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Long-term fatigue, neurotoxicity, cognitive and sexual disorders after chemotherapy in ovarian germ cell and sex cord–stromal tumors: subtype-specific findings from the GINECO-TMRG case control study

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Abstract

Purpose

Non-epithelial ovarian tumors, including germ cell tumors (GCTs) and sex cord–stromal tumors (SCSTs), have favorable survival rates but carry risks of long-term treatment sequelae. This study explored long-term quality-of-life (QoL) outcomes by tumor subtype using data from the French TMRG/GINECO VIVROVAIRE study.

Methods

Cancer-free GCT and SCST survivors (≥2 years post-treatment) were matched 1:2 to cancer-free women (CFW) by age and education. Participants completed validated questionnaires assessing QoL, fatigue, neurotoxicity, cognition, psychological distress, insomnia, physical activity, and sexuality.

Results

We included 144 patients (99 GCT, 45 SCST) and 284 CFW. Patients underwent surgery and platinum-based chemotherapy (median follow-up: 5.7 years). Compared to CFW, SCST survivors reported significantly higher fatigue (MFI 52.0 vs 42.5, p=0.03) and severe neuropathy (36% vs 7%, p<0.001). GCT survivors reported more cognitive complaints (37% vs 20%, p=0.002) and reduced sexual interest (29% vs 12%, p<0.001). Premature menopause was more frequent in both survivor groups compared to CFW. Psychological distress, insomnia, and physical activity levels were similar across groups.

Conclusions

Despite similar therapeutic management, long-term sequelae differ significantly by tumor subtype. SCST survivors predominantly experience fatigue and neuropathy, whereas GCT survivors are more affected by cognitive complaints and sexual dysfunction.

Implications for Cancer Survivors

Survivorship care plans should be tailored to the specific tumor subtype. Clinicians should screen SCST survivors for neuropathy and fatigue, while focusing on cognitive rehabilitation and sexual health support for GCT survivors.

Trial registration number: NCT03418844

Highlights

- Compared to CFW, long-term sequelae differ between GCT and SCST survivors.
- SCST survivors experience persistent fatigue and severe neuropathy.
- Overweight is associated with fatigue in SCST survivors.

- GCT survivors report more cognitive complaints and sexual impairment.
- Fatigue is associated with neurotoxicity in SCST and cognitive impairment in GCT.

INTRODUCTION

Germ Cell Tumors (GCTs) and Sex Cord–Stromal Tumors (SCSTs) are the most common subtypes of rare non-epithelial ovarian tumors. As these tumors are mostly diagnosed at an early stage and are associated with a favorable prognosis, their therapeutic management shares several similarities, mainly based on surgery and chemotherapy (1) (2). Although these tumors are treated similarly, patient and tumor characteristics differ between GCTs and SCSTs.

Approximately two-thirds of GCT are limited to stage I at diagnosis and affect young women with a median age at diagnosis of 22 years (0–93 years), 91% of the patients being < 40 years old (3). Fertility sparing surgery is recommended in women who desire future fertility (4). Patients with advanced stage are managed with debulking surgery followed by adjuvant chemotherapy (3 to 4 courses of BEP) (5). In stage I GCTs, the indication for adjuvant chemotherapy is more controversial (6). The BEP regimen remains the most commonly used (BEP : cisPlatine 20 mg/m²/j J1 à J5 + Etoposide 100 mg/m² /j J1 à J5 + Bleomycine 30 mg J1, J8, J15), with bleomycin omitted in patients over 40 years of age because of the risk of treatment-related pulmonary toxicity (3% mortality)(4).

SCST represent only 7% of all ovarian tumors, often diagnosed at a median age of 45–50 years (6) (7). They are mostly represented by granulosa cell tumors, which are declined between adult and juvenile forms; and Sertoli-Leydig cells tumors. These tumors are often indolent, but late recurrences can be observed more than 20 years after diagnosis (2). Surgery is a cornerstone in the management of ovarian SCST and is frequently combined with systemic chemotherapy for advanced disease (2) (5). To achieve complete surgery, extensive debulking is sometimes necessary including hysterectomy, bilateral adnexectomy, omentectomy, and removal of all macroscopic peritoneal lesions +/- digestive resections or splenectomy or other removals when needed. Although the data are very limited, the BEP regimen or carboplatin/paclitaxel (Carboplatin AUC5 + Paclitaxel 175mg/m2) are currently recommended for adjuvant postoperative chemotherapy and for patients with recurrent SCST (2) (5). Given the toxicity associated with BEP chemotherapy, a phase II study evaluating paclitaxel–carboplatin in ovarian SCST has been conducted, but non-inferiority to BEP could not be demonstrated (9). Conclusion from authors is to consider similar activity and less acute toxicity for paclitaxel–carboplatin but follow-up was not so long in the GOG trial. Currently, majority of patients of more than 40 years old received paclitaxel–carboplatin instead of BEP.

Management of ovarian GCT and SCST share multiple similarities even if patients and tumors profiles are quite different. Long-term effects of BEP have been well described in the male population of testicular GCT with long-term fatigue and deteriorated quality of life (QoL) (10) (11) (12). Concerning ovarian GCT, only few studies explored QoL outcomes. Among 132 ovarian GCT survivors, the impact of self-efficacy and social support on overall QoL outcomes have been reported (13). In a comparative

study with controls, ovarian GCT survivors reported sexual QoL impairment (13). A non-comparative cohort of 150 GCT and SCST explored some domains of QoL such as anxiety, as well as the impact of surgery and survivors QoL (14) (15).

Although these few studies have explored the impact of chemotherapy on the general health and some domains of QoL in survivors of ovarian GCT and SCST, none has specifically realized an in-depth assessment of QoLoutcomes differences between each of these two tumor subtypes compared to controls. In particular data remain scarce regarding the long-term outcomes.

Ovarian GCTs and SCSTs share similar care pathways in their initial therapeutic management, despite differences in their clinical presentation and tumor behavior. It therefore appears relevant to gain further insight into their distinct long-term outcomes in order to assess the differential impact of these treatments on the quality of life of patients in each of these subgroups. This study aims to characterize distinct long-term survivorship profiles in each subtype of ovarian GCT and SCST survivors, compared to matched cancer-free women (CFW) as controls. All patients were issued from a national rare gynecologic cancer network, and treated with surgery (with or without fertility-sparing) and chemotherapy.

METHODS

This is an ancillary study issued from a multicenter case-control study (Vivrovaire rare tumors case-control study “NCT03418844”) using the French network for rare malignant ovarian tumors TMRG (www.ovaire-rare.org; Tumeurs Malignes Rares Gynecologiques). TMRG network organization include : a systematic histological review, dedicated multidisciplinary tumor board to propose initial standard of care management, and options at relapse (16).

Vivrovaire rare tumors study design has been previously published (17). Eligible patients have been recruited from the INCa French network TMRG. They have been selected in 19 of the 22 centers of the French cooperative GINECO group (Groupe d’Investigateurs Nationaux pour l’Étude des Cancers Ovariens et du sein). CFW have been recruited from the Seintinelles® network (https://www.seintinelles.com), which is a collaborative research platform linking researchers and citizens to accelerate cancer research. Women of the Seintinelles® network are volunteers available to participate in cancer research surveys.Here, CFW volunteers have been contacted to complete online self-questionnaires.

We included women with histologically confirmed ovarian GCT or SCST who had received at least one line of platinum-based chemotherapy and were free of disease ≥ 2 years after their last treatment, either at primary diagnosis or relapse. Women treated with surgery alone or with hormonal therapy without chemotherapy were not considered in the present analysis. Here we present the results of a sub study assessing long-term QoL, as well as personal and professional outcomes, among each subtype of ovarian GCT and SCST survivors, both matched with CFW as controls.

Primary objective was to assess distinct long-term survivorship profiles in the 2 histological subtypes of non-epithelial ovarian tumors survivors: 1/ ovarian GCT survivors treated with surgery and chemotherapy, as compared with matched CFW; 2/ ovarian SCST survivors treated with surgery and chemotherapy, as compared with matched CFW. Matching (2:1 nearest neighbor propensity score matching without replacement) was adjusted on age (± 2 years) and level of education (primary/middle school, secondary school and higher education).

All participants completed self-reported questionnaires including standardized and validated instruments previously detailed in study protocol (17). Fatigue Questionnaire (Multidimensional Fatigue Inventory: MFI-20) (18) (19); Functional assessment of cancer therapy scale general (FACT-G) and module for ovarian cancer (FACT-O) (20); Hospital Anxiety and Depression Scale (HADS) (21); Peripheral Neurotoxicity Questionnaire (FACT/GOG-NTX) (22); Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog Questionnaire) (23); Insomnia Severity Index (ISI) (24); Physical Activity Questionnaire (IPAQ) (25); and a specific questionnaire adapted from the “living conditions” questionnaire used in previous studies (26). A minimal 5% difference of scores of FACT and MFI questionnaires between groups was considered as clinically relevant (27). HADS score ≥ 11 indicated elevated anxiety or depression. ISI Score 22–28 indicated severe clinical insomnia. Severe neurotoxicity was defined by Ntx score < 33 (28). Perceived cognitive impairment (PCI) categories were issued from the FACT-Cog normative data from a healthy population. Clinically significant symptoms of cognitive complaints were defined as ratings lower than the 10th percentile of a normative sample (29) (30) (31). Changes reported in the living conditions questionnaire were evaluated as follows: (i) in the patient questionnaire, changes referred to the period before cancer diagnosis compared with the time of the survey; (ii) in the CFW questionnaire, changes referred to the three-year period preceding the survey compared with the time of the survey.

Patients were asked to return completed questionnaires anonymously. For the CFW control group, the Seintinelles network published the study information, and the questionnaires were completed online. Patient’s medical data were collected from patient records.

Categorical variables are presented as frequencies and percentages and were compared using the chi-square test (or Fisher exact test if frequencies < 5), whereas continuous variables are displayed as mean ± SD and were compared using the Student t test (or Wilcoxon Mann Withney test for non-gaussian distributions). All tests were 2-tailed, and a p value < 0.05 was considered to indicate statistical significance.

Variables associated with the outcome at $p < 0.20$ in univariate analyses, together with age and group (patients vs HW), were entered into multivariable models. We used complete-case analyses; no imputation was performed. To further investigate the factors associated with fatigue in SCST patients identified in the multivariable models, we used linear regression models including an interaction term between group (SCST vs CFW) and insomnia to assess whether the association between insomnia and fatigue differed by group.

RESULTS

Among 231 ovarian GCT or SCST survivors who were included from 19 centers, 144 (45 SCST, 99 GCT) were treated with surgery and chemotherapy (≥ 1 cycle) and available for matching with 284 CFW (Figure 1).

Median delay from end of treatment was more than 5 years: 5.16 [IQR: 2.56-8.62] in SCST patients and 5.78 [IQR: 3.46-9.03] in GCT patients. Patients clinical characteristics are detailed in Table 1. SCST survivors were older than GCT (median age 50.6 years (21-71) vs 33.0 years (19-63), respectively) with more frequent comorbidities such as diabetes and hypertension. They were more frequently treated with radical surgery (including surgery at primary diagnosis and surgery at relapse) in comparison with GCT (31% vs 19%, respectively). Consecutively, menopause was more frequent in SCST patients than GCT (73% vs 27%, respectively). Patients characteristics according to menopausal status are described in Table S1. Compared with premenopausal patients, relapses occurred more frequently in the postmenopausal population, and these patients were more often treated with radical surgery. The number of CT lines was higher in SCST patients with 11% who received 2 CT lines, vs 4 % in GCT patients. Detailed chemotherapy regimen for relapsed patients treated with 2 lines are described in Table S2.

Patients and CFW socio-demographic characteristics are synthetized in Table 2. Overweight (BMI≥25) was more frequent among SCST patients than CFW (mean BMI 26.1 vs 23.6, respectively; p= 0.009). Menopause was more frequent in the 2 groups of patients compared with CFW: 27% of GCT survivors compared to 6% of CFW (p<0.001), with a median age at menopause of 36 vs 50 years (p<0.001); 73% of SCST survivors compared to 44% of CFW (p=0.004), with a younger age at menopause (45 vs 50 years, p=0.001). Patients clinical characteristics according to menopausal status are described in Table S2.

Patient-reported outcomes were compared between SCST survivors and matched CFW, as well as between GCT survivors and matched CFW (Table 3). Among SCST survivors, with a median age of 50.6 [21-71], fatigue was higher and clinically relevant compared with CFW (MFI fatigue median score 52 (26.0-82.0) vs 42.5 (24.0-86.0), p=0.03), particularly the general fatigue (MFI general fatigue median score 27 (14-39) vs 22 (13-43), p=0.02). Among GCT survivors, with a median age of 33 [19-63], fatigue was not different from CFW (MFI fatigue median score 47.0 (24.0-83.0) vs 43.5 (24.0-91.0), p=0.88).

FACT-G total score was similar in both SCST patients and CFW (78.7 vs 80.9, p=0.40), as well as in GCT patients and CFW (82.3 vs 78.3, p=0.04, but not clinically relevant. QoL assessed by ovarian cancer subscale, was deteriorated in SCST patients as compared with CFW (mean score 31.9 vs 34.4, p = 0.008, clinically relevant). Levels of anxiety, depression, insomnia and physical activity (IPAQ questionnaire) were globally similar among GCT vs matched CFW and SCST vs matched CFW.

Patient's sexual QoL, assessed by FACT-O items, was deteriorated for GCT survivors as compared with CFW, with patients having less interest in sex (29% vs. 12%, p<0.001) and being afraid not having children (41% vs. 13%, p<0.001). These differences were not observed in SCST survivors (39% vs 22%, p=

0.09 and 8% vs 13%, p= 0.53, respectively). Nonetheless, 48% of SCST patients (vs 28% CFW) and 29% of GCT patients (vs 23% CFW) declared having less fulfilling sexual life.

SCST survivors reported more severe neuropathy than CFW (36% vs 7%, respectively, p<0.001), whereas neuropathy was similar among GCT survivors and CFW (16% vs. 9%; p = 0.09). Conversely, GCT survivors experienced more cognitive impairment than CFW (37 % vs 20%, respectively; p=0.002), whereas SCST survivors had approximately similar cognitive impairment in comparison with CFW (20% vs 15%, respectively; p=0.643).

Factors associated with long-term fatigue and neuropathy in both univariate and multivariable analyses are described in Table 4 for SCST population. After adjustment on age and education level (which are matching criterias), physical activity (known to be correlated with fatigue) and factors associated with fatigue in univariate analysis, independent risk factors of fatigue in SCST survivors were insomnia (p=0.019), cognitive impairment (p=0.003), neuropathy (p<0.001) and overweight (BMI≥25) (p=0.005) (Table 4). Of note, levels of physical activity were similar across BMI categories in each, SCST patients, GCT patients, as well as CFW (data not shown). The interaction term between group (SCST vs CFW) and insomnia was not statistically significant, indicating similar insomnia related fatigue in both groups (Figure S1). Mediation analysis was conducted to decompose the total effect of SCST status on fatigue into direct and indirect effects through overweight (BMI≥25). The proportion mediated (33 %) was computed as the ratio of the indirect to total effect: overweightwas considered as mediation factor responsible of 33% of the correlation observed between SCST patients and fatigue (data not shown).

Factors associated with severe neuropathy in both univariate and multivariable analyses are described in Table 4 for SCST population. In multivariable models, independent risk factors for neuropathy were: fatigue (p = 0.005) as well as “patient group” (p<0.001) meaning that being a SCST survivor treated with surgery and chemotherapy was independently associated with neuropathy.

Factors associated with cognitive impairment, in both univariate and multivariable analyses are described in Table 5 for GCT population. In multivariable models, independent risk factors for cognition impairment were: fatigue (p<0.001), depression (p=0.003) and “patient group” (p<0.001) meaning that being a GCT survivor treated with surgery and chemotherapy was independently associated with cognition impairment.

DISCUSSION

To our knowledge, this is the largest study to date investigating long-term QoL outcomes in survivors of ovarian GCT and SCST, each compared with a matched population of CFW. At a median of follow-up of five years post-chemotherapy, SCST survivors reported higher levels of fatigue and peripheral neuropathy, compared to CFW. GCT patients were affected by premature menopause and sexual dysfunction. They reported more cognitive complaints than CFW.

Scores of QoL described in this study are consistent with previous reports in non-epithelial ovarian cancer survivors (14) (15). However, long-term QoL outcomes and cancer treatment-related sequelae in the subgroup of SCST survivors remain poorly documented in the literature. In a study of 86 granulosa cell tumor survivors, QoL was assessed using the 15D and EORTC QLQ-C30 questionnaires and compared with an age-standardized general female population (32). QoL scores were similar between survivors and controls, with slightly lower scores for sexual activity among granulosa cell tumor survivors (32). Previous publication, considering the overall VIVROVAIRE-TR study population, found similar levels of long-term fatigue between survivors and CFW (33). Here, when focusing on SCST survivors, fatigue was significantly higher than in CFW. Models performed to investigate the factors associated with fatigue in SCST patients, revealed that this increased fatigue could not be only explained by insomnia. Fatigue in SCST survivors was associated with overweight, cognitive impairment and neuropathy. Notably, SCST survivors exhibited more overweight, and a greater prevalence of premature menopause compared to CFW. Options for managing premature menopause in this SCST population, for whom hormone replacement therapy (HRT) is not recommended, are very limited. In contrast, effective management of overweight through lifestyle and dietary counseling, tailored physical activity, and appropriate health behaviors could potentially improve the long-term quality of life of SCST survivors and reduce the risk of fatigue. In this SCST subgroup, neurotoxicity was also associated with fatigue and with the fact of being a SCST survivor treated with surgery and chemotherapy. These results suggest a potential long-term impact of chemotherapy on neuropathy in this population, although causality cannot be formally established in this design. Potential explanations for this differential toxicity of chemotherapy in the SCST population, in contrast with GCT patients, may include older age, a higher burden of comorbidities (such as overweight, hypertension and diabetes), as well as a greater number of chemotherapy lines. Numerous studies have suggested that adjuvant chemotherapy does not improve the prognosis of patients with granulosa cell tumors (34). In light of these findings, the latest clinical guidelines have revised and de-escalated the indications of adjuvant CT in FIGO stage I SCST (35) (36). Given that long-term QoL remains impaired in SCST survivors treated with CT, with significant long-term fatigue and neurotoxicity, careful consideration is needed when managing this population, which is more prone to overweight and associated comorbidities.

In our study, the survivorship outcomes of GCT patients differed from that of SCST patients. We did not find some difference of fatigue and neuropathy, between GCT and CFW, however, GCT survivors reported particularly more cognitive impairment and a lower sexual QoL compared to CFW. While cancer-related cognitive impairment (CRCI) has been previously described in epithelial ovarian cancer survivors (37) and testicular GCT survivors (38), this is the first study to specifically assess CRCI in this particular population of GCT and SCST survivors, which is known to have a higher proportion of long-term survivors compared to other ovarian cancers. CRCI was associated with fatigue, depression and being a GCT survivor treated with surgery and chemotherapy. Our results are consistent with those found in breast cancer survivors where CRCI was associated with fatigue, chemotherapy, younger age and pre-treatment insomnia (39). These findings underscore the potential long-term impact of chemotherapy on cognitive functioning in this young population of GCT survivors. Particular attention should be given to

systematically assessing cognitive impairment in GCT survivors to mitigate its effects on quality of life. Furthermore, integrating specific intervention including cognitive rehabilitation, mental health interventions, fatigue management and coping strategies for CRCI into GCT survivorship care plans may significantly enhance long-term outcomes for these patients.

We also found that sexual life was impaired in both GCT and SCST subgroups even five years after surgery and chemotherapy. While long-term sexual concerns as captured by FACT-O items were more prominent in GCT survivors, a substantial proportion of SCST survivors also reported a less fulfilling sexual life than CFW, suggesting that sexual counseling may be relevant for both groups. This deterioration of sexual QoL is consistent with findings from previous studies (40) (41). Compared to controls, GCT survivors have been shown to report significantly more reproductive concerns, lower levels of sexual satisfaction, and diminished sexual QoL (40). In a cohort of 132 female GCT survivors, participants reported significantly greater reproductive concerns ($P < .0001$), reduced sexual pleasure ($P = .003$), and lower sexual QoL scores ($P = .001$) than controls (42). Interestingly, while these survivors expressed more distress related to fertility and sexual function, they also reported enhanced appreciation of life and higher levels of emotional social support (40), underscoring the complexity of psychosocial adaptation post-treatment. Surgical approach appears to play a role in sexual outcomes: sexual QoL has been shown to be better following conservative (fertility-sparing) surgery compared to radical procedures (15). Although recovery of menses and fertility following BEP chemotherapy is generally favorable (43) (44), the risk of premature menopause and premature ovarian insufficiency remains a significant concern (45). Despite the availability of international guidelines addressing survivorship care and reproductive health in GCT patients (46), including recommendation for HRT use which is not contraindicated in GCT, these are not consistently implemented in clinical practice, highlighting the need for more structured and personalized survivorship care pathways.

This multicentric (19 centers of the French national TMRG network) study, focusing on rare ovarian tumors, has a large population and a long follow-up period. Comprehensive assessment of the different dimensions of QoL as well as personal and professional outcomes has been exhaustively performed. The comparison with matched CFW allows for a more accurate assessment of deviations from the norm, thereby reinforcing the strength of the conclusion. Although direct comparison between GCT and SCST survivors was not possible because of population differences, the distinction between SCST and GCT survivors' outcomes, in comparison with matched CFW, brights new light on the specificities of survivorship outcomes in each subgroup. A limit of this study concerns the CFW group, sourced from the "Seintinelles" network, which consists of volunteers who are informed about cancer and its risk factors. Other limitations are the lack of statistical power due to the small sample size of subgroups (which is inevitable when studying rare tumors), and the number of statistical comparisons performed, which may increase the risk of type I error. This cross-sectional study is not able to assess the temporal sequence of onset of the adverse effects and sequelae identified in the patients. Although this study is not a longitudinal assessment of QoL over time, the evaluation of the different QoL domains is comprehensive and reported major information to prepare future long-term survivorship care plans for these patients.

CONCLUSIONS

For the first time, this study highlights distinct long-term survivorship profiles in ovarian GCT and SCST survivors treated with the same combination of surgery and chemotherapy. Compared with CFW, GCT survivors experience higher rates of premature menopause, impaired sexual quality of life, and cancer-related cognitive impairment, with potential socio-professional implications. In contrast, SCST survivors are particularly affected by persistent fatigue and severe peripheral neuropathy, with overweight emerging as a factor associated with these outcomes. Fatigue may represent a pivotal driver of long-term quality of life in this population, given its association with persistent sequelae such as neuropathy in SCST survivors and cognitive impairment in GCT survivors.

SCST and GCT patients experiment different type of sequelae that impact their survivorship in different manners for each. These findings underscore the need for tumor-specific survivorship strategies. Early detection and targeted management of these sequelae, may improve long-term QoL of this young population of rare ovarian cancer survivors.

Abbreviations

BEP
Bleomycine Etoposide Cisplatinum
BMI
Body Mass Index
CI
Confidence interval
CRCI
Chemotherapy related cognition impairment
CT
Chemotherapy
FACT-Cog
Functional assessment of cancer therapy scale, module for cognition
FACT-G
Functional assessment of cancer therapy scale, general
FACT/GOG-NTX
Functional assessment of cancer therapy scale, Peripheral Neurotoxicity Questionnaire
FACT-O
Functional assessment of cancer therapy scale, module for ovarian cancer
FIGO
International Federation of Gynecology and Obstetrics
GCT
Germ cell tumors
GINECO group

Groupe d’Investigateurs Nationaux pour l’Étude des Cancers Ovariens et du sein
GOG
Gynecologic Oncology Group
HADS
Hospital Anxiety and Depression Scale
HRT
Hormone replacement therapy
HW
Healthy Women
IPAQ
Physical Activity Questionnaire
IQR
Interquartile range
ISI
Insomnia Severity Index
MFI-20
Multidimensional Fatigue Inventory
PCI
Perceived cognitive impairment
POI
Premature ovarian insufficiency
QoL
Quality of life
SCST
sex cord and stromal tumors
TMRG
Tumeurs malignes rares gynécologiques

Declarations

Ethics approval and consent to participate

The study was approved by Ile de France V ethics committee on 10th January 2018, ID RCB: 2017-A03028-45. Informed consent form was signed by every patient who has been included in the study (inform consent form available on request).

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author, Coraline DUBOT, upon reasonable request. Restrictions apply to the availability of these data due to ethical and privacy concerns.

Competing interests

Coraline Dubot: Payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events: GSK, AMGEN, MSD; Support for attending meetings and/or travel: Astra Zeneca, MSD, GSK, Eisai, Novartis, Lilly, AbbVie, PharmaAnd

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

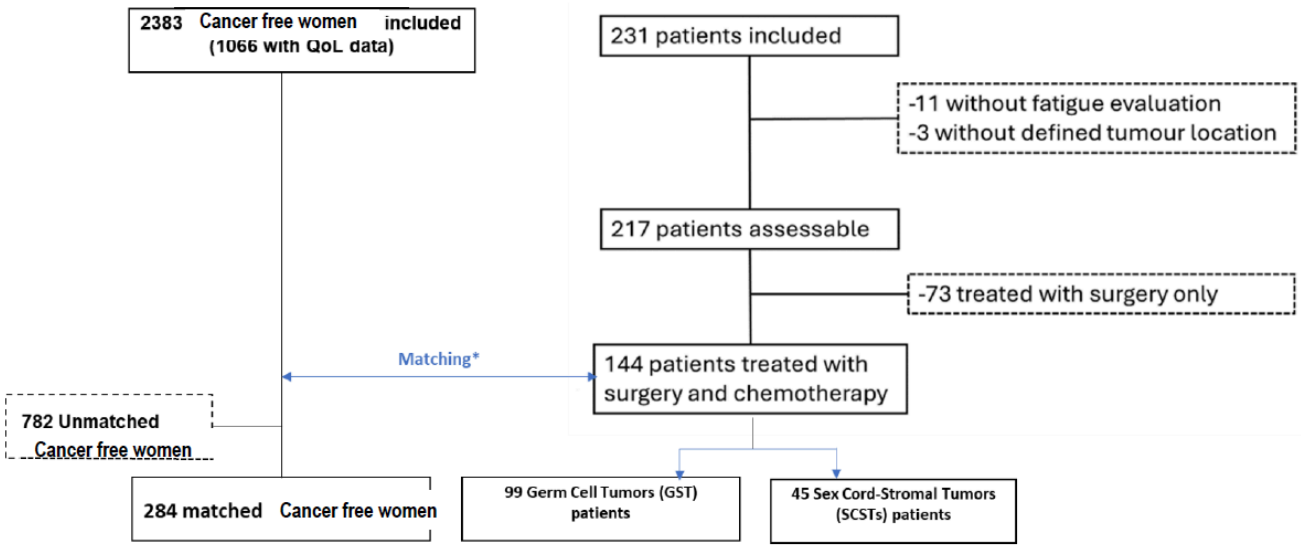

Figure 1

Flow-chart

* Matching (2 :1 by nearest neighbor propensity score matching) on age and level of education

Supplementary Files

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