

Gynecological malignancies and hormonal therapies: Clinical management and recommendations

Anna Myriam Perrone, Federica Pozzati, Donatella Santini, Martina Rossi, Martina Procaccini, Lucia Casalini, Erica Santi, Marco Tesei, Claudio Zamagni, Pierandrea De Iaco

Anna Myriam Perrone, Federica Pozzati, Martina Rossi, Martina Procaccini, Lucia Casalini, Erica Santi, Marco Tesei, Pierandrea De Iaco, Oncologic Gynecology Unit, Sant'Orsola-Malpighi Hospital, 40138 Bologna, Italy

Donatella Santini, Pathology Unit, Sant'Orsola-Malpighi University Hospital, 40138 Bologna, Italy

Claudio Zamagni, Medical Oncology Unit, Sant'Orsola-Malpighi University Hospital, 40138 Bologna, Italy

Author contributions: All authors contributed equally to the work presented in this paper.

Correspondence to: Anna Myriam Perrone, PhD, SSD, Oncologic Gynecology Unit, Sant'Orsola-Malpighi Hospital, Via Massarenti 9, 40138 Bologna, Italy. amperrone@libero.it

Telephone: +39-51-6364368 Fax: +39-51-6364392

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Abstract

Every year in the world a large number of women receive a diagnosis of gynecological cancer and undergo a therapy such as surgery, chemotherapy and radiotherapy to the pelvic region. A large portion of these patients are already in menopause, but for younger patients therapies are responsible of early menopause. The physical and psychological symptoms due to iatrogenic menopause significantly reduce the quality of life; however hormone replacement therapy (HRT) has a high efficacy in reducing menopausal symptoms. The prescription of HRT in patients with story of gynecological cancer is debated because its safety has not been completely proven. The main criticism is based on the theory that the hormone replacement could stimulate growth of residual cancer cells increasing the risk of recurrence.

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Key words: Iatrogenic menopause; Gynecological can-

cer; Hormone replacement therapy; Risk of recurrence; Climateric symptoms; Cardiovascular benefits; Clinical practice

Core tip: In this paper we analyze the role of hormone replacement therapy (HRT) in patients affected by gynecological neoplasms with iatrogenic menopause symptoms. We have analysed more than 70 articles with the aim to evaluate the possibility of using HRT in different gynaecological malignancies related to stage and grade of the neoplasm. The literature shows that the use of HRT is controversial in type I of endometrial cancer, endometrioid type of ovarian cancer, uterine cervix adenocarcinoma and endometrial stroma and leiomyosarcoma.

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INTRODUCTION

Hormone replacement therapy (HRT) consists in the administration of synthetic or natural female hormones to compensate the diminution or deprivation of natural hormones. Estrogenic therapy is useful in reducing menopausal symptoms like night sweats, insomnia, hot flushes, sexual disorder and dyspareunia^[1-7]. Moreover Estrogens are effective in preventing the acceleration of bone turnover and the bone loss associated with menopause, and in reducing cardiovascular accident a diabetes insurrence. HRT is the use of Estrogen alone (ERT) or, in women with an intact uterus Estrogen combined with a Progestin (EPT) to prevent endometrial proliferation

that can exacerbate an endometrial cancer. In fact, Estrogen brings an endometrial proliferation by increasing estrogen/progesterone receptors and cellular mitosis in the endometrial glandular epithelium. The association of Progestin creates a down-regulation of these receptors and moreover an induction of the activity of the 17 β -estradiol dehydrogenase which transforms Estradiol into Estrone that has an inferior activity. The association of Progestin thereby reduces the estrogenic stimulus on the endometrium^[8]. Under the progestin influence, the histology of the endometrium changes from proliferative to secretive, and this reduces the risk of insurance of hyperplasia^[9]. In the past 10 years much confusion has been generated regarding the use of HRT in the general population^[10]. In fact HRT led to some important risk like breast cancer, venous thromboembolic events, stroke and coronary artery events^[11]. After the publication of "Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health"^[11] a general consensus on HRT has been agreed. However in oncological environment the use of HRT remains subject of debate. Women treated for gynecological cancer invariably incur the consequences of Estrogen deficiency due to the surgical resection of the ovaries, irradiation and chemotherapy^[12]. Because of the underlying fear of cancer survivors, the insecurity of the clinicians, the lack of national or societal guidelines and the possibility of litigation should the woman develop a recurrence whilst taking oestrogen therapy, most clinicians do not prescribe HRT to these patients^[12] regardless of tumour type and disease stage^[13]. This has led to many women being denied the use of HRT thereby increasing the number of young patients who experience the effects of iatrogenic menopause. This is severely more intense than the natural onset both because of the sudden decline in estrogen/androgen levels and because of the younger age of the patients^[14-16]. In particular severe hot flushes, vaginal dryness, sexual dysfunction, sleep disturbances, and cognitive changes may significantly affect quality of life^[17]. The purpose of this review is to analyze the possibility of using ERT or EPT in patients who have been treated for gynecological malignancies with the aim of establishing recommendations for clinical practice.

RESEARCH

We reviewed the literature using the terms: HRT, ovarian cancer, cervical cancer, uterine sarcoma, endometrial cancer, borderline ovarian tumor. We analyzed more than 70 articles for the present study.

OVARIAN CANCER

Epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer and the leading cause of gynaecological cancer related mortality^[18,19]. It typically develops

as an insidious disease^[18,20,21], with few distinct symptoms until the tumour has become large or disseminated^[19]. Currently, cytoreductive surgery combined with platinum-based chemotherapy is the standard treatment also for patients of child-bearing age. Cytoreductive surgery for a malignant ovarian tumour frequently results in the loss of ovarian function and menopausal symptoms^[22]. HRT use for these patients is controversial because of the potential stimulation of residual cancer cells and the induction of new hormone-dependent disease^[23]. Epidemiological investigations have suggested that malignancies of the genital tract may be associated with hormonal stimuli and with the ingestion of long-term oral estrogen^[24,25]. *In vitro* experiments have yielded inconsistent results regarding the estrogen stimulation of cancer cell proliferation. Certain *in vitro* experiments have shown that estrogen is capable of stimulating the proliferation of malignant cells^[26,27]. While some results of these studies showed tumour cell growth inhibition by estrogen^[28], other authors found no effect of estrogen on malignant cell growth^[29,30]. There are 4 different histological types of epithelial ovarian cancer: serous, endometrioid, clear cell and mucinous carcinoma. The 70% of EOC are serous type and probably derive from the ovary epithelium or the fallopian tube^[23]. Endometrioid and clear cell tumours normally occur in patients that have ovarian inclusion cyst or foci of endometriosis. Endometrioid type of adenocarcinoma is similar to histological type of endometrioid adenocarcinoma of endometrium^[31,32]. Endometrioid EOC express estrogen receptors and for this reason it is retained that HRT can stimulate post-surgical residual cancer. Even so, there are no studies that have shown a real association between HRT and the development of EOC after treatment^[33]. Studies about HRT use after treatment of endometrioid cancer shows that HRT can be used in patients affected by early stage of endometrioid EOC. Although in patients with Stage 3 endometrioid adenocarcinomas because of the high possibility of residual disease after surgery the use of HRT is not secure in clinical practice^[23]. Two meta-analyses with contrasting data about the impact of HRT on EOC follow up have been published, the first demonstrating no increase in relative risk of EOC in patients having HRT and the second demonstrating a little but significant raise in risk after long use (10 years plus)^[34,35]. Different studies have investigated the possible adverse effects of HRT in patients who have undergone surgery and chemotherapy for EOC. Guidozzi *et al.*^[12] realized a prospective randomized study of 130 patients diagnosed with advanced stage, high grade serous ovarian cancer to analyze the effects of HRT on survival. That women who had earlier taken estrogens or had ovarian low malignant cancer were excluded. All of these patients underwent cytoreductive surgery and after cisplatin-based chemotherapy were randomized to have either oral Premarin *vs* placebo. After a follow up of 48 mo no considerable divergence in survival was noted between the two groups and the study establishing that HRT can be somministrated with the purpose of

Table 1 Epithelial ovarian cancer

Ref.	Study design	HRT vs control	Stage	Type of HRT	Months HRT	Months follow up	Recurrence HRT vs controls	Study conclusions
Eeles <i>et al</i> ^[37]	Retrospective case-control	78/295	1-2: 55% 3-4: 45%	Oral Estrogen	Median 28	Median 42	-	No effects of HRT on prognosis
Guidozzi <i>et al</i> ^[12]	Randomized controlled trial	59/66	1-2: 27% 3-4: 73%	Estrogen + Progestogen				
Bebar <i>et al</i> ^[36]	Retrospective cohort study	31/0	NS	Conjugate Estrogen	28	Mean 42	32 vs 41	No effect of HRT on DFS and OFS
Ursic-Vrscaj <i>et al</i> ^[38]	Retrospective case-control	24/48	1-2: 54% 3-4: 46%	Non-conjugated-Estrogen + Progestogen	Mean 25	Mean 55	3	No effect of HRT on progression of EOC
Mascarenhas <i>et al</i> ^[33]	Prospective cohort study	649 EOC 150 BOT	1-2: 60% 3-4: 40%	Estrogen + Progestogen	Mean 24	Mean 49	5 vs 15	No effect of HRT on survival
Li <i>et al</i> ^[39]	Prospective cohort study	31/45	1-2: 28% 3-4: 72%	Estrogen + Progestogen Conjugated-Estrogen + Progestogen	Up to 24 Mean 28.7	60 Mean 31.4	-	Better survival in HRT users vs non users No effect of HRT on cumulative survival HRT improve quality of life

HRT: Hormone replacement therapy; EOC: Epithelial ovarian cancer; NS: Not specified; BOT: Borderline ovarian tumor; DFS: Disease free survival; OFS: Overall free survival.

improving quality of life in young EOC survivors without increasing risk of recurrence^[12].

A prospective cohort study by Mascarenhas *et al*^[33] considered 649 women with EOC and 150 women with borderline ovarian tumours who were clustered according to pre and post cancer utilization of HRT using self-questionnaires. The work analyzed the effects of HRT before and after the diagnosis of both tumors on 5-year survival. There were found no significant divergence in EOC survival between the group of women who had HRT before cancer diagnosis and that who did not have it. Some data indicated a better survival for patients who had HRT before the arising of EOC, but there is not a clear explanation according to period or recent time of use. There are analogous data and no proof of an association between HRT use before diagnosis of endometrioid EOC was found. Better survival was reported for serous type women but a better survival after endometrioid tumours was suggested too^[33]. A retrospective cohort by Bebar *et al*^[36] describe 31 women with ovarian cancer treated with surgery and following chemotherapy who had non-conjugate estrogens for a mean period of 25 mo. Median follow up was 35 mo. Progression of disease occurred in only three patients, and one patient developed early stage breast cancer^[36]. A retrospective study by Eeles *et al*^[37] illustrated 373 women with endometrial cancer (EC) who had primary surgery after that, 78 of these patients had HRT in different formulations and 259 did not. In the group who had HRT there was a higher number of younger women most between the ages of 30 and 40 years, with earlier and well differentiated cancers. There was no considerable dissimilarity in disease free survival between those who had HRT and those who had not after checking for age, disease stage, tumor grade and interval to recurrence^[37]. Ursic-Vrscaj *et al*^[38] compared every patient with EOC at Stage I - III treated with estrogen, with two non treated patients at the same stage of disease. They found similar disease free and overall survival in the two groups. Li *et al*^[39] carried out a study aimed at assessing the impact of post-surgical HRT on life quality and prognosis in women with ovarian malignancies. HRT was administered in 31 patients, 44 patients did not receive HRT. A long-rank test revealed no difference in survival between patients with and without HRT. HRT administered following surgery exhibited no apparent negative effects on prognosis in EOC, while post-surgical HRT aided in the stabilization of serum calcitonin levels and improved quality of life in these patients^[39].

Current literature does not support the view that HRT facilitates the development and recurrence of ovarian cancer^[36,38]. Thus, ovarian malignancy after clinical management of cytoreduction and adequate chemotherapy is not a contraindication for HRT. HRT may be a good option for patients with serious symptoms of menopause and osteoporosis. Nevertheless, the use of HRT still lacks the support of large-scale multi-center prospective double-blind randomized studies, particularly regarding its effect on tumour growth in patients with gross residual tumours. Therefore, care should be taken to limit the use of HRT as much as possible to patients with satisfactorily controlled ovarian malignancy. The suitable duration of HRT is currently under debate with no definite conclusions based on large-scale studies. Consideration should be given to an individual's specific clinical circumstances as well as the severity of menopausal symptoms. The results of the studies we have analyzed are listed in Table 1.

Borderline ovarian tumour

Borderline ovarian tumors (BOTs) comprise approximately 15%-20% of all epithelial ovarian malignancies^[40,41]. They are known for their low malignant potential and for unclear associated risk factors. Patients with BOTs are, in general, younger than women with EOC: their average age at diagnosis is between 45 years old^[42], and 30% of patients are less than 40 years old. BOTs can be unilateral or bilateral. Similarly to carcinoma, they can spread to the peritoneum and, eventually, to the lymphonodes^[43]. Standard surgical treatment is based on bilateral salpingo-oophorectomy with or without hysterectomy. After comprehensive surgical staging, cystectomy or unilateral annessiectomy can be offered to patients who want to preserve their fertility^[44]. However, young patients for whom fertility-sparing surgery is not feasible (because of BOTs diffusion or recurrent disease) will suffer from iatrogenic menopause. For these patients HRT is an important issue. In 2006 Mascarenhas *et al*^[33] showed that out of 150 patients with BOTs, 93% survived at least five years and out of these, 51% had used HRT after diagnosis. In 2012, Fischerova *et al*^[45] concluded that HRT should be offered to these patients.

In literature, no prospective randomized study on HRT after BOTs was found, but we agree with the idea that HRT should be proposed in patients with bothersome symptoms for the same reasons that HRT is offered to patients with ovarian cancer.

Germ cell ovarian tumour

Ovarian germ cell tumors (OGCT) includes benign or malignant. Dysgerminoma, yolk sac tumour, embryonal carcinoma, polyembryoma, non-gestational choriocarcinoma, mixed germ cell tumours, and teratomas (immature, mature, and monodermal types)^[46] are all OGCTs. The age of insurance is between 10 and 30 years of age^[47]. Fertility sparing surgery is possible but most patients are submitted to adjuvant chemotherapy (*e.g.*, bleomycin + etoposide + cisplatin)^[48] and radiotherapy. This results in a gonadal dysfunction leading to transient or permanent ovarian failure^[49]. There is no evidence that hormones increase recurrence or decrease overall survival of ovarian cancer survivors and, although the research has been almost exclusively in epithelial ovarian cancer survivors, there seems to be no reason why HRT should not be given to survivors of OGCT^[50]. On this basis, in 2009 Singh *et al*^[23] concluded that these patients can benefit from the use of HRT.

Sex cord ovarian tumour

Sex cord-stromal tumours include granulosa cell tumours (GCTs), thecomas, Sertoli-Leydig cell tumours, gynandroblastoma. The most malignant and the most common sex cord stromal neoplasms is GCT^[51] which are also the most common. They secrete steroid hormones and diagnosis is frequently secondary to hypoeestrogenism symptoms onset. Fertility preserving surgery can be offered in Stage 1 patients; a total abdominal hysterectomy

with bilateral salpingo-oophorectomy is mandatory for all other patients^[23]. Regarding the possible use of hormonal treatment to restore patients from menopausal symptoms, although no studies have been published, the general consensus is that HRT should not be used because of their hormone-dependent nature. In fact about 30% of GCTs are Estrogen Receptor Positive and 100% are Progesterone Receptor positive^[52]. In 2013, Guidozi^[50] confirmed that it may be prudent to avoid estrogen therapy in women who are survivors of ovarian stromal tumours, in particular if the tumour was a GCT.

EC

EC is the most frequent gynaecological cancer. We can divide EC into 2 different types: Type I is the endometrioid histotype, which express estrogen and progesterone receptor and normally has a low grade. Major risk factors are prolonged use of estrogen, obesity and physiological hyperestrogenism. Type II EC normally has a serous-papillary or clear cell histotype, it doesn't express Estrogen and Progesterone receptors and habitually it has a high histological grade and for this reason it is more offensive than type I^[53]. This malignancy principally affects post-menopausal women, although about 20%-25% of women with EC are pre-menopausal and about 5% have less than 40 years of age^[54]. This cancer is normally diagnosed at an early stage (85% of patients in Stage I or II) because of abnormal uterine bleeding as a prevalent symptom of the neoplasm^[55]. Surgery represents the principal treatment: the typical surgical intervention is total hysterectomy and bilateral salpingo-oophorectomy to leave out the risk of ovarian metastasis or ovarian cancer. In advanced stages or precarious clinical conditions of the patient the primary treatment is radiotherapy. Because of the important role played by estrogens in the onset of the most common endometrial cancer, HRT may stimulate the growth of occult tumour cells remaining after surgical treatment. For this reason replacement of this hormones after disease treatment seems to be contraindicated. However there is no evidence that HRT may adversely affect disease free survival and the recurrence rate in women treated for endometrial cancer^[56,57]. Several studies have analyzed patients affected by endometrial cancer treated with HRT to reduce iatrogenic menopausal symptoms. Creasman *et al*^[58] and Lee *et al*^[59] in 1986 and in 1990 respectively, published case control studies on HRT in endometrial cancer Stage 1 patients finding a lower recurrence rate, longer disease-free and overall survival in users against non-users. In fact in the Lee series no recurrences occurred in estrogen users while HRT had been prescribed only in patients with low risk of recurrence (Stage 1A or 1B and low grade). The control group had a higher recurrence rate because of the higher-risk disease (Stage 1C grade 3). When only low-risk patients were compared Lee found no difference in recurrence rate. In 1990 two separate retrospective studies published by Bryant^[60] and Baker^[61], examined

Table 2 Endometrial cancer

Ref.	Study design	HRT vs control	Stage	Type of HRT	Months HRT	Months follow up	Recurrence HRT vs controls	Study conclusions
Creasman <i>et al</i> ^[58]	Retrospective case-control	47/174	1	Oral/Vaginal/Oral + Vaginal Estrogen	Mean 32	25-150	2 vs 15	Estrogen has a good effect on DFS an OS
Lee <i>et al</i> ^[59]	Case-control	44/99	1	Oral Estrogen	Median 64	24-84	0 vs 8	Estrogen are safe in low risk patients
Bryant ^[60]	Retrospective cohort	20	1-2	Conjugated Estrogen ± Depo Provera	12-132	42-168	NS	No recurrences in patients treated with HRT
Baker ^[61]	Retrospective cohort	31	NS	Oral/Vaginal/transdermal Estrogen		192	NS	No increase of recurrence or mortality in HRT users
Chapman <i>et al</i> ^[62]	Retrospective case-control	62/61	1-2	Oral/Vaginal Estrogen ± MPA 2.5 mg	Mean 49.1	Median 57.1	2 vs 8	No decreased DFI or increased recurrence in users vs non users in early stage
Suriano <i>et al</i> ^[63]	Retrospective cohort with matched controls	75/75	1-3	Oral Estrogen ± MPA 2.5 mg	Mean 83	Mean 83	2 vs 11	HRT ± Progesterone do not increase recurrence rate
Barakat <i>et al</i> ^[64]	Randomised double blind trial	618 vs 618	1-2	Oral Estrogen	Planned 36	Median 35.7	14 vs 12	Not completed. Low recurrence rate
Ayhan <i>et al</i> ^[65]	Prospective case-control	50/52	1-2	Conjugated Estrogen + Progesteron	Mean 49.1	Mean 49.1	0 vs 1	Postoperative HRT did not increase recurrence or death rate

HRT: Hormone replacement therapy; MPA: Medroxyprogesterone acetate; DFS: Disease free survival; OS: Overall survival; DFI: Disease free interval; NS: Not specified.

cancer survivors who received estrogen therapy after treatment and were followed up for 4-16 years. The stage of neoplasm was I - II in the Bryant study and was not specified in the Baker study. No recurrence of endometrial cancer was noted in either the studies. Chapman *et al*^[62] examined women with stage 1 or 2 EC. There was no significant difference in recurrence rate between HRT users and non-users, however the groups were not homogeneous because patients in the non-users group had often a greater frequency of high grade and stage, and were older than patients submitted to HRT. In the year 2001 Suriano *et al*^[63] studied women affected by stage I - II - III of EC and described a longer disease-free interval in HRT users vs non-users with a significant difference ($P = 0.006$). The study concludes that HRT with or without progestins does not seem to increase the risk of recurrence or death in patients treated for EC. The only randomized study was carried out by Barakat *et al*^[64] in 2006. It started in 1997 and stopped in 2003 after the publication of the Women's Health Initiative results that made accrual impossible. For this reason they did not reach their goal of 2108 patients but they randomized 1236 patients who received either estrogen or non-estrogen therapy after undergoing surgery. The authors concluded that, although the study could not clearly define the safety of estrogen therapy in endometrial cancer survivors, there is a low recurrence rate (2.1%) and minimal incidence of new neoplasm. Ayhan *et al*^[65] published in 2006 the first prospective case control study which showed that HRT administered immediately after surgical intervention did not amplify the recurrence or the mortality rate in Stage 1 and 2 EC survivors. The main limitation of this study was the small sample size and lack of randomization. These results were shown in a 2010 review by Singh *et al*^[23], however the author underlined that in endometrioid cancer of the endometrium the reason why HRT did not showed adverse effects may be due to the radical tumor excision because of early stage. In fact in advanced stage Type I of endometrial cancer there may be some residual cells after surgical treatment that can be stimulated by HRT and subsequently change the prognosis of the patient. The use of estrogen-progesterone HRT would probably suppress estrogen stimulated cell growth because of the progesterone combination, but there are no clear evidence data about this theory^[23]. The studies listed above are resumed in Table 2.

UTERINE SARCOMA

Uterine sarcomas constitute a disparate category of malignancies which includes leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), undifferentiated endometrial sarcoma and carcinosarcoma. The data available in literature on the role of estrogen therapy after surgical treatment for uterine sarcomas are limited because they are uncommon tumors (3%-8% of all uterine malignancies in women). Most ESSs express steroid receptors and are considered to be hormone-sensitive. Many studies have shown a regression or stabilization of recurrent low-grade ESS with endocrine therapy based on medroxyprogesterone acetate and Letrozolo (aromatase inhibitor)^[66]. Patients with a history of ESS should not be treated with estrogen therapy or tamoxifen and, if present, withdrawal of estrogen therapy is strongly recommended^[67]. LMSs are the most common

Table 3 Recommendations

Site	Tumour type	HRT
Ovary	EOC	
	Endometrioid	No ¹
	Others	Yes
	Germ cell ovarian tumour	Yes
	Sex cord ovarian tumour	No
Uterus	Endometrial cancer	
	Type 1	No ¹
	Type 2	No ¹
	Uterine sarcoma	
	Endometrial stroma sarcoma	No
Cervix	Leiomyosarcoma	No
	Adenocarcinoma	No
	Squamous	Yes

¹To evaluate in a multidisciplinary team. HRT: Hormone replacement therapy; EOC: Epithelial ovarian cancer.

of uterine pure sarcomas (42%-60%) and some express estrogen and progesterone receptors at different levels. Avoidance of estrogen therapy is generally recommended in surgically treated women with LMS because of their potential hormone sensitiveness^[68].

CERVICAL CANCER

Cervical cancer is the second most common gynaecological cancer with an important mortality and morbidity. Due to pap-test screening early diagnosis and therapies are increasing leading to a larger population of young women facing collateral gynaecological symptoms. Although fertility sparing treatment is possible in early stages, in advanced stages treatment consists of either radical surgery or primary chemo-radiotherapy. In squamous carcinoma, almost 80% of cervical cancers, ovary preservation is usually feasible and safe due to the low metastasis rate however for adenocarcinomas oophorectomy is usually recommended. Women with cervical cancer often undergo external radiotherapy or brachytherapy causing significant toxicity to the vagina. In addition to symptoms caused by iatrogenic menopausal status this may result in vaginal stenosis, dyspareunia and major sexual problems. Generally HRT is not refused in patients who complain of menopausal symptoms after treatment for squamous cervical cancer (SCC)^[69]. SCC is not considered an estrogen responsive tumour even though estrogen receptors have been described in this tissue too. A study by Ploch^[70] on 120 women showed no change in the survival rate or Disease Free Survival at five years in patients receiving HRT after treatment for cervical cancer Stage I / II. A higher risk seems to exist for cervical adenocarcinoma. It has been suggested that it should be treated in the same way as endometrial cancer because of the dependence of this histotype on oestrogen stimulation^[71]. The adverse effect of radiotherapy like vaginal stenosis can be treated with local oestrogen subministration but there is no clear evidence about a linkage between hormonal therapy and a worse prognosis of cervical cancer^[23].

BRCA MUTATION CARRIERS AFTER SALPINGO-OOPHORECTOMY

Women with germ line BReast CAncer type 1 (*BRCA1*) or *BRCA2* mutations have higher life time risk of ovarian (15%-56%) and breast (45%-80%) cancers than the general population (ovarian cancer 1.4%; breast cancer 12%)^[72]. In women between 35 and 40 years old prophylactic annessiectomy is recommended to reduce the risk of insurance of ovarian malignancies, causing the insurance of iatrogenic menopause with deterioration of quality of life. Two observational studies in women with *BRCA* mutation treated with prophylactic salpingo-oophorectomy showed no increase of breast cancer incidence in HRT users^[73,74]. On the contrary, Million Women Study compared HRT users with non users receiving placebo and it demonstrate an increased risk of breast cancer in the first group of patients^[75]. Current studies of women carrying *BRCA2* mutation are non randomized and there is little data about the increased risk of breast cancer in this group of patients.

Because of the increased risk of osteoporosis, cardiovascular event, cognitive problems and vasomotor symptoms related to hyatrogenic menopause, we agree with the idea that short-term HRT should be propose^[76].

CONCLUSION

HRT with Estrogen or Estrogen and Progestogen is the therapy with the highest efficacy in the treatment of physical and psychological symptoms of iatrogenic menopause. HRT can be administered in women with story of squamous cells carcinoma of the uterine cervix; conversely should not be prescribed in patients with endometrioid ovarian carcinoma, atypical histologies endometrial carcinoma, borderline ovarian tumour, germ cell ovarian tumours and *BRCA1-2* mutation carrier patients. The use of HRT in endometrioid EOC and endometrial cancer is debated because there are no studies that come to an agreement on this topic. We can speculate that the use could be stage-dependent, but in any case HRT should be discussed in a multidisciplinary team. HRT use is not safe endometrioid endometrial cancer, endometrioid ovarian cancer adenocarcinoma of the uterine cervix, endometrial stroma sarcoma and leiomyosarcoma. In these groups of patients non hormonal therapies are rational alternative to HRT to reduce vasomotor symptoms. These recommendations are resumed in Table 3. HRT should start after six months from the last treatment (chemotherapy or radiation therapy) to reduce thrombotic risk due to cancer, chemotherapy and hormone therapy.

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