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LiFE | Literature for ENYGO

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Reviews covering publications from August 15 – November 15, 2015

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Contents

Pathology/pathogenesis of malignant ovarian tumours

Editor Dogan Vatansever

Descriptive summary

Four reviews and nine original pieces of research found relevant.

Tang et al. reviewed the role of exosomes. These are extracellular vesicles functioning in the intercellular communication between tumour cells and major cells in the tumour microenvironment as well as in extracellular matrices, which may play a crucial role in metastasis of ovarian cancer. Alli et al. from Stanford reviewed the role of BRCA1 other than double-strand DNA breaks repair such as nucleotide-excision repair, base-excision repair (BER). They also highlighted the clinical implications of these roles of BRCA1, which is a hot topic after the discovery of PARP inhibitors. Katz et al. reviewed studies regarding small, non-coding RNAs that post-transcriptionally regulate gene expression, MicroRNAs (miRNAs). miRNAs seem to be potential biomarkers, predictive markers, and prognostic factors in ovarian cancer. Earp et al. reviewed alterations of DNA methylation in different types of epithelial ovarian cancer. They focused on the consequences of epigenetic changes for therapy response, risk, and prognosis of ovarian cancer.

Most of the original research articles retrieved reported on molecular markers, genetic mutations, etc., in high-grade serous ovarian cancer (HGSC). One of them, CD73, is an enzyme that generates extracellular adenosine, a potent immunosuppressive metabolite in the tumour microenvironment. A high expression of CD73 in HGS ovarian tumours is associated with poor survival and in its presence, tumour-infiltrating CD8+ are no longer associated with a better prognosis. CD73 is also validated as a potential target in HGS ovarian cancer (Turcotte et al.). Epithelial-Mesenchymal Transition (EMT), which is a fundamental change with the increased ability to migrate and is considered an important step in metastasis. Collagen triple helix repeat-containing 1 (CTHRC1) underlies the onset of EMT and the aggressive metastasis of EOC. CTHRC1 over-expression has been reported to be positively correlated with tumour size, stage, lymph node metastasis, and poorer prognosis (Hou et al.). PTEN positivity was reported to be associated with decreased recurrence, free survival independent of debulking status, and platinum resistance. It was postulated that the presence of positive IHC expression of PTEN may be predictive for targeted chemotherapy response in patients entering targeted therapy clinical trials and patients with tumours showing positive PTEN IHC expression may require more cycles of neoadjuvant chemotherapy or addition of another agent (Bakkar et al.). Chien et al. mainly studied the early events in early stage HGSC and stated that earliest events are deleterious TP53 mutations, loss of heterozygosity of chromosomes carrying TP53, BRCA1, and BRCA2. Quaruccio et al. also suggested that p53 mutation may be the initial event but not sufficient alone. A study from the Australian Ovarian Cancer Group identified genetic markers of progression from borderline to LGSCs. It is suggested that mTOR inhibitors may be drugs that are worthwhile to explore as companion treatment for targeted therapy in trials with MEK or BRAF inhibitors.

Moh et al. and Strickland et al. showed that SATB2 is highly specific for distinguishing primary ovarian mucinous tumours from appendiceal mucinous tumours metastatic to the ovary. Novak et al. stated that the discriminatory capacity of p16 and STMN1 could be particularly powerful in identifying or diagnosing p53-negative STICs with marginally elevated Ki-67 index and borderline atypia or p53-negative STICs within reactive/proliferative epithelium where the utility of Ki-67 index is limited. This could improve the diagnostic accuracy of STIC.

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Pathology/pathogenesis of malignant ovarian tumours

- Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	BRCA1: Beyond double-strand break repair.	Alli E et al.	DNA Repair (Amst).	http://www.ncbi.nlm.nih.gov/pubmed/25956865	
2	DNA methylation changes in epithelial ovarian cancer histotypes.	Earp MA et al.	Genomics.	http://www.ncbi.nlm.nih.gov/pubmed/26363302	
3	Exosomes: Emerging biomarkers and targets for ovarian cancer.	Tang MK et al.	Cancer Lett.	http://www.ncbi.nlm.nih.gov/pubmed/26189430	
4	MicroRNAs in Ovarian Cancer.	Katz B et al.	Hum Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26216350	
5	CD73 Is Associated with Poor Prognosis in High-Grade Serous Ovarian Cancer.	Turcotte M et al.	Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26363007	
6	High expression of CTHRC1 promotes EMT of epithelial ovarian cancer (EOC) and is associated with poor prognosis.	Hou M et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26452130	
7	Intact PTEN Expression by Immunohistochemistry is Associated With Decreased Survival in Advanced Stage Ovarian/Primary Peritoneal High-grade Serous Carcinoma.	Bakkar RM et al.	Int J Gynecol Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26166715	
8	Molecular profiling of low grade serous ovarian tumours identifies novel candidate driver genes.	Hunter SM et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26506417	
9	Mutant p53 expression in fallopian tube epithelium drives cell migration.	Quartuccio SM et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/25810107	
10	TP53 mutations, tetraploidy and homologous recombination repair defects in early stage high-grade serous ovarian cancer.	Chien J et al.	Nucleic Acids Res.	http://www.ncbi.nlm.nih.gov/pubmed/25916844	✓
11	SATB2 Expression Distinguishes Ovarian Metastases of Colorectal and Appendiceal Origin From Primary Ovarian Tumors of Mucinous or Endometrioid Type.	Moh M et al.	Am J Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26551622	
12	Stathmin 1 and p16INK4A are sensitive adjunct biomarkers for serous tubal intraepithelial carcinoma.	Novak M et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26206555	
13	Immunohistochemical characterization of appendiceal mucinous neoplasms and the value of SATB2 in their distinction from primary ovarian mucinous tumors.	Strickland S et al.	Histopathology.	http://www.ncbi.nlm.nih.gov/pubmed/26542609	

Surgical treatment of primary ovarian cancer

Editor Syuzanna Babloyan

Descriptive summary

Factors influencing optimal surgery.

The amount of residual disease (RD) is one of the most important prognostic factors influencing survival in advanced epithelial ovarian cancer (AEOC). Liu et al. showed that genes associated with stromal activation are differentially expressed in ovarian tumour samples of patients that couldn't be optimally cytoreduced despite aggressive surgery. Due to the fact that stromal activation was also linked with tumour invasiveness and chemoresistance they suggested that agents targeting tumour stroma (before or concurrently with chemotherapy) might increase therapeutic benefit in suboptimally cytoreduced patients.

A retrospective study of Vidal et al. of 148 patients treated in 7 centres explored whether the extent of surgery matters in patients with incomplete cytoreduction. Among patients that underwent incomplete (both <10mm and >10 mm) upfront or interval standard (hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection, infragastric omentectomy, pelvic and aortic lymphadenectomy, and, when applicable, appendectomy) or radical (upper abdominal surgery (UAS), hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection, infragastric omentectomy, pelvic and aortic lymphadenectomy) surgical treatment, both approaches led to similar outcomes despite the amount of RD. Although authors still support performing complete cytoreduction whenever possible, results of their study suggest that standard surgery with lower risk of morbidity can be considered over radical treatment when complete cytoreduction is impossible to achieve.

Discussing the results of the AGO-OVAR 12 study (standard first-line chemotherapy with or without nintedanib), Kehoe emphasises not only the need for standardization of surgical treatment, but also of patient selection for cytoreductive surgery as factors that potentially affect the results of clinical trials.

Laparoscopy in ovarian cancer.

Two Italian groups published their prospective (Gueli Alletti et al. MISSION Trial - NCT02324595, 30pts) and retrospective (Corrado et al., 30pts) studies evaluating the feasibility and morbidity of total laparoscopic interval debulking surgery in stage III-IV EAOC. Results indicate that in patients with clinical complete response to neoadjuvant chemotherapy, it seems to be feasible and safe in terms of perioperative outcomes, psycho-oncological impact and survival rate. Further studies with longer follow-up comparing to open surgery are indicated.

A Roman group presents a laparoscopy-based scoring system that has been updated after the introduction of upper abdominal surgery (Petrillo et al., 2015). On the basis of 234 included patients the following modifications have been inserted in the new model: laparoscopic assessments of mesenterial retraction and miliaric carcinomatosis on the serosa of the small bowel were omitted; while massive peritoneal involvement, a miliary pattern of distribution for parietal peritoneal carcinomatosis, widespread infiltrating carcinomatosis, confluent nodules to the most part of the diaphragmatic surface, tumour diffusion along the omentum up to the large stomach curvature, possible large/small bowel resection (excluding recto-sigmoid involvement), obvious neoplastic involvement of the stomach, lesser omentum, spleen and liver surface lesions larger than 2 cm were included in the updated model. The updated laparoscopy-based predictive index model showed improved discriminating performance (AUC = 0.885), with a lower rate (33.2%) of inappropriate laparotomic explorations at the established cut-off value of 10.

Education and centralisation of care.

Naik et al. described the results of the survey carried out among UK gynaecological oncologists. Results showed their readiness to undertake additional training in ultraradical surgery. However, the survey also demonstrated a considerable variability in the practice of ultraradical surgery across the country. Butler et al. published a retrospective analysis of the English cancer registry between 2000 and 2009. The data showed an improvement in ovarian cancer survival in England, which was still inferior, compared to other countries.

Lymphadenectomy and thoracic exploration.

Schwartz et al. retrospectively analysed a group of 101 initially inoperable AEOC that underwent neoadjuvant chemotherapy followed by cytoreductive surgery. In patients with no RD, pelvic and para-aortic lymphadenectomy did not seem to improve survival. Similarly, Iwase et al. demonstrated retrospectively that systematic retroperitoneal lymphadenectomy during interval debulking surgery may predict outcome but it does not confer therapeutic benefits. LaFargue et al. published a video demonstrating the surgical technique used to perform full-thickness diaphragm resection and cardiophrenic lymph node dissection.

Although transdiaphragmatic thoracic exploration is shown by Yin et al. to be a feasible procedure that might change pathological stage of the disease, one should not forget about the risk of complications (13.6%). The surgical indications might consider an untapped pleural effusion and full-depth diaphragmatic invasion.

Surgical treatment of primary ovarian cancer

Descriptive summary (cont.)

HIPEC

Huo et al. indicated in their systematic review and meta-analysis that the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to cytoreductive surgery and chemotherapy improves overall survival rates for both primary and recurrent EOC.

Cascales-Campos et al. and Oseledchyk et al. reviewed the major advantages and controversies of the different modalities of intraperitoneal chemotherapy in ovarian cancer.

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Suboptimal cytoreduction in ovarian carcinoma is associated with molecular pathways characteristic of increased stromal activation.	Liu et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26348314	
2	Which Surgical Attitude to Choose in the Context of Non-Resectability of Ovarian Carcinomatosis: Beyond Gross Residual Disease Considerations.	Vidal F et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26542592	
3	Nintedanib and ovarian cancer: standardise surgery in trials?	Kehoe S.	Lancet Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26590674	
4	Minimally Invasive Interval Debulking Surgery In Ovarian Neoplasm (MISSION Trial - NCT02324595): a feasibility study.	Gueli Alletti S et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26529370	
5	Laparoscopic Debulking Surgery in the Management of Advanced Ovarian Cancer After Neoadjuvant Chemotherapy.	Corrado G et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26111273	
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/26196319	
7	Patient Support Groups Identifying Clinical Equipoise in UK Gynaecological Oncology Surgeons as the Basis for Trials in Ultraradical Surgery for Advanced Ovarian Cancer.	Naik R et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26512783	
8	Specialist surgery for ovarian cancer in England.	Butler J et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26196319	
9	Impact of Pelvic and Para-aortic Lymphadenectomy in Advanced Ovarian Cancer After Neoadjuvant Chemotherapy.	Schwartz L et al.	Anticancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26408716	
10	Clinical significance of systematic retroperitoneal lymphadenectomy during interval debulking surgery in advanced ovarian cancer patients.	Iwase H et al.	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26197771	
11	Role of Transdiaphragmatic Thoracic Exploration in Bulky Stage IIIC Ovarian Cancer Patients Who Underwent Diaphragmatic Surgery.	Yin S et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26222485	
12	Transdiaphragmatic cardiophrenic lymph node resection for Stage IV ovarian cancer.	LaFargue CJ et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26049122	
13	Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer: A systematic review and meta-analysis.	Huo YR et al.	Eur J Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26453145	
14	HIPEC in ovarian cancer: Treatment of a new era or is it the end of the pipeline?	Cascales-Campos P et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26091936	
15	Intraoperative Hyperthermic Intraperitoneal Chemotherapy in Patients With Advanced Ovarian Cancer.	Oseledchyk A et al.	Oncology (Williston Park).	http://www.ncbi.nlm.nih.gov/pubmed/26384807	

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Surgical treatment of recurrent ovarian cancer

Editor Patriciu Achimas-Cadariu

Descriptive summary

Since the appearance of the first Issue of LiFE - Literature for ENYGO in October 2015, no randomised phase III data has emerged on the surgical treatment of recurrent ovarian cancer and results are still awaited for the three on-going randomised trials DESKTOP III (NCT01166737), GOG 213 (NCT00565851), and SOCceR (NTR3337).

A study aimed to propose the selection criteria for secondary cytoreductive surgery (SCS) through identifying predictive factors for successful SCS. Treatment-free interval >12 months, absent distant metastasis, solitary disease, and performance status 0 were independently associated with better survival and complete resection of visible tumours was achieved in 79 % of patients with 3–4 factors. Thus, the authors recommended SCS for patients with 3–4 of the above favourable factors at recurrence. As for patients with 2 factors, SCS may be considered if complete resection is expected to be achieved (1).

Another study looked at the associations between quantitative 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) uptake metrics, optimal debulking (OD), and progression-free survival (PFS) in patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery. Metabolically active tumour volumes (MTV), and total lesion glycolysis (TLG) were significantly associated with OD although the odds ratios were very close to 1, and patients with an MTV above 7.52 mL and/or a TLG above 35.94 g had significantly shorter PFS (2).

The last study identified within the search period also investigated the benefits of FDG-PET in patients with SCS for recurrent epithelial ovarian cancer in a PET group and a control group of patients evaluated by conventional imaging methods. A Cox model showed that PFS correlated significantly with FDG-PET evaluation [relative risk (RR)=0.432; p=0.001], sensitivity to platinum-based chemotherapies (RR=0.604; p=0.034), and resection completeness (RR=0.679; p=0.039), (3).

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Proposal for selection criteria of secondary cytoreductive surgery in recurrent epithelial ovarian, tubal, and peritoneal cancers.	Minaguchi T et al.	Int J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=26475355	
2	Volume-based quantitative FDG PET/CT metrics and their association with optimal debulking and progression-free survival in patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery.	Vargas HA et al.	Eur Radiol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=25916387	
3	Benefits of fluorine-18 fludeoxyglucose positron emission tomography in secondary cytoreductive surgery for patients with recurrent epithelial ovarian cancer.	Peng P et al.	Br J Radiol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=25989698	

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

- Editor Ignacio Zapardiel

- Descriptive summary

During the search period we found 35 articles, from which 4 seemed to be relevant. Those articles are focused on 2 main topics as described below:

1 Prognostic factors and management:

The only prognostic factor affecting overall survival in borderline ovarian tumours is the presence of invasive implants. Authors considered it optional to perform a complete surgical staging including lymph node dissection in order to identify cases with high possibility of recurrence. However, radiotherapy, chemotherapy or hormonal therapy is still not recommended.

2 Diagnosis:

Regarding the initial diagnosis, HE 4 levels and ROMA index could be useful in differentiating borderline ovarian tumours from invasive disease. Other authors tend to use only the ultrasound for the diagnosis of these tumours that could help preoperatively for surgical planning and fertility sparing of the patients.

- Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	The Factors Predicting Recurrence in Patients With Serous Borderline Ovarian Tumor.	Ureyen I et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26512785	
2	Controversies in borderline ovarian tumors.	Seonj SJ et al.	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26404125	
3	Clinical value of human epididymis protein 4 and the Risk of Ovarian Malignancy Algorithm in differentiating borderline pelvic tumors from epithelial ovarian cancer in early stages.	Kotowicz C et al.	Eur J Obstet Gynecol Reprod Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26398337	
4	Ultrasound diagnosis of serous surface papillary borderline ovarian tumor: A case series with a review of the literature.	Ludovisi M et al.	J Clin Ultrasound.	http://www.ncbi.nlm.nih.gov/pubmed/25706035	

Emerging molecular targeted therapies or early preclinical trials in ovarian cancer

Editor Muhammad Rizki Yaznil

Descriptive summary

Studies on early preclinical trials and targeted therapies in ovarian cancer covered by this second edition of the LiFE report focus on the following topics:

1 Tumour cell capture device

Alexandre de la Fuente et al. used an in vivo murine model of ovarian metastasis to demonstrate the efficacy of a fabricated tumour cell capture device. This was comprised of exosomes embedded on a 3D scaffold where metastatic tumour cells preferentially reside – a metastatic trap (M-Trap). The M-Trap device disrupts the crosstalk between metastatic cells and their environment, i.e. peritoneal surface. The authors suggest that by placing the M-Trap device, the metastatic cells may be collected only around the device. This may facilitate the transformation of a systemic, fatal disease into a localised disease that can be cured by surgery or radiation.

2 Intraperitoneal administration of antibodies

Mony et al. report the results of a preclinical study in a murine model. Ovarian tumours that are aggressive and non-immunogenic may benefit from intraperitoneal administration of antibody that blocks PD-L1 (programmed death ligand 1). That led to substantial T cell infiltration within the tumour and significantly increased survival. Screening for baseline anti-tumour antibodies could identify patients who may benefit from more personalised approaches, through dose adjustment or combination regimens.

3 New model of fallopian epithelium provides insight into the role of mutant p53 in epithelial ovarian cancer (EOC) formation and the role of Slug in epithelial-mesenchymal transition (EMT)

Quartuccio et al. (see also chapter on "Pathology/pathogenesis of malignant ovarian tumours") explore the role of a mutation in the p53 tumour suppressor (R273H) in fallopian tube epithelium cells. They found that the mutation was insufficient to drive cellular transformation, but significantly increased cell migration, a process not observed with ovarian surface epithelium cells traditionally associated with ovarian cancer. The authors speculate that this phenotype might support the spread of cancer cells from the fallopian tube to organs in the peritoneal cavity including the ovaries. Hou et al. found that increased expression of collagen triple helix repeat-containing (CTHRC1) in EOC tissue strongly correlates with prognosis. They explored the molecular mechanisms by which CTHRC1 activates the migration of EOC cells. Both groups found that Slug is a prominent biomarker and a possible target for therapies to prevent EMT.

4 Anti-cancer and anti-angiogenic potentials of tetrathiomolybdate (TM) and Vasohibin-1 (VASH1)

Kwang et al. studied ovarian and endometrial cancer cell lines and showed that TM inhibits HIF-1 protein accumulation and impairs the activation of its transcriptional targets relating to glucose metabolism and angiogenesis. They suggest a therapeutic potential as a method of blocking angiogenesis in ovarian and endometrial tumours. Takahashi et al. investigated the effect of VASH1 (regulator of angiogenesis) on ovarian cancer progression in vitro and in an animal model. They proved its antitumor effect on ovarian cancer by inhibiting angiogenesis in the tumour environment. These findings suggest that a novel therapy based on VASH1 could be a useful therapeutic strategy for ovarian cancer.

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Emerging molecular targeted therapies or early preclinical trials in ovarian cancer

- Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Anti-PD-L1 prolongs survival and triggers T Cell but not humoral anti-tumor responses in a human MUC1-expressing preclinical ovarian cancer model.	Mony JT et al.	Cancer Immunol Immu-nother.	http://www.ncbi.nlm.nih.gov/pubmed/25998800	
2	M-Trap: Exosome-Based capture of tumor cells as a new technology in peritoneal metastasis.	de la Fuente A et al.	J Natl Cancer Inst.	http://www.ncbi.nlm.nih.gov/pubmed/26150590	
3	Mutant p53 expression in fallopian tube epithelium drives cell migration.	Quartuccio SM et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/25810107	
4	High expression of CTHRC1 promotes EMT of epithelial ovarian cancer (EOC) and is associated with poor prognosis.	Hou M et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26452130	✓
5	The angiogenesis regulator vasohibin-1 inhibits ovarian cancer growth and peritoneal dissemination and prolongs host survival.	Takahashi Y et al.	Intl J Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26460696	✓
6	Tetrathiomolybdate inhibits mitochondrial complex IV and mediates degradation of hypoxia inducible factor-1 in cancer cells.	Kim KK et al.	Sci Rep.	http://www.ncbi.nlm.nih.gov/pubmed/26469226	✓

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

Editor Sara Giovannoni

Descriptive summary

Early Risk-Reducing Salpingectomy (RRS) and delayed Risk-Reducing Oophorectomy (RRO) to improve QoI in BRCA1/2 mutations carriers: "TUBA study": [1]

Harmsen et al. described an innovative, on-going, non randomised multicentre trial in premenopausal BRCA mutation carriers, comparing the standard strategy to reduce ovarian cancer risk, i.e., RRSO (Risk-Reducing Salpingo-Oophorectomy), at the recommended ages of 35-40 in BRCA1 and 40-45 in BRCA2 mutation carriers, with an innovative strategy including early RRS (upon completion of childbearing) and subsequent RRO, which is delayed for five years compared to the currently recommended age for the standard strategy. The trial is based on recent insights into the fallopian tube as possible site of origin of serous ovarian carcinomas and on the short- and long-term comorbidities associated to premature menopause. The primary outcome measure is menopause-related QoL. Secondary outcome measures include safety, histopathological findings of surgery specimens, cardiovascular risk factors and cost effectiveness. Furthermore there are two other on-going studies (an American and a French one) investigating the role of RRS in women with BRCA mutation (NCT01907789; NCT01608074).

Suppression of Homologous Recombination (HR) by Insulin-like growth factor type 1 receptor (IGF-1R) inhibition sensitises cancer cells to PARP inhibitors: [2]

Tumours with BRCA1 mutations show increased expression of IGF-1R and the inhibition of IGF-1R results in growth inhibition and apoptosis of ovarian tumour cells. Using ovarian and breast cancer cellular models with known BRCA1 status, they demonstrated that cells with mutated/methylated BRCA1 showed an impaired HR function, and had an overactivation of the IGF-1R pathway. These cells were more sensitive to IGF-1R inhibition compared to HR proficient cells. In addition, the IGF-IR inhibitor reduced RAD51 expression at mRNA and protein levels in HR proficient cells, and sensitised these cells to PARP inhibitor, so targeting both PARP and IGF-1R might increase the clinical efficacy in HR deficient patients and increase the population of patients who may benefit from PARP inhibitors.

Olaparib- PARP inhibitors: [3,4,5]

Bixel and Hays published an interesting review article focused on olaparib. They summarised, with a complete overview, all the trials with olaparib as single agent or in combination therapy for the treatment of recurrent ovarian cancer phase I-II). The authors emphasised the positive results of phase I and II trials of olaparib in combination with cediranib (oral ATP-competitive tyrosine kinase inhibitor of VEGF 1,2,3), with a PFS of 9 months vs. 17.7 months (HR 0.42) in the phase II trial, with a trend toward improved OS at 2 years. Finally they point out the future perspectives of olaparib in ovarian cancer treatment.

Lheureux et al analysed the safety profile of olaparib in ovarian cancer, concluding that common toxicities - nausea/vomiting, fatigue anaemia - are mild or moderate and appear consistent across subgroups (BRCA carriers/wild-type). Though the risk is low, long-term monitoring of patients is warranted to determine the potential risk for haematological complications.

The review by Musella et al. summarises the most recent research and clinical findings on PARP inhibitors in the treatment of ovarian cancer.

BRCA mutation detection: [6]

Minucci et al. highlight the need of an integrated MPS (Massive Parallel Sequencing) BRCA1/2 molecular workflow fulfilling the standardised requirements needed in the routine clinical laboratory practice.

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

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Early salpingectomy (TUbectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers (TUBA study): a prospective non-randomised multicentre study.	Harmsen MG et al.	BMC Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26286255	✓
2	Suppression of Homologous Recombination by insulin-like growth factor-1 inhibition sensitizes cancer cells to PARP inhibitors.	Amin O et al.	BMC Cancer	www.ncbi.nlm.nih.gov/pubmed/26510816	✓
3	Olaparib in the management of ovarian cancer.	Bixel K et al.	Pharmgenomics Pers Med.	http://www.ncbi.nlm.nih.gov/pubmed/26309417	✓
4	Safety evaluation of Olaparib for treating ovarian cancer.	Lheureux S et al.	Expert Opin Drug Saf.	http://www.ncbi.nlm.nih.gov/pubmed/26051946	
5	PARP inhibition: A promising therapeutic target in ovarian cancer.	Musella A et al.	Cell Mol Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26518896	✓
6	Clinical impact on ovarian cancer patients of massive parallel sequencing for BRCA mutation detection: the experience at Gemelli hospital and a literature review.	Minucci A et al.	Expert Rev Mol Diagn.	http://www.ncbi.nlm.nih.gov/pubmed/26306726	
7	Rescreening for genetic mutations using multi-gene panel testing in patients who previously underwent non-informative genetic screening.	Frey MK et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26296696	
8	Should risk-reducing surgery in women from hereditary breast ovarian cancer families be confined to removal of the fallopian tubes with ovarian conservation?	Snyder CL et l.	Womens Health (Lond Engl).	http://www.ncbi.nlm.nih.gov/pubmed/26246179	

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

Editor Kastriot Dallaku

Descriptive summary

The most relevant studies that touch on endometrial hyperplasia cover predominantly two aspects:

1 Diagnosis, biology, and follow-up for patients with endometrial hyperplasia (EH).

El-Sharkawi et al. evaluated endometrial lesions according to their nuclear and glandular morphometric parameters, their D score, and their DNA ploidy, concluded that these examinations may be used as an ancillary technique in the diagnosis of atypical changes occurring in precancerous endometrial lesions.

Kiraz et al. performed Micronucleus (MN) testing of patients with pre-postmenopausal EH for detection of genetic damages and DNA instability. They concluded that MN scoring can be used as adjunct in endometrial cancer (EC) screening.

Kadirogullari et al. studied the prevalence of co-existing EC in EH and recommended preoperative ultrasound and magnetic resonance imaging in patients with complex atypical EH. Concurrent endometrial carcinoma should be suspected and endometrial sampling should be considered in young or obese patients who present with atypical endometrial hyperplasia (Byun et al.).

Dueholm et al. reported on the diagnosis of EH in postmenopausal women evaluating the accuracy of hysteroscopy, transvaginal and gel infusion sonography. Tariq et al. reported the histopathological findings in endometrial biopsy samples in patients with a clinical history of postmenopausal bleeding.

2 Conservative and definitive treatment for patients with endometrial hyperplasia.

A systematic review of randomised trials (Abu Hashim et al.) reported that for the treatment of non-atypical EH, LNG releasing intrauterine systems achieved higher therapeutic effect rates and lower hysterectomy rates than oral progestins, and should be offered as an alternative to oral progestins in these cases.

Reyes et al. report that downregulation of FOXO1 mRNA levels may serve as a biomarker for response to therapy and an indicator of progesterone receptor function in patients being conservatively managed with a progestin-containing IUD. Another potential prognostic marker of EC treatment with progestin may be SPAG9, a recently characterised oncogene (Li et al.).

Management options and fertility-preserving therapy in EH and EC was another topic addressed by some authors. Gressel et al. reviewed the conservative management options for carefully selected women with complex atypical EH or early-stage EC who desire future fertility. Regarding fertility-sparing management of complex EH, Chen et al. confirmed that oral progestin is an effective treatment, however, obesity is associated with a lower probability of long-term success.

Chandra et al. provide an update for therapeutic options of EH, emphasises that future studies should focus on evaluation of the novel therapeutic agents precisely targeting the inhibition of ER, growth factor receptors, and signal transduction pathways which are likely to constitute an optimal approach for treatment of EH.

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LiFE | Literature for ENYGO

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

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Prevalence of Co-existing Endometrial Carcinoma in Patients with Preoperative Diagnosis of Endometrial Hyperplasia.	Kadirogullari P et al.	J Clin Diagn Res.	http://www.ncbi.nlm.nih.gov/pubmed/26557570	✓
2	Therapeutic Options for Management of Endometrial Hyperplasia.	Chandra V et al.	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26463434	
3	Management options and fertility-preserving therapy for premenopausal endometrial hyperplasia and early-stage endometrial cancer.	Gressel GM et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26384790	
4	Morphometric and DNA Image Analysis of Endometrial Hyperplasia and Carcinoma.	El-Sharkawy SL et al.	Appl Immunohistochem Mol Morphol.	http://www.ncbi.nlm.nih.gov/pubmed/26469331	
5	Endometrial cancer arising from atypical complex hyperplasia: The significance in an endometrial biopsy and a diagnostic challenge.	Byun JM et al.	Obstet Gynecol Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26623410	✓
6	Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer.	Chen M et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26493012	
7	Micronucleus testing as a cancer detector: endometrial hyperplasia to carcinoma.	Kiraz A et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26342824	
8	Levonorgestrel-releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials.	Abu Hashim H et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/25797236	
9	Pigment Epithelium-Derived Factor Alleviates Tamoxifen-Induced Endometrial Hyperplasia.	Goldberg K et al.	Mol Cancer Ther.	http://www.ncbi.nlm.nih.gov/pubmed/26450919	
10	SPAG9 May Be a Potential Prognostic Marker of Endometrial Hyperplasia and Grade 1 Endometrioid Adenocarcinoma Treated with Progestin.	Li C et al.	Gynecol Obstet Invest.	http://www.ncbi.nlm.nih.gov/pubmed/26334303	✓
11	Prognostic factors of oncological and reproductive outcomes in fertility-sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin in Chinese patients.	Zhou R et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26428941	
12	The importance of age and menopausal status in endometrial complex hyperplasia with atypia.	Ureyen I et al.	J Obstet Gynaecol.	http://www.ncbi.nlm.nih.gov/pubmed/26440514	
13	Endometrial Synovial-like Metaplasia Associated With Levonorgestrel-releasing Intrauterine System.	Stewart CJ et al.	Int J Gynecol Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26447355	
14	Downregulation of FOXO1 mRNA levels predicts treatment failure in patients with endometrial pathology conservatively managed with progestin-containing intrauterine devices.	Reyes HD et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26524723	
15	Endometrial polyps: when to resect?	de Azevedo JM et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26305029	
16	Spectrum of Histopathological Findings in Postmenopausal Bleeding.	Tariq MU et al.	J Coll Physicians Surg Pak.	http://www.ncbi.nlm.nih.gov/pubmed/26577963	
17	Expression of HE4 in Endometrial Cancer and Its Clinical Significance.	Li X et al.	Biomed Res Int.	http://www.ncbi.nlm.nih.gov/pubmed/26539494	✓

LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Surgical treatment of primary uterine cancer

Editor Piotr Lepka

Descriptive summary

Alagkiozidis et al. studied the correlation between extend node dissection and overall survival in uterine carcinosarcoma, papillary serous and endometrioid adenocarcinoma. The results showed a positive association between the total and positive lymph node count (LNC) and improved OS independent of histological types. Also, total LNC was associated with significant reduction in risk of death during the first two years after surgery.

Mahdi et al. demonstrated that tumour size is highly correlated with lymph node metastasis and has an impact on disease-specific survival in patients with endometrioid cancer confined to the uterus. Positive nodes occurred only in 2.7% when tumour size was less than 2cm, 5.8% in tumours of 2-5cm, and 11% in tumours of > 5cm. In multivariate analysis, in patients with tumours > 5cm, tumour size was an independent predictor of disease-specific survival.

Backer et al. analysed survival outcomes in patients with EC who underwent surgical treatment in hospitals with varying surgical volume in the Netherlands. The author found no relation between number of cases done by hospital per year and relative survival. The authors state that concentration of care for women with EC may have limited value in improving survival outcomes.

Trans-tubal spread of carcinoma may be of clinical significance in EC prognosis. Ashley et al. compared clinical features of EC diagnosis between patients who developed endometrial carcinoma after tubal ligation (TL) and EC patients who had not undergone TL. Patients were recruited to the GOG 210 trial where data on TL history was collected. Women after TL had lower-stage disease compared to woman who without TL and were less likely to have peritoneal metastasis. In patients with high risk histology (carcinosarcoma, serous and clear cell tumours) patients after TL had better cancer-specific survival. However, when adjusted for stage, this difference remained significant only in clear cell carcinomas.

Neff et al. used a Markov state transition model to analyse the presumable benefits for patient's quality of life and cost-effectiveness of offering bariatric surgery to morbidly obese patients with early stage endometrial cancer. The results showed that decrease in BMI after weight loss surgery is associated with significant reduction in costs (26,080 $/QALYs (quality-adjusted life years) compared to routine care) and also improvement in patients' quality of life.

Bouwman et al. summarised the impact of BMI on surgical complications and outcomes in endometrial cancer surgery and emphasised that many of those complications may be avoided with a laparoscopic approach.

Solmaz et al. reviewed 104 EC patients with stage III-IV disease treated over 18 years. The results showed that LVSI and optimal cytoreduction are the most significant factors that affect survival rates in advanced endometrial cancer.

Five articles retrospectively compared open surgery with a minimal invasive approach. The favourable outcomes in terms less of intraoperative and less postoperative complications after minimal invasive surgery were confirmed.

Glasgow et al. compared minimal invasive techniques (robotic and laparoscopic) with open surgery. Patients who underwent laparotomy had more comorbidities and were more likely to have prior malignancies. Also, they were two times less likely to undergo adjuvant treatment. The extent of surgical staging and progression-free survival was similar for the surgical approaches. Overall survival was superior in the laparoscopy group.

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ENYGO ESGO European Network of Young Gynae Oncologists

Surgical treatment of primary uterine cancer

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Extent of lymph node dissection and overall survival in patients with uterine carcinosarcoma, papillary serous and endometrioid adenocarcinoma: A retrospective cohort study.	Alagkiozidis I et al.	Int J Surg.	http://www.ncbi.nlm.nih.gov/pubmed/26476418	
2	Tumor size is an independent predictor of lymph node metastasis and survival in early stage endometrioid endometrial cancer.	Mahdi H et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/25549769	
3	Effects of surgical volumes on the survival of endometrial carcinoma.	Becker JH et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26348315	
4	Relationships of Tubal Ligation to Endometrial Carcinoma Stage and Mortality in the NRG Oncology/ Gynecologic Oncology Group 210 Trial.	Felix AS et al.	J Natl Cancer Inst.	http://www.ncbi.nlm.nih.gov/pubmed/26089540	
5	Bariatric surgery as a means to decrease mortality in women with type I endometrial cancer - An intriguing option in a population at risk for dying of complications of metabolic syndrome.	Neff R et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26232518	
6	Stage-III and -IV endometrial cancer: A single oncology centre review of 104 cases.	Solmaz U et al.	J Obstet Gynaecol.	http://www.ncbi.nlm.nih.gov/pubmed/26467294	
7	Laparoscopy Versus Laparotomy in the Treatment of High-Risk Endometrial Cancer: A Propensity Score Matching Analysis.	Gao H et al.	Medicine (Baltimore).	http://www.ncbi.nlm.nih.gov/pubmed/26222865	
8	A comparison of outcomes following robotic-assisted staging and laparotomy in patients with early stage endometrioid adenocarcinoma of the uterus with uterine weight under 480 g.	Ulm MA et al.	GMIT	http://www.sciencedirect.com/science/article/pii/S2213307015001410	
9	Robotic versus laparoscopic versus open surgery in morbidly obese endometrial cancer patients - A comparative analysis of total charges and complication rates.	Chan JK et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26363212	
10	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/26002986	
11	The impact of BMI on surgical complications and outcomes in endometrial cancer surgery - An institutional study and systematic review of the literature.	Bouwman F et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26407479	
12	Early stage uterine serous carcinoma: Does surgical approach impact survival?	M. Clark et al.	JMIG	http://www.jmig.org/article/S1553-4650%2815%2900742-6/abstract	

LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Medical (chemo and radiotherapy) treatment of recurrent uterine cancer

Editor Ewa Surynt

Descriptive summary

There are three different issues discussed in the literature:

1 The medical treatment of recurrent endometrial cancer (EC):

a) Results of two II phase trials have been published: One of trebananib (selective angiopoietin 1/2 neutralizing peptibody) and another of cediranib (multi-tyrosine kinase inhibitor) in the treatment of recurrent or persistent EC. Please see report on "Emerging molecular targets in endometrial cancer" for details.

b) The review "The Therapeutic Challenge of Targeting HER2 in Endometrial Cancer" summarises the role of HER2 in endometrial cancer, with a focus on uterine serous carcinoma. The current limitations of anti-HER2 therapy in this disease site are reviewed, and mechanisms of drug resistance are outlined based on the experience in breast cancer. Potential opportunities to overcome inherent resistance to anti-HER2 therapy in EC are discussed, offering opportunities for further clinical studies with the goal to improve outcomes of these patients.

2 Another discussed problem was radiotherapy in recurrent EC.

Iwashita et al. reported a case of patient with a uterine clear cell adenocarcinoma (UCCA) who responded to radiotherapy on each relapse (vaginal wall and lungs), also including stereotactic radiotherapy.

During the subsequent 36-month follow-up, there has been no relapse. Although UCCA is resistant to treatment, radiotherapy may be effective in some cases, even after multiple recurrences. Radiotherapy may be considered as a treatment option in localised recurrent disease.

3 The last topic covers leiomyosarcomas and genetic heterogeneity of these tumours.

De Graaff et al. identified translocation t(6;14) in two cases. FISH breakpoint mapping of case L1339 reveals a breakpoint at chromosome 6p21.31 close to HMGA1, and a small deletion was observed on the distal side of the gene. A small homozygous deletion was also found in the breakpoint region of chromosome 14q24.1 involving ACTN1. The second case revealed a der(6)t(6;14)(p21.1;q21.3), with a duplication adjacent to the breakpoint at chromosome 6.

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	A phase II evaluation of cediranib in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group study.	Bender D et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26186911	
2	A phase II trial of trebananib (AMG 386; IND#111071), a selective angiopoietin 1/2 neutralizing peptibody, in patients with persistent/recurrent carcinoma of the endometrium: An NRG/Gynecologic Oncology Group trial.	Moore KN et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26171911	
3	A translocation t(6;14) in two cases of leiomyosarcoma: Molecular cytogenetic and array-based comparative genomic hybridization characterization.	de Graaff MA et al.	Cancer Genet.	http://www.ncbi.nlm.nih.gov/pubmed/26361850	
4	Successful radiotherapy for repeated recurrent uterine clear cell adenocarcinoma.	Iwashita A et al.	J Obstet Gynaecol Res.	http://www.ncbi.nlm.nih.gov/pubmed/26310385	
5	The Therapeutic Challenge of Targeting HER2 in Endometrial Cancer.	Diver EJ et al.	Oncologist.	http://www.ncbi.nlm.nih.gov/pubmed/26099744	

LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Emerging molecular targets in endometrial cancer

Editor Ines Vasconcelos

Descriptive summary

This last quarter two positive phase II trials for metastatic/recurrent endometrial cancer were published. These evaluated cediranib (a multi-tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) receptors) and ridaforolimus (a mTOR inhibitor).

The phase II study on cediranib enrolled 53 patients with persistent or recurrent endometrial cancer, resulting in a partial response in 12.5% and six-month EFS of 29%. Median PFS was 3.65 months and median OS was 12.5 months, thus meeting the trial's objectives. The trial evaluating ridaforolimus versus a progestin or investigator choice of chemotherapy in metastatic and recurrent endometrial cancer enrolled 130 patients, 64 receiving ridaforolimus. 38% of the patients in the ridaforolimus arm versus 71% of the patients in the comparator arm discontinued treatment as a result of disease progression. Median PFS was 3.6 months for ridaforolimus and 1.9 months for the comparator, while PFS rate for ridaforolimus versus comparator was 48% versus 18% at 16 weeks and 38% versus 15% at 24 weeks. 33% stopped treatment due to adverse events in the ridaforolimus arm versus 6% with the comparator. The most common (> 10%) grade 3 toxicities were hyperglycaemia, anaemia, and diarrhoea.

Moore et al. published a negative trial on trebananib (a selective angiopoietin 1/2 neutralizing peptibody) in persistent/recurrent endometrial cancer, enrolling 32 patients. Because only 3.1% of the patients showed a partial response with a PFS of 1.97 months and an OS of 6.6 months, trebananib showed insufficient single-agent activity to warrant further investigation at this dose/schedule.

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	A phase II evaluation of cediranib in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group study.	Bender D et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26186911	
2	Randomized Phase II Trial of Ridaforolimus in Advanced Endometrial Carcinoma.	Oza AM et al.	J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26077241	
3	A phase II trial of trebananib (AMG 386; IND#111071), a selective angiopoietin 1/2 neutralizing peptibody, in patients with persistent/recurrent carcinoma of the endometrium: An NRG/Gynecologic Oncology Group trial.	Moore KN et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26171911	

LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Cervical pre-invasive disease (diagnosis, management)

- Editor Geanina Dragnea

- Descriptive summary

Efficacy of vaccination

Dorton at al. retrospectively analysed registry data of 1,662 patients. Cytology and histology were compared between patients who were previously HPV-vaccinated and unvaccinated patients. Vaccinated patients had fewer high-grade lesions on both cytology (53% reduced odds) and histology (36% reduced odds) (1).

Screening tests

Cytology

A Dutch registry study compared the efficacy of SurePath, ThinPrep (both liquid-based cytology tests). SurePath was associated with increased CIN2+ detection (by 8%), but with increased CIN1 detection (by 14%) more false-positive tests for CIN compared to conventional cytology (2,3). Cervical cancer detection rates were unaffected

Human papillomavirus (HPV) detection

- 13 or 14 high-risk HPV types are recommended to be included for triage of ASCUS cytology. Testing for more possibly oncogenic types of HPV did not add benefit in detection of CIN2+ but increased the number of colposcopy biopsies (4).
- The high-risk HPV E6/E7 RNA assay may be used as a safe and effective adjunctive cervical cancer screening method (5). After 3 years of follow-up, women who had either neg HPV DNR or RNA test had a very low risk of CIN2+ (<0.3%).
- HPV16 RNA patterns assay-positivity in HPV16 DNA-positive women may help to distinguish between the need for immediate colposcopy and continued observation and may have a role in predicting disease progression (6).

New tests

- Compared to HPC hybrid capture 2, the flow cytometry (FCM) cervical cancer screening system had a high sensitivity and specificity and was able to evaluate the severity of disease quantitatively (7).
- POU4F3, FAM19A4 or PAX1 gene methylation testing (DNA methylation tests) can be used for the triage of high-risk HPV-positive women for detecting CIN3+ lesions (8,9,10).

Therapeutic vaccines

- This randomised phase IIb study assessed if VGX-3100, a synthetic plasmids targeting HPV-16 and HPV-18 E6 and E7 proteins could cause histopathological regression of CIN2/3 lesions. 167 patients were treated either with VGX-3100 or placebo. 49.5% of the VGX-3100 recipients showed regression compared to 30.5% in the placebo group. VGX-3100 is suggested to be further explored as a non-surgical treatment option in patients with CIN2/3 (11).
- A phase I dose escalation trial studied PepCan, with peptides covering the HPV type 16 E6 protein with a Candida skin test reagent as adjuvant in 24 patients with biopsy-proven CIN2/3. A dose-dependant regression rate of CIN 2/3 of 52-83% was observed, with evidence of a Th1 promoting effect by the adjuvant (12).
- Cervicovaginal vaccination with HPVE6/E7 recombinant vaccinia vaccine induced potent local HPV-16 E7 antigen-specific CD8+ T cell immune response in a mouse model of HPV16+ cervical cancer (13).

Pharmacological treatment

One review described the current evidence of imiquimod as a treatment modality in VIN, VAIN, and CIN. Complete response rates for CIN 2-3 and VAIN 1-3 ranged from 67 to 75% and 57 to 86% respectively. The use of imiquimod as a treatment modality in VIN, VAIN, and CIN has been reported to have an encouraging effect, but more randomised controlled trials, especially with longer follow-up data are necessary to determine the attributive therapeutic value (14).

Complications

This Cochrane review reports on fertility and early pregnancy outcomes (less than 24 weeks of gestation) in women with a history of CIN treatment (excisional or ablative) as compared to women that had not received treatment. Overall pregnancy rate were higher in the treated group, but the inter-study heterogeneity was high. Pregnancy rates in women with the intent to conceive were the same in both groups. Treatment for CIN was associated with an increased risk of miscarriage in the second trimester (1.6% versus 0.4%, RR 1.89, 95% CI 1.50-2.39). However, most of the studies were of retrospective design and small (15).

A nested case-control study assessed the risk of preterm birth following treatment for cervical disease. The increased risk following deep excision treatments (≥15 mm) remains high (17-18% versus 6.5% before CIN treatment) throughout the reproductive life (16).

Follow-up

This cohort study reported that women (all HIV negative) with a history of high-grade cervical, vulvar, or vaginal cytology, dysplasia, or cancer (high risk group) are more likely to test positive for HPV in the anal canal and have higher risk of anal intraepithelial neoplasia.

Cervical pre-invasive disease (diagnosis, management)

Descriptive summary (cont.)

13.4% in the high-risk group had anal dysplasia with 4.2% having anal intraepithelial neoplasia 2 or greater (17).

A meta-analysis suggests that treatment for CIN does not affect fertility but increases the risk of miscarriage in the second trimester (19).

The risk of preterm birth following deep excision treatments (≥15 mm) remains high (17-18% versus 6.5% before CIN treatment) throughout the reproductive life (20).

Recurrence

HPV-16/18 infection, CIN3+ excision, type 3 transformation zone, positive excision margins, crypt involvement, persistent HPV infection at 6-12 months and abnormal liquid-based cytology tests at 3-month follow-up are strong risk factors for residual/recurrent CIN2/3 after LEEP (21,22,23,24,25,26).

Follow-up

Women with a history of high-grade cervical, vulvar, or vaginal cytology, dysplasia, or cancer are more likely to have anal intraepithelial neoplasia (27).

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Comparing Cervical Cytology and Histology Among Human Papillomavirus--Vaccinated and -Unvaccinated Women in an Academic Colposcopy Clinic.	Dorton BJ et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26348184	
2	Comparing SurePath, ThinPrep, and conventional cytology as primary test method: SurePath is associated with increased CIN II+ detection rates.	Rozemeijer K et al.	Cancer Causes Control.	http://www.ncbi.nlm.nih.gov/pubmed/26458884	
3	Cervical histology after routine ThinPrep or SurePath liquid-based cytology and computer-assisted reading in Denmark.	Rebolj M et al.	Br J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26448176	
4	Impact of Possibly Oncogenic High-Risk Human Papillomavirus (HPV) Types in Triage for ASC-US Cervical Cytology Results.	Amarosa EJ et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/26125096	
5	Human Papillomavirus Oncogenic mRNA Testing for Cervical Cancer Screening: Baseline and Longitudinal Results From the CLEAR Study.	Reid JL et al.	Am J Clin Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26276778	
6	HPV16 RNA patterns defined by novel high-throughput RT-qPCR as triage marker in HPV-based cervical cancer precursor screening.	Höfler D et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26148764	
7	A novel highly sensitive and specific flow cytometry system for cervical cancer screening.	Han X et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26212521	
8	Triage of high-risk human papillomavirus-positive women by methylated POU4F3.	Pun PB et al.	Clin Epigenetics.	http://www.ncbi.nlm.nih.gov/pubmed/26300990	✓
9	Comparing the performance of FAM19A4 methylation analysis, cytology and HPV16/18 genotyping for the detection of cervical (pre)cancer in high-risk HPV-positive women of a gynecologic outpatient population (COMETH study).	Luttmer R et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26317579	
10	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	
11	Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial.	Trimble CL et al.	Lancet.	http://www.ncbi.nlm.nih.gov/pubmed/26386540	

Cervical pre-invasive disease (diagnosis, management)

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

No	Title	Authors	Journal	Link to abstract	Available as full free text
12	A phase I dose-escalation clinical trial of a peptide-based human papillomavirus therapeutic vaccine with Candida skin test reagent as a novel vaccine adjuvant for treating women with biopsy-proven cervical intraepithelial neoplasia 2/3.	Greenfield WW et al.	Oncoimmunology.	http://www.ncbi.nlm.nih.gov/pubmed/26451301	
13	Local HPV Recombinant Vaccinia Boost Following Priming with an HPV DNA Vaccine Enhances Local HPV-Specific CD8+ T Cell Mediated Tumor Control in the Genital Tract.	Sun YY et al.	Clin Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26420854	
14	Imiquimod in cervical, vaginal and vulvar intraepithelial neoplasia: A review.	de Witte CJ et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26335596	
15	Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia.	Kyrgiou M et al.	Cochrane Database Syst Rev.	http://www.ncbi.nlm.nih.gov/pubmed/26417855	
16	Is the increased risk of preterm birth following excision for cervical intraepithelial neoplasia restricted to the first birth post treatment?	Castañon A, et al.	BJOG.	http://www.ncbi.nlm.nih.gov/pubmed/25854594	
17	Anal Cytology and Human Papillomavirus Genotyping in Women With a History of Lower Genital Tract Neoplasia Compared With Low-Risk Women.	Robison K et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26551180	

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ENYGO ESGO European Network of Young Gynae Oncologists

Pathology of cervical cancer

Editor Borja Otero

Descriptive summary

MicroRNA

Research on invasive cervical cancer (ICC) microRNAs is lately rendering promising results both in cell lines and in cervical tissue samples. Preclinical studies in cell lines have demonstrated that miR-720 could play an important role in ICC development by promoting cell migration. (1) Once ICC has appeared an early and precise diagnosis would be desirable. 383 miRNAs have been found to be differentially expressed in ICC tissue samples compared to normal and cervical precancer tissue samples, 182 of them being differentially expressed in HPV-16/18-positive cell lines compared with HPV-negative cell lines. (2)

Two studies investigated the expressions of several mi-RNA in ICC tissues and corresponding non-cancer tissues using qRT-PCR and demonstrated that low expression of miR-203 is significantly associated with lymph node metastases and that low expression of mirR-7 is correlated with advanced FIGO stage, lymph node metastases, and advanced histological grade. Down regulation of these mRNAs and up regulation of miR-20a and miR-10a are linked to poor prognosis. (3,4) On the other hand, miR-195 acts as suppressor of proliferation and cell cycle. (5) mi-RNAs may be potential novel therapeutic targets in cervical cancer also because of their relation other to other growth factors (EGFR). (6,7)

ICC development

Expression of the cell polarity regulator Atypical protein kinase C λ /1 (aPKC / 1) has been studied as a prognostic factors in CIN, showing that overexpression of aPKC λ /1 in the lesion and its nuclear localization are independent risk factors for CIN progression. (8) Epstein-Bar virus may be a co-factor in cervical carcinogenesis. (9) Different DNA methylation patterns of HPV types and HPV infected cells have been investigated concluding that increased methylation of both of them are highly associated with the development of ICC. (10,11) Other metabolism-related proteins such as glucose 6 phosphate dehydrogenase (G6PD) and VEGF family members have been related to tumour growth and proliferation in ICC tissue samples. (12,13) Apart form all these external factors, there is evidence of an individual susceptibility as Human Leukocyte Antigen (HLA) class II DRB1*1301 allele may protect against ICC. (14)

ICC diagnosis

New markers for ICC diagnosis have been investigated, both in serum and in histological samples. Higher serum levels of lysophosphatidylcholine have been reported in ICC in opposition to phosphatidylcholine serum levels suggesting that both molecules could be used as novel biomarkers to facilitate ICC diagnosis. (15)

Studying DNA methylation of certain candidate genes in CIN lesions, JAM3-M4 locus has shown to have a significantly increased specificity for CIN 3 and ICC compared to a triage marker of high risk HPV. (16)

ICC prognosis

One of the most important prognostic factors of ICC is the presence of lymph node metastases. High DLL4 expression may predict pelvic lymph node metastases and poor survival in cervical cancer based on results of one study comparing its expression in cancer and normal tissues samples. (17) Moreover tumour free but HPV-mRNA positive sentinel lymph nodes are independent prognostic factors. (18) Other prognostic factors are the presence of satellite lymphovascular space invasion, the tumour area occupied by Tbet+cells, and sphingokinase1 expression. (19-21) Finally, high-risk HPV determination after ICC treatment increases the specificity of cervical or vaginal cytology in predicting recurrence. (22)

ICC treatment outcome

DNA methylation is important not only for ICC development and diagnosis but also for treatment. Global DNA methylation in cervical cancer cell lines is associated with the development of drug resistance. (23)

Trying to reduce chemotherapy toxicity is an important goal and a study in cervical cancer lines has shown that inhibiting mTOR prior to Cisplatin treatment increased the cytotoxicity of a low concentration of Cisplatin. The authors speculate that a lower but equally effective dose of Cisplatin can be administered when give together with an mTOR inhibitor. This may help to decrease the dose-dependant toxicity associated with Cisplatin. This may be particularly important, as mTOR is over-expressed in both LSIL and ICC tissue. (24)

Novel therapeutic approaches

Finally, the study of several molecules such as programmed death ligand 1 (PDL1) and MCT1 have been shown to be key elements of ICC development and may serve as potential therapeutic targets in ICC. (25,26)

Pathology of cervical cancer

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	MicroRNA-720 promotes in vitro cell migration by targeting Rab35 expression in cervical cancer cells.	Tang Y et al.	Cell Biosci.	http://www.ncbi.nlm.nih.gov/pubmed/26413265	✓
2	Novel MicroRNA signatures in HPV-mediated cervical carcinogenesis in Indian women.	Sharma S et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26508022	
3	Identification of microRNAs (miR-203/miR-7) as potential markers for the early detection of lymph node metastases in patients with cervical cancer.	Seifoleslami M et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26490989	
4	Upregulation of miR-20a and miR-10a expression levels act as potential biomarkers of aggressive progression and poor prognosis in cervical cancer.	Safari A et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26427662	
5	MicroRNA-195 inhibits proliferation of cervical cancer cells by targeting cyclin D1a.	Wang N et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26511972	
6	miR-133a inhibits cervical cancer growth by targeting EGFR.	Song X et al.	Oncol Rep.	http://www.ncbi.nlm.nih.gov/pubmed/26134491	
7	MicroRNA-142-3p inhibits cell proliferation and invasion of cervical cancer cells by targeting FZD7.	Deng B et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/25976503	
8	Aberrant Expression of the Cell Polarity Regulator aPKC / is Associated With Disease Progression in Cervical Intraepithelial Neoplasia (CIN): A Possible Marker for Predicting CIN Prognosis.	Mizushima T et al.	Int J Gyn Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26535980	
9	Possible contributing role of Epstein-Barr virus (EBV) as a cofactor in human papillomavirus (HPV)-associated cervical carcinogenesis.	Aromseree S et al.	J Clin Virol.	http://www.ncbi.nlm.nih.gov/pubmed/26551071	
10	Different DNA methylation pattern of HPV16, HPV18 and HPV51 genomes in asymptomatic HPV infection as compared to cervical neoplasia.	Simanaviciene V et al.	Virol.	http://www.ncbi.nlm.nih.gov/pubmed/26119875	
11	Methylation of Cervical Neoplastic Cells Infected With Human Papillomavirus 16.	Ki EY et al.	Int J Gyn Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26552048	
12	Reprogramming energy metabolism and inducing angiogenesis: co-expression of monocarboxylate transporters with VEGF family members in cervical adenocarcinomas.	Pinheiro C et al.	BMC Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26525902	✓
13	Elevated glucose-6-phosphate dehydrogenase expression in the cervical cancer cases is associated with the cancerigenic event of high-risk human papillomaviruses.	Hu T et al.	Exp Biol Med (Maywood).	http://www.ncbi.nlm.nih.gov/pubmed/25616277	
14	Human leukocyte antigen class II DRB1*1302 allele protects against cervical cancer: At which step of multistage carcinogenesis?	Matsumoto K et al.	Cancer Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26235935	✓
15	Identification of phosphatidylcholine and lysophosphatidylcholine as novel biomarkers for cervical cancers in a prospective cohort study.	Yin MZ et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26566624	
16	JAM3 methylation status as a biomarker for diagnosis of preneoplastic and neoplastic lesions of the cervix.	Yin A et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26517242	
17	DLL4 as a predictor of pelvic lymph node metastasis and a novel prognostic biomarker in patients with early-stage cervical cancer.	Yang S et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26546434	
18	Prognostic value of HPV-mRNA in sentinel lymph nodes of cervical cancer patients with pN0-status.	Dürst M et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26008982	
19	Satellite lymphovascular space invasion: An independent risk factor in early stage cervical cancer.	Pol FJ et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26126782	
20	The tumor area occupied by Tbet+ cells in deeply invading cervical cancer predicts clinical outcome.	Gorter A et al.	J Transl Med.	http://www.ncbi.nlm.nih.gov/pubmed/26357849	✓

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Pathology of cervical cancer

Relevant articles retrieved May-Nov 2015 (cont.)

No	Title	Authors	Journal	Link to abstract	Available as full free text
21	Sphingosine kinase 1 is a reliable prognostic factor and a novel therapeutic target for uterine cervical cancer.	Kim HS et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26311741	
22	The Role of High-Risk Human Papilloma Virus Testing in the Surveillance of Cervical Cancer After Treatment.	Yu MC et al.	Arch Pathol Lab Med.	http://www.ncbi.nlm.nih.gov/pubmed/26516940	✓
23	Changes in DNA methylation are associated with the development of drug resistance in cervical cancer cells.	Chen CC et al.	Cancer Cell Int.	http://www.ncbi.nlm.nih.gov/pubmed/26464562	✓
24	The role of mTOR during cisplatin treatment in an in vitro and ex vivo model of cervical cancer.	Leisching GR et al.	Toxicology.	http://www.ncbi.nlm.nih.gov/pubmed/26201060	
25	Enhanced expression of PD L1 in cervical intraepithelial neoplasia and cervical cancers.	Mezache L et al.	Mod Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26403783	
26	STAT3:FOXM1 and MCT1 drive uterine cervix carcinoma fitness to a lactate-rich microenvironment.	Silva LS et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26563366	

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Surgical treatment of primary cervical cancer

Editor Mandic Aljosa and Matteo Morotti

Descriptive summary

Several studies evaluated the role of conservative surgery in cervical cancer. Togami et al. showed that patients with tumour size ≤2 cm had a significantly lower incidence of parametrial invasion, lymph node metastasis, lymph vascular space involvement, and recurrence than patients with tumour size >2 cm, suggesting that less radical surgery may be appropriate in these cases.

Yamazaki et al. determined pre-treatment risk factors for parametrial invasion (PI) in stage IB1 cervical cancer. Less radical surgery may become an option for patients with MRI-based tumour diameter <25 mm, MRI-based volume index <5,000 mm3, and negativity for SCC-Ag and CA-125.

Kong et al. investigated clinicopathologic prognostic factors associated with recurrence after treatment with laparoscopic/robotic radical hysterectomy (LRH/RRR). Multivariate analysis demonstrated that laparoscopic intracorporeal colpotomy represented a strong prognostic factor related to disease recurrence. Disease recurrence was higher in the LRH/RRH-IC group than in the LRH-VC group (16.3% vs. 5.1%, P = 0.057), with five patients in the LRH/RRH-IC group experiencing intraperitoneal spreads.

Chiantera et al. analysed 71 patients, FIGO stage IA2–IB1 treated with laparoscopic total mesometrial resection (L-TMMR). The median operative time was 260 min, estimated blood loss was 100 cm^3, and the median length of hospital stay was 6 days. Only 8 intra-operative complications were observed. The authors concluded that L-TMMR can be safely performed in selected cervical cancer patients and further larger prospective trials are needed to evaluate the oncological outcomes of patients undergoing this surgical procedure.

Other studies reported on the primary treatment of patients with bulky early stage cervical cancer (primary surgery, neoadjuvant chemotherapy (NACT) followed by surgery or primary chemoradiation (CT+RT)). Derks et al. included 129 patients who underwent a radical hysterectomy with pelvic lymphadenectomy for stage IB2/IIA2 cervical cancer and found a five-year disease specific survival of 84%, with pelvic recurrences in only 8% of the cases. Musaev et al. compared the radical surgery group with the NACT group. No significant difference in survival was observed among the groups. Regarding surgical training purposes, Kong et al. found that gynaeoncology fellows, even without abdominal RH experience, might reach an acceptable level of surgical proficiency in LRH after approximately 20 cases.

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Surgical treatment of primary cervical cancer

- Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Is It Possible to Perform Less Radical Surgery for Invasive Uterine Cervical Cancer?	Togami S et al.	Gynecol Obstet Invest.	http://www.ncbi.nlm.nih.gov/pubmed/26584181	
2	Pretreatment risk factors for parametrial involvement in FIGO stage IB1 cervical cancer.	Yamazaki H et al.	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26197769	✓
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	Treatment strategies for stage IB cervical cancer: A cost-effectiveness analysis from Korean, Canadian and US perspectives.	Lee JY et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26548733	
5	Learning curve analysis of laparoscopic radical hysterectomy for gynecologic oncologists without open counterpart experience.	Kong TW et al.	Obstet Gynecol Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26430662	✓
6	Prognostic and Safety Roles in Laparoscopic Versus Abdominal Radical Hysterectomy in Cervical Cancer: A Meta-analysis.	Cao T et al.	J Laparoendosc Adv Surg Tech.	http://www.ncbi.nlm.nih.gov/pubmed/26584414	
7	Survival rate comparisons amongst cervical cancer patients treated with an open, robotic -assisted or laparoscopic radical hysterectomy: A five year experience.	Mendivil AA et al.	Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26409687	
8	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	
9	Results of radical surgery in patients with stage IB2/IIA2 cervical cancer.	Derks M et al.	Acta Obstet Gynecol Scand.	http://www.ncbi.nlm.nih.gov/pubmed/26575692	
10	Assessment of primary radical hysterectomy and neoadjuvant chemotherapy followed by radical hysterectomy in Stage IB2, IIA bulky cervical cancer.	Musaev A et al.	Eur J Gynaecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26513887	

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Radiotherapy in the management of primary cervical cancer

Editor Sabita Nair

Descriptive summary

1. Bradbury et al. performed a retrospective study of 92 women with stage IB2 cervical cancer treated with surgery or CT+RT. Lymph node metastasis was a significant risk factor of OS and PFS. Most women required adjuvant therapy after surgery because of positive lymph nodes. Overall survival and PFS were higher for women undergoing surgery alone (91.7% and 83.3%) compared with women requiring adjuvant treatment after surgery (54.8% and 51.4%) and those having primary CT+RT (60% and 56%). Nodal assessment should guide definite treatment in those patients in order to identify a group of low-risk women who can be offered surgical treatment alone.

2. Samerdokiene et al. studied the occurrence of second primary malignancy (SPM), which is the most serious late adverse effect after radiotherapy. Patients were treated between 1989 and 1999 with 60 Co teletherapy and HDR brachytherapy with either 252 Cf or 60 Co. 5 SPMs were observed, 5.3% of all patients with no difference between the two HDR brachytherapies (p=0.68). As cure rates are continuously improving, monitoring of long-term treatment effects is important.

3. A prospective phase II clinical trial enrolled 24 patients with locally advanced squamous cell carcinoma of the cervix (IIB - IIIB) to study the feasibility, efficacy, and response rate of neoadjuvant low-dose radiation and chemotherapy with paclitaxel and carboplatin (three weekly for two cycles) (LDCRT) before chemoradiation (CRT).

Radiological complete or partial response rate was 40% and 60%, respectively after LDCRT with acceptable toxicity and PFS of 84% at 2.5 years.

4. A retrospective analysis of patients with localised cervical carcinoma treated with chemoradiation showed that chemoradiotherapy using image-guided intensity –modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) has excellent tumour control and tolerability, based on both disease free survival and toxicity and could be successfully delivered in a rural cancer setting.

5. This study assessed cost-effectiveness of three strategies in the treatment of Stage Ib cervical cancer in the US, Canada, and Korea: (1) radical hysterectomy followed by tailored adjuvant therapy (primary surgery), (2) primary chemoradiation, and (3) an MRI-based triage strategy, in which patients without risk factors in preoperative MRI underwent primary surgery and those with risk factors underwent primary chemoradiation. The MRI based triage strategy was shown to be more cost effective than primary surgery or primary chemoradiation.

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Pathological Risk Factors and Outcomes in Women With Stage IB2 Cervical Cancer Treated With Primary Radical Surgery Versus Chemoradiotherapy.	Bradbury M et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26244756	✓
2	Second primary malignancies after radiotherapy including HDR 252Cf brachytherapy for cervical cancer.	Samerdokiene V et al.	Brachytherapy.	http://www.ncbi.nlm.nih.gov/pubmed/26194049	
3	Low-dose fractionated radiation and chemotherapy prior to definitive chemoradiation in locally advanced carcinoma of the uterine cervix: Results of a prospective phase II clinical trial.	Das S et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26013695	
4	Definitive Chemoradiotherapy for Carcinoma of the Cervix using Image-Guided IMRT and VMAT: Outcomes from a Rural Regional Cancer Centre.	Mohd Tahir AR et al.	Poster presented at The Royal Australian and New Zealand College of Radiologists Annual Scientific Meeting, 2015	http://posterng.netkey.at/ranzcr/viewing/index.php?module=viewing_poster&task=&pi=131348	✓
5	Treatment strategies for stage IB cervical cancer: A cost-effectiveness analysis from Korean, Canadian and US perspectives.	Lee J Y et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26548733	

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Medical treatment of primary or recurrent cervical cancer

Editor Kristina Lindemann

Descriptive summary

1. Sage et al.: The core purpose of this GCIG roadmap was to develop consensus around several concepts, which could be taken forward by GCIG for international collaborative trials in cervical cancer. Even though is was acknowledged that the development of clinical trials in underdeveloped countries was an often unmet medical need, suggesting economic and operational changes were beyond the scope of this meeting. The GCIG seeks to increase its participation in phase II trials in order to avoid the risk of becoming irrelevant to the new world of targeted therapies. Areas of priority for further research: (1) Fertility-sparing surgery: What is the optimal management for bulky, early stage disease (2-5 cm)? A trial to study the role of surgical evaluation of lymph nodes before neoadjuvant chemotherapy (NACT) (imaging vs. laparoscopic staging), the ideal chemotherapy regimen, and optimal fertility-preserving surgery after NACT is suggested. (2) Sentinel-node mapping: Still not considered standard treatment, as validation by more large-scale practices is lacking. The significance and the therapeutic consequences of micrometastases detected by ultrastaging are still unknown. GCIG proposes a prospective multicentre international trial, evaluating the role of SN mapping including quality assurance, ultrastaging, and a standardization of the procedure. (3) The potential role of intensity-modulated radiotherapy (IMRT) was highlighted. (4) Patients with positive para-aortic nodes are those at highest risk of systemic relapse (>40%). Trials testing additional novel maintenance systemic therapies could be feasible in this population. (5) Some challenges with regard to clinical trial design in patients with metastatic disease were highlighted. All combination treatments come at the cost of increased toxicity and may therefore not be tolerated by the often frail patients with metastatic disease. New initiatives should be proposed for these patients who is not able to receive the triple combination (CT+Bev) that may become standard as the control arm in clinical trials. (6) Smaller biomarker driven phase II trials are considered to be feasible and potential drugable pathways are discussed.

2. Symonds et al. enrolled 69 relapsed/metastatic cervical cancer patients in a randomised, double-blind, placebo-controlled phase II trial of chemotherapy (Carbo/Taxol) +/- cediranib 20 mg until progression. PFS was significantly longer in the cediranib arm (median 8.1 vs. 6.7 months, one-sided p=0·032). There was no difference in overall survival (underpowered). Diarrhoea was again shown to be the most common non-haematological side effect of cediranib (16% grade 3). The increase in neutropenia in the cediranib arm was associated with a small but significant increase in neutropenic sepsis. Serum VEGFR2 was significantly decreased in the cediranib arm, but the number of evaluable patients was small, and the reductions were not associated with response or PFS.

3. Cibula: The role of neoadjuvant chemotherapy for locally advanced cervical cancer with focus on the potential to safely reduce surgical radicality is discussed. There may also be the potential to reduce the necessity for adjuvant radiochemotherapy by decreasing lymph node involvement.

4. Lapresa et al: Review regarding the use of neoadjuvant chemotherapy. The roles of NACT prior to radiotherapy and radical surgery are discussed separately. The control arm in all studies to date has not been chemo-radiation, which is now the standard of care for locally advanced cervical cancer. Therefore, the control arm in most trials is underperforming.

4. and 5. ESGO 2015: Two trials were presented as posters on the role of dose-dense paclitaxel and carboplatin in the neoadjuvant setting before fertility preserving surgery. The regimen achieved comparable RECIST and pathologic response rates as reported with TIP but no formal comparison was made.

6. Menderes et al.: This review discussed the molecular biology of cervical cancers and the potential mechanisms by which the immunotherapy approach could be a valid therapeutic strategy.

7. Angioli et al.: 200 stage Ib2-IIb patients were randomised to 4 or 6 cycles of cisplatin+paclitaxel after NACT plus radical surgery. Initially, 249 were assessed for the protocol. Due to exclusions (i.e., 15% were excluded prior to surgery due to progression/stable disease on NACT), 200 were finally randomised. Oncological outcomes were comparable, with expected less toxicity when less chemo was given. No formal comparison with chemoradiation was made, even though the OS data seems favourable. More efforts should be made to identify reliable prognostic factors that would allow choosing the best combination of available treatment modalities.

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Medical treatment of primary or recurrent cervical cancer

- Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Advances and Concepts in Cervical Cancer Trials - A Road Map for the Future.	Sagae S et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26569057	✓
2	Cediranib combined with carboplatin and paclitaxel in patients with metastatic or recurrent cervical cancer (CIRCCa): a randomised, double-blind, placebo-controlled phase 2 trial.	Symonds P et al.	Lancet Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26474517	✓
3	A Novel Perspective of Neoadjuvant Chemotherapy in Locally Advanced Cervical Cancer.	Cibula D.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26603625	
4	Neoadjuvant chemotherapy in cervical cancer: an update.	Lapresa et al.	Expert Rev Anticancer Ther.	http://www.ncbi.nlm.nih.gov/pubmed/26402247	
5	Neoadjuvant chemotherapy followed by large cone resection as fertility-sparing therapy in stage IB cervical cancer.	Salihi R et al.	ESGO-0980	http://eacademy.esgo.org/esgo/2015/19th/108169/rawand.salihi.neoadjuvant.chemotherapy.followed.by.large.cone.resection.as.html?f=m2	✓
6	Neoadjuvant dose dense weekly paclitaxel - carboplatin in cervical cancer.	Salihi R et al.	ESGO-0984	http://eacademy.esgo.org/esgo/2015/19th/108172/rawand.salihi.neoadjuvant.dose.dense.weekly.paclitaxel.-.carboplatin.in.html?f=m2	✓
7	Immunotherapy and targeted therapy for cervical cancer: an update.	Menderes G et al.	Expert Rev Anticancer Ther.	http://www.ncbi.nlm.nih.gov/pubmed/26568261	
8	A randomized controlled trial comparing four versus six courses of adjuvant platinum-based chemotherapy in locally advanced cervical cancer patients previously treated with neo-adjuvant chemotherapy plus radical surgery.	Angiolo R et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26428942	

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

Editor Kamil Zalewski

Descriptive summary

The majority of articles published in this period of time focused on vaginal squamous intraepithelial lesions. Sopracordevole et al. reviewed the incidence of occult invasive vaginal cancer in a group of 86 women with previously diagnosed vaginal high-grade squamous intraepithelial lesions (HSILs). They concluded that women diagnosed with VaIN3 should be treated with excisional procedures as a first-line surgical approach, given the risk of occult invasive disease in 10% of the cases. Women diagnosed with VaIN2 and with previous hysterectomy for human papillomavirus-related cervical diseases should always be carefully evaluated and possibly excised, given the higher risk of histopathological upgrading of lesions (33.3%) and the potential risk of occult vaginal cancer.

Other authors studied different modalities of VAIN treatment. Zolciak-Siwinska et al. retrospectively evaluated the efficacy of high-dose-rate brachytherapy of vaginal intraepithelial neoplasia. They found it to be an effective method of treatment, with a low recurrence rate (1/20; 5%). As expected, the study indicated that EQD2 ≥70Gy should not be applied to the vagina as this dose generates unacceptable toxicity (71.4%). Tainio et al. conducted a highly appreciated prospective randomised study evaluating the effectiveness of laser vaporization and vaginal imiquimod for that disease. Although the study group was not large the preliminary results indicate a tendency for higher HPV clearance rates among patients treated with vaginal imiquimod when comparing with laser (63% vs. 100%) and equal effectiveness in histological regression from VAIN at 4 months (75% and 78%). Choi et al. presented photodynamic therapy (PDT) and its long-term efficacy in preserving normal anatomy and function in women with premalignant lesions of the lower genital tract. Effectiveness of such treatment should be interpreted with caution because of the small and heterogenic cohort. Due to the fact that VAIN patients are thought to have a quite long life expectancy, long-term side effects of their treatment should be considered. The treatment method should take into account sparing reproductive and sexual abilities and preserving organ function.

Regarding premalignant lesions of the vulva, Pepas et al. reviewed the value of medical interventions for high-grade vulvar intraepithelial neoplasia. They concluded that topical imiquimod is a safe and effective treatment for high-grade VIN (uVIN), even though local side effects may necessitate dose reductions. The study also highlighted the need for longer-term follow-up data to assess the risk of progression to vulvar cancer. Gentile et al. didn't find a lower recurrence rate in a prospective study comparing patients with VIN treated with surgery alone and patients treated with surgery plus imiquimod. Patients after surgical treatments do not require adjuvant treatment.

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Vaginal Intraepithelial Neoplasia: Histopathological Upgrading of Lesions and Evidence of Occult Vaginal Cancer.	Sopracordevole F et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/26461231	
2	Brachytherapy for vaginal intraepithelial neoplasia.	Zolciak-Siwinska A et al.	Eur J Obstet Gynecol Reprod Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26334358	
3	Medical interventions for high-grade vulval intraepithelial neoplasia.	Pepas L et al.	Cochrane Database Syst Rev.	http://www.ncbi.nlm.nih.gov/pubmed/26284429	
4	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	
5	Randomised trial of treatment and follow-up of vaginal intraepithelial neoplasia.	Tainio K et al.	Poster presented at the 19th International Meeting of the European Society of Gynaecological Oncology (ESGO 2015)	http://eacademy.esgo.org/esgo/2015/19th/107751/michael.friedrich.evaluation.of.sentinel.lymphnodebiopsy.in.vulvar.cancer.html	

Vulvovaginal adenocarcinoma/melanoma/sarcoma

Editor Anna Dückelmann

Descriptive summary

Since these entities are quite rare and there are not very many articles covering these subjects, I decided to extend the search period to 6 months. Chokoeva et al. give a very good overview about malignant tumours of the vulva, in particular adenocarcinomas and malignant melanoma of the vulva. Biopsy for histological investigations is a prerequisite for early diagnosis. Introducing proper treatment requires an interdisciplinary approach of dermatologists with gynaecologists, urologists, radiotherapists, and oncologists.

An Australian study on melanomas of the vulva or vagina present 85 patients affected by this rare disease. Significant predictors of poorer disease-free survival included increasing Breslow thickness, increasing tumour mitotic rate, and ulceration. The authors recommend utilising the American Joint Committee on Cancer (AJCC) cutaneous melanoma staging system for vulval and vaginal melanomas. Surgery remains the mainstay of vulval and vaginal melanoma treatment with a pathologic margin of at least 1mm. Further staging with sentinel node biopsy may be advantageous. The authors suggest the establishment of an international data registry for melanomas of the vulva and vagina.

Filippetti et al. report a rare case of amelanotic melanoma in a young girl, originally suspected to be a pyogenic granuloma.

Rouzbahman et al. present in their study molecular characteristics and specifically, the frequency of BRAF, C-KIT, and NRAS mutations in vulvar and vaginal melanomas.

Kita et al. report an interesting case of mucinous adenocarcinoma at the anterior aspect of the neovagina in a 67-year-old female with a history of neovagina construction for Rokitansky syndrome 40 years ago. The authors stress the importance of performing screening and surveillance endoscopy in both the colon and neovagina.

Tunitsky-Bitton et al. present a case of Ewing sarcoma in an adolescent. According to the authors these rare tumours should be considered part of the differential diagnosis of a vulvar or vaginal mass. Complete surgical resection should be the first step in managing a firm mass in the vulva or vagina. Appropriate molecular and histopathological studies are crucial in determining the correct diagnosis. Specific treatment recommendations are lacking for extraosseous ES, and the treatment management should follow the recommended therapy for osseous Ewing sarcoma, which includes complete resection, multiagent chemotherapy, and, possibly, the addition of local radiation therapy.

Chokoeva et al. cover the extensive topic of vulvar sarcomas in a comprehensive way. Sarcomas of the vulva are characterised by non-specific clinical manifestations, aggressive behaviour, high metastatic potential, and mortality. Prognosis is poor, and depends mainly on the size of the primary lesion, tumour invasion, and mitotic activity. Lesions greater than 5 cm in diameter, with infiltrating margins, extensive necrosis, and with more than five mitotic figures per 10 highpower fields, are associated with even poorer prognosis, and indicative of possible recurrence after surgical resection.

Wang et al. collected 8 patients with primary vaginal sarcoma. They conclude: given that squamous cell carcinoma of the vagina occurs at a relatively older age, sarcoma should be taken into account when a younger patient presents with vaginal mass. The therapy and prognosis of vaginal sarcoma require further exploration.

Bassa et al. present the rare case of primary vaginal leiomyosarcoma in pregnancy.

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Vulvovaginal adenocarcinoma/melanoma/sarcoma

- Relevant articles retrieved Mar-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Amelanotic Vulvar Melanoma: A Case Report.	Filippetti R et al.	Am J Dermatopathol.	http://www.ncbi.nlm.nih.gov/pubmed/25993407	
2	Melanoma of the vulva and vagina: principles of staging and their relevance to management based on a clinicopathologic analysis of 85 cases.	S Seifried et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/25384702	
3	MRI findings in primary vaginal melanoma-a report of four cases.	QY Liu et al.	Clin Imaging.	http://www.ncbi.nlm.nih.gov/pubmed/25560672	
4	Vulvar cancer: a review for dermatologists.	AA Chokoeva et al.	Wien Med Wochenschr.	http://www.ncbi.nlm.nih.gov/pubmed/25930015	
5	Mucinous adenocarcinoma emerging in sigmoid colon neovagina 40 years after its creation: a case report.	Y Kita et al.	World J Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26159897	
6	Malignant Melanoma of Vulva and Vagina: A Histomorphological Review and Mutation Analysis-A Single-Center Study.	M Rouzbahman et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/26225944	
7	Primary Ewing Sarcoma Presenting as a Vulvar Mass in an Adolescent: Case Report and Review of Literature.	E Tunitsky-Bitton et al.	J Pediatr Adolesc Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26211932	
8	Vulvar sarcomas: Short guideline for histopathological recognition and clinical management. Part 1.	AA Chokoeva et al.	Int J Immunopathol Pharmacol.	http://www.ncbi.nlm.nih.gov/pubmed/25816394	
9	Vulvar sarcomas: Short guideline for histopathological recognition and clinical management. Part 2.	AA Chokoeva et al.	Int J Immunopathol Pharmacol.	http://www.ncbi.nlm.nih.gov/pubmed/25816393	
10	Primary vaginal sarcoma: Experience of a regional cancer center in China.	Y Wang et al.	J Obstet Gynaecol Res.	http://www.ncbi.nlm.nih.gov/pubmed/26111799	
11	Leiomyosarcoma of the vagina in pregnancy.	B Bassa et al.	Eur J Gynaecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26189266	

LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Treatment of primary vulvar cancer

Editor Alejandro Aragona

Descriptive summary

Radical treatment of vulvar cancer may be mutilating and often entails aesthetical, functional, sexual, and psychological complications. Consequently, reconstruction of the acquired defects represents an important challenge for gynaecologic oncologists. Nowadays, there is no consensus on which reconstructive approach should be adopted for vulvoperineal defects. Options range from local and regional flaps (inferior gluteal flap, lotus petal flap), myocutaneous flaps (transverse rectus abdominis myocutaneous flap and gracilis myocutaneous flap) to perforator skin flaps such as deep inferior epigastric perforator (DIEP) flap and anterolateral thigh (ALT) flap or fasciocutaneous flaps such as pudendal thigh flap (PTF) and gluteal fold V-Y advancement flap. In this regard, five recent studies have been retrieved for the second issue of the LiFE report. A Chinese study evaluated the outcomes of vulvar reconstruction in patients with advanced or recurrent vulvar. According to the authors, perforator skin techniques, punctually ALT and DIEP flaps, are associated with a low rate of postoperative complications, decreased pain, and improved functional status (1). An Italian study reported a reconstructive algorithm based on the topography of the external vulvar defect and their experience with lotus petal flap and DIEP flap in defects consequent to half-vulvar resection or to total vulvar resection and in those defects involving also the vagina, respectively (2). A Spanish article also reached successful results with lotus petal flaps stressing the low complexity of this technique and its feasibility (3). A Japanese study showed promising results in terms of postoperative morbidity with the use of a V-Y advancement flap designed on the medial thigh (4). Finally, another Chinese group conducted a matched case-control study, in this instance with the aim of evaluating intraoperative measures that tend to improve postoperative complications rates. In this way, the authors highlighted the advantages of sartorius tendon transposition in comparison to sartorius standard transposition during inguinal lymphadenectomy in terms of improved patient recovery and improved life quality without compromised radicality (5).

Because the disease is rare and surgery is the mainstay treatment for early vulvar cancer, limited data are available on the outcomes of primary radiotherapy for vulvar cancer. Kim et al. retrospectively evaluated the prognostic factors and clinical outcomes of 56 patients with vulvar cancer treated with curative radiotherapy or concurrent chemoradiotherapy. They found that clinical tumour size ≥3 cm was a significant prognostic factor for disease-free survival and age ≥70 years was the most important prognostic factor for both disease-free and overall survival. In this study, modality treatment was chosen at the discretion of the treating physicians and radiation technique/doses given were variable, adjusting to tumour characteristics and technology available over the years of recruitment (6).

Two more retrospective studies were retrieved. The first one failed to determine an optimal value of the surgical margins after radical surgery (7). The second study, which focused on the role of adjuvant radiotherapy in patients with close or positive surgical margins (8), showed that the aforementioned approach reduced the mortality risk in patients with positive/close resection margins. The recently published American College of Radiology consensus guidelines suggest that patients with negative lymph nodes and surgical margins >8 mm for the primary tumour can be observed after surgery, whereas the optimal method of adjuvant therapy is yet to be established (9).

Continued on the next page ➲

LiFE | Literature for ENYGO

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Treatment of primary vulvar cancer

- Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Outcome of vulvar reconstruction in patients with advanced and recurrent vulvar malignancies.	Zhang W et al.	BMC Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26542779	✓
2	Vulvar Reconstruction by Perforator Flaps. Algorithm for Flap Choice Based on the Topography of the Defect.	Negosanti L et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26035125	
3	Vulvar reconstruction in vulvar cancer: "lotus petal" suprafascial flap.	Herraiz Roda L et al.	Gynecol Surg.	http://link.springer.com/article/10.1007%2Fs10397-015-0911-7	
4	Vulvar Reconstruction Following Surgery for Vulvar Cancer Using a Stepladder V-Y Advancement Medial Thigh Flap.	Nomura H et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26222487	
5	Clinical application of sartorius tendon transposition during radical vulvectomy: a case control study of 58 cases at a single institution.	Li L et al.	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26404124	✓
6	Treatment outcomes of curative radiotherapy in patients with vulvar cancer: results of the retrospective KROG 1203 study.	Kim Y et al.	Radiat Oncol J.	http://www.ncbi.nlm.nih.gov/pubmed/26484303	✓
7	How important is the pathological margin distance in vulvar cancer?	Baiocchi G et al.	Eur J Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26507171	
8	Adjuvant radiotherapy for vulvar cancer with close or positive surgical margins.	Ignatov T et al.	J Cancer Res Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26498775	
9	ACR Appropriateness Criteria® Adjuvant Therapy in Vulvar Cancer.	Jolly S et al.	Oncology (Williston Park).	http://www.ncbi.nlm.nih.gov/pubmed/26568534	✓

LiFE | Literature for ENYGO
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Prevention and management of complications in surgical treatment of gynaecological malignancies (i.e., lymphocele, urological, wound, etc.)

Editor Elisa Piovano

Descriptive summary

During the period covered by the second edition of the LiFE report, the majority of published studies focused on the factors affecting postoperative complications.

Ovarian cancer

Barber et al. showed in a retrospective study of 1072 patients that preoperative thrombocytosis and leukocytosis are associated with an increased risk of major postoperative complications. Patients with both of them experienced twice the rate of major complications and a fourfold increase in postoperative deaths.

Barber et al. published another retrospective study of 751 elderly patients who underwent primary surgery for the treatment of ovarian cancer. They developed a predictive model to estimate their risk of major postoperative complications. The model is based on variables that are known preoperatively: Laboratory values, ascites, race, smoking status, and albumin. The observed area under the receiver operator curve for this model was 0.725. They suggest a 50% rate of postoperative complication as a threshold, which produced model sensitivity of 9.8% and specificity of 98%.

Kumar et al. aimed to refine another model based on age, ASA score, preoperative albumin, and BMI to predict 90-day mortality after primary debulking surgery for advanced epithelial ovarian cancer. Another model based on the same variables plus surgical complexity predicted 30-day morbidity. Nomograms were created for each final model.

These models might be a useful tool for counselling patients and to best individualise primary treatment.

Doo et al. conducted a retrospective study of 1807 patients on the association between preoperative chemotherapy and postoperative morbidity and mortality. Postoperatively, the chemotherapy group had a higher blood transfusion rate and higher rate of infections (other than the incision site) when compared to the upfront-surgery group.

Matsuo et al. conducted a multicentre case-control study of 1308 patients (370 with ovarian clear cell carcinoma (OCCC) and 938 with serous ovarian carcinoma (SOC)) and reported that patients with advanced OCCC have the highest 2-year cumulative venous thromboembolism rate (43.1%).

Endometrial cancer

Backes et al. set up a retrospective study on 543 patients who underwent robotic staging surgery. They didn't find any statistically significant relationship between increasing BMI or preoperative comorbidities and postoperative complications. There appeared to be only a trend toward higher rates of complications with greater (3 or more) number of comorbidities.

Others

Kim et al.: This retrospective study of 533 patients determined the relationship between preoperative hypoalbuminemia and the development of complications after gynaecological cancer surgery. Hypoalbuminemic patients were more likely to develop postoperative complications compared to non-hypoalbuminemic patient (34.3% vs. 17.8%, P=0.022), had significantly longer median time to resumption of normal diet (3.3 vs. 2.8 days, P=0.005), and a longer length of postoperative hospital stay. In conclusion, these patients should be preoperatively identified and either be nutritionally supported or be considered with alternative treatment strategies that delay a potentially complicated surgery.

Studies cited below have not been conducted in patients with gynaecological cancers, but their results can certainly also be implemented in this field.

In a multicentre, double-blind randomised controlled trial, Deerenberg et al. compared the large bites suture technique (bites of 1 cm every 1 cm) with the small bites technique (bites of 5 mm every 5 mm) for fascial closure of midline laparotomy incisions, in terms of incisional hernia. Patients in the small bites group had a longer closure time but a lower incidence of incisional hernia. As this incision also is standard for debulking procedures, the small bites technique should be considered.

Two interesting retrospective studies (Kiran et al., Scarborough et al.) evaluated the role of bowel preparation with mechanical cleansing (MBP) and oral antibiotics (OAP) in elective colorectal resection: Both studies (8442 and 4999 patients, respectively) showed a significantly lower incidence of incisional surgical site infection, anastomotic leakage, and hospital readmission when complete bowel preparation is compared to no preparation. It should be noted that they did not find preoperative administration of either mechanical or oral antibiotics cleansing alone to significantly decrease the incidence of postoperative infective complications. Taken together, these findings provide strong support for the routine utilization of combined MBP and OAP in patients who are scheduled to undergo cytoreductive surgery for ovarian cancer. Of note, a Cochrane review from 2011 did not find any statistically significant evidence that patients benefit from mechanical bowel preparation, nor the use of rectal enemas.

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

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Association of Preoperative Thrombocytosis and Leukocytosis With Postoperative Morbidity and Mortality Among Patients With Ovarian Cancer.	Barber EL et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26551182	
2	A preoperative personalized risk assessment calculator for elderly ovarian cancer patients undergoing primary cytoreductive surgery.	Barber EL et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26432038	
3	Risk-prediction model of severe postoperative complications after primary debulking surgery for advanced ovarian cancer.	Kumar A et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26541980	
4	Association Between Preoperative Chemotherapy and Postoperative Complications in Patients Undergoing Surgery for Ovarian Cancer.	Doo DW et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26542594	
5	Venous thromboembolism, interleukin-6 and survival outcomes in patients with advanced ovarian clear cell carcinoma.	Matsuo K et al.	Eur J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26238017	
6	Robotic Hysterectomy for Endometrial Cancer in Obese Patients With Comorbidities: Evaluating Postoperative Complications.	Backes FJ et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26017249	
7	Preoperative hypoalbuminemia is a risk factor for 30-day morbidity after gynecological malignancy surgery.	Kim J et al.	Obstet Gynecol Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26430660	
8	Small bites versus large bites for closure of abdominal midline incisions (STITCH): a double-blind, multicentre, randomised controlled trial.	Deerenberg EB et al.	Lancet.	http://www.ncbi.nlm.nih.gov/pubmed/26188742	
9	Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery.	Kiran RP et al.	Ann Surg.	http://www.ncbi.nlm.nih.gov/pubmed/26258310	✓
10	Combined Mechanical and Oral Antibiotic Bowel Preparation Reduces Incisional Surgical Site Infection and Anastomotic Leak Rates After Elective Colorectal Resection: An Analysis of Colectomy-Targeted ACS NSQIP.	Scarborough JE et al.	Ann Surg.	http://www.ncbi.nlm.nih.gov/pubmed/26083870	

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Sentinel node mapping in gynaecological malignancies

Editor Anton Ilin

Descriptive summary

Wuntakal et al. retrospectively studied patients with early-stage cervical cancer (FIGO IA1 with LVSI to IIA) after SN detection with the gamma probe and blue dye. Most commonly, the sentinel lymph node (SLN) was located in the external iliac (38.6%), obturator (25.3%) or internal iliac (23.6%) regions.

Kleppe. et al. performed anatomical studies of the lymphatic drainage of the ovaries in 3 human female foetuses and tissues samples from 1 human cadaveric specimen. In all, 3 lymphatic pathways were detected: via the proper ligament of the ovaries toward the lymph nodes in the obturator fossa and the internal iliac artery, via the suspensory ligament toward the para-aortic and para-caval lymph nodes and via the round ligament to the inguinal lymph nodes. These pathways may play a role for detection techniques like sentinel node procedure, even though not standard in ovarian cancer, yet.

Tax et al. reviewed the current literature on the use of sentinel node detection in cervical cancer. Data of 4130 patients of whom 1275 had undergone ultrastaging were reviewed. Early stage cancer without suspicious pre-, and perioperative lymph nodes and bilateral negative SLNs after ultrastaging, were shown to have a very low residual risk of 0.08% (1/1257) of occult metastases. Based on this data, the authors recommend that a full pelvic lymph node dissection may be safe to omit in such cases.

Among all markers which are used in SLN procedure currently, indocyanine green (ICG) is the most commonly used. Buda et al. compared methylene blue (38 cases) and ICG (43 cases) for SLN mapping among patients with cervical and endometrial cancer. The overall detection rate was significantly higher in the ICG group with 100% (43 of 43) compared to 84% (34 of 38) for methylene blue. Also, bilateral detection rate was significantly higher, potentially reducing the need for complete node dissection.

Laios et al. studied a novel custom-made Near InfraRed fluorescence imaging system, which allows simultaneous bright-field imaging during open surgery and laparoscopic procedures. They present a prospective study of 49 women with early stage vulvar, cervical and endometrial cancer. According to their results, SLN detection rate approached 100% for all cancer types with no false negative cases after exclusion of cases performed in the learning curve (>30 cases) and dye optimisation process.

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review.	Tax C el al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26416173	
2	A prospective pilot study of detection of sentinel lymph nodes in gynaecological cancers using a novel near infrared fluorescence imaging system.	Laios A el al.	BMC Res Notes	http://www.ncbi.nlm.nih.gov/pubmed/26502876	✓
3	Optimizing Strategies for Sentinel Lymph Node Mapping in Early-Stage Cervical and Endometrial Cancer: Comparison of Real-Time Fluorescence With Indocyanine Green and Methylene Blue.	Buda A el al.	Int J of Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26397069	✓
4	Location of Sentinel Lymph Node in Cervical Carcinoma and Factors Associated With Unilateral Detection.	Wuntakal R el al.	Int J of Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26270124	✓
5	Understanding Lymphatic Drainage Pathways of the Ovaries to Predict Sites for Sentinel Nodes in Ovarian Cancer.	Kleppe M el al.	Int J of Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26397066	✓

Fertility sparing treatment in gynaecological malignancies

Editor Dimitris Papatheodorou

Descriptive summary

In this literature search on fertility sparing treatments in gynaecological malignancies, four (4) retrospective studies and four (4) literature reviews were retrieved plus a letter to the editor. A very interesting systematic review about the impact of fertility preservation counselling and treatment on psychological outcomes among women with cancer comes from Deshpande et al., published in Cancer. There is evidence supporting the psychological benefit of prompt fertility preservation counselling, but future research must be conducted to elucidate the long-term psychosocial effects of fertility preservation. Data regarding sexual satisfaction after fertility sparing surgery is published by Chan et al.. The authors recruited patients from the California Cancer Registry, and they concluded that while Fertility Sparing Surgery (FSS) may allow for post-treatment fertility, it may not confer a significant benefit with regard to sexual satisfaction or sexual QOL. Thus, the decision to perform FSS should not be dictated based on preservation of sexual functioning. Another review by Gressel et al. addresses the management options and fertility-preserving therapy for premenopausal endometrial hyperplasia and early-stage endometrial cancer (See also the chapter "Treatment of endometrial hyperplasia (biology, conservative and definitive treatment, follow-up"). The main results focus on risk reduction with lifestyle modification, weight loss, and glycaemic control, which can improve regression and overall health. A retrospective study comes from Laurelli et al. regarding fertility-sparing management of low-grade endometrial stromal sarcoma. Although this is a small cohort (6 patients), these preliminary data are promising and larger series will further evaluate the safety and efficacy of this particular standard of care. The last retrospective study comes from Chen et al. (See also the chapter "Treatment of endometrial hyperplasia (biology, conservative, and definitive treatment, follow-up"). This study evaluates the oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer. This study confirms previous findings about the efficacy of oral progestin, however obese patients have a lower probability of long-term success. Tomao et al. published a review of the most recently debated options for fertility preservation in gynaecologic oncology, including uterine transplantation after cervical cancer and FSS in malignant ovarian germ cell tumours. This update in FSS ends with a letter to the editor of J Gynecol Oncol by Ditto et al. regarding fertility-sparing surgery in high-risk ovarian cancer (stage IC, IA & IB grade 3). The authors conclude that this subgroup of patients should not be denied FSS. Accurate counselling and strict follow-up are necessary. Their opinion is based on a subanalysis of a group of patients with early-stage ovarian cancer (please check the first issue of the LiFE report for the reference by Ditto et al.). A final comment should be made on the latest consensus of the European Organisation for Treatment of Trophoblastic Diseases on the management of gestational trophoblastic diseases in Eur J Cancer by Bolze et al. In this consensus it is stated that: "Surgery is not recommended as first line treatment of low risk GTD for reproductive age women wishing to conceive". A more detailed view in this consensus can be found in the LiFE section for GTD.

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Fertility sparing treatment in gynaecological malignancies

- Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Fertility-sparing management of low-grade endometrial stromal sarcoma: analysis of an institutional series and review of the literature.	Laurelli G et al	Eur J Obs Gyn Repr Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26476800	
2	Recent advances for improving fertility in gynaecological cancer patients.	Liu Y et al.	Eur Rev Med Pharma Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26400526	
3	Management options and fertility-preserving therapy for premenopausal endometrial hyperplasia and early-stage endometrial cancer.	Gressel GM et al.	Int J Gyne Obst.	http://www.ncbi.nlm.nih.gov/pubmed/26384790	
4	Impact of fertility preservation counseling and treatment on psychological outcomes among women with cancer: A systematic review.	Deshpande NA al.	Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26264701	
5	Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer.	Chen M et al.	Int J Gyne Obst.	http://www.ncbi.nlm.nih.gov/pubmed/26493012	
6	Prognostic factors of oncological and reproductive outcomes in fertility-sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin in Chinese patients.	Zhou R et al.	Gynec Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26428941	
7	Special issues in fertility preservation for gynecologic malignancies.	Tomao F et al.	Crit Rev Oncol Hematol.	http://www.ncbi.nlm.nih.gov/pubmed/26358422	
8	Sexual satisfaction and quality of life in survivors of localized cervical and ovarian cancers following fertility-sparing surgery.	Chan JL et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26232519	
9	Fertility-sparing surgery in high-risk ovarian cancer.	Ditto A et al	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26197775	✓
10	Formalised 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	

Cancer in pregnancy

Editor Michael J. Halaska

Descriptive summary

In total, 13 publications were published within the selected period. One publication reported a summary of 20 cervical cancer patients. There were several reports on breast cancer, thyroid cancer, and non-small cell lung cancer.

A retrospective study of 50 pregnancy-associated melanomas compared with 122 non-pregnancy-associated melanomas found similar proliferation rates using mitotic count and two immunohistochemical markers of proliferation, phosphohistone H3 and Ki-67.

Advances in surgery for cervical cancer were described in two patients with cervical cancer diagnosed during pregnancy. Indocyanine green was used for detection of sentinel lymph nodes for the first time in the literature without any adverse effects.

Fetal doses from radiotherapy using CyberKnife were evaluated in a patient with a brain tumour, finding a maximum of 4,4 cGy which is below the safety threshold of 10 cGy.

A pivotal publication was presented in NEJM, presenting a prospective study evaluating cardiac and psychomotoric examinations of children prenatally exposed to chemotherapy. In it, 129 patients and matched controls were found to have similar outcomes without negative effects of prenatal treatment on the children at the age of 18 and 36 months.

The Leuven group reported on 3 incidental diagnosis of cancer during pregnancy after by non-invasive prenatal testing (NIPT) of over 4000 prospective pregnancies.

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	A comparative study of proliferative activity and tumor stage of pregnancy-associated melanoma (PAM) and non-PAM in gestational age women.	Merkel EA et al.	J Am Acad Dermatol.	http://www.ncbi.nlm.nih.gov/pubmed/26545488	
2	Laparoscopic Indocyanine Green Sentinel Lymph Node Mapping in Pregnant Cervical Cancer Patients.	Papadia A et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26476388	
3	Radiation dose to the fetus during CyberKnife radiosurgery for a brain tumor in pregnancy.	Pantelis E et al.	Phys Med.	http://www.ncbi.nlm.nih.gov/pubmed/26508017	
4	Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy.	Amant F et al.	N Engl J Med.	http://www.ncbi.nlm.nih.gov/pubmed/26415085	✓
5	Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing.	Amant F et al.	JAMA Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26355862	

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

Editor Manuela Undurraga

Descriptive summary

The articles published during the period were mainly case reports, retrospective studies and reviews/updates. There were no meta-analysis or randomised controlled trials, and there was 1 patient information summary written by the National Cancer Institute of the US. There was also 1 article by Golfier that described the approach taken by the French for the development of a GTD biobank.

Pathology

Lertkhachonsuk et al. looked at the LINE-1 methylation patterns and found that a reduction in its partial methylation occurs early before the clinical appearance of malignant transformation. They suggest that further studies are needed, as it seems to be a promising marker. Mirkovic studied the GATA3 transcriptor factor that seems to be present in GTD, but the investigation of this marker is just beginning. Bynum et al. demonstrated in their study a higher frequency of heterozygous/dispermic complete hydatidiform moles among invasive cases compared with those lacking invasion, but do not support the use of zygosity data for risk assessment of invasion.

Diagnosis

Cormano et al. present a new case report detailing the hook effect that can delay diagnosis of GRD, due to the saturation of antibodies used in pregnancy tests that can occur with hCG values over 500,000. Eysbouts et al. report that incidence rates since 2004 have remained stable, associated with a decrease in unspecified molar pregnancies, both probably due to the improvement in diagnostic techniques. The same stability in incidence was found by Sun et al. with lower levels of hCG at diagnosis and an increase in age at diagnosis.

Treatment

Bolze et al. found that patients with a FIGO score of >= 13 had an increased risk of death (38.4% vs. 12%), particularly early death, as 75% of patients that died within 4 weeks of treatment initiation had a FIGO score of >=13. Vree et al., in a retrospective study, found that lung metastasis do not influence MTX resistance, but seem to increase the risk for recurrence and death of disease.

Follow-up

In a retrospective study, the Charing Cross team confirmed the harmlessness of using hormonal contraception in the follow-up of GTD, as it does not increase time to hCG remission, GTN development or high-risk FIGO score. Braga et al. also suggest that follow-up may need to be increased in patients that develop GTN with spontaneous hCG normalisation after molar pregnancy evacuation, as the median time to development of GTN was 18 months in their cohort, even though this was a rare occurrence. Rathod et al. studied the use of paclitaxel and carboplatin in refractory gestational trophoblastic neoplasia, and found a response rate in 75% of their cohort, with a median 30-month remission in 62.5% of the patients. All their patients had been previously treated with EMA-CO and EMA-EP.

Pregnancy

Gaducci et al. reviewed the reproductive outcome of patients treated for GTD. They found the risk of recurrence 0.7 to 2.6% after one complete hydatidiform mole, and 10% after two. Among patients who received chemotherapy, they found an increased risk of myeloid leukaemia related to the cumulative dose of etoposide. They also found the menopause occurred 3 years earlier in the population treated with chemotherapy. There was no increased risk of congenital abnormalities in this population except a slight increase in stillbirth. They advise to carefully choose patients considered for fertility sparing treatment for placental site trophoblastic tumour.

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

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Gestational Trophoblastic Disorders: An Update in 2015.	Stevens FT et al.	Geburtshilfe Frauenheilkd.	http://www.ncbi.nlm.nih.gov/pubmed/26556906	✓
2	Mortality of gestational trophoblastic neoplasia with a FIGO score of 13 and higher.	Bolze PA et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26433171	
3	The influence of lung metastases on the clinical course of gestational trophoblastic neoplasia: a historical cohort study.	Vree M et al.	BJOG.	http://www.ncbi.nlm.nih.gov/pubmed/26456952	
4	LINE-1 Methylation Patterns as a Predictor of Postmolar Gestational Trophoblastic Neoplasia.	Lertkhachonsuk R et al.	Biomed Res Int.	http://www.ncbi.nlm.nih.gov/pubmed/26448937	✓
5	Hormonal contraceptive use before hCG remission does not increase the risk of gestational trophoblastic neoplasia following complete hydatidiform mole: a historical database review.	Braga A et al.	BJOG.	http://www.ncbi.nlm.nih.gov/pubmed/26444183	
6	Update on the diagnosis and management of gestational trophoblastic disease.	Ngan HY et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26433668	
7	Gestational Trophoblastic Disease Treatment (PDQ®): Patient Version.	PDQ Adult Treatment Editorial Board	PDQ Cancer Information Summaries [Internet].	http://www.ncbi.nlm.nih.gov/pubmed/26425750	✓
8	Gestational trophoblastic neoplasia after spontaneous human chorionic gonadotropin normalization following molar pregnancy evacuation.	Braga A et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26383828	
9	Elaboration of a national biobank for the study of gestational trophoblastic diseases.	Bolze PA et al.	J Gynecol Obstet Biol Reprod (Paris).	http://www.ncbi.nlm.nih.gov/pubmed/26323857	
10	Reproductive outcomes after hydatiform mole and gestational trophoblastic neoplasia.	Gadducci A et al.	Gynecol Endocrinol.	http://www.ncbi.nlm.nih.gov/pubmed/26288335	
11	Gestational Trophoblastic Disease Diagnosis Delayed by the Hook Effect.	Cormano J et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26132453	
12	Trends in incidence for gestational trophoblastic disease over the last 20years in a population-based study.	Eysbouts YK et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26586414	
13	Gestational trophoblastic diseases - clinical guidelines for diagnosis, treatment, follow-up, and counselling.	Niemann I et al.	Dan Med.	http://www.ncbi.nlm.nih.gov/pubmed/26522484	
14	Optional management of low-risk gestational trophoblastic neoplasia.	Goldstein DP et al.	Expert Rev Anticancer Ther.	http://www.ncbi.nlm.nih.gov/pubmed/26517533	
15	Clinical Characteristics of Gestational Trophoblastic Neoplasia: A 15-Year Hospital-Based Study.	Sun R1 et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26512786	
16	GATA3 expression in gestational trophoblastic tissues and tumours.	Mirkovic J et al.	Histopathology.	http://www.ncbi.nlm.nih.gov/pubmed/25753145	
17	Invasive Complete Hydatidiform Moles: Analysis of a Case Series With Genotyping.	Bynum J et al.	Int J Gynecol Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26535984	
18	Refractory Gestational Trophoblastic Neoplasia: A Novel Drug Combination With Paclitaxel and Carboplatin Produces Durable Complete Remission.	Rathod PS et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26401644	

Immunotherapy in gynaecological cancers

Editor Zoltan Novak

Descriptive summary

In this update, two recently published clinical trials of cancer immunotherapy in humans can be reported. A phase I trial investigated whether a combination of carboplatin/doxorubicin, blockade of interleukin 6 receptor (IL-6R; tocilizumab), and immune enhancer interferon-α was feasible, safe, and able to enhance immunity in patients with recurrent epithelial ovarian cancer (EOC) patients. In the trial, 11 of 21 assessable patients responded and the results demonstrated that the effective blocking of IL-6 signalling during chemotherapy resulted in a series of functional immunological changes that could be considered as a change toward an immune response less associated with suppression (1). The same group reported a study using combination of gemcitabine, therapeutic vaccination immunotherapy with p53 synthetic long peptide (SLP) vaccine and interferon- in platinum-resistant p53-positive EOC patients. It was a small dose finding study, underpowered to demonstrate efficacy, but the treatment had an acceptable safety profile and a possible immunological benefit showing a shift towards an increased cytotoxic T cell/regulatory T-cell ratio (2). An interesting clinical study including 171 patients with high-grade serous ovarian cancer showed that prognostic benefit for patients with high intratumoural CD8+ tumour infiltrating lymphocytes (TIL) was observed only if primary surgery had resulted in a complete cytoreduction. By contrast, optimal (<1 cm of residual tumour) or incomplete cytoreduction fully abrogated the prognostic effect of CD8+ TIL (3) (see also chapter "Pathology/pathogenesis of malignant ovarian tumours").

The second part of this update is a selection of murine experimental studies based on the subjective evaluation of their possible clinical impact. Authors of the paper published in Nature studied the role of epigenetic silencing in cancer immunopathology and immunotherapy using murine model of ovarian cancer. Histone modifications and DNA methylation were negatively associated with tumour-infiltrating CD8(+) T-cells and patient outcome, thus epigenetic silencing of TH1-type chemokines is a novel immune-evasion mechanism of tumour. The authors suggest that epigenetic reprograming may condition tumours from poor T-cell infiltration to rich T-cell infiltration and ultimately potentiate cancer therapy (4). In a murine model of cervical cancer, complete regression of large established tumours depended on the tumour-infiltrating macrophages that were induced by a synthetic long peptide vaccine immunotherapy. The authors showed that therapeutic peptide vaccination could induce cytokine-producing T-cells with strong macrophage-skewing capacity necessary for tumour shrinkage, and suggest that the development of macrophage-polarizing, rather than macrophage-depleting, agents is warranted (5). In another study, the antitumor effects of a related DNA methyl transferase inhibitor, decitabine (DAC), were demonstrated in a syngeneic murine ovarian cancer model. While neither DAC nor immune checkpoint blockade conferred durable responses as a monotherapy in this model, the efficacy of anti-CTLA-4 was potentiated by combination with DAC. This combination promoted differentiation of naïve T-cells into effector T-cells and prolonged cytotoxic lymphocyte responses as well as mouse survival (6).

The remaining 3 papers are high-quality reviews about the advances of tumour infiltrating lymphocyte therapy for ovarian cancer (7), about immunotherapy and targeted therapies, including recently completed or currently on-going trials in cervical cancer patients (9) (see the chapter "Medical treatment f primary and recurrent cervical cancer"), and about a new DNA-based vaccine approach targeting tumour vasculature in ovarian cancer models (10).

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Immunotherapy in gynaecological cancers

Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	A phase 1/2 study combining gemcitabine, Pegintron and p53 SLP vaccine in patients with platinum-resistantovarian cancer.	Dijkgraaf EM et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26334096	
2	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/26/10/2141.long	
3	Treatment Regimen, Surgical Outcome, and T-cell Differentiation Influence Prognostic Benefit of Tumor-Infiltrating Lymphocytes in High-Grade Serous Ovarian Cancer.	Wouters MC et al.	Clin Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26384738	
4	Epigenetic silencing of TH1-type chemokines shapes tumour immunity and immunotherapy.	Peng D et al.	Nature.	http://www.nature.com/nature/journal/v527/n7577/full/nature15520.html	
5	Therapeutic Peptide Vaccine-Induced CD8 T Cells Strongly Modulate Intratumoral Macrophages Required for Tumor Regression.	van der Sluis TC et al.	Cancer Immunol Res.	http://www.ncbi.nlm.nih.gov/pubmed/25888578	
6	Decitabine Enhances Lymphocyte Migration and Function and Synergizes with CTLA-4 Blockade in a Murine Ovarian Cancer Model	Wang L et al.	Cancer Immunol Res.	http://www.ncbi.nlm.nih.gov/pubmed/26056145	
7	Tumor infiltrating lymphocyte therapy for ovarian cancer and renal cell carcinoma.	Andersen R et al.	Hum Vaccin Immunother.	http://www.ncbi.nlm.nih.gov/pubmed/26308285	
8	Immunotherapy and targeted therapy for cervical cancer: an update.	Menderes G et al.	Expert Rev Anticancer Ther.	http://www.ncbi.nlm.nih.gov/pubmed/26568261	
9	Targeting tumor vasculature: expanding the potential of DNA cancer vaccines.	Ugel S et al.	Cancer Immunol Immunother.	http://www.ncbi.nlm.nih.gov/pubmed/26267042	

LiFE | Literature for ENYGO

ENYGO ESGO European Network of Young Gynae Oncologists

Quality of life in gynaecological cancers/Palliative care

Editor Stef Cosyns

Descriptive summary

In this new literature report I would like to focus on 4 topics: The impact of radiation therapy for endometrial cancer, depression and anxiety, the use of hormone replacement therapy in ovarian cancer patients and sexual health in gynaecologic cancer patients.

On radiation therapy for endometrial cancer, the long-term impact of the PORTEC-2 trial was presented in November. Comparison between the post-radiation effects within patients undergoing external beam radiation therapy (EBRT) or vaginal brachytherapy (VBT) showed significant persisting decreased QOL in the patients undergoing EBRT. For EBRT and VBT, respectively, the results showed faecal leakage in 11% vs. 2%, diarrhoea in 8% vs. 1%, limitations due to bowel symptoms in 10% vs. 2%, bowel urgency in 23% vs. 7%, and urinary urgency in 39% vs. 25% of the patients. No difference in sexual activity was seen.

A similar study by Karabuga et al. reported better physical functioning, role functioning and sexual enjoyment in the VBT group vs. EBRT. QOL was overall higher when the BMI was within normal limits.

The study of Pisani et al. found a good overall QOL (82%) after adjuvant radiotherapy for endometrial and cervical cancers. For symptomatic patients (urinary/abdominal) a significant correlation with dose-volume parameters on bladder, vagina, trigonum, and lumbo-sacral plexus was noted.

A new report on the effects of RT showed an association between lymph-node positivity and risk of lymphedema in EC patients.

On ovarian cancer, a nice meta-analysis was published on the prevalence of depression and anxiety pre-treatment, during treatment, and post-treatment. The prevalence of both is, as expected, significantly higher than in the healthy female population.

Depression prevalence varied from 25% over 23% to 13% (resp pre/on/post-treatment). The prevalence of anxiety was 19% over 26% to 27% (resp pre/on/post-treatment). These results stress the necessity of diagnosing and treating psychological distress during and after treatment for ovarian cancer. This will have a major positive influence on the QOL of these patients.

Smits et al. described a negative impact on QOL of obesity and inactivity among ovarian cancer survivors.

In fertility sparing surgery, due to localised cervical and ovarian cancers, no benefit was seen with regard to sexual satisfaction or QOL (Chan et al.). (See chapter "Fertility sparing treatment for gynaecological malignancies").

The results of an exceptional randomised, controlled trial initiated by Eeles et al. in 1990 on the use of hormone replacement therapy in patients (pre/postmenopausal) with recent diagnosis and treatment for epithelial ovarian cancer were published. Even if the trial was closed early as a result of difficult patient recruitment, some astonishing conclusions were made. The question was 'to treat or not to treat' patients after debulking procedure. In patients who suffered from vasomotoric symptoms, QOL improved after oestrogen alone HRT. But is it safe? Does it increases relapse rate, risk of progression, breast cancer risk, coronary heart disease, or even all-cause mortality? The authors found a significantly improved OS and a better PFS in patients taking HRT with only a median HRT exposure of 1.14 years. Although there are known risks from taking HRT, one should not forbid patients oestrogen alone therapy in EOC patients complaining of vasomotor symptoms if they have no other contra-indications for HRT. Their QOL will only improve with even a possible positive outcome by reducing ovarian cancer relapse, ovarian cancer-specific death, and other causes of death.

If I can suggest one more article that deserves your attention, it would be 'Maintaining sexual health throughout gynaecologic cancer survivorship' from Huffmann et al. They comprehensively describe the negative impact of sexual dysfunction on QOL among gynaecologic cancer survivors as a result of surgery, radiation, and chemotherapy. They also provide some simple strategies to address sexual health concerns in clinical practice.

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Quality of life in gynaecological cancers/Palliative care

- Relevant articles retrieved May-Nov 2015

No	Title	Authors	Journal	Link to abstract	Available as full free text
1	Depression and anxiety in ovarian cancer: a systematic review and meta-analysis of prevalence rates.	Watts S et al.	BMJ Open.	http://www.ncbi.nlm.nih.gov/pubmed/26621509	✓
2	The effect of lifestyle interventions on the quality of life of gynaecological cancer survivors: A systematic review and meta-analysis.	Smits A et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26441008	
3	Sexual satisfaction and quality of life in survivors of localized cervical and ovarian cancers following fertility-sparing surgery.	Chan JL et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26232519	
4	Quality of life in patients treated by adjuvant radiotherapy for endometrial and cervical cancers: correlation with dose-volume parameters.	Pisani C et al.	Clin Transl Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26607932	
5	Maintaining sexual health throughout gynecologic cancer survivorship: A comprehensive review and clinical guide.	Huffman LB et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26556768	
6	Assessing the Quality of Life in Patients With Endometrial Cancer Treated With Adjuvant Radiotherapy.	Karabuga H et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26207785	
7	The risk of lymphedema after post-operative radiation therapy in endometrial cancer.	Mitra D et al.	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26463430	✓
8	Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial.	de Boer SM et al.	Int J Radiat Oncol Biol Phys.	http://www.ncbi.nlm.nih.gov/pubmed/26530748	
9	Adjuvant Hormone Therapy May Improve Survival in Epithelial Ovarian Cancer: Results of the AHT Randomized Trial.	Eeles RA et al.	J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26417001	

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