Histological Classification of Ovarian Cancer

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Gonads

Gonads appear in a 2 week embryo as a genital ridge on either side of the midline between mesonephros and dorsal mesentry. These are formed by proliferation of coelomic epithelium and condensation of the underlying mesenchyme.

Germ Cells

Germ cells appear in the genital ridge in the 6th week. They migrate by amoeboid movement from the wall of yolk sac. Coelomic epithelium of the genital ridge proliferates and the epithelial cells penetrate the underlying mesenchyme forming irregular shaped cords which surround the germ cells = Primitive sex cords.

They disappear and a second generation of cords appear which also surround the germ cells but remain close to the surface. In the 4th month these cords split into isolated cell clusters each surrounding primitive germ cells and later develop into granulosa cells (Fig. 1a & 1b).

Therefore ovarian tumors are divided into:

1. Primary
   Tumors of surface epithelium.
   Sex cord stromal tumors.
   Tumors of germ cell origin.
   Miscellaneous.

2. Metastatic

Purpose of classification of Ovarian Tumors

Ovarian tumors show remarkable diversity and are classified into different histologic groups mainly because treatment of one malignant ovarian tumor differs from the other.

1. Natural history and response to treatment vary, from one group of tumors to another.
2. In the field of Oncology, therapeutic approach may be highly specific for a single type of neoplasm.

Hence accurate histologic diagnosis is critical, in achieving an optimum treatment response. Accordingly communication between Pathologist responsible for the diagnosis, and the Gynaecologist and Oncologist responsible for the treatment is extremely important.

The classification used in any discussion of new therapeutic techniques must be understandable, otherwise the Pathologist report is useless.
4. It is important that the Pathologist and Epidemiologists work together more closely as they search for meaningful relationships between incidence and geographic distribution of various types of ovarian carcinomas. Berg and Baylor (Human Pathology 1973) pointed out the importance of making accurate and specific Pathological diagnosis in epidemiological studies of ovarian cancer.

5. The classification should reflect the present concepts of histogenesis (i.e. cell or tissue of origin) in as uncomplicated a manner as possible.

The WHO CLASSIFICATION of ovarian tumors is primarily histogenetic and was published in 1973. Several new entities have since been described and new concepts relating to these neoplasm have evolved. This required further modifications and extension.

Many other classifications including FIGO are also in use.

### Tumors Derived From the Surface Epithelium

The epithelial tumors of the ovary are derived from coelomic epithelium from which are derived the mullarian ducts and the tissues to which these give rise i.e. tubal endocervical and endometrial epithelium.

Neoplasms arising from the indifferent cells in the surface epithelium retain their embryonic potential to differentiate along mullarian epithelium.

In some, the cells may differentiate along an endocervical pathway. They give rise to Mucinous neoplasms. These may be:-

- Benign
- Borderline
- Malignant

If they differentiate along tubal type of epithelium then they give rise to serous tumors these may also be:-

- Benign
- Borderline
- Malignant

Thirdly the cell may differentiate along endometrial line to produce endometrioid neoplasms. These are mostly malignant. Surface epithelium also has a potential for differentiating along Wolffian lines to form urothelium. Such neoplasm = Brenners Tumors (nearly all are benign; but borderline and malignant forms exist).

Clear cell tumors (so called mesonephroma) are now considered to be of mullarian origin and morphological variant of endometriod groups of neoplasm, although they differ histologically from them and have a poor prognosis.

### Tumors of Surface Epithelium

#### A. SEROUS TUMORS

1. Benign cystadenoma.
   Cystadeno-fibroma.
   Papillary cystadenoma.
2. Borderline serous tumors.
3. Malignant serous cystadenocarcinoma.
   (Papillary carcinoma)

#### B. MUCINOUS TUMORS

1. Benign mucinous cystadenoma.
2. Borderline mucinous tumors.

#### C. ENDOMETROID TUMORS

1. Benign (Cystic Endometriosis).
2. Borderline (Rare Lesions).
   (Resemble atypical endometrial Hyperplasia)
3. Malignant.
   Adeno-carcinomas-Well differentiated, poorly differentiated.
   Adenosquamous.
   Endometriod stromal sarcoma.
   Mixed mullarian tumor.

There is co-existence of endometriod tumors of the ovary with endometrial carcinoma. This is important. Ovarian endometriod carcinoma have been found in association with endometriod carcinoma of uterus in 5-29% of cases and with endometrial hyperplasia in 12-20% cases.

#### D. CLEAR CELL TUMORS

1. Benign clear cell tumor (Cystadeno-fibroma).
2. Borderline clear cell tumors.
3. Malignant clear cell adenocarcinoma.

#### E. BRENNER TUMOR

1. Benign.
2. Borderline (Proliferating brener tumor).
3. Malignant.

#### F. MIXED (e.g. serous + mucinous)

1. Benign.
2. Borderline.
3. Malignant.

G. UNDIFFERENTIATED CARCINOMA
(Always malignant).

TUMORS OF SURFACE EPITHELIUM
1. Constitute 60% of all ovarian tumors 90% of
malignant ovarian tumors.
2. All exist in benign, "Borderline" and malignant
forms.
3. Borderline tumors are defined by WHO as those
tumors which are microscopically benign but on
L/M show changes in the epithelium suggestive of
malignancy i.e. varying combination of epithelial
stratification, detachment of cell cluster, mitosis
and nuclear abnormalities. It is preferable to call
these "Tumors of low malignant potential" rather
than borderline. Their course is clearly malignant
over a prolonged interval.
4. Studies have shown co-existence of areas of
benign, borderline and frankly malignant tissue
within a single tumor. Therefore multiple sections
should be examined because the clinical behaviour
is equated to the most malignant portion of the
tumor.
5. The malignant epithelial tumors are collectively
called
Ovarian Adenocarcinoma. They are the
commonest fatal tumor of female reproductive
system. They infiltrate locally and form implants.
Five years survival is only 30%.
6. It is accepted that among the epithelial tumors of
the ovary there is a simple relationship between
histologic type and outcome, the serous tumors
having a poor prognosis, mucinous tumors a
relatively good prognosis & endometroid tumors a
prognosis intermediate between the two. However
it is difficult to substantiate such relationships,
because:

1. Mixed patterns are seen in ovarian tumors
and only small areas are normally sampled
histologically.
2. Undifferentiated tumors are difficult to classify &
often many tumors are undifferentiated.

Epithelial tumors of all histological types are
equally lethal when compared by stage and grade.

Tumors of Sex Cord and Stromal Origin

The epithelium which envelops the germ cells (sex
cords) during the early embryonic stages of gonadal
development are capable of developing into either the
ovary or testis. If differentiation is in an ovarian
direction, Granulosa cells/theca cells are formed. If
differentiation is in testicular direction, then sertoli cells/
leydig cells are formed.

Stromal component differentiates accordingly,
because there is an interaction between the sex cord and
the adjacent primitive gonadal stroma.

Therefore the neoplastic tissue may also show
differentiation either into ovarian tissue i.e. Granulosa
cell/theca cell tumors or into testicular tissue i.e.
sertoli cells/leydig cell i.e. sertoli cells/leydig cell
tumors.

Sex Cord stormal Tumors
A. Grannulosa-thcca cell tumors
1. Grannulosa cell tumors. A variant is called
Juvenile Grannulosa cell tumor.
2. Thecoma.
3. Fibroma.
4. Mixed and indeterminate types.
B. Sertoli - Leydig cell Tumors
(Andro-blastomas, "Arrheno-blastomas).
1. Pure sertoli cell.
2. Pure leydig cell.
3. Mixed-Well differentiated Intermediately
differentiated Poorly differentiated.
C. Gynandro-blastoma.
It is composed of mixture of grannulosa & sertoli
cells.

Tumors of Germ Cell Origin

1. Germ cell may show no evidence of embryonic or
extra embryonic differentiation. such
undifferentiated germ cell neoplasms are known
as dysgerminomas.
2. A germ cell may differentiate along extra
embryonic pathways into either
a). Placental tissue resulting in an ovarian
chorio-carcinoma.
b). Or yolk sac tissue, which would produce an
EST (Endodermal sinus tumor).
3. Germ cell may differentiate into embryonic tissue forming a teratoma. (15-20% of all ovarian neoplasm). These tumors may be
   (i) Mature (Benign are usually cystic being composed of mature adult type tissue.
   (ii) Immature (Malignant are usually solid and are composed of immature tissue) Struma Ovari carcinoind.
   (iii) Monodermal-when the tumor is composed of only one tissue line e.g Struma Ovari contain only thyroid tissue.

4. If germ cell shows differentiation into primitive embryonic type cells then the tumor is called an Embryonal Carcinoma.

   Tumors of Germ Cell Origin
   a. Dysgerminoma.
   b. EST(YST).
   c. Embryonal carcinoma (Polyembryoma).
   d. Choriocarcinoma.
   e. Teratomas.
      1. Mature.
      2. Immature.
   f. Mixed Forms.
   g. Gonadoblastoma.

   Germ cell tumors may be encountered in all ages but are seen most frequently from 1st to 6th decade. They constitute 60% of ovarian neoplasms in children and adolescents and 1/3 of these are malignant. Incidence of malignancy is relatively low among ovarian tumors (5%) c.f. testicular tumors (90%).

Miscellaneous
   This group comprises of tumors which may be grouped as follows:
   1. Unknown histogenesis which are extremely rare
   2. Primary malignant Lymphomas.
   3. Tumors derived from non-specific cells of the ovary.
      Lipoma. Liposarcoma
      Haemangioma, Haemangioscarcoma
      Leiomyoma, Leiomyosarcoma
      Struma Ovari Carcinoid
      Haemangio-pericytoma
      Rhabdomyosarcoma.

Metastatic Tumors
   Ovary represents the most frequent recipient of metastases.
   The frequency varies and appears to depend at least in part on,
   1. Hormonal function.
   2. Rich premenopausal blood supply.
   3. Anatomic defect in the ovarian capsule from ovulation which may form nidi for metastatic growth.

   From Extragenital sites.
      Breast.
      Stomach.
      Colon.
      Haematopoetic malignancies.

   From Intragenital sites.
      Endometrium is the most common.