A prospective study of adjuvant radiotherapy concomitant with cisplatin followed by paclitaxel, carboplatin in high-risk early stage endometrial cancer.

Thesis

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List of Abbreviations

AH	Atypical hyperplasia
BMI	Body mass index
BRCA	Breast Cancer
BTH	Brachytherapy
CEA	Carcino Embryonic Antigen
CTCAE	Common terminology criteria for adverse events
CTH	Chemotherapy
CTV	Clinical target volume
D & C	Dilatation and curettage
DFS	Disease free survival
EBRT	External beam radiotherapy
EC	Endometrial cancer
EEC	Endometrioid endometrial cancer
EMA	Epithelial membrane antigen
ER	Estrogen Receptor
ESGO	European Society of Gynecological Oncology
ESMO	European Society for Medical Oncology
ESTRO	European SocieTy for Radiotherapy & Oncology
FIGO	International Federation of Gynecology and Obstetrics
GI	Gastrointestinal
GOG	Gynecology Oncology Group
HDR	High dose rate
HER 2	Human epidermal growth factor receptor 2
HR	Hazards ratio
IHC	Immunohistochemistry
IGF_I	Insulin growth factor I
IMRT	Intensity Modulated Radiotherapy
IR	Intermediate risk

IUD	Intra uterine devise
LENT	late effect of normal tissue
LND	Lymph node dissection
LNM	Lymph node metastasis.
LOE	Level of evidence
LR	Low risk
LVI	Lymphovascular invasion
MLH1	MutL homolog 1
MRI	Magnetic resonance imaging
MSH2	MutS protein homolog 2
MSH6	MutS homolog 6
MI	Myometrial invasion
OS	Overall survival
OR	Odd ratio
PFS	Progression free survival
PTEN	Phosphatase and tensin homolog
PR	Progesteron Receptor
RCT	Randomized controlled trial
RR	Response rate
RTH	Radiotherapy
SLN	Sentinal Lymph node
UCS	Uterine Carcinosarcoma
US	Ultrasound
WT_1	Wilms tumor 1

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Aim of the work

The aim of this study is to determine the efficacy and toxicity with adjuvant radiotherapy concomitant with cisplatin, followed by 4 cycles of paclitaxel carboplatin in patients with early stages, high risk endometrial cancer and the impact of this regimen on the rate and sites of recurrence.

Introduction

Endometrial cancer is the most common gynecological malignancy in the United States, and it's the sixth most common malignancy worldwide .It is estimated that 54,870 new uterine cancer cases will occur in 2015, with 10,170 deaths resulting from the disease ***(Siegel et al, 2015).***

The highest incidence is recorded in North America, followed by central and eastern Europe, while the lowest incidence is found in developing countries in mid and western Africa ***(WHO Globocan 2008).***

In Egypt according to Garbiah Cancer registry the incidence of uterine cancer is approximately 1.3% of all cancer cases. ***(Ibrahim et al, 2007).***

Furthermore, a study was done comparing urban-rural differences of gynecological malignancies in the Gharbeyah province of Egypt (1999-2002), the most striking finding was almost six times higher incidence of uterine cancer in urban areas than in rural areas of Gharbeyah ***(Dey et al,2010).***

At Ain Shams university hospital, from 2001-2010 473 cases of endometrial cancer were recorded which formed 31.4% of the female genital system tumors and 4 % of the total malignancies. Time trend analysis showed increase in the number of cases

during 2006-2010 (283 cases) compared to 2001-2005 (190 cases) ***(Helal et al, 2015).***

More than 70% of cases of EC are stage I at the time of diagnosis when the reported 5 years survival rate is 90% ***(Creasman et al, 2006).*** The mean age of diagnosis in the United States is 63 years ***(Howlader et al, 2014).***

Stage is the most important prognostic factor for EC, early stage patient have the best outcome and survival decrease with advanced stage. Overall the 5 year survival rates for all grades and histological subtypes are approximately 78-90% for stage I, 74% for stage II, 36-57% for stage III, and 20% for stage IV ***(Lewin et al, 2010).*** In addition to the lymph node status, the histological subtype, grade, depth of myometrial invasion are factors used to assess the risk of recurrence and the need for adjuvant treatment ***(*Tejerizo-Garcia *et al ,2013).***

According to Federation of Gynecology and Obstetrics FIGO 1997 stage IIIA EC is defined as tumor involvement either as direct extension or metastasis to serosa, parametria, adnexa, and or cancer cells in peritoneal washings ***(Hermanek et al, 1997).*** Due to this broad definition, patient with stage IIIA have a heterogeneous prognosis. In FIGO 2009 the definition of IIIA has changed, being involvement either direct extension or metastasis to serosa and/or adenexa only , parametrial invasion

became stage IIIB , and the presence of abnormal cells in peritoneal washings no longer affect staging.

According to the new FIGO 2009 definition EC stage IIIA with isolated involvement of adnexa or serosa only has a comparable disease specific survival of 71.8% and 75.4% at 7 years. Locoregional control for patients with adenxal involvement is excellent with 2.2% recurrences, but worse for patients with serosal involvement at 14.3% ***(Jobsen et al, 2011).***

To date, no level 1 evidence supports adjuvant therapy of any form in patients with early stage endometrial cancer when the end point is overall 5 years survival. Radiotherapy proved to reduce local recurrence but not overall survival. Further complicating the decision process is the fact that early stage actually comprises two types of patients; those who are comprehensively staged and have received appropriate nodal evaluation and those who are not comprehensively staged, those who have higher risk factors than others.

The GOG-99 trial randomized patient with FIGO IA/II G3 tumors to follow–up or pelvic EBRT. After 2 years, the pelvic recurrence rate in the control arm was 12% and in the radiotherapy arm 3%; this difference did not influence overall survival .Of particular relevance to this study is that in the subgroup of patients with high-intermediate risk disease, the risk of any recurrence without

adjuvant treatment was 27%, predominantly due to distant recurrence (19%) **(Keys et al 2004).**

This high rate of distant recurrence prompted evaluation of adjuvant chemotherapy in high-risk early stage disease.

Etiology

There are many established risk factors for type I EC related to prolonged unopposed estrogen exposure and other risk factors , however little is known about risk factor for type II tumors, mainly because most epidemiological studies have lacked enough cases to study these less common histological subtypes separately.

- Estrogen replacement therapy:

In the mid-1970s, estrogen replacement therapy prescribed to control post menopausal symptoms, was shown to substantially increase the risk of endometrial cancer by 2 to 20 folds, with an increased risk correlating with the duration of use. The concomitant administration of progestins continuously or intermittently (10 to 15 days/month) significantly reduces this increased risk.

A population based case control study of 833 cases and 791 control subjects was conducted, the results showed that the addition of a progestin to estrogen replacement therapy for a short term less than ten days reduced the increased risk of EC by 26%, while the addition of a progestin for 10 days or more abolished this increased risk, as did combined replacement therapy. The overall adjusted Odd ratio per 5 years of use of estrogen only

replacement therapy and sequential estrogen progestin replacement therapy (short progestin use: 7 days) were 2.17 and 1.87, respectively, while the comparable Odds ratio for the long progestin use (>10 days) or continuous combined were both 1.07 ***(Pike et al, 1997).***

- Selective Estrogen Receptor Modulators:

A selective estrogen receptor modulator acts as antagonist in breast tissues but as agonist in endometrial and bone tissues. The use of tamoxifen is associated with a 6 to 8 fold increase in the incidence of endometrial cancer; however, net benefit greatly outweighs risk ***(Fisher et al, 1994).***

The ability of Tamoxifen to induce endometrial malignancy and other histopathological conditions appear to differ between premenopausal and post menopausal women. (Committee opinion No 601.American College of Obstetricians and Gynecologist.2014)

In the National Surgical Breast and Bowel Project prevention trial of high risk women, there was no statistically significant differences in EC rates between women treated with Tamoxifen and others in the placebo group in the age subgroup of 49 years and younger, however women 50 years and older, the risk ratio

was 4.01(95% CI, 1.70-10.90) for those treated with Tamoxifen versus those receiving the placebo. ***(Fisher et al, 1998)***

Raloxifen, which is another oral selective estrogen receptor modulators used to reduce the risk of breast cancer as well as reducing recurrence, does not increase the risk of EC ***(Nelson et al, 2013).***

- Obesity

Obesity is associated with an increased incidence of endometrial cancer, mainly due to the associated high levels of endogenous estrogen because of the conversion of androstenedione to estrone in peripheral adipose tissue. ***(Renehan et al 2008)***

The level of risk related to the degree of obesity. Women with BMI>32 kg/m2 have a relative risk of 4.0 and women with BMI> 35 kg/m2 have a higher relative risk of 6.0 when compared to women with BMI of 23kg/m2. ***(Bianchini et al 2002)***

Five epidemiologic studies examined risk factor for type II EC with two of them were mainly focusing on BMI. The largest study with 992 women of type II EC, found that high BMI was associated with both type II as well as type I, and that the magnitude of risk was somewhat stronger for type I than type II tumors. However the lack of control for potential confounders (ie parity, exogenous hormone use, and smoking) in that study