

## Advances in surgical pathology of the ovary

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### Laparoscopic surgery of the ovary: The pathologist's role

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Inspection of the abdominal cavity and the pelvic organs by means of a lensed instrument has been known by many different names. Currently, the available instruments are called laparoscopes and the technique, laparoscopy.

In 1834, Blundell first removed a portion of the Fallopian tube for sterilization. Subsequently, in 1880, Lundgren performed an actual tubal ligation. Currently, laparoscopy has become a minimally morbid and simple procedure for tubal sterilization. In 1982, according to the National Center for Health Statistics, sterilization was the most common contraceptive practice among women between the ages of 15 and 44 years in the United States. Although this technique has long been performed to examine patients with abdominal and pelvic diseases, only recently has it become a diagnostic and therapeutic tool, due to the development of pneumoperitoneum, video endoscopy, electrosurgery and laser technologies. Today, laparoscopy has revolutionized the practice of gynecology, particularly in the field of reproductive surgery. In terms of the ablation of lesions, functional recovery and the achievement of pregnancy, the results of endosurgery are identical to those of open surgery but with the further benefits of reduced hospitalization and morbidity.

The creation of pneumoperitoneum is a crucial step. The typical site for the insertion of the insufflation needle is the umbilical area and either carbon dioxide or nitrous oxide may be used for insufflation. Few techniques differ in the method of entering the abdomen, equipment used, timing of insufflation and type of abdominal closure. The addition of the low weight video camera enhanced the use and popularity of operative laparoscopy. The surgeon operates from the video monitor and the role of the assistant is extremely important. Video equipment gives a panoramic view of the abdomen from every angle and by using differently sized lenses, ample magnification is obtained.

Electrosurgery is the controlled transfer of energy to tissue in the form of electrons in contrast to electrocautery and endothermy in which the transfer of energy is in the form of heat. With the unipolar electrosurgical method, which immediately became the standard technique for the electrocoagulation and electrosection of the Fallopian tube at the cornu, a high-voltage, high-frequency current was used and a ground plate (return electrode) attached to the patient completed the electrical circuit. This method has been almost totally replaced by the safer bipolar system, which does not require a separate return electrode. The coagulated tissue should be surrounded by the forceps to reduce bowel burns and other accidental injuries. The tissue effects include vaporization, coagula-

tion, fulguration and cautery. The system has also been adapted to the laser, in which the tissue effect depends on absorption and transformation of light energy. Video-laseroscopy offers many advantages over traditional macro- and microsurgery and is currently widely used.

Laparoscopy has created a picture window in the abdomen and opened new surgical possibilities. Routine endoscopic surgical procedures include adhesion lyse, bowel repair, treatment of hydrosalpinx and ectopic pregnancy, removal of endometriosis, ovarian cysts and uterine fibroids. In addition, tubes, ovaries, particularly in cases of torsion, pelvic and abdominal nodes, as well as the appendix can all be removed. Occasionally, subtotal and total hysterectomies have been performed.

Numerous studies have emphasized the role of laparoscopy in the diagnosis and treatment of benign adnexal masses and ovarian cysts. Treatment includes aspiration of the cyst fluid and fenestration (which are currently rarely performed) as well as cyst excision. The most frequent ovarian masses removed include dermoids, epithelial and functional cysts and, with increasing frequency, borderline epithelial tumors. The prerequisite of this approach is the preoperative evaluation of the patient to avoid the discovery of an unexpected malignant tumor. There are several guidelines for preoperative differential diagnosis between benign and malignant tumors (particularly ovarian tumors), such as a combination of sophisticated ultrasonography and serum tumor markers. The incidence of unexpected malignancy at laparoscopy is low (0.4-2.9%).

The indications for gynecologic endoscopic surgery of malignant tumors have increased in recent years but this procedure is not yet universally accepted. In some centers, laparoscopic salpingo-oophorectomy is followed by vaginal hysterectomy for atypical hyperplasia and low-grade endometrioid carcinoma. Laparoscopic lymphadenectomy may follow hysterectomy in low-stage high-grade endometrial carcinoma with myometrial invasion and may be used in cases of cervical and vaginal cancer. The role of laparoscopy in ovarian cancer is still being debated since this technique is inferior to laparotomy and carries the risk of tumor dissemination. However, it can be used in selected cases.

Endosurgery would allow a new approach in which diagnosis and therapy could be achieved simultaneously rather than consecutively. The pathologist can be consulted for i) conventional diagnosis on biopsies or surgical specimens; ii) intraoperative diagnosis on frozen sections; and ii) consultation in the operating room at the video camera during laparoscopy. In each of these situations, his role should be adjusted to the endoscopist's requests.

Peritoneal endometriosis can be diagnosed, classified and followed by laparoscopy. The pathologist may be requested by the laparoscopist to confirm typical as well as subtle endometriosis and even to provide more sophisticated information, such as evaluation of the degree of hormonal stimulation on conventional slides using quantitative immunohistochemistry and receptor studies, morphometric evaluation of vascularization before and after gonadotropin-

releasing hormone agonist therapy and three-dimensional architecture of the ectopic endometrium. Ovarian and extra ovarian endometriosis can be classified into superficial, hemorrhagic and deeply infiltrating. Adhesions are classified laparoscopically and an evaluation of their age (fibrosis) and nerve proliferation can be requested from the pathologist.

Tissue on either frozen or permanent sections may be altered by artifact and clinical information is, therefore, essential. For instance, tubal fimbriae and mesothelial hyperplasia are difficult to distinguish from papillary serous proliferations. In ovarian biopsies, theca external cells may mimic a primary stromal tumor. In leiomyomas, as well as in samples of ovarian stroma, the cellular vacuolization that results from electrosurgery can be confused with mucin droplets ("signet-ring like cells"). The presence of the pathologist in the operating room is important in difficult cases, particularly in borderline tumors of the ovary. Experienced gynecologic pathologists may have some initial difficulty, since examination with the naked eye differs from the video image due to the magnifying effect of the lens.

## References

- Candiani M, Canis M, Luciano A et al. *Chirurgia laparoscopica in ginecologia. Test Atlanta*. Mosby Doyma Italia, Milano 1997.
- Canis M, Pouly JL, Wattiez A et al. *Laparoscopic management of adnexal masses suspicious at ultrasound*: *Obstet Gynecol* 1997; 89: 679-683.
- Childers JM, Nassari A, Surwit EA. *Laparoscopic management of suspicious adnexal masses*. *Am J Obstet Gynecol* 1996; 175: 1451-1459.
- Granberg S, Wikland M, Janason J. *Macroscopic characterization of ovarian tumors and relation to the histologic diagnosis. Criteria to be used for ultrasound evaluation*. *Gynecol Oncol* 1989; 35: 139-144.
- McGowan L, Lasher P, Norris L et al. *Misstaging of ovarian carcinoma*. *Obstet Gynecol* 1985; 65: 568-572.
- Obiakor I, Maiman M, Mittal K et al. *The accuracy of frozen sections in the diagnosis of ovarian neoplasms*. *Gynecol Oncol* 1991; 43: 61-63.
- The Board of Trustees of the American Association of Gynecologic Laparoscopists: *Manual of Endoscopy*. In: Martin JM (Ed.). *International Congress of Gynecologic Endoscopy*. Washington, DC, 1997.

## Mucinous borderline tumors

Mucinous borderline tumors (MBTs) are almost as common as serous borderline tumors and constitute 40-50% of all mucinous malignant tumors (1) and 71% of those that are stage I (4). Recently, MBTs have been subclassified into two different clinicopathological forms: the most common form is composed of intestinal-type epithelium and has been designated MBT of the intestinal type (IMBT). A second and less common variant of MBT contains endocervical-type epithelium and has been named MBT of the endocervical type (EMBT) (5).

IMBT (85% of MBTs), occur most frequently in the fourth to seventh decades of life with an average age of 41 years (4, 5). Most of them (80-90%) are stage I and less than 10% are bilateral (4, 5). It should be realized that metastatic mucinous tumors in the ovary often mimic primary ovarian mucinous neoplasms, particularly adenocarcinomas of the pancreas and large intestine (6, 7). The metastatic tumor may appear deceptively "benign", "borderline" or malignant. Bilaterality is exceptional in stage I ovarian mucinous tumors; consequently, tumor involvement of both ovaries should arouse the suspicion of metastatic carcinoma.

Grossly, these tumors average 19 cm in diameter and are usually multilocular (4). They cannot be distinguished from mucinous cystadenomas and cystadenocarcinomas. These tumors should be sampled extensively since variations in the degree of epithelial proliferation and nuclear atypia (from benign to borderline, and to carcinoma) are common within an individual neoplasm. Microscopically, IMBTs are composed of cysts and glands lined by atypical epithelium of intestinal type. The cysts may contain papillae, which are typically thin and branching. The lining epithelium almost always contains goblet cells. The epithelial cells are usually stratified to two or three layers, nuclear atypia is mild to moderate and mitotic figures vary from few to numerous.

The criteria used to distinguish IMBTs from mucinous carcinomas have varied, resulting in considerable confusion in the literature. In the classification of the World Health Organization (WHO) (8), the former were defined as showing a degree of epithelial proliferation greater than that seen in benign cystadenomas, but lacking "destructive" stromal invasion. Nevertheless, the morphological evaluation of stromal invasion is more difficult for these tumors than for stromal borderline tumors (SBTs); the stroma, instead of being desmoplastic, may resemble ovarian stroma, and in cystadenomas, the irregular distribution of the glands in the stroma may suggest that invasion has occurred. To resolve this problem, Hart and Norris (9) proposed that noninvasive carcinoma should be diagnosed when the lining epithelial cells show a nuclear stratification of four or greater. Subsequently, Hart (4) added other cytologic and architectural criteria to support the diagnosis of noninvasive carcinoma. These criteria included malignant features of the epithelial cells, an obvious cribriform pattern and the presence of solid cellular papillae without fibrovascular cores. Using these criteria, these authors were able to distinguish accurately between IMBT, which had an excellent prognosis (96% 10-year survival for stage I tumors) and mucinous carcinomas, which were associated with only a 67% survival (9). These "Hart-Norris" criteria became widespread in the United States but many pathologists elsewhere followed the WHO criteria. Because of this disparity in criteria, the cumulative data in the literature does not allow reliable conclusions to be drawn about which of the two sets of criteria (WHO vs. Hart-Norris) better distinguishes IMBT from noninvasive carcinomas (10). Nevertheless, the comparative analysis of some series in which

## Recent advances in mucinous tumors

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Mucinous tumors account for 10-15% of all ovarian tumors (1). Approximately 75% are benign, 10% are borderline and 15% are carcinomatous (1). Although they generally occur in older women (mean ages 51-54 years); mucinous borderline tumors and carcinomas are more common in the first two decades of life than analogous serous tumors (1).

Some mucinous tumors may be of germ cell origin but neometaplasia of the ovarian surface epithelium is an alternative explanation for their development (1). Mucinous ovarian tumors may be associated dermoid cysts, Brenner tumors and mucinous tumors of other organs such as the uterine cervix and the appendix (1). Mucinous tumors are among the most common non endocrine ovarian tumors associated with hormonal manifestations (2). The serum level of alpha-inhibin is considered to be a tumor marker for mucinous borderline tumors and carcinomas (3).

both diagnostic approaches were used has shown no difference in survival whether or not the noninvasive "carcinomas" of Hart and Norris were included in the borderline category (11). Such tumors appear to be of low malignant potential and do not behave like invasive mucinous tumors (10).

In a comparative analysis of 32 IMBTs and 15 stage I noninvasive, well-differentiated mucinous carcinomas reported recently by De Nictolis et al. (12), statistically significant differences in quantitative nuclear morphology were found between IMBTs and noninvasive carcinomas. None of the 15 carcinomas produced metastases and the authors proposed that patients with stage IA, well-differentiated noninvasive carcinomas could be grouped together with stage I IMBTs as far as prognosis and treatment are concerned, providing that the patients have been adequately staged, the tumors extensively sampled and metastatic carcinoma excluded. Recently, Scully (10) and coworkers (1) have proposed maintaining the WHO diagnostic criteria and additionally have divided IMBTs into forms with epithelial atypia and variants with intraepithelial carcinoma. The latter diagnosis is based mainly on cytologic features. The term carcinoma would only be used for tumors exhibiting obvious invasion of the stroma.

Otherwise typical IMBTs may occasionally contain small foci or clusters of tumor cells with atypical nuclei within a reactive stroma. The upper size limit for microinvasion has been arbitrarily set at 10 mm<sup>2</sup> (10). Too few cases of microinvasive IMBTs have been reported to determine its significance (11, 13-15).

Mucinous intestinal cystic tumors of the ovary, whether benign, borderline or malignant, may be associated with mural nodules of various types. These intriguing nodules were initially classified as true sarcomas and sarcoma-like mural nodules (SLMNs) (16, 17). Subsequently, foci of anaplastic carcinoma were also described as nodules in the walls of mucinous cystic ovarian tumors (18). Keratin immunostaining is typically strongly positive in the nodules of anaplastic carcinoma but only focally or weakly positive in the SLMNs (19). Although the distinction between the foci of anaplastic carcinoma and true sarcomatous nodules may not prove to have prognostic significance, both types of nodule should be separated from SLMNs because of the latter's favorable prognosis (17). Over the last 20 years, several additional cases of mural nodules in cystic ovarian tumors have been reported. However, the nature of these mysterious nodules remains unclear. A surprising finding is that combinations of any of the three types of nodules can occur (20). A recent immunohistochemical study of SLMNs suggested a submesothelial origin for these lesions (21). In our experience, SLMNs appear to be self-limiting lesions; if they are well circumscribed, their presence does not influence the prognosis based on the main mucinous cystic tumor (21).

According to the annual report of the International Federation of Gynecology and Obstetrics (FIGO)(22), MBTs are confined to one or both ovaries in 82% of the cases, are stage II in 6%, stage III in 10% and stage IV in 2%. The corresponding figures for mucinous carcinomas are 49%, 11%, 29% and 10% of the cases. Almost all stage II-III IMBTs are associated with pseudomyxoma peritonei and there is convincing evidence that most of these tumors are secondary to mucinous tumors of the appendix (see below). This finding, as well as the almost 100% 5-year survival rate of stage I IMBTs, has raised the question of whether the noninvasive mucinous ovarian tumors have any malignant potential (23). Nevertheless, Scully (10) has recommended that all cases of pseudomyxoma peritonei associated with a mucinous cystic ovarian

tumor should be diagnosed as stage II or stage III ovarian tumors to avoid confusion in the clinical evaluation of these cases. However, the inclusion of these metastatic tumors in the category of IMBTs will result in overestimating their malignant potential.

While performing a frozen section, the pathologist should be aware that additional postoperative sampling of an apparently benign mucinous tumor may disclose a carcinomatous component and the surgeon should be informed that the diagnosis could be changed after examination of the permanent sections. When this is done, the surgeon is more likely to undertake appropriate staging. If there are pseudomyxoma peritonei or bilateral ovarian tumors, removal of the appendix as well as exploration of the abdomen for a possible source of metastasis are recommended.

### **Synchronous mucinous tumors of the appendix and the ovary associated with pseudomyxoma peritonei**

In cases in which ovarian IMBTs are associated with pseudomyxoma peritonei, the appendix is also involved by a similar mucinous lesion in 60% of the cases and appears normal in the remaining 40% (10, 23-26). These findings indicate that in some cases pseudomyxoma peritonei results from a primary ovarian IMBT. The synchronous ovarian and appendiceal tumors were traditionally considered as independent primary neoplasms but there is now convincing evidence that in most cases the ovarian tumors represent metastasis from the appendiceal lesions (23-25).

The gross and microscopic evidence includes: i) simultaneous presentation of the ovarian and appendiceal tumors in cases of pseudomyxoma peritonei; ii) their histologic similarity; iii) high frequency of bilaterality of the ovarian tumors (ovarian IMBTs are usually unilateral and only occasionally associated with pseudomyxoma peritonei); iv) right-sided predominance of unilateral ovarian tumors; v) presence of pools of mucin dissecting through the ovarian stroma (pseudomyxoma ovarii), a rare finding in primary mucinous ovarian tumors; vi) unusually tall mucinous epithelium of the ovarian tumors in the presence of appendiceal and peritoneal involvement; and vii) appendiceal tumors always showing the histologic features of a primary tumor, being either adenomas or adenocarcinomas (23-25).

Features against the secondary nature of ovarian tumors are: i) large size and presence of a benign-looking epithelial component in ovarian tumors; ii) small size, low grade or benign microscopic appearance of the appendiceal tumors with intact appendiceal wall on gross inspection or even microscopic examination; iii) occasional presentation of the appendiceal tumor months or years after the discovery of the ovarian tumor; iv) differences in the histologic grade of the ovarian and appendiceal tumors; v) discordant epithelial immunohistochemical staining in the ovarian and appendiceal tumors; and vi) more favorable clinical behavior in these patients than that expected from patients with metastatic carcinomas (24, 27).

Authors in favor of the metastatic nature of ovarian tumors have contended all of the above points and stated that the appendiceal source of the pseudomyxoma can only be excluded after adequate sampling and microscopic examination of the appendix (23-25). The appendiceal tumors may be small and rupture sites can be sealed after evacuation of mucus and retraction of the appendiceal wall (24). Differences in histologic appearance and immunohistochemical staining between appendiceal and ovarian tumors may reflect tumor heterogeneity or incomplete sampling of the neoplasms (1). Moreover, mucinous tumors metastatic to the ovary typically show a much higher degree of differentiation than

do primary neoplasms and may appear deceptively "benign" in some areas (1, 24). Concordant negative immunostaining reactions for HAM 56 and cytokeratin 7 in both tumors also support their appendiceal origin (28).

At least three molecular genetic studies have addressed this problem (29-31). An analysis of loss of heterozygosity on chromosomes 17q (nm23), 3p (VHL) and 5q in 12 cases disclosed divergent findings in ovarian and appendiceal tumors in three cases (supporting two separate primaries) and similar findings in another three (supporting a single primary tumor with metastatic spread) (29). Although genetic progression of the metastatic tumors could account for the disparity of these results, it should also be noticed that the authors of this study did not interpret the synchronous lack of loss of heterozygosity in six of their cases as concordant results.

c-Ki-raspoint mutations at codons 12 and 13 occur with increasing frequencies in benign (55%), borderline (73%) and carcinomatous (85%) mucinous tumors of the ovary (32). They appear to be an early event in mucinous ovarian tumorigenesis. Recently, we performed a clinicopathological study and a comparative analysis of c-Ki-ras mutations in six cases of synchronous ovarian and appendiceal tumor (30). Their clinicopathologic features (simultaneous presentation, bilaterality or right-sided predominance, similar histopathological findings and presence of pseudomyxoma peritonei) suggested that they were primary appendiceal tumors metastatic to the ovaries. Moreover, the concordance of c-Ki-ras mutational pattern in both tumors in each patient also suggested their clonal nature and supported that they were not separate neoplasms but originated from the same clone which, in the light of the clinicopathologic data, was most likely to be of appendiceal origin. Our results have recently been confirmed by a similar study of 16 additional cases (31).

In Rutgers and Scully's series (5), EMBTs accounted for approximately 15% of MBTs. These tumors differed in many respects from IMBTs, as shown in Table 1.

The prognosis of EMBTs is excellent and approximates that of SBTs. All the patients were alive at an average of 3.7 years of follow-up. Two patients, initially treated by a unilateral salpingo-oophorectomy, had recurrent tumors in the contralateral ovary. One-half of the patients with higher-stage tumors were treated with chemotherapy and none had tumor progression or recurrence.

**Table 1. Comparative analysis of endocervical-like and intestinal mucinous borderline tumors (5).**

	EMBT(a)	IMBT(b)
Average age (years)	34	41
Bilaterality (%)	40	6
Diameter (cm)	8	19
Multilocularity (%)	20	72
Gross papillae (%)	87	17
Stromal papillae	++++	+
Cellular tufting	++++	+
Goblet cells (%)	0	100
Grimelius + cells (%)	3	86
Acute inflammation (%)	100	0
Endometriosis, either ovary (%)	30	6
Stage II-III (%)	24	10
Discrete implants +/- or node mets (%)	20	0
Pseudomyxoma peritonei (%)	0	17

(a)EMBT = endocervical mucinous borderline tumors. (b)IMBT = intestinal mucinous borderline tumors.

There is no evidence that chemotherapy is helpful, even for patients with higher-stage disease (5).

**Mucinous carcinomas**

Recently, Hoeri and Hart (14) have summarized the clinicopathological features of these tumors as follows: i) mucinous carcinomas of the ovary are very uncommon tumors, after metastatic carcinomas and tumors associated with pseudomyxoma peritonei have been excluded; ii) they are rarely bilateral; iii) FIGO stage is the single most important prognostic factor, and stage I carcinomas have an excellent prognosis; iv) stage I carcinomas that metastasize have extensive stromal invasion; v) extensive stromal invasion is found only in tumors with intraepithelial carcinoma; vi) high-stage carcinomas invariably contain extensively invasive carcinoma and have very poor prognosis; and vii) stromal microinvasion (<1 mm) does not change the good prognosis of either carcinomas or borderline tumors at stage I.

**References**

- Scully RE, Young RH, Clement PB. *Tumors of the ovary, maldeveloped gonads, Fallopian tube, and broad ligament.* Atlas of Tumor Pathology. Third Series. Fascicle 23. AFIP, Washington, DC, 1998; 51-168.
- Matias-Guiu X, Prat J. *Ovarian tumors with functioning stroma: An immunohistochemical study with hCG mono and polyclonal antibodies,* cancer 1990; 65: 2001-2005.
- Healy DL, Burger HG, Mamer P et al. *Elevated serum inhibin concentrations in postmenopausal women with ovarian tumors.* N Eng J Med 1993; 329: 1539-1542.
- Hart WR. *Ovarian epithelial tumors of borderline malignancy (carcinomas of low malignant potential).* Hum Pathol 1977; 8:541-549.
- Rutgers JL, Scully RE. *Ovarian mullerian mucinous papillary cystadenomas of borderline malignancy A clinicopathologic analysis:* Cancer 1988; 61: 340-348.
- Lash RH, Hart WR. *Intestinal adenocarcinomas metastatic to the ovaries: A clinicopathologic evaluation of 22 cases.* Am J Surg Pathol 1987; 11: 114-121.
- Young RH, Hart WR. *Metastases from carcinomas of the pancreas simulating primary mucinous tumors of the ovary: A report of seven cases.* Am J Surg Pathol 1989; 13: 748-756.
- Serov SF, Scully RE, Sobin LH. *International histological classification of tumours, vol 9, Histological typing of ovarian tumours.* World Health Organization, Geneva 1973; 17-18.
- Hart WR, Norris HJ. *Borderline and malignant mucinous tumors of the ovary Histologic criteria and clinical behavior.* Cancer 1973; 31:1031-1045.
- Silva EG, Kurman RJ, Russell P et al. *Symposium: Ovarian tumors of borderline malignancy* Int J Gynecol Pathol 1996; 15: 281 -302.
- Siriaunkgul 5, Robbins KM, McGowan Let al. *Ovarian mucinous tumors of low malignant potential: A clinicopathologic study of 54 tumors of intestinal and mullerian type.* Int J Gynecol Pathol 1995; 14:198-206.
- De Nictolis M, Montironi R, Tommasoni Set al. *Benign, borderline and well-differentiated malignant intestinal mucinous tumors of the ovary: A clinicopathologic, histochemical, immunohistochemical and nuclear quantitative study of 57 cases.* Int J Gynecol Pathol 1994; 13: 10-21.
- Nayar R, Siriaunkgul 5, Robbins KM et al. *Microinvasion in low malignant potential tumors of the ovary.* Hum Pathol 1996; 27: 521-527.
- Hoerl HO, Hart WR. *Primary ovarian mucinous cystadenocarcinomas. A clinicopathologic study of 49 cases with long term follow-up.* Am J Surg Pathol 1998; 22: 1449-1462.
- Riopel MA, Ronnett BM, Kumman RJ. *Diagnostic criteria and behavior of mucinous ovarian tumors: Borderline, microinvasive, invasive and metastatic.* Modern Pathol 1998; 11: 113 (abstract).
- Prat J, Scully RE. *Sarcomas in ovarian mucinous tumors.* Cancer 1979; 44: 1327-1331.
- Prat J, Scully RE. *Ovarian mucinous tumors with sarcoma-like mural nodules.* Cancer 1979; 44:1332-1344.
- Prat J, Young RH, Scully RE. *Ovarian mucinous tumors with foci of anaplastic carcinoma.* Cancer 1982; 50: 300-304.
- Matias-Guiu X, Aranda I, Prat J. *Immunohistochemical study of sarcoma-like mural nodules in a mucinous cystadenocarcinoma of the ovary.* Virchows Archly A Pathol Anat 1991; 419: 89-92.

20. Fujii S, Konishi J, Kobayashi F. *Sarcoma-like mural nodules combined with a microfocus of anaplastic carcinoma in mucinous ovarian tumor*. *Gynecol Oncol* 1985; 20: 219-233.
21. Prst J. *Sarcoma-like mural nodules in mucinous cystic tumors of the ovary*. *Modern Pathol* 1997; 10:107 (Abst.).
22. Pettersson F. Annual Report of the Results of Treatment in Gynecological Cancer. International Federation of Gynecology and Obstetrics, Stockholm 1991.
23. Ronnett BM, Kurman RJ, Zahn CM et al. *Pseudomyxoma peritonei in women: A clinicopathologic analysis of 30 cases with emphasis on site of origin, prognosis, and relationship to ovarian mucinous tumors of low malignant potential*. *Hum Pathol* 1995; 26: 509-524.
24. Young RH, Gilka CB, Scully RE. *Mucinous tumors of the appendix associated with mucinous tumors of the ovary and pseudomyxoma peritonei: A clinicopathologic analysis of 22 cases supporting an origin in the appendix*. *Am J Surg Pathol* 1991; 15: 415-429.
25. Prayson RA, Hart WR, Petras RE. *Pseudomyxoma peritonei: A clinicopathologic study of 19 cases with emphasis on site of origin and nature of associated ovarian tumors*. *Am J Surg Pathol* 1994; 18: 591-603.
26. Michael H, Sutton G, Roth LM. *Ovarian carcinoma with extracellular mucin production: Reassessment of "pseudomyxoma ovarii et peritonei"*. *Int J Gynecol Pathol* 1987; 6: 298-312.
27. Seidman JD, Elsayed AM, Sobin LH et al. *Association of mucinous tumors of the ovary and appendix. A clinicopathologic analysis of 22 cases*. *Am J Surg Pathol* 1993; 17: 22-34.
28. Ronnett BM, Shmookler BM, Diener-West M et al. *Immunohistochemical evidence supporting the appendiceal origin of pseudomyxoma peritonei in women*. *Int J Gynecol Pathol* 1997; 16:1-9.
29. Chuaqui RF, Zhuang Z, Emmert-Buck MR et al. *Genetic analysis of synchronous mucinous tumors of the ovary and appendix*. *Hum Pathol* 1996; 27: 165-171.
30. Cuatrecasas M, Matias-Guiu X, Prat J. *Synchronous mucinous tumors of the appendix and the ovary associated with pseudomyxoma peritonei: A clinicopathologic study of six cases with comparative analysis of c-Ki-ras mutations*. *Am J Surg Pathol* 1996; 20: 739-746.
31. Ronnett BM, Szych C, Staebler A et al. *Molecular genetic evidence supporting the appendiceal origin of pseudomyxoma peritonei (PMP) in women*. *Modern Pathol* 1999; 123 (abstract).
32. Cuatrecasas M, Villanueva A, Matias-Guiu X et al. *K-ras mutations in mucinous ovarian tumors. A clinicopathologic and molecular study of 95 cases*. *Cancer* 1997; 79:1581-1586.

## Simultaneous carcinomas involving the endometrium and ovaries

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The simultaneous occurrence of multiple primary cancers in the upper female genital tract is well known (1-5). In fact, ovarian carcinomas may be associated with endometrial malignancies as well as with involvement of the contralateral ovary or even the cervix (6).

The occasional finding of simultaneous primary tumors in the ovaries and endometrium should not be surprising. The surface epithelium of the ovary has the same embryologic derivation as the Mullerian duct and therefore, in adults, a given carcinogenic stimulus may produce similar epithelial proliferations in both structures. Cancers developing concomitantly in these locations are not infrequently misdiagnosed as metastatic tumors (3). However, the overall survival of these patients suggests multifocal rather than metastatic

disease (3). These tumors should be separated from true metastatic carcinomas from one to another organ of the female genital tract, since each of these two categories carries a different prognosis and clinical implications.

Several clinicopathological features can be helpful for the correct classification of the into these two groups (stage, size, bilaterality and pattern of ovarian involvement, histological types and grades, presence of endometrial hyperplasia or ovarian endometriosis, myometrial, tubal, lymphatic and blood vessel invasion, as well as follow-up of the patients) (2-5). In some cases, however, it may be difficult to distinguish between metastatic and independent malignancies because the tumors may share features of both categories.

Seven years ago, we studied 18 cases of adenocarcinoma, simultaneously involving both the endometrium and the ovary, and tried to assess the importance of clinical, pathological, immunohistochemical and DNA flow cytometric parameters in the differential diagnosis (6). Of the nine cases with independent primary tumors, seven showed different immunohistochemical profiles (CAM 5.2, wide spectrum keratin, vimentin carcinoembryonic antigen, CEA 125, and CA 19.9) in the ovarian and uterine tumors but only four of the nine metastatic tumors had similar staining characteristics in both locations. In contrast, when one of the two simultaneous tumors was metastatic from the other, identical aneuploid DNA indexes were encountered (6). Therefore, in synchronous tumors with different DNA indexes, the possibility of independent primaries has to be considered. Our data indicated that immunohistochemical and DNA flow cytometric analysis may be of some value when distinguishing between metastatic and independent tumors. The differential diagnosis, however, still largely relies upon conventional clinicopathological criteria (6).

Molecular pathology techniques can also be of some help in distinguishing independent primaries from metastatic tumors. Recent studies have shown a different pattern of loss of heterozygosity on chromosome 17 in the ovary and endometrium in several cases of synchronous tumors of both locations (7, 8). Also, X-chromosome inactivation, *K-ras* mutations and mutations or allelic losses of p53 have been applied (9). Moreover, the demonstration of microsatellite instability in endometrial carcinomas and its absence in the ovarian tumors can also be taken as strong evidence of their independent origin. Indeed, we have successfully used such an approach in the evaluation of several cases of synchronous endometrioid tumors of the ovary and endometrium (10).

### References

1. Eitel P, Hendrikson M, Ross J et al. *Simultaneous presentation of carcinoma involving the ovary and the uterine corpus*. *Cancer* 1982; 50: 163-170.
2. Ulbright TM, Roth LM. *Metastatic and independent cancers of the endometrium and the ovary: A clinicopathologic study of 34 cases*. *Hum Pathol* 1985; 16: 28-34.
3. Woodruff JD, Solomon D, Sullivant H. *Multifocal disease in the upper genital canal*. *Obstet Gynecol* 1985; 65: 695-698.
4. Rusell P, Bannatyne PM, Solomon HJ et al. *Multifocal tumorigenesis in the upper female genital tract: Implications for staging and management*. *Int J Gynecol Pathol* 1985; 4: 192-210.
5. Young RH, Scully RE. *Metastatic tumors of the ovary*. In: Kurman R. (Ed.). *Blaustein's Pathology of the Female Genital Tract*. 3th ed. Springer-verlag, New York 1987; 742-768.
6. Prat J, Matias-Guiu X, Barreto J. *Simultaneous carcinoma involving the endometrium and the ovary. A clinicopathologic, immunohistochemical, and DNA flow cytometric study of 18 cases*. *Cancer* 1991; 11: 2455-2459.
7. Shenson DL, Gallion HH, Powell DE et al. *Loss of heterozygosity and genomic instability in synchronous endometrioid tumors of the ovary and endometrium*. *Cancer* 1995; 4: 650-657.

8. Emmert-Buck MR, Chuaqui R, Zhuang Z et al. *Molecular analysis of synchronous uterine and ovarian endometrioid tumors*. *Int J Gynecol Pathol* 1997; 16: 143-148.
9. Fujita M, Enomoto T, Wads H et al. *Application of clonal analysis. Differential diagnosis for synchronous primary ovarian and endometrial cancers and metastatic cancer*. *Am J Olin Pathol* 1996; 105: 350-359.
10. Catusus LI, Machin P, Lerma E et al. *Microsatellite instability in endometrial carcinomas. Clinicopathologic correlations in a series of 42 cases*. *Hum Pathol* 1998; 29: 1160-1164.

## Recent advances in sex cord-stromal tumors

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Sex cord-stromal tumors of the ovary are rare, making up approximately 8% of all ovarian tumors. Granulosa cells, theca cells and their luteinized derivatives, Sertoli cells, Leydig cells and fibroblasts of gonadal stromal origin, in pure or combined forms and in variable degrees of differentiation, may be present.

Fibromas, which are almost never associated with endocrine manifestations, are the most frequent subtype, accounting for half of sex cord-stromal tumors; most of the other subtypes are granulosa cell tumors.

Granulosa cell tumors comprise two different subtypes, with distinct clinical settings and microscopic appearance: adult and juvenile types. Adult-type granulosa cell tumors occur more often in postmenopausal women and are the most common clinically estrogenic ovarian tumor. Granulosa cells grow in a wide variety of patterns, which are very commonly admixed. The better differentiated tumors typically have microfollicular, macrofollicular, insular, trabecular, solid or hollow-tubular patterns. The less well differentiated forms include watered-silk and gyriform diffuse (sarcomatoid) pattern alone or in combination. Whatever the histologic pattern may be, the best morphological markers of adult-type granulosa cell tumors are the presence of small cavities similar to Call-Exner bodies and cells with pale nuclei and prominent grooves.

Juvenile granulosa cell tumors usually occur in the first three decades of life. The microscopic appearance is that of a solid neoplasia with focal follicle formation. In contrast to the adult type, neoplastic cells have abundant cytoplasm and round nuclei, usually without grooves. Nuclear atypia varies from slight to severe and the mitotic rate may be high. Despite these histological features, stage is the only reliable prognostic factor in these tumors.

Sertoli-Leydig cell tumors are another interesting group of gonadal sex cord-stromal tumor. They usually occur in young women, most of them under 30 years of age and about one-third of the patients develop signs of virilization.

Different histological subtypes are described: well differentiated, of intermediate differentiation and poorly differentiated, with heterologous elements and retiform pattern. Well-differentiated tumors have a nodular architecture with fibrous bands intersecting lobules of neoplastic cells, arranged in hollow or solid tubules. Nuclear atypia is usually absent or minimal and mitotic figures are rare.

Tumors of intermediate differentiation are composed of Sertoli and Leydig cells with varying degrees of immaturity, growing in dif-

fuse sheets, nests, solid tubules and thin cords resembling the sex cords of the embryonic testis. Poorly differentiated Sertoli-Leydig cell tumors have been classified as sarcomatoid because, in addition to the presence of specifically diagnostic elements, they resemble sarcomas.

Retiform pattern, present in 15% of these tumors is characterized by a network of irregularly branching tubules and cysts into which papillae or polypoid structures may project.

In approximately 20% of these tumors of intermediate or poor differentiation, the presence of heterologous elements such as glands of intestinal-type epithelium and foci of carcinoid, cartilage, hepatocytes, embryonal rhabdomyosarcoma, retinal, as well as other tissues, is described.

### Differential diagnosis

Pathological diagnosis of sex cord-stromal tumors is one of the most difficult problems in ovarian pathology. Extensive sampling of the specimen is mandatory but sometimes it is not enough to provide an accurate diagnosis.

Endometrioid carcinomas (Sertoliform type) and metastatic adenocarcinomas (tubular Krukenberg's tumor) may simulate Sertoli cell tumors, Sertoli-Leydig cell tumors and granulosa cell tumors, which are of the well-differentiated type.

Carcinoid tumors, especially those of trabecular pattern, may be confused with intermediate Sertoli-Leydig cell tumors. The retiform pattern of Sertoli-Leydig cell tumors has to be distinguished from endodermal sinus tumors, serous cystadenoma of borderline malignancy, serous or endometrioid carcinoma and mesodermal mixed tumors.

The diffuse and/or sarcomatoid pattern of granulosa cell tumors may resemble an endometrial stromal sarcoma, an undifferentiated carcinoma or a small cell carcinoma of the hypercalcemic type.

Steroid cell tumors (NOS) may be confused with other neoplasms, particularly luteinized granulosa cell tumors and thecomas, clear cell carcinomas, metastatic renal cell carcinoma and malignant melanoma.

Sex cord-stromal tumors have a rather nonspecific immunohistochemical profile. Their expression of intermediate filaments is quite variable and this variability is misleading when making a differential diagnosis. The absence of epithelial membrane antigen in these tumors has diagnostic value, since most of the histologic look-alikes of granulosa and Sertoli-Leydig cell tumors, such as metastatic and primary carcinomas, are positive to epithelial membrane antigen.

Recent reports have emphasized the importance of the immunodetection of inhibin in sex cord-stromal tumors in providing a reliable differential diagnosis with epithelial neoplasms, melanoma, lymphoma and soft tissue tumors.

Inhibin is a glycoprotein produced by granulosa cells, theca cells and Sertoli cells. Immunostaining by antibodies against alpha-inhibin has been strongly positive in granulosa cell tumors, Sertoli cell tumors, and consistently negative in carcinomas, germ cell tumors, melanomas and lymphomas. Antibodies against the alpha-subunit of human inhibin may also be useful in identifying, late metastases of granulosa cell tumors, especially when the previous diagnosis is unknown.

Furthermore, inhibin appears to be a sensitive serological marker of the presence or progression of these tumors and their metastases. It may be valuable in assessing response to chemotherapy or in predicting recurrent disease. Serum inhibin level evaluation

should be incorporated into large-group trials of therapy for sex cord-stromal tumors.

## Prognosis

The behavior of these tumors has not been easy to define because they may have a long clinical course with late recurrences and metastases. Prognosis is closely related to stage and degree of differentiation. In stage I Sertoli-Leydig cell tumors, only those of intermediate differentiation (11%), poor differentiation (59%) and those with heterologous elements (19%) have been clinically malignant. The retiform pattern also seems to be associated with more aggressive behavior. In contrast to granulosa cell tumors, recurrences of Sertoli-Leydig cell tumors usually occur early, in the first year after diagnosis.

Granulosa cell tumors are characterized by indolent growth with a significant capacity to recur many years after an apparent clinical cure.

Several pathological features have been evaluated as prognostic factors. Nuclear atypia, high mitotic rate, high Ki67 PI and the absence of Call-Exner bodies seem to be pathologic predictors of recurrence.

Other studies have investigated biological and molecular parameters by means of immunohistochemistry (c-myc, p21-ras, c-erbB2, p53), but results have been inconsistent.

DNA ploidy, percent S-phase fraction, proliferative index and morphometric studies have been performed in series of granulosa cell tumors. Aneuploidy, S-phase fraction >10%, large nuclear area and nuclear perimeter seem to be adverse prognostic factors. Nevertheless, using these clinical, pathologic or biological parameters, it is difficult to predict early recurrences and impossible to predict late recurrences.

Trisomy of chromosome 12 has frequently been described in various neoplasms, particularly in tumors of the female genitourinary tract. Recently, this chromosomal abnormality has been found in a large proportion of sex cord-stromal tumors, including thecoma-fibromas, granulosa cell tumors and Sertoli-Leydig cell tumors. The prognostic significance of trisomy 12 in these tumors is unknown.

Sex cord-stromal tumors of the ovary may present in a wide variety of morphological pictures, creating serious problems of differential diagnosis with other neoplasia. Recent advances have provided key markers to facilitate the correct diagnosis. The behavior of these tumors remains somewhat unpredictable, especially because of the lack of prognostic factors in early stage disease.

Further studies are needed to go deeper into the pathogenesis of these fascinating tumors.

## References

- Bogges JF, Soules MR, Gaff BA et al. *Serum inhibin and disease status in women with ovarian granulosa cell tumors.* Gynecol Oncol 1997; 64: 64-69.
- Costis MJ, Ames PF, Walls J et al. *Inhibin immunohistochemistry applied to ovarian neoplasms: A novel, effective, diagnostic tool.* Hum Pathol 1997; 28: 1247-1254.
- Fleming P, Wellmann A, Maschek H et al. *Monoclonal antibodies against inhibin represent key markers of adult granulosa cell tumors of the ovary even in their metastases. A report of three cases with late metastases, being previously misinterpreted as hemangiopericytoma.* Am J Surg Pathol 1997; 19: 927-933.
- Haba R, Miki H, Kobayashi S et al. *Combined analysis of flow cytometry and morphometry of ovarian granulosa cell tumor.* Cancer 1993; 72: 3258-3262.
- King LA, Okagaki T, Gallup DG et al. *Mitotic count, nuclear atypia, and immunohistochemical determination of Ki67, c-myc, p21-ras, c-erbB2, and p53 expression in granulosa cell tumors of the ovary: Mitotic count and Ki67 are indicators of poor prognosis.* Gynecol Oncol 1996; 61: 227-232.
- Kommoas F, Oliva E, Bhan AK et al. *Inhibin expression in ovarian tumors and tumor-like lesions: An immunohistochemical study* Mod Pathol 1998; 11: 656-664.

- Matias Guiu X, Pans C, Prat J. *Mullerian inhibiting substance, alpha-inhibin, and CD99 expression in sex cord-stromal tumors and endometrioid ovarian carcinomas resembling sex cord-stromal tumors.* Hum Pathol 1998; 29: 840-845.
- Miller BE, Barron BA, Wan JY et al. *Prognostic factors in adult granulosa cell tumor of the ovary.* Cancer 1997; 79: 1951-1955.
- Persona DL, Hartmann LC, Herath JF et al. *Fluorescence in situ hybridization analysis of trisomy 12 in ovarian tumors.* Am J Clin Pathol 1994; 102: 775-779.
- Riopel MA, Perlman EJ, Seidman JD et al. *Inhibin and epithelial membrane antigen immunohistochemistry assist in the diagnosis of sex cord-stromal tumors and provide clues to the histogenesis of hypercalcemic small cell carcinomas.* Int J Gynecol Pathol 1998; 17: 46-53.
- Rishi M, Howard LN, Brattauer GL et al. *Use of monoclonal antibody against human inhibin as a marker for sex cord-stromal tumors of the ovary.* Am J Surg Pathol 1997; 21: 583-589.
- Roush GR, el Naggari AK, Abdul Karim FW. *Granulosa cell tumor of ovary: A clinicopathologic and flow cytometric DNA analysis.* Gynecol Oncol 1995; 56: 430-434.
- Shashi V, Golden WL, von Kap Herr C et al. *Interphase fluorescence in situ hybridization for trisomy 12 on archival ovarian sex cord-stromal tumors.* Gynecol Oncol 1994; 55: 349-354.
- Taruscio D, Carcangiu ML, Ward DC. *Detection of trisomy 12 on ovarian sex cord-stromal tumors by fluorescence in situ hybridization.* Diagn Mol Pathol 1993; 2: 94-98.

## Neuroendocrine tumors of the ovary

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Neuroendocrine tumors are a heterogeneous group of separate clinicopathological entities, which have a common characteristic, *i.e.*, expression of endocrine differentiation potential. In order to diagnose endocrine differentiation within a tumor, we should first see the histological characteristics suggesting such differentiation and apply special studies only to confirm the suspicion. In the ovary, the term "neuroendocrine" relates mainly to the widely known carcinoids but it may also be applied to rare neuroendocrine carcinomas of non-small-cell type and small-cell carcinomas of pulmonary type, which have been described in recent years.

### Neuroendocrine carcinomas of non small-cell type

Neuroendocrine carcinomas of non small-cell type are characterized by the presence of islands, sheets and trabeculae with little intervening stroma (organoid growth pattern) as well as by cellular homogeneity. Palisading of cells at the periphery of nests may be seen, particularly in low-grade tumors. Neuroendocrine carcinomas are higher grade than carcinoids. To date, nine such tumors have been reported and all developed in association with glandular müllerian-type component (seven mucinous-type tumors, one endometrioid carcinoma and one carcinosarcoma). Microscopically, the neuroendocrine component grew in the background of a surface-epithelial tumor but both components could be still recognized as separate. The tumor cells were medium-sized to large. Other cytological characteristics, *i.e.*, the amount of cytoplasm, chromatin and

nucleoli pattern were not consistent. In nearly all of the cases, the neuroendocrine tumor presented with moderate to marked atypia, high mitotic activity as well as extensive and/or single cell necrosis. The neuroendocrine differentiation was confirmed by the presence of two or more specific markers, *i.e.*, argyrophilic and/or argentaffinic granules, chromogranin A and less frequently serotonin, synaptophysin and neuron specific enolase. Interestingly, most cells in the glandular components were also positive for chromogranin and serotonin.

The prognosis for neuroendocrine carcinomas of the ovary appears worse than that for typical surface epithelial carcinomas. In the series published by Eichhorn *et al.*, three of three patients with available follow-up data died after 3, 8, and 36 months, despite early clinical stage in two cases. Patients reported by other authors died within 3 to 10 months of metastases to the liver, peritoneum or brain, despite postoperative chemotherapy.

### **Small-cell carcinomas of the pulmonary type**

Primary ovarian small-cell carcinomas of the pulmonary type do not differ histologically from their counterparts in other organs. They are composed of small cells with scanty cytoplasm, with oval to spindle-shaped nuclei and inconspicuous nucleoli. The cells are arranged in closely packed sheets, islands and trabeculae. About 13 cases of this tumor type in the ovary have been reported. Eight of 11 tumors described by Eichhorn *et al.* had a component of müllerian tumor or epithelium, *i.e.*, endometrioid carcinoma in four cases, squamous differentiation in one, and atypical mucinous epithelium in another; two small-cell carcinomas were associated with Brenner tumors. This suggests that, like non-small-cell neuroendocrine carcinomas, at least some primary ovarian small cell carcinomas of the pulmonary type develop in preexisting benign or malignant ovarian tumors. In the series published by Eichhorn *et al.*, only two of nine tumors studied by histochemical and immunohistochemical techniques showed argyrophilia and positive chromogranin A staining. NSE was positive in six of nine tumors. These results are similar to those reported for pulmonary smallcell carcinomas (reviewed by Eichhorn) but different from the neuroendocrine carcinomas of non-small-cell type. The prognosis for this tumor type is poor. Most patients with available follow-up data died within 1 year or had early recurrence.

### **Ovarian carcinoids**

Ovarian carcinoids develop in pure form or in association with other tumors, mainly teratomas. They originate from endocrine cells, either of teratomatous, or possibly also of indigenous. There are four histological types of ovarian carcinoids: insular, trabecular, strumal and mucinous. Mucinous carcinoid and its special form, goblet cell carcinoid, are only exceptionally described as primary in the ovary. In the

mucinous carcinoid, enterochromaffin cells are intimately admixed with mucin-filled neoplastic cells. In the goblet cell type, signet-ring cells (with no atypia or mitoses) create glands or solid structures similar to Brunner glands. One can also see cells with granular, eosinophilic cytoplasm, some of which are positive for serotonin. The nuclei are small, round or oval. Electron microscopy studies show either cells with secretory granules or goblet cells, or intermediate cells with both characteristics. Talerman also mentions a more atypical form of the ovarian mucinous carcinoid. The tumor is comparable to "argentaffin cell carcinoma", described by Soga *et al.* This carcinoid has adenocarcinoma architecture and is composed of glandular and solid structures with hyperchromatic nuclei and frequent mitoses. Most glandular and solid structures are argentaffinic and/or argyrophilic. Among enterochromaffin cells, one can also observe cells negative for these stainings but positive for mucicarmine. The material present in the glandular lumina is mucicarmophilic. Immunohistochemistry reveals chromogranin A in many cells. Serotonin and gastrin may be present in some.

The mucinous type of ovarian carcinoid has a worse prognosis than other types. It behaves similarly to the mucinous carcinoid of the vermiform appendix; *i.e.*, it spreads via the lymphatics and may extend beyond the ovary at the time of diagnosis.

### **References**

- Alenghat E et al. *Primary mucinous carcinoid tumor of the ovary.* Cancer 1986; 58: 777-783.
- Collins RJ et al. *Primary mixed neuroendocrine and mucinous carcinoma of the ovary.* Arch Gynecol Obstet 1991; 248: 39-143.
- Eichhorn JH et al. *Primary ovarian small cell carcinoma of pulmonary type. A clinicopathologic, immunohistologic and flow cytometric analysis of 11 cases.* Am J Surg Pathol 1992; 16: 926-938.
- Eichhorn JH et al. *Ovarian neuroendocrine carcinomas of non small-cell type associated with surface epithelial adenocarcinomas. A study of five cases and review of the literature.* Int J Gynecol Pathol 1996; 15: 303-314.
- Jones K et al. *Neuroendocrine carcinoma arising in an ovarian mucinous cystadenoma.* Int J Gynecol Pathol 1996; 15: 167-170.
- Khurana KK et al. *Ovarian neuroendocrine carcinoma associated with a mucinous neoplasm.* Arch Pathol Lab Med 1994; 118: 1032-1034.
- Kupryjanczyk, J. *Neuroendocrine tumours of the ovary. A review.* Verh Otach Ges Path 1997; 81: 253-259.
- Malut HM, Koerner FC. *Carcinomas of the breast with endocrine differentiation: A review.* Virchows Arch 1994; 425: 449-457.
- Scully RE. *Argyrophilia, serotonin, and peptide hormones in the female genital tract and its tumors.* Int J Gynecol Pathol 1984; 3: 51-70.
- Sobin LH. *New techniques and tumor nomenclature.* APMIS 1991; 23(Suppl.): 9-12.
- Soga J et al. *Argentaffin cell adenocarcinoma of the stomach: An atypical carcinoid?* Cancer 1971; 28: 999-1003.
- Talerman A. *Germ cell tumors of the ovary.* In: Kurman RJ. (Ed.). *Blaustein's Pathology of the Female Genital Tract.* Springer 1994.
- Wolpert RW et al. *Primary mucinous carcinoid tumor of the ovary. A case report.* Int J Gynecol Pathol 1989; 8: 156-162.