



UNIVERSITAS  
GADJAH MADA

Kadar VEGF, Interleukin-6, Interleukin-10 dan TNF alfa pada Cairan Peritoneum, Tumor Infiltrating Lymphocyte (TIL) dan Lymphovascular Space Invasion (LVSI) pada Jaringan Tumor Sebagai Prediktor

**Progression-free Survival (PFS) Karsinoma Ovarium**

Moh Nailul Fahmi, Prof. Dr. Dr. Heru Pradjatmo, SpOG(K), MKes; Dr. Med. Dr. Indwiani Astuti; dr. Didik Setyo Heriyadi  
Universitas Gadjah Mada, 2023 | Diunduh dari <http://etd.repository.ugm.ac.id/>

## DAFTAR PUSTAKA

- Abiko, K., Matsumura, N., Hamanishi, J., Horikawa, N., Murakami, R., Yamaguchi, K., et al., 2015. IFN- $\gamma$  from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. *Br. J. Cancer* 112: 1501–1509. doi:10.1038/bjc.2015.101
- AD, S., PL, H., A, R., S, B., JJ, R., CV, S., et al., 2001. Phenotypic and Functional Analysis of Tumor-Infiltrating Lymphocytes Compared with Tumor-Associated Lymphocytes from Ascitic Fluid and Peripheral Blood Lymphocytes in Patients with Advanced Ovarian Cancer. *Gynecol. Obstet. Investig.* 7199: 254–261.
- Aggarwal, B.B., 2003. Signalling Pathways of The TNF Superfamily: A Double-Edged Sword. *Nat. Rev. Immunol.* 3: 745–756. doi:10.1038/nri1184
- Ahmed, N., & Stenvers, K.L., 2013. Getting to Know Ovarian Cancer Ascites: Opportunities for Targeted Therapy-Based Translational Research. *Front. Oncol.* 3: 1–12. doi:10.3389/fonc.2013.00256
- Alberts, D.S., Marth, C., Alvarez, R.D., Johnson, G., Bidzinski, M., Kardatzke, D.R., et al., 2008. Randomized phase 3 trial of interferon gamma-1b plus standard carboplatin/paclitaxel versus carboplatin/paclitaxel alone for first-line treatment of advanced ovarian and primary peritoneal carcinomas: Results from a prospectively designed analysis of prog. *Gynecol. Oncol.* 109: 174–181. doi:10.1016/j.ygyno.2008.01.005
- Antony, M.L., Nair, R., Sebastian, P., & Karunagaran, D., 2010. Changes in expression, and/or mutations in TGF- $\beta$  receptors (TGF- $\beta$  RI and TGF- $\beta$  RII) and Smad 4 in human ovarian tumors. *J. Cancer Res. Clin. Oncol.* 136: 351–361. doi:10.1007/s00432-009-0703-4
- Asschert, J.G.W., Vellenga, E., Ruiters, M.H.J., & De Vries, E.G.E., 1999. Regulation of spontaneous and TNF/IFN-induced IL-6 expression in two human ovarian-carcinoma cell lines. *Int. J. Cancer* 82: 244–249. doi:10.1002/(SICI)1097-0215(19990719)82:2<244::AID-IJC15>3.0.CO;2-N
- Baert, T., Timmerman, D., Vergote, I., & Coosemans, A., 2015. Immunological



parameters as a new lead in the diagnosis of ovarian cancer. *Facts, views Vis. ObGyn* 7: 67–72.

Bamias, A., Gavalas, N.G., Karadimou, A., & Dimopoulos, M.A., 2010. Immune response in ovarian cancer: How is the immune system involved in prognosis and therapy: Potential for treatment utilization. *Clin. Dev. Immunol.* doi:10.1155/2010/791603

Bamias, A., Koutsoukou, V., Terpos, E., Tsiantas, M.L., Liakos, C., Tsitsilonis, O., et al., 2008. Correlation of NK T-like CD3+CD56+ Cells and CD4+CD25+(hi) Regulatory T Cells with VEGF and TNF $\alpha$  in Ascites from Advanced Ovarian Cancer: Association with Platinum Resistance and Prognosis in Patients Receiving First-Line, Platinum-Based chemotherapy. *Gynecol. Oncol.* 108: 421–427. doi:10.1016/j.ygyno.2007.10.018

Batchu, R., Gruzdyn, O., Kolli, B., Dachepalli, R., Umar, P., Rai, S., et al., 2021. IL-10 Signaling in the Tumor Microenvironment of Ovarian Cancer, Advances in Experimental Medicine and Biology.

Berek, J.S., Kehoe, S.T., Kumar, L., & Friedlander, M., 2018. Cancer of the ovary, fallopian tube, and peritoneum. *Int. J. Gynecol. Obstet.* 143: 59–78. doi:10.1002/ijgo.12614

Bhatla, N., & Jones, A., 2018. The World Ovarian Cancer Coalition Atlas, World Ovarian Cancer Coalition 2018.

Bonneau, C., Rouzier, R., Geyl, C., Cortez, A., Castela, M., Lis, R., et al., 2015. Predictive markers of chemoresistance in advanced stages epithelial ovarian carcinoma. *Gynecol. Oncol.* 136: 112–120. doi:10.1016/j.ygyno.2014.10.024

Bridget, C., Goode, E.L., Kalli, K.R., Knutson, K.L., & DeRycke, M.S., 2013. The immune system in the pathogenesis of ovarian cancer. *Crit. Rev. Immunol.* 33: 137–164. doi:10.1615/CritRevImmunol.2013006813

Browning, L., Patel, M.R., Horvath, E.B., Tawara, K., & Jorcyk, C.L., 2018. IL-6 and ovarian cancer: Inflammatory cytokines in promotion of metastasis. *Cancer Manag. Res.* 10: 6685–6693. doi:10.2147/CMAR.S179189

Bryant, A., Hiu, S., Kunonga, P.T., Gajjar, K., Craig, D., Vale, L., et al., 2022. Impact of residual disease as a prognostic factor for survival in women with



advanced epithelial ovarian cancer after primary surgery. *Cochrane Database Syst. Rev.* 2022. doi:10.1002/14651858.CD015048.pub2

Budiana, I.N.G., Angelina, M., & Pemayun, T.G.A., 2019. Ovarian cancer: Pathogenesis and current recommendations for prophylactic surgery. *J. Turkish Ger. Gynecol. Assoc.* 20: 41–46. doi:10.4274/jtgga.galenos.2018.2018.0039

Burger, R.A., Brady, M.F., Bookman, M.A., Fleming, G.F., Monk, B.J., Huang, H., et al., 2012. Incorporation of Bevacizumab in The Primary Treatment of Ovarian Cancer. *Obstet. Gynecol. Surv.* 67: 289–290. doi:10.1097/OGX.0b013e3182547170

Cai, D.L., & Jin, L.-P., 2017. Immune Cell Population in Ovarian Tumor Microenvironment. *J. Cancer* 8: 2915–2923. doi:10.7150/jca.20314

Cantón-Romero, J.C., Miranda-Díaz, A.G., Bañuelos-Ramírez, J.L., Carrillo-Ibarra, S., Sifuentes-Franco, S., Castellanos-González, J.A., et al., 2017. Markers of Oxidative Stress and Inflammation in Ascites and Plasma in Patients with Platinum-Sensitive, Platinum-Resistant, and Platinum-Refractory Epithelial Ovarian Cancer. *Oxid. Med. Cell. Longev.* 2017. doi:10.1155/2017/2873030

Castells, M., Thibault, B., Delord, J.P., & Couderc, B., 2012. Implication of tumor microenvironment in chemoresistance: Tumor-associated stromal cells protect tumor cells from cell death. *Int. J. Mol. Sci.* doi:10.3390/ijms13089545

Chan, J.K., Urban, R., Cheung, M.K., Osann, K., Husain, A., Teng, N.N., et al., 2006. Ovarian cancer in younger vs older women: A population-based analysis. *Br. J. Cancer* 95: 1314–1320. doi:10.1038/sj.bjc.6603457

Chang, L.C., Huang, C.F., Lai, M.S., Shen, L.J., Wu, F.L.L., & Cheng, W.F., 2018. Prognostic factors in epithelial ovarian cancer: A population-based study. *PLoS One* 13: 1–11. doi:10.1371/journal.pone.0194993

Chen, C.A., Cheng, W.F., Lee, C.N., Chen, T.M., Kung, C.C.S., Hsieh, F.J., et al., 1999. Serum vascular endothelial growth factor in epithelial ovarian neoplasms: Correlation with patient survival. *Gynecol. Oncol.* 74: 235–240. doi:10.1006/gyno.1999.5418



- Chen, D.S., & Mellman, I., 2013. Oncology meets immunology: The cancer-immunity cycle. *Immunity*. doi:10.1016/j.jimmuni.2013.07.012
- Chen, G., Zhu, L., Yang, Y., Long, Y., Li, X., & Wang, Y., 2018. Prognostic role of neutrophil to lymphocyte ratio in ovarian cancer: A meta-analysis. *Technol. Cancer Res. Treat.* 17: 1–8. doi:10.1177/1533033818791500
- Chen, M., Jin, Y., Bi, Y., Li, Y., Shan, Y., & Pan, L., 2015. Prognostic significance of lymphovascular space invasion in epithelial ovarian cancer. *J. Cancer* 6: 412–419. doi:10.7150/jca.11242
- Chen, Y.L., Cheng, W.F., Chang, M.C., Lin, H.W., Huang, C.T., Chien, C.L., et al., 2013. Interferon-gamma in ascites could be a predictive biomarker of outcome in ovarian carcinoma. *Gynecol. Oncol.* 131: 63–68. doi:10.1016/j.ygyno.2013.07.105
- Chen, Y.L., Chou, C.Y., Chang, M.C., Lin, H.W., Huang, C.T., Hsieh, S.F., et al., 2015. IL17a and IL21 combined with surgical status predict the outcome of ovarian cancer patients. *Endocr. Relat. Cancer* 22: 703–711. doi:10.1530/ERC-15-0145
- Coward, J., Kulbe, H., Chakravarty, P., Leader, D., Vassileva, V., Leinster, D.A., et al., 2011. Interleukin-6 as a Therapeutic Target in Human Ovarian Cancer. *Clin. Cancer Res.* 17: 6083–6096. doi:10.1158/1078-0432.CCR-11-0945
- Dalal, V., Kumar, R., Kumar, S., Sharma, A., Kumar, L., Sharma, J.B., et al., 2018. Biomarker potential of IL-6 and VEGF-A in ascitic fluid of epithelial ovarian cancer patients. *Clin. Chim. Acta* 482: 27–32. doi:10.1016/j.cca.2018.03.019
- Darb-Esfahani, S., Kunze, C.A., Kulbe, H., Sehouli, J., Wienert, S., Lindner, J., et al., 2015. Prognostic Impact of Programmed Cell Death-1 (PD-1) and PD-Ligand 1 (PD-L1) Expression in Cancer Cells and Tumor Infiltrating Lymphocytes in Ovarian High Grade Serous Carcinoma. *Oncotarget* 7: 1486–1499.
- Drakes, M.L., & Stiff, P.J., 2018. Regulation of ovarian cancer prognosis by immune cells in the tumor microenvironment. *Cancers (Basel)*. 10. doi:10.3390/cancers10090302
- Dunn, G.P., Bruce, A.T., Sheehan, K.C.F., Shankaran, V., Uppaluri, R., Bui, J.D.,



- et al., 2005. A critical function for type I interferons in cancer immunoediting. *Nat. Immunol.* 6: 722–729. doi:10.1038/ni1213
- Ezzati, M., Abdullah, A., Sharifabrizi, A., Hou, J., Kopf, M., Stedman, J.K., et al., 2014. Recent advancements in prognostic factors of epithelial ovarian carcinoma. *ISRN Obstet. Gynecol.* doi:10.1155/2014/953509
- Fahmi, M.N., Pradjatmo, H., Astuti, I., & Nindrea, R.D., 2021. Cytokines as Prognostic Biomarkers of Epithelial Ovarian Cancer (EOC): A Systematic Review and Meta-Analysis. *Asian Pacific J. Cancer Prev.* 22: 315–323. doi:10.31557/APJCP.2021.22.2.315
- Fanale, D., Dimino, A., Pedone, E., Brando, C., Corsini, L.R., Filorizzo, C., et al., 2022. Prognostic and Predictive Role of Tumor-Infiltrating Lymphocytes (TILs) in Ovarian Cancer. *Cancers (Basel)*. 14: 1–16. doi:10.3390/cancers14184344
- Folkman, J., 2003. Angiogenesis and Apoptosis. *Semin. Cancer Biol.* 13: 159–167. doi:10.1016/S1044-579X(02)00133-5
- Freedman, L.S., 1982. Tables of the number of patients required in clinical trials using the logrank test. *Stat. Med.* 1: 121–129. doi:10.1002/sim.4780010204
- Freedman, R.S., Kudelka, A.P., Kavanagh, J.J., Verschraegen, C., Edwards, C.L., Nash, M., et al., 2000. Clinical and biological effects of intraperitoneal injections of recombinant interferon- $\gamma$  and recombinant interleukin 2 with or without tumor-infiltrating lymphocytes in patients with ovarian or peritoneal carcinoma. *Clin. Cancer Res.* 6: 2268–2278.
- Fujita, K., Ikarashi, H., Takakuwa, K., Kodama, S., Tokunaga, A., Takahashi, T., et al., 1995. Prolonged Disease-free Period in Patients with Advanced Epithelial Ovarian Cancer after Adoptive Transfer of Tumor-infiltrating Lymphocytes1, Clinical Cancer Research.
- Gasparri, M.L., Attar, R., Palaia, I., Perniola, G., Marchetti, C., Donato, V. Di, et al., 2015. Tumor Infiltrating Lymphocytes in Ovarian Cancer. *Asian Pacific J. Cancer Prev.* 16: 3635–3638. doi:10.7314/APJCP.2015.16.9.3635
- Gavalas, N.G., Lontos, M., Trachana, S.P., Bagratuni, T., Arapinis, C., Liacos, C., et al., 2013. Angiogenesis-related pathways in the pathogenesis of ovarian



cancer. *Int. J. Mol. Sci.* doi:10.3390/ijms140815885

- Gawrychowski, K., Szewczyk, G., Skopińska-Różewska, E., Małecki, M., Barcz, E., Kamiński, P., et al., 2014. The angiogenic activity of ascites in the course of ovarian cancer as a marker of disease progression. *Dis. Markers* 1–5. doi:10.1155/2014/683757
- Geomini, P., Kruitwagen, R., Bremer, G.L., Cnossen, J., & Mol, B.W.J., 2009. The accuracy of risk scores in predicting ovarian malignancy: A systematic review. *Obstet. Gynecol.* 113: 384–394. doi:10.1097/AOG.0b013e318195ad17
- Ghoneum, A., Afify, H., Salih, Z., Kelly, M., & Said, N., 2018. Role of tumor microenvironment in ovarian cancer pathobiology. *Oncotarget* 9: 22832–22849. doi:10.18632/oncotarget.25126
- Gonzalez, H., Hagerling, C., & Werb, Z., 2018. Roles of the immune system in cancer: From tumor initiation to metastatic progression. *Genes Dev.* 32: 1267–1284. doi:10.1101/GAD.314617.118
- Gupta, D., & Lis, C.G., 2009. Role of CA125 in predicting ovarian cancer survival - A review of the epidemiological literature. *J. Ovarian Res.* 2: 1–20. doi:10.1186/1757-2215-2-13
- Gupta, M., Babic, A., Beck, A.H., & Terry, K., 2016. TNF- $\alpha$  expression, risk factors, and inflammatory exposures in ovarian cancer: Evidence for an inflammatory pathway of ovarian carcinogenesis? *Hum. Pathol.* 54: 82–91. doi:10.1016/j.humpath.2016.03.006
- Hendry, S., Salgado, R., Gevaert, T., Russell, P.A., John, T., Thapa, B., et al., 2017. Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immuno-Oncology Biomarkers Working Group: Part 2: TILs in Melanoma, Gastrointestinal Tract Carcinom. *Adv. Anat. Pathol.* 24: 311–335. doi:10.1097/PAP.0000000000000161
- Hisamatsu, T., Mabuchi, S., Sasano, T., Kuroda, H., Takahashi, R., Matsumoto, Y., et al., 2015. The significance of lymphatic space invasion and its association with vascular endothelial growth factor-C expression in ovarian cancer. *Clin. Exp. Metastasis* 32: 789–798. doi:10.1007/s10585-015-9751-0



Hsieh, S.F., Lau, H.Y., Wu, H.H., Hsu, H.C., Twu, N.F., & Cheng, W.F., 2019.

Prognostic factors of early stage epithelial ovarian carcinoma. *Int. J. Environ. Res. Public Health* 16: 1–12. doi:10.3390/ijerph16040637

Huang, Q.-T., Zhong, M., Zhou, L., Zeng, W.-J., Ma, Q.-Q., Wang, W., et al., 2017.

Prognostic Significance of Neutrophil-to- Lymphocyte Ratio in Ovarian Cancer: A Systematic Review and Meta-Analysis of Observational Studies.

*Cell Physiol Biochem* 41: 2411–2418. doi:10.1159/000475911

Hwang, C., Lee, S.J., Lee, J.H., Kim, K.H., Suh, D.S., Kwon, B.S., et al., 2019.

Stromal tumor-infiltrating lymphocytes evaluated on H&E-stained slides are an independent prognostic factor in epithelial ovarian cancer and ovarian serous carcinoma. *Oncol. Lett.* 17: 4557–4565. doi:10.3892/ol.2019.10095

Hwang, W.T., Adams, S.F., Tahirovic, E., Hagemann, I.S., & Coukos, G., 2012.

Prognostic Significance of Tumor Infiltrating T cells in Ovarian Cancer: A Meta-Analysis. *Gynecol. Oncol.* 124: 192–198.

doi:10.1016/j.ygyno.2011.09.039

James, F.R., Jiminez-Linan, M., Alsop, J., Mack, M., Song, H., Brenton, J.D., et al., 2017. Association between tumour infiltrating lymphocytes, histotype and clinical outcome in epithelial ovarian cancer. *BMC Cancer* 17: 1–7. doi:10.1186/s12885-017-3585-x

Jochems, C., & Schlom, J., 2011. Between Conventional Cancer Therapy and Immunity. *J. Exp. Med.* 236: 567–579. doi:10.1258/ebm.2011.011007. Tumor-infiltrating

Jones, V.S., Huang, R.Y., Chen, L.P., Chen, Z.S., Fu, L., & Huang, R.P., 2016. Cytokines in cancer drug resistance: Cues to new therapeutic strategies. *Biochim. Biophys. Acta - Rev. Cancer* 1865: 255–265. doi:10.1016/j.bbcan.2016.03.005

Kheiri, S.A., Kunna, A., Babiker, A.Y., Alsuhaibani, S.A., Ahmed, R.Y., & Alsammani, M.A., 2018. Histopathological pattern and age distribution, of malignant ovarian tumor among sudanese ladies. *Open Access Maced. J. Med. Sci.* 6: 237–241. doi:10.3889/OAMJMS.2018.067

Kim, S., Kim, B., & Song, Y.S., 2016. Ascites modulates cancer cell behavior,



- contributing to tumor heterogeneity in ovarian cancer. *Cancer Sci.* 107: 1173–1178. doi:10.1111/cas.12987
- Kim, S.J., Rosen, B., Fan, I., Ivanova, A., McLaughlin, J.R., Risch, H., et al., 2017. Epidemiologic factors that predict long-term survival following a diagnosis of epithelial ovarian cancer. *Br. J. Cancer* 116: 964–971. doi:10.1038/bjc.2017.35
- Kolomeyevskaya, N., Eng, K.H., Khan, A.N.H., Grzankowski, K.S., Singel, K.L., Moysich, K., et al., 2015. Cytokine profiling of ascites at primary surgery identifies an interaction of tumor necrosis factor- $\alpha$  and interleukin-6 in predicting reduced progression-free survival in epithelial ovarian cancer. *Gynecol. Oncol.* 138: 352–357. doi:10.1016/j.ygyno.2015.05.009
- Kurman, R.J., & Shih, I.M., 2016. The dualistic model of ovarian carcinogenesis revisited, revised, and expanded. *Am. J. Pathol.* 186: 733–747. doi:10.1016/j.ajpath.2015.11.011
- Lane, D., Matte, I., Garde-Granger, P., Bessette, P., & Piché, A., 2018. Ascites IL-10 Promotes Ovarian Cancer Cell Migration. *Cancer Microenviron.* 11: 115–124. doi:10.1007/s12307-018-0215-3
- Lane, D., Matte, I., Garde-Granger, P., Laplante, C., Carignan, A., Rancourt, C., et al., 2015. Inflammation-regulating factors in ascites as predictive biomarkers of drug resistance and progression-free survival in serous epithelial ovarian cancers. *BMC Cancer* 15: 1–11. doi:10.1186/s12885-015-1511-7
- Lane, D., Matte, I., Rancourt, C., & Piché, A., 2011. Prognostic significance of IL-6 and IL-8 ascites levels in ovarian cancer patients. *BMC Cancer* 11. doi:10.1186/1471-2407-11-210
- Lee, L., Hellendall, R.P., Wang, Y., Haskill, J.S., Mukaida, N., Matsushima, K., et al., 2000. IL-8 Reduced Tumorigenicity of Human Ovarian Cancer In Vivo Due to Neutrophil Infiltration. *J. Immunol.* 164: 2769–2775. doi:10.4049/jimmunol.164.5.2769
- Li, J., Wang, J., Chen, R., Bai, Y., & Lu, X., 2017. The prognostic value of tumor-infiltrating T lymphocytes in ovarian cancer. *Oncotarget* 8: 15621–15631. doi:10.18632/oncotarget.14919



- Li, Y.L., Zhao, H., & Ren, X.B., 2016. Relationship of VEGF/VEGFR with immune and cancer cells: staggering or forward? *Cancer Biol. Med.* 13: 206–214. doi:10.20892/j.issn.2095-3941.2015.0070
- Li, Z., Yin, H., Ren, M., & Shen, Y., 2020. Prognostic significance of CA125 dynamic change for progression free survival in patients with epithelial ovarian carcinoma. *Med. Sci. Monit.* 26: 1–8. doi:10.12659/MSM.925051
- Liang, B., Guo, Z., Li, Y., & Liu, C., 2013. Elevated VEGF concentrations in ascites and serum predict adverse prognosis in ovarian cancer. *Scand. J. Clin. Lab. Invest.* 73: 309–314. doi:10.3109/00365513.2013.773593
- Ligament, B., 2018. Special Section : Ovarian Cancer. *Am. Cancer Soc.* 45: 28–43.
- Markmann, S., Gerber, B., & Briese, V., 2007. Prognostic value of Ca 125 levels during primary therapy. *Anticancer Res.* 27: 1837–1839.
- Masoumi Moghaddam, S., Amini, A., Morris, D.L., & Pourgholami, M.H., 2012. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. *Cancer Metastasis Rev.* doi:10.1007/s10555-011-9337-5
- Matsuo, K., Hasegawa, K., Yoshino, K., Murakami, R., Hisamatsu, T., Stone, R.L., et al., 2015. Venous thromboembolism, interleukin-6 and survival outcomes in patients with advanced ovarian clear cell carcinoma. *Eur. J. Cancer* 51: 1978–1988. doi:10.1016/j.ejca.2015.07.012
- Matsuo, K., Yoshino, K., Hiramatsu, K., Banzai, C., Hasegawa, K., Yasuda, M., et al., 2014. Effect of Lymphovascular Space Invasion on Survival of Stage I Epithelial Ovarian Cancer. *Obstet. Gynecol.* 123: 957–965. doi:10.1097/AOG.0000000000000240
- Matte, I., Lane, D., Laplante, C., Rancourt, C., & Piché, A., 2012. Profiling of cytokines in human epithelial ovarian cancer ascites. *Am. J. Cancer Res.* 2: 566–80.
- Minor, D.R., Moores, S.P., & Chan, J.K., 2017. Prolonged survival after intraperitoneal interleukin-2 immunotherapy for recurrent ovarian cancer. *Gynecol. Oncol. Reports* 22: 43–44. doi:10.1016/j.gore.2017.09.009
- Monk, B.J., Brady, M.F., Aghajanian, C., Lankes, H.A., Rizack, T., Leach, J., et



- al., 2017. A Phase 2, Randomized, Double-Blind, Placebo- Controlled Study of Chemoimmunotherapy Combination using Motolimod with Pegylated Liposomal Doxorubicin in Recurrent or Persistent Ovarian Cancer: A Gynecologic Oncology Group partners study. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* 28: 996–1004. doi:10.1093/annonc/mdx049
- Musrap, N., & Diamandis, E.P., 2012. Revisiting the Complexity of the Ovarian Cancer Microenvironment--Clinical Implications for Treatment Strategies. *Mol. Cancer Res.* 10: 1254–1264. doi:10.1158/1541-7786.MCR-12-0353
- Nash, M.A., Ferrandina, G., Gordinier, M., Loercher, A., & Freedman, R.S., 1999. The role of cytokines in both the normal and malignant ovary. *Endocr. Relat. Cancer* 6: 93–107. doi:10.1677/erc.0.0060093
- National Collaborating Centre, 2011. Ovarian cancer: The recognition and initial management of ovarian cancer. *Heal. (San Fr.)* NICE clini.
- Nelson Brad H, 2008. The Impact of T-Cell Immunity on Ovarian Cancer Outcomes.
- O'Toole, S.A., Sheppard, B.L., Laios, A., O'Leary, J.J., McGuinness, E.P.J., D'Arcy, T., et al., 2007. Potential predictors of chemotherapy response in ovarian cancer-How do we define chemosensitivity? *Gynecol. Oncol.* 104: 345–351. doi:10.1016/j.ygyno.2006.08.039
- Oge, T., Ozalp, S.S., & Yalcin, O.T., 2011. Prognostic Factors In Epithelial Ovarian Carcinoma: A Reference Institution Experience. *J. Turkish Soc. Obstet. Gynecol.* 8: 51–56. doi:10.5505/tjod.2011.05902
- Öge, T., Özalp, S.S., & Yalçın, Ö.T., 2011. Prognostic factors in epithelial ovarian carcinoma: A reference institution experience. *Turk Jinekoloji ve Obstet. Dern. Derg.* 8: 51–56. doi:10.5505/tjod.2011.05902
- Paoletti, X., Lewisley, L.A., Daniele, G., Cook, A., Yanaihara, N., Tinker, A., et al., 2020. Assessment of Progression-Free Survival as a Surrogate End Point of Overall Survival in First-Line Treatment of Ovarian Cancer: A Systematic Review and Meta-analysis. *JAMA Netw. Open* 3: 1–15. doi:10.1001/jamanetworkopen.2019.18939
- Paradkar, P.H., Joshi, J.V., Mertia, P.N., Agashe, S.V., & Vaidya, R.A., 2014. Role



- of cytokines in genesis, progression and prognosis of cervical cancer. *Asian Pacific J. Cancer Prev.* doi:10.7314/APJCP.2014.15.9.3851
- Parveen, A., Subedi, L., Kim, H., Khan, Z., Zahra, Z., Farooqi, M., et al., 2019. Phytochemicals Targeting VEGF and VEGF-Related Multifactors as Anticancer Therapy. *J. Clin. Med.* 8: 350. doi:10.3390/jcm8030350
- Paul, M.S., Saibil, S.D., Lien, S.C., Han, S.J., Sayad, A., Mulder, D.T., et al., 2020. IL6 induces an IL22+ CD8+ T-cell subset with potent antitumor function. *Cancer Immunol. Res.* 8: 321–333. doi:10.1158/2326-6066.CIR-19-0521
- Peres, L.C., Cushing-Haugen, K.L., Köbel, M., Harris, H.R., Berchuck, A., Rossing, M.A., et al., 2019. Invasive epithelial ovarian cancer survival by histotype and disease stage. *J. Natl. Cancer Inst.* 111. doi:10.1093/jnci/djy071
- Perren, T.J., Swart, A.M., Pfisterer, J., Ledermann, J.A., Pujade-Lauraine, E., Kristensen, G., et al., 2011. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. *N. Engl. J. Med.* 365: 2484–2496. doi:10.1056/nejmoa1103799
- Prat, J., & Committee, F., 2014. International Journal of Gynecology and Obstetrics Staging classification for cancer of the ovary , fallopian tube , and peritoneum ☆. *Int. J. Gynecol. Obstet.* 124: 1–5. doi:10.1016/j.ijgo.2013.10.001
- Qian, X., Xi, X., & Jin, Y., 2010. The grading of lymphovascular space invasion in epithelial ovarian carcinoma. *Int. J. Gynecol. Cancer* 20: 895–899. doi:10.1111/IGC.0b013e3181e02fc7
- Rao, U.N.M., Lee, S.J., Luo, W., Mihm, M.C., & Kirkwood, J.M., 2010. Presence of Tumor-Infiltrating Lymphocytes and A Dominant Nodule Within Primary Melanoma are Prognostic Factors for Relapse-Free Survival of Patients with Thick (T4) Primary Melanoma: Pathologic Analysis of The E1690 and E1694 Intergroup Trials. *Am. J. Clin. Pathol.* 133: 646–653. doi:10.1309/AJCPTXMEFOVYWDAA6
- Rodriguez, G.M., Galpin, K.J.C., McCloskey, C.W., & Vanderhyden, B.C., 2018. The tumor microenvironment of epithelial ovarian cancer and its influence on response to immunotherapy. *Cancers (Basel)*. doi:10.3390/cancers10080242
- Rosenberg, S.A., Lotze, M.T., Yang, J.C., Aebersold, P.M., Linehan, W.M., Seipp, C.A., et al., 1989. Experience with the Use of High-Dose Interleukin-2 in the



Treatment of 652 Cancer Patients. *Ann. Surg.* 210: 474–485.  
doi:10.1097/00000658-198910000-00008

Rudlowski, C., Pickart, A.K., Fuhljahn, C., Friepoertner, T., Schlehe, B., Biesterfeld, S., et al., 2006. Prognostic significance of vascular endothelial growth factor expression in ovarian cancer patients: A long-term follow-up. *Int. J. Gynecol. Cancer* 16: 183–189. doi:10.1111/j.1525-1438.2006.00307.x  
Rustin, G.J.S., Vergote, I., Eisenhauer, E., Pujade-Lauraine, E., Quinn, M., Thigpen, T., et al., 2011. Definitions for response and progression in ovarian cancer clinical trials incorporating recist 1.1 and CA 125 agreed by the gynecological cancer intergroup (GCIG). *Int. J. Gynecol. Cancer* 21: 419–423. doi:10.1097/IGC.0b013e3182070f17

Saad, A.F., Hu, W., & Sood, A.K., 2010. Microenvironment and Pathogenesis of Epithelial Ovarian Cancer. *Horm. Cancer* 1: 277–290. doi:10.1007/s12672-010-0054-2

Saito, T., Berens, M.E., & Welander, C.E., 1987. Interferon-gamma and cytotoxic agents studied in combination using a soft agarose human tumor clonogenic assay. *Cancer Chemother. Pharmacol.* 19: 233–239. doi:10.1007/BF00252978

Santoiemma, P.P., & Powell, D.J., 2015. Tumor infiltrating lymphocytes in ovarian cancer. *Cancer Biol. Ther.* 16: 807–820. doi:10.1080/15384047.2015.1040960

Savant, S.S., Sriramkumar, S., & O'Hagan, H.M., 2018. The Role of Inflammation and Inflammatory Mediators in the Development, Progression, Metastasis, and Chemoresistance of Epithelial Ovarian Cancer. *Cancers (Basel)*. 10. doi:10.3390/cancers10080251

Scambia, G., Testa, U., Panici, P.B., Foti, E., Martucci, R., Gadducci, A., et al., 1995. Prognostic significance of interleukin 6 serum levels in patients with ovarian cancer. *Br. J. Cancer* 71: 354–356. doi:10.1038/bjc.1995.71

Schauer, I.G., Zhang, J., Xing, Z., Guo, X., Mercado-Uribe, I., Sood, A.K., et al., 2013a. Interleukin-1  $\beta$  Promotes Ovarian Tumorigenesis through a p53 / NF- $\kappa$  B – Mediated Inflammatory Response in. *Neoplasia* 15: 409–420.



doi:10.1593/neo.121228

- Schauer, I.G., Zhang, J., Xing, Z., Guo, X., Mercado-Uribe, I., Sood, A.K., et al., 2013b. Interleukin-1 $\beta$  promotes ovarian tumorigenesis through a p53/NF- $\kappa$ B-mediated inflammatory response in stromal fibroblasts. *Neoplasia (United States)* 15: 409–420. doi:10.1593/neo.121228
- Siegel, R.L., Miller, K.D., & Jemal, A., 2019. Cancer statistics, 2019 (US statistics). *CA. Cancer J. Clin.* 69: 7–34. doi:10.3322/caac.21551
- Strandmann, E.P. von, Reinartz, S., Wager, U., & Müller, R., 2017. Tumor–Host Cell Interactions in Ovarian Cancer: Pathways to Therapy Failure. *Trends in Cancer* 3: 137–148. doi:10.1016/j.trecan.2016.12.005
- Szlosarek, P.W., Grimshaw, M.J., Kulbe, H., Wilson, J.L., Wilbanks, G.D., Burke, F., et al., 2006. Expression and regulation of tumor necrosis factor  $\alpha$  in normal and malignant ovarian epithelium. *Mol. Cancer Ther.* 5: 382–390. doi:10.1158/1535-7163.MCT-05-0303
- Szulc-Kielbik, I., Kielbik, M., Nowak, M., & Klink, M., 2021. The implication of IL-6 in the invasiveness and chemoresistance of ovarian cancer cells. Systematic review of its potential role as a biomarker in ovarian cancer patients. *Biochim. Biophys. Acta - Rev. Cancer* 1876: 188639. doi:10.1016/j.bbcan.2021.188639
- Testa, U., Petrucci, E., Pasquini, L., Castelli, G., & Pelosi, E., 2018. Ovarian Cancers: Genetic Abnormalities, Tumor Heterogeneity and Progression, Clonal Evolution and Cancer Stem Cells. *Medicines* 5: 16. doi:10.3390/medicines5010016
- Tjokroprawiro, B.A., Fadli, S., & Budiono, B., 2021. Evaluating the Association between Clinical Characteristics with Progression-Free Survival and 3-Year Survival in Patients with Epithelial Ovarian Cancer. *Indones. J. Cancer* 15: 162. doi:10.33371/ijoc.v15i4.815
- Trachana, S., Pilalis, E., Gavalas, N.G., & Tzannis, K., 2016. The Development of an Angiogenic Protein “Signature” in Ovarian Cancer Ascites as a Tool for Biologic and Prognostic Profiling 1–16. doi:10.1371/journal.pone.0156403
- Van Der Zee, A.G.J., De Bruijn, H.W.A., Krans, M., De Cuyper, E.M.J., Hollema,



- H., Limburg, P.C., et al., 1995. Higher levels of interleukin-6 in cystic fluids from patients with malignant versus benign ovarian tumors correlate with decreased hemoglobin levels and increased platelet counts. *Cancer* 75: 1004–1009. doi:10.1002/1097-0142(19950215)75:4<1004::AID-CNCR2820750416>3.0.CO;2-G
- Wall, L., Burke, F., Barton, C., Smyth, J., & Balkwill, F., 2003. IFN- $\gamma$  induces apoptosis in ovarian cancer cells in vivo and in vitro. *Clin. Cancer Res.* 9: 2487–2496.
- Wang, Y., Van Boxel-Dezaire, A.H.H., Cheon, H., Yang, J., & Stark, G.R., 2013. STAT3 activation in response to IL-6 is prolonged by the binding of IL-6 receptor to EGF receptor. *Proc. Natl. Acad. Sci. U. S. A.* 110: 16975–16980. doi:10.1073/pnas.1315862110
- Webb, P.M., & Jordan, S.J., 2017. Epidemiology of epithelial ovarian cancer. *Best Pract. Res. Clin. Obstet. Gynaecol.* doi:10.1016/j.bpobgyn.2016.08.006
- Winter, W.E., Maxwell, G.L., Tian, C., Carlson, J.W., Ozols, R.F., Rose, P.G., et al., 2007. Prognostic factors for stage III epithelial ovarian cancer: A Gynecologic Oncology Group study. *J. Clin. Oncol.* 25: 3621–3627. doi:10.1200/JCO.2006.10.2517
- Woolery, K.T., & Kruk, P.A., 2011. Ovarian Epithelial-Stromal Interactions: Role of Interleukins 1 and 6. *Obstet. Gynecol. Int.* 2011: 1–9. doi:10.1155/2011/358493
- Worzfeld, T., von Strandmann, E.P., Huber, M., Adhikary, T., Wagner, U., Reinartz, S., et al., 2017. The unique molecular and cellular microenvironment of Ovarian cancer. *Front. Oncol.* 7. doi:10.3389/fonc.2017.00024
- Wu, L., Deng, Z., Peng, Y., Han, L., & Liu, J., 2017. Ascites-derived IL-6 and IL-10 synergistically expand 8: 76843–76856.
- Yeung, T.L., Leung, C.S., Yip, K.P., Yeung, C.L.A., Wong, S.T.C., & Mok, S.C., 2015. Cellular and molecular processes in ovarian cancer metastasis. A review in the theme: Cell and molecular processes in cancer metastasis. *Am. J. Physiol. - Cell Physiol.* 309: C444–C456. doi:10.1152/ajpcell.00188.2015
- Yin, X., Wu, L., Yang, Hui, & Yang, Hongbo, 2019. Prognostic significance of



neutrophil-lymphocyte ratio (NLR) in patients with ovarian cancer. *Medicine (Baltimore)*. 98: e17475. doi:10.1097/MD.00000000000017475

Yuan, Y., Jiang, Y.C., Sun, C.K., & Chen, Q.M., 2016. Role of the tumor microenvironment in tumor progression and the clinical applications (Review). *Oncol. Rep.* 35: 2499–2515. doi:10.3892/or.2016.4660

Zhang, L., Conejo-Garcia, J.R., Katsaros, D., Gimotty, P.A., Massobrio, M., Regnani, G., et al., 2003. Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer. *N. Engl. J. Med.* 348: 203–213. doi:10.1056/NEJMoa020177

Zhang, Y.-L., Li, J., Mo, H.-Y., Qiu, F., Zheng, L.-M., Qian, C.-N., et al., 2010. Different Subsets of Tumor Infiltrating Lymphocytes Correlate with NPC Progression in Different Ways.

Zhou, J., & Brune, B., 2006. Cytokines and Hormones in the Regulation of Hypoxia Inducible Factor-1a; (HIF-1a). *Cardiovasc. Hematol. Agents Med. Chem.* 4: 189–197. doi:10.2174/187152506777698344