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Conservative therapeutic approach in young patients with endometrial cancer: is it really possible?

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Abstract

Fertility preservation in young patients with early stage endometrial cancer, represents a great therapeutic challenge nowadays. The eligible patients should have strong desire for future fertility, informed consent about conservative approach and no contraindications regarding medical treatment with progestins. Moreover, they should have an extensive counselling regarding disease recurrence, fertility and childbearing issues. Before starting conservative treatment, a thorough evaluation should be performed in every patient with both endometrial sampling and detailed visualization of the entire abdomen. Then, the carefully selected young patients, could initiate fertility sparing treatment which is mainly based on progestin regimens and should be taken for a period of 6 months. All patients should have a very close surveillance during and after conservative management. The overall response rate after fertility sparing treatment in endometrial cancer, is quite encouraging reaching approximately 75%. However, the overall recurrence rate in these patient subgroup, is essentially high ranging between 30% and 40%. This is the main reason why systematic surgical staging should be performed in all these patients after completion of childbearing. In conclusion, fertility sparing treatment is really possible only in young patients with FIGO stage IA, grade 1 and type I endometrial cancer. However, conservative management in endometrial cancer is not the standard of care and patients should be informed about the future need of systematic surgical staging in any treatment failure, disease recurrence or after completion of childbearing.

Key words: conservative treatment, fertility preservation, endometrial cancer.

Introduction

Endometrial cancer (EC) is the 2nd most frequent cancer of the female genital tract and the 5th most

common malignancy among women worldwide.^{1,2} The estimated annual incidence of EC is significantly greater in more developed countries in North and West Europe and North America.^{1,2} However, the mortality rate of EC is substantially higher in less developed countries in North Africa and Melanesia.^{1,2}

Although EC usually affects postmenopausal population, there is a small subgroup of premenopausal patients and approximately 4% are younger than 40 years.³⁻²⁰ This is the main reason why, fertility preservation in young patients with EC remains a great therapeutic challenge nowadays.³⁻²⁰

Current treatment guidelines

Based on recently published treatment guidelines, systematic surgical staging represents an essential part in EC treatment by providing a wide variety of benefits in diagnosis, treatment and prognosis for both type I (endometrioid) and type II (serous, clear cell, undifferentiated) EC.^{3-5,9-15,18,20-26} Moreover, the administration of postoperative adjuvant treatment with either radiotherapy, chemotherapy or a combination of both, has an equally important role in EC management especially in patients with increased risk of recurrence or at advanced disease stage.^{3-5,9-15,27}

Nevertheless, the extent of initial surgical procedure as well as the type of postoperative adjuvant treatment should be carefully individualized according to type of EC, disease stage, childbearing plans and performance status.^{3-5,9-16,18-26}

Patient selection

In this light, fertility sparing treatment should be considered only in young patients with FIGO stage IA, grade 1 and type I EC.^{3-5,7,16,19,20,28-31} The eligible patients should have strong desire for future fertility, informed consent about conservative management and no contraindications regarding medication with progestin regimens.^{3,4,7,16,19,20} Furthermore, the selected patients should be further referred to special-

ized oncology centres with well documented experience in fertility sparing management.^{3,4,7,16,19,20}

It is interesting to note, that all patients should be informed that conservative treatment is not the standard of care in EC and there are only few data available regarding oncologic outcome.^{3-5,7,16,19,20,28-31} Moreover, all patients should have a thorough counselling concerning disease recurrence, fertility and childbearing issues.^{3-5,7,16,19,20,28-31} Furthermore, they should be able to comply with a very close surveillance for an extended time period.^{3-5,7,16,19,20,28-31} Additionally, they should be aware of the fact that systematic surgical staging is inevitable in any treatment failure, disease recurrence and after completion of childbearing.^{3-5,7,16,19,20,28-31}

Pre-treatment evaluation

Before starting conservative treatment, a proper endometrial specimen should be obtained from every patient using either office endometrial biopsy, hysteroscopy or dilatation and curettage.^{3,4,7,16,19,20,32-37} Among them, dilatation and curettage is the most preferable technique, mainly because of the quality of sample.^{3,4,7,16,19,20,32-37}

Following endometrial sampling, the whole specimen should be evaluated by an experienced pathologist, in order to diagnose accurately the grade and type of EC.^{3,4,7,16,19,20,35} Moreover, a complete assessment of the hormone receptor profile (estrogen, progesterone) and the expression of molecular prognostic markers (p53, Ki-67, HE-4) in tissue specimen, may provide useful data about the nature and biologic behavior of EC.^{3,4,6,7,16,19,20,38} It can be easily understood the essential role of pathologist in patient's selection process, as women with highly aggressive types of EC should be excluded from any conservative treatment.^{3-5,7,16,19,20}

Furthermore, a thorough visualization of the entire abdomen should be performed in every patient, in order to assess accurately the depth of myometrial

invasion and recognize any suspicious findings or disease extension in ovaries, pelvic and para-aortic lymph nodes and omentum.^{3, 4, 7, 16, 19, 20, 35, 39-41} The detailed visualization could be implemented using either ultrasound, computerized tomography (CT) or magnetic resonance imaging (MRI).^{3 4 7 16 19 20 35 39-41} Among them, MRI is the most preferable technique mainly because of the better visualization of anatomical structures.^{3, 4, 7, 16, 19, 20, 35, 39-43} The crucial role of radiologist in patient's selection process is quite obvious, as women with advanced stage EC should be excluded from any further conservative approach.^{3, 4, 7, 16, 19, 20, 35, 39-41}

In addition, the utilization of laparoscopy in patient's pre-treatment evaluation, could provide useful data about disease stage.^{3, 7, 16, 19, 20} Nevertheless, in EC patients laparoscopy remains an optional evaluation method, when considering fertility sparing approach.^{3, 7, 16, 19, 20}

Fertility sparing treatment

After completion of pre-treatment assessment, the carefully selected young patients could initiate fertility sparing approach which is mainly based on oral progestins.^{3-5, 7, 16, 19, 20, 27, 44, 45} In daily practise, medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are the most commonly used oral progestin regimens.^{3-5, 7, 14, 19, 20, 27, 35, 44, 45} Among them, MPA should be recommended at a daily dose of 400-600 mg, while MA at a daily dose of 160-320 mg.^{3-5, 7, 16, 19, 20, 35, 46} Treatment with oral progestins should be taken for a period of 6 months.^{3-5, 7, 16, 19, 20, 35, 46-48} In the past many patients received progestin regimens for more extended time periods.^{3-5, 7, 16, 19, 20, 35, 46-48} Currently, there are no evidence to support the prolonged administration of oral progestins in EC, in order to achieve late response.^{3-5, 7, 16, 19, 20, 35, 46-48}

In addition, the use of levonorgestrel releasing intrauterine system alone or in combination with gonadotropin releasing hormone analogues (GnRH

analogues), has shown encouraging results for EC patients.^{4, 5, 16, 19, 20, 35, 44, 49} However, future studies are needed, in order to consider them as an alternative in fertility sparing management of EC.^{4, 5, 16, 19, 20, 35, 44, 49}

Patient follow-up

All EC patients with fertility sparing approach, should have a very close surveillance during and after conservative management.^{3-5, 7, 16, 19, 20, 28-31} During treatment with oral progestins, patients should be routinely evaluated with endometrial sampling at 3-month intervals, in order to assess the response to treatment.^{3, 4, 7, 16, 19, 20, 35, 44, 50} The endometrial specimen could be obtained using either hysteroscopy or dilatation and curettage.^{3, 4, 7, 16, 19, 20, 35, 44 50}

After completion of the 6-month protocol with oral progestins, the overall response to treatment should be further evaluated using both endometrial sampling and MRI.^{3, 4, 7, 16, 19, 20, 35, 40, 50}

Post-treatment plan

If there is no response to the fertility sparing treatment, then systematic surgical staging is unavoidable based on current treatment guidelines for EC.^{3-5, 7, 9-16, 18-22, 25, 26, 35, 47, 48} It is interesting to note, that prolonged administration of oral progestins in order to achieve late response, is not supported by clinical evidence.^{3-5, 7, 16, 19, 20, 35, 46-48}

On the other hand, if there is complete response to the conservative treatment, then patients should be further referred to a specialized fertility centre in order to start an assisted conception program as soon as possible.^{3, 4, 7, 16, 19, 20, 51-54} In case that they do not wish a pregnancy straight away, then treatment with oral progestins should be prolonged and patients should be re-evaluated at 6-month intervals.^{3, 4, 7, 16, 19, 20, 35, 44, 51} However, they should be aware of the fact that pregnancy associated with a reduced risk of disease recurrence.^{3, 4, 7, 16, 19, 20, 44, 51}

Oncologic outcome

According to recent publications, the overall response rate in EC patients after fertility sparing management with oral progestins is quite encouraging reaching approximately 75%.^{3,4,7,16,19,20,30,35,51,55} Additionally, there is evidence that pregnancy plays a beneficial role and reduces the risk of disease recurrence.^{3,4,7,16,19,20,44,51}

However, the overall recurrence rate in EC patients having fertility sparing treatment is essentially high ranging between 30% and 40%.^{3,4,7,16,19,20,30,35,51,55} This is the main reason why, systematic surgical staging should be performed in all these patients after completion of childbearing.^{3,4,7,16,19,20,30,35,51,55}

Conclusion

In conclusion, fertility sparing treatment is really possible only in young patients with FIGO stage IA, grade 1 and type I EC.^{3-5,7,16,19,20,28-31} However, conservative treatment in EC is not the standard of care, because there are only few data regarding oncologic outcome.^{3-5,7,16,19,20,28-31} In this light, all patients should have a thorough counselling concerning disease recurrence, fertility issues and childbearing and be informed about the necessity of systematic surgical staging in any treatment failure, disease recurrence or after completion of childbearing.^{3-5,7,16,19,20,28-31}

Conflict of interest

We declare that we have no conflict of interest.

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