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Review article

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Management of surgical menopause in female patients with bladder cancer undergoing radical cystectomy

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Abstract

Radical cystectomy is the gold-standard treatment for patients with muscle-invasive and very high-risk non-muscle-invasive bladder cancer. In female patients, radical cystectomy has traditionally included removal of the uterus, ovaries, fallopian tubes and anterior vaginal wall. The majority of female patients undergoing radical cystectomy are postmenopausal, but a subset of patients are premenopausal and experience surgical menopause as a result of bilateral oophorectomy. Surgical menopause results from an abrupt loss of sex steroid hormones, resulting in symptoms such as vasomotor instability and sexual dysfunction, while also increasing the long-term risk of osteoporosis, cardiovascular disease and cognitive decline. The importance of ovarian preservation during radical cystectomy is increasingly recognized; however, oophorectomy might still be indicated in selected premenopausal patients for oncological control. In these individuals, awareness and management of surgical menopause among urologists is often limited, resulting in avoidable morbidity. Thus, when surgical menopause is unavoidable, patients should be counselled regarding symptom management, cardiovascular risk and bone protection; and appropriate hormonal and non-hormonal therapeutic strategies should be implemented where indicated.

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Key points

- Surgical menopause occurs following radical cystectomy when bilateral oophorectomy is carried out in a premenopausal woman.
- Surgical menopause results in an abrupt cessation of ovarian sex hormone production, causing symptoms including hot flushes and sexual dysfunction.
- Beyond symptomatic effects, surgical menopause is associated with important long-term risks including an increased risk of all-cause mortality, cardiovascular disease, cognitive decline and loss of bone mineral density.
- Female patients experiencing surgical menopause should receive evidence-based counselling regarding expected symptoms, hormone replacement therapy and appropriate non-hormonal treatment options.
- Management of surgical menopause should be multidisciplinary, involving urology, gynaecology and/or menopause specialists, and primary care and allied health professionals, to ensure coordinated symptom control, risk reduction and survivorship care.

Introduction

Bladder cancer is the 17th most common cancer in women worldwide, with a global age-standardized incidence rate of 2.4 per 100,000 (ref. 1). Radical cystectomy remains the gold-standard treatment for muscle-invasive bladder cancer (MIBC) and very high-risk non-muscle-invasive bladder cancer (NMIBC). In female patients, radical cystectomy is conventionally carried out alongside removal of the ovaries, fallopian tubes, uterus and anterior vaginal wall[2].

Most female patients with bladder cancer are postmenopausal, but a small number are premenopausal. The exact incidence of bladder cancer in this young cohort of patients is unknown but is presumed to be low, considering that less than 2% of new diagnoses occur in individuals under the age of 45 years[3]. In these patients, bilateral oophorectomy carried out at the time of radical cystectomy before natural menopause results in surgical menopause.

Surgical menopause leads to an abrupt and complete cessation of ovarian hormone production, often leading to the onset of menopausal symptoms. This sudden hormone withdrawal is associated with substantial short- and long-term health consequences, including an increase in all-cause mortality[4–7]. Owing to the relative rarity of premenopausal female individuals undergoing radical cystectomy, many urologists are unfamiliar with the consequences of surgical menopause and its management, especially the appropriate use of hormone replacement therapy (HRT)[8]. To date, no formal guidance exists to support the perioperative care of this specific patient cohort. Conversely, evidence-based guidelines for the management of surgical menopause are well established within gynaecological practice, where bilateral salpingo-oophorectomy (BSO) is frequently performed with or without hysterectomy[5–13]. However, real-world adherence to these guidelines remains suboptimal, with results from several studies showing that only ~50% of female patients with premature surgical menopause receive HRT and, in these individuals, treatment duration falls short of guideline recommendations[14,15]. Data regarding the use of HRT in female patients with surgical menopause following radical cystectomy are lacking, but the scale of under-treatment might be assumed to be particularly great in this population owing to low awareness of surgical menopause-related morbidity among urologists. This inadequate recognition and management of surgical menopause exposes individuals to substantial, yet largely preventable, morbidity. Thus, urologists carrying out radical cystectomy must be equipped to identify patients at risk, pursue ovarian preservation where oncologically appropriate, and, when oophorectomy is indicated, ensure coordinated multidisciplinary follow-up monitoring that includes timely initiation of HRT.

In this Review, we highlight the pathophysiology and clinical consequences of surgical menopause in premenopausal female patients undergoing radical cystectomy and summarize current evidence-based strategies to mitigate associated symptoms and long-term health risks. The rationale for ovarian-sparing cystectomy and available data on the oncological safety of this procedure are additionally discussed. We also outline current management strategies, with a particular focus on HRT, and provide practical recommendations for follow-up monitoring and survivorship care in this often overlooked population. These efforts align with the growing recognition of the need to address female-specific considerations in the management of bladder cancer.

Pathophysiology of menopause

Ovarian ageing is marked by dysregulation of the hypothalamic–pituitary–ovarian axis and progressive depletion of the ovarian reserve, resulting in a decline in both follicle quantity and quality[16]. The effect of this process is a gradual reduction in ovarian hormone production and, ultimately, the onset of natural menopause. The underlying mechanisms responsible for decline in the follicle pool and oocyte quality remain incompletely understood but include genomic instability, impaired autophagy, cellular senescence, deregulated nutrient sensing, mitochondrial dysfunction, oxidative stress and chronic inflammation[17]. Ovarian function typically begins to decline at around 35 years of age, with a more marked deterioration after 37 years, and eventual loss of ovarian function between the ages of 50 and 52 years on average[10,11]. Menopause is defined as the permanent cessation of menstruation and indicates the end of a woman's reproductive years. Menopause can occur naturally any time after the age of 45 years to beyond 55 years. Menopause occurring before the age of 45 years is termed early menopause, whereas onset before the age of 40 years is referred to as premature ovarian insufficiency.

During natural menopause, levels of oestradiol and progesterone decline gradually — often to undetectable levels — whereas testosterone production also falls, albeit more modestly, with partial compensation through adrenal production[16]. Conversely, surgical menopause as a result of bilateral oophorectomy results in an abrupt and complete cessation of ovarian hormone production. This sudden hormonal disruption is responsible for the rapid onset and potentially greater severity of menopausal symptoms experienced in patients undergoing surgical menopause compared with women who have natural menopause[12]. In a study including 189 female patients, those who experienced surgical menopause ($n = 94$) reported higher rates of hot flushes ($P = 0.001$), poor memory ($P = 0.04$) and change in sexual desire ($P = 0.04$) compared with female patients undergoing natural menopause[17]. Results from another study involving 274 female patients showed reduced self-esteem and body satisfaction among those with surgical menopause, as assessed by using the Body Cathexis Scale, Rosenberg Self-Esteem Scale and the Dyadic Adjustment Scale[18]. Direct comparisons between surgical and natural menopause are inherently challenging, as age is a major

confounder in many of the relevant outcome measures. Nonetheless, results from a large prospective UK Biobank study including data from 139,691 postmenopausal female patients showed that surgical menopause was more strongly associated with depression requiring hospitalization than premature natural menopause (HR (95% CI) surgical menopause 1.76 (1.43–2.16) versus premature natural menopause 1.27 (1.17–1.38))[19]. The mechanisms underpinning these differences in symptom burden and long-term risk remain incompletely understood; however, continued steroidogenic activity of the postmenopausal ovary has been proposed as a contributing factor[12,20].

Clinical consequences of surgically induced menopause

Surgical menopause is associated with a broad spectrum of adverse effects, including vasomotor symptoms (VMS), sexual dysfunction and cognitive decline as well increased risk of a number of conditions including cardiovascular disease, metabolic syndrome and loss of bone mineral density (BMD)[10,11] (Fig. 1). Surgical menopause has also been associated with an increased risk of all-cause mortality[4–7].

Vasomotor symptoms

VMS, characterized by hot flushes and night sweats, are a defining feature of menopause and have a well-established negative effect on quality of life[21,22]. In the What Happens After Menopause (WHAM) study — a large prospective study including premenopausal female patients undergoing reducing bilateral oophorectomy compared with age-matched individuals who did not undergo bilateral oophorectomy — the prevalence of hot flushes and night sweats markedly increased within the first 3 months following surgery, from 6% to 58% and from 21% to 41%, respectively[23]. Symptom bother, assessed using the Menopause-Specific Quality of Life-Intervention (MENQOL-I) questionnaire, peaked at 3 months in the vasomotor domain, with most participants describing their symptoms as 'mildly' bothersome. These findings show that VMS are common following surgical menopause and are particular prominent in the early postoperative period.

Genitourinary symptoms associated with menopause and sexual function

Oestrogen deficiency within the genitourinary tract leads to thinning of the vaginal epithelium, reduced vaginal blood flow and loss of microbial diversity[24]. Thus, oestrogen deficiency can result in a range of symptoms including vaginal dryness, irritation and dyspareunia[10]. The term 'genitourinary syndrome of the menopause' is used in some regions to encompass these symptoms, although no consensus on the number of signs or symptoms required for diagnosis exists[10,11,25]. In other regions, the term 'genitourinary symptoms associated with menopause' is preferred[26].

Sex steroids have a crucial role in maintaining sexual function. Oestrogen facilitates increased vaginal blood flow and lubrication during arousal, whereas testosterone promotes sexual desire through central neurotransmitters, such as dopamine, and also contributes to peripheral arousal[27]. Thus, sexual dysfunction following surgical menopause is multifactorial, and might be further exacerbated by changes in body image following radical cystectomy[28,29]. Evidence from the WHAM study showed impairment across multiple domains of sexual function in patients who experienced surgical menopause and were not using HRT. At 12 months post-surgery, participants undergoing surgical menopause showed greater declines from baseline in Female Sexual Function Index scores for sexual arousal (mean change −2.53; 95% CI −4.86 to −0.19), lubrication (−3.40; 95% CI −5.85 to −0.96), orgasm (−1.64; 95% CI −3.23 to −0.06) and pain (−2.70; 95% CI −4.59 to −0.82), compared with women who did not undergo oophorectomy[23]. Hypoactive sexual desire disorder (HSDD) is defined as the persistent or recurrent absence of sexual interest or desire for at least 6 months, which causes personal distress and is not better explained by any other conditions[30]. HSDD was shown to be more prevalent in the surgical menopause population than in normal menopause or premenopausal aged-matched women, although evidence comes largely from survey-based studies[31,32]. In the Women's International Study of Health and Sexuality survey, the reported rate of HSDD was significantly higher in women aged 20–49 years who underwent surgical menopause than in premenopausal women (26% versus 14%, $P = 0.002$); HSDD in the natural menopause population was 9% in this study[31]. Similarly, in a survey including 1,345 European women aged 20–70 years, women who had undergone BSO were twice as likely to experience HSDD than their premenopausal or naturally menopausal counterparts (odds ratio (OR) 2.1; 95% CI 1.4–3.4; $P = 0.001$)[32]. The reasons for higher rates of HSDD in the surgical menopause versus natural menopause population are not clear, as HSDD is a consequence of both hormonal changes and psychosocial components[10,11].

Cognitive function and neurological disorders

Data from retrospective studies suggest that female patients who undergo surgical menopause — particularly before the age of 45 years — might be at an increased risk of cognitive decline and neurological disorders; however, the pathogenic mechanisms remain unclear[10,11,33,34]. Data from the WHAM study — including premenopausal women undergoing risk-reducing BSO compared with age-matched individuals who did not undergo BSO — have shown a modest adverse effect of surgical menopause on verbal learning at 24 months after surgery, with participants experiencing surgical menopause performing worse on the delayed-recall component of the Hopkins Verbal Learning Test-Revised than age-matched individuals who did not have a risk-reducing BSO (estimate = 0.44; 95% CI 0.05–0.75, $P = 0.02$)[23]. Results from retrospective cohort studies have further shown that female patients undergoing bilateral oophorectomy before natural menopause and before the age of 46 years were at an increased risk of mild cognitive impairment (assessed using a battery of nine cognitive tests covering four domains) compared with female patients who did not undergo oophorectomy (adjusted OR 2.21; 95% CI 1.41–3.45)[33]. However, this association was not confirmed in another study, in which patients reported subjective cognitive complaints following surgical menopause (self-perceived changes in memory and concentration) without corresponding objective impairment on formal neuropsychological testing[34]. The association between surgical menopause and neurological disorders remains poorly defined, as available evidence is limited to retrospective observational studies[35,36]. In one population-based cohort, surgical menopause was associated with an increased risk of Parkinson disease in female patients undergoing bilateral oophorectomy before the age of 43 years (HR 5.00; 95% CI 1.10–22.70)[35]. Additionally, a pooled analysis of six observational studies showed an increased risk of ischaemic stroke following surgical menopause[36]. However, these findings require further validation in long-term prospective studies.

Bone health

Bone turnover and remodelling cycle are directly affected by oestrogen and, in the setting of oestrogen deficiency, bone resorption exceeds

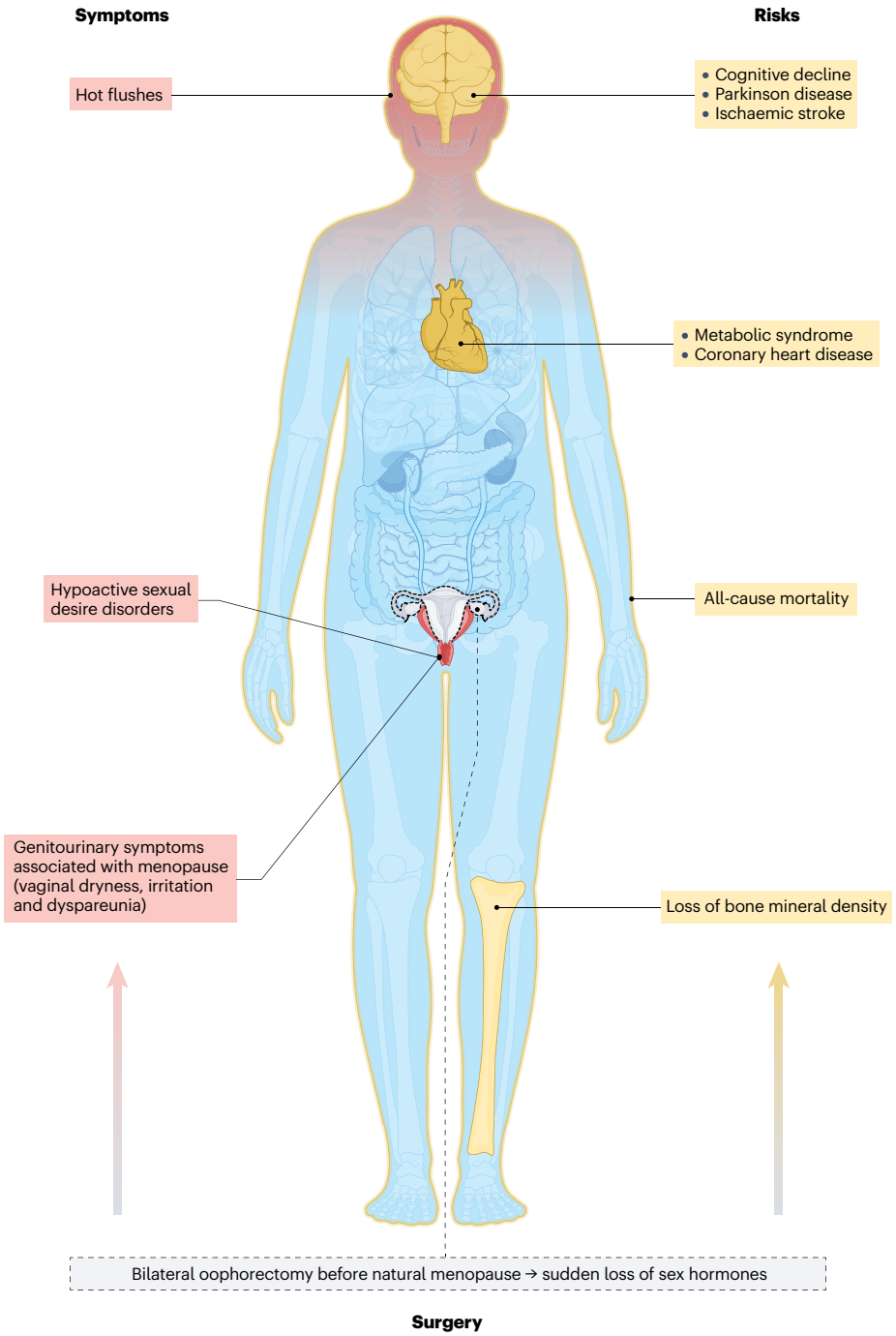

Fig. 1 | Symptoms and risks associated with surgical menopause. Symptoms (red) and risks (yellow) associated with surgical menopause are shown. Symptoms and risks are distinguished according to the distinct management approaches. Symptoms might be transient, and response can be assessed soon after treatment, whereas risks are continuous and require extended monitoring and mitigation.

bone formation, resulting in a net bone loss[10]. In a meta-analysis of ten studies, BMD after surgical menopause was significantly lower than that of age-matched premenopausal women (mean difference lumbar spine −0.15 g/cm^2 (95% CI −0.19 to −0.11 g/cm^2); mean difference femoral neck −0.17 g/cm^2 (95% CI −0.23 to −0.11 g/cm^2)), but not lower than that reported in women with natural menopause (mean difference lumbar spine −0.02 g/cm^2 (95% CI −0.04 to 0.00 g/cm^2); mean difference femoral neck 0.04 g/cm^2 (95% CI −0.09 to 0.16 g/cm^2))[37]. Low BMD is associated with increased fracture risk. Thus, monitoring and treatment of low BMD is important in the surgical menopause population[10,11].

Metabolic syndrome and cardiovascular disease

Results from large retrospective[38,39] and prospective[23,40] cohort studies have provided evidence that surgical menopause is associated with an increased risk of metabolic syndrome and cardiovascular disease.

In the WHAM study, surgical menopause was associated with increased weight and increased abdominal visceral fat at 24 months compared with women who did not undergo BSO (mean difference in weight 0.94 kg (95% CI −1.12 to 2.61 kg, $P = 0.431$); mean difference in visceral fat 0.10 kg (95% CI 0.01–0.19 kg, $P = 0.032$))[23]. No difference was observed in lipid profile or blood pressure at 12 months. The increase in weight was not observed in the surgical menopause group who were using HRT, suggesting that this treatment mitigates the risk of weight gain in the surgical menopause population. In the Nurses' Health Study, in which 121,700 women aged 30–55 years were evaluated at baseline and every 2 years through mailing questionnaires between 1976 and 1982, women undergoing bilateral oophorectomy were at an increased risk of coronary heart disease (rate ratio 2.2, 95% CI 1.2–4.2) compared with premenopausal individuals of the same age[40]. The pathogenesis of cardiovascular disease in surgical menopause is multifactorial, as the loss of oestrogen results in endothelial dysfunction, vascular stiffness as well as changes to oxidative stress and systemic inflammation[41].

Overall mortality

Results from several observational studies have shown that surgical menopause is associated with increased all-cause mortality, especially if occurring before the age of 45 (refs. 4–7). In the large, population-based Mayo Clinic Cohort Study of Oophorectomy and Aging, 1,293 female patients who underwent unilateral oophorectomy and 1097 who underwent bilateral oophorectomy between 1950 and 1987 were identified[42]. Each participant was age-matched to a reference individual from the same population who had not undergone oophorectomy. In this cohort, prophylactic bilateral oophorectomy before the age of 45 years was associated with a higher risk of all-cause mortality than that observed in age-matched individuals who did not undergo oophorectomy (HR 1.67; 95% CI 1.16 to 2.40). Notably, this excess mortality was largely confined to women who did not receive oestrogen therapy up to the age of 45 years, whereas no increase in mortality was observed among those who underwent unilateral oophorectomy. These findings suggest that premature and complete loss of ovarian oestrogen, rather than oophorectomy per se, is a crucial driver of the observed mortality risk.

Consistent findings were reported in a large UK population-based cohort study including >200,000 female patients undergoing hysterectomy for benign indications. In this study, BSO was associated with increased all-cause mortality in individuals aged <45 years (HR 1.31; 95% CI 1.18–1.45; $P < 0.001$) and 45–49 years (HR 1.16; 95% CI 1.04–1.30; $P = 0.007$), but not in those aged 50–54 years (HR 0.83; 95% CI 0.72–0.97) or ≥55 years (HR 0.92; 95% CI 0.82–1.03). These age-stratified findings support the conclusion that excess mortality is specifically associated with surgical menopause occurring before the average age of natural menopause, rather than bilateral oophorectomy per se. Analysis from the National Health and Nutrition Examination Survey (1999–2018) and National Health and Nutrition Examination Survey III (1988–1994), including a total of 14,161 postmenopausal women, showed that age at surgical menopause correlated linearly inversely with all-cause mortality, with age <40 years linked to a 39% increased risk of overall death[42]. The mechanisms underlying this association remain incompletely understood. It is unclear whether surgical menopause directly contributes to increased mortality or serves as a marker of heightened risk mediated through downstream morbidity — including cardiovascular disease, ischaemic stroke and neurodegenerative conditions, which are more prevalent following premature loss of ovarian function.

Prevention of surgical menopause

The routine practice of concomitant bilateral oophorectomy during radical cystectomy has historically been predicated on the goal of achieving negative surgical margins; concerns about potential ovarian involvement by bladder cancer (either at the time of surgery or as a site of future metastasis)[2]; the risk of developing a primary ovarian malignancy (extrapolated from historical practice patterns supporting elective oophorectomy at the time of benign hysterectomy rather than from evidence of an intrinsically increased ovarian cancer risk)[43]; and the perception that ovarian preservation adds technical complexity to cystectomy[8]. However, national and international clinical guidance has evolved to support gynaecological organ preservation in carefully selected patients. Both the European Association of Urology (EAU) and the American Urological Association (AUA) endorse consideration of gynaecological organ-sparing radical cystectomy in the absence of direct tumour involvement of the organs to be preserved. This shift was formally incorporated into the EAU guidelines in 2023 and the AUA/ASCO/SUO guidelines in 2024. However, both sets of guidelines acknowledge that specific criteria for patient selection remain poorly defined. Despite increasing support for ovarian preservation in contemporary practice, clinical practice remains heterogeneous. Results from a 2018 survey of 101 US uro-oncologists showed that ~50% of participants still routinely perform oophorectomy in premenopausal women with organ-confined disease during radical cystectomy[44], with many unaware of the long-term sequalae associated with bilateral oophorectomy[8].

Importantly, in the gynaecology literature it is indicated that premenopausal women undergoing hysterectomy with ovarian preservation also experience an earlier onset of menopause, potentially ascribed to a reduction in ovarian blood flow following surgery[45,46]. This evidence underscores the importance of considering uterine preservation alongside the ovaries in premenopausal women undergoing radical cystectomy.

One of the primary arguments in favour of pelvic organ preservation during radical cystectomy is the relatively low incidence of gynaecological organ involvement at the time of surgery. Overall, the incidence of malignant gynaecological involvement at the time of radical cystectomy ranges from 4.8% to 23.0%, depending on cohort characteristics[47–51]. Among these, the anterior vaginal wall is most frequently involved, whereas ovarian involvement is rare, with a reported incidence between 0% and 12%. Ovarian involvement, when present, is typically macroscopic and associated with locally advanced or node-positive disease. These findings support ovarian preservation in carefully selected patients with organ-confined disease and normal-appearing ovaries[50,51].

Concerns about future primary ovarian malignancy are used by urologists as justification for concomitant oophorectomy at the time of radical cystectomy[8]. However, in a study including 1,347 female patients with bladder cancer, only 3.4% of patients undergoing radical cystectomy harboured genomic mutations associated with ovarian cancer, suggesting a low baseline risk in this population[52]. Additionally, analysis of Surveillance, Epidemiology, and End Results data from 1,851 women undergoing anterior exenteration identified only two cases of subsequent ovarian malignancy[53]. Furthermore, high-grade serous ovarian carcinoma, the most prevalent and aggressive type of ovarian cancer, is increasingly understood to originate in the fallopian tubes from serous tubal intraepithelial carcinoma, rather than from the ovaries. Thus, bilateral salpingectomy at the time of radical cystectomy should be offered to premenopausal women for whom ovarian preservation is planned. Evidence from systematic reviews and meta-analyses in the

general gynaecological population (rather than cystectomy-specific cohorts) shows that salpingectomy is associated with a reduction in lifetime ovarian cancer risk of up to 80%[54].

Collectively, these data suggest that ovarian preservation is oncologically safe in appropriately selected women. Available data on pelvic organ-sparing radical cystectomy is generally favourable, but remains limited by its retrospective, single-centre nature, small patient numbers and immature follow-up monitoring[55–58]. In a multicentre study including 269 women undergoing robot-assisted radical cystectomy, no significant differences in cancer-specific ($P = 0.12$) or overall ($P = 0.78$) survival were observed between women who received pelvic organ-sparing surgery with intracorporeal urinary diversion ($n = 81$) and those who underwent non-organ-sparing procedures ($n = 188$) at a median follow-up time of 34.2 months[59]. These findings are encouraging, but prospective randomized data are ultimately needed to establish the long-term safety of this approach.

Patient selection is crucial when considering ovarian preservation during radical cystectomy. Tumour location is a crucial determinant, with both AUA and EAU guidelines supporting organ preservation in the absence of direct tumour extension or involvement of the area to be preserved[60,61]. Historically, organ preservation has been limited to patients with cT2 disease. However, emerging data suggest that organ preservation might be feasible beyond these traditional boundaries in carefully selected patients. In a single-centre retrospective cohort study, patients were selected for pelvic organ-sparing radical cystectomy based on multidisciplinary risk assessment incorporating preoperative cross-sectional imaging and intraoperative findings, including tumour location, depth of invasion and absence of macroscopic gynaecological organ involvement. In this cohort, neither advanced pathological stage (≥pT3) nor the presence of variant histology was associated with worse oncological outcomes than those after non-organ-sparing radical cystectomy. Specifically, positive surgical margin rates in organ-sparing and non-sparing procedures were comparable (4.3% versus 7.9%; $P = 0.19$), similar to median recurrence-free survival (26.1 versus 15.3 months; $P = 0.94$; HR 1.02) and cancer-specific survival (36.3 versus 28.6 months; $P = 0.76$; HR 0.90)[55]. Importantly, high-risk subtype histologies were under-represented in this study, with only one patient harbouring micropapillary disease and no patients with plasmacytoid carcinoma — subtypes known to show aggressive behaviour and an increased risk of occult extension beyond the bladder[62]. This limitation restricts the generalizability of these findings to patients with high-risk variant histology and, therefore, is clinically relevant. In a single-centre study involving 18 premenopausal female patients with predominantly squamous cell carcinoma of the bladder who underwent pelvic organ-sparing radical cystectomy, no instances of ovarian recurrence were detected at a median follow-up time of 70 months[63]. Notably, patient selection was limited to those with ≤T2b tumours away from the bladder neck and posterior wall.

Results from these studies suggest that organ preservation might be safe in selected patients with subytpe histology. However, evidence is limited, and further studies are needed to determine whether outcomes vary by histological subtype. Preoperative MRI might provide additional value in evaluating the feasibility of gynaecological organ preservation by delineating the extent of tumour invasion and the proximity to adjacent gynaecological organs.

Management of surgical menopause

Guidance on management and follow-up monitoring of female patients who have experienced surgical menopause following radical cystectomy for bladder cancer has not been specifically defined. Thus, recommendations outlined in this manuscript are largely extrapolated from guidance developed for patients with prematurely induced menopause following surgical or hormonal treatment for risk reduction in women with gynaecological cancers (Box 1).

Hormone replacement therapy

HRT consists of two principal components: oestrogen and progestogen, which can be used alone or in combination, and in topical and systemic preparations depending on the indication and patient-specific risk factors. HRT has been shown to improve some menopause symptoms, although the evidence of the role of HRT in reducing the risk of complications, including cardiovascular disease and all-cause mortality, remains inconclusive. Currently, national and international clinical guideline groups recommend initiating HRT following premature surgical menopause and continuing it until the age of an expected natural menopause (51–52 years old)[9–13,22,64].

Risks of hormone replacement therapy. HRT is associated with risks that can be grouped in two categories: hormone-dependent cancer (breast and endometrial cancer) and venous thromboembolism (VTE)[64].

Unopposed oestrogen increases endometrial cancer risk[65,66]. Thus, combined preparations of oestrogen and progesterone should be used if the uterus is retained and HRT is initiated to manage symptoms or risks of menopause[9–11,26,64]. However, given that bilateral oophorectomy during radical cystectomy is almost always carried out in conjunction with hysterectomy, this will be a rare scenario, and the risk of endometrial cancer is not clinically relevant.

The evidence base regarding HRT and breast cancer risk has evolved over time, with contemporary evaluations by international guideline committees indicating that oestrogen-only HRT confers minimal or no increase in breast cancer risk[9–11,26,64]. Evidence from the Women's Health Initiative — a large, randomized, double-blind, placebo-controlled trial involving over 10,000 women who had undergone hysterectomy and bilateral oophorectomy — showed a reduced incidence of invasive breast cancer among those receiving oestrogen-only HRT[67]. Specifically, the group receiving oral conjugated equine oestrogen (0.625 mg daily) had a significantly lower annual incidence of breast cancer (0.27%) than patients receiving a placebo (0.35%), corresponding to a hazard ratio of 0.77 (95% CI 0.62–0.95; $P = 0.02$). Thus, current guidance indicates that female patients <50 years old undergoing surgical menopause do not face an increased breast cancer risk with HRT[9–11].

Oestrogen receptor expression has been described in both normal and neoplastic urothelium, with mixed data available on the association between expression levels and malignancy[68]. Preclinical data in bladder cancer cell lines showed that oestrogen receptor modulation with tamoxifen increased cisplatin sensitivity[68]. However, these findings were not replicated in a clinical study including 30 patients[69]. Thus, the potential effect of HRT on bladder cancer outcomes is unknown, and, considering the paucity of evidence, caution is warranted if adjuvant cisplatin therapy is being considered.

With regard to VTE, no increased risk of VTE has been associated with transdermal oestrogen[70]; thus, transdermal oestrogen should be prescribed as first-line therapy when HRT treatment of the surgical menopause is sought. However, transdermal oestrogen is still contraindicated in female patients with previous or current VTE, or with known thrombophilic disorders[9–11,22,26,64,71].

Box 1 | Recommendations for prevention, management and monitoring of risks in surgical menopause

Prevention of surgical menopause: ovarian preservation
- Select patients for ovarian-sparing cystectomy based on:
  - Low risk of bladder cancer involving ovaries, based on clinical, histological and imaging findings
  - Low ovarian cancer risk, based on family and personal history
  - Premenopausal status and younger age (<45 years old, noting that the natural age of menopause is 51– 52 years)
- Offer bilateral salpingectomy when ovarian preservation is planned to reduce subsequent ovarian cancer risk

Systemic hormone replacement therapy (HRT)
- Recommended HRT in patients aged <45 years and continue until the age of natural menopause (51–52 years). Offer HRT to patients aged 45–50 years depending on symptoms and patient wishes. Specific recommendations include:
  - Start HRT >6 weeks after cystectomy
  - Discuss risks and benefits of different preparations; identify and rule out contraindications
  - Transdermal formulations might be preferred as first-line treatments owing to a reduced venous thromboembolism risk
  - Titrate the dose according to the aim and assess response at 6–12 weeks, and then annually

Other therapeutic considerations
- Vasomotor symptoms:
  - Healthy weight maintenance, reduction of alcohol and caffeine, smoking cessation
  - Use of selective serotonin re-uptake inhibitors or serotonin–noradrenaline reuptake inhibitors or neurokinin B antagonists (fezolinetant)
- Genitourinary symptoms:
  - Provide vulval skin care advice and suggest using barrier cream and vaginal moisturiser
  - Suggest using vaginal oestrogen in the form of cream, pessaries or rings
- Sexual function:
  - Use a holistic approach including psychosexual counselling, use of lubricants, pelvic floor therapy
  - After full evaluation, consider pharmacological therapy for hypoactive sexual desire disorder, defined as the persistent or recurrent absence of sexual interest or desire for at least 6 months, which causes personal distress and is not better explained by any other conditions[30]

Monitoring of risks associated with surgical menopause
- Bone health
  - Recommend baseline dual-energy X-ray absorptiometry scan and Fracture Risk Assessment Tool scoring; proceed with treatment and repeat scans based on individual risk
  - Measure vitamin D levels and replace vitamin D and calcium if required
- Cardiovascular and metabolic health
  - Recommend baseline measurement and optimization of blood pressure, lipid profile, glucose and weight
  - Annual monitoring of cardiovascular risk, including blood pressure, lipid profile, glucose and weight

An increased risk of VTE has been shown in patients receiving oral oestrogen preparations compared with no HRT, with mixed results observed when patient groups were stratified according to age. Specifically, results from a Cochrane meta-analysis suggested an increased risk of VTE in (naturally) postmenopausal women under the age of 60 years (risk ratio 1.74; 95% CI 1.11–2.73); but a subsequent updated analysis showed a risk only in women >60 years old, suggesting that this risk might not be relevant to the surgical menopause population, in whom treatment is recommended until the average age of natural menopause (51–52 years)[72,73]. Overall, VTE risk should be considered in all women receiving oral preparations, and the lowest dose of oestrogen should be used[9,26,64].

Timing, duration and dosing of hormone replacement therapy. The British Gynaecological Cancer Society and British Menopause Society guidelines advise initiating HRT as soon as possible following treatment resulting in the surgical menopause, but this recommendation primarily applies to patients undergoing premenopausal risk-reducing bilateral oophorectomy[9]. In female patients undergoing radical cystectomy, most urologists prefer to delay HRT by 4–6 weeks to avoid an increased risk of VTE in the immediate postoperative period. HRT treatment is then recommended until the average age of natural menopause (50–52 years old). Continuation after this threshold should be carried out on an individual basis with particular consideration given to cardiovascular disease factors. No specific guidance on continuation of therapy exists, but the British Menopause Society does not recommend using HRT in women with known cardiovascular disease or uncontrolled risk factors, including uncontrolled hypertension (blood pressure ≥180/110 mmHg) or abnormal lipid profile (total cholesterol >7.8 mmol/l and triglycerides >4.5 mmol/l)[74].

With regard to HRT dosing, the aim should be to use the lowest effective dose that is consistent with treatment goals, either symptom response or risk reduction[9,26,64]. Once HRT has been started, effectiveness and adverse effects should be monitored through clinical consultation and symptom inquiry, as the dose and preparation might require modification. A review at 3 months and then at least annually is recommended by international guideline groups including European Society of Human Reproduction and Embryology (ESHRE), National Institute for Health and Care Excellence (NICE) and the North American Menopause Society[10,11,26,64]. High doses of oestrogen might be needed to reduce the risk of BMD loss, even if other symptoms are controlled, with a dose of at least 2 mg oral or 100 µg transdermal oestradiol recommended to reliably prevent bone loss[10,11]. These reviews are often best conducted by a family physician, gynaecologist or menopause specialist. Thus, the urology team should refer appropriately to ensure appropriate follow-up monitoring and continuity of care.

Hormone replacement therapy preparation selection. HRT is available in oral and topical preparations. Topical preparations include transdermal patches, creams, pessaries, intra-uterine devices and vaginal rings.

In patients who received radical cystectomy and have also undergone hysterectomy, a transdermal oestrogen-only patch is a preferred first-line option, as this preparation is associated with a lower VTE risk than oral preparations. British Menopause Society and NICE guidance states that any patient at an increased VTE risk should avoid oral preparations and recommend that all women at an increased risk of VTE, including women with a BMI >30 kg/m^2, should be offered transdermal preparations[9,26].

Topical vaginal oestrogen can be added if patients experience ongoing predominant genital symptoms after receiving systemic oestrogen. Vaginal oestrogen is only absorbed locally and, therefore, can be used in addition to systemic HRT[9].

Hormone replacement therapy to reduce the risks associated with surgical menopause. Evidence of the role of HRT in reducing the risks associated with the surgical menopause is not uniformly conclusive. Results from the WHAM study showed a positive effect of HRT in the surgical menopause group at 24 months after oophorectomy on cognitive function — verbal learning was higher in HRT users (66th percentile of normed scores) versus non-users (42nd percentile); HRT also prevented tibial BMD losses compared with non-users, and mitigated losses at the lumber spine — losses in lumbar spine (5.8%) and tibia (2.3%) were observed in non-HRT users, whereas with HRT use, no tibial losses were seen, and reduced loss in the lumbar spine (2.3%) was observed ($P = 0.01$)[23,75]. However, results from this study did not show any effect of HRT on the measured cardiovascular or metabolic surrogates, including weight, body composition, blood pressure and lipid profile[23]. Currently, no data are available on the effect of HRT on mortality. Thus, the British and Australian Menopause Societies, NICE and ESHRE guideline groups and international consensus recommend HRT to reduce the risk of BMD loss and subsequent fragility fractures, but acknowledge that the effect on cardiovascular risk is less certain[9–12,26]. HRT is recommended until the age of natural menopause and oestrogen therapy alone can be used for bone protection, always considering contraindications of unopposed oestrogen if the uterus is preserved.

Symptom management

The management of the symptoms of surgical menopause should be undertaken in a holistic manner. Clinicians should focus on individualizing advice and understanding the specific wishes and needs of female patients after radical cystectomy.

Vasomotor symptoms

Non-pharmacological approaches to the management of VMS include the optimization of lifestyle factors that can contribute to VMS, such as maintaining a healthy weight, reducing alcohol and caffeine and smoking cessation. Other non-pharmacological techniques are designed to reduce the perception of bother of hot flushes — such as cognitive behavioural therapy and clinical hypnosis[9–11,26,64]. Changing diet to increase dietary oestrogens to manage VMS is not recommended, as the benefit of this modification is challenging to prove, mainly owing to variable oestrogen absorption, which is ascribable to differences in individual microbiome and genetics as well as food preparation[64].

From a pharmaceutical perspective, HRT is an effective treatment for VMS symptoms. In the WHAM study — in which the MENQOL-I menopause-specific questionnaire was used to capture VMS symptoms such as hot flushes and night sweats — the prevalence of night sweats at 24 months after risk-reducing BSO was halved in HRT users compared with non-users (28% versus 60%) and the change from baseline to 24 months in the MENQOL-I VMS domain was lower in HRT users than in non-users (mean between-group difference 1.55; 95% CI −2.51 to −0.59, $P = 0.001$)[23]. Other pharmaceutical approaches to the management of VMS include the use of selective serotonin re-uptake inhibitors and serotonin–noradrenaline reuptake inhibitors such as gabapentin and venlafaxine; the effectiveness of these drugs is supported by high-level evidence[9–11,26,64,76]. Monitoring treatment effectiveness is crucial, as depending on the agent, dose titration might be required to achieve symptom relief. Neurokinin B antagonists — a new class of drugs that work through the inhibition of the kisspeptin–gonadotrophin-releasing hormone axis — have also been developed to treat VMS associated with natural menopause, with fezolinetant being the first in this class to be approved by the FDA[77].

Genitourinary symptoms associated with menopause

Vaginal oestrogen is recommended for the management of genitourinary symptoms associated with menopause[9–11,26,64]. Several different preparations (including creams, pessaries, rings or gels) are available, and the choice is often based on patient preference and the predominant symptom. Creams that can be applied directly to the labia and vestibule, which are areas not well-targeted by inserted formulations, might be preferred. However, some women might find creams inconvenient or messy and opt for pessaries instead.

All patients experiencing surgical menopause must receive guidance on appropriate vulval skin care. Women with a neobladder — who might require continence pads and are at an increased risk of developing vulvitis — should be advised to change pads regularly and avoid perfumed products or those containing additives, which might irritate the skin. Using a barrier cream (such as Epaderm) might help to protect the skin and reduce inflammation. Patients should be encouraged to wash with water or a soap substitute, as many commercial products can disrupt vaginal pH and exacerbate genitourinary symptoms associated with menopause. Vaginal moisturisers might offer additional benefit, but are often unnecessary when vaginal oestrogen is adequately prescribed. Care should be taken in selecting these products, as some formulations, particularly those containing glycerine, might cause irritation[78]. To date, laser therapy is not recommended for genitourinary symptoms associated with menopause owing to limited evidence of efficacy[10,11,26,79].

Sexual function

Although HRT might improve sexual function in women experiencing surgical menopause, particularly manifestations associated with genitourinary symptoms of menopause, a holistic approach to sexual dysfunction remains essential and the role of psychosexual counselling should not be overlooked[10,25,80]. Vaginal lubricants and pelvic floor physiotherapy might alleviate pelvic floor muscle weakness, as well as dyspareunia and orgasmic dysfunction that can result from genitourinary symptoms associated with the menopause, although specific data are lacking in the menopause population as most studies involved premenopausal women and those with chronic pain[81].

Low libido might be observed in women undergoing surgical menopause owing to reduced testosterone levels, although no definitive reference range exists for diagnostic purposes and causality is not

established[10,11,30]. In women with low libido who meet the diagnostic criteria for HSDD and have undergone a full biopsychosocial evaluation, testosterone supplementation can be considered, although several guidelines recommend a course of conventional HRT first[9,26,82,83]. One option for testosterone supplementation is AndroFeme, which is licenced for use in women in Australia and was approved by the Medicines and Healthcare products Regulatory Agency (UK) in 2025 (ref. 84). In countries where this preparation is unavailable, approved male formulations might be used off-label. Baseline measurement of testosterone and sex hormone binding globulin, as well as liver function and lipid profile, are recommended in women receiving testosterone supplementation, and monitoring is required to ensure that the testosterone levels remain within the physiological range[83]. In addition to hormonal approaches, non-hormonal pharmacological therapies, such as FDA-approved flibanserin and bremelanotide — which are a serotonin receptor and melanocortin receptor agonist, respectively — might also be considered[85].

Contraindications to hormone replacement therapy

A small proportion of patients undergoing surgical menopause have contraindications to HRT. This population includes individuals with a personal history of breast cancer, hormone-sensitive ovarian or endometrial cancer, VTE, recent arterial thromboembolic events, liver disease or known thrombophilic disorders. In the case of uncertainty, early consultation with a menopause specialist is essential. Historically, the risks of HRT have often been overstated. Thus, decisions around initiating or withholding HRT must be based on a careful, individualized assessment of risks and benefits.

Follow-up monitoring

Women who experience the surgical menopause require follow-up monitoring addressing symptoms and response to treatment, as well as the risks of BMD loss and cardiovascular disease.

Bone health

The British Menopause Society and international consensus groups recommend that baseline BMD assessment is carried out in all premenopausal women with treatment-induced menopause by using either a dual-energy X-ray absorptiometry scan alone or in conjunction with Fracture Risk Assessment Tool scoring to evaluate future fracture risk[9,22]. After baseline assessment, guidelines recommend tailoring the intensity of monitoring to the individual's risk of osteoporosis. The dual-energy X-ray absorptiometry-based screening system classifies bone density by using the World Health Organization T-score criteria, defining a normal bone density as a T-score ≥−1.0, osteopenia as a T-score between −1.0 and −2.5, and osteoporosis as a T-score ≤−2.5. In patients with a normal T-score, repeat assessment at 5 years is recommended, whereas in those with osteopenia, follow-up imaging is advised at 1–3-year intervals[9,13]. For women with either osteoporosis or osteopenia with a Fracture Risk Assessment Tool-calculated 10-year fracture risk >20% or a fragility fracture, prompt referral to an endocrinologist or bone health specialist for pharmacological intervention is recommended[9,13]. First-line pharmacological options would include bisphosphates, denosumab or selective oestrogen receptor modulators.

Other modifiable risk factors for osteoporosis should also be addressed in women undergoing surgical menopause, including low body mass index (<18 kg/m^2), low physical activity, insufficient calcium (<1,000–1,200 mg/day), low vitamin D (<15–20 mcg/day) and insufficient protein intake (<1.2 g/kg/day), smoking and excessive consumption of alcohol (>2 drinks/day)[9,22,86]. Thus, lifestyle modifications should be emphasized alongside clinical monitoring. Guidelines also recommend that all women with premature menopause have baseline vitamin D levels assessed, and those with vitamin D deficiency should have dietary supplementation to achieve recommended levels (1,000–1,200 mg/day of calcium and at least 600–800 IU/day of vitamin D)[9,22].

Cardiovascular health

ESHRE, the British Menopause Society and international consensus groups recommend assessing cardiovascular risk in women undergoing surgical menopause and informing women of the lifestyle factors that can be undertaken to modify this risk, including smoking cessation, a healthy diet and minimizing sedentary behaviour[9–11,22]. Annual weight and blood-pressure monitoring as well as the optimization of glucose and lipid profiles is also recommended[9–11,22].

In the WHAM study, no substantial changes in blood pressure or fasting circulating cardiometabolic markers (from baseline to 12 months) were seen in women undergoing premenopausal risk-reducing BSO, including systolic and diastolic blood pressure, fasting glucose, lipid profiles, and high-sensitivity C-reactive protein[87]. This evidence led the authors to conclude that routine measurement of these parameters within the first postoperative year is not routinely indicated. Conversely, early anthropometric changes were observed, with a greater increase in waist circumference after risk-reducing BSO (~2.5 cm) than in comparators not undergoing risk-reducing BSO (~1.1 cm), suggesting that waist measurements might identify early central adiposity that precedes later cardiometabolic risk.

Conclusions

Premenopausal women undergoing radical cystectomy for bladder cancer will experience surgical menopause if concomitant bilateral oophorectomy is performed. The abrupt cessation of ovarian hormone production as a result of surgical menopause is associated with a range of short- and long-term consequences, including VMS, sexual dysfunction, cognitive decline, osteoporosis, cardiovascular disease and increased all-cause mortality.

Emerging evidence suggests that ovarian preservation is oncologically safe in carefully selected patients, and this approach should be actively pursued in all eligible premenopausal women undergoing radical cystectomy. HRT has not been shown to reduce all risks associated with surgical menopause, but remains the cornerstone of bone protection and symptom management when bilateral oophorectomy is unavoidable. In the absence of contraindications, HRT should be continued at least until the average age of natural menopause. A multidisciplinary approach is essential to ensure comprehensive postoperative care, including risk stratification, symptom management, with access to hormonal and non-hormonal treatment, and long-term monitoring of bone and cardiovascular health.

Available evidence to date underscores the urgent need to increase awareness, improve urologist education and develop consensus guidelines to support the optimal care of premenopausal women undergoing radical cystectomy. Incorporating female patient-specific considerations into bladder cancer management will improve survivorship and also reduce the burden of avoidable morbidity in this vulnerable patient cohort.

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Author contributions

N.L., E.D. and F.P.B. researched data for the article. N.L., E.D. and C.M. contributed substantially to discussion of the content. N.L., E.D., F.P.B., C.M. and J.D.K. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

Additional information

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