Recent advances in gynecologic oncopathology

Over the years, significant advances have appeared in gynecologic oncopathology, especially with regards to the changing trends of cancers developing in different regions of the female genital tract (cervical, endometrial, ovarian, and vulvar), as well as specific managements for individual tumor subtypes.

It has been reported that uterine cancer, especially cervical cancer mortality rates are declining in East Asia, while uterine corpus cancer mortality has relatively increased. Ovarian cancer mortality has been stable.[1] Among various gynecological cancers in Indian population, there has been an increasing trend in the incidence rate of ovarian cancer in most of the registries.[2] Accordingly, over the years there have been developments and updates related to the diagnosis of these tumors.

Cervical cancer is declining in urban population, in contrast to rural population, where it seems to have a high prevalence. Despite cervical cancer being one of the preventable cancers, there has been a challenge in the implementation of a nationwide quality assured cervical cancer screening in India. Various screening techniques for cervical cancer include Papanicolau (Pap) test, visual inspection of cervix, and Human Papilloma virus (HPV) DNA testing with variable sensitivities, and specificities, including higher specificity, but relatively lower sensitivity for conventional Pap test.[3,4] The updated version of the Bethesda System (TBS) for reporting of cervicovaginal smears appeared in 2014.[5] The other changes that have occurred over the years include increased use of liquid-based cytology (LBC), incorporation of co-testing (Pap and high-risk HPV) and of late, primary high-risk HPV screening. P16INK4 is a useful surrogate marker for testing HPV infection. According to the LAST (Lower Anogenital Squamous Terminology Standardization Project) recommendation, this immunohistochemical antibody marker should be tested in cases of diagnostic difficulty between preinvasive cancer (intraepithelial neoplasia grade 2 or 3) and mimics (invariably benign) of these lesions, namely, atrophy, squamous metaplasia, tangential cut sections, and reactive/reparative changes. A diffuse block p16 staining in conjunction with morphological features is interpreted as precancer (high-grade squamous intraepithelial lesion).[6]

The classification of endometrial cancers has evolved from the clinicopathologic type-1 (endometrioid) and type-2 (serous, clear cell, mucinous, mixed) toward molecular classification or rather integrated genomic characterization of endometrial carcinoma, as per the Cancer Genome Atlas (TCGA). Accordingly, endometrial cancers have been reclassified into four molecular subtypes, namely, POLE (DNA polymerase epsilon, catalytic subunit) ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high.[7] Subsequently, Talhouk et al.[8] proposed a simple, genomics-based clinical classifier for endometrial cancer, which essentially includes testing for POLE mutation and combining immunohistochemical profiling to classify endometrial cancers in a more updated manner. In fact, immunohistochemistry has emerged as a powerful tool for a more accurate diagnosis, in uncovering some rare tumors with specific immunohistochemical markers, in prognostication of cancers as well as in the form of certain predictive markers, which help in tailoring specific therapy in certain cancers.[9,10]

One of the major clinical studies in endometrial carcinomas has been the postoperative radiation therapy for endometrial carcinoma (PORTEC), followed by American oncology of clinical practice guideline endorsement of the American society of radiation oncology evidence-based guideline. Accordingly, in women with grade 1 or 2 cancer and with more than, equal to 50% myometrial invasion or grade 3 cancer, and less than 50% myometrial invasion, vaginal brachytherapy is as effective as pelvic radiation therapy at preventing vaginal recurrence and is therefore recommended.[11] This underpins the value of including various clinicopathologic parameters while reporting endometrial carcinomas, or rather various oncology specimens.

Within the realm of ovarian cancers, while most cancers arise either from the ovary or the fallopian tube, it has been realized in clinics that epithelial ovarian cancers (EOCs) are not a single disease entity, but are a heterogeneous group of various subtypes, each characterized by specific histopathological features, biologic features, and underlying genetic events. Clinically, these are stratified into Type-I, which includes histopathologic subtypes such as low-grade serous, endometrioid, clear cell and mucinous and Type II, comprising high-grade serous, carcinomas, and undifferentiated carcinomas.[12] Various immunohistochemical markers have
emerged, which are useful in reinforcing a morphological impression of a particular tumor type, as well as in resolving diagnostic dilemmas, associated with therapeutic implications.

While the most commonly occurring, high-grade serous adenocarcinomas are chemosensitive, clear cell adenocarcinomas are relatively chemoresistant. Despite their initial chemosensitivity, nearly 70% patients develop relapse. One of the challenges in this arena has been to identify certain biomarkers that could be prognostic of the survival outcomes. Certain markers, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) receptor family proteins, and drug transporters, such as hCtr 1 (drug influx pump) and more recently, insulin-like growth factor 1 receptor (IGF1R) have been explored. 

Other recent developments in gynecologic oncology have been related to revised (The International Federation of Gynecology and Obstetrics) FIGO cancer staging. The FIGO Committee for Gynecologic Oncology has brought out the third edition of the FIGO cancer report. 

The Special Issue 1 on gynecologic oncopathology includes an insightful review on various biomarkers associated with chemoresistance, especially in certain subtypes of epithelial ovarian cancers, by Deo et al, [16] reinforcing the value of an exact histopathologic subtyping and need for evaluation of certain specific predictive biomarkers, in order to design improved therapeutic strategies for an optimal response in such cases, which constitutes an important aspect of personalized medicine. There is another illustrated review article on the applications of immunohistochemistry, especially with respect to treatment implications, in gynecologic oncopathology practice, by Rekhi. [17] Furthermore, there are original articles on topics, such as uterine tumor resembling ovarian sex cord tumor (UTROSGT), by Kaur et al, [18] abnormal placentation by Heena et al, [19] along with some interesting case reports, dedifferentiated endometrioid carcinomas, by Boler et al. [20]

Bharat Rekhi
Department of Surgical Pathology, Tata Memorial Centre, HBNI University, Mumbai, Maharashtra, India. E-mail: rekhi.bharat@gmail.com

REFERENCES

1. Lee JY, Kim EY, Jung KW, Shin A, Chan KK, Aoki D, et al. Trends in gynecologic cancer mortality in East Asian regions. J Gynecol Oncol 2014;25:174-82.

2. Murthy NS, Shalini S, Suman G, Pruthvish S, Mathew A. Changing trends in incidence of ovarian cancer - The Indian scenario. Asian Pac J Cancer Prev 2009;10:1025-30.

3. Aggarwal P, Batra S, Gandhi G, Zutshi V. Comparison of papanicolaou test with visual detection tests in screening for cervical cancer and developing the optimal strategy for low resource settings. Int J Gynecol Cancer 2010;20:862-8.

4. Kolopodulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PP, Mustafa RA, et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database Syst Rev 2017;8:CD008587.

5. Nayyar R, Wilbur DC. The Pap test and Bethesda 2014 “The reports of my demise have been greatly exaggerated.” (after a quotation from Mark Twain). Acta Cytol 2015;59:121-32.

6. Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al. The lower anogenital squamous terminology standardization project for HPV-associated lesions: Background and consensus recommendations from the college of American pathologists and the American society for colposcopy and cervical pathology. Arch Pathol Lab Med 2012;136:1266-97.

7. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73.

8. Talhouk A, McConkey MK, Leung S, Yang W, Lum A, Senz J, et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer 2017;123:802-13.

9. McCluggage WG. Immunohistochemical and functional biomarkers of value in female genital tract lesions. Int J Gynecol Pathol 2006;25:101-20.

10. Kaspar HG, Crum CP. The utility of immunohistochemistry in the differential diagnosis of gynecologic disorders. Arch Pathol Lab Med 2015;139:39-54.

11. Meyer LA, Bohlke K, Powell MA, Fader AN, Franklin GE, Lee LJ, et al. Postoperative radiation therapy for endometrial cancer: American society of clinical oncology clinical practice guideline endorsement of the American society for radiation oncology evidence-based guideline. J Clin Oncol 2015;33:2908-13.

12. Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: A proposed unifying theory. Am J Surg Pathol 2010;34:433-43.

13. Huang J, Hu W, Sood AK. Prognostic biomarkers in ovarian cancer. Cancer Biomark 2010‑2011;8:231-51.

14. Deo A, Chaudhury S, Kannan S, Rekhi B, Maheshwari A, Gupta S, et al. IGF1R predicts better survival in high-grade serous epithelial ovarian cancer patients and correlates with hCtr1 levels. Biomark Med 2019;13:511-21.

15. Bhatia N, Denny L. FIGO cancer report 2018. Int J Gynaecol Obstet 2018;143(Suppl 2):2-3.

16. Deo A, Mukherjee S, Rekhi B, Ray P. Subtype specific biomarkers associated with chemoresistance in epithelial ovarian cancer. Indian J Pathol Microbiol. 2020;63(Spl Issue):S64‑9.

17. Rekhi B. Role of immunohistochemistry in Gynaec Oncopathology, including Specific Diagnostic Scenarios, with associated Treatment Implications. Indian J Pathol Microbiol 2020;63(Spl Issue):S70‑80.

18. Kaur K, Rajeshwari M, Gurung N, Kumar H, Sharma MC, Yadav R, et al. Uterine tumor resembling sec cord tumor: A series of six cases displaying varied histopathological patterns and clinical profiles. Indian J Pathol Microbiol 2020;63(Spl Issue):S59‑1.

19. Boler AK, Bandhopadhyay A, Roy S. A report of two cases of dedifferentiated endometrioid carcinomas: A newly described unrecognized tumor of poor prognosis. Indian J Pathol Microbiol 2020;63(Spl Issue):S91‑3.