Gynecologic Oncology 148 (2018) 213–221

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The roles of pathology in targeted therapy of women with gynecologic cancers

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HIGHLIGHTS

- Pathologists play a central role in the management (including targeted therapy) of women with gynecologic cancer.
- Pathology is important in identification of targetable tumors based on morphologic features and biomarkers.
- Pathology is key to monitoring therapeutic response, and to discovery of novel biomarkers and therapeutic targets.

ARTICLE INFO

Article history:
Received 18 September 2017
Received in revised form 14 November 2017
Accepted 15 November 2017
Available online 23 November 2017

Keywords:
Cancer
Cervix
Endometrium
Gynecologic cancer
Ovary
Pathology
Precision medicine
Targeted therapy
Treatment

ABSTRACT

The role of the pathologist in the multidisciplinary management of women with gynecologic cancer has evolved substantially over the past decade. Pathologists' evaluation of parameters such as pathologic stage, histologic subtype, grade and microsatellite instability, and their identification of patients at risk for Lynch syndrome have become essential components of diagnosis, prognostic assessment and determination of optimal treatment of affected women.

Despite the use of multimodality treatment and combination cytotoxic chemotherapy, the prognosis of women with advanced-stage gynecologic cancer is often poor. Therefore, expanding the arsenal of available systemic therapies with targeted therapeutic agents is appealing. Anti-angiogenic therapies, immunotherapy and poly ADP ribose polymerase (PARP) inhibitors are now routinely used for the treatment of advanced gynecologic cancer, and many more are under investigation. Pathologists remain important in the clinical management of patients with targeted therapy, by identifying potentially targetable tumors on the basis of their pathologic phenotype, by assessing biomarkers that are predictive of response to targeted therapy (e.g. microsatellite instability, PD1/PDL1 expression), and by monitoring treatment response and resistance. Pathologists are also vital to research efforts exploring novel targeted therapies by identifying homogenous subsets of tumors for more reliable and meaningful analyses, and by confirming expression in tumor tissues of novel targets identified in genomic, epigenetic or other screening studies.

In the era of precision gynecologic oncology, the roles of pathologists in the discovery, development and implementation of targeted therapeutic strategies remain as central as they are for traditional (surgery-chemotherapy-radiotherapy) management of women with gynecologic cancers.

Contents

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https://doi.org/10.1016/j.ygyno.2017.11.020
0090-8258/

1. Introduction

In 2017 in the USA, it is estimated that 107,470 women will be diagnosed with gynecologic cancers, and that 31,600 women will die of gynecologic tumors (Table 1) [1]. This corresponds to 12.6% and 11.2%, respectively, of all cancers in women. The traditional management of women with gynecologic cancer largely rests upon surgery, cytotoxic chemotherapy and radiotherapy, singly or in combination as dictated by the clinical circumstances, with the stage of disease largely determining the need for adjuvant or first-line chemotherapy or radiation. In those with recurrent disease, the choice of cytotoxic chemotherapy is generally most dependent upon time since last platinum-based chemotherapy, with the platinum-free interval determining platinum sensitivity versus resistance. More recently, ever-increasing numbers of targeted therapies directed against a variety of molecular targets in gynecologic cancers and their microenvironments are being developed and used in women with these malignancies.

2. Traditional roles of pathology in treatment of gynecologic cancers

Pathologists have long played a central role in the multidisciplinary management of patients with gynecologic cancer by providing fundamental items of risk-stratification information that guide optimal treatment, such as pathologic stage of disease, histologic subtype and grade [2].

Pathologists are also key to assessment of other parameters that are useful in management. An important example of this is pathologic evaluation of DNA mismatch repair deficiency in endometrial cancer, which has become part of the standard of care for women with these tumors. DNA mismatch repair defects are found in 25–30% of endometrial cancers, and lead to a high-level microsatellite instability (MSI-H) phenotype [3–5]. A few MSI-H endometrial cancers are associated with Lynch syndrome-associated germline alterations in DNA mismatch repair genes (*MLH1*, *PMS2*, *MSH2*, *MSH6*) or *EPCAM*, but the majority are due to a sporadic epigenetic change, namely hypermethylation of the promoter region of *MLH1*, which leads to gene silencing [3,6,7]. Both germline and sporadic alterations are associated with loss of expression of protein products of the affected genes [3,5]. Patients with tumors that exhibit loss of expression of MLH1/PMS2 by immunohistochemistry but which lack *MLH1* promoter hypermethylation are likely to harbor germline *MLH1* mutations as seen in Lynch syndrome. Should the presence of a *MLH1* germline mutation be confirmed, they and their family members would be at increased risk for Lynch-syndrome-associated malignancies, and would require exploration of these risks, including personal and familial genetic counseling and consideration of increased cancer screening. In contrast, tumors that exhibit loss of expression of MLH1/PMS2 by immunohistochemistry and which show *MLH1* promoter hypermethylation are likely to be sporadically hypermethylated tumors, and women with these tumors and their families do not have increased cancer risk [8,9].

Table 1
Estimated numbers of gynecologic tract cancers in 2017 (adapted from [1]).

	Estimated new cases	Estimated deaths
Ovary	22,440	14,080
Uterine corpus	61,380	10,920
Cervix	12,820	4210
Vagina	4810	1240
Vulva	6020	1150
Total	107,470	31,600

3. Targeted therapy

During the past decade, there have been changes in histologic classification that affect surgical management, adjuvant therapies and prognostic assessment; recognition of areas of diagnostic difficulty (such as histologic subtyping of high-grade endometrial carcinomas); and discovery of molecular genetic alterations and genetically defined prognostic subgroups of gynecologic cancer. Most patients with early stage gynecologic cancer (when many endometrial cancers are diagnosed) have good clinical outcomes. Nevertheless, between 1987 and 2008, it is believed that the number of women who died from endometrial cancer in the US increased substantially, while relative survival has declined over the past decade [10]. The clinical course in patients with advanced-stage gynecologic cancer (which is frequent in ovarian cancer) is often aggressive and the prognosis is poor, despite the use of combination cytotoxic chemotherapy. Furthermore, many ovarian cancer patients who

Table 2
A selected summary of targeted therapy in gynecologic cancer.

Targets	Class	Examples
Signaling pathways	PI3K/AKT/mTOR inhibitors MAPK inhibitors JAK1/JAK2 inhibitors NTRK/ROS1/ALK inhibitors	Temsirolimus Trametinib[a] Ruxolitinib[a] Entrectinib[a]
Homologous recombination deficiency	PARP inhibitors	Olaparib, niraparib, rucaparib, veliparib[a]
Hormone receptors	Progesterone receptor Estrogen receptor Gonadotropin-releasing hormone agonists Androgen receptor	Progestins Tamoxifen, aromatase inhibitors Leuprolide Enzalutamide[a]
Angiogenesis	Anti-VEGF/VEGFR	Bevacizumab, cediranib
Immunologic factors	Immune checkpoint inhibitors (e.g. anti-PD1 and anti-CTLA4) Adaptive T cells Vaccines	Pembrolizumab, nivolumab[a], ipilimumab[a]

[a] Undergoing investigation.