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Reviews covering publications from May 15 – August 15, 2015

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Screening for ovarian and fallopian tube cancer

Editor Lucas Minig

Descriptive summary

The main publications regarding ovarian cancer screening include a publication of the results of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). This is the largest published randomized trial where the combination of transvagina ultrasound and CA-125, called multimodal strategy (MMS), was tested in 46,237 women older than 50 years. MMS was compared with pelvic ultrasound or no screening, and a specific algorithm (ROCA) established the risk of ovarian cancer. Thus, annual screening was offered to women with normal ROCA value; CA-125 was repeated 12-weeks later in women with intermediate risk; and a second MMS was done 6 weeks later in case of high risk. If high risk persisted, women were clinically evaluated. Specificity was lower for ultrasound compared to MMS, resulting in nine times as many surgeries performed in the ultrasound group to detect one cancer. MMS had a sensitivity and specificity to detect ovarian cancer of 85.8% (95% CI, 79.3% to 90.9%) and 99.8% (95% CI, 99.8% to 99.8%), respectively, with 4.8 surgeries per ovarian cancer diagnosed. Of the 155 women with ovarian cancer, ROCA detected 86.4%, whereas using annual serum CA-125 fixed cut-offs of more than 35, more than 30, and more than 22 U/mL would have identified only 41.3%, 48.4%, and 66.5%, respectively. The area under the curve for ROCA was significantly higher than that for a single-threshold rule (0.869 versus 0.915; p=0.0027). Therefore, CA-125 rise within normal range can be detected by ROCA long before any abnormality is detected with trans-svaginal ultrasound. However, whether this is associated with less mortality is under investigation. In this regard, should the UKCTOCS report a negative outcome, then other screening strategies will need to be considered and developed.

A sub-analysis of the same trial, demonstrated that sixteen percent (3499/21,733) of women requiring a repeat screening test in addition to annual screen withdrew from the study: 12.9% (1560/12,073) from the multimodal group and 20.1% (1939/9660) from the US group. An estimated relative risk of withdrawal is 1.46 (95% confidence interval, 1.36-1.56; P<0.001) for the US arm. High anxiety trait and increased psychological morbidity significantly influenced withdrawal, even when age, screening center, and group were taken into account (P< 0.001).

Cancer precursor lesions in the BRCA population at the time of prophylactic salpingo-oophorectomy are another potential surrogate marker for ovarian cancer prevention. As Lheureux L et al. states in an interesting clinical commentary, the most reproducible interpretation and optimal identification of carcinomas and precursor lesions from samples obtained from women who have undergone risk reduction salpingo-oophorectomy with germline BRCA1/2 mutations require comprehensive processing (SEE-FIM) alongside the use of a validated diagnostic algorithm that combines histologic features (routine H&E morphological assessment) and immunohistochemical expression of p53 and Ki-67. Future large and prospective preventive trial in HGSOC, should consider these aspects.

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening.	Menor U et al.	J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25964255	✓
2	Psychosocial Factors Associated With Withdrawal From the United Kingdom Collaborative Trial of Ovarian Cancer Screening After 1 Episode of Repeat Screening.	Jenkins V et al.	Int J Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26222482	
3	Screening the molecular targets of ovarian cancer based on bioinformatics analysis.	Du L et al.	Tumori	http://www.ncbi.nlm.nih.gov/pubmed/25953442	
4	Quality Assurance and its impact on ovarian visualisation rates in the multicentre United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).	Sharma A et al.	Ultrasound Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26095052	
5	Cancer precursor lesions in the BRCA population at the time of prophylactic salpingo-oophorectomy: Accuracy of assessment and potential surrogate marker for prevention.	Lheureux Set al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26072440	

Hereditary ovarian cancer (BRCA1/2 mutation, genetic counseling, management)

- Editor Sara Giovannoni

- Descriptive summary

The articles selected focus mainly on the following points :

- OVA301 TRIAL-exploratory analysis. The role of BRCA1 mutation:

Monk et al published the results of the exploratory analysis concerning the effect of BRCA1 mutation on treatment response to Trabectedin and PLD in patients enrolled on phase III OVA 301 trial. The study compared TrabectedinPLD vs PLD alone in patients with recurrent ovarian cancer. The patients carrying BRCA1mutation had improved outcomes with Trabectedin + PLD versus PLD alone (RR 49% vs 28%; PFS 13.5 vs 5.5 months; OS 23.8 vs 12.5 months p= 0.0086).

- PARP inhibitors:

Coleman et al. published in Gynecol Oncol (June 2015), the results of the phase II trial of a new PARP inhibitor, Veliparib, in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer in patients with gBRCA1 or gBRCA2 mutation. This trial was conducted by the NRG Oncology Group study.
The trial included 50 patients, 60% with platinum resistent disease. The ORR was 26%. For platinum resistant and platinum sensitive patients the proportion responding was 20% and 35% respectively. Median PFS was 8.18 months. So, the trial showed the efficacy of Veliparib as single agent for BRCA mutation associated recurrent ovarian cancer with a good toxicity profile.

- Olaparib:

As we know, on October 2014 CHMP approved Olaparib monotherapy, fallopian, relapsed for maintenance treatment for patients with platinum sensitive relapsed BRCA mutated high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who responded to platinum based chemotherapy; while the FDA on December 2014 approved Olaparib for the treatment of patient with BRCA mutated ovarian cancer who have been treated with three or more prior chemotherapies.

Kim et al and Tewari et al summarized the scientific data linked to FDA approval. An international single arm trial enrolled 137 patients with BRCA mutated-associated ovarian cancer treated with three or more chemotherapies. Patients received Olaparib, 400 mg daily until progression or unacceptable toxicity. The ORR was 34% with median response duration of 7.9 months in this cohort.

Furthermore Tewari summarized the ongoing clinical trials concerning Olaparib alone or in combination.

Finally Walsh in his review, summarized the recent clinical trials concerning PARP inhibitors and how the genetic testing landscape has changed over the last few years.

The role of the CTLA-4 blockage in BRCA-1 deficient ovarian cancer: Higuchi et al. have recently published the results of an interesting study reporting that BRCA deficient ovarian cancer tumors would be vulnerable to immunological checkpoint blockage. CTLA-4 blockage seems to be able to synergize PARP inhibitors, resultig in immune-mediated tumour clearance and increased long term survival compared to PARP inhibitors alone in murine models ($p < 0.0001$).

The lack of appropiate models and guidelines for genetic counselling: Ricci et al in a retrospective analysis underlined the need for introducing ovarian cancer genetic risk assessment in oncology practice. Furthermore De Geus et al developed an Informing Relatives Inventory (IRI) in order to assess index patients' knowledge, motivation and self efficacy regarding the disclosure of hereditary cancer risk information. This could be very useful in order to improve genetic counseling.

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Hereditary ovarian cancer (BRCA1/2 mutation, genetic counseling, management)

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Effect of BRCA1 and XPG mutations on treatment response to trabectedin and pegylated liposomal doxorubicin in patients with advanced ovarian cancer: exploratory analysis of the phase 3 OVA-301 study.	Monk BJ et al.	Ann Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25722380	
2	A phase II evaluation of the potent, highly selective PARP inhibitor velipa-rib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study.	Coleman RL et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25818403	
3	FDA Approval Summary: Olaparib Monotherapy in Patients with Delete-rious Germline BRCA-Mutated Advanced Ovarian Cancer Treated with Three or More Lines of Chemotherapy.	Kim G et al.	Clin Cancer Res	http://www.ncbi.nlm.nih.gov/pubmed/26187614	
4	Development of Olaparib for BRCA-Deficient Recurrent Epithelial Ovarian Cancer.	Tewari KS et al.	Clin Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26169965	
5	Two decades beyond BRCA1/2: Homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy.	Walsh CS	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25725131	✓
6	Safety evaluation of olaparib for treating ovarian cancer.	Lheureux S et al	Expert Opin Drug Saf	http://www.ncbi.nlm.nih.gov/pubmed/26051946	
7	CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer.	Higuchi T et al.	Cancer Immunol Res	http://www.ncbi.nlm.nih.gov/pubmed/26138335	
8	Referral of Ovarian Cancer Patients for Genetic Counselling by Oncologis-ts: Need for Improvement.	Ricci MT et al.	Public Health Genomics	http://www.ncbi.nlm.nih.gov/pubmed/26111740	✓
9	Development of the Informing Relatives Inventory (IRI): Assessing Index Patients' Knowledge, Motivation and Self-Efficacy Regarding the Disclosu-re of Hereditary Cancer Risk Information to Relatives.	de Geus E et al.	Int J Behav Med	http://www.ncbi.nlm.nih.gov/pubmed/25515913	
10	Feelings of Women With Strong Family Histories Who Subsequent to Their Breast Cancer Diagnosis Tested BRCA Positive.	Joseph M et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25675043	
11	BRCA1 and BRCA2 genetic testing-pitfalls and recommendations for managing variants of uncertain clinical significance.	Eccles DM et al.	Ann Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26153499	✓
12	How medical choices influence quality of life of women carrying a BRCA mutation.	Harmsen MG et al.	Crit Rev Oncol Hematol	http://www.ncbi.nlm.nih.gov/pubmed/26299336	
13	Pre-test genetic counseling services for hereditary breast and ovarian cancer delivered by non-genetics professionals in the state of Florida.	Vadaparampil ST et al.	Clin Genet	http://www.ncbi.nlm.nih.gov/pubmed/24735105	
14	Hereditary ovarian cancer: not only BRCA 1 and 2 genes.	Toss A et al.	Biomed Res Int	http://www.ncbi.nlm.nih.gov/pubmed/26075229	✓
15	Olaparib tablet formulation: effect of food on the pharmacokinetics after oral dosing in patients with advanced solid tumours.	Plummer R et al.	Cancer Chemother Pharmacol	http://www.ncbi.nlm.nih.gov/pubmed/26242220	

Surgical treatment of recurrent ovarian cancer

Editor Patriciu Achimas-Cadariu

Descriptive summary

Within the search period two narrative reviews present the current knowledge on the surgical treatment of relapsed ovarian cancer and summarize the articles that address the surgical efforts beyond it and in combination with HIPEC [1,2].

A randomized phase III trial that assessed the role of HIPEC in combination with cytoreductive surgery (CRS) in recurrent epithelial ovarian cancer indicated a significant survival benefit that applies both to platinum sensitive and platinum resistant disease in the HIPEC arm, with a maximum efficacy of HIPEC when complete cytoreduction was achieved [3].

Regarding Quality of Life (QOL) in platinum sensitive recurrent ovarian cancer, in the first prospective case control study using diagnostic laparoscopy for the group enrollment of patients, both surgery followed by chemotherapy and chemotherapy alone seemed to have a similar impact on QOL as assessed, with a survival advantage in the first group, although this remains to be evaluated within prospective trials [4].

Significant effort has been invested in the search for prediction models of complete secondary CRS due to its significant impact on survival. A recent study performed the external validation of the two most known prediction models of complete secondary CRS, the AGO score and the Tian model. The two models showed high positive predictive values but also high false negative rates. The authors concluded that the clinical effectiveness has to be further investigated with or without the addition of laparoscopy or other predictive factors when the benefit of secondary CRS will eventually be demonstrated by the three randomized ongoing trials [5].

The AGO score was also retrospectively analyzed in a single institution series with similar results, with a sensitivity of 73.2% and a specificity of only 43.9%. In comparison with the DESKTOP I study, the rate of complete tumor resection was higher, probably due to procedures performed in a tertiary center by experienced surgeons as stated by the author of this work. Hence, the AGO score is a useful predictor for operability in patients with ovarian cancer with a first recurrence but patients with a negative score may still have a 50% chance of achieving optimal tumor resection [6].

Since predictors play an increasingly important role, a recently published retrospective study found that obesity is not a risk factor for suboptimal surgical management of recurrent ovarian cancer, although in a multivariate analysis obesity remained a negative independent prognostic factor for overall survival as is has been previously demonstrated with primary CRS, suggesting an effect of excess weight on tumor biology and/or response to treatment [7].

Furthermore, a recent review summarizes the available literature of the role of 18F-FDG PET/CT in the surgical management of recurrent disease, making it a useful tool in the selection of patients who might benefit from secondary CRS [8].

Before establishing the definitive role of secondary CRS, results are still awaited from the DESKTOP III (NCT01166737), GOG 213 (NCT00565851) and SOCceR (NTR3337) randomized trials.

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Surgical treatment of recurrent ovarian cancer

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No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	The role of cytoreductive surgery and HIPEC in epithelial ovarian cancer.	Halkia E et al.	Journal of BUON	http://www.ncbi.nlm.nih.gov/pubmed/26051328	✓
2	The next steps in improving the outcomes of advanced ovarian cancer.	Openshaw MR et al.	Womens Health	http://www.ncbi.nlm.nih.gov/pubmed/?term=26102473	
3	Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study.	Spiliotis J al.	Ann Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25391263	
4	Quality of Life in Platinum-Sensitive Recurrent Ovarian Cancer: Chemotherapy Versus Surgery Plus Chemotherapy.	Plotti F et al.	Ann Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25582738	
5	External validation of two prediction models of complete secondary cytoreductive surgery in patients with recurrent epithelial ovarian cancer.	Van De Laar R et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25677063	
6	AGO score as a predictor of surgical outcome at secondary cytoreduction in patients with ovarian cancer.	Muallem MZ al.	Anticancer Res	http://www.ncbi.nlm.nih.gov/pubmed/?term=26026105	
7	Impact of obesity on secondary cytoreductive surgery and overall survival in women with recurrent ovarian cancer.	Tran AQ et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=26037901	
8	PIpelle Prospective ENDOmetrial carcinoma (PIPENDO) study, pre-operative recognition of high risk endometrial carcinoma: a multicentre prospect Fludeoxyglucose F 18 PET-computed tomography: Management changes effecting patient outcomes in gynecologic malignancies. ive cohort study.	Brunetti JC	PET Clinics	http://www.ncbi.nlm.nih.gov/pubmed/?term=26099674	

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Medical treatment of recurrent ovarian cancer

Editor Elisabeth Chereau

Descriptive summary

Lots of phase 1/2 studies without significant results in terms of survival, furthers studies are warranted.

Some interesting datas concerning the targeted therapies alone or in addition to standard chemotherapy:

- combination chemotherapy and bevacizumab prolongs PFS and OS compared with bevacizumab alone in recurrent, heavily pretreated epithelial ovarian cancer (1)
- in the OCEANS study (randomized, placebo (PL)-controlled, phase 3 trial evaluating the efficacy and safety of bevacizumab combined with gemcitabine+carboplatin (GC) for patients with platinum-sensitive recurrent ovarian cancer (ROC): already published data showed improved PFS with GC+bevacizumab compared with GC+PL. Results of final OS showed no significant difference in OS for patients treated with GC+bevacizumab compared with GC+PL. (2)
- Veliparib (inhibitor of PARP-1/2) in ovarian cancer patients carrying a germline BRCA1 or BRCA2 mutation (gBRCA).
- The single agent efficacy and tolerability of veliparib for BRCA mutation-associated recurrent ovarian cancer warrants further investigation. (3)
- Cediranib (VEGFR inhibitor): significant activity in recurrent platinum sensitive OC. The toxicities were expected and manageable at the dose of 30mg od. (4)
- RO4929097 (a gamma-secretase inhibitor) in patients with recurrent platinum-resistant ovarian cancer: insufficient activity as a single-agent in platinum-resistant ovarian cancer to warrant further study as monotherapy. (5)

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Comparison of Bevacizumab Alone or with Chemotherapy in Recurrent Ovarian Cancer Patients.	Fuh KC et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26144600	
2	Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer.	Aghajanian C et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26271155	
3	A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study.	Coleman RL et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25818403	
4	Quality Assurance an A phase 2 study of cediranib in recurrent or persistent ovarian, peritoneal or fallopian tube cancer: a trial of the Princess Margaret, Chicago and California Phase II Consortia. d its impact on ovarian visualisation rates in the multicentre United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).	Hirte H et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25895616	
5	A phase II study of single-agent RO4929097, a gamma-secretase inhibitor of Notch signaling, in patients with recurrent platinum-resistant epithelial ovarian cancer: A study of the Princess Margaret, Chicago and California phase II consortia.	Diaz-Padilla I et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25769658	

Treatment of ovarian tumors of low malignant potential (borderline ovarian tumors)

Editor Ignacio Zapardiel

Descriptive summary

The articles retrieved are focused mainly on the preoperative differential diagnosis of borderline ovarian tumors and adnexal masses, and on inmunological and genetic factors of the disease with currently no application to the clinical practice. However we found 5 papers considering treatment options. Most of them will probably not change the current management but add interesting data:

1. The removal of a normal-appereant appendix in mucinous borderline ovarian tumors does not seem to be necessary and does not add information to the tumor staging.
2. Follow-up of advanced stage bordeline ovarian tumors must be mantainen for a long period in order to detect late recurrences that are more common in this subgroup of patients.
3. Fertility preservation in advanced borderline ovarian tumors could be considered. Fertility preservation was not found to be associated with an increased risk of relapse in young patients with advanced disease and may be feasible.

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Management of Borderline Ovarian Tumors Based on Patient and Tumor Characteristics.	Black JD et al.	Gynecol Obstet Invest	http://www.ncbi.nlm.nih.gov/pubmed/26067608	
2	Epithelial borderline ovarian tumor: Diagnosis and treatment strategy.	Ushijima K et al.	Obstet Gynecol Sci	http://www.ncbi.nlm.nih.gov/pubmed/26023666	
3	Safety of ovarian conservation and fertility preservation in advanced borderline ovarian tumors.	Helpman L et al.	Fertil Steril	http://www.ncbi.nlm.nih.gov/pubmed/25956371	
4	Should we remove the normal-looking appendix during operations for borderline mucinous ovarian neoplasms?: A retrospective study of 129 cases.	Ozcan A et al.	Int J Surg	http://www.ncbi.nlm.nih.gov/pubmed/25907325	
5	Outcome of patients with advanced-stage borderline ovarian tumors after a first peritoneal noninvasive recurrence: impact on further management.	Uzan C et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25828751	

Emerging molecular targeted therapies or early preclinical trials in ovarian cancer

Editor Muhammad Rizki Yaznil

Descriptive summary

For ovarian cancer, there is a lot of research about potential targeted molecules or pathways and preclinical trials/laboratory trials on new agents. Sometimes a well known drug that is currently used for other indications is investigated for the potential use in cancer treatment.

Here I have summarized some of the potential targeted molecules / pathways:

1. Bone morphogenetic protein pathway inhibited by DMH1
2. NOTCH signaling inhibited by -secretase inhibitors
3. Exosomes -> a key mediator of intercellular communications between tumor cells and tumor microenvironment
4. miR-140-5p acts as a tumor suppressor during ovarian carcinogenesis
5. PPAR induce growth inhibition of cancer cells, mediated by the upregulation of miR-125b
6. ARMc8 overexpression may enhance the invasion and metastasis of ovarian cancer cells
7. OCT4 is an essential mediator in FSH-induced EMT and invasion
8. Overexpression of ABC transporter increases chemoresistance
9. Overexpression of Claudin-4 to poor chemo response
10. MiR-498 acted as a tumor suppressor by targeting the FOX03 gene
11. Dub3 expression increased proliferation of cancer cells and worsened survival
12. miR-205 promotes invasion and proliferation of ovarian cancer cells, mediated by VEGF
13. PI3K/AKT/mTOR pathway is frequently activated in ovarian cancer, especially in clear cell carcinoma and endometrioid adenocarcinoma

And the preclinical trials that include well known drugs that are currently used for other indications:

1. AMG 386 (trebananib) neutralize interaction between angipoietins (Ang 1/2) and their Tie2 receptor to inhibit angiogenesis
2. Metformin alters the metabolism in ovarian cancer cells, prevents tumor growth and increases sensitivity to chemotherapy in vitro and mouse models
3. Ormeloxifene (non steroid SERM) currently used for contraception efficiently inhibits cell growth and induces apoptosis in ovarian cancer cell lines including cisplatin resistant cell lines
4. HO-4200 & HO-4318 capable of selectively inhibit STAT3 activation, translocation and DNA binding capacity
5. PNC-27 (derived from HDM-2 binding domain of p53, binds to HDM-2 in cancer cell membrane) leading to rapid cell necrosis
6. HMG-CoA reductase inhibitor (simvastatin)
7. Itraconazole has anticancer effects via inhibiton of angiogenesis, hedgehog and mTOR pathway
8. HO-3867

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Emerging molecular targeted therapies or early preclinical trials in ovarian cancer

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Small molecule inhibitor of the bone morphogenetic protein pathway DMH1 reduces ovarian cancer cell growth	Laura D et al.	Cancer Lett	http://www.sciencedirect.com/science/article/pii/S0304383515004875	
2	Notch pathway promotes ovarian cancer growth and migration via CXCR4/SDF1 chemokine system	Chiaramonte R et al.	Int J Biochem Cell Biol	http://www.sciencedirect.com/science/article/pii/S1357272515002009	
3	Exosomes: Emerging biomarkers and targets for ovarian cancer	Maggie KS et al.	Cancer Lett	http://www.sciencedirect.com/science/article/pii/S0304383515004565	
4	miR-140-5p inhibits ovarian cancer growth partially by repression of PDGFRA	Lan H et al.	Biomed Pharmacoth	http://www.sciencedirect.com/science/article/pii/S0753332215001791	
5	PPAR inhibits ovarian cancer cells proliferation through upregulation of miR-125b	Luo S et al.	Biochemi Biophys Res Comm	http://www.sciencedirect.com/science/article/pii/S0006291X15006890	✓
6	A novel biomarker ARMc8 promotes the malignant progression of ovarian cancer	Jiang G et al.	Hum Pathol	http://www.sciencedirect.com/science/article/pii/S0046817715002099	
7	OCT4 mediates FSH-induced epithelial–mesenchymal transition and invasion through the ERK1/2 signaling pathway in epithelial ovarian cancer	Liu L et al.	Biochemi Biophys Res Comm	http://www.sciencedirect.com/science/article/pii/S0006291X15007512	
8	The role of ABC transporters in ovarian cancer progression and chemoresistance	Ween MP et al.	Crit Rev Oncology Hematol	http://www.sciencedirect.com/science/article/pii/S1040842815001018	
9	Claudin-4 in ovarian cancer and its relation to platinum compounds resistance	Hegab HM et al.	Progresos de Obstetricia y Ginecología	http://www.sciencedirect.com/science/article/pii/S0304501315000709	
10	Advances in anti-angiogenic agents for ovarian cancer treatment: The role of trebananib (AMG 386)	Marchetti C et al. Muzii L et al.	Crit Rev Oncology Hematol	http://www.sciencedirect.com/science/article/pii/S1040842815000256	
11	MiR-498 regulated FOXO3 expression and inhibited the proliferation of human ovarian cancer cells	Liu R et al.	Biomed Pharmacother	http://www.sciencedirect.com/science/article/pii/S0753332215000967	
12	Subtype-specific binding peptides enhance the therapeutic efficacy of nanomedicine in the treatment of ovarian cancer	Shen YA et al.	Cancer Let	http://www.sciencedirect.com/science/article/pii/S0304383515000889	
13	Metformin inhibits ovarian cancer growth and increases sensitivity to paclitaxel in mouse models	Lengyel E et al.	AJOG	http://www.sciencedirect.com/science/article/pii/S0002937814010813	
14	Dub3 expression correlates with tumor progression and poor prognosis in human epithelial ovarian cancer	Zhou B et al.	Biomed Pharmacother	http://www.sciencedirect.com/science/article/pii/S075333221500030X	
15	Ormeloxifene efficiently inhibits ovarian cancer growth	Diane M et al.	Cancer Lett	http://www.sciencedirect.com/science/article/pii/S0304383514005977	
16	The role of miR-205 in the VEGF-mediated promotion of human ovarian cancer cell invasion	Li J et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900535-1/abstract	
17	The PI3K/AKT/mTOR pathway as a therapeutic target in ovarian cancer	Mabuchicorresponden-ceemail S et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258(15)00606-X/abstract	
18	Anticancer potential of diarylidenyl piperidone derivatives, HO-4200 and HO-4318, in ovarian cancer	ElNaggar, AC et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900512-0/abstract	
19	Evaluating anti-cancer activity of a novel p53-derived peptide against multidrug resistant ovarian cancer	Shaikh MF et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900295-4/abstract	
20	The HMG-CoA reductase inhibitor, simvastatin, has anti-tumorigenic effects in ovarian cancer cell lines and a genetically engineered serous ovarian cancer mouse model	Stine JE et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900153-5/abstract	
21	The effects of itraconazole as anti-cancer agent in epithelial ovarian cancer	Lee JW et al	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900514-4/abstract	
22	Suppression of ovarian cancer growth and metastasis with HO-3867, a STAT3 inhibitor, in human tissue culture and in an orthotopic mouse model	Naidu S et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900511-9/abstract	
23	Investigating the role of phosphodiesterase 10A as a novel target in ovarian cancer	da Silva LM et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900609-5/abstract	

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Treatment of endometrial hyperplasia (biology, conservative and definitive treatment, follow-up)

Editor Kastriot Dallaku and Elko Gliozheni

Descriptive summary

1. Short overview over the most relevant studies with endometrial hyperplasia (EH).

a. Some of articles selected are about endometrial hyperplasia classification systems (Committee Opinion N631, 2015).

b. Other articles are about EH diagnosis through ultrasound examination and surgery (Goyal et al, 2015), including endometrial curettage, pipelle aspiration biopsy, and hysteroscopy. Identification of predictive clinic-pathologic factors for concurrent endometrial carcinoma in patients with endometrial hyperplasia, was another topic selected from literature (Kyoung Kim et al., 2015).

c. Some articles collected were about molecular profiling and biomarkers for premalignant and malignant endometrial lesions, relapse and appropriate follow up of patients with EH (Berg et al.,2015).

d.Regarding management of EH and early stages of endometrial carcinoma surgical and non-surgical or hormonal treatment are compared. Hormonal treatment includes oral progestogens (micronized progesterone and lynestrenol, cyclic medroxyprogesterone acetate) and progesterone intrauterine releasing systems (Emarh 2015; Bian et al., 2015).

e. Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma have been reported (Pronin et al., 2015). Some other authors reported on EH in patients with long term exposure to tamoxifen (Rong Hu 2015).

2. Study design.

In the selected articles the design of the studies was mainly observational, some were descriptive studies and some were cohort, case control and cross-sectional studies. Only few were randomized controlled trials, mainly those comparing different hormonal treatments for EH. Some other studies were systematic reviews of the literature.

3. Results

a. According to authors in the selected literature, the sensitive and accurate diagnosis of true premalignant endometrial lesions can reduce likelihood of developing invasive endometrial cancer.

b. Berg et al. (2015) report that molecular alterations in patients with EH such as PIK3CA mutations, PTEN loss, PI3K and KRAS activation, are early events in endometrial carcinogenesis. Also it was reported that oncoprotein Stathmin might improve preoperative diagnostic distinction between premalignant and malignant endometrial lesions.

c. Dias et al. (2015) concluded that ultrasonographic parameters and endothelial markers (CD34 and CD105) did not enable differentiation of endometrial polyps from endometrial neoplasia. Relapse of endometrial hyperplasia after initial regression with hormonal therapy occurs often, and long-term follow-up is advised in these cases.

d. Some of the predictive factors for concurrent endometrial carcinoma in EH are older age, obesity, diabetes mellitus, and complex atypic hyperplasia (CAH) of endometrium, as reported by Matsuo et al. (2015).

e. Fertility-sparing treatment for CAH and grade 1 endometrial cancer was feasible with progestin therapy and leads to clinically meaningful rates of pregnancy in young women who wish to preserve fertility (Pronin et al., 2015).

f. Some authors determine important areas for future research, such as increasing the diagnostic reproducibility of EH, improving the discri-mination between AH and carcinoma, and identifying biomarkers to stratify risks or serve as indicators of response to clinical treatment. Dusp6 could be a predicting marker for deciding the effectiveness of progestin therapy in atypic EH (Zhang et al., 2015).

Relevant articles retrieved May-Aug 2015

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ENYGO ESGO European Network of Young Gynae Oncologists

Treatment of endometrial hyperplasia (biology, conservative and definitive treatment, follow-up)

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Prediction of concurrent endometrial carcinoma in women with endometrial hyperplasia.	Matsuo K et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26238457	
2	Comparison of diagnostic accuracy between endometrial curettage and pipelle aspiration biopsy in patients treated with progestin for endometrial hyperplasia: a Korean Gynecologic Oncology Group Study (KGOG 2019)	Mi Kyoung Kim et al.	Jpn J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26206899	✓
3	Folate receptor expression and significance in endometrioid endometrium carcinoma and endometrial hyperplasia	Senol S et al.	Int J Clin Exp Pathol	http://www.ncbi.nlm.nih.gov/pubmed/26191275	✓
4	Tamoxifen-associated polypoid endometriosis mimicking an ovarian neoplasm.	Choi IH et al.	Obstet Gynecol Sci	http://www.ncbi.nlm.nih.gov/pubmed/26217606	✓
5	Endometrial evaluation by ultrasonography, hysteroscopy and histopathology in cases of breast carcinoma on Tamoxifen therapy.	Jindal A et al.	J Midlife Health	http://www.ncbi.nlm.nih.gov/pubmed/26167055	✓
6	Hysteroscopic Resection in Fertility-Sparing Surgery for Atypical Hyperplasia and Endometrial Cancer: Safety and Efficacy.	De Marzi P et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26092080	
7	Management of Endometrial Hyperplasia: A Survey of Members of the Korean Gynecologic Oncology Group.	Kim MK et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26067858	✓
8	Risk Factors Associated with the Malignant Changes of Symptomatic and Asymptomatic Endometrial Polyps in Premenopausal Women.	Elfayomy AK et al.	J Obstet Gynaecol India	http://www.ncbi.nlm.nih.gov/pubmed/26085741	
9	Cyclic versus continuous medroxyprogesterone acetate for treatment of endometrial hyperplasia without atypia: a 2-year observational study.	Emarh M	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/26015309	✓
10	The American College of Obstetricians and Gynecologists Committee Opinion no. 631. Endometrial intraepithelial neoplasia.	Committee on Gynecologic Practice, Society of Gynecologic Oncology.	Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25932867	✓
11	Fertility-Sparing Treatment of Early Endometrial Cancer and Complex Atypical Hyperplasia in Young Women of Childbearing Potential	Pronin SM et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25950126	✓
12	Effects of genistein in combination with conjugated estrogens on endometrial hyperplasia and metabolic dysfunction in ovariectomized mice.	Kim JH et al.	Endocr J	http://www.ncbi.nlm.nih.gov/pubmed/25877295	✓
13	Long-term Clinical Outcomes After Resectoscopic Endometrial Ablation of Nonatypical Endometrial Hyperplasia in Women With Abnormal Uterine Bleeding.	Vilos GA et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25749467	
14	An estrogen-induced endometrial hyperplasia mouse model recapitulating human disease progression and genetic aberrations.	Yang CH	Cancer Med	http://www.ncbi.nlm.nih.gov/pubmed/25809780	✓
15	Levels of Regulatory Proteins Associated With Cell Proliferation in Endometria From Untreated Patients Having Polycystic Ovarian Syndrome With and Without Endometrial Hyperplasia.	Bacallao K et al.	Reprod Sci	http://www.ncbi.nlm.nih.gov/pubmed/26239387	✓
16	Expression and clinical significance of ghrelin in endometrial hyperplasia and carcinoma of Egyptian patients.	Younes SF et al.	Ultrastruct Pathol	http://www.ncbi.nlm.nih.gov/pubmed/25569277	
17	PTEN sequence analysis in endometrial hyperplasia and endometrial carcinoma in Slovak women.	Gbelcová H et al.	Anal Cell	http://www.ncbi.nlm.nih.gov/pubmed/26114084	✓
18	Efficacy of the Levonorgestrel-Releasing Intrauterine System on IVF-ET Outcomes in PCOS With Simple Endometrial Hyperplasia.	Bian J et al.	Reprod Sci	http://www.ncbi.nlm.nih.gov/pubmed/25536958	✓
19	Dual-specificity phosphatase 6 predicts the sensitivity of progestin therapy for atypical endometrial hyperplasia.	Zhang H et al.	Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25451692	

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ENYGO ESGO European Network of Young Gynae Oncologists

Treatment of endometrial hyperplasia (biology, conservative and definitive treatment, follow-up)

Relevant articles retrieved May-Aug 2015 (cont.)

No	Title	Authors	Journal	Link to abstract	Available as full freetext
20	Hysteroscopic transcervical resection is useful to diagnose myometrial invasion in atypical polypoid adenomyoma coexisting with atypical endometrial hyperplasia or endometrial cancer with suspicious myometrial invasion.	Yamagami W et al.	J Obstet Gynaecol Res.	http://www.ncbi.nlm.nih.gov/pubmed/25491392	✓
21	Molecular profiling of endometrial carcinoma precursor, primary and metastatic lesions suggests different targets for treatment in obese compared to non-obese patients.	Berg A et al.	Oncotarget	http://www-ncbi-nlm-nih-gov.emedien.ub.uni-muenchen.de/pubmed/25415225	✓
22	Accuracy of endometrial sampling compared to conventional dilatation and curettage in women with abnormal uterine bleeding.	Abdelazim IA et al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/25367600	
23	Immunohistochemical and genetic profiles of endometrioid endometrial carcinoma arising from atrophic endometrium.	Geels YP et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25773202	
24	Strong correlation between molecular changes in endometrial carcinomas and concomitant hyperplasia.	Zauber P et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25768080	✓
25	Endometrial histology in severely obese bariatric surgery candidates: an exploratory analysis.	Kaiyrlykyzy A et al.	Surg Obes Relat Dis	http://www.ncbi.nlm.nih.gov/pubmed/25820079	
26	Hysteroscopy in women with abnormal uterine bleeding: a meta-analysis on four major endometrial pathologies.	Gkrozou F et al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/25524536	✓
27	Project for the National Program of Early Diagnosis of Endometrial Cancer Part I.	Bohîl ea RE et al.	J Med Life	http://www.ncbi.nlm.nih.gov/pubmed/26351531	✓
28	Referring survivors of endometrial cancer and complex atypical hyperplasia to bariatric specialists: a prospective cohort study.	Jernigan AM et al.	Am J Obstet Gyneco	http://www.ncbi.nlm.nih.gov/pubmed/25981846	
29	Type 2 Endometrial Cancer is Associated With a High Density of Tumor--Associated Macrophages in the Stromal Compartment.	Kelly MG et al.	Reprod Sci	http://www.ncbi.nlm.nih.gov/pubmed/25701837	✓
30	Relation of metabolic syndrome with endometrial pathologies in patients with abnormal uterine bleeding.	Özdemir S et al.	Gynecol Endocrinol	http://www.ncbi.nlm.nih.gov/pubmed/26182187	
31	Efficacies and pregnant outcomes of fertility-sparing treatment with medroxyprogesterone acetate for endometrioid adenocarcinoma and complex atypical hyperplasia: our experience and a review of the literature.	Ohyagi-Hara C et al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/25118836	✓
32	Reproducibility of Endometrial Pathologic Findings Obtained on Hysteroscopy, Transvaginal Sonography, and Gel Infusion Sonography in Women With Postmenopausal Bleeding.	Dueholm M et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26044592	
33	Hysteroscopic Resection in Fertility-Sparing Surgery for Atypical Hyperplasia and Endometrial Cancer: How Important Are Intrauterine Adhesions?	Shokeir T	J Minim Invasive Gyne- col	http://www.ncbi.nlm.nih.gov/pubmed/26205575	
34	Mig-6 regulates endometrial genes involved in cell cycle and progesterone signaling.	Yoo JY et al.	Biochem Biophys Res Commun	http://www.ncbi.nlm.nih.gov/pubmed/25976672	

Pathology in endometrial cancer (prognostic factors, EIN, EIC)

Editor Santiago Scasso

Descriptive summary

Not many articles are applying the term EIN or EIC recommended by the Endometrial International Collaborative group. This is highlighted by the ACOG COMMITTEE OPINION Number 631 published in May 2015 titled Endometrial Intraepithelial Neoplasia.

On the other hand the research lines are working behind biomarkers which may identify the high-risk early stage, establish diagnosis, monitor disease progression and probably responders to target therapy.

Endometrial cancer is a heterogeneous disease with 5-year survival rates ranging from > 90% to 42% for women with clinical stage I disease. LN metastasis also occur in low-risk patients with stage I endometrial cancer. Therefore, new prognostics markers are being studied to be able to identify high-risk features among patients otherwise being considered to be at low-risk according to traditional clinic-pathologic factors. A number of studies have reported that DNA aneuploidy is associated with other prognostic factors and recurrence. In the low-risk group, the recurrence rate was 2.1% for diploid tumors and 12.5% for aneuploid tumors (P = 0.038).

Leupaxin is expressed in breast and endometrial carcinomas. Downregulation of leupaxin expression is associated with decreased migration and invasion of tumor cells.

The l-asparaginase (ASRGL1) protein was identified as a prognostic marker for endometrial carcinoma. Loss of ASRGL1 is a powerful predictor for poor prognosis and impact on survival. A recent study showed that L1CAM is the best predicting prognostic factor in FIGO stage I, type I EC and superior to the standard risk factors (myometrial invasion, tumour grade and lymph space or vascular invasion). L1CAM immunohistochemistry may identify patients at increased risk for recurrent disease.

However, all the mentioned biomarkers are lacking validation on pre-operative histological samples and are based on mainly retrospective, singles studies. Two important prospective multicenter trials are in the way but it should be "on the way" and waiting for FU results to validate these promising results.

1) Molecular Markers in Treatment in Endometrial Cancer (MoMaTEC), the purpose of this prospective multicenter study (started recruitment in 2001, n=1000) is to investigate the predictive value of molecular markers in endometrial cancer for lymph node metastasis, prognosis and treatment. The expression of p53, p16, ER, PR and HER2neu in curettage material is studied in relation to lymph node metastasis and prognosis among EC patients. Distribution of genetic alterations in fresh frozen tumor tissue based on molecular profile are also under investigation to study targetable pathways, such as inhibitors of Her2/NEU, EGFR, receptor tyrosine kinase, mTOR, PTEN and hormone receptor pathways.

2) PIpelle Prospective ENDOmetrial carcinoma (PIPENDO) study, pre-operative recognition of high risk endometrial carcinoma: a multi-centre prospective cohort study in nine hospitals in the Netherlands. From Sept-2011 till Dec-2013 and two years of FU. Identification of a panel of immunohistochemical (IHC) markers may be helpful to establish a reliable preoperative risk classification.

The objectives are to select a panel of the most accurate biomarkers that can be used in daily practice for preoperative diagnosis and establish prognosis to tailor the appropriate treatment.

Relevant articles retrieved May-Aug 2015

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Pathology in endometrial cancer (prognostic factors, EIN, EIC)

- Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	The American College of Obstetricians and Gynecologists Committee Opinion no. 631. Endometrial intraepithelial neoplasia	Committee on Gynecologic Practice, Society of Gynecologic Oncology	Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25932867	
2	Leupaxin is expressed in mammary carcinoma and acts as a transcriptional activator of the estrogen receptor .	Kaulfuss S et al.	Int J Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25955236	✓
3	PI3K/mTOR pathway inhibition overcomes radioresistance via suppression of the HIF1- /VEGF pathway in endometrial cancer.	Miyasaka A et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25913131	✓
4	Loss of ASRGL1 expression is an independent biomarker for disease-specific survival in endometrioid endometrial carcinoma.	Edqvist PH et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25858696	
5	DNA ploidy in curettage specimens identifies high-risk patients and lymph node metastasis in endometrial cancer.	Njolstad TS et al.	Br J Cancer	http://www.ncbi.nlm.nih.gov/pubmed/?term=DNA+ploidy+in+curettage+specimens+identifies+high-risk+patients+and+lymph+node+metastasis+in+endometrial+cancer	
6	Molecular Markers in Treatment in Endometrial Cancer (MoMaTEC)	Salvesen HB et al.	clinicaltrials.gov	https://clinicaltrials.gov/ct2/show/study/NCT00598845	
7	Molecular cues on obesity signals, tumor markers and endometrial cancer	Daley-Brown D et al.	Horm Mol Biol Clin Invest		
8	PIpelle Prospective ENDOmetrial carcinoma (PIPENDO) study, pre-operative recognition of high risk endometrial carcinoma: a multicentre prospective cohort study.	Visser NC et al.	BMC Cancer	http://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+26123742	✓
9	Multivariate Analysis of Prognostic Biomarkers in Surgically Treated Endometrial Cancer	Li J et al.	PLoS One	http://www.ncbi.nlm.nih.gov/pubmed/26107255	✓
10	The role of microRNAs in the pathogenesis of endometrial cancer: a systematic review.	Sianou A et al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/25697925	

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Medical (chemo and radiotherapy) treatment of primary uterine cancer

Editor David Lindquist

Descriptive summary

The evidence for adjuvant treatment of primary uterine cancer is still very limited with only few randomized clinical trials addressing this question. Those are in general old and have different subgroups making them quite difficult to compare. In this search only four relevant articles for the current update were found.

One study is a phase I clinical trial (GOG 9920) which determined the maximum tolerated dose for intraperitoneally administered chemotherapy in endometrial cancer patients with intraperitoneal disease spread (FIGO stages IIIA/IIIC and IV). The toxicity profile was acceptable and further study of this treatment strategy is recommended by the authors.

Next study was comparing early stage high-grade endometrial cancer with those with non-endometrioid histology. 123 patients were investigated during a 6 year period with a median follow-up time of 27.9 months. No significant differences were found in distant recurrent rate or in 5 year recurrent-free survival when comparing high-grade endometroid, serous, and clear cell carcinomas.

The third study investigated the effect of adjuvant chemotherapy and pelvic irradiation. This was a multi-institution retrospective study including 115 patients with stage IA non-invasive uterine papillary serous carcinoma. Lymphadenectomy in this patient group was the only factor associated with improved outcome in multivariate analysis. Adjuvant treatment was associated with improved outcome in unstaged patients but this group included a limited number of patients.

The fourth study evaluated 55 patients with FIGO stage IIIA or positive cytology. In this retrospective study including only surgically staged patients, survival was improved by adjuvant chemotherapy and radiotherapy, both for either treatment alone, and for the combination.

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	A phase I study of IV doxorubicin plus intraperitoneal (IP) paclitaxel and IV or IP cisplatin in endometrial cancer patients at high risk for peritoneal failure (GOG9920): An NRG Onclogy/ Gynecologic Oncology Group study	McMeeking et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900867-7/abstract	
2	Impact of adjuvant chemotherapy and pelvic radiation on pattern of recurrence and outcome in stage I non-invasive uterine papillary serous carcinoma. A multi-insitution study	Mahdi et al.	Gynecol Oncol	http://www.gynecologiconcology-online.net/article/S0090-8258%2815%2900587-9/abstract	
3	Survival Analysis of Cancer Patients With FIGO Stage IIIA Endometrial Cancer	Lum et al.	Am J Clin Oncol	http://www.ingentaconnect.com/content/wk/ajco/2015/00000038/00000003/art00009	
4	Comparable Outcome Between Endometroioid and Non-Endometrioid Tumors in Patients With Early-Stage High-Grade Endometrial Cancer	Reynaers et al.	J Surg Oncol	http://onlinelibrary.wiley.com/doi/10.1002/jso.23871/abstract	

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ENYGO ESGO European Network of Young Gynae Oncologists

Surgical treatment of primary uterine cancer

Editor Piotr Lepka

Descriptive summary

Articles reviewed in this update mainly focus on four issues linked to surgical treatment.

1. Preoperative preparation. Visser et al published a multicenter prospective cohort study, in which preoperative histology diagnosis correspond poorly to final histology. As a result patients are often over- or under treated. This study is designed to determine whether standardization of endometrial biopsies with additional immunohistochemical analysis could better predict final histological type, tumor grade and stage to improve surgical treatment. Other factors like cytology may additionally improve risk classification. Follow-up will be completed in 2015.
2. Range of surgery and adjuvant therapy. Reynaers et al compare distant recurrence and disease-related mortality between endometrioid and non-endometrioid high grade tumors in early stage EC. All patients underwent hysterectomy and bilateral salpingo-oophorectomy. Different types of adjuvant treatment were given. After 27,9 months follow-up 27,6% of enrolled patients had recurred, regardless of histological type. The authors suggest that treatment approaches should differ by histological subtypes in early-stage endometrial cancers.

   Peled et al focused on patients who where pre-operatively diagnosed as endometrioid carcinoma but showed uterine papillary serous carcinoma on final histopathology. Misdiagnosed women received inadequate surgical staging without omentectomy. The authors state that restaging of those patients with omentectomy may have only limited value as mean disease free interval was 24,5 versus 30,5 months with and without omentectomy, respectively. Overall survival was 33 months after omentectomy and 29 months after no omentectomy. Recurrence patterns did not differ.

   Koskas et al analyzed accuracy of preoperative staging followed ESMO guidelines in endometrial cancer. University hospitals were divided into two groups. Those who treat less than 20 cases EC and more than 20 cases/year. The results showed that preoperative staging and lymphadenectomy in the presumed low- and high-risk patients was homogenous in both groups. The only difference was the number lymphadenectomies in patients with presumed intermediate risk. Centers with more than 20 EC tend to perform lymphadenectomy more frequently.
3. Postoperative lower-extremity lymphedema as a consequence surgical procedures was studied in articles by Yukiharu et al. and Hyo Sook. In addition Agar et al also considered benefits of pelvic and para-aortic lymphadenectomy in EC after recommendations of INCa 2010. Lymphadenectomy was associated with high postoperative morbidity and 2.5% mortality.
4. Sentinel lymph nodes. Touhami et al investigated metastasis in non-sentinel lymph nodes when SLN is positive in endometrial cancer. Only size of a SLN was associated with increased risk of metastasis in non-SLN. Cutoff diameter was 2mm - below that size risk of metastasis in non-SLN was low. How et al compared usefulness different markers in detection SLN like Indocyanine green, technetium and blue dye to improve surgical staging. Ideally this should lead to decreased number of lymphadenectomies. Plante et al published a pilot study in which they demonstrate SLN mapping using indocyanine green with endoscopic near-infrared fluorescence imaging. 50 patients were enrolled in this study (42 with endometrial cancer and 8 with cervical cancer). The overall SLN detection rate was 96%, with a high bilateral detection rate of 88%.

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Surgical treatment of primary uterine cancer

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Comparable outcome between endometrioid and non-endometrioid tumors in patients with early-stage high-grade endometrial cancer.	Reynaers EA et al.	J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25900897	
2	PIpelle Prospective ENDOmetrial carcinoma (PIPENDO) study, pre-operative recognition of high risk endometrial carcinoma: a multicentre prospective cohort study.	Visser NC et al.	BMC Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26123742	
3	Uterine papillary serous carcinoma pre-operatively diagnosed as endometrioid carcinoma: Is omentectomy necessary?	Peled Y et al.	Aust N Z J Obstet Gynaecol	http://www.ncbi.nlm.nih.gov/pubmed/26235227	
4	Risk-adjusted outcomes in elderly endometrial cancer patients: implications of the contrasting impact of age on progression-free and cause-specific survival	AlHilli MM et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25895615	
5	Impact of surgical case volume on the accuracy of preoperative staging and compliance with the guidelines for the management of endometrial cancer	Koskas M et al.	Anticancer Res	http://www.ncbi.nlm.nih.gov/pubmed/25964572	
6	Morbidity of pelvic lymphadenectomy and para-aortic lymphadenectomy in endometrial cancer	Agar N et al.	Bull Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25956349	
7	Does debulking of enlarged positive lymph nodes improve survival in different gynaecological cancers?	Somashekhar SP	Best Pract Res Clin Obstet Gynaecol	www.ncbi.nlm.nih.gov/pubmed/26043964	
8	Close relationship between removal of circumflex iliac nodes to distal external iliac nodes and postoperative lower-extremity lymphedema in uterine corpus malignant tumors	Todo Y et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26186910	
9	Predictors of non-sentinel lymph node (non-SLN) metastasis in patients with sentinel lymph node (SLN) metastasis in endometrial cancer.	Touhami O et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25891803	
10	Comparing indocyanine green, technetium, and blue dye for sentinel lymph node mapping in endometrial cancer.	How J et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25870917	
11	Sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial cancer. A pilot study and review of the literature.	Plante M et al.		http://www.ncbi.nlm.nih.gov/pubmed/25771495	
12	Preoperative imaging of uterine malignancy: A low-value service.	Baker W et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25724793	
13	Postoperative Lower Extremity Edema in Patients with Primary Endometrial Cancer.	Bae HS et al.	Ann Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25986870	
14	Preoperative CT-based nomogram for predicting overall survival in women with non-endometrioid carcinomas of the uterine corpus.	Lakhman Y et al.	Abdom Imaging	http://www.ncbi.nlm.nih.gov/pubmed/25549782	

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Surgical treatment of recurrent uterine cancer

Editor Arun Kalpdev

Descriptive summary

There is limited literature available on the role of surgical management of recurrent endometrial cancer. Recurrence in endometrial cancer is being reported to be around 6–13%. Recurrence patterns have been reported ranging from isolated lesions to distant metastasis. To date, non-surgical treatment has been preferred as treatment of recurrence in endometrial cancer. Since past few decades radiotherapy has been the first line of treatment for locally recurrent disease. Chemotherapy is often recommended for patients with metastatic recurrences. The role of surgery in patients with recurrent endometrial cancer is undefined. Surgery has mostly been used when the extent of the disease or other factors indicating that radiotherapy could not be curative.

Success rate of surgical treatment is governed by various factors e.g. previous treatment modality (surgery, radiotherapy, hormonal therapy, combined), extent of recurrence (local recurrence, distant or multifocal) histopathology etc. Surgical treatment aims at optimal cytoreduction with complete removal of malignant tissue. Pelvic exenterative procedures with / without removal of adjacent viscera along with salvage cytoreduction have been performed in various series. Surgery in this group of patients has been associated with high rates of morbidity & mortality. Even after surgery, overall survival rate and disease free survival are reported to give variable results. Over last few decades surgical intervention for recurrent endometrial cancer has also undergone a paradigm shift towards less radical surgery. Also, refinement in surgical approach e.g. with the increase of of minimal invasive surgery, inherent cons of open abdominal surgery, morbidity and mortality are expected to decrease. Randomized controlled studies are required to gain further insight into the role of surgery in the management of patients with recurrent endometrial cancer.

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Atypical paracaval recurrence of uterine endometrial stromal sarcoma: a case report.	Bacalbaşa N et al .	Anticancer Res	http://www.ncbi.nlm.nih.gov/pubmed/26026102	
2	Obstructing Colonic Mass: A Case of Recurrent Endometrial Cancer.	Chedid V et al.	Case Rep Gastrointest Med	http://www.ncbi.nlm.nih.gov/pubmed/26199767	✓

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ENYGO ESGO European Network of Young Gynae Oncologists

Medical (chemo and radiotherapy) treatment of recurrent uterine cancer

- Editor Surynt Ewa

- Descriptive summary

There are two areas of studies with patients with endometrial and non-endometrial recurrent uterine neoplasm.

In the first group of trials the problem of target molecular alterations specific to this subset of recurrent endometrial tumors is discussed.

1. The multicenter, open label, randomized phase III study was to determine whether ixabepilone resulted in improved overall survival (OS) compared to single-agent chemotherapy (doxorubicin or paclitaxel) in women with locally advanced, recurrent, or metastatic endometrial cancer with at least one failed prior platinum-based chemotherapeutic regimen. A favorable benefit ratio was not observed for ixabepilone versus control at the time of the interim analysis. 2. The two-stage phase II study assessed activity of single agent dalantercept in patients with recurrent/persistent endometrial carcinoma (EMC). Dalantercept has insufficient single agent activity in recurrent EMC to warrant further investigation at this dose level and schedule. 3. There are numerous correlative scientific investigations demonstrating that the HER2 (ERBB2) gene is amplified in 17%-33% of carcinosarcoma, uterine serous carcinoma, and a subset of high-grade endometrioid endometrial tumors. This review explores the literature surrounding HER2 expression in endometrial cancer, focusing on trastuzumab and other anti-HER2 therapy and resistance mechanisms characterized in breast cancer but germane to endometrial tumors. This review summarizes the role of HER2 in endometrial cancer, with a focus on uterine serous carcinoma. The limitations of anti-HER2 therapy in this disease site are examined, and mechanisms of drug resistance are outlined based on the experience in breast cancer.

The second area of recurrent uterine carcinoma concerns leiomyosarcoma. 1. The treatment of advanced uterine leiomyosarcomas (U-LMS) represents a considerable challenge. For recurrent or disseminated U-LMS, cytotoxic chemotherapy remains the mainstay of treatment. There have been few active chemotherapy drugs approved for advanced disease, although newer drugs such as trabectedin with its pleiotropic mechanism of actions represent an important addition to the standard front-line systemic therapy with doxorubicin and ifosfamide. In this review the therapeutic potential and in particular the emerging evidence-based strategy of therapy with trabectedin in patients with advanced U-LMS is discussed.

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Medical (chemo and radiotherapy) treatment of recurrent uterine cancer

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	The Therapeutic Challenge of Targeting HER2 in Endometrial Cancer.	Diver EJ et al.	Oncologist	http://www.ncbi.nlm.nih.gov/pubmed/26099744	
2	Management Strategies in Advanced Uterine Leiomyosarcoma: Focus on Trabectedin.	Amant F et al.	Sarcoma	http://www.ncbi.nlm.nih.gov/pubmed/26089739	✓
3	Postoperative Lower Extremity Edema in Patients with Primary Endometrial Cancer.	Bae HS et al.	Ann Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25986870	
4	Comparable outcome between endometrioid and non-endometrioid tumors in patients with early-stage high-grade endometrial cancer.	Reynaers EA et al.	J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25900897	
5	Pelvic Exenteration in Gynecologic Cancer: La Paz University Hospital Experience.	Moreno-Palacios E et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25853383	
6	Potential proton beam therapy for recurrent endometrial cancer in the vagina.	Yanazume S et al.	J Obstet Gynaecol Res	http://www.ncbi.nlm.nih.gov/pubmed/25369803	
7	Treatment of recurrent metastatic uterine leiomyosarcoma of the spine: a multimodality approach using resection, radiosurgery, and chemotherapy.	Strong MJ et al.	J Neurosurg Spine	http://www.ncbi.nlm.nih.gov/pubmed/26186448	
8	STUMP un"stumped": anti-tumor response to anaplastic lymphoma kinase (ALK) inhibitor based targeted therapy in uterine inflammatory myofibroblastic tumor with myxoid features harboring DCTN1-ALK fusion.	Subbiah V et al.	J Hematol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26062823	✓
9	Patient and physician factors associated with participation in cervical and uterine cancer trials: an NRG/GOG247 study.	Brooks SE et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25937529	✓
10	Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer.	McMeekin S et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25925990	
11	Comparable outcome between endometrioid and non-endometrioid tumors in patients with early-stage high-grade endometrial cancer.	Reynaers EA et al.	J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25900897	
12	Phase II evaluation of dalantercept, a soluble recombinant activin receptor-like kinase 1 (ALK1) receptor fusion protein, for the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study 0229N.	Makker V et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25887099	
13	A phase II evaluation of selumetinib (AZD6244, ARRY-142886), a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study.	Coleman RL et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25887099	

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Emerging molecular-targeted therapies in endometrial cancer

Editor Inês Vasconcelos

Descriptive summary

Mutation and loss of PTEN function with overexpression of mTOR signalling pathway is involved in the pathogenesis of endometrial cancer, with endometrial cancer being the cancer type that shows the highest incidence of mutations in this pathway. Therefore the PIK3/AKT/mTOR pathway is a particularly attractive target in endometrial cancer.

AZD6244 (Selumetinib) is an TKI orally bioavailable inhibitor of AKT. The phase II trial did not meet pre-trial specifications for clinical efficacy. 54 patients were enrolled and ran ORR of 6% as reported (1).

mTOR inhibitors have shown therapeutic efficacy alone or in combination therapy, regardless of the status of PTEN mutation.

Ridaforolimus is a thoroughly studied rapalog. The latest phase II trial enrolled 130 patients, of which 64 received ridaforolimus. Treatment discontinuation as a result of adverse events was 33%. Median PFS at the protocol pre-specified interim analysis was 3.6 months for ridaforolimus and 1.9 months for the comparator. Oral ridaforolimus showed encouraging activity in advanced endometrial cancer but was associated with significant toxicity (2).

Regarding mTOR inhibitors, particularly the results of the phase II trial evaluating PF-05212384 are eagerly awaited, as are the results of the phase II trial evaluating paclitaxel, carboplatin, and bevacizumab or paclitaxel, carboplatin, and temsirolimus or ixabepilone, carboplatin, and bevacizumab (NCT00977574).

Attempts to block VEGFR family have shown good results in other cancer types, but efforts to block VEGF in endometrial cancer have obtained disappointing results. TKI258 (Dovitinib) is an orally bioavailable lactate salt of a benzimidazole-quinolinone compound that strongly binds to several members of the receptor tyrosine kinase superfamily (RTK). It binds to the fibroblast growth factor receptor 1, 2 and 3 (FGFR-1, FGFR-2 and FGFR-3), VEGF, platelet-derived growth factor receptor type 3 (PDGF-3), FMS-like tyrosine kinase 3, stem cell factor receptor (c-KIT) and colony-stimulating factor receptor 1 (CSFR-1). It has been evaluated in the treatment of patients with FGFR2 mutated (mut) or wild-type (WT) advanced and/or metastatic endometrial cancer. Second-line dovitinib in FGFR2(mut) and FGFR2(WT) advanced or metastatic endometrial cancer had single-agent activity, but it did not reach the pre-specified study criteria. Of 248 patients with FGFR2 pre-screening results, 27 (11%) had FGFR2(mut) endometrial cancer, of which 22 patients FGFR2(mut) and 31 patients FGFR2(WT) were recruited. Seven (31.8%) FGFR2(mut) patients and nine (29.0%) FGFR2(WT) patients were progression-free at 18 weeks. On the basis of predefined criteria, neither group continued to stage two of the trial (3).

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No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	A phase II evaluation of selumetinib (AZD6244, ARRY-142886), a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group study.	Coleman RL et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25887099	
2	Randomized Phase II Trial of Ridaforolimus in Advanced Endometrial Carcinoma.	Oza AM et al.	JCO	http://www.ncbi.nlm.nih.gov/pubmed/21788564	
3	Second-line dovitinib (TKI258) in patients with FGFR2-mutated or FGFR2-non-mutated advanced or metastatic endometrial cancer: a non-randomised, open-label, two-group, two-stage, phase 2 study.	Konecny GE	Lancet Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25981814	

Cervical pre-invasive disease (diagnosis, management)

Editor: Geanina Dragnea

Descriptive summary

Prevention

- Early data on the impact of the vaccination programs shows that although there has been a noticeable drop in CIN2+ incidence rates, the magnitude of vaccine effectiveness should become more obvious (1).
- A Danish study showed that the reduction of positive screening results with liquid-based cytology is small after HPV vaccination, and the expected decline in PPV is very limited. In this situation, the information general practitioners will have to provide to their patients will be largely unchanged (2).

Genetics

- Human leukocyte antigen (HLA) class II DRB1*1302 allele has a protective effect against progression from CIN1 to CIN2/3 (3).

Detection

- False-negative (FN) liquid-based cytology diagnoses is associated with scanty, isolated, small, atypical cells and dense cell groups. Prior to final diagnosis, pathologists should systematically review the entire surface of the dotted slides, with special attention being devoted to slides with multiple cell layers and tridimensional groups (4).
- p16/Ki-67 dual-stained cytology has comparable or lower sensitivity for CIN2+, but higher levels of specificity compared with HC2 HPV testing in both ASC-US and LSIL cases. This may help to reduce the number of unnecessary colposcopy referrals (5).
- The profile of viral load evolution over time could distinguish non-progressive from progressive (carcinogenic) infections and could be used for future triage in HPV-based cervical screening programs (6).
- Methylation of the gene PAX1 (a transcription factor) could be used as a biomarker in cervical cancer screening to increase the specificity of HPV DNA by detecting women with more advanced cervical abnormalities (CIN 2+) (7).

Treatment

- See-and-treat management is justified in the case of a high-grade smear and a high-grade colposcopic impression, with the pooled over-treatment rate at least comparable with the two-step procedure (8).
- Conization using electrosurgical knife for cervical intraepithelial neoplasia or microinvasive carcinomas is a reliable technique for diagnosis and treatment with relatively low rate of recurrence (4.6%) and complications (6.0%) (9).
- The residual lesion and its progression in the cervical canal after positive endocervical margins on LEEP specimens are more difficult to screen and control. Patients unable to comply with regular colposcopic follow-up could benefit from repeat conization (10).

Follow-up

- Co-testing (HPV testing and cytology) at 6 and 12 months after loop electrosurgical excision procedure (LEEP) predict recurrent disease at a sensitivity of 90-100% (11). Additional visit at 3 months is recommended in cases with positive section margins or microinvasive carcinoma (12).
- High risk factors of recurrence after electrosurgical excision are: positive surgical margins (9,12, 13), microinvasive carcinoma (9), high grade lesion (12), positive endocervical curettage (1), menopause (13), ≥50 years old (13), gland involvement (13), high risk HPV infection after 6-12 months (12, 13), family history of virus-associa- ted malignancies (9).

Complications

- Within a German cohort off 144 cervical conisations the risk of preterm birth, cesarean section or poor fetal outcome did not increase (14).

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Cervical pre-invasive disease (diagnosis, management)

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1	Trends in cervical intraepithelial neoplasia Grade 2+ after human papillomavirus vaccination: The devil is in the details	Brar, H et al.	Cancer	http://onlinelibrary.wiley.com/doi/10.1002/cncr.29264/abstract	
2	The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark.	Hestbech MS et al.	BMJ Open	http://bmjopen.bmj.com/content/5/8/e007921.full	✓
3	The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark.	umoto K et al.	Cancer Sci	http://www.ncbi.nlm.nih.gov/pubmed/26235935	
4	Retrospective Rescreening of Negative Cervical Cytology Samples Preceding Histologically Proven CIN2-3 and Squamous Cell Carcinoma: An Educational Opportunity to Understand and Prevent Laboratory Errors	Feoli F et al.	Acta Cytol	http://www.ncbi.nlm.nih.gov/pubmed/26279075	
5	Prospective evaluation of p16/Ki-67 dual-stained cytology for managing women with abnormal Papanicolaou cytology: PALMS study results	Bergeron C et al.	Cancer Cytopathol	http://www.ncbi.nlm.nih.gov/pubmed/25891096	
6	Serial type-specific human papillomavirus (HPV) load measurement allows differentiation between regressing cervical lesions and serial virion productive transient infections	Christophe E et al.	Cancer Medicine	http://onlinelibrary.wiley.com/doi/10.1002/cam4.473/epdf	✓
7	PAX1 methylation as an auxiliary biomarker for cervical cancer screening: A meta-analysis	Nikolaidis C et al.	Cancer Epidemiol	http://www.ncbi.nlm.nih.gov/pubmed/26234429	
8	Evidence supporting see-and-treat management of cervical intraepithelial neoplasia: a systematic review and meta-analysis.	Ebisch R et al.	BJOG	http://www.ncbi.nlm.nih.gov/pubmed/26177672	
9	Conization Using an Electrosurgical Knife for Cervical Intraepithelial Neoplasia and Microinvasive Carcinoma.	Xiang L et al.	PLoS One.	http://www.ncbi.nlm.nih.gov/pubmed/26153692	✓
10	Positive endocervical margins at conization: repeat conization or colposcopic follow-up? A retrospective study.	Chambo Filho A et al.	J Clin Med Res	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4432896/	✓
11	Human papillomavirus combined with cytology and margin status identifies patients at risk for recurrence after conization for high-grade cervical intraepithelial neoplasia	Ruano Y et al.	Eur J Gynaecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26189247	
12	Long-Term Clinical Outcome after Treatment for High-Grade Cervical Lesions: A Retrospective Monoinstitutional Cohort Study	Del Mistro A et al.	BioMed Research International	http://www.hindawi.com/journals/bmri/2015/984528/	✓
13	Meta-analysis of high risk factors of residue or relapse of cervical intraepithelial neoplasia after conization	Jin J et al.	J Biol Regul; Homeost Agents	http://www.ncbi.nlm.nih.gov/pubmed/26122236	
14	Cervical conisation and the risk of preterm delivery: a retrospective matched pair analysis of a German cohort	Kirn V et al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/25234516	

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Cervical cancer pathology

Editor Borja Otero

Descriptive summary

MicroRNA

- MicroRNAs are noncoding RNAs aberrantly expressed in cervical cancer. Therefore, these particles have recently gained much interest.
- Thinking of miRNAs as biomarkers of cancer development, miR-125b could be a good predictor of ICC development from premalignant lesions whereas the study of miR-34a has shown contradictory results. (1,2)
- Its aberrant expression in ICC has led to the proposale of the expression of nine of these miRNAs as a prognostic signature for ICC. Although a study has failed to demonstrate such relation, its authors point several ways of enhancing this type of signature. On the other hand, a low expression of mir-26b in ICC has been associated with short disease free and overall survival. (3)
- Again mi-RNA analysis has demonstrated that miR-7, 506, 373 and 92-a can be potential novel therapeutic targets of cervical cancer. (4-7)

ICC development

- HPV 16 is the most frequent genotype of ICC related HPV, but there is a wide variety of different subtypes according to E6 gene variants. AA-a has shown the highest association with the development of ICC. (8)
- The study of other particles such as CARD8 (caspase recruitment domine family member 8) has shown that its variant rs7248320 could be a marker of susceptibility to HPV related ICC (9) similarly to certain genetic polymorphisms of several genes related to reactive oxygen species inactivation. (10)
- Finally, a new study demonstrates that survivin, p16, COX-2 and Ki-67 expression in HPV infected tissues play a critical role on ICC development and progression. (11)

ICC diagnosis

- From a histological point of view, amplification of the 3q chromosomal region can help to distinguish healthy tissues and CIN 2/3 lesions. (5)
- Moreover, combining the analysis of HPV E6/7 expression and hTERT mRNA levels could be a complementary method for distinguishing high grade premalignant lesions and ICC. (6)
- A new approach to ICC diagnosis has been developed discovering that circulating soluble neuropilin-1 could serve as new biomarker for this tumor. (13)

ICC prognosis

- Several variants of galectin have been analyzed as prognostic markers in ICC showing galectin 1 as an independent predictor of poor survival and galectin 9 as a marker of a trend toward improved survival. (14)
- Again, tumor-stroma ratio has failed to demonstrate a prognostic role in patients with cervical adenocarcinoma. (15)

ICC treatment outcome

- Whereas high osteopontin and low E-cadherin expression can be considered as indicators of radiation resistance and poor prognosis for cervical carcinoma. (16)
- miR-145a over-expression in these tumors enhances radiosensitivity indicating a novel radiosensitizing strategy. (17)
- On the other hand, NRF2 is associated with resistance to chemotherapy and its expression can be a marker of poor prognosis in patients with cervical cancer. (18)

Novel therapeutic approaches

- Apart from the aforementioned analysis of several mi-RNAs other pathways such as the CCR6-CCL20 pathway, CIP2A and PDGF beta have been shown as promising targets for the development of new treatments. (19-21)
- Finally, different somatic mutations have been described in ICC and cervical adenocarcinoma thus suggesting different routes of malignant development and indicating new options for the development of new treatments. (22)

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Cervical cancer pathology

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1	MiR-34a and mir-125b expression in HPV infection and cervical cancer development.	Ribeiro J et al.	Biomed Res Int	http://www.ncbi.nlm.nih.gov/pubmed/26180794	✓
2	Aberrant expression of microrna-26b and its prognostic potential in human cervical cancer.	Luo M et al.	Int J Clin Exp Pathol	http://www.ncbi.nlm.nih.gov/pubmed/26191262	
3	Expression quantitative trait loci for CARD8 contributes to risk of two infection-related cancers-hepatocellular carcinoma and cervical cancer.	Yin J et al.	PLoS One	http://www.ncbi.nlm.nih.gov/pubmed/26147888	✓
4	Expressions of survivin, P16(ink4a), COX-2, and ki-67 in cervical cancer progression reveal the potential clinical application.	Zhou WQ et al.	Eur J Gynaecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25872337	
5	Amplification of the 3q chromosomal region as a specific marker in cervical cancer.	Wright TC et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25659466	
6	Galectin-1, -3 and -9 expression and clinical significance in squamous cervical cancer.	Punt S et al.	PLoS One	http://www.ncbi.nlm.nih.gov/pubmed/26066796	✓
7	Prognostic evaluation of tumor-stroma ratio in patients with early stage cervical adenocarcinoma treated by surgery.	Pongsuvareeyakul T et al.	Asian Pac J Cancer Prev	http://www.ncbi.nlm.nih.gov/pubmed/26028100	
8	Functional role of NRF2 in cervical carcinogenesis.	Ma JQ et al.	PLoS One	http://www.ncbi.nlm.nih.gov/pubmed/26247201	
9	Precise classification of cervical carcinomas combined with somatic mutation profiling contributes to predicting disease outcome.	Spaans VM et al.	PLoS One	http://www.ncbi.nlm.nih.gov/pubmed/26197069	

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Surgical treatment of primary cervical cancer

Editor Matteo Morotti and Mandic Aljosa

Descriptive summary

Advances in surgical techniques along with multimodality treatment have expanded the range of options available for diagnosing and treating early-stage cervical cancer. In this summary we review the recent advances in cervical cancer surgery in terms of lymph node assessment (sentinel node), fertility sparing and radical surgery.

Recent data suggest that conservative approaches to lymph node assessment/dissection may reduce morbidity without affecting survi- val. Imboden et al. found in their retrospective study that the bilateral detection rate of sentinel lymphnodes using indocyanin green (ICG) was much higher than technetium and blue dye (95.5 % and 61%). This study suggests ICG SLN mapping in cervical cancer provides higher overall and bilateral detection rates than the current standard of care. Results from prospective studies (PIONIR, CRUK Oxford) are expected to address the role of ICG in gynaecological cancers. In terms of fertility surgery, Vieira et al. examined the safety and outcomes of minimally invasive (laparoscopic or robotic) surgery (MIS) versus abdominal radical trachelectomy (RT) in 100 patients. They found that RT via MIS resulted in less blood loss and a shorter hospital stay. Fertility rates appeared higher in patients undergoing abdominal RT, however, data was limited by a short follow-up time. Hauerberg et al. reviewed clinical and obstetrical outcomes of 120 patients who underwent vaginal RT from the Danish Gynecological Cancer Database. 113 patients (94.2%) had a tumour size less than 2 cm. Overall, six recurrences (5.1%) and 2 deaths (1.7%) occurred. 72 women (60.0%) desired to conceive and 55 women obtained a total of 77 pregnancies. This study confirms that vaginal RT is a safe procedure with good obstetrics outcome in carefully selected patients with lesions with a diameter of 2 cm or less.

Pareja et al. found in their review that the global pregnancy rate was 16.2%, 24% and 30.7% for abdominal RT, vaginal RT, and neoadjuvant (NACT) chemotherapy followed by surgery; respectively. The recurrence rate was 3.8%, 4.2%, 6%, 7.6% and 17% for abdominal RT (all sizes), vaginal RT (all sizes), abdominal RT (tumors >2cm), suggest that NACT followed by conization, and vaginal RT (tumors >2cm). These outcomes must be considered when offering a fertility sparing technique to patients with a tumour larger than 2cm.

Eleven cases of a more conservative approached (NACT followed by large cone resection in patients responding to treatment) were reviewed by Salihili et al. In 9 patients fertility sparing surgery could be performed (7 patients underwent conisation only and 2 patients conisation followed by hysterectomy after 2 and 3 years, respectively. Six of them (67%) got pregnant. None needed cerclage. This study su- ggest that NACT followed by conization might be a promising fertility sparing option in patients with cervical carcinoma stage IB1, but further studies are needed.

Regarding surgery, Gallotta et al. demonstrated in a phase II study that total laparoscopic radical surgery is feasible in patients with advanced cervical cancer receiving preoperative CT/RT, with only 21.4% grade 2 and 14.3% 3 complications.

Kohler et al demonstrated in a randomized clinical trial that surgical staging (pelvic and paraaortic lymphadenectomy) is feasible, safe and does not delay primary chemoradiotherapy in patients with locally advanced cervical cancer. Moreover, it led to upstaging in 40 of 121 (33%) patients, demonstrating that it might be a useful procedure to better tailor medical treatments in this subset of patients. Chiantera et al. described the laparoscopic technique and assessed the feasibility, efficacy and safety of the total mesometrial resection (TMMR) in a multi-institutional case-series of women with early cervical cancer FIGO IA2–IB1.

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Surgical treatment of primary cervical cancer

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1	A Comparison of Radiocolloid and Indocyanine Green Fluorescence Imaging, Sentinel Lymph Node Mapping in Patients with Cervical Cancer Undergoing Laparoscopic Surgery	Imboden S et al.	Ann Surg Onc	http://www.ncbi.nlm.nih.gov/pubmed/26122376	
2	Radical trachelectomy in early-stage cervical cancer: A comparison of laparotomy and minimally invasive surgery	Vieira MA et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26095894	
3	The potential for less radical surgery in women with stage IA2-IB1 cervical cancer.	Bai H et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26070225	
4	Neoadjuvant chemotherapy followed by large cone resection as fertility-sparing therapy in stage IB cervical cancer.	Salihi R et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26050921	
5	Vaginal Radical Trachelectomy for early stage cervical cancer. Results of the Danish National Single Center Strategy.	Hauerberg L et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26026821	
6	Immediate radical trachelectomy versus neoadjuvant chemotherapy followed by conservative surgery for patients with stage IB1 cervical cancer with tumors 2cm or larger: A literature review and analysis of oncological and obstetrical outcomes.	Pareja R et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25827293	
7	Laparoscopic Radical Hysterectomy After Concomitant Chemoradiation in Locally Advanced Cervical Cancer: A Prospective Phase II Study.	Gallotta V et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25929741	
8	Perioperative morbidity and rate of upstaging after laparoscopic staging for patients with locally advanced cervical cancer: results of a prospective randomized trial.	Köhler C et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25986030	
9	Primary surgery versus primary radiation therapy for FIGO stages I-II small cell carcinoma of the uterine cervix: A retrospective Taiwanese Gynecologic Oncology Group study.	Chen TC et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25797082	
10	Success Factors of Laparoscopic Nerve-sparing Radical Hysterectomy for Preserving Bladder Function in Patients with Cervical Cancer: A Protocol-Based Prospective Cohort Study.	Kim HS et al.	Ann Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25465377	
11	Laparoscopic radical hysterectomy in cervical cancer as „total mesometrial resection (L-TMMR)": A multicentric experience.	Chiantera V et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26166805	

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Medical treatment of primary and recurrent cervical cancer

- Editor Kristina Lindemann

- Descriptive summary

The articles selected for this update cover mainly two different aspects of current treatment strategies:

1. The treatment of recurrent or metastatic cervical cancer was studied in two recent randomized trials. Tewari et al have previously reported a significant increase in overall survival (OS) of women with metastatic/recurrent cervical cancer who were treated with bevacizumab in combination with chemotherapy. Pfaendler et al have now published a summary of this study but also a literature review of the available evidence for current treatment strategies in metastatic cervical cancer. Another important study stems from the Japanese group who has compared Cisplatin/Paclitaxel and Carboplatin/Paclitaxel. Carboplatin/Paclitaxel showed non-inferiority apart from patients who had not been treated with platinum-containing regimen before. The results have been published in J Clin Oncol. One may still argue that also dose-dense regimen may be an option in these patients and Vergote et al report toxicity and safety data from a small Phase II study where they included different gyne cancers.
2. Another area of discussion is the use of neoadjuvant chemotherapy prior to fertility sparing surgery in early cervical cancer. This updates includes a very comprehensive review of M. Plante and another by Robova et al. Both reviews focus on oncological as well as obstetrical outcomes which are equally important when treatment strategies are discussed. Both authors conclude that the current evidence for offering NACT followed by fertility-sparing surgery to patients with bulky Stage IB1 is based on currently sparse data available in the literature. The reviews may help clinical decision making and to inform patients. There are also efforts to conduct a clinical trial addressing the management of bulky IB1 cervical cancer in young women wishing to preserve fertility.

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Medical treatment of primary and recurrent cervical cancer

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1	Long-Term Clinical Benefits of Neoadjuvant Chemotherapy in Women With Locally Advanced Cervical Cancer: Validity of Pathological Response as Surrogate Endpoint of Survival.	Buda A et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26222484	
2	Changing paradigms in the systemic treatment of advanced cervical cancer.	Pfaendler KS et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26212178	
3	Platinum sensitivity and non-cross-resistance of cisplatin analogue with cisplatin in recurrent cervical cancer.	Takekuma M et al.	J Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26197856	✓
4	Clinical Features of Neuroendocrine Carcinoma of the Uterine Cervix: A Single-Institution Retrospective Review.	Nagao S et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26166556	
5	Optimal management of cervical cancer in HIV-positive patients: a systematic review.	Ntekim A et al.	Cancer Med	http://www.ncbi.nlm.nih.gov/pubmed/26136407	✓
6	Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: A study in 108 patients by the Belgian Gynaecological Oncology Group	Vergote et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26049123	
7	Review of neoadjuvant chemotherapy and trachelectomy: which cervical cancer patients would be suitable for neoadjuvant chemotherapy followed by fertility-sparing surgery?	Robova et al.	Curr Oncol Rep	http://www.ncbi.nlm.nih.gov/pubmed/25893880	
8	Bulky Early-Stage Cervical Cancer (2-4 cm Lesions): Upfront Radical Trachelectomy or Neoadjuvant Chemotherapy Followed by Fertility-Preserving Surgery: Which Is the Best Option?	Plante M	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25764351	
9	Nomograms Predicting Progression-Free Survival, Overall Survival, and Pelvic Recurrence in Locally Advanced Cervical Cancer Developed From an Analysis of Identifiable Prognostic Factors in Patients From NRG Oncology/Gynecologic Oncology Group Randomized Trials of Chemoradiotherapy	Rose PG et al.	J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25764351	
10	Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505.	Kitagawa R	J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25732161	
11	A randomized trial comparing concurrent chemoradiotherapy with single-agent cisplatin versus cisplatin plus gemcitabine in patients with advanced cervical cancer: An Asian Gynecologic Oncology Group study.	Wang CC et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25827291	

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Preinvasive disease of vulva and vagina (etiology, diagnosis, management, follow-up)

Editor Kamil Zalewski

Descriptive summary

In the period covered by the review, a couple of studies evaluating different treatment modalities in vulvar and vaginal precancerous lesions were covered. Ramirez et al. evaluated in his prospective study the efficacy of laser vaporisation surgical technique in patients with: vulvar intraepithelial neoplasia (VIN) 2/3, vaginal intraepithelial neoplasia (VaIN), or condylomata acuminata, Piovano E et al. CO2 laser for the treatment of VaIN, Ko Yi et al. focused on the effect of oraly administrated poly-gamma-glutamic acid on the treatment of VaIN and Choi MC et al. measured responses to photodynamic therapy (PDT) and its long-term efficacy in women with VIN, VAIN and Paget's disease. Although all authors reported satisfactory results, those studies are limited by their observational character, low number of patients, lack of control group and used inconsistent terminology of the intraepithelial leasions of the lower genital tract.

Second aspect which found its place in publications was the potential implication of a new nanovalent HPV vaccine on occurrence of HPV-related cancers. Mona Saraiya and colleagues showed based on data from the United States that HVP DNA is detected in 68.8% of vulvar and 75.0% of vaginal cancers. It is estimated that nanovalent HPV vaccine will add a small additional reduction to the currently avalaible vaccine and may prevent an additional 14.2% to 18.3% (respectively) of lower genital tract cancers. Based on data from 6 multicenter retrospective studies, the European study of Riethmuller D al. studied the absolute additional impact (% of additional prevented cases) estimates that nanovalent vaccine might prevent from 12.3% to 22.7% new cases of vulvar cancers.

Women with vulvar lichen sclerosus (VLS) are at increased risk of developing squamous cell cancer (SCC) of the vulva. Lee A et al. present the results of the largest prospective clinical cohort study to date including 507 women with VLS. The authors present evidence that in contrast to patients with good compliance with topical corticosteroid (TCS) treatment those with poor compliance are predisposed to the development of SCC and VIN (0% vs 4,7%, p<0,001) and scarring (3,4% vs 40%, p<0,001). They propose that initial treatment regimens should be selected using a variety of corticosteroid potencies based on the severity of signs at presentation. They also propose that maintenance treatment for VLS should be the norm, increasing or decreasing the potency of treatment as necessary. The authors recommend life-long specialist follow-up.

During the XXIII World Congress of the International Society for the Study of Vulvovaginal Diseases (NYC, July 2015) its Terminology Committee presented a new 3-tier classification of vulvar intraepithelial lesions where they were divited into 1. Low grade squamous intraepithelial lesion (Flat condyloma or HPV effect), 2. High grade squamous intraepithelial lesion (VIN usual type) and 3. Intraepithelial neoplasia, differentiated. This is an interesting upgrade of existing WHO classification (taking into account clinical aspect of the disease) and addendum of LAST consensus that doesn't consider non-HPV-related leasions.

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Laser vaporization in vulvar intraepithelial neoplasia (vin), vaginal intraepithelial neoplasia (vain) and condylomata acuminata: igcs-0093 vulvar and vaginal cancer.	Ramirez S et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25955950	
2	Efficacy of Poly-Gamma-Glutamic Acid in Women with High-Risk Human Papillomavirus-Positive Vaginal Intraepithelial Neoplasia: an Observational Pilot Study.	Koo YJ et al.	J Microbiol Biotechnol	http://www.ncbi.nlm.nih.gov/pubmed/25907060	
3	Photodynamic therapy for premalignant lesions of the vulva and vagina: A long-term follow-up study.	Choi MC et al.	Lasers Surg Med	http://www.ncbi.nlm.nih.gov/pubmed/26174756	
4	CO2 laser vaporization for the treatment of vaginal intraepithelial neoplasia: Effectiveness and predictive factors for recurrence	Vapiano E et al.	Europ J Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26390687	
5	US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines.	Saraiya M et al.	J Natl Cancer Inst	http://www.ncbi.nlm.nih.gov/pubmed/25925419	
6	Potential impact of a nonavalent HPV vaccine on the occurrence of HPV-related diseases in France.	Riethmuller D et al.	BMC Public Health	http://www.ncbi.nlm.nih.gov/pubmed/25934423	
7	Long-term Management of Adult Vulvar Lichen Sclerosus: A Prospective Cohort Study of 507 Women.	Lee A et al.	JAMA Dermatol	www.ncbi.nlm.nih.gov/pubmed/26070005	
8	New ISSVD Terminologies: VIN – Presentation of the Proposal and Discussion	Bornstein J et al.	The XXIII World Congress of the International Society for the Study of Vulvovaginal Diseases (ISSVD)	Oral report. Data not published.	

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Pathology of epithelial and non-epithelial malignant tumours of vagina and vulva

Editor Kamil Zalewski

Descriptive summary

Malignant tumors of the vulva and vagina account for about 6% of cancers of the female genital tract. Due to their rarity, little is known about the genetic aberrations carried by these tumors. In the period covered by the review a couple of studies evaluating expressions of different genes and their impact on clinical presentation were published. Agostini A. et al. reported a detailed study of 25 vulva tumors [22 squamous cell carcinomas (SCC), 2 malignant melanomas (MM), 1 atypical squamous cell hyperplasia (AH)] analyzed for expression of the high-mobility group AT-hook family member genes HMGA2 and HMGA1, for mutations in the IDH1, IDH2 and TERT genes, and for methylation of the MGMT promoter. Their study suggests that HMGA2 and TERT may be of importance in the genesis and/or the progression of tumors of the vulva. Vulvar MM was also explored by Rouzbahman M et al. who reported that C-KIT and NRAS mutations exists with higher frequency in vulvar MM than in those of other sites. These mutations are suggested to be potential therapeutic targets in patients harboring them. BRAF mutations were infrequent (most commonly reported mutations in other malignant melanomas).

Although Dong F et al. reviewed the morphology, immunophenotype, and selected molecular features of a consecutive series of 97 patients with vulvar SCC with a detailed clinical follow-up, the relationship between clinical, morphologic, immunohistochemical, and molecular features and patient outcome was firm. These data demonstrate that the utility of biological markers of vulvar SCCs and patient outcome is still controversial. Wang Z and colleagues searched for abnormal expression of cyclin B1 and CDK1 that so far have been reported in several types of tumors, but no previous study has investigated them in vulvar cancer. That study proved them to have an associations with malignancy and aggressive phenotypes and to be an independent prognostic factor. Their expression may be involved in tumorigenesis and progression of SCC.

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	HMGA2 expression pattern and TERT mutations in tumors of the vulva.	Agostini A et al.	Oncol Rep	http://www.ncbi.nlm.nih.gov/pubmed/25823555	
2	Squamous Cell Carcinoma of the Vulva: A Subclassification of 97 Cases by Clinicopathologic, Immunohistochemical, and Molecular Features (p16, p53, and EGFR).	Dong F et al.	Am J Surg Pathol	http://www.ncbi.nlm.nih.gov/pubmed/26171917	
3	Malignant Melanoma of Vulva and Vagina: A Histomorphological Review and Mutation Analysis-A Single-Center Study.	Rouzbahman M et al.	J Low Genit Tract Dis	http://www.ncbi.nlm.nih.gov/pubmed/26225944	✓
4	Expression of CDK1 Tyr15, pCDK1 Thr161, Cyclin B1 (total) and pCyclin B1 Ser126 in vulvar squamous cell carcinoma and their relations with clinicopatological features and prognosis.	Wang Z et al.	PLoS One	http://www.ncbi.nlm.nih.gov/pubmed/25849598	

Treatment of recurrent vulvar cancer

Editor M. de los Reyes Oliver

Descriptive summary

1. Squamous cell carcinoma (SCC):

The rate of SCC recurrence ranges from 20% to 50% . There has been little in the literature regarding treatment for recurrent vulvar cancer. Reports often are based on a limited number of cases observed over long periods of time with nonuniform criteria.

Soderini A. [1] have carried out a retrospective study including 105 patients with primary vulvar SCC traetd with radical surgery. After multivariate analysis, tumor size and stage were the only independent prognostic factors for DFS and OS. Survival drops remarkably in tumors ≥ 6 cm.

1.1. Treatment of local/nodal recurrences:

1.1.1. Surgical treatment: No randomized prospective studies are reported. Previous retrospective studies suggest that wide radical local excision, ipsilateral lymphadenectomy, and pelvic exenteration (PE) can be performed.

Moreno-Palacios et al. [2] retrospectively analyzed 10 patients who underwent PE because of recurrent gynecologic cancer, including one vulvar cancer. Their postoperative complications were related to the urinary diversion (50%), reconstructive technique (30%) and systemic/pelvic infections (20%). 70% of the patients recurred, with a median time to recurrence of 12 months. Regarding the case of vulvar cancer, 7 months after PE, the patient experimented a second recurrence and died.

Zang et al. [3] retrospectively reviewed 24 patients who received anterolateral thigh flap for vulvar reconstruction, 20 of them due to a recurrence. They studied the rate of complications (mayor complications: 20.8% and minor complications: 12.5%) and it's impact on quality of life. 58.3% patients recurred with a median interval of 5 months. OS was 56.4%. They concluded that it might be considered as an option for reconstructing vulvar defects.

1.1.2. Systemic treatment: Manher et al. [4] have published an exhaustive review about systemic treatment and emerging strategies for vulvar cancer. No large prospective trials are available for palliative treatment of patients with metastatic or extensive locally recurrent disease. The use of radiotherapy combining 5-fluorouracil with cisplatin and mitomycin-C and/or Bleomycin has given promising results. Overall response rates differ quite extensively among the studies. The importance of postoperative radiation after residual microscopic disease remains to be elucidated. [4]

1.1.3. Radiotherapy: Amsbaugh et al. [5] retrospectively reviewed their results in 21 patients with recurrent gynecological cancers (3 recurrent vulvar cancers) treated with computed tomography planned interstitial brachytherapy. They described a rate of ≥grade 3 vaginal, urinary, and rectal toxicity of 28.5%, 9.5%, and 19%. They emphasized the tumor size as negative prognostic factor.

1.2. Treatment of metastatic disease(mayor complications: 20.8% a: No large prospective trials are available. Treatment should be individualized [4].

1.3. Emerging strategies [4]: Targeted therapies might serve as an alternative therapeutic approach beyond chemotherapy in metastatic and/or inoperable vulvar carcinoma.

1.3.1 Increased epidermal growth factor receptor (EGFR) expression has been observed in 40–67% of vulvar carcinomas. Controlled clinical phase II trial with Erlotinib (EGFR inhibitor) with 41 patients with locally advanced, primary, recurrent or metastatic SCC observed an overall clinical benefit rate of 67.5%.

1.3.2. Vascular endotelial growth factor (VEGF) overexpression has been associated with tumor progression and poor prognosis. It has been recently reported that the combination of bevacizumab and chemotherapy improves OS.

2. No SSC vulvar cancer: Chokoeva et al. [6] performed a review concerning different subtypes of vulvar cancer and their clinical characteristics and management.

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Treatment of recurrent vulvar cancer

- Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Prognostic significance of tumor size in squamous cell carcinoma of the vulva: igcs-0107 vulvar and vaginal cancer	Soderini A	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25955951	
2	Pelvic Exenteration in Gynecologic Cancer: La Paz University Hospital Experience	Moreno-Palacios E et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25853383	
3	Outcome of vulvar reconstruction by anterolateral thigh flap in patients with advanced and recurrent vulvarmalignancy.	Zang W et al.	J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25974742	
4	Systemic treatment of vulvar cancer	Mahner S et al.	Expert Rev Anticancer	http://www.ncbi.nlm.nih.gov/pubmed/25997120	
5	Computed tomography planned interstitial brachytherapy for recurrent gynecologic cancer.	Amsbaugh MJ et al.	Brachytherapy	http://www.ncbi.nlm.nih.gov/pubmed/26087868	
6	Vulvar cancer: a review for dermatologists.	Chokoeva AA et al.	Wien Med Wochenschr	http://www.ncbi.nlm.nih.gov/pubmed/25930015	

Minimal Invasive Surgery in Gynaecological Cancer (laparoscopic, robotics)

Editor Marc Barahona Orpinell

Descriptive summary

Comparing 2 surveys (conducted in 2007 and 2012) to evaluate the role of minimally invasive surgery (MIS) in gynaecologic oncology fellowship, Ring KL et al. conclude that fellowship programs should develop a systematic approach to training in MIS and in individual MIS platforms as they become more prevalent. Fellowship programs should also develop and apply an objective assessment of minimum proficiency in MIS to ensure that programs are adequately preparing trainees.

The learning curve of robotic-assisted laparoscopic surgery appears to be short.

Cervical cancer: Laparoscopic staging for patients with locally advanced cervical cancer (LACC) led to upstaging in 40 of 121 (33%), is safe and does not delay primary combined chemoradiation (CT/RT) in a randomized study. Robotic preperitoneal para-aortic lymphadenectomy for staging of local advanced cervical cancer is feasible and safe.

Comparing approaches for radical trachelectomy (RT), minimal invasive results in less blood loss and a shorter hospital stay. Laparoscopic radical histerectomy (RH) reduced blood loss compared with vaginal assisted RH, and could be an alternative option for patients with large tumours. Fertility rates appear higher in patients undergoing open radical trachelectomy.

In a survey of radical trachelectomy (RT) and conservative surgery in patients with early-stage cervical cancer, significant proportion of all respondents believe that less radical surgery may be a consideration for patients with low-risk early-stage cervical cancer.

Robotic radical histerectomy (RRH) may be superior to abdominal radical hysterectomy with lower blood loss, shorter hospital stay, less febrile morbidity and wound-related complications. RRH and laparoscopic radical histerectomy appear equivalent in intraoperative and short-term postoperative outcomes.

In patients with LACC who has received preoperative radical CT/RT, total laparoscopic radical surgery, within 6 to 8 weeks after CT/RT, is feasible resulting perioperative outcomes comparable to those registered in early-stage disease.

Sarcomas: Only anaemia and myoma size (>7 cm) may be associated with occult leiomyosarcoma. However, these criteria are not sufficiently discriminating to allow for pre-operative identification of patients with uterine sarcoma. Future large multicenter studies are necessary to detect uterine leiomyosarcoma before surgery.

Ovarian cancer: Staging laparoscopy is confirmed as an accurate tool in the prediction of complete R0 ovarian surgery in women with advanced epithelian epithelial ovarian cancer, in order to avoid laparotomies with suboptimal debulking surgery.

Endometrial cancer: Minimally invasive approach has a number of established advantages over laparotomy for endometrial cancer staging, especially in obese patients (lower complication rate, shorter hospital stay, and higher likelihood of receiving lymphadenectomy). Comparing robotic vs laparoscopic endometrial cancer surgery, despite more comorbidities in the robotic group, compared with laparoscopy, the former have shorter hospital admissions, a greater rate of lymph node dissection and similar postoperative morbidity and mortality, albeit at greater total cost. It can also be done with the same ports for pelvic and paraortic lymphadenectomy. There is no difference in postoperative pain scores and narcotic use in robotic-assisted versus laparoscopic approach. In terms of oncological outcomes the three groups (abdominal, laparoscopy and robotics) are equivalent. Despite these results, only 38% of endometrial cancers, are treated with minimal invasive surgery.

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Minimal Invasive Surgery in Gynaecological Cancer (laparoscopic, robotics)

- Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Impact of obesity on surgical treatment for endometrial cancer: a multi-center study comparing laparoscopy vs. Open surgery, with propensity-matched analysis.	Uccella S et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26282516	
2	Extraperitoneal Para-aortic Lymphadenectomy by Robot-Assisted Laparoscopy in Gynecologic Oncology: Preliminary Experience and Advantages and Limitations.	Narducci F el al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26270116	
3	Risk Factors for Occult Uterine Sarcoma among Women undergoing Minimally Invasive Gynecologic Surgery.	Oduyebo T et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26253281	
4	Feasibility and efficacy of laparoscopic restaging surgery for women with unexpected ovarian malignancy.	Bae J et al.	Eur J Obstet Gynecol Reprod Biol	http://www.ncbi.nlm.nih.gov/pubmed/26232726	
5	Robotic high para-aortic lymph node dissection with high port placement using same port for pelvic surgery in gynecologic cancer patients.	Kim TL et al.	J Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=26197858	✓
6	Definition of a dynamic laparoscopic model for the prediction of incomplete cytoreduction in advanced epithelial ovarian cancer: Proof of a concept.	Petrillo M et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=26196319	
7	Laparoscopic and robot-assisted hysterectomy for uterine cancer: a comparison of costs and complications.	Zakhari A et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/?term=26188114	
8	Minimally invasive surgery for endometrial cancer	Rabinovich A	Curr Opin Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/?term=26134173	
9	Radical trachelectomy in early-stage cervical cancer: A comparison of laparotomy and minimally invasive surgery.	Vieira MA et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=26095894%5D	
10	Make New Friends But Keep the Old: Minimally Invasive Surgery Training in Gynecologic Oncology Fellowship Programs.	Ring KL et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/?term=26067857	
11	Robotic radical hysterectomy in early stage cervical cancer: A systematic review and meta-analysis.	Shazly SA et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=26056752	
12	Surgical and oncological outcome of robotic surgery compared to laparoscopic and abdominal surgery in the management of endometrial cancer.	Corrado G et al.	Eur J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=26002986	
13	Perioperative morbidity and rate of upstaging after laparoscopic staging for patients with locally advanced cervical cancer: results of a prospective randomized trial	Köhler C et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25986030	
14	Dramatically reduced incidence of vaginal cuff dehiscence in gynecologic patients undergoing endoscopic closure with barbed sutures: A retrospective cohort study	Rettenmaier MA	Int J Surg	http://www.ncbi.nlm.nih.gov/pubmed/?term=25980394	
15	Postoperative Pain Scores and Narcotic Use in Robotic-assisted Versus Laparoscopic Hysterectomy for Endometrial Cancer Staging.	Turner TB el al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25967934	
16	The centralization of robotic surgery in high-volume centers for endometrial cancer patients--a study of 6560 cases in the U.S.	Chan JK et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25933680	
17	Laparoscopic Radical Hysterectomy After Concomitant Chemoradiation in Locally Advanced Cervical Cancer: A Prospective Phase II Study.	Gallotta V et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25929741	
18	Role of Minimally Invasive Surgery in Gynecologic Oncology: An Updated Survey of Members of the Society of Gynecologic Oncology.	Conrad LB et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/?term=25860841	
19	New approach of learning curve for robotic-assisted gynecologic oncology surgery	Yaribakht S et al.	Gynecol Obstet Fertil	http://www.ncbi.nlm.nih.gov/pubmed/?term=25813433	
20	Outcome of robotic surgery for endometrial cancer as a function of patient age.	Zeng XZ et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/?term=25723778	
21	Implementing robotic surgery to gynecologic oncology: the first 300 operations performed at a tertiary hospital.	Mäenpää M et al.	Acta Obstet Gynecol Scand	http://www.ncbi.nlm.nih.gov/pubmed/?term=25721212	

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Minimal Invasive Surgery in Gynaecological Cancer (laparoscopic, robotics)

- Relevant articles retrieved May-Aug 2015 (cont.)

No	Title	Authors	Journal	Link to abstract	Available as full freetext
22	Step-by-step Type C Laparoscopic Radical Hysterectomy With Nerve-sparing Approach.	Centini G et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25708951	
23	Radical Trachelectomy for Early-Stage Cervical Cancer: A Survey of the Society of Gynecologic Oncology and Gynecologic Oncology Fellows-in--Training.	Churchill SJ et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/?term=25675042	
24	Obesity and perioperative pulmonary complications in robotic gynecologic surgery.	Wysham WZ et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25637843	
25	Uterine sarcomas and parasitic myomas after laparoscopic hysterectomy with power morcellation.	Tan-Kim J et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25499259	
26	Outcomes of abdominal radical trachelectomy: results of a multicenter prospective cohort study in a Tohoku Gynecologic Cancer Unit.	Tokunaga H et al.	Int J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25391812	
27	Perioperative Outcomes of Radical Trachelectomy in Early-Stage Cervical Cancer: Vaginal Versus Laparoscopic Approaches	Yoon A et al.	Int J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=25675039	

Prevention and management of complications in surgical treatment of gyneacological malignancies (i.e. lymphocele, urological, wound, etc.)

Editor Elisa Piovano

Descriptive summary

Relevant articles focus on different and very interesting topics. Starting with ovarian cancer (OC), Ataseven set up a retrospective study on 604 patients who underwent primary cytoreductive surgery. Preoperative hypoalbuminemia is a negative prognostic factor and a predictive factor for severe post-operative complications.

The role of preoperative albumin level is confirmed by Patankar who extracts data from the "National Surgical Quality Improvement Program" (NSQIP) database. 2870 women surgically treated for OC are included. Preoperative serum albumin level and the number of extended cytoreductive procedures performed are the factors most consistently associated with morbidity.

Benedetti Panici studied 121 women retrospectively who were treated for advanced OC. The study confirms diaphragmatic resection , hepatic resection, pancreatectomy and biliary surgery as independent predictors of severe (G3-G4) complications.

Ramzan conducted a retrospective study to examine intra- and postoperative complication rates for surgical staging combined with panniculectomy for endometrial cancer in obese patients. Although panniculectomy-combined surgery is associated with an increased risk of postoperative complications, the author highlights that the majority of patients recovers uneventfully, making this approach feasible especially for superobese patients.

Another study on obese patients is reported by Wysham, performing a retrospective chart review on 1032 obese patients submitted to robo- tic gynecological surgery. The primary outcome was pulmonary compli- cations (only 3%), the secondary outcome is all-cause complications (14%). The author concludeed that the vast majority of obese patients can successfully tolerate robotic gynecological surgery, the degree of obesity not predicting subsequent complications.

Garabedian studied retrospectively the morbidity of laparoscopic radical hysterectomy in patients with early-stage cervical cancer. Two factors appear as independent risk factors for perioperative and/or postoperative complications: the tumor size and operative time.

A very interesting retrospective study comes from Chapman who suggests that postoperative oral immune modulating diets are associated with fewer wound complications in patients undergoing laparotomy for gynecologic malignancy.

In his retrospective study Deura highlight 2 risk factors for lower limb lymphedema after gynecologic cancer surgery: adjuvant concurrent chemoradiotherapy and age ≥ 55 years.

Zikan analyzes lymphoceles in a prospective study on 800 patients undergoing pelvic or combined pelvic and paraaortic lymphadenectomy for gynecological cancer. Lymphadenectomy in OC, a higher number of lymph nodes obtained (>27), and radical hysterectomy in cervical cancer are independent risk factors for symptomatic lymphoceles.

Swenson finds that risk factors for venous thromboembolism (VTE) after hysterectomy are: BMI 35 or greater, abdominal hysterectomy, increasing surgical time and cancer as the indication for surgery.

Corr suggests to use a single-dose unfractionated heparin on the operating room table prior to the time of anesthesia induction combined with two weeks of thromboprophylaxis in gynecologic cancer patients to reduce the risk of VTE.

Tan-Kim describes the incidence and risk factors for uterine sarcomas and parasitic myomas at the time of power morcellation. In this study 941 out of 3523 patients underwent power morcellation at the time of hysterectomy; 1.1% were subsequently diagnosed subsequently with uterine sarcomas or parasitic myomas; uterine sarcomas were not associated significantly with any preoperative factors.

Akdemir focuses on an interesting innovative technique for enclosed morcellation using a surgical glove in a case series of 30 women.

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Prevention and management of complications in surgical treatment of gyneacological malignancies (ie lymphocele, urological, wound, etc.)

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Incidence and risk factors for lower limb lymphedema after gynecologic cancer surgery with initiation of periodic complex decongestive physiotherapy	Deura I et al.	Int J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/24993674	
2	Uterine sarcomas and parasitic myomas after laparoscopic hysterectomy with power morcellation.	Tan-Kim J et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25499259	✓
3	Obesity and perioperative pulmonary complications in robotic gynecologic surgery	Wysham WZ et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25637843	✓
4	Minimally invasive surgical management of early-stage cervical cancer: an analysis of the risk factors of surgical complications and of oncologic outcomes.	Garabedian C et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25647258	✓
5	A prospective study examining the incidence of asymptomatic and symptomatic lymphoceles following lymphadenectomy in patients with gynecological cancer.	Zikan M et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25720294	
6	Predictors of postoperative morbidity after cytoreduction for advanced ovarian cancer: Analysis and management of complications in upper abdominal surgery.	Benedetti Panici P et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25824857	
7	Post-operative enteral immunonutrition for gynecologic oncology patients undergoing laparotomy decreases wound complications.	Chapman JS et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25888979	
8	Risk factors for venous thromboembolism after hysterectomy.	Swenson CW et al.	Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25932841	
9	Innovative technique for enclosed morcellation using a surgical glove.	Akdemir A et al.	Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25932842	
10	Risk stratification and outcomes of women undergoing surgery for ovarian cancer.	Patankar S et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25976399	
11	Pre-operative serum albumin is associated with post-operative complication rate and overall survival in patients with epithelial ovarian cancer undergoing cytoreductive surgery.	Ataseven B et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26163893	
12	Effectiveness and safety of expanded perioperative thromboprophylaxis in complex gynecologic surgery.	Corr BR et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26186912	
13	Relative Morbidity and Mortality of Panniculectomy-Combined Surgical Staging in Endometrial Cancer.	Ramzan AA et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26270120	✓

Sentinel node mapping in gynaecological malignancies

Editor Anton Ilin

Descriptive summary

In 1977 Cabanas published first results of sentinel node evaluation of patients with penile cancer. In gyneoncology first publication belong to Levenback et al. Author used blue dye on 9 vulvar cancer patients.

Nowadays sentinel nodes mapping depends on the methodology of the study and surgical approach. More often following markers are used: blue dye, radiocolloid (technetium-99m) or fluorescent dye (indocyanine green).

Endometrial cancer

Frequency of lymph node metastasis lesions for local uterine cancer ranges from 12.4% to 22%. It depends on the stage of disease, histological type and grade.

According to review of Plante et al. combination of blue dye and radiocolloid showed better results then isolated use of these markers. Sensitivity of combined method ranges from 81% to 92% and frequency of false positives does not exceed 11-16%. [1].

For fluorescent dye sensitivity reaches 94.1% and specificity about 100% [2].

The frequency of sentinel nodes detection also depends on the way of mapping. Rossi et al. in their meta-analysis obtained the following results: 84,9%, 73,9%, 69,7%, 86,1% and 50% for cervical, sub-endometrial, subserosal, cervical/subserosal, and sub-endometrial/subserosal injections.

Cervical cancer

Frequency of lymph node metastasic lesions is 0-4.8% for IA stage, 17% for IB, 12-27% for IIA and 25-30% for IIB. That means that in IB stage in more than 80% of cases we can avoid lymphadenectomy, as well as possible complications.

Altgassen C. et al. retrospectively analyzed over 500 cases of signal lymph nodes mapping. The sensitivity was below expected – 77%. In similar studies of Lecuru et al. (139 cases), Cormier et al. (122 cases), and Cibula et al. (645 cases) the average sensitivity was 87.5-92%, and specificity 96.8-98.2%.

Combination of preoperative lymphoscintigraphy with SPECT/CT results in superior overall SLN detection in comparison with planar lymphoscintigraphy [3].

The most commonly proposed technique consists of a two- or four-point peritumoural injection closest to the cervix-tumor interface with a 25-G spinal needle.

By data of Ayhan et al. separate use of blue due, radiocolloid or combination of the markers did not show significant difference in sentinel node detection.

Darin M.C. et al. reviewed 825 cases of indocyanine green / isosulfan blue administration for endometrial (701 pt.) and cervical cancer (124 pt.). The majority of patients (97.2%) had a cervical injection. Sentinel node detection rate for cervical injection ranged from 83–100%.

Ovarian cancer

More often regional lymph nodes are affected in serous and non-differentiated ovarian cancer (69% and 50%, respectively); more rare in mucinous (7%) and clear-cell (14%) ovarian cancer. For T1 frequency of regional lymph nodes involvement is 10%, for 2-27%, for 3-62%. Currently there are only few publications dedicated to sentinel lymph nodes mapping in ovarian cancer.

Negishi et al. used activated charcoal solution, which was injected into ovarian cortex during laparotomy. Accumulation of the marker in lymph nodes was detected in 100% (11 patients). In 2011 Nyberg et al. published the results of study of sentinel lymph nodes in 16 patients. Technetium and blue dye were injected directly in right and left ovary during laparotomy. One to three sentinel nodes per patient were identified in all but 1 patient (15 of 16,94%).

In 2014 Kleppe et al. demonstrated the efficiency of injecting of radioisotope drug and blue dye into the ligamentum ovarii proprium and the ligamentum infundibulo-pelvicum. Accumulation of markers was detected in 100% (67% - paracaval lymph nodes, 9% - pelvic lymph nodes and 24% - pelvic and paracaval/paraaortic lymph nodes).

Vulvar/vaginal cancer

Inguinofemoral lymph node dissection in patients with invasive vulvar cancer is related to increased risks of postoperative complications, such as wound breakdown, lymphorrhea, lymphostasis, which significantly complicate postoperative period. Determination of sentinel nodes with subsequent selective lymphadenectomy significantly decreases the risk of this complications.

More often for mapping procedure are reported technecium-99, blue dye or combination of these markers. Meads et al. showed next detection rates: 94.0% for technecium-99, 68.7% for blue stain and 97.7% for combined method. Schaafsmaet al. also published data about efficiency of fluorescent dye (indocyanine green). Detection rate was comparable to the one for technecium-99. Verbeek et al. reported about 100% intraoperative node detection using combination indocyanine green–technetium-99m. Method also allows the administration of a 5-times lower injected dose of ICG (compared with ICG and ICG absorbed to human serum albumin) and can be injected up to 20 hours before surgery.

One of the major studies is GROINSS-V, which included 403 patients with T1-T2. Results were published by Van der Zee et al. At the median follow-up period of 35 weeks 6 groin recurrences (2,3%) were detected. It shows the high sensitivity of the method. However there is certain probability to get a false negative result. In study GOG-173, which included 453 patients, frequency of false negative results was 4.3%. It means that in 4.3% metastases in lymph nodes remains unrecognized.

Conclusions

Detection of sentinel lymph nodes is a prospective direction for vulvar, endometrial and cervical cancer; however the scope of use of this method in ovarian cancer requires further studies.

Sentinel node mapping in gynaecological malignancies

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial cancer. A pilot study and review of the literature	Plante M et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25771495	
2	Sentinel node detection in endometrial cancer using indocyanine green and fluorescence imaging—a case report	Anupama R et al.	Ecancermedicalscience	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494816/	
3	99mTc SPECT/CT Versus Planar Lymphoscintigraphy for Preoperative Sentinel Lymph Node Detection in Cervical Cancer: A Systematic Review and Metaanalysis.	Hoogendam JP et al.	J Nucl Med	http://www.ncbi.nlm.nih.gov/pubmed/25858041	
4	Role of indocyanine green (ICG) in sentinel node mapping in gynecologic cancer: a time for a new standart of care?: IGCS 0083 Imaging / Staging	Darin MC et al.	Int J Gynecol Cancer	http://journals.lww.com/ijgc/Fulltext/2015/05001/ROLE_OF_INDOCYANINE_GREEN__ICG__IN_SENTINEL_NODE.34.aspx?sessionEnd=true&sessionEnd=true	✓
5	Sentinel Lymph Node Biopsy in Vulvar Cancer Using Combined Radioactive and Fluorescence Guidance	Verbeek F et al.	Int J Gynecol Cancer	http://journals.lww.com/ijgc/Fulltext/2015/07000/Sentinel_Lymph_Node_Biopsy_in_Vulvar_Cancer_Using.21.aspx?sessionEnd=true	✓
6	The Incidence and Clinical Significance of the Micrometastases in the Sentinel Lymph Nodes During Surgical Staging for Early Endometrial Cancer	Ferraioli D et al.	Int J Gynecol Cancer	http://journals.lww.com/ijgc/Fulltext/2015/05000/The_Incidence_and_Clinical_Significance_of_the.20.aspx	✓
7	Sentinel Lymph Node Biopsy in Endometrial Cancer—Comparison of 2 Detection Methods.	Sawicki S et al.	Int J Gynecol Cancer	http://journals.lww.com/ijgc/Fulltext/2015/07000/Sentinel_Lymph_Node_Biopsy_in_Endometrial.15.aspx?sessionEnd=true	✓
8	Sentinel node mapping with radiotracer alone in vulvar cancer: a five year single-centre experience and literature review.	Bogliolo S at al.	Eur J Gynaecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25872327	
9	Sentinel node biopsy in vulvar cancer: Implications for staging	Oonk MH et al.	Best Pract Res Clin Obstet Gynaecol	http://www.ncbi.nlm.nih.gov/pubmed/25962357	

Fertility sparing treatment in gynecological malignancies

- Editor Dimitris Papatheodorou

- Descriptive summary

Fertility sparing treatment in gynecological cancer mainly applies to early cervical, ovarian and endometrial cancer. This literature search rated 15 articles as relevant.

The most important update comes from the ESGO Task force for fertility preservation in young endometrial cancer patients. This article is a list of clinical recommendations for the management of endometrial cancer in young patients based on the most recent evidence from the literature. Furthermore two publications from the Japan Clinical Oncology Group focus on the selection of fertility sparing surgery for patients with epithelial ovarian cancer (non-randomized confirmatory study) and a review on the minimization of curative surgery for the treatment of early cervical cancer. An interesting literature review was published regarding radical trachelectomy versus neo-adjuvant chemotherapy followed by conservative surgery for patients with large IB1 tumors (>2cm). Finally the list includes 11 additional articles (cohort studies and reviews) covering several aspects related to fertility sparing surgery such as atypical polypoid adenomyomas, endometrial complex atypical hyperplasia and ovarian germ cell tumors in pediatric and adolescent girls.

- Relevant articles retrieved May-Aug 2015

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Fertility sparing treatment in gynecological malignancies

- Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Reproductive outcomes after hydatiform mole and gestational trophoblastic neoplasia	Gadducci A at al.	Gynecol Endocrinol	http://www.ncbi.nlm.nih.gov/pubmed/26288335	
2	Long-term outcomes of fertility sparing treatment of atypical polypoid adenomyoma with medroxyprogesterone acetate	Nomura H at al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/26209972	
3	Fertility sparing surgery for localized ovarian cancers maintains an ability to conceive but is associated with diminished reproductive potential diminished	Letourneau J at al.	J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26193338	
4	European Society of Gynecological Oncology Task Force for Fertility preservation: Clinical Recommendations for fertility Sparing management in young endometrial cancer patients	Rodolakis A at al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26186070	
5	Fertility -sparing management of gynecological cancers	Fastrez M at al.	Maturitas	http://www.ncbi.nlm.nih.gov/pubmed/26160684	
6	Long-term follow-up of patients with an isolated ovarian recurrence after conservative treatment of epithelial ovarian cancer: review of the results of a international multicenter study comprising 545 patients.	Bentivegna E at al.	Fertil Steril	http://www.ncbi.nlm.nih.gov/pubmed/26149354	
7	Hysteroscopic resection in Fertility - Sparing Surgery for Atypical Hyperplasia and Endometrial Cancer: Safety and Efficacy	De Marzi P at al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26092080	
8	A non-randomized confirmatory study regarding selection of fertility sparing surgery for patients with epithelial ovarian cancer: Japan Clinical Oncology Group Study (JCOG1203).	Satoh T at al.	Jpn J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26059697	
9	Neoadjuvant chemotherapy followed by large cone resection as fertility-sparing treatment in stage IB cervical cancer.	Salihi R at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26050921	
10	Incidence, risk factors and treatment of cervical stenosis after radical trachelectomy: A systematic review.	Li X at al.	Eur J Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26049687	
11	Long-term safety of fertility sparing surgery in early stage ovarian cancer: comparison to standard radical surgical procedures.	Ditto A at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25969349	
12	Fertility-Sparing treatment of early Endometrila cancer and Complex Atypical Hyperplasia in Young Women of Childbearing Potential	Pronin SM at al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25950126	
13	Minimazation of curative surgery for treatment of early cervical cancer: a review	Arimoto T at al.	Jpn J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25888708	
14	Outcomes of pediatric and adolescent girls with malignant ovarian germ cell tumours. girls	Park JY at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25842162	
15	Immediate radical trachelectomy versus neoadjuvant chemotherapy followed by conservative surgery for patients with stage IB1 cervical cancer with tumors 2cm or larger: A literature review and analysis of oncological and obstetrical outcomes.	Pareja R at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25827293	

Treatment of elderly patients with gynaecological cancers

- Editor Alex Mutombo

- Descriptive summary

Some articles emphasized prognostic factors and outcomes in older patients with gynaecological cancers. Sabatier et al. assessed the treatment outcomes of invasive ovarian carcinoma in older patients compared to young patients. They found that prognosis was poorer in older women, but they were suboptimally treated. Doll KM et al. in North Carolina, USA, reported an overall 34 % increase in all-cause mortality after diagnosis with a gynecologic cancer in women aged >64 years who were dually enrolled in Medicare and Medicaid, compared with the non-dually enrolled Medicare population. In another case-control study by Elliott SP et al. women >65 years old with nonmetastatic cervical cancer were more likely to present with urinary adverse events after treatment. According to Rauh-Hain et al. a diagnosis of venous thromboembolism was associated with decreased survival in elderly patients with endometrial cancer. Another set of studies are related to treatment modalities and their necessity in older women. In general, several comorbidities expose them in specific toxicities, resulting in frequent readjustment of treatment protocols in elderly patients. For example, Stuckey A et al. demonstrated that death from intercurrent disease or treatment complications was higher in elderly patients.

In general, there is a need for prospective research to evaluate the best treatment options in this growing population with regard to cost-effectiveness, survival benefit, toxicity and death from intercurrent disease or treatment complications.

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Treatment of elderly patients with gynaecological cancers

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Prognostic factors for ovarian epithelial cancer in the elderly: a case-control study	Sabatier R et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25768081	
2	Incidence and effects on mortality of venous thrombo-embolism in elderly women with endometrial cancer	Rauh-Hain JA et al.	Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26000507	
3	Gynecologic cancer outcomes in the elderly poor: A population-based study	Doll KM et al.	Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26230631	
4	Radiotherapy in elderly patients, recommendations for the main localizations: Breast, prostate and gynaecological cancers	Hennequin C et al.	Cancer Radiother	http://www.ncbi.nlm.nih.gov/pubmed/?term=Radiotherapy+in+elderly+patients%2C+recommendations+for+the+main+localizations%3A+Breast%2C+prostate+and+gynaecological+cancers	
5	Cost-Effectiveness of Neoadjuvant Chemotherapy versus Primary Surgery in Elderly Patients with Advanced Ovarian Cancer	Poonawalla IB et al.	Value Health	http://www.ncbi.nlm.nih.gov/pubmed/26091592	
6	Costs of treatment for elderly women with advanced ovarian cancer in a Medicare population	Forde GK et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=Costs+of+treatment+for+elderly+women+with+advanced+ovarian+cancer+in+a+Medicare+population	
7	Propensity-Weighted Comparison of Long-Term Risk of Urinary Adverse Events in Elderly Women Treated For Cervical Cancer	Elliott SP et al.	Int J Radiat Oncol Biol Phys	http://www.ncbi.nlm.nih.gov/pubmed/?term=Comparison%2C+Long-Term+Risk%2C+Events%2C+Elderly+Women+%2C+Treated%2C+Cervical+Cancer	
8	Locally advanced vulvar cancer in elderly women: is chemoradiation beneficial?	Stuckey A et al	Am J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=Locally+advanced+vulvar+cancer+in+elderly+women%3A+is+chemoradiation+beneficial%3F	
9	Definitive chemoradiotherapy for advanced cervical cancer: should it be different in the elderly?	Caires IQ et al.	Eur J Obstet Gynecol Reprod Biol	http://www.ncbi.nlm.nih.gov/pubmed/26182837	
10	Cost-utility comparison of neoadjuvant chemotherapy versus primary debulking surgery for treatment of advanced-stage ovarian cancer in patients 65 years old or older	Rowland MR et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25644442	
11	Long-term safety of fertility sparing surgery in early stage ovarian cancer: comparison to standard radical surgical procedures.	Ditto A at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25969349	
12	Fertility-Sparing treatment of early Endometrila cancer and Complex Atypical Hyperplasia in Young Women of Childbearing Potential	Pronin SM at al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25950126	
13	Minimazation of curative surgery for treatment of early cervical cancer: a review	Arimoto T at al.	Jpn J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25888708	
14	Outcomes of pediatric and adolescent girls with malignant ovarian germ cell tumours. girls	Park JY at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25842162	
15	Immediate radical trachelectomy versus neoadjuvant chemotherapy followed by conservative surgery for patients with stage IB1 cervical cancer with tumors 2cm or larger: A literature review and analysis of oncological and obstetrical outcomes.	Pareja R at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25827293	

Nutritional support/status in gynaecological cancer

Editor Jiri Presl

Descriptive summary

The first search was targeted strictly on nutritional support/status in gynaecological cancer. Only one study was published during the selected period. This phase III multi-centre randomised clinical trial by Baker et al. focused on difference quality of life (QoL) after early enteral feeding versus standard postoperative diet as tolerated in patients with advanced ovarian cancer. Authors conclude that there is no significant improvement in QoL in comparison early enteral feeding versus stan- dard care but early intervention may improve nutritional status.

The second search was conducted with a wider entry - nutritional status / support in abdominal surgery. Again, it was found that during the period under review only one trial was published. The study by Wang et al. focused on impact of enteral nutrition on postoperative immune function and nutritional status in gastric cancer patient. This study indicates that appropriate preoperative enteral nutrition support for gastric cancer patients can improve their postoperative nutritional status and immune function and is more conducive to the recovery of patients. The conclusions may still potentially be applicable to our specialty mainly in patients with advanced ovarian cancer.

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Quality of life after early enteral feeding versus standard care for proven or suspected advanced epithelial ovarian cancer: Results from a randomised trial.	Baker J et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/?term=Quality+of+life+after+early+enteral+feeding+versus+standard+care+for+proven+or+suspected+advanced+epithelial+ovarian+cancer%3A+Results+from+a+randomised+trial.	✓
2	Impact of enteral nutrition on postoperative immune function and nutritional status.	Wang F et al.	Gener Mol Res	http://www.ncbi.nlm.nih.gov/pubmed/26125807	

Follow-up after gynaecological malignancies

- Editor Anne van Altena

- Descriptive summary

A (non-systematic) research of the recent literature since 2001 by Faubian et al. showed general recommendations for the surveillance of gynecological cancer survivors. An overview on (the limitations of) clinical tests, like tumor markers and imaging was given as well as on side effects like postmenopausal complaints. Recommendations for general health screening, fertility preservation and contraception were given.

The role of the ultrasound in surveillance of gynecological cancer is only mentioned briefly in a study on ultrasound in gynecological cancer (Fischerova et al.). It is a reliable navigator for tru-cut biopsies and easier to undergo for patients.

An Italian group (Cheli et al., abstract only) studied the role of cognitive behavioral therapy in breast and gynecological cancer patients. They looked at the effect of this eight weekly therapy on the level of depressive, and anxious symptoms, psychological distress and quality of life in 32 women. A large intent to treat effect was observed. Depressive and anxious symptoms and distress were reduced but no difference in quality of life was seen. A larger, controlled study is recommended.

A Thai study (Suprasert et al., abstract only) looked at reducing the burden and the costs of surveillance of gynecologic oncology patients. They initiated a network program with 5 provincial hospitals and its general gynecologists. These gynecologists participated in a special training before doing follow-up checks . A total of 854 patients participated in the study. The most common disease was cervical cancer. After a year 604 patients and 21 health care workers were interviewed. 85.2% of the patients and 100% of the health care workers were satisfied. In the group of 60 patients that had withdrawn the most mentioned reason was the lack of confidence in the provincial hospital.

629 Women 3-5 years after a diagnosis of endometrial cancer were studied to examine the prevalence, predictors and correlates of supportive care needs. Almost a quarter of these women reported one or more needs in the last month. Several socio demographic, clinical and psychosocial factors were associated with having more needs. Recommendations for how to assess these needs were done.

A study (Faubian) was performed following the ESGO conference in Turin. The researchers looked at the current surveillance strategies in ovarian, endometrial and cervical cancer patients. Since they saw that recommendations are mainly based on retrospective data and opinions, they advised to perform prospective studies comparing the effect on survival, detection of recurrences, quality of life and costs.

Another study (Pagano) also looked at the costs of follow-up in gynecologic oncology. A literature search was performed in Medline and NHS CRD databases. In total they found 21 eligible studie. However, the studies appeared to be based on weak evidence of effectiveness and they lacked formal methodological approaches. The general impression was that these studies rely on small sample sizes, most often are observational studies and suffer from a lack of financial support. Again the conclusion of this study was that well designed randomized trials should be performed in which cost effectiveness should be looked at.

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LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Follow-up after gynaecological malignancies

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Surveillance and Care of the Gynecologic Cancer Survivor	Faubion S at al.	J Womens Health	http://www.ncbi.nlm.nih.gov/pubmed/26208166	
2	Follow-up in Gynecological Malignancies: A State of Art.	Zola P at al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26207784	
3	Role of MR Imaging and FDG PET/CT in Selection and Follow-up of Patients Treated with Pelvic Exenteration for Gynecologic Malignancies.	Lakhman Y at al.	Radiographics	http://www.ncbi.nlm.nih.gov/pubmed/26172364	
4	Outcome of the Gynecologic Oncology Patients Surveillance Network Program	Suprasert P at al.	Asian Pac J Cancer Prev	http://www.ncbi.nlm.nih.gov/pubmed/26163612	
5	Economic Considerations on the Follow-Up Practice in Gynecologic Cancers: Few Lights and Many Shadows From a Literature Review.	Pagano E at al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25950132	
6	How to lead the new psycho-oncologists toward a third wave: A mindfulness-based and metacognition-based intervention for women in follow-up cancer care.	Cheli S at al.	Psycho-Oncology	http://onlinelibrary.wiley.com/doi/10.1002/pon.3874/pdf (P1-15, page 8)	
7	Ultrasound in Gynecological Cancer: Is It Time for Re-evaluation of Its Uses?.	Fischerova D at al.	Current Oncology Reports	http://www.ncbi.nlm.nih.gov/pubmed/25980344	
8	Prevalence, predictors, and correlates of supportive care needs among women 3-5 years after a diagnosis of endometrial cancer.	Rowlands IJ at al.	Supportive Care in Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25304121	

Gestational trophoblastic disease management (pathology, diagnosis, follow-up, pregnancies)

Editor Manuela Undurraga

Descriptive summary

The articles published during this period were mainly case reports and literature reviews or retrospective chart studies. There were no meta-analysis or randomized controlled trials. There was one formalized consensus published by the European Organisation for Treatment of Trophoblastic Diseases on management of gestational trophoblastic diseases.

Pathology

Zheng et al. looked at the clinicopathological characteristics of stage I placental site tumor and found that serum B HCG of more than 100 000 and mitotic index of more than 5 per 10 HPFs were associated with lower DFS.

Diagnosis

In their prospective study Wang et al. found that power doppler may be a useful tool in the diagnosis of GTD based on the features found in the resistance index, vascularisation index and flow index of healthy myometrium.

Price et al. looked whether lesions found on computed tomography (CT) imaging of the thorax would affect FIGO risk score or alter clinical management.

Treatment

Maestà et al. showed no relationship between response to chemotherapy and BMI. Another retrospective study by Neubauer et al. revealed that most deaths occur due to resistant disease and not hemorrhage, as shown in earlier series. They stated that 1/3 of women who died of resistant disease had not received adequate first line therapy

Follow up

Sun et al. found (as was already seen in other populations) that earlier diagnosis did not decrease the risk of persistent GTD. Savage et al. in their interesting study showed that the risk of a second malignancy overall was not signifi- cantly increased, with some variation between treatments. MTX and EMA-CO alone showed no overall increase in second malignany, while the adjunction of alkylating agents increased the risk, mainly for leukemia. They also noted that MTX-FA appears to have a minimal effect of early menopause, in contrast to EMA-CO that led to an overall increase in risk of premature menopause, with the risk being greater for women older than age 30.

Di Mattei et al. found higher depression and anxiety scores in women with GTD, particularly in younger women.

Pregnancy

Gaducci et al. reviewed the reproductive outcome of patients treated for GTD, including the risk of recurrence, the chance of subsequent pregnancy, and analyses also the risk of second tumors and premature menopause.

Relevant articles retrieved May-Aug 2015

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Gestational trophoblastic disease management (pathology, diagnosis, follow-up, pregnancies)

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Changing presentation of complete Ihydatidiform mole at the New England Trophoblastic DIsease Center over the past three decades: does early diagnosis alter risk for gestational trophoblastic neoplasia?	Sun SY et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25969351	
2	Response to chemotherapy in overweight/obese patients with low-risk gestational trophoblastic neoplasia.	Maestà I et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25675037	
3	Effects of single agent and combination chemotherapy for gestational trophoblastic tumors on risks of second malignancy and early menopause	Savage P et al.	J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25547507	
4	An investigative study into psycological and fertility sequelae of gestational trophoblastic disease: the impact on parients' perceived fertility, anxiety and depression	Di Mattei VE et al.	PLOS one	http://www.ncbi.nlm.nih.gov/pubmed/26030770	✓
5	Characeristics of three dimension power doppler in gestational trophoblastic disease	Wang W et al.	Disease Markers	http://www.ncbi.nlm.nih.gov/pubmed/26257463	✓
6	The rose of computed tomography scanning of the thorax in the initial assessment of gestational trophoblastic neoplasia	Price J et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26270122	
7	Reproductive outcomes after hydatiform mole and trophoblastic neoplasia	Gadducci A et al.	Gynecol Endocrin	http://www.ncbi.nlm.nih.gov/pubmed/26288335	
8	Formalized consensus of the European Organisation for treatment of trophoblastic diseases on management of gestational trophoblastic diseases	Bolze PA et al.	Eur J Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26092638	
9	Fatal gestational trophoblastic neoplasia: an alaysis of treatment failure at the Brewer Trophoblastic Disease center from 1979-2012 compared to 1962-1978	Neubauer NL et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26047591	
10	Retrospective analysis of the clinicopathologic and pronostic characteristics of stage I placental site trophoblastic tumora	Zheng Y et al.	Int J Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/25572983	

Quality of life in gynaecological cancers/Palliative care

- Editor Stef Cosyns

- Descriptive summary

The topic I was assigned to is rather broad and can be divided according to different tumor groups. As a start of these consecutive reviews I tried to make a first summary of data published since the beginning of the year. The impact of gynecological cancer treatments on quality of life (QOL) is logically related to the extensiveness of the surgical treatment and/or type of adjuvant treatment.

I do want to point out that many QOL issues are not fully integrated in our routine counselling or follow up. Probably because it is time consuming and sometimes embarrassing to address.

Important to take into account is that outpatient treatment and hospitalisation cause organisational efforts in both professional and private lives. Despite the increasing emphasis of the high-priority of symptom assessment and management, systematic reviews continue to indicate that pain and other symptoms associated with cancer and its treatment are not optimally controlled.

Cancer related fatigue (CRF) caused by cancer and its treatment occurs more pervasively, persistently and profoundly than any other symptom. Fatigue is also the most prevalent symptom for cancer survivors who have no evidence of active disease. No accepted pathophysiological evidence to explain whether a combination of mechanisms or a centrally mediated disorder causes CRF.

For cervical cancer patients global health studies and physical and role functioning show a highly significant decline during treatment, before returning to near the baseline levels three months after end of treatment. The most frequently reported substantial complaints are fatigue, diarrhea, urinary frequency and nausea recovering in some degree after 3 months. Fatigue however persists in half of them and limb edema is often observed (22%). A predominant focus on sexuality/intimacy and information seeking issues in noted. These needs probably evolve over time from diagnosis to treatment and subsequently to survivorship. The prevalence of poor sleep quality of stages I and II cervical cancer patients was approximately twice than that of the other women in the communities. Cancer treatment had an important effect on sleep quality. Psychological distress, depression, anxiety, high grade of chemo-induced peripheral neurotoxicity, and chemotherapy combined with radiotherapy during treatment were the factors associated with poor sleep quality. Performing exercise during treatment was a protective factor for poor sleep quality.

In ovarian cancer treatment, severe pain and fatigue occur for years after treatment even when in remission. Detection and aggressive symptom management are critical in monitoring QOL. Multidisciplinary consultations are critical to optimise outcome and symptom control.

Understandably, lymphadenectomy has a negative influence on patient's sexual function after surgical treatment for vulvar cancer.

In endometrial cancer treatment, the risk of developing lymphedema varies markedly with the number of lymph nodes removed and, to a lesser extent, the use of of adjuvant radiation or chemotherapy treatment. In the study of Beesley et al. the absolute risk of developing lymphedema was >50% for women with 15+ nodes removed and 2-3 additional risk factors like adjuvant chemotherapy, adjuvant radiation or NSAID's use prior to diagnosis were identified. General incidence rates of lower limb lymphedema in women following endometrial cancer have been reported between 1-18%.

The impact of lower limb lymphedema can be significant including physical discomfort, pain, and reduction in mobility, body image issues, sexuality issues and distress.

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LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Quality of life in gynaecological cancers/Palliative care

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Disease-free ovarian cancer patients report severe pain and fatigue over time: prospective quality of life assessment in a consecutive series.	Shinde S at al.	Eur J Gynaecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26050353	
2	Central nervous system metastasis in gynecologic cancer: symptom management, prognosis and palliative management strategies.	Walter AC at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25752572	
3	Comprehensive care in gynecologic oncology: The importance of palliative care.	Landrum LM at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25749723	
4	Quality of life and sexual function after surgery in early stage vulvar cancer.	Forner DM at al.	Eur J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25468750	
5	Health related quality of life and patient reported symptoms before and during definitive radio(chemo)therapy using image-guided adaptive brachytherapy for locally advanced cervical cancer and early recovery - a mono-institutional prospective study.	Kirchheiner K at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25462202	
6	A systematic review of the supportive care needs of women living with and beyond cervical cancer.	Maguire R at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25462200	
7	Cancer-related and treatment-related fatigue.	Wang XS at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25458588	
8	Incidence, risk factors and estimates of a woman's risk of developing secondary lower limb lymphedema and lymphedema-specific supportive care needs in women treated for endometrial cancer.	Beesley VL at al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25448454	
9	Sleep status of cervical cancer patients and predictors of poor sleep quality during adjuvant therapy.	Tian J at al.	Support Care Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25370891	
10	Dietary habits changes and quality of life in patients undergoing chemotherapy for epithelial ovarian cancer.	Mardas M at al.	Support Care Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25270849	
11	Psychosexual support for gynecological cancer survivors: professionals' current practices and need for assistance.	Vermeer WM at al.	Support Care Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25218609	
12	Addressing anxiety and insecure attachment in close relationships could improve quality of life for gynaecological cancer survivors.	Andrykowski M.	Evid Based Nurs	http://www.ncbi.nlm.nih.gov/pubmed/25147309	
13	Quality of life and sexual function in patients with borderline tumors of the ovary. A substudy of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) study group ROBOT study.	Farthmann J at al.	Support Care Cancer	http://www.ncbi.nlm.nih.gov/pubmed/24996831	

Immunotherapy in gynaecological cancers

Editor Zoltan Novak

Descriptive summary

In this update two human trials of cancer immunotherapy are reported. An interesting clinical study including nine patients show that durable, complete regression of metastatic cervical cancer can occur after a single infusion of tumor-infiltrating T cells selected for human papillomavirus E6 and E7 reactivity (1). A Phase I clinical study investigated a combination of chemotherapeutics, blockade of IL-6 receptor (tocilizumab) and immune enhancer interferon-γ. This combination has proven to be safe with 11 of 21 evaluable patients showing clinical response (7).

An in vitro study investigating patient blood samples found that a survivin protein-specific immune response may be induced spontaneously in patients, further fortifying the eligibility of survivin as an immunotherapeutic target (2).

In a murine model of ovarian cancer, the efficacy of a monoclonal antibody blocking programmed death-1 signaling pathway was demonstrated when used with a novel anticancer agent, trabectedin (3).

The remaining 3 papers are high-quality reviews about the vaccine-based immunotherapeutic modalities for human papillomavirus-induced cancer (5), dendritic cell immunotherapy in ovarian cancer (6) and cellular immunotherapies against ovarian cancer, especially targeting cancer stem cells (4).

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells.	Stevanović S et al.	J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25823737	✓
2	Combined Trabectedin and anti-PD1 antibody produces a synergistic antitumor effect in a murine model of ovarian cancer.	Guo Z et al.	J Transl Med	http://www.translational-medicine.com/content/13/1/247	
3	In Vitro Validation of Survivin as Target Tumor-associated Antigen for Immunotherapy in Uterine Cancer.	Vanderstraeten A et al.	J Immunother	http://www.ncbi.nlm.nih.gov/pubmed/26049547	
4	Cellular immunotherapy in ovarian cancer: Targeting the stem of recurrence.	Wefers C et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/25727651	
5	New approaches in vaccine-based immunotherapy for human papillomavirus-induced cancer.	van der Sluis TC et al.	Curr Opin Immunol	http://www.ncbi.nlm.nih.gov/pubmed/26001120	
6	A view on dendritic cell immunotherapy in ovarian cancer: how far have we come?	Coosemans A et al.	Facts Views Vis Obgyn	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4402447/	
7	A phase I trial combining carboplatin/doxorubicin with tocilizumab, an anti-IL-6R monoclonal antibody, and interferon- 2b in patients with recurrent epithelial ovarian cancer.	Dijkgraaf EM et al.	Ann Oncol	http://annonc.oxfordjournals.org/content/early/2015/07/26/annonc.mdv309.abstract	

LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Cancer in pregnancy

Editor Michael J. Halaska

Descriptive summary

The topic of cancer and pregnancy was covered by 24 articles. Majority of them were case reports from diagnosis such as breast (37 cases), cervix (27 cases), ovary (2 cases), endometrial cancer (2 cases), haematological malignancies (21 cases), nasopharyngeal carcinoma (36 cases), colorectal and gastrointestinal cancers (5 cases), melanoma and lung cancer (1 case).

Several articles need more attention:

- A Scandinavian epidemiological study by Andresson et al. describes most common malignancies diagnosed during pregnancy between the years 1963 to 2007: malignant melanoma, breast cancer, cervical cancer followed by ovarian, colon, endocrine glands and thyroid cancers.
- In cervical cancer a large retrospective study by Kärrberg et al. with 47 pregnancy associated cervical cancer concentrated on the method of detection which was in 74,5 % done by follow-up of abnormal cytology, though majority was asymptomatic supporting a screening programs in Cx Ca. Other case reports presented conservative management using radical trachelectomy and chemotherapy performed during pregnancy.
- A study of 21 patients analysis transplacental passage of neoadjuvant chemotherapy using cisplatine into cord blood and amniotic fluid with concentrations of 23-65% and 11-42% of maternal blood respectively.
- Based on a metaanalysis of Byrom et al. it seems that pregnancy-associated melanomas have poorer outcomes than outside of pregnancy eventhough several bias have been commented towards this article. Prithviraj et al described based on a in-vitro and in-vivo models the explanation for this finding due to an increased migration capability of melanoma cells due to PAPP-A protein produced by placenta.
- A follow-up of 57 children exposed prenatally to chemotherapy were evaluated by Cardonick et al with no significant differences found between children exposed and not exposed to chemotherapy.

Relevant articles retrieved May-Aug 2015

No	Title	Authors	Journal	Link to abstract	Available as full freetext
1	Cancer during pregnancy and the postpartum period: A population-based study.	Andersson TM et al.	Cancer	http://www.ncbi.nlm.nih.gov/pubmed/25737403	
2	Support for down-staging of pregnancy-associated cervical cancer.	Andersson TM et al.	Acta Obstet Gynecol Scand	http://www.ncbi.nlm.nih.gov/pubmed/25845736	
3	How much platinum passes the placental barrier? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy.	Köhler C et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25731691	
4	Increased mortality for pregnancy-associated melanoma: systematic review and meta-analysis.	Byrom L et al.	J Eur Acad Dermatol Venerol	http://www.ncbi.nlm.nih.gov/pubmed/25690106	
5	Pregnancy associated plasma protein-A links pregnancy and melanoma progression by promoting cellular migration and invasion.	Prithviraj P et al.	Oncotarget	http://www.ncbi.nlm.nih.gov/pubmed/25940796	
6	Development of children born to mothers with cancer during pregnancy: comparing in utero chemotherapy-exposed children with nonexposed controls.	Cardonick EH et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/25434835	

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