Bölüm 39

Overin Seks Kord Stromal Tümörleri

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Seks kord stromal tümörler (SKST), overin non-germ ve non-epitelyal bileşenlerinden gelişen, benign ve malign olabilen heterojen bir neoplazm grubudur (Young,2005). Malign SKST'ler nadirdir ve tüm primer over kanserlerinin sadece %1,2'sini oluştururlar. Epitelyal over kanserinin aksine, malign seks kordstromal tümörleri erken evrede tanı alır,%57'sinde tümör over ile sınırlıdır ve genellikle düşük dereceli olarak kabul edilirler(Quirk,2005). Yayılım genellikle lokaldir ve lenf nodu metastazı bu tümörlerde nadir görülür (Brown,2009;Abu-Rustum,2006; Thrall,2011).

Epidemiyoloji

Overin seks kord stromal tümörleri nadirdir. Amerika Birleşik Devletleri'ndeki, SEER verilerine göre görülme sıklığı, 100.000 kadında 0.2'dir (Quirk,2005). Bu oran, siyah kadınlarda beyazlara oranla daha yüksektir. Epitelyal over tümörlerine göre biraz daha genç yaşta görülürler ve tanı anındaki ortalamayaş 50'dir (Quirk,2005). SKST tanısı alan kadınların %12'si 30 yaşından genç, %57'si 30-59 yaşları arasındadır.

Genetik

FOXL2 geni, granüloza hücrelerinin gelişiminde kritik öneme sahip olan nükleer bir proteini ekspresse eden transkripsiyon faktörünü kodlar. FOXL2'deki somatik mutasyon, granüloza hücreli tümör gelişimi ile ilişkilendirilmiştir (Shah,2009). FOXL2 için immünohistokimyasal boyamanın da tanıda yardımcı olabileceği gösterilmiştir(Al-Agha,2011; Kommoss,2014).

DICER1, RNase III ailesinden, mikroRNA'ların işlenmesi için gerekli olan bir endoribonükleazdır (Heravi-Moussavi,2012). DICER1'deki mutasyonlar Sertoli-Leydig hücre tümörleri ve diğer non-epitelyal over kanserleri ile ilişkilidir (Heravi-Moussavi,2012). DICER1'deki germ mutasyonlarının önemi, Sertoli-Leydig hücreli tümörler dışında; plöropulmoner blastoma, akciğer kistleri, kistik nefroma, tiroid nodüler hiperplazi ve servikal botryoid sarkomu gibi birçok klinik durum ile ilişkili olmasıdır. Bu klinik durumlardan herhangi birinin hastada tespit edilmesi, risk altında olabilecek diğer aile üyelerinin taranmasını gündeme getirmektedir. Seks kord stromal tümörlerinin BRCA mutasyonları veya meme kanserine genetik yatkınlık ile bilinen bir ilişkisi yoktur.

Histopatoloji

Overin seks kord stromal tümörleri; granüloza, teka, Sertoli, Leydig hücrelerinden veya stromadaki fibroblastlardan kaynaklanabilir. Bu tümörlerde belirgin gonodal diferansiasyon (granüloza, teka, Sertoli, Leydig hücreleri) görülebileceği gibi, nonepitelyal (fibroblast, kıkırdak veya iskelet kası) veya heterelog elemanlar içeren epitelyal diferensiasyon da görülebilir. Çoğu overe ait hücrelerden oluşmaktayken, testis veya her iki dokuya ait hücreleri de kapsayabilir.

paklitaksel/karboplatin veya BEP gibi platin bazlı kemoterapi rejimleri önerilmektedir.

Diğer platin bazlı rejimler, ikinci basamak tedavi için alternatiflerdir. Bunlar arasında siklofosfamid, doksorubisin, artı sisplatin; karboplatin, epirubisin, artı etoposid; sisplatin, vinblastin, artı bleomisin; ve taksan/platin kombinasyon terapileri(Brown,2004; Tomlinson,1997;Fujimoto,1995; van der Meer,1985;Homesley,1999; Gershenson, 1996)sayılabilir.

Prognoz ve takip:

Prognoz, evre ve histolojik diferansiyasyon derecesi ile ilişkili olmakla beraber genel beş yıllık sağkalım oranı %70-90'dır. İyi, orta ve kötü diferansiye tümör oranı sırasıyla % 11, 54 ve13 olan ve %22'si heterolog eleman içeren 207 Sertoli-Leydig hücreli tümörlü hastadan oluşan büyük bir seride, uzun süreli takipte hastaların % 18'inde rekürrens veya metastaz izlendiği rapor edilmiştir(Young,1985). İyi diferansiye tümörlerin hepsi benign, orta diferansiye tümörlü hastaların %11'inde, kötü diferansiye tümörlü hastaların %59'unda ve heterolog eleman içeren tümörlü hastaların ise %19'unda malign davranış tespit edilmiştir.

Bu hastalar, fizik muayene ve testosteron seviyeleri ile ilk iki yıl için her üç ila dört ayda bir ve sonraki üç yıl altı ayda bir takip edilmeleri gerekmektedir. Tanı anında, inhibin, estradiol veya alfa-fetoprotein gibi diğer belirteçlerde yükselme tespit edilmiş ise takipte kullanılmalıdır). Bilgisayarlı tomografi veya diğer görüntüleme yöntemleri, semptomatik ve serum tümör marker seviyeleri yükselen hastaların değerlendirilmesinde kullanılabilir.

Kaynaklar

1. Abu-Rustum NR, Restivo A, Ivy J, Soslow R, Sabbatini P, Sonoda Y, et al.: Retroperitoneal nodal metastasis in primary and recurrent granulosa cell tumors of the ovary, *Gynecol Oncol*, 103:31-34,2006.
2. Adamian RT: Hyperplastic processes and endometrial cancer in patients with hormone-producing ovarian tumors, *Vopr Onkol,*37:48-51,1991.
3. Ala-Fossi SL, Mäenpää J, Aine R, Koivisto P, Koivisto AM, Punnonen R: Prognostic significance of p53 expression in ovarian granulosa cell tumors. *Gynecol Oncol*, 66:475-479,1997.
4. Alhilli MM, Long HJ, Podratz KC, Bakkum-Gamez JN: Aromatase inhibitors in the treatment of recurrent ovarian granulosa cell tumors: brief report and review of the literature,*J Obstet Gynaecol Res,*38:340-344,2012.
5. Al-Agha OM, Huwait HF, Chow C, Yang W, Senz J, Kalloger SE, et al.: FOXL2 is a sensitive and specific marker for sex cord-stromal tumors of the ovary,*Am J Surg Pathol*, 35:484-494,2011.
6. Auranen A, Sundström J, Ijäs J, Grénman S: Prognostic factors of ovarian granulosa cell tumor: a study of 35 patients and review of the literature,*Int J Gynecol Cancer,*17:1011-1018,2007.
7. Bahar B, Hu Z, Szpaderska A,Liotta M, Potkul RK, Smith D, et al.: Fatal case of luteinized thecoma with sclerosing peritonitis in a 40-year-old woman,*Int J Gynecol Pathol,* 33:30-34,2014.
8. Berek JS, Hacker NF:Granulosa–StromalCell Tumors, *Berek & Hacker's Gynecologic Oncology*, 6th edition, Wolters Kluwer, Philadelphia, 2015,p.546-553.
9. Bergamini A, Cormio G, Ferrandina G, Lorusso D, Giorda G, Scarfone G,et al.: Conservative surgery in stage I adult type granulosa cells tumors of the ovary: Results from the MITO-9 study,*Gynecol Oncol*, 154:323-327,2019.
10. Bianco R, de Rosa G, Staibano S, Somma P, Bianco AR: Ovarian luteinized thecoma with sclerosing peritonitis in an adult woman treated with leuprolide and toremifene in complete remission at 5 years,*Gynecol Oncol*,96:846-849,2005.
11. Björkholm E, Silfverswärd C: Prognostic factors in granulosa-cell tumors,*Gynecol Oncol,*11:261-274,1981.
12. Boggess JF, Soules MR, Goff BA,Greer BE, Cain JM, Tamimi HK; Serum inhibin and disease status in women with ovarian granulosa cell tumors,*Gynecol Oncol*, 64:64-69,1997.
13. Boyce EA, Costaggini I, Vitonis A,Feltmate C, Muto M, Berkowitz R, et al.: The epidemiology of ovarian granulosa cell tumors: a case-control study,-*Gynecol Oncol*, 115:221-225,2009.
14. Briasoulis E, Karavasilis V, Pavlidis N: Megestrol activity in recurrent adult type granulosa cell tumour of the ovary,*Ann Oncol,*8:811-812,1997.
15. Brown J, Brady WE, Schink J,Van Le L, Leitao M, Yamada SD, et al.: Efficacy and safety of bevacizumab in recurrent sex cord-stromal ovarian tumors: results of a phase 2 trial of the Gynecologic Oncology Group,*Cancer,* 120:344-351,2014.
16. Brown J, Shvartsman HS, Deavers MT,Burke TW, Munsell MF, Gershenson DM, et al.: The activity of taxanes in the treatment of sex cord-stromal ovarian tumors, *J Clin Oncol,* 22:3517-3523,2004.
17. Brown J, Shvartsman HS, Deavers MT, Ramondetta LM, Burke TW, Munsell MF,et al.: The activity of taxanes compared with bleomycin, etoposide, and

cisplatin in the treatment of sex cord-stromal ovarian tumors,*Gynecol Oncol,* 97:489-496,2005.
18. Brown J, Sood AK, Deavers MT, Milojevic L, Gershenson DM: Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted? *Gynecol Oncol*, 113:86-90,2009.
19. Brun JL: Demons syndrome revisited: a review of the literature,*Gynecol Oncol*, 105:796-800,2007.
20. Burton ER, Brady M, Homesley HD, Rose PG, Nakamura T, Kesterson JP,et al.: A phase II study of paclitaxel for the treatment of ovarian stromal tumors: An NRG Oncology/ Gynecologic Oncology Group Study, Gynecol Oncol, 140:48-52,2016.
21. Castro CY, Malpica A, Hearne RH, Silva EG: Androgenic adult granulosa cell tumor in a 13-year-old prepubertal patient: a case report and review of the literature,*Int J Gynecol Pathol*, 19:266-271,2000.
22. Chan JK, Zhang M, Kaleb V, Loizzi V, Benjamin J, Vasilev S, et al.: Prognostic factors responsible for survival in sex cord stromal tumors of the ovary-a multivariate analysis,*Gynecol Oncol,* 96:204-209,2005.
23. Chang HL, Pahlavan N, Halpern EF, MacLaughlin DT: Serum Müllerian Inhibiting Substance/anti-Müllerian hormone levels in patients with adult granulosa cell tumors directly correlate with aggregate tumor mass as determined by pathology or radiology,*Gynecol Oncol*,114:57-60,2009.
24. Chechia A, Attia L, Temime RB, Makhlouf T, Koubaa A: Incidence, clinical analysis, and management of ovarian fibromas and fibrothecomas, *Am J Obstet Gynecol,* 199:473-476,2008.
25. Clement PB, Young RH, Hanna W, Scully RE: Sclerosing peritonitis associated with luteinized thecomas of the ovary. A clinicopathological analysis of six cases, *Am J Surg Pathol,*18:1-13,1994.
26. Cohen I, Shapira M, Cuperman S, Goldberger S, Siegal A, Altaras M, et al.: Direct in-vivo detection of atypical hormonal expression of a Sertoli-Leydig cell tumour following stimulation with human chorionic gonadotrophin,*Clin Endocrinol (Oxf)*, 39:491-495,1993.
27. Colombo N, Sessa C, Landoni F, Sartori E, Pecorelli S, Mangioni C: Cisplatin, vinblastine, and bleomycin combination chemotherapy in metastatic granulosa cell tumor of the ovary,*Obstet Gynecol*,67:265-2681986.
28. Crew KD, Cohen MH, Smith DH, Tiersten AD, Feirt NM, Hershman DL: Long natural history of recurrent granulosa cell tumor of the ovary 23 years after initial diagnosis: a case report and review of the literature,*Gynecol Oncol,*96:235-240,2005.
29. Cronjé HS, Niemand I, Bam RH, Woodruff JD: Review of the granulosa-theca cell tumors from the emil Novak ovarian tumor registry,*Am J Obstet Gynecol*, 180:323-327,1999.
30. DiSaia PJ, Creasman WT, Germ cell, stromal and other ovarian tumors. In: *Clinical Gynecologic Oncology,* 5th ed, St Louis: Mosby YearBook, 1997, p.351-374.
31. DiSaia PJ, Creasman WT, Germ cell, stromal and other ovarian tumors. In: *Clinical Gynecologic Oncology*, 7th ed, St Louis: Mosby YearBook, 2007, p.381-393.
32. Disaia P, Saltz A, Kagan AR, Rich W: A temporary response of recurrent granulosa cell tumor to adriamycin,*Obstet Gynecol*,52:355-359,1978.
33. Elghorori MR, Al-Taher H, Redwood NF: Ovarian fibrothecoma: a benign neoplasm with potential adverse consequences,*J Obstet Gynaecol*,23:677-678,2003.
34. Emons G, Schally AV: The use of luteinizing hormone releasing hormone agonists and antagonists in gynaecological cancers,*Hum Reprod,*9:1364-1379,1994.
35. Evans AT 3rd, Gaffey TA, Malkasian GD Jr, Annegers JF: Clinicopathologic review of 118 granulosa and 82 theca cell tumors,*Obstet Gynecol*,55:231-238,1980.
36. Fishman A, Kudelka AP, Tresukosol D, Edwards CL, Freedman RS, Kaplan AL, et al.: Leuprolide acetate for treating refractory or persistent ovarian granulosa cell tumor, *J Reprod Med*, 41:393-396,1996.
37. Fujimoto A, Saitou M, Ishihara O, Takeda S, Kinoshita K, Itoyama S: [A case of ovarian malignant Sertoli-Leidig cell tumor treated with CBDCA, etoposide and epirubicin chemotherapy],*Gan To Kagaku Ryoho,*22:1843-1846,1995.
38. Färkkilä A, Koskela S, Bryk S,Alfthan H, Bützow R, Leminen A, et al.: The clinical utility of serum anti-Müllerian hormone in the follow-up of ovarian adult-type granulosa cell tumors-A comparative study with inhibin B, *Int J Cancer*, 137:1661-1671,2015.
39. Gershenson DM, Copeland LJ, Kavanagh JJ, Stringer CA, Saul PB, Wharton JT: Treatment of metastatic stromal tumors of the ovary with cisplatin, doxorubicin, and cyclophosphamide,*Obstet Gynecol*,70:765-769,1987.
40. Gershenson DM: Management of early ovarian cancer: germ cell and sex cord-stromal tumors,*Gynecol Oncol,* 55:S62-72,1994.
41. Gershenson DM, Morris M, Burke TW, Levenback C, Matthews CM, Wharton JT: Treatment of poor-prognosis sex cord-stromal tumors of the ovary with the combination of bleomycin, etoposide, and cisplatin, Obstet Gynecol,87:527-531,1996.
42. Gershenson DM, Dowdy SC, Young RH. Ovarian sex cord stromal tumors. In: Principles and Practice of Gynecologic Oncology, 7th ed, Chi D, Berchuck

A, Dizon DS, Yashar CM, Lippincott Williams & Wilkins, Philadelphia, 2017,p1343-1354.
43. Gui T, Cao D, Shen K, Yang J, Zhang Y, Yu Q, et al.: A clinicopathological analysis of 40 cases of ovarian Sertoli-Leydig cell tumors, *Gynecol Oncol,* 127:384-389,2012.
44. Gustafson ML, Lee MM, Scully RE,Moncure AC, Hirakawa T, Goodman A, et al.: Müllerian inhibiting substance as a marker for ovarian sex-cord tumor,*N Engl J Med*, 326:466-471,1992.
45. Hardy RD, Bell JG, Nicely CJ, Reid GC: Hormonal treatment of a recurrent granulosa cell tumor of the ovary: case report and review of the literature,*Gynecol Oncol*,96:865-869,2005.
46. Healy DL, Burger HG, Mamers P, Jobling T, Bangah M, Quinn M, et al.:Elevated serum inhibin concentrations in postmenopausal women with ovarian tumors,*N Engl J Med,* 329:1539-1542,1993.
47. Heravi-Moussavi A, Anglesio MS, Cheng SW, Senz J, Yang W, Prentice L, et al.: Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers,*N Engl J Med*, 366:234-242,2012.
48. Hildebrandt RH, Rouse RV, Longacre TA: Value of inhibin in the identification of granulosa cell tumors of the ovary,*Hum Pathol*,28:1387-1395,1997.
49. Homesley HD, Bundy BN, Hurteau JA, Roth LM: Bleomycin, etoposide, and cisplatin combination therapy of ovarian granulosa cell tumors and other stromal malignancies: A Gynecologic Oncology Group study,*Gynecol Oncol,*72:131-137,1999.
50. Horny HP, Braumann W, Weiss E, Dietl J, Kaiserling E: Virilizing stromal Leydig cell tumor (Leydig cell-containing thecoma) of the ovary in pregnancy. A case report with extensive immunohistochemical investigation of the tumor cells,*Gen Diagn Pathol,*141:57-60,1995.
51. Hölscher G, Anthuber C, Bastert G, Burges A, Mayr D, Oberlechner E, et al.: Improvement of survival in sex cord stromal tumors - an observational study with more than 25 years follow-up,*Acta Obstet Gynecol Scand*, 88:440-448,2009.
52. Ishiko O, Yoshida H, Sumi T, Hirai K, Ogita S: Vascular endothelial growth factor levels in pleural and peritoneal fluid in Meigs' syndrome,*Eur J Obstet Gynecol Reprod Biol,*98:129-130,2001.
53. Jobling T, Mamers P, Healy DL,MacLachlan V, Burger HG, Quinn M, et al.: A prospective study of inhibin in granulosa cell tumors of the ovary, *Gynecol Oncol,* 55:285-289,1994.
54. Kommoss S, Gilks CB, Penzel R,Herpel E, Mackenzie R, Huntsman D, et al.:A current perspective on the pathological assessment of FOXL2 in adult-type granulosa cell tumours of the ovary, *Histopathology*, 64:380-388,2014.
55. Korach J, Perri T, Beiner M,Davidzon T, Fridman E, Ben-Baruch G: Promising effect of aromatase inhibitors on recurrent granulosa cell tumors,*Int J Gynecol Cancer*,19:830-833,2009.
56. Köbel M, Gilks CB, Huntsman DG: Adult-type granulosa cell tumors and FOXL2 mutation,*Cancer Res,*69:9160-9162,2009.
57. Lack EE, Perez-Atayde AR, Murthy AS,Goldstein DP, Crigler JF Jr, Vawter GF:Granulosa theca cell tumors in premenarchal girls: a clinical and pathologic study of ten cases,*Cancer*,48:1846-1854,1981.
58. Lane AH, Lee MM, Fuller AF Jr, Kehas DJ, Donahoe PK, MacLaughlin DT: Diagnostic utility of Müllerian inhibiting substance determination in patients with primary and recurrent granulosa cell tumors, Gynecol Oncol,73:51-55,1991.
59. Lappöhn RE, Burger HG, Bouma J, Bangah M, Krans M, de Bruijn HW: Inhibin as a marker for granulosa-cell tumors,*N Engl J Med,* 321:790-793,1989.
60. Lauszus FF, Petersen AC, Greisen J, Jakobsen A:Granulosa cell tumor of the ovary: a population-based study of 37 women with stage I disease,*Gynecol Oncol*,81:456-460,2001.
61. Lee YK, Park NH, Kim JW,Song YS, Kang SB, Lee HP: Characteristics of recurrence in adult-type granulosa cell tumor, Int J Gynecol Cancer,18:642-647,2008.
62. Li B, Wu LY, Zhang WH,Li L, Ma SK, Liu LY: [Clinical analysis of 11 cases of ovarian Setoli-Leydig cell tumor], *Zhonghua Fu Chan Ke Za Zhi,*39:334-337,2004.
63. Liu H, Hao SH, Li WM: Giant malignant ovarian fibrothecoma involved with retroperitoneal structures mimicking a retroperitoneal sarcoma,*Arch Gynecol Obstet*, 279:763-765,2009.
64. Lo WK, Chan KT, Leung AC, Pang SW, Tse CY: Sclerosing peritonitis complicating prolonged use of chlorhexidine in alcohol in the connection procedure for continuous ambulatory peritoneal dialysis, *Perit Dial Int,*11:166-172,1991.
65. Malmström H, Högberg T, Risberg B, Simonsen E:Granulosa cell tumors of the ovary: prognostic factors and outcome, *Gynecol Oncol,*52:50-55,1994.
66. Mangili G, Sigismondi C, Frigerio L, Candiani M, Savarese A, Giorda G,et al.: Recurrent granulosa cell tumors (GCTs) of the ovary: a MITO-9 retrospective study,*Gynecol Oncol*, 130:38-42,2013.
67. Marshall AJ, Baddeley H, Barritt DW, Davies JD, Lee RE, Low-Beer TS, et al.: Practolol peritonitis. A study of 16 cases and a survey of small bowel function in patients taking beta adrenergic blockers,*Q J Med,*46:135-149,1977.
68. Martikainen H, Penttinen J, Huhtaniemi I, Kauppila A: Gonadotropin-releasing hormone agonist analog therapy effective in ovarian granulosa cell malignancy,*Gynecol Oncol,*35:406-408,1989.

69. McCluggage WG: Recent advances in immunohistochemistry in the diagnosis of ovarian neoplasms;*J Clin Pathol;*53:327-334,2000.
70. Meigs JV: Fibroma of the ovary with ascites and hydrothorax; Meigs' syndrome,*Am J Obstet Gynecol*,67:962-985,1954.
71. Mellembakken JR, Engh V, Tanbo T,Czernobilsky B, Edelstein E, Lunde O, et al.: Mitotically active cellular luteinized thecoma of the ovary and luteinized thecomatosis associated with sclerosing peritonitis: case studies, comparison, and review of the literature,*Pathol Res Pract,* 206:744-748,2010.
72. Miller BE, Barron BA, Wan JY, Delmore JE, Silva EG, Gershenson DM: Prognostic factors in adult granulosa cell tumor of the ovary,*Cancer,*79:1951-1955,1997.
73. Mom CH, Engelen MJ, Willemse PH, Gietema JA, ten Hoor KA, de Vries EG,et al.:Granulosa cell tumors of the ovary: the clinical value of serum inhibin A and B levels in a large single center cohort,*Gynecol Oncol,* 105:365372,2007.
74. Mooney EE, Nogales FF, Tavassoli FA: Hepatocytic differentiation in retiform Sertoli-Leydig cell tumors: distinguishing a heterologous element from Leydig cells,*Hum Pathol,*30:611-617,1999.
75. Movahedi-Lankarani S, Kurman RJ: Calretinin, a more sensitive but less specific marker than alpha-inhibin for ovarian sex cord-stromal neoplasms: an immunohistochemical study of 215 cases,*Am J Surg Pathol*,26:1477-1483-2002.
76. Muntz HG, Goff BA, Fuller AF Jr: Recurrent ovarian granulosa cell tumor: role of combination chemotherapy with report of a long-term response to a cyclophosphamide, doxorubicin and cisplatin regimen,*Eur J Gynaecol Oncol*, 11:263-268,1990.
77. Nakashima N, Young RH, Scully RE: Androgenic granulosa cell tumors of the ovary. A clinicopathologic analysis of 17 cases and review of the literature,*Arch Pathol Lab Med*, 108:786-791,1984.
78. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (Accessed on February 20, 2019).
79. Nauen DW, Martin A, Katz A,Cohen D, Ranganathan S: A case of luteinizing thecoma with sclerosing peritonitis: revisiting a link with anti-epileptic drugs,*Pediatr Blood Cancer,* 54:470472,2010.
80. Nowak M, Podciechowski L, Krawczyk T, Wilczynski J: Meigs' syndrome and virilizing ovarian fibrothecoma complicating pregnancy. A case report and review of the literature,*Neuro Endocrinol Lett,* 30:192-194,2009.
81. Noyes N, Perretta RC, Fino ME, Matulewicz T, Barakat R: Use of hormone suppression then oocyte freezing to preserve reproductive capability in an adolescent girl with ovarian luteinized thecoma associated with sclerosing peritonitis,*Fertil Steril,*92:393-396,2009.
82. Ohashi M, Hasegawa Y, Haji M,Igarashi M, Nawata H: Production of immunoreactive inhibin by a virilizing ovarian tumour (Sertoli-Leydig tumour),*Clin Endocrinol,* 33:613-618,1990.
83. Ohel G, Kaneti H, Schenker JG:Granulosa cell tumors in Israel: a study of 172 cases,*Gynecol Oncol,*15:278-286,1983.
84. Oliva E, Alvarez T, Young RH: Sertoli cell tumors of the ovary: a clinicopathologic and immunohistochemical study of 54 cases,*Am J Surg Pathol*,29:143-156,2005.
85. Outwater EK, Wagner BJ, Mannion C, McLarney JK, Kim B: Sex cord-stromal and steroid cell tumors of the ovary,*Radiographics*,18:1523-1546,1998.
86. Pankratz E, Boyes DA, White GW,Galliford BW, Fairey RN, Benedet JL:Granulosa cell tumors. A clinical review of 61 cases,*Obstet Gynecol*,52:718-723,1978.
87. Pectasides D, Alevizakos N, Athanassiou AE: Cisplatin-containing regimen in advanced or recurrent granulosa cell tumours of the ovary,*Ann Oncol,*3:316-318,1992.
88. Peparini N, Chirletti P: Ovarian malignancies with cytologically negative pleural and peritoneal effusions: demons' or meigs' pseudo-syndromes,*Int J Surg Pathol,*17:396-397,2009.
89. Powell JL, Otis CN: Management of advanced juvenile granulosa cell tumor of the ovary, *Gynecol Oncol*,64:282-284,1997.
90. Powell JL, Connor GP, Henderson GS: Management of recurrent juvenile granulosa cell tumor of the ovary, *Gynecol Oncol*,81:113-116,2001.
91. Quirk JT, Natarajan N: Ovarian cancer incidence in the United States, 1992-1999,*Gynecol Oncol*,97:519-523,2005.
92. Rey RA, Lhommé C, Marcillac I,Lahlou N, Duvillard P, Josso N, et al.: Antimüllerian hormone as a serum marker of granulosa cell tumorsof the ovary: comparative study with serum alpha-inhibin and estradiol, *Am J Obstet Gynecol,* 174:958-965,1996.
93. Robertson DM, Stephenson T, Pruysers E,McCloud P, Tsigos A, Groome N, et al.: Characterization of inhibin forms and their measurement by an inhibin alpha-subunit ELISA in serum from postmenopausal women with ovarian cancer, *J Clin Endocrinol Metab*, 87:816-824,2002.
94. Robertson DM, Stephenson T, Pruysers E, Burger HG, McCloud P, Tsigos A,et al.: Inhibins/activins as diagnostic markers for ovarian cancer,*Mol Cell Endocrinol,* 191:97-103,2002.
95. Roth LM, Sternberg WH: Ovarian stromal tumors containing Leydig cells. II. Pure Leydig cell tumor, non-hilar type,*Cancer,*32:952-960,1973.

96. Roth LM, Czernobilsky B: Perspectives on pure ovarian stromal neoplasms and tumor-like proliferations of the ovarian stroma,*Am J Surg Pathol,*35:15-33,2011.
97. Roush GR, el-Naggar AK, Abdul-Karim FW:Granulosa cell tumor of ovary: a clinicopathologic and flow cytometric DNA analysis, Gynecol Oncol,56:430-434,1995.
98. Salani R, Backes FJ, Fung MF,Holschneider CH, Parker LP, Bristow RE, et al.:Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations, *Am J Obstet Gynecol*, 204:466-478,2011.
99. Savage P, Constenla D, Fisher C, Shepherd JH, Barton DP, Blake P, et al.:Granulosa cell tumours of the ovary: demographics, survival and the management of advanced disease, *Clin Oncol (R Coll Radiol),* 10:242-245,1998.
100. Schneider DT, Calaminus G, Wessalowski R,Pathmanathan R, Selle B, Sternschulte W, et al.: Ovarian sex cord-stromal tumors in children and adolescents,*J Clin Oncol,* 21:2357-2363,2003.
101. Schonman R, Klein Z, Edelstein E,Czernobilsky B, Fishman A: Luteinized thecoma associated with sclerosing peritonitis--conservative surgical approach followed by corticosteroid and GnRH agonist treatment--a case report,*Gynecol Oncol*, 111:540-543,2008.
102. Schultz KA, Pacheco MC, Yang J, Williams GM, Messinger Y, Hill DA, et al.: Ovarian sex cord-stromal tumors, pleuropulmonary blastoma and DICER1 mutations: a report from the International Pleuropulmonary Blastoma Registry,*Gynecol Oncol*, 122:246-250,2011.
103. Schumer ST, Cannistra SA:Granulosa cell tumor of the ovary,*J Clin Oncol,* 21:1180-1189,2003.
104. Segal R, DePetrillo AD, Thomas G: Clinical review of adult granulosa cell tumors of the ovary,*Gynecol Oncol*,56:338-344,1995.
105. Sehouli J, Drescher FS, Mustea A,Elling D, Friedmann W, Kühn W, et al.:Granulosa cell tumor of the ovary: 10 years follow-up data of 65 patients,*Anticancer Res,* 24:1223-1229,2004.
106. Shah SP, Köbel M, Senz J,Morin RD, Clarke BA, Wiegand KC, et al.: Mutation of FOXL2 in granulosa-cell tumors of the ovary,*N Engl J Med*, 360:2719-2729,2009.
107. Sigismondi C, Gadducci A, Lorusso D, Candiani M, Breda E, Raspagliesi F, et al.: Ovarian Sertoli-Leydig cell tumors. a retrospective MITO study,*Gynecol Oncol,*125:673-676,2012.
108. Staats PN, McCluggage WG, Clement PB, Young RH: Luteinized thecomas (thecomatosis) of the type typically associated with sclerosing peritonitis: a clinical, histopathologic, and immunohistochemical analysis of 27 cases, *Am J Surg Pathol*, 32:1273-1290,2008.
109. Stenwig JT, Hazekamp JT, Beecham JB:Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up, Gynecol Oncol,7:136-152,1979.
110. Tao X, Sood AK, Deavers MT,Schmeler KM, Nick AM, Coleman RL, et al.: Anti-angiogenesis therapy with bevacizumab for patients with ovarian granulosa cell tumors, *Gynecol Oncol*, 114:431-436,2009.
111. Thrall MM, Paley P, Pizer E, Garcia R, Goff BA: Patterns of spread and recurrence of sex cord-stromal tumors of the ovary,*Gynecol Oncol,* 122:242-245,2011.
112. Tomlinson MW, Treadwell MC, Deppe G: Platinum based chemotherapy to treat recurrent Sertoli-Leydig cell ovarian carcinoma during pregnancy,*Eur J Gynaecol Oncol*,18:44-46,1997.
113. Tresukosol D, Kudelka AP, Edwards CL, Charnsangavej C, Narboni N, Kavanagh JJ: Recurrent ovarian granulosa cell tumor: a case report of a dramatic response to Taxol, *Int J Gynecol Cancer*,5:156-159,1995.
114. Tsuji T, Catasus L, Prat J: Is loss of heterozygosity at 9q22.3 (PTCH gene) and 19p13.3 (STK11 gene) involved in the pathogenesis of ovarian stromal tumors,*Hum Pathol*,36:792-796,2005.
115. Uygun K, Aydiner A, Saip P, Basaran M, Tas F, Kocak Z, et al.: Granulosa cell tumor of the ovary: retrospective analysis of 45 cases, *Am J Clin Oncol*, 26:517-521,2003.
116. van der Meer J, de Vries EG, Vriesendorp R, Willemse PH, Donker AJ, Aalders JG: Hemolytic uremic syndrome in a patient on cis-platinum, vinblastine and bleomycin, *J Cancer Res Clin Oncol,* 110:119-122,1985.
117. van Meurs HS, van Lonkhuijzen LR, Limpens J,-van der Velden J, Buist MR: Hormone therapy in ovarian granulosa cell tumors: a systematic review, *Gynecol Oncol,* 134:196-205,2014.
118. Varras M, Vasilakaki T, Skafida E, Akrivis C: Clinical, ultrasonographic, computed tomography and histopathological manifestations of ovarian steroid cell tumour, not otherwise specified: our experience of a rare case with female virilisation and review of the literature, *Gynecol Endocrinol*,27:412-418,2011.
119. Wolf JK, Mullen J, Eifel PJ, Burke TW, Levenback C, Gershenson DM: Radiation treatment of advanced or recurrent granulosa cell tumor of the ovary,-*Gynecol Oncol*,73:35-41,1999.
120. World Health Organization Classification of Tumours of Female Reproductive Organs, 4th edition, Kurman RJ, Carcangiu ML, Herrington CS, Young RH, International Agency for Research on Cancer, Lyon 2014. Vol 6.

121. Young R, Clement PB, Scully RE, The ovary. In: Surgical Pathology, Sternberg SS, Raven Press, New York, 1989, p.1687-1690.
122. Young RH, Scully RE: Well-differentiated ovarian Sertoli-Leydig cell tumors: a clinicopathological analysis of 23 cases,*Int J Gynecol Pathol,*3:277-290,1984.
123. Young RH, Scully RE: Ovarian Sertoli-Leydig cell tumors. A clinicopathological analysis of 207 cases,*Am J Surg Pathol,* 9:543-569,1985.
124. Young RH: Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems,*Mod Pathol,*18:81-98,2005.
125. Zanagnolo V, Pasinetti B, Sartori E: Clinical review of 63 cases of sex cord stromal tumors,*Eur J Gynaecol Oncol,*25:431-438,2004.
126. Zhang M, Cheung MK, Shin JY,Kapp DS, Husain A, Teng NN, et al.: Prognostic factors responsible for survival in sex cord stromal tumors of the ovary-an analysis of 376 women,*Gynecol Oncol,*104:396-400,2007.