Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 111 (2018) 51-63 EISSN 2392-2192

Contemporary management and novel therapies in ovarian cancer – literature review

Krzysztof Kotowski[1], Dawid Przystupski[1], Stanisław Kwiatkowski[1,*], Karolina Kolasińska[1], Weronika Bartosik[2], Agata Górska[3], Jolanta Saczko[4], Dagmara Baczyńska[4,5], Julita Kulbacka[4]

[1] Faculty of Medicine, Wroclaw Medical University, J. Mikulicza-Radeckiego 5, 50-345 Wroclaw, Poland

[2] Faculty of Biotechnology, University of Wroclaw, Fryderyka Joliot-Curie 14a, 50-383 Wroclaw, Poland

[3] Department of Biological Sciences, Institute of Experimental Biology, University of Wroclaw, Kanonia 6/8, 50-328 Wroclaw, Poland

[4] Department of Molecular and Cellular Biology, Wroclaw Medical University, Borowska 211A, 50-556, Wroclaw, Poland

[5] Department of Forensic Medicine, Molecular Techniques Unit, Wroclaw Medical University, J. Mikulicza-Radeckiego 4, 50-345 Wroclaw, Poland

*E-mail address: stkwiatek@gmail.com

ABSTRACT

Ovarian cancer is characterized by an extremely poor prognosis in women with an advanced stage of this carcinoma. In United States every year 20,000 women are diagnosed with ovarian cancer. It is the fifth most frequent cause of death from cancer in females and the most common cause of death for 15 years after diagnosis in women with stage III-IV tumors. Among ovarian neoplasms the most frequent are surface epithelial-stromal tumors. Moreover, non-epithelial ovarian tumors are distinguished. This group matters 10% of patients with diagnosed ovarian tumors. Due to a huge variety of ovarian tumors, the following work focuses mainly on the current clinical treatment of the epithelial ovarian cancer. The following paper summarizes current clinical treatment of epithelial ovarian cancer, including surgical procedure, chemo- and immunotherapy including modern therapeutic approaches.

(Received 04 September 2018; Accepted 21 September 2018; Date of Publication 22 September 2018)

***Keywords*:** ovarian cancer, immunotherapy, Interval Debuking Surgery, Interval Cytoreductive Surgery, bevacizumab, Anti-VEGF monoclonal IgG1 antibody, electrochemotherapy, hormone therapy, photodynamic therapy

1. INTRODUCTION

Ovarian cancer is characterized by an extremely poor prognosis in women with an advanced stage of this carcinoma [1]. In United States every year 20,000 women are diagnosed with ovarian cancer [2]. It is the fifth most frequent cause of death from cancer in females [3] and the most common cause of death for 15 years after diagnosis in women with stage III-IV tumors [4]. The mean survival time in case of ovarian cancer is 19 months [5] and the 5-year survival for women with advanced disease's stage reaches only 50% [6]. Among ovarian neoplasms the most frequent are surface epithelial-stromal tumors. They are subdivided into serous, mucosal, clear-cell, adenocarcinomas and those derived from transitional epithelium (Table 1). All above-mentioned tumors present a different histological image [7]. Moreover, non-epithelial ovarian tumors are distinguished. This group matters 10% of patients with diagnosed ovarian tumors. Among these, SCST-sex cord stromal tumors [8] or GCT germ cell tumors are distinguished [9]. Such heterogeneity of ovarian tumors results from the presence of three cell types present in a normal ovary:

- cells of multipotential surface epithelium,
- totipotent germ cells,
- sex cord cells.

Each of the following cells' type can proliferate pathologically and develop numerous, different cancers. Moreover, metastases from other organs can be found in oncologically managed ovary. The most common cancers that give metastases to the ovaries are tumors originating from the so-called *Muller's ducts*, as well as: breast cancers, malignant melanoma or carcinomas of gastrointestinal tract [2][10]. Highly characteristic for ovaries is metastasis from the gastrointestinal system - *the Krukenberg tumor*. This is the most common type of metastasis from gastric cancer located in the pylorus [11]. Due to a huge variety of ovarian tumors, the following work focuses mainly on the current clinical treatment of the epithelial ovarian cancer.

Table 1. Simplified classification of ovarian tumors according to World Health Organization based on [2].

Surface epithelial – stromal tumors
Serous
Mucous
Endometrial
Clear cell
Transitional cell carcinoma (Brenner tumors)

Cord stromal tumors
Granulosa cell tumor
Thecoma, fibrothecoma, fibroma
Androblastoma
Tumor with a lipid cell origin
Germ cell tumors
Dysgerminoma
Yolk sac tumor
Carcinoma embrionale
Choriocarcinoma
Teratoma
Mixed tumors
Unclassified tumors
Metastatic tumors

2. ETIOPATHOGENESIS

The following risk factors are related to the more frequent occurrence of ovarian cancer:

- low number or lack of deliveries [12],
- BRCA1, BRCA2 gene mutations [13],
- congenital syndromes of breast and ovarian cancer and hereditary ovarian cancer [14],
- family occurrence of Lynch syndrome (*hereditary nonpolyposis colorectal cancer*) [15].

Nulliparous women exhibit an increased risk of ovarian cancer [16]. The controversial is the risk of cancer related to the fertility drug use and it needs further, large, well-designed investigations with sufficient follow-up time [17][18].

The nest risk factor involves BRCA1, BRCA2 gene mutations. The BRCA1 gene is located in locus 17q21 [19] and BRCA2 on 13 chromosome [20]. The average cumulative risks for ovarian cancer in BRCA1-mutation carriers by age 70 years is 39% (18%–54%)[21]. The Lynch syndrome is the next hereditary disorder associated with an increased risk in women. It is also known as *hereditary nonpolyposis colorectal cancer* (HNPCC) [22]. The syndrome is responsible as well for the increased risk of other tumors occurrence such as: colorectal cancer, endometrial cancer, digestive adenoma (gastric, pyloric gland, duodenal, intestinal adenoma) [23]. The Lynch syndrome is caused by mutations within the genes responsible for mismatch repair such as hMSH2 (*human mutS protein homolog 2*) in the 2p21-22 locus, hMLH1 (*human mutL homolog 1*) in the locus 3p21.3-23, hPMS1 (human postmeiotic segregation 1) at the 2q31-33 locus, hPMS2 (*human postmeiotic segregation 2*) at the 7p22 locus, hMSH6 at the 2p16 locus, hMSH3 at the 5q11.2-q13.2 locus [24]. The

diagnosis of this syndrome is based on the guidelines set out in the Amsterdam system and the Bethesda criteria [25][26].

The other important risk factor seems to be chronic exposure to asbestos[27]. Also viral diseases, such as epidemic parotitis (mumps) [28][29][30] or rubella [31] may play a significant role in the pathogenesis of some types of ovarian cancer. Several factors associated with the reduction of the ovarian cancer risk were indicated: uterine excision, tubal occlusion and breastfeeding [29].

3. CLINICAL SYMPTOMS

Ovarian cancer usually develops insidiously. The first signs of the disease are often absent or uncharacteristic; thus, often ignored or misdiagnosed. In many cases some of them exist for several months before the diagnosis. The most common symptoms include bloating, abdominal pain or discomfort, loss of appetite, changes in bowel movements, fatigue, back pain, irregular menstruation or postmenopausal vaginal bleeding and pain or bleeding after or during sexual intercourse. Urinary symptoms such as more frequent or urgent need to urinate may also be present [32]. The majority of women have stage III or stage IV at diagnosis and they mostly present with ascites, abdominal pain or compression symptoms, such as bowel obstruction or urinary retention [33]. Symptoms may vary due to localization of metastases. Interestingly, metastases may cause Sister Mary Joseph nodule. It is a palpable tumor in the umbilical region resulting from the metastatic disease located within peritoneal lymph nodes. Ovarian cancer is the most common metastatic tumor in the umbilical region in women [34]. Clinical representation of patients depends mostly on the stage of the disease and involvement of adjacent anatomical structures[35].

4. RECOGNITION CRITERIA AND DETERMINATION OF THE LEVEL OF ADVANCEMENT

Table 2. FIGO Ovarian Cancer Staging - Effective Jan. 1, 2014 based on https://www.sgo.org/wp-content/uploads/2012/09/FIGO-Ovarian-Cancer-Staging_1.10.14.pdf

Stage		**Characteristic**
I	**Tumor confined to ovaries**	
	IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
	IB	Tumor involves both ovaries otherwise like IA.
	IC	Tumor limited to 1 or both ovaries
	IC1	Surgical spill
	IC2	Capsule rupture before surgery or tumor on ovarian surface
	IC3	Malignant cells in the ascites or peritoneal washings.

II	**Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer**		
	IIA	Extension and/or implant on uterus and/or Fallopian tubes	
	IIB	Extension to other pelvic intraperitoneal tissues	
III	**Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes**		
	IIIA	Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis	
	IIIA1	Positive retroperitoneal lymph nodes only	
		IIIA1(i)	Metastasis ≤ 10 mm
		IIIA1(ii)	Metastasis > 10 mm
	IIIA2	Microscopic, extra-pelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes	
	IIIB	Macroscopic, extra-pelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	
	IIIC	Macroscopic, extra-pelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.	
IV	**Distant metastasis excluding peritoneal metastasis**		
	IVA	Pleural effusion with positive cytology	
	IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

The basis for the diagnosis of the ovarian cancer is based on the pathomorphological evaluation of the material collected from the patient during the surgery. The biopsy performed under the control of imaging methods is important as well. The stage of the assessment is based on the FIGO criteria (*The International Federation of Gynecology and Obstetrics*), based on the surgical evaluation and the histopathological picture. The current classification from 2014 is presented in the Table 2.

5. TREATMENT

The treatment of the ovarian cancer is based on combined treatment based on surgery and chemotherapy. In addition, the following paper presents current information on the effectiveness of other available therapeutic methods e.g. immunotherapy and biological treatment.

5. 1. Surgical procedure

Surgical treatment is the treatment of choice. The scope of the surgery is closely related and depends on the classification according to FIGO. Due to the frequent bilateral occurrence of the tumor and tendency to endometrial infiltration, the surgical procedure is relatively extensive, because in the low stages and thus in stage I-IIA the total hysterectomy is performed - which means removal of the uterus along with bilateral removal of the fallopian tubes with ovaries. Additionally, the procedure includes the removal of the greater omentum and pelvic and aortic lymph nodes excision. During the procedure, samples of biological material are also collected - smears and random peritoneum sections [36].

However, there are a few deviations and modifications of this procedure. The most important is the surgical development of cancer in women of childbearing age with a single-sided FIGO stage IA in a situation where the patient wants to preserve fertility. In this situation, it is acceptable to leave the uterus and the second ovary [37].

In the case of tumors in the stage IA and equal to IIB, the complete cytoreduction is required [38]. In this case, the extent of resection includes not only these organs as in the case of less advanced tumor but also segmental resections of the large intestine, small intestine and all existing changes on the surface of the liver [39]. An important issue is IDS/ICS, so-called Interval Debuking Surgery / Interval Cytoreductive Surgery. This procedure is based on the resection only after 3 cycles of chemotherapy and continuation of chemotherapy after the procedure. The application of this type of surgery seems to be promising [40][41].

5. 2. Chemotherapy

The duration, cycles and doses of CTH are also dependent on the stage of the cancer. It is extremely important to start chemotherapy as early as it is possible from the time of diagnosis. The basis of chemotherapy for ovarian cancer is biphasic therapy. CT scheme protocols include the following cytostatics and its combinations: platinium combined with taxoid [42], carboksilplatin and paclitaxel [43], futhermore, cisplatin and docetaxel [44]. The most commonly used treatments are based on the individual stages according to FIGO. The promising diagnose was presented for a group of patients with tumors in stage IA or IB G1. Authors indicated the withdraw from chemotherapy, but only after careful examination of the pelvic and para-aortic lymph nodes [45]. In other cases, it was recommended to apply 6 cycles of carboxyplatatin with paclitaxel. There was also demonstrated a good efficacy of the treatment with carboxyplatin with pegylated liposomal doxorubicin. However this method of treatment requires further investigation to assess its effectiveness and mechanisms in more details [46].

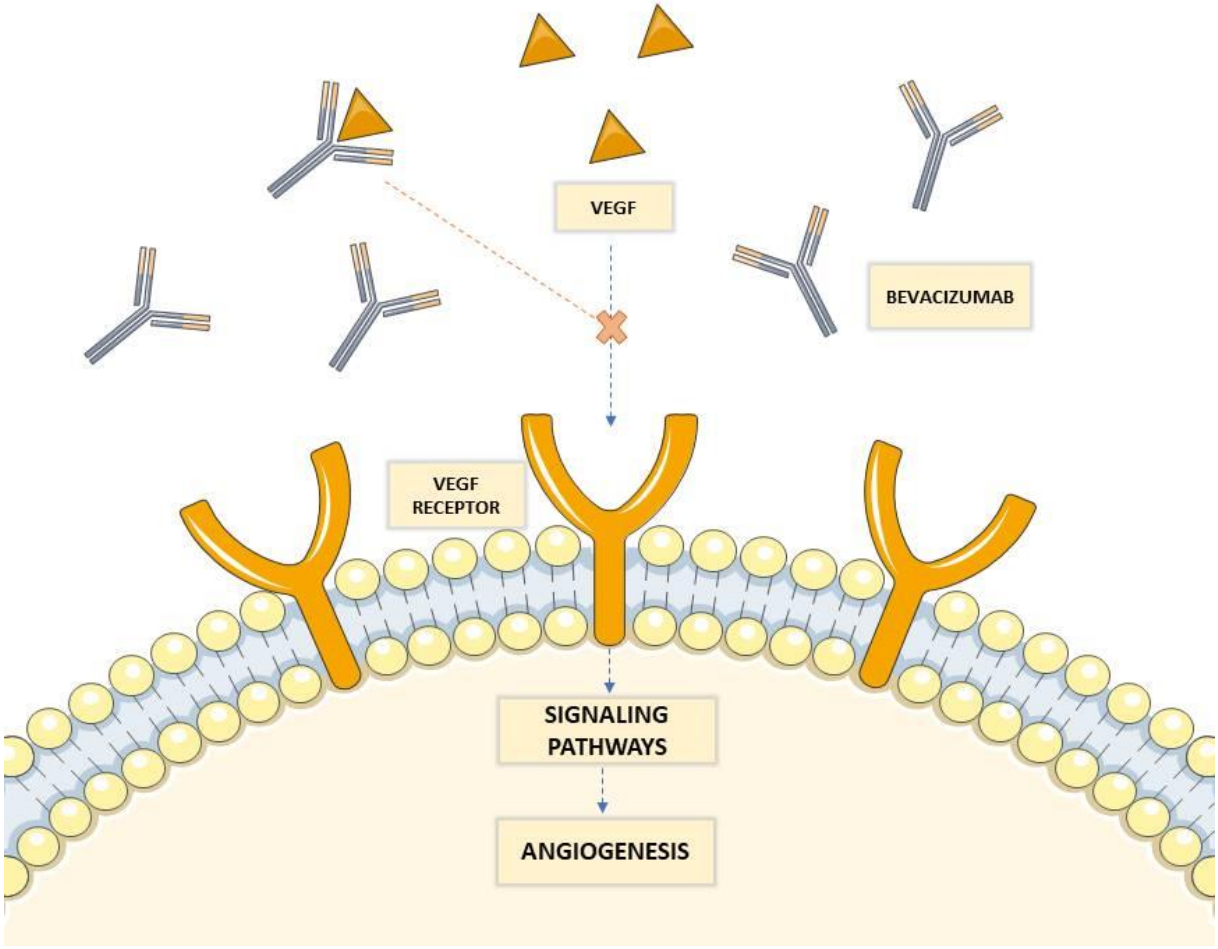
The noteworthy method of chemotherapy used in patients with left over 1cm tumor residue is an intraperitoneal chemotherapy [47]. Chochrane's (2016) meta-analyzes demonstrated the high efficacy of a combination of standard intravenous and IP chemotherapy[48].

5. 3. Immunotherapy

Immunotherapy can be also called targeted therapy. Targeted therapy (TT) includes the usage of drugs which can access cancer cells in a specific or unique way. TT is mostly concentrated on the specific proteins or inhibition of action of molecules that are essential to cancer growth. An example of biological treatment used in the treatment of ovarian cancer is

the use of bevacizumab [49]. This drug is a recombinant, humanized anti-VEGF monoclonal IgG1 antibody [50]. Cells under hypoxia conditions increase the VEGF's transcription [51]. Epithelial cells presents receptors for vascular endothelial growth factor (VEGFR) -1 [52] and VEGFR-2 [53] on their surface. In addition, neuropilin NRP -1 and NRP-2 are also responsible for binding to VEGF. This factor is responsible for the angiogenesis and stimulation of epithelial cell division [54].

The mechanism of action of bevacizumab is based on selective combining with circulating VEGF to inhibit the binding of VEGF to its cell surface receptors [49]. It caused reduction in blood vessels. The compound appears to be effective, however, it is capable of also inducing side effects like hypertension, asymptomatic proteinuria, thromboembolic events. However, these disadvantages do not undermine its role in anti-cancer therapy [55]. Furthermore its approved in the treatment of metastatic breast cancer, glioblastoma multiforme and renal cell cancer [54].



Scheme 1. The mechanism of action of bevacizumab.
(Modified from: https://www.healio.com/hematology-oncology/learn-immuno-oncology/clinical-indications/colorectal-cancer and Servier Medical Art website, http://smart.servier.com/)

5. 4. Hormone therapy

Hormone therapy (HT) includes the application of hormones or drugs that inhibit hormones crucial for cancer cells. HT is rather not used in case of epithelial ovarian cancer but is more often used in ovarian stromal tumors. In clinical practice is implemented luteinizing-hormone-releasing hormone (LHRH) agonists to modulate estrogen levels, tamoxifen which acts anti-estrogens, and aromatase inhibitors which reduce estrogen production [56][57]. These procedures can be also combined as a novel strategies with other standard protocols to improve the expected effect.

5. 5. Therapy on place of action

Personalized medicine selected individually for patient is becoming still more popular. One of the most known methods defined as a personalized treatment applied directly on tumor tissue is photodynamic therapy (PDT). PDT is marginally invasive and effective method, which requires simultaneous application of photoactive drug (photosensitizer), presence of oxygen and a proper wavelength to drug activation [58][59]. Photodynamic method is widely and successfully applied in United States, where ovarian cancer is one of the fourth most frequent cancers in woman [60]. This method is mainly advised for patients not qualified for surgery or characterized by platinum-resistant ovarian carcinoma. Moreover, the photosensitiser is highly selective in detecting minimal tumor residuals, what enables better tumor tissue detection because [60].

The other tumour targeted approach is electrochemotherapy (ECT), which is commonly applied for various tumours, but in case ovarian treatment is still in basic [61] and clinical trials [62]. This method is based on the application of pulsed electric fields utilizing short pulses (100μs) and electric field intensity up to few kV/cm. This phenomenon causes temporary cell membrane permeabilization and drug particles can easily and more efficiently target cancer cell interior [63]. Presently, during ECT clinical protocols are applied two drugs, which exposed the highest efficacy, i.e.: bleomycin and cisplatin. ECT in experimental approach occurred particularly beneficial for cancer with multidrug resistance [64][65]. Moreover, there was also proved a promising potential of electroporation in combination with photodynamic therapy [66][67] and nanocarriers delivery [68].

6. CONCLUSIONS

The above considerations demonstrated that ovarian tumors are frequently appeared cancers in women and described current guidelines, classifications as well as guidelines for the treatment of this cancer. This review revealed also new perspectives in ovarian cancer treatment that might be useful in the future, however further research is required to broaden the basic biological mechanisms to be implicated in clinical practice.

Acknowledgments

The work was created as part of the activity of the Student Research Group "Biology of Cancer Cell" at the Wroclaw Medical University (SKN No. 148) and partially by Statutory Funds of Wroclaw Medical University No.: ST.E130.17.013 (PI: J. Zalewski)

References

[1] Zhou Y, Layton O, Hong L. Identification of Genes and Pathways Involved in Ovarian Epithelial Cancer by Bioinformatics Analysis. *J Cancer* 9(17) (2018) 3016–3022.

[2] Kumar V, Cotran RS, Robbins SL, Perkins JA, Olszewski W. *Robbins pathology*, Elsevier Urban & Partner (2005).

[3] Tomao F *et al.* Emerging role of cancer stem cells in the biology and treatment of ovarian cancer: basic knowledge and therapeutic possibilities for an innovative approach. *J Exp Clin Cancer Res* 32(1) (2013) 48.

[4] Dinkelspiel HE *et al.* Long-term mortality among women with epithelial ovarian cancer. *Gynecol. Oncol.* 138(2) (2015) 421–8.

[5] Dvoretsky PM, Richards KA, Angel C, Rabinowitz L, Beecham JB, Bonfiglio TA. Survival time, causes of death, and tumor/treatment-related morbidity in 100 women with ovarian cancer. *Hum. Pathol.* 19(11) (1988) 1273–9.

[6] Heintz A *et al.* Carcinoma of the Ovary. *Int. J. Gynecol. Obstet.* 95 (2006) S161–S192.

[7] Kurian AW, Balise RR, McGuire V, Whittemore AS. Histologic types of epithelial ovarian cancer: have they different risk factors? *Gynecol. Oncol.* 96(2) (2005) 520–530.

[8] 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(1) (2009) 86–90.

[9] Ulbright TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. *Mod. Pathol.* 18(S2) (2005) S61–S79.

[10] Troiano RN, McCarthy SM. Müllerian Duct Anomalies: Imaging and Clinical Issues. *Radiology* 233(1) (2004) 19–34.

[11] Yakushiji M, Tazaki T, Nishimura H, Kato T. Krukenberg tumors of the ovary: a clinicopathologic analysis of 112 cases. *Nihon Sanka Fujinka Gakkai Zasshi* 39(3), (1987) 479–85.

[12] Cramer DW, Welch WR. Determinants of Ovarian Cancer Risk. II. Inferences Regarding Pathogenesis. *JNCI J. Natl. Cancer Inst.* 71(4) (1983) 717–721.

[13] Couch FJ *et al.* Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. *PLoS Genet.* 9(3) (2013) e1003212.

[14] Struewing JP, Lerman C, Kase RG, Giambarresi TR, Tucker MA. Anticipated uptake and impact of genetic testing in hereditary breast and ovarian cancer families. *Cancer Epidemiol. Biomarkers Prev.* 4(2) (1995) 169–73.

[15] Cohen SA, Leininger A. The genetic basis of Lynch syndrome and its implications for clinical practice and risk management.. *Appl. Clin. Genet.* 7 (2014) 147–58.

[16] Whittmore AS, Harris R, Itnyre J. Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of 12 US Case -Control Studies. *Am. J. Epidemiol.* 136(10)

(1992) 1184–1203.

[17] Kurta ML *et al.* Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol. Biomarkers Prev.* 21(8) (2012) 1282–92.

[18] Diergaarde B, Kurta ML. Use of fertility drugs and risk of ovarian cancer. *Curr. Opin. Obstet. Gynecol.* 26(3) (2014) 125–9.

[19] Nowacka-Zawisza M, Forma E, Walczak M, Różański W, Bryś M, Krajewska WM. Loss of heterozygosity for chromosomal regions 15q14-21.1, 17q21.31, and 13q12.3-13.1 and its relevance for prostate cancer. *Med. Oncol.* 32(11) (2015) 246.

[20] F. Xia *et al.* Deficiency of human BRCA2 leads to impaired homologous recombination but maintains normal nonhomologous end joining. *Proc. Natl. Acad. Sci.* 98(15) (2001) 8644–8649.

[21] Antoniou A *et al.* Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. *Am. J. Hum. Genet.* 72(5) (2003) 1117–1130.

[22] Steinke V, Engel C, Büttner R, Schackert HK, Schmiegel WH, Propping P. Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome. *Dtsch. Arztebl. Int.* 110(3) (2013) 32–8.

[23] Watson P *et al.* The Clinical Features of Ovarian Cancer in Hereditary Nonpolyposis Colorectal Cancer. *Gynecol. Oncol.* 82(2) (2001) 223–228.

[24] Martín-López JV Fishel R. The mechanism of mismatch repair and the functional analysis of mismatch repair defects in Lynch syndrome. *Fam. Cancer* 12(2) (2013) 159–68.

[25] Vasen HFA, Watson P, Mecklin J, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology* 116(6) (1999) 1453–1456.

[26] Bermejo JL, Büchner FL, Hemminki K. Familial risk of endometrial cancer after exclusion of families that fulfilled Amsterdam, Japanese or Bethesda criteria for HNPCC. *Ann. Oncol.* 15(4) (2004) 598–604.

[27] Graham J, Graham R. Ovarian cancer and asbestos. *Environ. Res.* 1(2) (1967) 115–128.

[28] Cramer DW, Welch WR, Cassells S, Scully RE. Mumps, menarche, menopause, and ovarian cancer. *Am. J. Obstet. Gynecol.* 147(1) (1983) 1–6.

[29] Menczer J, Modan M, Ranon L, Golan A. Possible role of mumps virus in the etiology of ovarian cancer. *Cancer* 43(4) (1979) 1375–1379.

[30] Holschneider CH, Berek JS. Ovarian cancer: Epidemiology, biology, and prognostic factors. *Semin. Surg. Oncol.* 19(1) (2000) 3–10.

[31] Shu XO, Brinton LA, Gao YT, Yuan JM. Population-based case-control study of ovarian cancer in Shanghai. *Cancer Res.* 49(13) (1989) 3670–4.

[32] Longo DL, *Harrison's principles of internal medicine.* McGraw-Hill (2012).

[33] Áyen A, Jiménez Martínez Y, Marchal JA, Boulaiz H. Recent Progress in Gene Therapy for Ovarian Cancer. *Int. J. Mol. Sci.* 19(7) (2018).

[34] Wroński M, Kluciński A, Krasnodębski IW. Sister Mary Joseph Nodule. *J. Ultrasound Med.* 33(3) (2014) 531–534.

[35] Shoupe D. *Handbook of gynecology* (2017).

[36] Benedet JL, Bender H, Jones H, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. *Int. J. Gynaecol. Obstet.* 70(2) (2000) 209–62.

[37] Zanetta G *et al.* Conservative surgery for Stage I ovarian carcinoma in women of childbearing age. *BJOG An Int. J. Obstet. Gynaecol.* 104(9) (1997) 1030–1035.

[38] Eisenkop SM, Friedman RL, Wang HJ. Complete Cytoreductive Surgery Is Feasible and Maximizes Survival in Patients with Advanced Epithelial Ovarian Cancer: A Prospective Study. *Gynecol. Oncol.* 69(2) (1998) 103–108.

[39] Hoskins WJ, Bundy BN, Thigpen JT, Omura GA. The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume Stage III epithelial ovarian cancer: A gynecologic oncology group study. *Gynecol. Oncol.* 47(2) (1992) 159–166.

[40] Vergote I, De Wever I, Tjalma W, Van Gramberen M, Decloedt J, van Dam P. Neoadjuvant Chemotherapy or Primary Debulking Surgery in Advanced Ovarian Carcinoma: A Retrospective Analysis of 285 Patients. *Gynecol. Oncol.* 71(3) (1998) 431–436.

[41] Jacob JH, Gershenson DM, Morris M, Copeland LJ, Burke TW, Wharton JT. Neoadjuvant chemotherapy and interval debulking for advanced epithelial ovarian cancer. *Gynecol. Oncol.* 42(2) (1991) 146–50.

[42] Piccart MJ *et al.* Randomized Intergroup Trial of Cisplatin-Paclitaxel Versus Cisplatin-Cyclophosphamide in Women With Advanced Epithelial Ovarian Cancer: Three-Year Results. *J. Natl. Cancer Inst.* 92(9) (2000) 699–708.

[43] du Bois A *et al.* A Randomized Clinical Trial of Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel as First-Line Treatment of Ovarian Cancer. *CancerSpectrum Knowl. Environ.* 95(17) (2003) 1320–1329.

[44] Francis P *et al.* Phase II trial of docetaxel in patients with platinum-refractory advanced ovarian cancer. *J. Clin. Oncol.* 12(11) (1994) 2301–8.

[45] Wei W, Li N, Sun Y, Li B, Xu L, Wu L. Clinical outcome and prognostic factors of patients with early-stage epithelial ovarian cancer. *Oncotarget* 8(14) (2017) 23862–23870.

[46] Pujade-Lauraine E *et al.* Pegylated Liposomal Doxorubicin and Carboplatin Compared With Paclitaxel and Carboplatin for Patients With Platinum-Sensitive Ovarian Cancer in Late Relapse. *J. Clin. Oncol.* 28(20) (2010) 3323–3329.

[47] Levine EA *et al.* Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1,000 patients. *J. Am. Coll. Surg.* 218(4) (2014) 573–85.

[48] Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst. Rev.* (2016).

[49] Willett CG *et al.* Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat. Med.* 10(2) (2004) 145–147.

[50] Sousa F, Cruz A, Fonte P, Pinto IM, Neves-Petersen MT, Sarmento B. A new paradigm for antiangiogenic therapy through controlled release of bevacizumab from PLGA nanoparticles. *Sci. Rep.* 7(1) (2017) 3736.

[51] Xiao B *et al.* HIF-1 contributes to hypoxia adaptation of the naked mole rat. *Oncotarget* 8(66) (2017) 109941–109951.

[52] Lacal PM, Graziani G. Therapeutic implication of vascular endothelial growth factor receptor-1 (VEGFR-1) targeting in cancer cells and tumor microenvironment by competitive and non-competitive inhibitors. *Pharmacol. Res.* 136 (2018) 97–107.

[53] AbdElhameid MK, Labib MB, Negmeldin AT, Al-Shorbagy M, Mohammed MR. Design, synthesis, and screening of *ortho*- amino thiophene carboxamide derivatives on hepatocellular carcinomaas VEGFR-2Inhibitors. *J. Enzyme Inhib. Med. Chem.* 33(1) (2018) 1472–1493.

[54] Kazazi-Hyseni F, Beijnen JH, Schellens JHM. Bevacizumab. *Oncologist* 15(8) (2010) 819–25.

[55] Pavlidis ET, Pavlidis TE. Role of bevacizumab in colorectal cancer growth and its adverse effects: a review. *World J. Gastroenterol.* 19(31) (2013) 5051–60.

[56] Simpkins F, Garcia-Soto A, Slingerland J. New insights on the role of hormonal therapy in ovarian cancer. *Steroids* 78(6) (2013) 530–7.

[57] Gershenson DM, Bodurka DC, Coleman RL, Lu KH, Malpica A, Sun CC. Hormonal Maintenance Therapy for Women With Low-Grade Serous Cancer of the Ovary or Peritoneum. *J. Clin. Oncol.* 35(10) (2017) 1103–1111.

[58] Hamblin MR, Mróz P. *Advances in photodynamic therapy : basic, translational, and clinical*. Artech House (2008).

[59] Kwiatkowski S *et al.* Photodynamic therapy – mechanisms, photosensitizers and combinations. *Biomed. Pharmacother.* 106 (2018) 1098–1107.

[60] Shishkova N, Kuznetsova O, Berezov T. Photodynamic therapy for gynecological diseases and breast cancer. *Cancer Biol. Med.* 9(1) (2012) 9–17.

[61] Saczko J *et al.* The effectiveness of chemotherapy and electrochemotherapy on ovarian cell lines in vitro. *Neoplasma* 63(3) (2016) 450–455.

[62] Belehradek M, Domenge C, Luboinski B, Orlowski S, Belehradek J, Mir LM. Electrochemotherapy, a new antitumor treatment. First clinical phase I-II trial. *Cancer* 72(12) (1993) 3694–700.

[63] Sersa G, Miklavcic D. Electrochemotherapy of tumours. *J. Vis. Exp.* 22 (2008).

[64] Michel O *et al.* Electroporation with Cisplatin against Metastatic Pancreatic Cancer: *In*

Vitro Study on Human Primary Cell Culture. *Biomed Res. Int.* 2018 (2018) 1–12.

[65] Kulbacka J *et al.* Doxorubicin delivery enhanced by electroporation to gastrointestinal adenocarcinoma cells with P-gp overexpression. *Bioelectrochemistry* 100 (2014) 96–104.

[66] Kulbacka J, Nowak M, Skołucka N, Saczko J, Kotulska M. The influence of electroporation on in vitro photodynamic therapy of human breast carcinoma cells. *Folia Biol. (Praha)* 57(3) (2011) 112–8.

[67] Kotulska M, Kulbacka J, Saczko J. Advances in photodynamic therapy assisted by electroporation. *Curr. Drug Metab.* 14(3) (2013) 309–18.

[68] Kulbacka J *et al.* The Effect of Millisecond Pulsed Electric Fields (msPEF) on Intracellular Drug Transport with Negatively Charged Large Nanocarriers Made of Solid Lipid Nanoparticles (SLN): In Vitro Study. *J. Membr. Biol.* 249(5) (2016) 645–661.