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Male-specific late effects in adult hematopoietic cell transplantation recipients:

a systematic review from the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research and Transplant Complications Working Party of the European Society of Blood and Marrow Transplantation

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Abstract

Background: Male-specific late effects after hematopoietic cell transplantation (HCT) include genital chronic graft-versus-host disease (GvHD), hypogonadism, sexual dysfunction, infertility, and subsequent malignancies, such as prostate, penile, and testicular cancer. They may be closely intertwined and cause prolonged morbidity and decreased quality of life after HCT.

Objective: Here, we provide a systematic review of male-specific late effects in a collaboration between transplant physicians, endocrinologists, urologists, dermatologists, and sexual health professionals through the Late Effects and Quality of Life Working Committee of the Center for International Blood and Marrow Transplant Research, and the Transplant Complications Working Party of the European Society of Blood and Marrow Transplantation.

Study Design: We utilized systematic review methodology to summarize incidence, risk factors, screening, prevention and treatment of these complications and provide consensus evidence-based recommendations for clinical practice and future research.

Results: Most of the evidence regarding male GvHD is still based on limited data, precluding strong therapeutic recommendations. We therefore recommend to systematically screen for male genital GvHD regularly and report it to large registries to allow for a better understanding. Future research should also address treatment since little published evidence is available to date. Male-specific endocrine consequences of HCT include hypogonadism which may also affect bone health. Since the evidence is scarce, current recommendations for hormone substitution and/or bone health treatment are based on similar principles as for the general population. Following HCT, sexual health decreases and this topic should be addressed at regular intervals. Future studies should focus on interventional strategies to address sexual dysfunction. Infertility remains prevalent in patients having undergone myeloablative conditioning, which warrants offering sperm preservation in all HCT candidates. Most studies on fertility rely on descriptive registry analysis

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and surveys, hence the importance of reporting post-HCT conception data to large registries. Although the quality of evidence is low, the development of cancer in male genital organs does not seem more prevalent than in the general population; however, subsequent malignancies in general seem to be more prevalent in males than females, and special attention should be given to skin and oral mucosa.

Conclusion: Male-specific late effects, probably more under-reported than female-specific complications, should be systematically considered during the regular follow-up visits of male survivors who have undergone HCT. Care of patients with male-specific late effects warrants close collaboration between transplant physicians and specialists from other involved disciplines. Future research should be directed towards better data collection on male-specific late effects and on studies about the interrelationship between these late effects, to allow the development of evidence based effective management practices.

Keywords

Survivorship; Late Effects; Male-Specific; Hematopoietic Cell Transplantation; Genital Chronic Graft-versus-Host Disease; Hypogonadism; Sexual Dysfunction; Infertility; Subsequent Malignancies

Introduction

Hematopoietic cell transplantation (HCT) is a treatment option for a variety of malignant and non-malignant disorders [1, 2]. Overall survival has improved substantially over the last decades; however, HCT remains associated with considerable early and late treatment-related morbidity and mortality [3–5]. It is essential for clinicians caring for transplant survivors to be aware of sex-specific complications for appropriate diagnosis, management, and counseling of patients.

Male-specific late effects include genital skin and mucosal manifestations with or without graft-versus-host disease (GvHD), hypogonadism, sexual dysfunction, infertility, and subsequent malignancies (such as prostate, penile, testicular and breast cancer). These late effects can be closely intertwined and may be under-recognized in HCT survivors. Similar to previous initiatives aimed at female survivors, [6–8] we propose a summary of guidelines for clinicians on the appropriate surveillance, management, and counseling for adult male HCT recipients, to increase awareness of these complications and to standardize practice for HCT clinicians or primary care providers. In the scope of this review, we do not address cardiovascular disease, as data suggests that while male gender is a risk factor for cardiovascular disease in general, it may not be a significant factor for developing cardiovascular disease after HCT.

Our aim is to provide an overview of male-specific late effects of adult survivors after HCT with evidence-based recommendations for clinical practice and future research. Since the approach of sex-specific late effects presents relevant differences when HCT has taken place during childhood [9], results regarding survivors who underwent transplantation during childhood or adolescence will be reported in a different manuscript.

Methods

The protocol for this review was registered at the International Prospective Register of Systematic Reviews (PROSPERO 2020 Registration ID: CRD4202014764099)[10]. Literature searches were conducted in MEDLINE (Ovid), Scopus, Web of Science Core Collection, PsycINFO (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost), and the Cochrane Library databases with the assistance of a medical librarian (ES). The results were limited to articles printed in English published between January 2000 - October 2020. A base search used keywords and subject headings to describe the topics of hematopoietic cell transplantation: stem cell, bone marrow, cord blood, peripheral blood, tandem transplant; and to describe late effects: long term, delayed, sequalae, late onset, survivor, survivorship. Additional search terms were developed by each of five subgroups, including GvHD, hypogonadism, sexual health, infertility and subsequent malignancies, and the terms were combined with the base search (see Supplemental Material 1). In the GvHD subgroup specifically, the GvHD keywords were only combined with hematopoietic cell transplantation keywords and not the late effects keyword, due to low initial search results. The reference lists and citing references of relevant reviews were searched to identify additional articles that may have been missed in the database searches. Web of Science was used to search citing references.

Search results were screened and data extracted as previously described [11, 12]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) frameworks were used for assessing quality of evidence and strength of recommendation for an intervention (See Supplemental Material Table 2) [13].

The detailed study flow for each subgroup is documented in PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowcharts (Figures 1a-1e)[14]. Detailed results from the different sub-groups are available in Supplemental Material Tables 3-7.

Genital chronic GvHD

In the past 10 years, several case reports[15–24] and a few cohort studies[25–28] have specifically reported on manifestations of genital male chronic GvHD (cGvHD), often associated with systemic cGvHD. The incidence of genital cGvHD in men varies between 5%[26] and 20%[25, 27], depending upon the evaluated cohort (i.e., asymptomatic patients vs patients who seek care for symptoms). The only cross-sectional cohort study to investigate the co-existence of genital lesions with cGvHD elsewhere, [3] reported a significantly higher incidence of oral, ocular, and/or cutaneous cGvHD when compared with patients without male genital lesions. The reported time of presentation in all publications exceeded two years (range 2-6 years) after transplantation (See Supplemental Material Table 3). The literature on GvHD and sexual function is relatively unclear, and will be discussed in the section on sexual dysfunction

Diagnosis

The National Institutes of Health (NIH) GvHD consensus development project was updated in 2014 to include male genital cGvHD. It now provides guidelines for diagnosis and

organ scoring to determine severity [29]. In male cGvHD of the genital tract, the glans penis, urethra or meatus may be affected. Symptoms may include painful intercourse or a burning sensation. Signs and diagnostic features based on NIH consensus criteria include include noninfectious inflammation with balanoposthitis, lichen sclerosis-like or lichen planus-like features, phimosis, urethral or meatal scarring or stenosis (Figure 1). Distinctive features of male genital cGvHD (which require additional evidence of cGvHD via pertinent specialist evaluation, biopsy, laboratory, imaging or other tests in the same or other organ for diagnosis) include erosions, fissures and ulcers. Contracture secondary to Peyronie's disease (characterized by penile deformity, pain and erectile dysfunction) due to a localized, fibrotic disorder is well described[16, 17], but it has not yet been integrated into the NIH diagnostic and scoring criteria of cGvHD. The NIH consensus criteria suggests organ scoring based on symptoms and genital exam, with lichen planus-like features categorized as mild, lichen sclerosis-like categorized as moderate, and phimosis or urethral/meatal scarring categorized as severe [29].

The reported cases have often been confirmed by histopathological findings, compatible with manifestations of cGvHD. Biopsies have revealed parakeratosis, focal hypergranulosis and dense lichenoid infiltrate, but also hyperkeratosis and epidermal atrophy, mild lymphocytic infiltrate and mild basal vacuolar change, dermal fibrosis and apoptotic bodies in the epithelium [15, 16, 19, 20]. Histopathology is not required for confirmation of cGvHD if lichenoid changes are present, but can be performed to exclude (pre-) malignant changes and/or concomitant infections.

Screening and Treatment

Genital cGvHD manifestations can translate into genitourinary and sexual dysfunction, which can have an impact on quality of life. Moreover, genital cGvHD in males seems to be under-reported since it is seldom described in GvHD trials but affected 13% of males in a study specifically aimed at genital involvement, where it was often associated with manifestations of extragenital mucocutaneous cGvHD[27]. Patients often do not report genital symptoms (especially if not sexually active) and health-care providers do not specifically investigate this aspect[30]. Moreover, most studies to date have primarily focused on the genital issues in female recipients. Screening for genital cGvHD in male survivors should be a standard part of the routine follow-up history and physical examination on an annual basis [31]. For patients with known or suspected genital cGvHD, multidisciplinary evaluation by the HCT provider, urologist and dermatologist is important to pursue the correct diagnosis (in particular to exclude subsequent malignancies) as well as suggest specific and supportive therapy. A systematic evaluation is essential and can provide a multimodal approach to treatment. Although there is no definitive consensus regarding treatment, topical and systemic immunosuppression as well as surgical intervention (circumcision for complete phimosis) have been reported (Table 2).[27] More research is needed in the area of treatment for male genital cGvHD.

Hypogonadism

Hypogonadism affects approximately 15% of young male cancer survivors (age 25-45 years) [32], but there is a wide range of prevalence (6.9-84%) reported in studies of adults following both allogeneic and autologous HCT (See Supplemental Material Table 4). The prevalence has been difficult to quantify in part due to variations in definitions and lack of diagnostic criteria. Age at transplant, type of conditioning, underlying conditions and previous treatment for underlying conditions are important factors. Leydig cells, where testosterone is produced, are less vulnerable to chemotherapy and radiation compared to germinal epithelium, where spermatozoa are produced[33]. As such, patients may experience azoospermia and infertility, but normal testosterone levels. Patterns of Leydig cell dysfunction post-HCT include patients with elevated luteinizing hormone (LH) and normal testosterone levels (compensated hypogonadism) or elevated LH and low testosterone levels (hypogonadism)[34]. Recovery of hypogonadism does occur, and can sometimes be as early as within the first year after transplant[34–43] . Low testosterone levels are seen in patients with acute and cGvHD after HCT, likely due to the inhibitory effects on the hypothalamic-pituitary-gonadal axis from immunosuppressive treatments such as steroids and cyclosporine.[41] Iron overload, which is a common complication after HCT, is also known to lower testosterone levels in men[44]. In adult patients, specific symptoms of hypogonadism include loss of body hair, small testes and erectile dysfunction. Non-specific symptoms include loss of libido, anemia, fatigue, lack of motivation, reduced muscle mass and increased fat mass.[44] Bone density loss is a complication of HCT survivors and can be related to hypogonadism[45], immunosuppression, prolonged steroid use and/or cGvHD [46].

Diagnosis

For patients who have undergone high dose chemotherapy and/or radiation and HCT, there are insufficient data to recommend screening for gonadal dysfunction in asymptomatic patients. Guidelines for HCT survivors recommend testing and consideration of hormone replacement therapy based on symptoms, and to assess gonadal function through testing levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone if symptoms warrant (lack of/reduced libido or erectile dysfunction), with consideration for referral to an endocrinologist/urologist to discuss the potential risks and benefits of testosterone therapy.[31]

Total testosterone concentrations should be measured in the mornings when the patient is fasting. If abnormal, this should be repeated. Low testosterone levels (<250-300 mg/dL) should be confirmed, because 30% of men with initial low testosterone levels will have normal levels on repeat measurement, and because HCT survivors may recover normal testosterone levels within a year after HCT [44, 47, 48]. Free testosterone levels should be determined for patients with borderline low levels, or those on glucocorticoids, as these can impact sex hormone binding globulin (SHBG) levels. Free testosterone levels should only be measured by an equilibrium dialysis method if available, otherwise calculated from total testosterone, SHBG, and albumin, using a formula that accurately reflects free testosterone by equilibrium dialysis. Reference ranges of the laboratory or formula being used should serve to determine abnormal levels, as there is no standard reference range[44].

Treatment

The efficacy of testosterone replacement therapy in men with symptomatic hypogonadism in the general population has been associated with improvement in libido, erectile function, sexual activity, sexual satisfaction, areal and volumetric bone mineral density, bone strength, fat-free mass, muscle strength, as well as improvements in the positive and reductions in the negative aspects of mood[49].

Guidelines for testosterone therapy and management of men with hypogonadism from the Endocrine Society Practice Guidelines and American Urologic Association have been published[44, 50], though data for testosterone therapy in patients with hypogonadism and low testosterone after HCT specifically are limited[31]. One large randomized, placebo-controlled study of testosterone replacement in young male cancer survivors between 25 and 50 years (including a minority of HCT recipients) with low or borderline low testosterone showed that testosterone replacement therapy improved body composition with a reduction in fat mass and increase in lean body mass[51]. Another randomized controlled trial in men who received cytotoxic chemotherapy, including 14 patients who underwent HCT, who had compensated hypogonadism (elevated LH and low/normal testosterone level) but no overt hypogonadism, showed that testosterone replacement improved fatigue and lowered low density lipoprotein (LDL), but had no effect on bone mineral density, quality of life, body composition, or other lipid levels (Table 2).[52] In addition, Combination testosterone and sildenafil treatment in this patient population has been shown to improve erectile dysfunction[53]

Risks of testosterone replacement therapy need to be considered and balanced with the potential benefits. Testosterone replacement may induce polycythemia, in which case the dose may need to be reduced with close follow up of the patient[49]. It may decrease spermatogenesis as it silences the hypothalamus-pituitary-gonadal axis, but this will usually recover if testosterone is stopped[49]. According to the Endocrine Society Clinical Practice Guideline, testosterone should not be given to patients with prostate cancer, with palpable nodule or induration, a prostate-specific antigen level >4 ng/mL or >3 ng/mL combined with a high risk of prostate cancer (e.g., African American or men with a first-degree relative with prostate cancer), or elevated hematocrit [44]. In the previously mentioned randomized controlled trials of testosterone therapy in cancer survivors and those who underwent cytotoxic chemotherapy, skin reaction was the most common side effect, while heartburn/ indigestion, chest pain, arterial hypertension, fatigue, insomnia, and anxiety were rare; there were no reported urinary symptoms or prostatic effects[51, 52]. Detailed information about toxicities and monitoring practices for men on testosterone replacement are available in published guidelines and reviews [44].

Hypogonadism should be treated in patients with premature gonadal failure; however, this alone will not prevent bone loss[54]. Therefore, standard screening and preventive practices that may include calcium, vitamin D, and bisphosphonates are warranted for patients at risk for bone loss after HCT, even in patients on testosterone replacement therapy.[31] This includes discussion about preventive practices and a dual energy X-ray absorptiometry (DEXA) scan performed 1 year after HCT on all patients who underwent allogeneic HCT and earlier for those who did not have a baseline evaluation prior to transplant or those

who received high dose steroids early post-HCT [31, 55]. Guidelines from the American Society for Transplantation and Cellular Therapy on bone health management after HCT have been recently published and include pre-HCT evaluation recommendations as well as post-HCT guidance on bone health screening practices, vitamin supplementation, and the use of bisphosphonates and other pharmacological therapies[55]. Future research will need to include the impact of testosterone replacement therapy on male HCT survivors with hypogonadism, and in those with decreased bone density.

Sexual Dysfunction

Sexual difficulties occur when an individual is unable to fully engage in all phases of the human response cycle (i.e., desire, arousal, plateau, orgasm, and resolution).[56] Sexual dysfunction may be diagnosed when these difficulties are accompanied by sexual distress, i.e. the psychological and emotional strain resulting from disturbances in sexual functioning.[57] Sexual dysfunction following HCT is common[58] (ranging from 28% to 80% depending upon domain of sexual dysfunction), as patients who undergo either autologous or allogeneic HCT tend to experience greater problems in sexual functioning than non-transplant, matched controls[59] and their counterparts with similar diseases who did not undergo HCT.[60, 61] Evidence suggests that sexual distress and dysfunction in men who underwent autologous versus allogeneic HCTs are comparable.[28, 62–64] Additionally, in comparison to sexual function pre-HCT, satisfaction with sexual activity, ability to achieve orgasm, and frequency of intercourse decrease after HCT.[65] A majority of male HCT survivors report sexual dysfunction (52%) [66], often manifesting as erectile dysfunction (ED) (12%-78%) [26, 38, 66–68], loss of sexual interest/decreased libido (23.5-62%) [26, 38, 67, 68], and decreased enjoyment of sex (33%) [26] (See Supplemental Material Table 5).

Sexual difficulties in patients with cGvHD have been described but the literature remains unclear. Some studies have suggested an association between sexual dysfunction and the presence of GvHD[26, 28, 69, 70], but this has not been confirmed by others[27, 71]. One study specifically reported on gender differences and noted that less severe cGvHD was associated with higher sexual satisfaction in males[70]. Another study found that cGvHD was associated with sexual dysfunction in females, but not in males.[72]

It has been demonstrated that the effects of HCT on sexuality can be long lasting. In one study, male survivors at one year post-HCT reported increased concerns related to perceived attractiveness (56%), erectile dysfunction (50%), issues experiencing ejaculation (33%), and orgasm (22%) compared to baseline (time of HCT), although libido improved at one year following HCT [73]. At three years post-HCT, attractiveness concerns increased further (61%), whereas other sexual concerns remained similar or decreased since one-year follow-up (22% reported concerns related to ability to achieve erection, ejaculation, or orgasm). These findings of prevalent sexual health concerns were also noted in another study assessing HCT survivors who were 1-3 years post-transplant[74]. Notably, males stillreport lower sexual function compared to healthy controls[67, 68], even five years post-HCT.[75]

Other factors are known to impact sexual functioning, such as body changes, mastering one’s own life, and experiencing changes to identity [76]. In comparison to female

counterparts, male HCT survivors with malignant hematological disorders have been shown to be most concerned about whether their partner(s) were still attracted to them, rather than being affected by an altered body image.[76] Relationship quality can also impact sexual functioning. . Male survivors have been found to be more sexually active than female HCT survivors[70, 77],but they seem to be more likely to experience decreased sexual desire and report more relationship strain related to sexual dysfunction after HCT[78]. Spousal caregivers of HCT survivors report a negative impact of HCT on their sexual life[79],[80] and also report worse marital satisfaction at six- and 12-month follow-up compared to the patients themselves (of note, this finding was limited to female caregivers of male patients).[81] Additional factors such as older age, physical problems, level of education, and physical inactivity have also been associated with lower sexual satisfaction, function[67], and activity[68] in HCT survivors.

Screening and Treatment

Despite the prevalence of sexual dysfunction following HCT, the majority of health care professionals does not address these issues (68% among both physicians and nurses) and typically wait until the patient introduces any relevant concerns.[30] In a qualitative single-center study in Canada, most HCT survivors indicated they had never been asked about sexual health, and those who had voiced their concerns felt that this had been insufficiently acknowledged or addressed.[82] Most survivors are willing to receive information about sexual health following HCT (79.4%), survivors with high levels of sexual health knowledge, were being 1.91 times more sexually active than those survivors with low knowledge.[83] While patients may prioritize survival over sexuality during treatment, these concerns become more important as time passes and survival becomes more of a reality.[84] We recommend that male HCT survivors be screened for sexual dysfunction at routine follow-up visits by the HCT or primary care provider (Table 2) [85].

Sildenafil is effective in treating ED in HCT survivors, regardless of the contributing factors (i.e., organic and psychogenic); however, it is less effective in those with reduced libido[53].. El-Jawahri et al delivered a multimodal intervention aimed at improving sexual functioning in allogeneic HCT survivors, both male and female survivors [86]. The intervention consisted of monthly visits (ranging from two to six) with clinicians who 1) assessed contributors to patients' sexual concerns, 2) educated, normalized, and empowered patients to address their sexual health needs, and 3) implemented therapeutic sexual health interventions (such as treating hormonal deficiencies or erectile dysfunction, psychoeducation, referral to a specialty sexual health clinic). All domains of sexual functioning (e.g. satisfaction, interest in sex, orgasm, and erectile function) improved significantly upon completion of the intervention, with no differences by sex. In addition to improvements in sexual function, participants experienced significant improvements in quality of life and mood (depression and anxiety) following the intervention. These findings emphasize the importance of recognizing sexual dysfunction after HCT. More research is needed in the area of effective pharmacologic and non-pharmacologic interventions for male HCT survivors with sexual dysfunction. In the meantime, following society ED guidelines which emphasize shared decision making and offering escalating therapies to achieve an erection (i.e. urethral

suppositories, penile injections, vacuum erection device, penile implants) should be offered [87].

Infertility

Fertility management in adult men is less problematic than in women [88], but impaired fertility in male survivors of HCT remains a frequent late effect of chemo-radiotherapy given before transplant as treatment or conditioning (between 20%-90% depending on the conditioning regimen) [42, 89–91]. Loss of fertility can be psychologically traumatic and options to preserve reproductive potential should be considered and planned before HCT[92–94]. Fertility preservation should occur as early as possible, ideally before initiating any therapy. Semen analysis is a pivotal examination evaluating fertility in male recipients after HCT. Since 2000, there are at least 11 publications in which semen samples were evaluated during follow-up after HCT[42, 89–91, 95–101]; seven of them report results of more than 30 samples, including one study with samples from 224 males[90], and 15 using self-reported data (See Supplemental Material Table 6).

Prevalence and risk factors

The probability of infertility following HCT depends on the cumulative dose of radiotherapy and chemotherapy, the type of chemotherapy and the age of the patient. Favorable factors for spermatogenesis recovery are age under 25-30 years at HCT, conditioning regimen without total body irradiation (TBI), long follow-up (>5years) after HCT, absence of ongoing cGvHD, and absence of underlying malignant disease[90, 91, 99].

Regarding conditioning regimens, recovery of spermatogenesis has been described after a median of 4 years in 90% of patients conditioned with cyclophosphamide alone, in 50% of patients with cyclophosphamide plus busulfan or thiotepa, and 17% of patients with cyclophosphamide plus TBI or thoracoabdominal irradiation[89]. A prospective study evaluating 35 semen samples one year after busulfan and cyclophosphamide conditioning regimen showed that all males had impaired spermatogenesis (91% azoospermia; 9% oligozoospermia)[42]. Non-obstructive azoospermia (i.e. spermatogenic dysfunction) is also particularly high after TBI-based conditioning regimen, with prevalence of up to 85%[90, 91, 95, 99, 100]. Of note, about 4-16% of males already had impairment of spermatogenesis before HCT[25, 90], mostly due to treatment of underlying malignancy. Patients with aplastic anemia, who typically do not require chemotherapy before HCT and receive a reduced intensity regimen as conditioning, frequently show a high rate (≥50%) of fertility recovery[100, 102] . Time after HCT is also an important factor, as one study showed that patients with detectable spermatozoa had longer interval since HCT (>9 years), suggesting a trend to spermatogenesis production with longer follow-up, particularly in patients younger than 25 years at transplantation[91].

The harmful effect of ongoing cGvHD on spermatogenesis has been discussed in three studies[90, 91, 96] , with only one demonstrating a significant negative influence on fertility[90]. A retrospective study by the European Society for Blood and Marrow Transplantation (EBMT) focusing on male fertility after transplantation found that independent from TBI, age over 25 years at the time of HCT and ongoing cGvHD were associated with

infertility after allogeneic HCT[90]. However, the mechanism by which GvHD may lead to azoospermia remains unclear. In an animal model[103], injury to Leydig cells correlated with an intra-testicular inflammatory response, suggesting a potential indirect effect of GvHD on spermatogenesis. In patients not conditioned with TBI, ongoing cGvHD is an adverse factor for sperm recovery.

Pregnancy and fatherhood

An important outcome to demonstrate fertility is conceiving a child. Multiple retrospective studies have reported the rates of conception for men after HCT[26, 89–91, 95, 96, 98–100, 102, 104–113]. With one exception[102] all studies consistently showed a low rate of paternity after HCT (See Supplemental Material Table 6). The true prevalence of fertility after HCT is difficult to determine because patients' wishes regarding fatherhood are often unreported in studies. The desire for paternity was evaluated in one study: a majority (78%) reported the wish of having a child, but only 15% of the HCT-recipients transplanted for a malignant or non-malignant disease, fathered eventually a child[114] . In another study 21 males had tried to conceive, with 11 pregnancies reported, six of them assisted by in vitro fertilization[26].. In a small series, of 13 male patients with severe aplastic anemia who attempted to be a father, 12 (92%) succeeded.[102] The reported pregnancies and deliveries from male recipients were usually uncomplicated: no excess of miscarriage, stillbirth, or congenital malformations were reported[91, 102, 106, 107, 112] .

Fertility preservation

Despite the fact that sperm banking is readily available, studies show that male patients often do not recall having been counseled about this before cancer therapy. Regarding fertility preservation utilization, one study showed that only 4.7% of men age 18-40 in a national insurance database had claims for fertility preservation counseling and/or procedures prior to transplant.[121] Sperm banking should be discussed with all male patients undergoing HCT, ideally before cancer treatment is initiated[92, 115] . At HCT, spermatogenesis might be already impaired due to treatment of the underlying disease (Table 2). Patients who already received chemotherapy before HCT will often fulfill the minimum criteria for semen cryopreservation, since reported pre-HCT azoospermia rates range from 16%[89] to 46%[116]. Patients who have no sperm in the ejaculate and children may be offered testicular biopsy to obtain sperm for cryopreservation (e.g., microscopic assisted testicular sperm extraction; mTESE) [117–119]. Stored spermatogonial stem cells obtained from testicular biopsy might be transplanted back to restore fertility. Remove contaminated malignant cells in stored material is a crucial step before auto-transplantation. Different techniques such as fluorescence-activated cell sorting (FACS), magnetic-activated cell sorting (MACS), selective matrix adhesion technique, and nanoparticle-targeted drug delivery to malignant cells have been evaluated in preclinical studies, but none have yet been completely successful[120]. Possible barriers to fertility preservation before HCT may include the perception of lack of time because of the urgency to start the transplant procedure, deficient awareness on this topic by the transplant team, underestimation of the future desire for paternity, the existence of an underlying malignancy, and issues related to the insurance coverage[116, 121]. The long-term care team should signal readiness to discuss issues on fertility, and if needed, to undertake further investigations and consider referral for a

specialized consult [31]. If appropriate, contraception counseling should be done in patients who are known to be fertile or when their fertility status is not known [31].

Subsequent Malignancies

Long-term survivors of HCT are at risk of subsequent malignancies, and subsequent solid cancers are a major cause of late treatment-related mortality.[122] While risk factors for the development of subsequent solid cancers, in general, are known, little is known about male-specific considerations. Sex-related differences for subsequent solid cancers include conditions that only affect male recipients because these cancers develop in the male reproductive system (prostate, testicular, penile cancers), and cancers which are more common in men than in women (See Supplemental Material Table 7).

Cancers with a higher likelihood in men

The cumulative incidence of subsequent solid malignancies for males and females ranges from approximately 1-6% at 10 years[123–125]. Male sex was identified as a risk factor for the development of subsequent solid cancers in several studies: overall after both autologous and allogeneic HCT[124, 126], and specifically in squamous cell carcinoma (SCC) after allogeneic HCT[125, 127], melanoma after autologous HCT[123], and any skin cancer after allogeneic HCT[128]. In one study, the increased risk of subsequent solid cancers was seen in male recipients of female donors, independent of GvHD [124]. Male sex has also been associated with an increased risk of death after subsequent solid cancer among survivors of autologous HCT.[129]

Male recipients undergoing autologous or allogeneic HCT have a 25-fold increase in the risk of oral cavity cancer compared to the general population in a single-center, case-control study.[130] In studies of allogeneic HCT survivors, male sex was associated with increased risks of SCC of the oral cavity and skin,[125, 127] and skin cancer including SCC and basal cell carcinoma,[128] while another study did not find significant associations[131]. It is unclear whether the higher incidence of skin and oral cancer in males is due to genetic causes or behavioral differences.

Male-specific cancers

Only one study of adult allogeneic and autologous HCT recipients reported the cumulative incidence of prostate cancer, which was 14% at 5 years.[132] Although prostate cancer may develop as a subsequent solid malignancy after HCT, its risk of development was not significantly increased compared to the general population [123, 125, 126, 133–138]. Of note, when compared to the general population, the risk of prostate cancer did not vary by the age at diagnosis, time since diagnosis, by diagnosis evaluated, or by conditioning intensity.[133, 135–137] In 3 retrospective studies that included 13,925 patients who underwent allogeneic HCT, a total of 365 subsequent solid cancers were observed at a median of 6 years post HCT, out of which only 6 were prostate cancers.[133, 135, 138] An increased risk of mortality in association with prostate cancer was documented when compared to the general population in one study[132] but this was not confirmed by others[129]. The overall survival

following the development of prostate cancer ranges from 69-91%, with no significant differences among allogeneic and autologous survivors.[129, 132]

Data on genitourinary cancers following HCT is scarce. When compared to the general population, the risk of genitourinary cancers among males is about two-fold higher among study populations focusing on adult and pediatric allogeneic HCT survivors.[127] Although testicular cancer may develop as a subsequent solid malignancy after HCT, its risk of development is not significantly increased compared to the general population when considering allogeneic HCT survivors.[125, 135, 136, 139] Moreover, the risk of testicular cancer when compared to the general population did not vary by age at diagnosis, time since diagnosis, by diagnoses evaluated, or by conditioning intensity.[125, 135, 136] A few cases of penile cancers have been reported after HCT.[125, 140] Single cases of squamous cell carcinoma have been reported in patients with genital lichen sclerosis, likely related to cGvHD.[23] Penile carcinoma might be underestimated, since carcinogenesis in male genital lichen sclerosis in the general population can be as high as 10%.[141]

Screening and management

Male survivors of HCT have a higher risk of developing subsequent solid cancers when compared to the general population. Special attention should be paid to the development of SCC of the skin and oral cavity. Screening protocols should focus on these high-risk sites in male survivors of HCT. Male genitourinary cancers such as prostate, testicular, and penile cancers are documented, although the risk does not seem significantly elevated when compared to the general population. However, these cancers might be underreported. Therefore, general population age-specific guidelines should be followed for screening and management for male-specific subsequent malignancies. There is no consensus about using prostate-specific antigen or digital rectal examination[31].

Summary and Recommendations for Research and Clinical Practice

This review summarizes the existing literature regarding the prevalence and long-term management of male-specific dysfunctions in adult patients who undergo HCT (Table 2). We note specific changes linked to GvHD, which tend to develop in long term-survivors and can be managed by local therapy and, if needed, by surgical urological interventions. Most of the evidence regarding male GvHD is still based on case-reports and limited case-series, precluding strong therapeutic recommendations. We therefore recommend to systematically screen for male genital GvHD and report it to large registries to allow for a better understanding of this HCT complication. Future research should also address treatment issues since almost no published evidence is available to date to support recommendations. Male-specific endocrine consequences of HCT concern hypogonadism which may also affect bone health; it can be addressed by hormonal substitution and/or appropriate osteopenia/osteoporosis treatment, if necessary. Again, the evidence is scarce and current recommendations are based on the same principles as for the general population. Sexual health decreases after HCT so this should be addressed as early as possible in the HCT trajectory and be screened for at regular intervals thereafter. Since only few studies have robustly investigated the best interventions to offer, future efforts should aim at comparing

interventional strategies to address sexual dysfunction. Fertility management in adult males is less problematic than in females, but remains extremely prevalent when patients having undergone a myeloablative conditioning, warranting offering sperm conservation in all HCT candidates. Most studies on fertility rely on descriptive registry analysis and surveys, so we stress here the importance of reporting post-HCT conception information to large registries such as EBMT and CIBMTR. Future options include involving patients to report this directly. Further research should address fertility prospectively to identify the predictors and factors associated with fertility issues after HCT. Finally, overall subsequent malignancies seem to be more prevalent in males than females, and special attention should be given to skin and oral mucosa, including genital skin changes. The development of cancer in male genital organs does not seem more prevalent than in the general population, but the quality of evidence is low and future studies should focus on a better understanding of how to prevent and treat these cancers in HCT recipients.

We are aware that there may be obstacles in addressing male-specific issues during the clinical visit. However, the high level of consent among long-term survivors to be examined specifically for genital changes has been demonstrated in a prospective study[27]. By systematically addressing questions on genital abnormalities, sexual dysfunction or fertility issues, the long-term care team signals readiness to discuss these issues, and if needed, to undertake further investigations and consider referral for a specialized consult. Many issues encountered by male survivors are closely intertwined. GvHD can potentially negatively impact fertility, sexual health and increase the risk of subsequent malignancies. Similarly, the advantages of substitution treatment for hypogonadism must be balanced against the potentially increased risk of prostate cancer. Therefore, a multidisciplinary approach is essential, with early referrals to urologist, sexual health specialists, dermatologist and endocrinologist when appropriate. Such collaborative clinical practices can be standardized, implemented and audited through standard operating procedures within the quality system of accredited HCT programs [142].

On behalf of the CIBMTR Late effects and Quality of Life Committee and EBMT Transplantation Complication Working Party, we provide consensus recommendations for screening and preventive measures for adult male-specific late effects after HCT. Significant knowledge gaps remain in all areas. Future research should be directed towards better data collection on male-specific late effects, on studies about the interrelationship between these late effects, and effective management practices. Care of patients with male-specific late effects warrants close collaboration between transplant physicians, dermatologists, urologists, endocrinologists, and specialists in sexual health, to improve the care of male survivors of HCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

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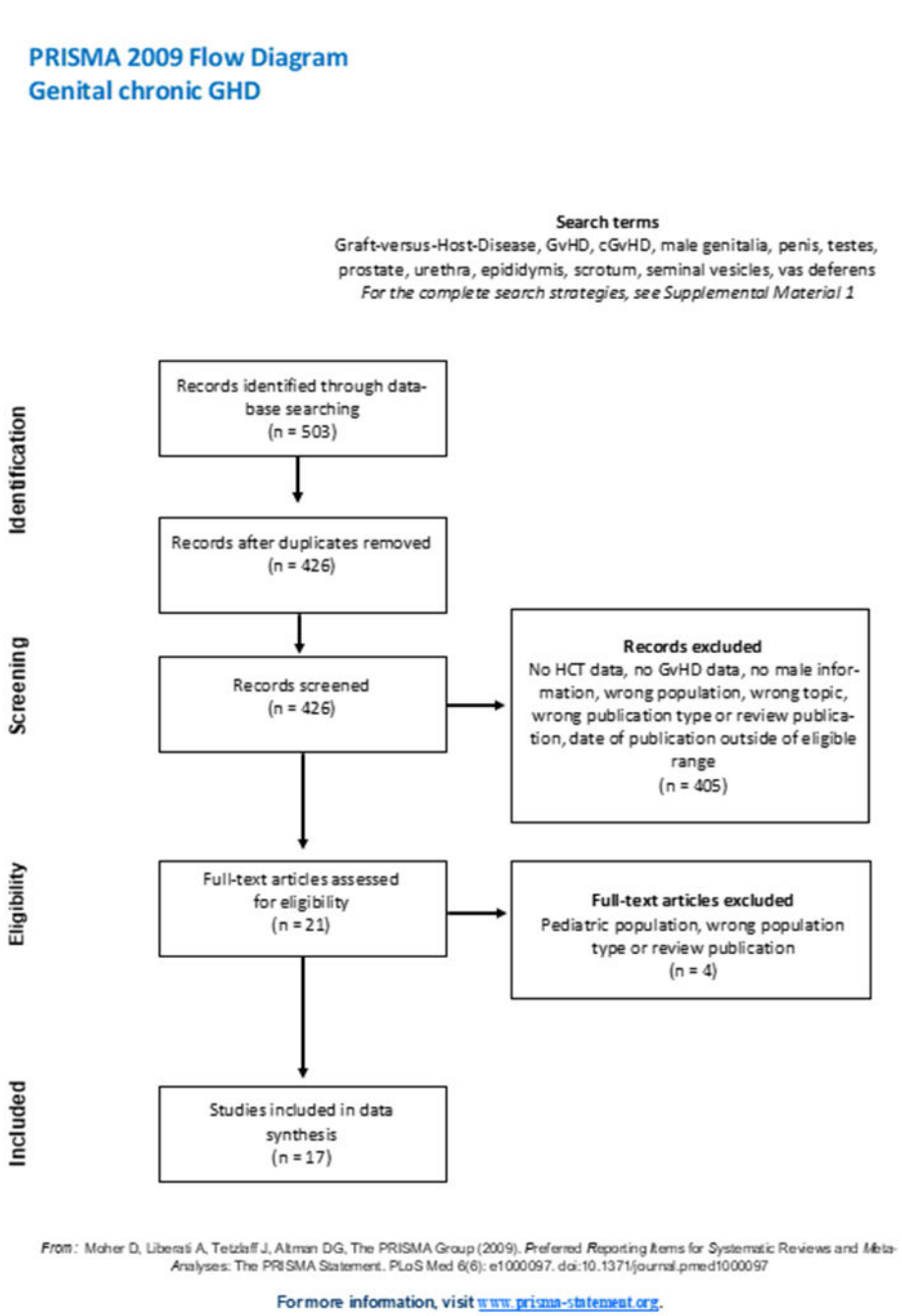
Highlights:

- Male-specific late effects after hematopoietic cell transplantation (HCT) may be closely intertwined and cause prolonged morbidity and decreased quality of life.
- We utilized systematic review methodology to summarize incidence, risk factors, screening, prevention and treatment of these complications and provide consensus evidence-based recommendations for clinical practice.
- Care of patients with male-specific late effects warrants close collaboration between transplant physicians and specialists from other involved disciplines.
- Future research should be directed towards better data collection and studies of the interrelationship between these late effects.

a



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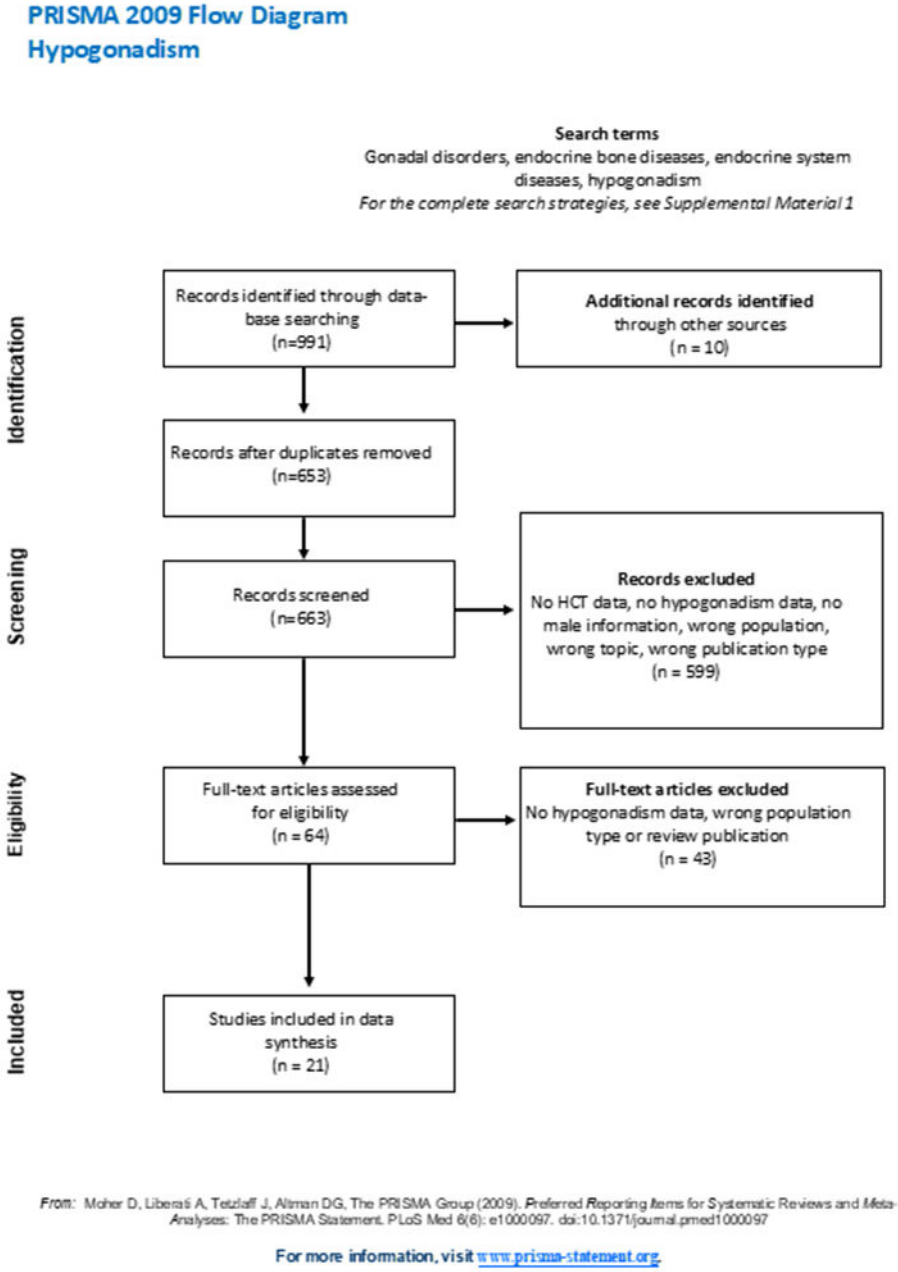

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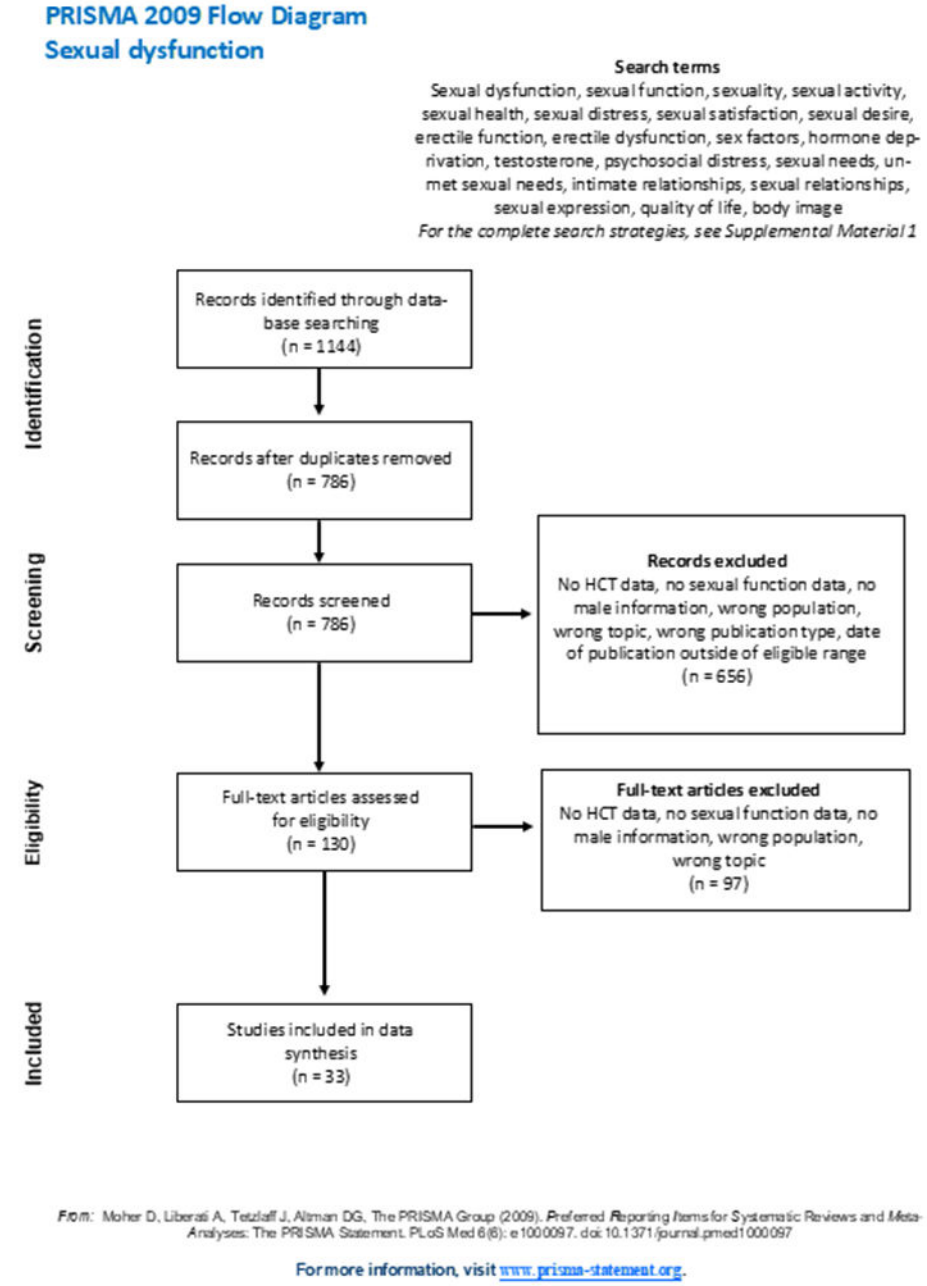

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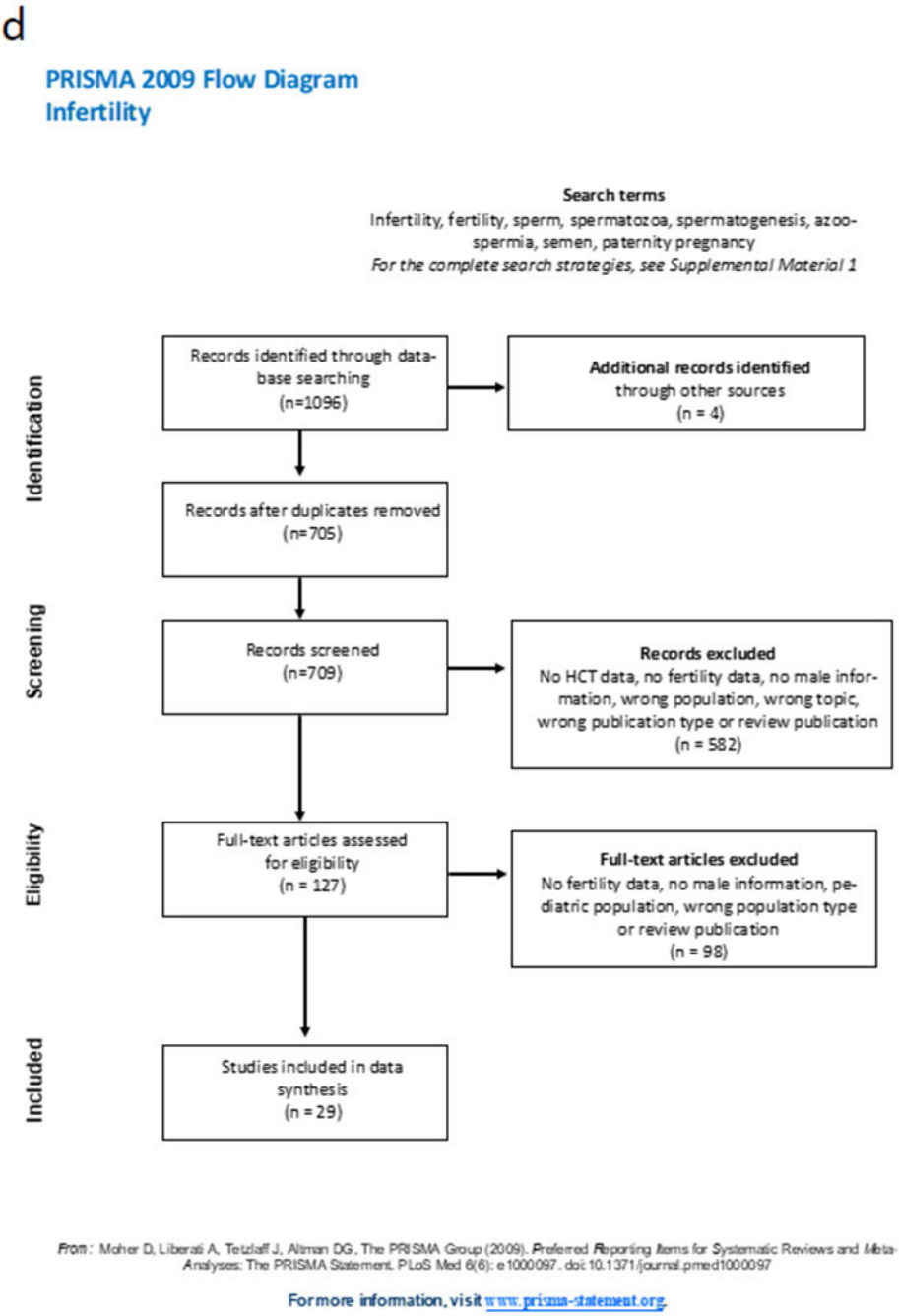

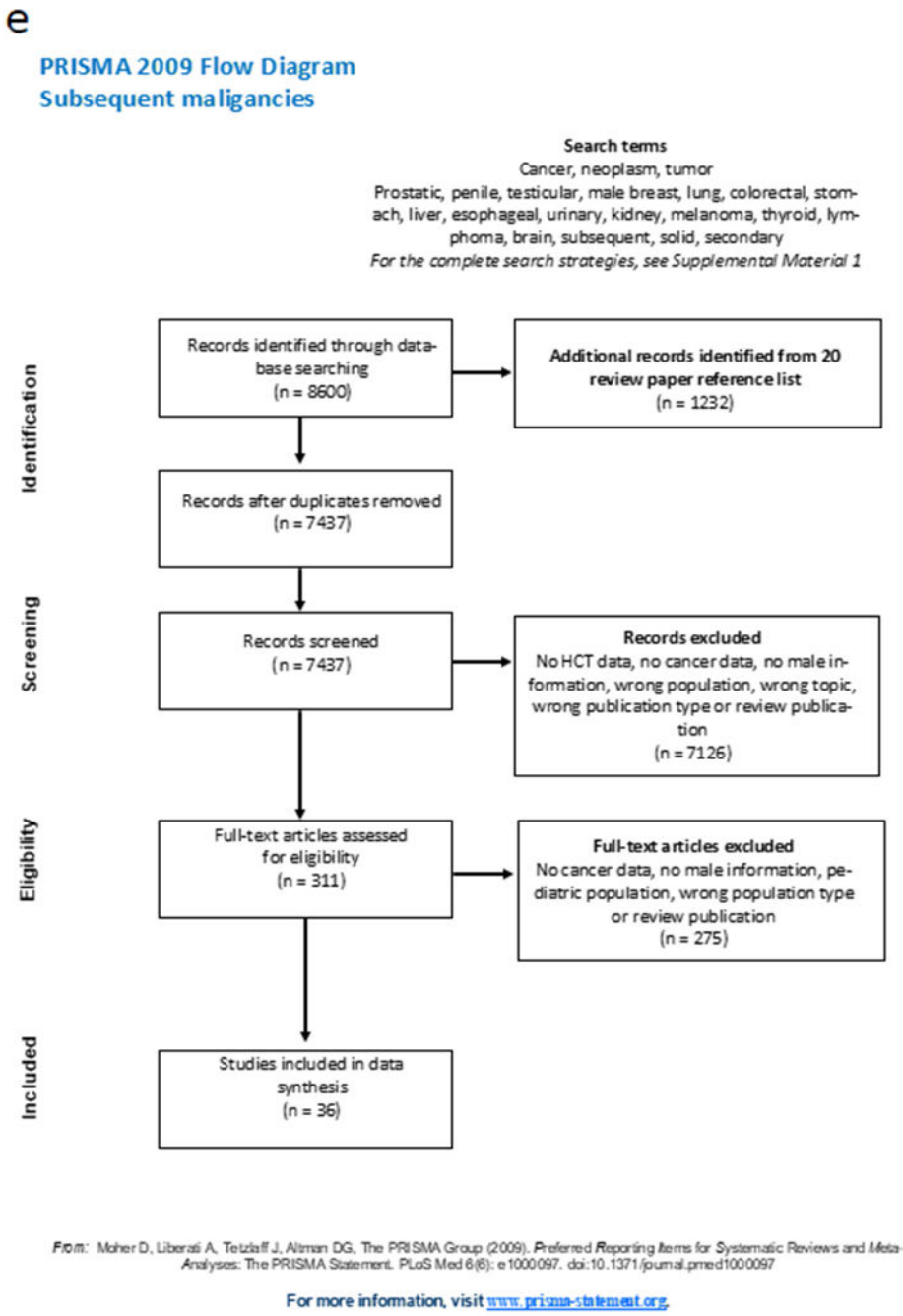

Figure 1.

PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowcharts for the 5 different subgroup analysis: figure 1a, genital chronic GvHD; 1b, hypogonadism; 1c sexual dysfunction; 1d infertility; 1e, subsequent malignancies.

Abbreviations: GvHD, graft-versus-host disease; cGvHD, chronic GvHD; HCT, hematopoietic cell transplantation;

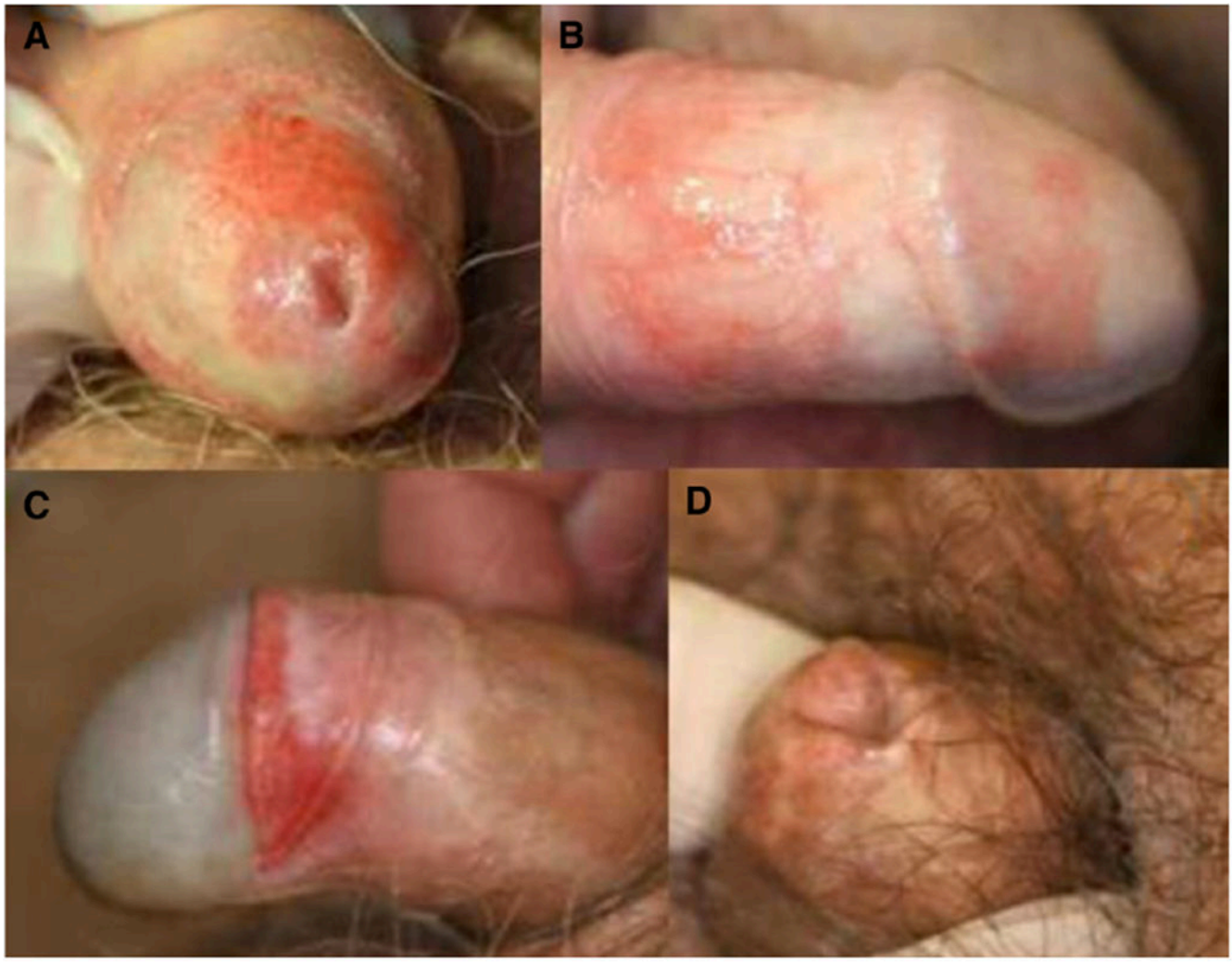

Figure 2. (from Müller at al. 2013[27])

Examples of post-transplantation inflammatory genital skin changes. (A) Inflammatory (noninfectious) balanoposthitis with reddish “cayenne-pepper spots” on the glans penis and partial phimosis. (B) Shiny plaques on the glans penis and the inner layer of the foreskin. (C) Lichen sclerosis-like skin changes with erythematous and whitish sclerotic areas on the foreskin. (D) Phimosis

Table 1:

Recommendations for screening and therapy for male-specific late effects in HCT adult patients

Potential late effects	Screening Recommendations	Therapeutic Implications	Quality of Evidence	Strength of Recommendation	Comments
Genital chronic GvHD	- Screening for symptoms (change in appearance of genitalia, a new burning sensation or painful intercourse) at each visit [27] - Genital exam, yearly [31] - Biopsy not required but can be done to exclude (pre-)malignant changes and infections	Topical therapy (e.g. high-potency topical corticosteroids [0.05%] or calcineurin inhibitors [0.1%]) and, if necessary, systemic immunosuppression	Low	Strong	- Consider multidisciplinary evaluation by the HCT provider, urologist and dermatologist for suspected genital GvHD - The occurrence of subsequent genital skin cancer remains a concern and patients should be educated on self-examination and symptoms
		Circumcision for complete phimosis	Low	Strong	
		Surgical interventions for meatal stenosis	Low	Strong	
Hypogonadism	- Screening for symptoms at each visit (lack of libido or erectile dysfunction, lack of motivation, reduced muscle mass and increased fat mass) [44] - Hormonal testing (testosterone, FSH, LH), ideally done in fasting patients, first thing in the morning in patients with symptoms [31] - Low testosterone should be confirmed by a repeat test [44, 47] - Annual screening for bone loss in allogeneic HCT recipients and patients at risk of bone loss [31, 55] - DEXA scan and fracture risk evaluation at 3 months for patients without pre-transplant evaluation or if patient received high dose steroids early post-transplant	Testosterone therapy in hypogonadal men to correct symptoms of testosterone deficiency [44]	Low	Weak	- Consider referral to an endocrinologist or urologist to discuss the potential risks and benefits of testosterone therapy - Consider toxicities of testosterone therapy: screening for polycythemia and prostate cancer before initiating treatment, and close monitoring during treatment
Sexual dysfunction	- Screen for sexual health regularly through the survivorship process (loss of sexual interest, concerns related to perceived attractiveness, problems obtaining erection, ejaculation or orgasm) [85]	Treatment of hormonal deficiencies, psychoeducation, referral to specialist in sexual health	Moderate	Strong	- Adapt interventions based on patient priorities - Consider referral to a psychologist for individual or couples-based interventions to address psychological contributors to sexual dysfunction
		Sildenafil treatment, vacuum erectile device, medicated urethral system for erection, or intra-cavernous injection for erectile dysfunction	Low	Weak	
Infertility	- Pre-transplant counseling about risk of infertility and fertility preservation (sperm banking offered to all adult male patients undergoing HCT) depending on the type of pretransplant therapy and the conditioning [92] - Post-transplant counseling and consideration of semen analysis	Pre-transplant fertility preservation (sperm banking)	Moderate	Strong	- Consider discussion about alternative options for fatherhood - Consider referral to appropriate specialists for patients having difficulties conceiving [31] Contraception counseling if fertile or fertility status not known
		Referral to reproductive health specialist for patients with infertility	Moderate	Strong	

Potential late effects	Screening Recommendations	Therapeutic Implications	Quality of Evidence	Strength of Recommendation	Comments
Subsequent malignancies - Cancers only affecting men - Cancers more prevalent in men than in women	- Cancers which affect only men (Prostate, testis and penile cancers) follow guidelines for the general population - Patients with ongoing chronic GvHD or a history of chronic GvHD should have regular full skin examination, including genitalia - Counsel patients about risk of subsequent cancers, including ones in which men are at higher risk and ones that only affect men	Follow the guidelines for the general population	Low	Strong	- Special attention to screening for symptoms of squamous cell cancers of the skin, oral cavity and genitalia

GvHD: graft-versus-host disease; HCT, hematopoietic cell transplantation; FSH, follicle stimulating hormone; LH, luteinizing hormone; DEXA, dual energy X-ray absorptiometry