. Hormonal and surgical treatment in trans-women with BRCA1 mutations: a controversial topic. J Sex Med. 2014;11:2496–9.
105. Nyberg T, Frost D, Barrowdale D, Evans DG, Bancroft E, Adlard J, et al. Prostate cancer risks for male BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Eur Urol. 2020;77:24–35.
106. Forbes C, Fayter D, de Kock S, Quek RG. A systematic review of international guidelines and recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of BRCA-mutated breast cancer. Cancer Manag Res. 2019;11:2321.
107. Clarke CN, Cortina CS, Fayanju OM, Dossett LA, Johnston FM, Wong SL. Breast cancer risk and screening in transgender persons: a call for inclusive care. Ann Surgical Oncol. 2022;29:2176–80.
108. D'Andrea S, Pallotti F, Senofonte G, Castellini C, Paoli D, Lombardo F, et al. Polymorphic cytosine-adenine-guanine repeat length of androgen receptor gene and gender incongruence in trans women: a systematic review and meta-analysis of case-control studies. J Sex Med. 2020;17:543–50.
109. Bostwick DG, Qian J, Civantos F, Roehrborn CG, Montironi R. Does finasteride alter the pathology of the prostate and cancer grading? Clin Prostate Cancer. 2004;2:228–35.
110. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17:479–505.
111. McClintock TR, von Landenberg N, Cole AP, Lipsitz SR, Gild P, Sun M, et al. Neoadjuvant androgen deprivation therapy prior to radical prostatectomy: recent trends in utilization and association with postoperative surgical margin status. Ann Surg Oncol. 2019;26:297–305.
112. Ginsburg KB, Curtis GL, Timar RE, George AK, Cher ML. Delayed radical prostatectomy is not associated with adverse oncologic outcomes: implications for men experiencing surgical delay due to the COVID-19 pandemic. J Urol. 2020;204:720–5.
113. Berli JU, Knudson G, Fraser L, Tangpricha V, Ettner R, Ettner FM, et al. What surgeons need to know about gender confirmation surgery when providing care for transgender individuals: a review. JAMA Surg. 2017;152:394–400.
114. Grigsby PW, Russell A, Bruner D, Eifel P, Koh W-J, Spanos W, et al. Late injury of cancer therapy on the female reproductive tract. Int J Radiat Oncol* Biol* Phys. 1995;31:1281–99.
115. Mayadev J, Merrick GS, Reed JR, Butler WM, Galbreath RW, Allen ZA, et al. Permanent prostate brachytherapy in prostate glands <20 cm(3). Int J Radiat Oncol Biol Phys. 2010;76:1450–5.
116. Chung E, Stenmark MH, Evans C, Narayana V, McLaughlin PW. Greater post-implant swelling in small-volume prostate glands: implications for dosimetry, treatment planning, and operating room technique. Int J Radiat Oncol Biol Phys. 2012;82:1944–8.
117. Kovtun KA, Wolfsberger L, Niedermayr T, Sugar EN, Graham PL, Murciano-Goroff Y, et al. Dosimetric quality and evolution of edema after low-dose-rate brachytherapy for small prostates: implications for the use of newer isotopes. Brachytherapy. 2014;13:152–6.
118. Sanguineti G, Marcenaro M, Franzone P, Tognoni P, Barra S, Vitale V. Is there a "curative" role of radiotherapy for clinically localized hormone refractory prostate cancer? Am J Clin Oncol. 2004;27:264–8.
119. Jackson WC, Hartman HE, Dess RT, Birer SR, Soni PD, Hearn JWD, et al. Addition of androgen-deprivation therapy or brachytherapy boost to external beam radiotherapy for localized prostate cancer: a network meta-analysis of randomized trials. J Clin Oncol. 2020;38:3024–31.
120. Almazan AN, Keuroghlian AS. Association between gender-affirming surgeries and mental health outcomes. JAMA Surg. 2021;156:611–8.
121. Chen YC, Lin PH, Jou YY, Lin VC. Surgical treatment for urinary incontinence after prostatectomy: a meta-analysis and systematic review. PLoS ONE. 2017;12:e0130867.
122. Purohit R, Blaivas Jerry G, Kalkan S. V12-03 autologous rectus fascial pubovaginal sling after vaginoplasty: an old trick for a new problem. J Urol. 2019;201:e1205–e1205.
123. Schaeffer E, Srinivas S, Antonarakis ES, Armstrong AJ, Bekelman JE, Cheng H, et al. NCCN guidelines insights: prostate cancer, version 1.2021: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw. 2021;19:134–43.
124. Sweeney CJ, Chen Y-H, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373:737–46.
125. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. New Engl J Med. 2022; https://doi.org/10.1056/NEJMoa2119115.
126. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol. 2019;30:1992–2003.
127. Markland C. Transexual surgery. Obstet Gynecol Annu. 1975;4:309–30.
128. Sada YH. A Dozen Eggs. J Clin Oncol. 2021;39:3645–6.
129. Molokwu CN, Appelbaum JS, Miksad RA. Detection of prostate cancer following gender reassignment. BJU Int. 2008;101:259; author reply 259–60.

AUTHOR CONTRIBUTIONS

The manuscript was conceptualised and designed by NK, RSP and DJL. Literature review was performed by FC, MM, SG and DJL. Tables and figures were prepared by FC, MM, SG and DJL. FC, MM, SG, NK and DJL wrote and prepared the initial draft. AKT, CT, MD, NK, RSJ and DJL reviewed, edited and revised the manuscript at all points. All authors read and approved the final version of the manuscript. Figure 1 was created with BioRender.com.

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AKT certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received or pending), are the following: AKT has served as a site PI on pharma/industry-sponsored clinical trials from Kite Pharma Inc., Lumicell, Inc., Dendron Pharmaceuticals, LLC, Oncovir Inc., Blue Earth Diagnostics Ltd., RhoVac ApS., Bayer HealthCare Pharmaceuticals Inc., and Janssen Research and Development, LLC; has received research funding (grants) to his institution from DOD, NIH, Axogen, Intuitive Surgical, AMBF and other philanthropy; has served as an unpaid consultant to Roivant Biosciences and advisor to Promaxo; and owns equity in Promaxo. The remaining authors declare no competing interests in relation to the work described.

ADDITIONAL INFORMATION

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