

## Estrogen and Progesterone Receptors in Endometrial Cancer: Where Are We Today?

Swasti\*

Senior Consultant, Department of Surgical Oncology (Gynaecology), Max Cancer Centre, Max Super Speciality Hospital, Vaishali, India

\*Corresponding author: Swasti, Senior Consultant, Department of Surgical Oncology (Gynaecology), Max Cancer Centre, Max Super Speciality Hospital, Vaishali, India, Tel: 9582036787; E-mail: swasti20@yahoo.com

Received date: February 13, 2018; Accepted date: February 15, 2018; Published date: February 22, 2018

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### Editorial

#### Introduction

Immunohistochemistry of estrogen receptor (ER) and progesterone receptor (PR) is not routinely adopted by clinicians for the management of endometrial cancers. However, they may have significant importance in determining tumor behaviour and selection of an appropriate treatment protocol. An insight into the role of ER and PR in endometrial cancers is needed for optimizing outcome. The mechanism of action of these receptors in endometrial carcinoma needs to be clearly understood.

#### Structure and Function

ER and PR are ligand dependent transcription factors belonging to the nuclear receptor superfamily. Their binding to different DNA sites initiates the expression of specific genes. There are two classes of ERs:

1. Nuclear ER (ER $\alpha$  and ER $\beta$ ) are members of nuclear receptor family. They are expressed distinctly in various tissues [1] particularly the endometrium leading to cellular proliferation and differentiation [2]. ER- $\alpha$  binds to estrogens with high affinity and low capacity and vice versa with ER- $\beta$ . ER- $\beta$  is needed for organization and adhesion of epithelial cells and hence for functional maturation of differentiated tissues [3,4].

2. Membrane estrogen receptors (mERs)-G protein coupled estrogen receptor (GPER)

Progesterone receptor (PR) also has 2 isoforms which are functionally distinct transcription factors:

1. PR-A-Has estrogen antagonistic action and modulates the anti-proliferative effects of progesterone in uterus
2. PR-B-Has estrogen agonist action and induces cell growth in absence of PR-A [5].

In most of the estrogen responsive cells, transcription of PR gene is induced by estrogen and inhibited by progesterone. There is coordination in the expression of ER and PR [6-8].

#### ER and PR in Endometrial Cancers

Endometrial cancer is hormone dependent. ER- $\alpha$ , PR-A and PR-B have been quantitatively associated with the tumour's histological differentiation [9,10], response to therapy [11] and metastatic potential [12]. Loss of these receptors occurs early in endometrial carcinogenesis. Endometrial carcinoma has lower level of these

receptors in comparison with normal endometrium or endometrial hyperplasia [13].

In endometrial cancer, ER- $\alpha$  expression decreases in both endometrial glands and stroma [14,15]. As the grade of tumor advances, there is further reduction in stromal expression [16]. Reduced or absent PR-A or PR-B expression is observed in endometrial cancers [16]. Similar pattern of expression of PR-A and ER- $\alpha$  is found in endometrial glands and stroma cells. The imbalance in PR-A to PR-B ratio is frequently associated with the development of endometrial cancer [16-18,19]. The relative over-expression of PR-B, which is referred to as an endometrial estrogen agonist [20], without transcriptional repression by PR-A, may be related to the metastatic potential and partially cause deviation from sex steroidal dependency in endometrial cancers [12]. PR-A/PR-B, if <1, has a shorter disease-free and overall survival [21]. Therefore, the expression of PR-B is more sinister. Whether this ratio could be used as a prognostic tool to determine progesterone responsiveness is still unclear. Conflicting evidences exist regarding the PR status in endometrial malignancies. PR-B predominance [22] or loss of both PR isoforms may be seen in advanced endometrial malignancies [16]. Poorly differentiated endometrial cancer cells may only express PR-A [23].

#### Impact on Clinical Decision Making

Five-year survival rate (stage I) and median survival time (stages II-IV, recurrences) for patients with PR positive endometrial cancers were significantly better as compared to PR negative cancers. ER does not have significant prognostic relevance [24].

Reduced expression of ER- $\alpha$  and PR-A in stromal cells of endometrium indicates invasiveness [25]. Loss of hormone receptors in endometrial biopsies prior to surgical staging independently predicts lymph node metastasis [26]. Simultaneous ER and PR negativity significantly adds predictive and prognostic information for low risk grade 1 or 2 endometrioid adenocarcinomas, both in need for lymphadenectomy and adjuvant therapy [26].

There exists a significant correlation between PR-positive tumors and grade, surgical stage, histology, adnexal spread, disease free survival and recurrence [26]. Thus, PR/ER immunohistochemistry appears to be a reliable means for predicting survival in endometrioid adenocarcinoma of endometrium, independent of other clinicopathological parameters [27].

Another challenge is the management of endometrial pre-cancers and cancers in the young women. The definitive treatment of endometrial cancers is surgical staging and hysterectomy. The need is to preserve fertility in these women. Progesterone therapy is utilized for fertility sparing in women with atypical endometrial hyperplasia or

early stage well differentiated endometrioid adenocarcinomas as per guidelines. If response to therapy is achieved, definitive treatment is delayed till after conception. The overall response rate to progestosterone therapy is 50-70% [28]. ER and PR positive tumors respond well to hormonal therapy. Only some PR negative tumors show good clinical response. ER and PR testing on endometrial biopsy specimen may be useful to determine response to progesterone therapy. However, this needs further research.

## Conclusion

In early or recurrent endometrial cancers, the utilization of ER/PR testing on tumor tissue is not yet routinely practised. Prior to initiation of definitive treatment, ER and PR on immunohistochemistry of endometrial biopsy specimen may be useful in predicting lymph node, adnexal involvement and myometrial invasion. These parameters are critical determinants of extent of surgery.

Some questions remain and yet need to be addressed. Can we rely on ER/PR testing for determining response to progesterone therapy? Can we predict the biologic nature of endometrial cancer? Can higher grade more aggressive endometrial cancers be treated with lesser cytotoxic hormonal agents?

We may not have the answers yet. The approach can be to perform ER/PR immunohistochemistry testing, collect data, formulate studies and trials and follow up endometrial cancer patients for the answers. Treatment algorithms may need reprisal in the near future based on use of ER/PR testing.

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