GCIG-Consensus guideline for long-term survivorship in gynecologic cancer

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GCIG-Consensus guideline for Long-term survivorship in gynecologic Cancer: A position paper from the gynecologic cancer Intergroup (GCIG) symptom benefit committee

H. Woopen [a,*], J. Sehouli [a], A. Davis [b], Y.C. Lee [b], P.A. Cohen [b], A. Ferrero [c], N. Gleeson [d], A. Jhingran [e], Y. Kajimoto [f], J. Mayadev [e], M.P. Barretina-Ginesta [g], S. Sundar [h], N. Suzuki [i], E. van Dorst [j], F. Joly [k]

[a] NOGGO-North-Eastern German Society of Gynecological Oncology, Germany
[b] ANZGOG - Australia New Zealand Gynaecological Oncology Group, Australia
[c] MANGO - Mario Negri Gynecologic Oncology Group, Italy
[d] Cancer Trials Ireland, Ireland
[e] GOG Foundation, Gynecologic Oncology Group Foundation, United States
[f] Gotic-North Kanto Gynecologic Cancer Clinical Trials Consortium, Japan
[g] GEICO-El Grupo Español de Investigación en Cáncer de Ovario, Spain
[h] NCRI/BGCS-British Gynaecological Cancer Society, United Kingdom
[i] JGOG-Japanese Gynecologic Oncology Group, Japan
[j] EORTC-DGOG-The Dutch Gynecological Oncology Group and European Organisation for Research and Treatment of Cancer, Belgium and The Netherlands
[k] GINECO-Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, France

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ABSTRACT

Introduction: Long-term survivors of gynecological cancers may be cured but still have ongoing health concerns and long-term side effects following cancer treatment. The aim of this brainstorming meeting was to develop recommendations for long-term follow-up for survivors from gynecologic cancer.

Methods: International experts, representing each member group within the Gynecologic Cancer InterGroup (GCIG), met to define long-term survival, propose guidelines for long term follow-up and propose ways to implement long term survivorship follow-up in clinical trials involving gynecological cancers.

Results: Long-term survival with/from gynecological cancers was defined as survival of at least five years from diagnosis, irrespective of disease recurrences. Review of the literature showed that more than 50% of cancer survivors with gynecological cancer still experienced health concerns/long-term side effects. Main side effects included neurologic symptoms, sleep disturbance, fatigue, sexual dysfunction, bowel and urinary problems and lymphedema. In this article, long-term side effects are discussed in detail and treatment options are proposed. Screening for second primary cancers and lifestyle counselling (nutrition, physical activity, mental health) may improve quality of life and overall health status, as well as prevent cardiovascular events. Clinical trials should address cancer survivorship and report patient reported outcome measures (PROMs) for cancer survivors.

Conclusion: Long-term survivors after gynecological cancer have unique longer term challenges that need to be addressed systematically by care givers. Follow-up after completing treatment for primary gynecological cancer should be offered lifelong. Survivorship care plans may help to summarize cancer history, long-term side effects and to give information on health promotion and prevention.

* Corresponding author at: Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Department of Gynecology with Center for Oncological Surgery, Augustenburger Platz 1, 13353 Berlin, Germany.

E-mail addresses: hannah.woopen@charite.de (H. Woopen), jalid.sehouli@charite.de (J. Sehouli), alison.davis@act.gov.au (A. Davis), yehchen.lee@ctc.usyd.edu.au (Y.C. Lee), paul.cohen@uwa.edu.au (P.A. Cohen), ferrero@unito.it (A. Ferrero), noreengleeson@dubgyn.org (N. Gleeson), ajhingra@mdanderson.org (A. Jhingran), ykajimoto234@gmail.com (Y. Kajimoto), jmayadev@ucsd.edu (J. Mayadev), mpbarretina@iconcologia.net (M.P. Barretina-Ginesta), s.s.sundar@bham.ac.uk (S. Sundar), nao@marianna-u.ac.jp (N. Suzuki), e.vandorst@umcutrecht.nl (E. van Dorst), f.joly@baclesse.unicancer.fr (F. Joly).

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Introduction

The incidence of gynecological cancers is rising due to the increasing age of the population and environmental factors, with 14 million new cancer diagnoses each year. However, due to improved screening methods and treatment strategies, the number of long-term gynecologic cancer survivors is also increasing. A large number of patients with endometrial, vulvar and cervical cancer are cured with treatment and a third of patients with ovarian cancers become long-term survivors [1]. Recommendations for cancer survivorship care have been published stressing the need for survivorship care planning and coordination between specialists and primary health care providers (i.e., general practitioners). These include strategies for surveillance for recurrence and second primary cancers, prevention and detection of post-treatment psychological and physical effects, and interventions to manage cancer and treatment sequelae [2,3]. However, these recommendations have generally focused on the first 5 years post diagnosis or end of treatments, when patients are generally under the supervision of their cancer specialist/s. After this period, patients are frequently referred back to their primary care physician or gynecologist as the risk of cancer recurrence at this stage is generally low. However patients may still have ongoing concerns and treatment related issues requiring attention [4] and primary care physicians and gynecologists are not necessarily aware of the specific needs of long-term gynecologic cancer survivors. Better information and guidance for the primary caregiver or gynecologist are therefore needed [5] as well as for the gynecologic cancer survivor who may have limited knowledge of the potential long-term side effects of cancer treatments and what the follow-up should include [6].

Given the increasing number of long-term gynecologic cancer survivors, it is important that clinical trials include long-term follow-up to assess not only survival outcomes, but also long-term toxicities and quality of life. This poses challenges for researchers in terms of feasibility and added cost. In parallel, there are many unanswered research questions relating to long-term gynecologic cancer survivors which need a new generation of dedicated studies. Examples include, i) how to better coordinate and deliver information, ii) how to prevent and treat long-term side effects, iii) how to predict patients who are likely to experience long-term side effects [7,8].

The Gynecologic Cancer Intergroup (GCIG) symptom benefit committee organized a brainstorming meeting in Athens in November 2019 with representatives from the different GCIG member groups to discuss different aspects of quality of life. The objectives of the survivorship working group were to consensually define long-term survival in gynecologic cancer patients, to summarize the existing literature regarding long-term toxicities and needs of patients, to propose guidelines for clinical long-term surveillance and implementation of long-term gynecologic cancer survivorship into clinical trials.

Methods

Long-term survivorship was one of four brainstorming topics discussed by delegates of the different international member groups of the Gynecologic Cancer Intergroup (GCIG) symptom benefit committee in Athens in November 2019. Fifteen delegates were chosen from the different international study group members of the GCIG. As part of the meeting preparation the goals of the working group for long-term survivorship were defined as follows: definition of long-term survival in gynecologic oncology, review of the existing literature, proposition of guidelines to follow long-term side effects and brainstorming how to implement gynecologic cancer survivorship in clinical trials.

Four meetings (three virtual and one face-to-face meeting) were conducted: the first one to define the objective of the brainstorming meeting; the second to identify the long-term problems among gynecologic cancer survivors; the third to discuss and validate (via votes) the list of long-term concerns and the proposed recommendations, and the last to endorse the survivorship plan.

Firstly, a comprehensive summary of the literature and experience of the participating study group members with long-term survival were circulated. The definition of long-term survivorship and the proposed guidelines were discussed extensively within the group before the face-to-face meeting so that voting was possible during the meeting. Experiences and country-specific practices were taken into account. During the meeting in Athens, voting took place not only on the definition of long-term survival but also on each point of the recommended guidelines outlined below. During the first meeting the group decided that long-term survival should also be addressed in clinical trials, as discussed below. After the meeting, the written proposal for a guideline on long-term follow-up was shared with the delegates again. All proposals were reviewed by patient advocacy groups and full consensus was reached.

Definition of long-term survivors with gynecologic cancer

There is no universally accepted, unique definition of long-term survival after gynecologic cancer. Definitions in the literature for survivorship range from time of completion of first-line treatment to five, eight or ten years after initial diagnosis [9–12]. This variability makes comparisons between studies on survivorship challenging and one goal of the meeting was to agree on a definition of long-term survival in gynecologic cancer that could be incorporated in future studies within the GCIG.

The brainstorming group reached a consensus that long-term survivorship be defined as survival for at least five years after initial diagnosis irrespective of the development of disease recurrence – this was the result of the group voting without a dissentient vote. This decision was based on the fact that follow-up is routinely performed by specialists treating gynecological cancers for the first five years in most countries; after this period the follow-up is delegated to the treating primary care physician or gynecologist.

State of the art

Quality of life and long-term toxicities in long-term survivors – Review of the literature

In general, patients report improvement in quality of life over the years after cancer diagnosis in all domains (physical function, role function, emotional function, cognitive function and social function) [13]. Although long-term survivors may be cured from cancer, they frequently experience long-term toxicities relating to their treatment. In a survey of long-term survivors with ovarian cancer, more than half of the survivors had at least one tumor-/therapy-related symptom after eight years [14]. Another survey of long-term survivors reported that higher numbers of cancer survivors consulted a general practitioner (90% vs 68%) or their oncologist/specialist (68% vs 15%) compared to an age-matched population in a timeframe of 12 months [15]. Three main domains have been defined to potentially impact cancer survivors: physical health, mental health and social health [13].

In a survey involving 1,029 long term survivors of gynecological cancers (median 4.9 years post diagnosis) many reported ongoing symptoms suggestive of residual side effects from prior treatment. The ten most common side-effects were fatigue (44.3%), sexual dysfunction (35.7%), sleep disturbance (35.3%), neurologic symptoms (35.2%), urinary dysfunction (33.0%), bowel problems (31.2%), memory problems (30.8%), depression (26.4%), anxiety (19.3%) and lymphedema (17.6%) [6]. Changes in sexuality after gynecological cancer treatment were noted in 55% of the women including distortion of self-image (45%), dry vaginal mucosa (25%), fear of physical harm and dyspareunia (20%) [16]. Gynecological cancer survivors state that they have a high need for information regarding side-effects, likelihood of a cure from cancer and different types of treatment including the different potential side effects [17]. Despite long-term toxicities and the patients'

wish for more information, there are no guidelines available for gynecological cancer survivorship.

Beyond the recognized long-term issues associated with systemic chemotherapy, including hypertension, renal impairment and neuropathy, future attention should also be given to long-term assessment of toxicity of the newer targeted therapies such as PARP- inhibitors (i.e. myelodysplastic syndrome, leukemia) and check point inhibitors (endocrinopathies such as diabetes and hypothyroidism) [18].

Cervical cancer

Long-term survivorship is very common in cervical cancer, especially in FIGO stage I with 5-year-survival rates of 92% and in locally advanced stages II and III with 5-year-survival rates of 58% according to the American Cancer Society (https://www.cancer.org/research/cancer-facts-statistics.html). In a study involving 168 long-term survivors after cervical cancer with a median follow-up of 6.8 years (range: 4.1–12.5 years) there was no significant difference in global quality of life between cervical cancer survivors and healthy controls. However, cervical cancer survivors (treated with combined radiation-chemotherapy in 84% and radiation therapy alone in 16%) showed higher scores regarding symptom experience, body image, sexual/vaginal dysfunction, lymphedema, peripheral neuropathy and sexual worry [19]. Cervical cancer survivors report more sexual discomfort, pain with penetration and vaginal dryness in a study comparing 51 survivors (5–10 year survival) and 50 age-matched controls. There are mixed results regarding long-term effects of radiation on sexuality [20].

Le Borgne et al. showed in a survey with 173 patients and 594 healthy controls that cervical cancer survivors had an impaired long-term global health status 15 years after initial diagnosis compared to healthy controls. Lower scores were also reached regarding emotional functioning, mental fatigue and lymphedema after 15 years with more symptoms in patients treated with radiotherapy [21]. Within the Cancer Registry in the Netherlands, secondary cancers occurred in 5.6% of patients after cervical cancer. Most secondary cancers were smoking- and irradiation related. Risk of secondary cancer remained high after ten years [22]. Overall quality of life was shown to have an impact in survival in cervical cancer survivors with a mean follow-up time of 9.3 years of follow-up in the California Cancer Surveillance Program [23]. Differences regarding financial concerns were found in five-year survivors, but were not reported among a group of women with more than 10 years of follow-up. In the same cohort there were no significant differences regarding marital status, education and employment status between cervical cancer survivors and controls [21].

Ovarian cancer

Despite the high mortality in ovarian cancer around a third of women diagnosed with ovarian cancer are long-term survivors [2425]. More than 50% of these long-term survivors report medical complaints which are independent of current treatments [14]. In a trial from Norway of 189 ovarian cancer survivors with a median follow-up of 6 years, survivors showed lower scores in physical, role, cognitive, emotional, and social function in the EORTC quality of life questionnaire QLQ-C30 compared to controls. There was no significant difference in global quality of life. Survivors consulted general practitioners more frequently and use of medications was more common. Levels of anxiety as well as somatic complaints such as fatigue and gastrointestinal symptoms were also higher [26].

In the French Vivrovaire study, from the GINECO study group, ovarian cancer survivors with a mean time from chemotherapy of six years reported higher levels of fatigue, poorer quality of sleep, more depression, and neurotoxicity in multivariate analyses. Global quality of life assessed with the FACT-G questionnaire did not differ between survivors and controls. [27] The international OvQuest survey, initiated by the ANZGOG study group, showed high levels of neuropathy (78%), fatigue (60%), mood disturbance (48%) and insomnia (59%) in ovarian cancer patients with a mean of 2 years after completion of adjuvant chemotherapy [28].

The international ENGOT and GCIG survey "Expression VI – Carolin meets HANNA" initiated by the NOGGO study group is recruiting long-term survivors who have survived at least eight years after initial diagnosis. Long-term survivors reported a very good, good, or satisfying health status in 90%. Symptoms were, however, reported in 53%. Side effects with the greatest impact during the course of the disease were alopecia, fatigue, nausea/vomiting, pain and gastrointestinal problems. At the timepoint of recruitment fatigue (24%), pain (20%), gastrointestinal complaints (18%), polyneuropathy (18%) and memory problems (17%) were the side effects that still had an impact on quality of life. There was no difference in side effects between survivors receiving current treatment and survivors without current cancer treatment. In total, 52% of long-term survivors still regard themselves as cancer patients [14]. Long-term survivors with fatigue experience more long-term side effects than long-term survivors without fatigue. Fatigue is associated with worse health status and higher distress levels [29].

Polyneuropathy was a long-lasting side effect in a survey of 129 ovarian cancer patients. In 20% of patients polyneuropathy was still present after five years and even at years 11–12 there were still 8% of survivors with polyneuropathy. Neuropathy symptoms were associated with lower levels of functioning and quality of life as well as other long-term side effects [30]. Sexual worries are also frequent in long-term survivors with ovarian cancer. In general, 63% of ovarian cancer patients say that their sexual life has changed after diagnosis and 46% are sexually active. Main sexual worries include pain/discomfort (in 77%) and vaginal dryness (in 87%) [31]. There was a lower overall score for long-term survivors compared to healthy controls for other items in the female sexual function index (FSFI) questionnaire such as dryness, discomfort, and desire, which could also be shown for sexually active long-term survivors (54% of long-term survivors were sexually active) [32]. The above mentioned Vivrovaire study from the GINECO study group showed that there is a high frequency of menopausal symptoms in ovarian cancer survivors: 73% of survivors with surgically induced menopause have menopausal symptoms while only 5.4% take hormonal replacement therapy although there were no contraindications [33]. Arora et al. published a population-based study from British Columbia with 6427 patients with ovarian cancer from 1990 to 2014 with 4246 deaths analyzing the causes of death in ovarian cancer patients. Ovarian cancer remains the primary cause of death within 15 years after initial cancer diagnosis. Mortality due to second primary cancers, cardiovascular disease, and external causes such as falls, increases with time since diagnosis. The authors postulated the importance of prevention/early detection of secondary cancer and fall prevention/prophylaxis of osteoporosis [34]. Secondary cancer was observed in 7.5% in an analysis of more than 4000 ovarian long-term survivors. The most common secondary cancers were breast cancer followed by colon cancer and rectal cancer [35].

Endometrial cancer

Most endometrial cancer patients are diagnosed in FIGO stage I with a 5-year survival rate of 95% according to the American Cancer Society so long-term survivorship is very common. Global quality of life was not significantly worse in endometrial cancer survivors in a survey of 328 patients (80% stage I) with at least three years follow-up [36]. This survey used the EORTC QLQ-C30 questionnaire and the only significant difference that was found was emotional functioning between survivors who were treated with surgery alone (mean score 84.83) and survivors who were treated with surgery and radiotherapy (mean score 57.43). There was no difference between survivors treated with surgery and controls [36]. Gao et al. have analyzed sexual worries in endometrial cancer patients (time since diagnosis: 33% $>$ 5 years, 27% 3–5 years and 40% $\leq$ 3 years). In this analysis 69% of survivors had sexual problems

and 56% never had sexual intercourse with their partners after cancer surgery. The main reasons were psychological problems in more than 30%, no interest in sex in almost 25% and no partner in more than 15% [37]. A large population-based cohort study with 2,648 endometrial cancer survivors compared long-term cardiovascular outcomes among endometrial cancer survivors and an age-matched general population. Cardiovascular risks were higher in the survivor group especially within the first five years after diagnosis. After 5–10 years after initial diagnosis, survivors were 33% more likely to be diagnosed with heart disease. The hazard ratio for the risk of hypertension was 1.25 (99% confidence interval 1.11–1.42) after five and ten years after initial diagnosis [38]. Within the same cohort Soisson et al. have also studied adverse genitourinary outcomes and could show that 37.4% of survivors were diagnosed with a urinary system disorder and 36.9% with a genital tract disorder. The risk of genitourinary disease was higher in survivors who were treated with chemotherapy or radiation compared to surgery alone [38,39,40].

However, recent methods of external beam radiotherapy used, i.e. tri-dimensional conformal (3DCRT), intensity-modulated radiotherapy (IMRT) or stereotactic ablative radiotherapy (SABR) have resulted in a significant reduction of acute and late toxicity [42]. In the same line, with the increasing use of three-dimensional image-guided brachytherapy, there is an opportunity to increase the level of expertise in the radiation oncology community who treat cancer of uterus and to better control the toxicities [43].

Proposed guidelines for long-term follow up

We identified a **minimum checklist** of the principal long-term concerns among gynecologic cancer survivors to focus the follow-up on: i) surveillance of recurrence; ii) prevention of new secondary cancers; iii) prevention, diagnosis and treatment of long-term side effects induced by the treatments (i. e. lymphedema, neuropathy, urinary/digestive disorders, fatigue, chronic pain, osteoporosis, sexual and hormonal disorders, cognitive complaints; (iv) other health concerns, particularly sleep disorders, emotional difficulties and social difficulties; v) secondary and tertiary prevention with a particular focus on cardiovascular disease with lifestyle counselling.

The minimum checklist of the most frequent long-term side effects is summarized in Table 1.

Gynecological cancer follow-up

Most relapses will occur within the first two years; follow-up care is usually offered within the first five years after initial diagnosis and patients are often discharged from gynecologic oncology clinics after five years in most countries. However, we propose routine oncology follow-up among gynecological survivors free of relapse based on annual thorough history taking, clinical and gynecological examination; laboratory investigations and imaging can be added if needed. Strategies for follow-up are to be adapted according to the countries practice and adjusted to risk factors [44,45].

Table 1
Minimum Checklist of potential main long-term concerns among gynecologic cancer survivors.

Fatigue
Chemotherapy induced polyneuropathy (CIPN)
Post-chemotherapy cognitive impairment (PCCI)
Pain
Depression and psychological concerns
Gastrointestinal concerns (nausea, constipation, diarrhea, loss of appetite etc.)
Urinary/stool incontinence
Sexuality concerns
Osteoporosis/Bone health
Cardiotoxicity
Lymphedema
Sleep disorders
Secondary and new primary cancers
Postmenopausal symptoms
Reproductive issues (if indicated)
Social issues

Secondary and new primary cancers

Gynecological cancer survivors and their treating physicians must be aware of the risk of secondary and new primary cancers, (particularly in case of pelvic irradiation or PARP inhibitor maintenance treatment) even if the risk is low. Second primary cancers could be found in 6.3% in a SEER database with 301,210 gynecological cancer survivors [46]. In ovarian cancer survivors secondary new cancer (not metastases) was diagnosed in 7.6% after a median of 6.5 years [47]. Information should also be given on the risk of cancers linked with other risk factors such as HPV, smoking, obesity as part of the lifestyle counselling [Table 2]. After pelvic irradiation the risk of a second pelvic cancer remains high, even several decades later and an annual clinical pelvic exam is the recommendation [40,48]. There is no specific recommendation for the follow-up of other cancers and the follow-up of new cancers from other sites is the same as the general population. Therefore cancer survivors should be actively offered the same cancer screening programs as the general population. For ovarian and endometrial cancer patients, during long-term follow-up, practitioners should verify that genetic risk assessment especially for breast and colorectal cancers has been proposed to all the patients at diagnosis. If patients have not received genetic counselling at primary diagnosis it is recommended to revisit this issue again during follow-up. An offer to repeat genetic counselling should be also made in patients with a family history of cancer even if there were no common pathogenic gene variants detected at diagnosis. For patients with a familial genetic predisposition, long-term follow-up is usually continued by oncologists or genetic specialists according to national guidelines and is not the focus of this article. Of special interest is

Table 2
New or second cancers.

Cancer types	RR	Whole population*	Specific population
Ovarian	Second primary cancer in 7.5% [35] Type: Solid tumors: breast, colon, lung Hematological malignancies (i.e. after PARP and chemotherapy)	Information Follow-up as general population Long-term gynecological follow-up Annual complete blood count if PARP inhibitors	Germline *BRCA1 or BRCA2* pathogenic variant carriers, MSI-high (Lynch syndrome) i.e. dedicated surveillance
Cervix/ Vulvar	Secondary primary cancer in 5.6% [22] Type: especially smoking- and irradiation-related tumors (pelvic cancers, head and neck cancers, pulmonary cancer)	Information Prevention: smoking cessation Long-term gynecological follow-up follow-up as general population	NA
Endometrial	Secondary primary Cancer in 7.0% [41] Type: ovarian, colorectal, bladder, kidney cancer Irradiation: sarcoma and other pelvic cancers	Information Long- term gynecological follow-up follow-up as general population	MSI-high (Lynch syndrome), germline *BRCA1* or *BRCA2* pathogenic variant carriers i.e. dedicated surveillance

RR: risk of second cancer, TT: treatments Sarcoma.
NA: not applicable * Participation to national cancer screening programs.
Reference: [48].

familial breast and ovarian cancer syndrome and Lynch-syndrome [49]. The incidence of breast cancer following an ovarian cancer diagnosis in carriers of germline *BRCA1/2* mutations increases over time and breast surveillance is recommended [50]. Preventative mastectomy may be warranted in germline BRCA1/2 mutation carrying ovarian cancer patients with early-stage disease and in those who have survived without recurrence for more than 10 years [51]. Gynecological cancer survivors without an identified germline mutation should participate in the standard breast, colorectal and melanoma national screening programs or follow the international guidelines; in the rare case of fertility preserving therapy, cervical cancer screening according to national guidelines is mandatory. An overview of recommendations regarding secondary/new cancers can be found in Tables 2 and 3.

Based on the broad introduction of PARP-inhibitors secondary hematological malignancies should also be considered in the monitoring and follow-up of patients who received or still under treatment with PARP inhibitors and other cancer treatments [18,52]. Long-term safety analyses of the ENGOT-Ovar16/NOVA trial as well as the study-19 showed that the onset of acute myeloid leukemia and myelodysplastic syndrome are rare but severe complications [52,53]. Side effects from maintenance therapy usually appear within the first months of treatment but may persist and can also develop after many months after treatment initiation [53].

In the era of immunotherapy and new targeted therapies new side effects are generated and should be closely monitored. Some side effects, especially endocrinological and neurological side effects may occur later during treatment and can persist. Long-term side effects are often underreported or may not be known yet [54].

Side-effects induced by treatments

Treatment-induced side effects may persist with a negative impact on quality of life [28,55]. It is particularly the case of fatigue, lymphedema, sexual disorders and neuropathy.

Patients undergoing pelvic surgery are particularly at risk for lower extremity ***lymphedema.*** Lymphedema risk increases over time with a negative impact on quality of life [56]. Detecting early lymphedema is important because it may be reversible or manageable with early physiotherapy. Regular examination is required even among patients without lymph node dissection (i.e. en-bloc-resection, bowel resection). Education of patients to reduce obesity, and increase physical activity, as well as infection risk minimization is recommended. If lymphedema needs treatment, patients should be referred to specialists (i.e. lymphedema therapists). The principle of treatment is decongestive therapy: physiotherapy and compression therapy. These approaches must be regularly repeated to maximize treatment effect [57]. If conservative treatment is not sufficient, micro vessel surgery was shown to be an effective treatment method and should be considered [58].

Table 3
Screening of breast, colorectal and cervical cancer, in women without genetic predisposition or mutation.

Cancer types	Breast	Colo-rectal	Cervix
Ovarian	- Genetic risk assessment should be offered to all patients - Standard screening*	- Genetic risk assessment - Standard screening	- NA unless if cervix retained
Cervix/ Vulvar	- Standard screening	-Standard screening	NA
Endometrial	- Genetic risk - Standard screening	- Genetic risk assessment - Standard screening	NA

* adjusted to national guidelines.

Table 4
Menopausal symptoms and osteoporosis.

Cancer types	HRT*	Hot Flashes TT**	Osteoporosis
Ovarian	No CI, excepted for hormone sensitive tumor (i.e. low-grade ovarian cancer, endometrioid ovarian cancer, granulosa cell tumors) Physical activity and lifestyle changes may also help	No CI	Prevention: Physical activity, smoking cessation, Calcium and Vitamin D alimentation +/-supplementation baseline DEXA, if abnormal continuous monitoring is recommended***
Cervix/ vulvar	No CI Combination HRT until natural age of menopause and then according to symptoms Physical activity and lifestyle changes may also help	No CI	Treatment: Bisphosphonates or denosumab, Vit D if osteoporosis is evident
Endometrial	No CI: serous Precaution: endometroid, low-grade tumors (including adenocarcinoma and sarcoma) Physical activity and lifestyle changes may also help	No CI	

CI: contraindication.
For all the patients with treatment induced menopause and for patients with symptoms of natural menopause.
* HRT: hormone replacement therapy: Oestrogens without progestins preferred if hysterectomy. Oral +/- local topics.
** Hot flushes treatments: if not improve by HRT or CI HRT: Selective Serotonin Reuptake Inhibitors (Venlafaxine), norepinephrine Reuptake inhibitors. Gabapentinoids, Clonidine,No pharmacological therapy: cognitive behavioral therapy.
*** DEXA (dual absorptiometry) particularly if early menopause.

Neuropathy

Neuropathy is an underestimated long-term side effect following taxane and/or platinum-based chemotherapy. The peripheral sensory neuropathy related to taxanes is dose-dependent and is more frequent in patients with comorbidities also associated with neuropathy such as diabetes (sensory) and older age; it may persist lifelong after treatment (15 to 40% after taxane chemotherapy) and can precipitate falls among elderly patients. There are predictors of chronic neuropathy or susceptibility for severe neuropathy symptoms based on the chemotherapy duration or dosage. Clinical identification of residual neuropathy intensity and impact on quality of life should be included in long-term follow-up. Self-reporting questionnaires dedicated to neuropathy can be used (for example the CIPN subscale of the EORTC QOL Questionnaire or the Module NTX of the FACT questionnaire). If neuropathy has been present for a long time, the objective of the treating physician is to detect and prevent comorbidities that may worsen the symptom and then give counselling to cope with it. Supportive care such as physiotherapy, physical activity, referral to podiatrists, patient education i.e. adequate footwear, acupuncture, support in daily activities can be helpful. Vitamin B supplementation can be discussed. If neuropathy induces chronic pain, patients can be referred to a neurologist for further investigation or to introduce medication including gabapentin, selective serotonin reuptake Inhibitor (i.e. venlafaxine), or norepinephrine reuptake inhibitor with usually limited efficacy [59].

Menopausal symptoms and osteoporosis *(Table 4)*

Gynecologic cancer patients are at risk of osteoporosis particularly if they experience early-induced menopause related to oophorectomy or treatment induced menopause and/or pelvic irradiation with higher risk of bone loss and insufficiency fractures [60]. Bone density status should be assessed after treatment and should be monitored over time. Immediate post-treatment baseline dual absorptiometry (DEXA scan) is recommended for all patients treated for a gynecologic cancer; with regular long-term monitoring considered if abnormal at baseline. Risk minimization is recommended with supplementation of calcium when dietary calcium intake is insufficient to achieve 1300 mg/day, and vitamin D, weight-bearing exercise, diet and smoking cessation. Osteoporosis is treated with bisphosphonates or denosumab and vitamin D. The prevention and management of osteoporosis should be the same as the general population.

Surgery-induced menopause often leads to vasomotor symptoms which may be more severe than after natural menopause. These symptoms that may persist for many years after surgery or after natural menopause and can have a negative impact on quality of life, sleep and mood [61]. Although the level of supportive evidence is variable, there are few formal contraindications for hormone replacement therapy among gynecological cancer survivors who suffer from menopausal symptoms. There is no evidence to contraindicate the use of systemic or topical hormone therapy for women with cervical, vaginal or vulvar cancers, as these tumors are not hormone-dependent. The risk/benefit profile of hormone therapy is favorable for most of the non-epithelial and epithelial ovarian cancers (high grade, clear cell and mucinous) and for early-stage endometrial cancer patients. Due to the lack of data and/or a potential link to hormonal status, hormone treatment is contraindicated in patients with low-grade serous epithelial ovarian cancer, granulosa cell tumors, certain types of sarcoma (leiomyosarcoma and stromal sarcoma) and advanced endometrioid uterine adenocarcinoma [62,63]. A *meta*-analysis that investigated associations of hormone replacement therapy on oncologic outcomes of endometrial cancer survivors showed a significantly increased recurrence risk in black American women. However, these findings should be interpreted with caution due to several limitations of the *meta*-analysis including the quality of included studies that were mostly observational, lack of data regarding molecular subtypes of endometrioid carcinoma, and the inclusion of patients with only early stage disease [64]. A short-term administration in symptomatic survivors can be discussed individually. In women with early or premature menopause without other contraindications, hormone replacement therapy is recommended at least until the average age of natural menopause. For other patients with menopausal symptoms, management needs to be individualized. Hormone replacement therapy is based on estrogens without progesterone if hysterectomy has been performed, either as oral medication or topical. If the uterus has not been removed the addition of progesterone to estrogen is mandatory. In cases where hormone replacement treatment is contraindicated or persistent hot flushes, selective serotonin reuptake or norepinephrine re-uptake inhibitors can be used in conjunction with non-pharmacological approaches such as cognitive based therapy, yoga, acupuncture, auriculotherapy [65,66].

Sexuality concerns

Concerns about treatment-induced sexual dysfunction affects a large group of gynecologic cancer patients even if they are not sexually active. However, this topic is largely under-addressed because of barriers by the patients themselves and the health care providers who often lack experience and confidence in addressing the subject [67]. During follow-up, caregivers should regularly ask patients if they have any concerns regarding the effects of their cancer or treatment on sexuality issues or want to address this topic. Screening and identification of patients' issues relating to sexual health difficulties should be integrated into follow-up and if needed, separate consultation can be proposed. Many documents and tools exist to inform and assess sexual difficulties in cancer survivors though are not frequently used [67].

Caregivers can assess vaginal sexual health with a brief checklist or self-reported quality of life questionnaire dedicated to sexuality to facilitate communication about patient needs (example for questionnaires: Female sexual function index (FSFI), Female Sexuality and Sexual Dysfunction (FSDS), Sexual Quotient - Female Version (SQF) However, there is no gold standard and they cannot substitute face-to face meetings.

To help women to manage their concerns about their sexuality, education and information should be proposed for all patients and their partners (alone and/or together) preferably by specialized professionals. If a problem has been identified, clinicians need to have referral networks of specialized persons (gynecologists with experience in cancer survivorship care, physiotherapists, specialists in urogynecology, sexual counsellors, psychologists and psychiatrists). In different countries, dedicated multidisciplinary clinics of onco-sexology associated with sexuality group counselling have been developed and can be proposed.

Vaginal stenosis as a result of radiotherapy can often lead to intractable long-term complications, loss of sexual function, pain during medical pelvic exams, predisposition to trauma and infections, and even complete vaginal occlusion [68].

Some medications can help to improve treatment-induced symptoms: i) topical therapy such as moisturizers, vaginal estrogens, lubrication, hormone replacement for vaginal dryness or pain due to sexual intercourse; ii) vaginal dilators +/- regular sexual activity, behavioral and creative therapies for fibrosis and stenosis post irradiation. Laser therapy showed promising results in the therapy of vaginal stenosis. However, more clinical trials are needed in gynecological cancer survivors [69].

Genito-urinary and digestive disorders

Gynecologic cancer survivors have a higher prevalence of pelvic floor disorders (which include urinary incontinence, fecal incontinence, and pelvic organ prolapse) mainly linked to pelvic surgery [70]. Long-term irritative bladder symptoms can also appear after pelvic irradiation. These sequelae should be detected early and patients referred to specialists; treatments usually include education on lifestyle, rehabilitation (pelvic floor physical therapy), conservative treatments (i.e. biofeedback, pessary), and if needed surgery.

Constipation is a frequent complaint and patients should be advised about simple lifestyle counselling: physical activity, diet counselling, hydration, use of laxatives if needed. In the case of increase in symptoms without explanation, patients should be referred to a gastroenterologist for further investigation. The possibility of cancer recurrence or progression should also be considered.

To manage chronic diarrhea reported by some patients after irradiation, lifestyle counselling including diet counselling is important and if needed medications (i.e. loperamide or bulking agents such as psyllium husk) may be useful.

Chronic pain

Chronic pain affects one third of survivors and is often associated with poor quality of life [71]. Different components of treatment-related pain (neuropathic pain, post-surgery pain, musculoskeletal, gastrointestinal or genito-urinary pain) must be identified and different approaches can be proposed: physiotherapy approach and if necessary analgesics (according to standard guidelines). The pain is often multifactorial and patients can be referred to a pain clinic for more specialized interventions with multidisciplinary approaches [72].

Fatigue

More than half of ovarian cancer patients report fatigue during the course of the disease and fatigue is still present in 23% of long-term survivors [73]. Fatigue is a multidimensional problem with huge effect on cognition and cannot be compared to simple tiredness. Differential diagnoses such as depression, anemia and infection should be ruled out. Fatigue has a significant impact on quality of life. There are some strategies to help the patients to cope with fatigue [74,75]. It has been shown that patient education on healthy lifestyle including physical activity, improvement of sleep quality and psychosocial interventions can improve fatigue.

Post-chemotherapy cognitive impairment (PCCI)

Cognitive impairment following chemotherapy is a frequent long-term side effect, often linked with psychosocial disorders. However, this is an area of ongoing research to define causes and measure impact. Several studies have reported that patients report this side effect commonly, and discuss it with their doctors [76]. Differential diagnoses such as dementia syndromes (i.e. Alzheimer disease or vascular dementia), cerebral metastases, paraneoplastic (limbic) encephalitis, pseudo-dementia in depression or anxiety disorders should be excluded. It is also important to screen and treat patients for depression, anxiety, fatigue, pain, and sleep disturbance, as these can worsen cognitive impairment. Patients should be referred to a neurologist if needed. So far there is no specific therapy for PCCI. Physical activity, cognitive training, psychoeducational strategies memory aids, strict daily routine and stress reduction are recommended.

General long-term concerns and comorbidities

Many general issues concern long-term survivors including psychological distress and sleep disturbance. In long term survivors they are mainly linked to psycho-affective distress.

These issues must be detected and discussed with the patients. General quality of life questionnaires (i.e. EORTC-QLQ-C30 or SF 36), fatigue questionnaires (MFI, FACT-F EORTC -FA12 –subscale, ….), distress scale (Distress thermometer), cognitive questionnaires (Fact-Cog, memory test) can be used to help identify the impaired domains of QoL but they cannot replace the face to face discussion.

The long-term follow-up visit is centered on prevention, detection, and education for a healthy life [5]. Counselling of modifiable lifestyle factors (obesity, alcohol consumption, physical inactivity, balance of healthy diet, smoking) must be included in long-term follow-up. Bioelectrical impedance analysis and a food diary can help to assess the patients' nutrition and weight management. If needed, patients can be referred to a nutritionist. Benefits of exercise on health, fatigue, and mood should be explained to patients and regular physical exercise should be systematically promoted during the follow-up clinics for all survivors; patients can be referred to dedicated centers (with supervised exercise programs) to encourage them to integrate physical activity in their routine life.

Mental health and wellbeing should also be promoted. Many long-term survivors still regard themselves as cancer patients and many report a constant fear of cancer recurrence. Psycho-oncological counselling should be routinely offered and cognitive behavioral therapy, mindfulness-based exercises, creative therapies (e.g. creative writing, art therapy) are also encouraged. This may also avoid/reduce medications; anxiolytics and anti-depressants should be considered only if the other approaches are not effective or in cases of persistent important anxio-depressive syndrome.

Social issues are multiple and can persist over time. Difficulties associated with returning to work for younger patients, negative financial issues due to cancer and treatments should be regularly followed with the help of social workers if needed. Financial toxicity is especially dependent on health care and social security systems which are different in countries. As patients may not mention financial problems by their own, caregivers should address financial toxicity [77]. Loss of autonomy and needs of partners and/or caregivers are particularly important to identify, to maintain elderly patients at home after cancer [1,78,79]. Advocacy groups can also give information on survivorship care needs.

Comorbidities such as cardiovascular disease and diabetes are particularly prevalent among endometrial and ovarian cancer survivors. Prevention, detection, and follow-up with regular blood pressure monitoring and assessment of blood cardio-vascular risk factors (i.e. cholesterol, glucose, HbA1c) are recommended as part of the regular long-term follow-up. If cardiotoxic agents were administered, cardiological work-up including longitudinal strain echocardiography should be regularly performed.

Coordination of long-term follow-up care: Proposal of the GCIG gynecologic long term survivorship plan

Despite no proven impact of a survivorship care plan on cancer survivor outcomes and the efficiency of health care professionals, it can help and improve the spread of the information. Several organizations recommend that cancer survivors receive a survivorship care plan after their cancer treatment [80]. This document summarizes both the cancer diagnosis and treatment details in addition to long-term side effects/health concerns. It can improve survivors' self-reported adherence to medical recommendations and health care professionals' knowledge of survivorship care and late effects [81] (Supplementary Fig. 1).

There are some national initiatives for survivorship care plans after gynecologic cancer treatments. However, they have limited focus on the long-term (post 5 years) period corresponding to the transition between the follow-up by oncologists in specialized centers and the primary care physicians and gynecologists [982]. Moreover, the long-term surveillance and late complications of treatments are not well known by the patients, the providers, primary care physicians and gynecologists [3,83].

A dedicated "survivorship" clinic at the time of transition of follow-up from a specialized center to the primary care physician is the ideal opportunity to check for potential late sequelae, in a multidisciplinary approach for each patient. During this clinic, specific individualized problems, risks, and needs can be identified, the patient can be informed and educated, and the long-term follow-up organized with the appropriate health care provider. However, as it is difficult to generalize and dictate practice in varying settings, the GCIG group proposes the initiative of a long-term survivorship care plan document at the time of transition from specialist care. This plan focuses on long-term side effects and health maintenance after gynecologic cancer. A long-term survivorship care plan can help to communicate with general health providers and give the opportunity to transmit important information to the patients on long-term follow-up, particularly when the surveillance is entrusted to the general practitioner or gynecologist [9,83]. The coordination of health-care providers is crucial as there is frequently more than one problem/long-term side-effect and it is therefore recommended to define one main coordinating person who may be part of the survivorship clinic, the general practitioner or the gynecologist.

Next generation of clinical trials

In general, clinical trials focus on short-term results and do not report long-term clinical outcomes. We strongly recommend that long term outcomes such as toxicity and QoL are reported in gynecological cancer clinical trials, whenever practicable, to enhance knowledge about long-term impacts of a diagnosis and treatment of a gynecological cancer. Furthermore, QoL questionnaires usually address acute disease and treatment-related symptoms. Long-term toxicities are not addressed and psychological issues like fear of recurrence or return to work are not

covered. Long term patient-reported outcome measures (PROMS) should cover the full range of long-term toxicities also relevant for disease-free survivors such as fatigue, lymphedema, and cognitive impairment. Long term follow-up may not be cost effective; however, with new technologies, web-applications with annually self-reported questionnaires may be useful. Furthermore, we recommend the establishment of an international *meta*-database to identify prognostic and predictive markers in long-term survivors. We recommend the reporting of data on long-term survivors of every study at recruitment and to report their outcome separately. The GCIG also encourages dedicated patient surveys (such as GCIG-NOGGO-EXPRESSION 6) and interventional trials on lifestyle and social aspects for long-term gynecologic cancer survivors to improve quality of life.

Conclusion

The number of long-term survivors of gynecologic cancers is increasing. Cancer survivors may be cured from cancer, but frequently still report cancer- or treatment-related symptoms such as fatigue and peripheral neuropathy. In this article, the GCIG group proposes guidelines for lifelong follow-up care for gynecologic cancer survivors as well as recommendations for implementing survivorship into clinical trials.

CRediT authorship contribution statement

H. Woopen: Conceptualization, Writing – original draft, Resources, Validation, Writing – review & editing. **J. Sehouli:** Conceptualization, Writing – original draft, Resources, Validation, Writing – review & editing. **A. Davis:** Resources, Validation, Writing – review & editing. **Y. C. Lee:** Resources, Validation, Writing – review & editing. **P.A. Cohen:** Resources, Validation, Writing – review & editing. **A. Ferrero:** Resources, Validation, Writing – review & editing. **N. Gleeson:** Resources, Validation, Writing – review & editing. **A. Jhingran:** Resources, Validation, Writing – review & editing. **Y. Kajimoto:** Resources, Validation, Writing – review & editing. **J. Mayadev:** Resources, Validation, Writing – review & editing. **M.P. Barretina-Ginesta:** Resources, Validation, Writing – review & editing. **S. Sundar:** Resources, Validation, Writing – review & editing. **N. Suzuki:** Resources, Validation, Writing – review & editing. **E. van Dorst:** Resources, Validation, Writing – review & editing. **F. Joly:** Conceptualization, Writing – original draft, Resources, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of Interest

AD received support to attend the meeting by the Canberra Hospital Private Practice Fund, was part of an ovarian cancer advisory board for Astra Zeneca and is the RAC chair of ANZGOG.

YCL has received honoraria for educational events from the Limbic and for participation on Advisory Board from GSK.PAC has received honoraria for educational events from Seqirus and Astra Zeneca.

AF received payment for an educational event by Clovis, was part of an advisory board for MSD and GSK and was an (unpaid) council member of ESGO from 2016-2019.

AJ received consulting fees from Genentech.

YK is now an employee of MSD K.K.

JSM received travel support from the GOG Foundation and consulting fees from Merck, Astra Zeneca, Varian Medical Systems, Primmune and is cervix-co-chair of NRG Oncology.

MPMG received honoraria for lectures and travel support from Clovis Oncology, Astra Zeneca, MSD, GSK, Roche. She was part of an advisory board for Clovis Oncology, Astra Zeneca, MSD, GSK, Roche and Pharmamar. Receipt of medical writing from Astra Zeneca and GSK.

SS has received honoraria for educational events from AZ and GSK and for participation on Advisory Board from AZ.

HW, EVD, NG, SN and FJ declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2022.102396.

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