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Estrogen therapy in gynecological cancer survivors

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ABSTRACT

Treatment of gynecological cancer has significant impact on a woman's quality of life because it commonly includes removal of the uterus and ovaries, both being the core of a woman's femininity, whilst irradiation and chemotherapy, be they as primary therapy or when indicated as postoperative adjuvant therapy, will lead to ablation of ovarian function if the ovaries had not been removed. This will lead to an acute onset of menopausal symptoms, which may be more debilitating than those occurring as a result of natural aging, and of which hot flushes, night sweats, insomnia, mood swings, vaginal dryness, decreased libido, malaise and a general feeling of apathy are the most common. About 25% of gynecological cancers will occur in pre- and perimenopausal women, a large percentage of whom will become menopausal as a result of their treatment. There are also the gynecological cancer survivors who are not rendered menopausal as a result of the treatment strategy but who will become menopausal because of natural aging. Concern among the medical attendants of these women is whether use of estrogen therapy or estrogen and progestogens for their menopausal symptoms will reactivate tumor deposits and therefore increase the rate of recurrence and, as a result, decrease overall survival among these women. Yet the data that are available do not support this concern.

There are eight retrospective studies and only one randomized study that have analyzed outcome in endometrial cancer survivors who used hormone therapy after their surgery, whilst, among ovarian cancer survivors, there are four retrospective studies and one randomized study. The studies do suffer from small numbers and, although the studies pertaining to endometrial cancer analyze mostly women with early-stage disease, a number of the studies in both the endometrial and ovarian cancer survivors do have a sizeable follow-up. These studies seem to support that estrogen therapy after the treatment for gynecological cancer does not impact negatively on outcome in endometrial and ovarian cancer survivors and that estrogen therapy can be considered as a plausible therapeutic option in survivors who are debilitated by their menopausal symptoms. It is prudent not to offer estrogen therapy to survivors of endometrial stromal sarcoma and women with granulosa cell tumors of the ovaries. Vulval, vaginal and cervical cancers are not considered hormone-dependent and therefore estrogen therapy can be given.

INTRODUCTION

Women who have been treated for gynecological cancer invariably have to face the consequences of estrogen deficiency, be it due to the surgical resection of the ovaries as part of their treatment strategy, the adjuvant postoperative irradiation, the pelvic irradiation and concomitant chemotherapy given to women with advanced cancer where surgery is not offered, or simply because of natural aging after treatment. These patients will therefore, of necessity, need to make an informed decision on how to treat their menopausal symptoms. Both the psychological and physical symptoms of menopause induced by these treatment strategies appear to be more intense and severe than those of natural menopause. Trinh and colleagues in 2006 showed that the hot flushes, night sweats, vaginal dryness and urinary incontinence experienced by breast cancer survivors are likely to be more severe than those in women not treated for breast cancer, irrespective of whether tamoxifen was used or not[1]. Associated stress due to

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the diagnosis and treatment strategies may further exacerbate the severity[1,2].

Improved screening modalities, surgical strategies and chemo-irradiation options have led to greater success in managing women with gynecological cancers and, therefore, an ever-increasing population of cancer survivors who will suffer significant menopausal symptoms as a result of their surgery, irradiation, chemotherapy, or simply because of their age when their cancer was initially diagnosed. Treatment of women with gynecological cancer commonly will induce premature menopause. Bilateral resection of the ovaries is part of the surgical strategy of treating ovarian cancer and endometrial cancer and will be performed by some practitioners in women with endocervical cancer, not only to decrease the estrogen level, but also because about 4% of patients will have ovarian metastases at the time of the diagnosis. The chemotherapeutic drugs that are administered as adjuvant or neoadjuvant therapy may result in ovarian failure, and factors that play a role in increasing the likelihood of ovarian failure include older age, concomitant exposure to irradiation and the use of alkylating agents, particularly platinum-based drugs and cyclophosphamide[3,4]. There is a significant risk of ovarian failure following exposure of the ovaries to irradiation. The magnitude of risk is related to radiation dose, schedule and age at treatment. The older the patient, the greater the impact on the ovaries. Irradiation doses to the pelvis of between 10 and 15.75 Gray are likely to result in ovarian failure in about 90% of the women, although doses from 6 Gray may have a permanent damaging impact on the ovaries[5,6].

Although estrogen therapy is quite commonly given to treat menopausal symptoms in women who are survivors of vulval, vaginal and cervical cancer, concern still persists in prescribing estrogen therapy to endometrial and ovarian cancer survivors because of the over-riding concern that the estrogen will specifically increase the likelihood of recurrent or metastatic disease or lead to the development of a second primary, particularly of breast cancer. In 2005, Creasman thoroughly reviewed the prevailing literature to that time and concluded that there appeared to be little, if any risk in giving hormone therapy to women who have had breast or endometrial cancer, and that there are very little data to support that estrogen therapy is contraindicated in cervical and ovarian cancer survivors[7]. This study was more positive in its message than a previous publication by the American College of Obstetricians and Gynecologists Committee of Gynecologic Practice, which in 2000 had stated that 'The decision to use hormone therapy in gynecological cancer survivors should be individualized according to potential benefit versus risk to the patient'[8]. Yet despite this, the use of hormone therapy to treat menopausal symptoms in women who are gynecological cancer survivors continues to be controversial, highly emotive and challenging, particularly because of the overwhelming opposition to its use by chemotherapists, radiotherapists, and invariably by the surgeons themselves. Be it because of the underlying fear of the cancer survivors, the insecurity of the medical attendants, the lack of national or societal guidelines and the possibility of litigation should the woman develop a recurrence whilst taking estrogen therapy, most clinicians will not prescribe hormone therapy to these patients.

METHODS

The intention of this review is to specifically analyze whether estrogen therapy is a plausible option in women with menopausal symptoms who have been treated for gynecological cancer and whether there is a negative impact on disease-free interval or survival amongst these women because of increased incidence of recurrence, metastatic disease or development of a second primary. The review was undertaken by performing a Medline search for all pertinent studies published in the English literature. The key words 'gynecological cancer survivors, endometrial cancer survivors, ovarian cancer survivors, cervical cancer survivors, vulval cancer survivors, vaginal cancer survivors, estrogen therapy, estrogen replacement therapy, hormone therapy' were used for the search. The search yielded 62 associated studies of which 55 were relevant and used for the review.

ENDOMETRIAL CANCER

Endometrial cancer is the most common gynecological cancer in the developed world, principally affecting postmenopausal women, although about 20–25% of affected women are premenopausal and about 5% will be less than 40 years of age[9]. Patients will invariably have early-stage disease because the most common presenting feature is abnormal vaginal bleeding, with about 85% of patients having stage 1 or 2 disease[10,11]. Treatment consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, commonly followed by intravaginal and whole pelvic irradiation. There are a number of studies which have addressed the question of hormone therapy for the treatment of menopausal symptoms in endometrial cancer survivors. In 1986, Creasman analyzed retrospectively 47 patients with stage 1 endometrial cancer who had been given estrogen therapy because of severe menopausal symptoms postoperatively which was commenced within a median of 15 months after surgery (0–81 months). Estrogen users had a lower recurrence rate (2% vs. 15%), a longer disease-free interval and overall survival when compared to patients who had not used therapy[12]. Four years later, Lee and colleagues published their findings of 44 women who had taken estrogen therapy for a median of 64 months after management of their stage 1 endometrial cancer and compared them to 99 women not taking hormone therapy. No recurrences occurred in the estrogen users while 8% of non-users developed a recurrence. In fairness though, hormone therapy had only been prescribed in low-risk patients (stage 1A, 1B grade 1 or 2) whilst 37% of controls had high-risk disease (stage 1C grade 3). If only the low-risk patients were compared, there was no difference in the development of recurrences[13]. There were no recurrences in another two separate retrospective studies published in 1990 by Bryant and Baker respectively, involving 20 and 31 endometrial cancer survivors respectively who were given

estrogen therapy after treatment and followed up for 4–16 years[14,15]. Chapman and colleagues reviewed 123 women who had been treated for stage 1 or 2 endometrial cancer, of which 62 had used hormone therapy from 8 months after surgery. There was no significant difference in recurrences among the users vs. the non-users[16]. In 2001, Suriano and colleagues identified 130 women who had used hormone therapy after having been treated for stage I–III endometrial cancer. Among this cohort, 75 matched treatment–control pairs were selected and were matched by using age at diagnosis and stage of the disease. Both groups were comparable in terms of parity, grade of tumor, depth of invasion, histology, surgical treatment, lymph node status, postoperative irradiation and concurrent disease. About half the hormone users were using estrogen only, whilst the other half were using estrogen and progestogens. The hormone users were followed for a mean of 83 months and the non-users for a mean of 69 months. There were two recurrences among the users vs. 11 recurrences in the non-users. Hormone users had a statistically significant longer disease-free interval than the non-users ($p = 0.006$)[17]. In early 2006, Barakat and colleagues published the only randomized study which has addressed whether hormone therapy is safe in endometrial cancer survivors. Even though the study did not reach its accrual goal of 2108 patients because the publication of the WHI results made accrual impossible, it was able to randomize 1236 patients to receive either estrogen or no estrogen therapy after undergoing surgery. The planned duration of hormone therapy vs. placebo treatment was 3 years, with an additional 2 years of follow-up. The median follow-up was 35.7 months. The median age of the 618 users of hormone therapy was 57 years (29–91 years) and, although 41% were compliant with their therapy for the entire period, recurrences occurred in 40 patients (6.5%), of which 26 died as a result of the disease (4.2%) whilst eight developed a new malignancy. The median age of the non-users was also 57 years (30–80 years) with recurrences occurring in 19 patients (4.0%), of which nine died (3.1%) as a result of the disease, whilst ten developed a new malignancy (1.6%). The authors concluded that, although the study could not definitively refute or support the safety of estrogen therapy in endometrial cancer survivors, it was important to note that the incidence of risk and demise from the disease in the users was low (relative risk 1.27; 80% confidence interval (CI) 0.91–1.77)[18]. In late 2006, Ayhan and colleagues published a prospective case–control study which also showed that immediate postoperative use of hormone therapy did not increase the recurrence or death rates in endometrial cancer survivors. Fifty patients were given continuous estrogen and progestogens which were commenced 4–8 weeks after surgery and the outcome was compared with a control group with similar characteristics not using hormone therapy. Seven patients stopped taking their hormones, whilst the rest used therapy for at least 24 months, for a mean of 49.1 months. At the end of their follow-up, there were no recurrences in the patients who used hormone therapy for the entire period, and there were no recurrences in those who started therapy but subsequently stopped[19].

There is still some concern about estrogen therapy and uterine sarcomas, which thankfully are not common and only constitute about 3–5% of all uterine malignancies. Even though there are a number of histological subtypes, namely leiomyosarcoma, endometrial stromal sarcoma and undifferentiated endometrial sarcoma, and even carcinosarcoma, there is a significant paucity of literature on the subject because of the rarity of the malignancies. The data that are available allude to the sarcomas collectively and there is some evidence to support that estrogen therapy is contraindicated in women with endometrial stromal sarcoma and not the other types, even though both leiomyosarcoma and endometrial stromal sarcoma express both estrogen and progesterone receptors to varying degrees[20–23].

There is very little to support that vaginal topical estrogen is contraindicated in endometrial cancer survivors even though there are no studies that have specifically addressed this issue. During the initial period of use, there does appear to be a mild increase in the systemic estradiol levels, but these levels do not persist, with negligible systemic absorption following estrogenization of the vaginal epithelium. In a randomized, double-blind study of 443 women who were using topical vaginal estradiol tablets and had endometrial biopsies, 85.6% had atrophic endometrium, 12.6% had non-evaluable samples, 1.1% had polyps, 0.2% were weakly proliferative, one showed complex hyperplasia without atypia and one was reported as endometroid adenocarcinoma. This study appears to support that the use of low-dose topical vaginal estrogen could be an option in endometrial cancer survivors who have significant vaginal atrophy[24].

A summary of the studies pertaining to estrogen therapy in endometrial cancer survivors is shown in Table 1.

OVARIAN CANCER

Management of women with invasive ovarian cancer invariably includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and bulk reduction of all tumor deposits followed by adjuvant chemotherapy. Optimal cytoreductive surgery is achieved when residual tumor deposits at the end of the surgery are no greater than 1.5 cm in diameter[25]. The impact of this treatment is the sudden onset of menopausal status in premenopausal or perimenopausal women, who account for about a third of women who develop ovarian cancer, and clearly is debilitating to these patients. Guidozzi interviewed 28 ovarian cancer survivors at 3-monthly intervals to determine the impact of treatment on two domains: activity, daily living, health, support and outlook as the one domain and sexual activity as the second domain. Treatment of ovarian cancer produced significant deterioration in both domains, with specific emphasis on behavioral disruption, emotional distress and sexual activity[26]. In 1991, Eeles and colleagues published the first retrospective analysis comparing overall survival and disease-free survival in ovarian cancer survivors who did or did not receive hormone therapy after treatment. The endpoints were measured in 78 patients who used hormone therapy vs. 295 who did not. There was no difference in survival between women using estrogen therapy

Table 1 Estrogen therapy in endometrial cancer survivors

Study	n	Stage				Interval to estrogen therapy after surgery (months)	Follow-up on estrogen therapy (months)	Recurrence
		IA	IB	IC	II			
Creasman[12]	47	30	17	–	0	0–18	25–150	0
Lee[13]	44	24	20	–	0	1 > 60	24–54	1
Bryant[14]	20	19	–	–	1	18–24	47–168	0
Baker[15]	31	–	–	–	–	0–20	–	0
Chapman[16]	62	–	60	–	2	0–108	57	2
Suriano[17]	75	14	44	6	7	0–120	83	2
Barakat[18]	618	232	305	48	31	–	35.7	14
Ayhan[19]	50	44	–	–	6	1–2	49.1	0

and those not using it. The risk of dying in those using hormone therapy was 0.73 (95% CI 0.44–1.20) and for disease-free interval 0.90 (95% CI 0.52–1.54). The authors felt that hormone therapy is unlikely to significantly impact on outcome in users[27]. Eight years later, Guidozzi and DaPonte published their findings of a randomized study involving 130 women who had been treated for invasive ovarian cancer and were randomized 6–8 weeks after the surgery to estrogen-only therapy or no hormone therapy. Nine patients originally randomized to hormone therapy refused or stopped taking their therapy, whilst five of the non-users commenced taking estrogen hormonal therapy. In the final analysis, disease-free interval and overall survival were measured in 59 estrogen therapy users and 66 non-users. The median disease-free interval was 34 months in users vs. 27 months in the non-users, respectively, whereas overall survival was 44 months vs. 34 months, respectively. The differences in disease-free interval and overall survival between the two groups were not statistically significant. Prognostic factors such as stage, differentiation, and suboptimal cytoreductive surgery did not have an adverse impact on disease-free interval or overall survival[28]. In 2000, Bebar and Ursic-Vrscaj published their analysis of 31 ovarian cancer survivors who received hormone therapy and were followed up for an average of 51 months. The mean duration of hormone therapy was 25 months, starting on average about 18 months after surgery. Recurrence occurred in three patients at 1, 2 and 10 months after starting hormone therapy, two of whom died from the disease. The authors concluded that hormone therapy was not significantly detrimental in ovarian cancer survivors[29]. One year later, the same authors analyzed outcome in 24 patients with invasive serous ovarian cancer who used hormone therapy after surgery. Each patient was compared with two patients who did not receive hormone therapy. In the final analysis, there was no difference in outcome[30]. In 2006, Moscarenhas and colleagues published the 5-year survival of 649 ovarian cancer survivors and 150 survivors with borderline ovarian tumors in a prospective nationwide study according to estrogen therapy before and after diagnosis. After 5 years, 45% of women with ovarian cancer and 93% of women with borderline ovarian tumors respectively were still alive. There was no overall difference in 5-year survival in women with ovarian cancer according to use of hormone therapy before diagnosis (hazard ratio (HR) 0.83, 95% CI 0.48–0.98), whilst analysis according to different hormonal preparations, duration or when commenced after treatment, did not affect survival in women with ovarian cancer. Of note, the authors of this study noted a better survival in those women using estrogen therapy than those who did not use hormone therapy (HR 0.57, 95% CI 0.42–0.78). Their conclusion was that hormone therapy before the diagnosis of ovarian cancer did not affect survival after treatment, whilst use after treatment may in fact be associated with improved survival, although they do acknowledge that their latter finding may have occurred because of selection bias[31].

A summary of the studies that analyzed estrogen therapy in ovarian cancer survivors is shown in Table 2.

Table 2 Estrogen therapy in ovarian cancer survivors

Study	n	Stage				Interval to estrogen therapy after surgery (months)	Follow-up on estrogen therapy (months)	Recurrence and overall survival
		I	II	III	IV			
Eeles[27]	78	33	10	27	8	0–120 (median 28)	1–200 (median 42)	no difference between estrogen therapy vs. placebo users
Guidozzi[28]	59	7	9	38	5	1–2	48	no difference between estrogen therapy vs. placebo users
Bebar[29]	31	–	–	–		0–41 (mean 18)	51	3
Ursic-Vrscaj[30]	24	10	3	11	–	21	49	5: no difference vs. placebo
Mascarenhas[31]	649	185	74	301	89	not stated	60	no significant difference in outcome

CERVICAL CANCER

Cervical cancer is still common and accounts for significant morbidity and mortality. According to the International Agency for Research on Cancer in 2008, it was estimated that globally about 530 000 women were diagnosed with cervical cancer and that about 275 000 died of the disease. Of this number, about 455 000 were seen in low-resource countries of which 241 818 died of the disease. There is a striking disparity in the incidence of and mortality from cervical cancer in different regions of the world, and it is evident that the number of deaths in low-resource countries is nearly 10 times greater than in high-resource countries. Lack of screening availability in the low-resource countries is a significant reason for this disparity. Globally, cervical cancer was the third most common cancer in 2008, ranking after breast and colorectal cancer[32-34]. Even though estrogen receptors are present in squamous cell cancer tissue, cervical cancer is not considered an estrogen-responsive tumor, with no evidence to support that there is an association with this tumor type and hormonal therapy. Data also do not support any role for estrogen therapy and HPV carriage or replication[35,36]. Fertility-sparing surgery is an option in very early invasive cervical cancer in women who wish to maintain fertility, although standard treatment is either radical surgery alone with preservation of the ovaries or radical surgery with ovarian preservation but followed by adjuvant irradiation and chemotherapy postoperatively in women with pelvic lymph nodal metastases. Alternatively, patients with advanced cervical cancer can have only primary chemo-irradiation without surgery as their modality of treatment. Irradiation not only results in ablation of ovarian function, but also in significant vaginal stenosis[37]. Use of topical vaginal estrogen early in the postoperative period is important to preserve vaginal function, with no evidence to support that topical vaginal estrogen preparations are detrimental to long-term survival[38,39]. In the case of women with adenocarcinoma of the cervix, bilateral salpingo-oophorectomy is far more commonly performed because the incidence of metastases to the ovaries is about 4%. Ploch analyzed prospectively the impact of hormone therapy in 120 women with stage 1 or 2 cervical cancer over 5 years, 80 of which took postoperative hormones, whilst 40 did not and acted as the control group. Histological subtypes were not included in the analysis but, overall, there was no difference in survival or recurrence rate in the two groups, whilst, amongst the users, there was a significant decrease in vasomotor symptoms, and symptoms secondary to urinary, rectal and vaginal irradiation changes[39]. Although the uterus will invariably be ablated if primary chemo-irradiation is given as part of the management for cervical cancer, it is prudent to give these patients combined hormone therapy to control menopausal symptoms after their treatment to ensure no possible stimulation of endometrium whenever the uterus is not removed as part of the recommended treatment[40].

VULVAL CANCER

Cancer of the vulva accounts for about 4% of gynecological cancers and in about 90% of cases will be squamous cell in nature. Surgical strategies include wide local resection of the cancer or simple vulvectomy and bilateral inguinal lymphadenectomy in advanced stages. Removal of ovaries is not part of the recommended treatment, but ovarian ablation occurs should postoperative irradiation be necessary. As with squamous cell cancers of the cervix, cancer of the vulva is not considered estrogen-dependent and postoperative hormone therapy in the form of topical vaginal preparations or oral supplementation is not contraindicated and has not shown to impact negatively on outcome. Very rarely, melanoma of the vulva is encountered with similar treatment strategies being offered. Observational studies on hormone therapy after the diagnosis and treatment of malignant melanoma mostly show no effect on recurrence rates. A cohort of 206 postmenopausal women with melanoma followed for an average of about 11 years showed a survival difference in favor of hormone therapy users (HR 0.17, 95% CI 0.05–0.62)[41]. Adenocarcinoma arising from Bartholin's gland or from Paget's disease are very rare and, although there are no specific data to refute or support a negative impact on recurrence rate or overall survival, estrogen therapy is commonly prescribed.

VAGINAL CANCER

Vaginal cancer is exceedingly rare and accounts for less than 1% of gynecological cancers. Invariably, the cancer will be squamous cell in nature, although even more rarely, in women below 20 years of age, adenocarcinoma is likely, probably secondary to diethylstilbestrol ingestion by the mother in pregnancy. Surgical resection of the tumor is the primary modality of treatment and removal of the ovaries is not necessary, although postoperative adjuvant irradiation or irradiation as the primary modality of treatment will ablate ovarian function. Squamous cell vaginal cancer is not considered to be estrogen-dependent and therefore hormone therapy following treatment is not contraindicated. There are no defined data pertaining to adenocarcinoma of the vagina and hormone therapy[42].

DISCUSSION

Gynecological cancer strikes at the core of femininity and is associated with many distressing and emotive issues in women, other than simply looking at long-term survival. Treatment strategies are radical and, as with all cancers, the need for total extirpation of the cancer is the central focus of treatment to ensure long-term prognosis. There are indeed three groups of gynecologiocal cancer survivors who will develop menopause as a result of their treatment. There are those who have a bilateral salpingo-oophorectomy at their

initial treatment, those who do not have a bilateral salpingo-oophorectomy but receive postoperative adjuvant irradiation, and those with advanced stage cancer who receive primary pelvic irradiation with concomitant chemotherapy. All these treatment strategies result in ovarian ablation and, as a consequence, the acute onset of menopause. Not only do the surgical and irradiation strategies have their own inherent complications, but the resulting symptoms associated with the menopause are more distressing and debilitating than the symptoms that occur following natural menopause. Quite commonly, depression in response to the cancer diagnosis and treatment strategy will compound the symptoms and cause further decline in coping mechanisms. The fourth group of survivors would be those women who had treatment but became menopausal simply because of natural aging. Gynecological cancer survivors will, therefore, not only confront their medical attendants for advice, but also seek options to manage their menopausal symptoms. It is well known that estrogen therapy is the most effective agent to treat women with such menopausal symptoms, but the greatest concern lurking in the mind of the medical attendants is whether estrogen therapy will impact negatively on the long-term outcome in these gynecological cancer survivors by increasing the risk of recurrences and hence decreasing overall survival. Further indecision in prescribing estrogen therapy is commonly brought about by the fact that many oncologists vehemently oppose the use of hormone therapy in gynecological cancer survivors. National guidelines are invariably non-existent or not specific enough to allow one to make an unbiased decision and there is always the fear of litigation should a recurrence occur. It is fact that medical attendants are invariably reluctant to prescribe estrogens to gynecological cancer survivors. Three recent studies show that only 15–48% of medical attendants will give estrogen to endometrial and ovarian cancer survivors[43–45].

Perhaps the greatest shortcoming of the data published on hormone therapy in gynecological cancer survivors is that the studies suffer from small numbers, mostly having women with early-stage disease with no consistency in dose, type, duration or when the estrogen therapy was commenced. Nevertheless, the data support that estrogen therapy does not increase the recurrence rate or decrease survival rate of gynecological cancer survivors[46–54]. Hormone therapy can be given to women who are survivors of vulval, vaginal and cervical squamous cell cancer and there are very little data to substantiate that hormone therapy is a problem in women who have been treated for early-stage endometrial cancer. In addition to that already addressed, Cairu and colleagues found that quality of life in 61 endometrial cancer survivors was significantly affected by treatment and they also supported the use of hormone therapy to overcome the menopausal symptoms[55]. The impact of hormones on adenocarcinoma of the endocervix has not been analyzed widely, but the data that do exist, albeit sparse, do not support any negative impact on outcome and hormones appear safe to use. It is, however, prudent to consider hormone therapy in survivors of endometrial stromal sarcoma as only the last option and to exhaust all other options to manage the menopausal symptoms before one offers it as a modality of treatment. There are no data to substantiate that hormones increase recurrences or decrease overall survival in ovarian cancer survivors and, although the research has been almost exclusively in epithelial ovarian cancer survivors, there seems no reason that hormone therapy should not be given to survivors of ovarian germ cell tumors. It may be prudent though to avoid estrogen therapy in women who are survivors of ovarian stromal tumors, particularly if the tumor was a granulosa cell tumor.

In conclusion, treatment of gynecological cancer brings with it a significant amount of emotional and physical strain, resulting in significant impairment in quality of life. Menopausal symptoms contribute significantly to this distress. In the long-term management of these survivors, it cannot only be longevity of life that is the sole priority. Estrogen therapy is very effective in eliminating menopausal symptoms and there is no obvious evidence to support that estrogen therapy in appropriately selected survivors of gynecological cancer is detrimental. It therefore does constitute a plausible option when menopausal symptoms are of concern.

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