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LiFE report
Literature for ENYGO

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Reviews covering publications from August 15, 2016 – February 15, 2017

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Preface

Dear colleagues,

This is the fifth consecutive edition of the LiFE report, containing reviews of publications in gynaecological oncology from August 15, 2016 – February 15, 2017. LiFE is an initiative of ENYGO supported by ESGO.

Some of the topics have found new authors, and we welcome Erbil Karaman (Turkey), and Ruben M. Betoret (Spain) to the LiFE team. We enjoy the close and continuing work with the individual authors and are very proud of this international collaboration. We would like to acknowledge the continuous effort from each author.

The LiFE team is very grateful for the support of Beth Green in proofreading and also of our graphic designer Tomas Grünwald, who ensures that LiFE is good-looking and its content is easy to navigate. We would also like to thank Helena Opolecka for her administrative and coordinating support. We could not do it without her.

This issue is again published as a supplement to the International Journal of Gynecological Cancer Volume 27, Supplement #1, which adds to the publicity of our work

We hope you will enjoy LiFE 5 and find it interesting! Please let us know if you have any comments or other feedback.

And, as there is constant fluctuation of the busy LiFE authors, please get in touch if you are interested in becoming an author by sending an email to enygo.life.project@esgomail.org.

Stay up to date!

Yours,

The LiFE team

Kristina Lindemann

Kamil Zalewski

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Pathology/pathogenesis of malignant ovarian tumours

Editor Dogan Vatansever

Descriptive summary

Four original research article and one review articles were considered relevant to this topic in the review period.

Original Research

- Endothelial cells (EC) are a major component of the tumour microenvironment. They provide angiocrine factors orchestrating tumour progression. Wieland, Rodriguez-Vita et al. revealed that activated Notch1 signalling in endothelial cells (ECs) in tumours and in the premetastatic niche induces VCAM1 expression, leading to increased neutrophil infiltration and metastasis. They also demonstrated that EC notch signalling controls peritoneal neutrophil infiltration in a mouse model of ovarian carcinoma and genetic ablation of EC Notch signalling inhibited peritoneal neutrophil infiltration.
- Germline BRCA1 or BRCA2 mutations in patients with high-grade serous ovarian cancer (HGSC) are associated with favourable responses to chemotherapy. However, secondary intragenic (reversion) mutations that restore protein function lead to clinically significant rates of acquired resistance. Christie et al. performed targeted amplicon, next-generation sequencing in circulating cell-free DNA (cfDNA) of 30 patients. In all, 14 had undergone primary cytoreduction and 16 had recurrent disease. Reversion mutations were only detected in tumour samples from patients with recurrent disease (five of 16) and all patients with reversions detected in tumour-derived DNA were resistant to platin- or poly ADP ribose polymerase inhibitor-based chemotherapy.
- Clustered regularly interspaced short palindromic repeats (CRISPR) systems are RNA-based adaptable immune mechanisms of bacteria and archaea to protect themselves from exogenous nucleic acids (viruses or plasmids). CRISPR-associated protein 9 (Cas9) is a double-stranded DNA nuclease that uses a small CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA) to specify the site of cleavage. Even though CRISPR-Cas9 has been widely applied in varieties of cell line- and embryo-based experiments, delivery poses a major challenge for their further development toward human therapeutics. Li et al. studied a new delivery method by using an artificial virus for delivering the CRISPR-Cas9 system for genome editing. Furthermore, the artificial virus effectively targets ovarian cancer via dual-receptor mediated endocytosis and had minimal side effects.
- It has been suggested that specialised pathology review prior to randomisation should become the standard procedure in study protocols. The reason for this was the probability of conflictive histopathological diagnoses not eligible for the study. But the time needed for an expert review may be troublesome. Kommoss et al. hypothesised that their internet-based high-throughput infrastructure would be capable of providing specialised pathology review within ten working days. A total of 880 patients with an original diagnosis of ovarian epithelial carcinoma meant to be included in the AGO OVAR17 ovarian carcinoma chemotherapy trial were registered for an expert pathology review from October 2011 to July 2013. The median number of working days required to complete the review was four, and in 848 out of 880 (97.5%) cases, it was ≤10 working days. In 2.5% (n=22) of cases, a major diagnostic discrepancy of potential clinical relevance was found leading to exclusion from the trial.

Review

- Zhan et al. reviewed autophagy. Autophagy is an evolutionarily conserved cellular self-digestion pathway for homeostasis maintenance by recycling lysosome-dependent intracellular soluble macromolecules, organelles, and microorganisms. Autophagy exists at a basal level in all cell types and could be dramatically activated by a wide diversity of stresses. The principal autophagic signalling that have been implicated in autophagy progression are the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway and liver kinase B1 (LKB1)/adenosine monophosphate activated protein kinase (AMPK) pathway. This review is noticeable since more attention is being paid to the role of autophagy in ovarian carcinoma and its potential as a promising therapeutic target.

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Pathology/pathogenesis of malignant ovarian tumours

- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Endothelial Notch1 Activity Facilitates Metastasis	Wieland E et al.	Cancer Cell	http://dx.doi.org/10.1016/j.ccell.2017.01.007
2	Reversion of BRCA1/2 germline mutations detected in circulating tumor DNA from patients with high-grade serous ovarian cancer	Christie EL et al.	J Clin Oncol	http://ascopubs.org/doi/full/10.1200/JCO.2016.70.4627
3	Artificial virus delivers CRISPR-Cas9 system for genome editing of cells in mice	Li L et al.	ACS Nano	http://dx.doi.org/10.1021/acsnano.6b04261
4	Better resource utilisation and quality of care for ovarian cancer patients using internet-based pathology review	Kommoss S et al.	Br J Cancer	http://dx.doi.org/10.1038/bjc.2016.416
5	Autophagy as an emerging therapy target for ovarian carcinoma	Zhan L et al.	Oncotarget	http://dx.doi.org/10.18632/oncotarget.13080

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Screening for ovarian and fallopian tube cancer

Editor Lucas Minig

Descriptive summary

In 2011, the Prostate Lung Colorectal and Ovarian (PLCO) randomised controlled trial (RCT) of ovarian cancer screening with CA 125 and transvaginal ultrasound (TVU) concluded that simultaneous screening with CA 125 and TVU, compared with usual care, did not reduce ovarian cancer mortality at a median follow-up of 12 years [1]. The authors recently reported the results of the study at a median follow-up of 14.7 years in each arm and a maximum follow-up of 19.2 years in each arm [2]. After analysing 39,105 women in the intervention group (TVU + CA 125) and 39,111 women in the "usual care" group, 187 (intervention) and 176 (usual care) deaths from ovarian cancer were observed, for a risk-ratio of 1.06 (95% CI: 0.87–1.30). Risk-ratios were similar for study years zero to seven (RR = 1.04), seven–14 (RR = 1.06), and 14+ (RR = 1.09). The risk ratio for all-cause mortality was 1.01 (95% CI: 0.97– 1.05). Ovarian cancer – specific survival was not significantly different across trial arms (p = 0.16). These findings are in accordance with the preliminary survival results of the UKCTOCS study [3] published in 2016, the biggest study regarding screening in ovarian cancer to date.

Two studies dealt with the UK Familial Ovarian Cancer Screening Study (UK FOCSS). Rosenthal et al. [4] report about a stage shif in scree-detected cancers. The significantly higher proportion of cancers diagnosed at stage IIIa or lower (i.e., microscopic abdominal disease at worst) during the study was associated with more primary surgery and with higher zero residual disease achieved with less complex surgery. The authors conclude that even though compliance might be a problem outside a clinical study, the screening algorithm could help avoiding a diagnosis of advanced incompletely resectable OC/FTC in the interim. Skates et al. [5] reported preliminary results of early detection of ovarian cancer using the risk of ovarian cancer algorithm (ROCA) with frequent CA 125 testing in women at increased familial risk. The screening strategy included CA 125 tests every three months and TVU annually regardless of CA 125 results. The screening strategy implemented ROCA, which individualised the screening test for each woman. The study combined the results of two trials with a similar screening strategy. The Cancer Genetics Network (CGN) study (NCT00039559) included women from families with a deleterious BRCA1/2 mutation, and/or multiple ovarian and/or breast cancers in first- or second-degree blood relatives. In addition, the GOG-0199 study (NCT-00043472) was a two-arm, non-randomised observational study of women at increased risk that chose between risk-reducing salpingo-oophorectomy (RRSO) and ROCA-based ovarian cancer screening. GOG-0199 had the same eligibility criteria as the CGN study, except that women after oophorectomy were ineligible. Specificity and PPV were compared with levels derived from general population screening (specificity 90%, PPV 10%), and stage-at-detection was compared with historical high-risk controls. Specificity for ultrasound referral was 92% vs. 90% (p=0.0001), and PPV was 4.6% vs. 10% (p>0.10). Eighteen of 19 malignant ovarian neoplasms were detected via screening or risk-reducing salpingo-oophorectomy (RRSO). Amongst incident cases, which best reflect long-term screening performance, three out of six invasive cancers were early-stage (50% versus 10% historical BRCA1 controls; p=0.016). Six of nine RRSO-related cases were stage I. ROCA flagged 3/6 (50%) incident cases before CA 125 exceeded 35 U/mL. Eight of nine early-stage ovarian cancer patients were alive at a median follow-up of six years. Despite these findings, the small number of incidental cases detected reinforces the necessity of a larger cohort of patients to modify the standard recommendations for women at high risk for ovarian cancer.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial	Buys SS et al.	JAMA	https://www.ncbi.nlm.nih.gov/pubmed/21642681
2	Extended mortality results for ovarian cancer screening in the PLCO trial with median 15 years follow-up	Pinsky PF et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27615399
3	Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial	Jacobs IJ et al.	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/26707054
4	Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom Familial Ovarian Cancer Screening Study	Rosenthal et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28240969
5	Early Detection of Ovarian Cancer using the Risk of Ovarian Cancer Algorithm with Frequent CA125 Testing in Women at Increased Familial Risk - Combined Results from Two Screening Trials	Skates SJ et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28143870

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Surgical treatment of primary ovarian cancer

Editor Sileny Han

Descriptive summary

A concise review on surgery for advanced epithelial ovarian cancer is provided by Hacker et al.[1]. The outcome of surgical cytoreduction is considered the most important modifiable prognostic factor in women with advanced ovarian cancer. This fact is confirmed again by Wallace et al. [2]. The authors assessed survival rate associated with residual disease and found that patients with no residual disease (R0) had the longest overall survival, but also that a survival advantage existed for RD1 when compared to RD>1cm.

"Ultra-radical" surgical procedures are listed as diaphragmatic peritonectomy, extensive peritonectomy, splenectomy, cholecystectomy, multiple bowel resections, gastrectomy, and liver resection. Turnbull et al. [3] assessed that in their tertiary center, 50.4% of patients with advanced disease required at least one of the aforementioned procedures. Cytoreduction to R0 disease and to disease with greater tumour diameter of less than 1 cm (optimal) was achieved in 54.1 and 34.1% of the cases, respectively. Without incorporating surgical procedures in the upper abdomen ("ultra-radical"), the combined rate of complete and optimal cytoreduction would be only 33.3%.

A ten-step standardised technique for en-bloc resection of the pelvis in patients with stage IIIc-IV ovarian cancer is proposed by Tozzi et al. [4] whereby all pelvic organs, except the bladder, are removed together with the peritoneum. A low rate of surgical morbidity was accompanied by reduced hemorrhage, a high rate of clear margins, and R0 resection in all patients (N=92) that underwent surgery via this technique.

Rungruang et al. [5] investigated the effect of retroperitoneal exploration (RE) on progression-free and overall survival in patients who underwent optimal debulking surgery (from 1,871 records of the GOG-182 study). RE was defined as defined as removal of nodal tissue from at least one pelvic or para-aortic lymph node site. Of these patients, 689 (36.8%) underwent RE, and 1,182 (63.2%) did not. RE at the time of primary surgery in patients with optimally debulked stage IIIc disease is associated with a survival benefit (PFS 18.5 vs 16.0 months; $P<.0001$; and OS 53.3 vs 42.8 months; $P<.0001$).

The impact of total parenteral nutrition (TPN) versus conservative management in patients who underwent debulking surgery and a bowel resection was assessed by Mendivil et al. [6] in a group of 147 patients (TPN n=69; conservative management n=78). TPN was associated with increased risk for complications, delayed postoperative recovery and increased hospital stay duration. Thus, postoperative TPN was found to be inadvisable in this subset of patients.

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Di Donato et al. [7] performed a systematic review of randomised clinical trials and observational studies (a total of 18,579 patients in 46 studies) to evaluate the mortality rate in patients who underwent primary cytoreduction. Disease stage was a strong predictor of mortality, with an estimated risk increase from 2.8% (95% CI 2.02-3.66) for stage III to 16.1% (95% CI 6.18-25.93) for stage IV disease. Metaregression demonstrated that increased age and advanced stage were independently associated with an increased risk of mortality, and the combined effects of both factors greatly increased the risk.

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- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Surgery for advanced epithelial ovarian cancer	Hacker NF et al.	Best Pract Res Clin Obstet Gynaecol	http://www.ncbi.nlm.nih.gov/pubmed/27884789
2	Efforts at maximal cytoreduction improve survival in ovarian cancer patients, even when complete gross resection is not feasible	Wallace S et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/28159407
3	The impact of ultra-radical surgery in the management of patients with stage IIIC and IV epithelial ovarian, fallopian tube, and peritoneal cancer	Turnbull HL et al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/27995370
4	En-bloc resection of the pelvis (EnBRP) in patients with stage IIIc-IV ovarian cancer: A 10 steps standardised technique. Surgical and survival outcomes of primary vs. interval surgery	Tozzi R et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/28073597
5	What is the role of retroperitoneal exploration in optimally debulked stage IIIC epithelial ovarian cancer? An NRG Oncology/Gynecologic Oncology Group ancillary data study	Rungruang BJ et al.	Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27864921
6	The impact of total parenteral nutrition on postoperative recovery in patients treated for advanced stage ovarian cancer	Mendivil AA et al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/27832350
7	Trends in mortality after primary cytoreductive surgery for ovarian cancer: A systematic review and metaregression of randomized clinical trials and observational studies	Di Donato V et al.	Ann Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27896508

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Surgical treatment of recurrent ovarian cancer

Editor Patriciu Achimas-Cadariu

Descriptive summary

A study of 103 patients diagnosed with recurrent epithelial ovarian cancer adds to the bulk of retrospective evidence that residual tumour at secondary cytoreductive surgery, disease-free interval, and the number of lesions were independent prognostic factors for secondary cytoreductive surgery. Patients that had a disease-free interval greater than 12 months and a single recurrent lesion were more likely to achieve a better cytoreduction [1].

A prospective pilot study assessed the role of whole-body diffusion-weighted magnetic resonance imaging (WB-DWI/MRI) for diagnosis and prediction of complete tumour resection in comparison with contrast-enhanced CT in 51 patients with recurrent ovarian cancer. WB-DWI/MRI showed 94% accuracy for detecting ovarian cancer recurrence, compared with 78% for CT. Also, WB-DWI/MRI correctly predicted complete resection in 94% of patients eligible for salvage surgery, in comparison with 49% of cases for CT. These results need to be validated in larger study populations, with regard to interobserver agreement and experience, the potential synergistic value of PET imaging, and issues of cost-effectiveness [2].

To have a better understanding of the potential benefit of secondary cytoreductive surgery, three randomised trials were designed. The Dutch trial (SOCceR, NTR3337) was stopped prematurely as a result of low recruitment (11.7% of the target accrual). Some of the reasons for low recruitment were discussed by the principal investigator in the article mentioned here: Personal beliefs of the treating physicians in favour of either surgery of chemotherapy, the late detection of recurrent disease due to the current lack of periodic measurement of CA-125 level, and the practice to treat patients with recurrent disease with neoadjuvant chemotherapy prior to secondary surgery, which was not allowed in the SOCceR trial [3].

The results of the other two trials (DESKTOP III, NCT01166737; GOG 213, NCT00565851) are still awaited, and their estimated primary completion date is 2019. The first results from DESKTOP III are expected to be presented at the ASCO 2017.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Secondary cytoreductive surgery in recurrent epithelial ovarian cancer: A prognostic analysis with 103 cases	Fan XM et al.	Int J Surg	https://www.ncbi.nlm.nih.gov/pubmed/?term=28027999
2	Whole-body diffusion-weighted magnetic resonance imaging in the diagnosis of recurrent ovarian cancer: a clinical feasibility study	Michielsen KL et al.	Br J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/?term=27585490
3	Correspondence: Premature Stop of the SOCceR Trial, a Multicenter Randomized Controlled Trial on Secondary Cytoreductive Surgery: Netherlands Trial Register Number: NTR3337	van de Laar R et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/?term=28002207

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Medical treatment of primary ovarian cancer

Editor Ilker Selcuk

Descriptive summary

In this prospective study, Veskimae K. et al. assessed poly ADP ribose polymerase (PARP) activity in fresh ovarian cancer tissue samples of patients with homologous recombination deficiency after primary (38 patients (p)) and interval (19) debulking surgery. PARP activity was assessed by enzymatic chemiluminescence assay in fresh frozen tumour tissue samples and PARP protein expression in paraffin embedded tumour tissue by immunohistochemistry. PARP concentration was used as an indirect indicator of PARP-1 activity and was available in 51 patients (89%). Platinum sensitive patients had high PARP concentrations in the whole group (p=0.022) and especially in the high grade subgroup (p=0.017), meanwhile neo-adjuvant chemotherapy was associated with low levels of PARP (p=0.014). Moreover, low PARP concentration was associated with an increased risk of recurrence both in univariate (HR 2.4; 95% CI 1.204-4.797) and multivariate analysis but not death. On the other hand, PARP immunostaining pattern (weak or strong) was not associated with any survival benefit.

Musella et al. reviewed unanswered questions for bevacizumab and they emphasised that in a front line setting, bevacizumab treatment should be limited to 15 months as we still await the results of the recently closed BOOST trial, 15 vs 30 months maintenance with bevacicumab.

Egloff et al. evaluated the importance of BRCA mutation in ovarian cancer patients during and just after front line chemotherapy to check if it had any additional effect on chemotherapy toxicity. Patients (n=482) were categorised due to family history of ovarian or breast cancer (94p), BRCA positivity (23p) or none. Hospitalisation or emergency department visits were not increased in patients with a family history (27%, odds ratio 0.88; 95% CI 0.52, 1.45; p = .62; 30%, odds ratio 0.90; 95% CI 0.49, 1.58; p = .71) or BRCA mutation (30%, odds ratio 1.09; 95% CI 0.41, 2.62; p = .85; 17%, odds ratio 0.88; 95% CI 0.25, 2.40; p = .81).

Akladios et al. analysed the association between the number of neoadjuvant chemotherapy (NACT) cyles and survival. This retrospective study included 75 (36.8%) patients with ≤ 4 NACT cycles (group 1) and 129 (63.2%) patients with ≥ 5 cycles (group 2). The patient groups were similar and most of the patients had a high grade serous tumour. Sugarbaker score to calculate the dissemination of tumour at the beginning of interval debulking surgery (IDS) was similar (median 8 vs. 7, group 1 and 2 respectively, p=0.64) and rate of achievement of complete debulking was also similar in both groups (56%, 60.5%, p=0.78). Median overall survival (OS) (36.8 months (m) and 33.1m, p=0.24) and progression-free survival (PFS) (10.5m and 9.4m, p=0.12) were similar between the two groups.

Luo et al. evaluated the risk factors for platinum-resistant recurrence after NACT-IDS and primary debulking surgery (PDS). NACT-IDS and PDS were performed for 58 (17%) and 283 (83%) patients, respectively. After NACT-IDS and PDS, 29 (50%) and 99 (35%) patients, respectively, developed platinum-resistant disease (p=0.033). NACT-IDS and postoperative residual tumour volume >1cm were detected as risk factors for chemoresistance, moreover postoperative tumour volume >1cm and platinum resistant disease were also correlated with shorter OS (adjusted hazard ratios 1.579 and 4.078; 95% CI 1.193–2.089 and 3.074–5.412, P=0.001 and 0.000, respectively).

Esselen et al. evaluated the role of CA-125 and computed tomography (CT) in clinical follow-up before and after the publication of results of a randomised trial in 2009 (Rustin et al.) showing no survival benefit when treatment is started based on a CA125 rise only. This prospective cohort study includes 1241 women diagnosed between 2004-2011 and analysed the use of CA-125 and CT imaging in two time periods. Before 2009 and after 2009; 95% vs. 96% of patients received 1 CA-125 test within 6 months of remission and 86% vs. 91% received 3 CA-125 test within 12 months of remission. Additionally, 68% vs 64% of patients received 1 CT scan within 6 months of remission and 30% vs. 29% received 3 CT scans within 12 months of remission. The median time to re-administer chemotherapy was 2.8 and 3.5 months before and after 2009, respectively. These differences were not statistically significant and CA-125 and CT imaging are still standard of care for the surveillance of ovarian cancer patients with the associated costs, and potential impact on quality of life.

Qu et al. analysed the pooled data of 13 randomised controlled trials (RCT) and compared the toxicities of first line chemotherapy regimens in advanced ovarian cancer patients. Eight chemotherapy regimens were evaluated and non-haematologic toxicities with pegylated doxorubicin plus carboplatin chemotherapy ware higher than other protocols. Gemcitabine plus carboplatin chemotherapy was the most toxic regimen in haematologic side effects especially for anaemia, febrile neutropenia and thrombocytopenia. Additionally, the toxicity profile of paclitaxel and carboplatin regimen was lower better than the others.

Zhu et al. evaluated the role of the Glasgow Prognostic Score (GPS), which is an inflammation based prognostic score system calculated with high levels of C-reactive protein and low levels of albumin. In all, 672 newly diagnosed patients were evaluated and higher GPS was related to lower complete remission rates after neoadjuvant chemotherapy (p<0.05), shorter PFS and OS (p<0.001). High GPS was an independent adverse predictor of PFS and OS.

Shen and Li analysed HE4 and CA-125 levels to predict surgical outcome (optimal debulking) after PDS (n=39) and IDS (n=43). In

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Medical treatment of primary ovarian cancer

Descriptive summary (cont.)

PDS, HE4 was superior to CA-125 (area under curve (AUC) 0.758 vs. 0.633), cut-off 353pmol/L with 77.4% and 75% sensitivity and specificity, respectively. HE4 was also superior to CA-125 in IDS after NACT (AUC was 0.793 vs. 0.663, respectively, and cut-off level was 154.3 pmol/L for HE4 before IDS with 92.9% and 69% sensitivity and specificity, respectively). Moreover, 70% change of HE4 after NACT was also a significant predictor of optimal debulking ($p<0.01$) .

Hain-Rauh et al. compared OS results with respect to PDS (86.4%) and IDS (13.6%) in a national population cohort of stage IIIC and IV epithelial ovarian cancers. Patients (22,962) treated between 2003 and 2011, under 70 years of age and with a Charlson comorbidity index of 0 were evaluated. For PDS and IDS groups, median follow-up was 56.5 (54.5-59.2) vs. 56.3 months (54.5-59.8), median OS was 37.3m (35.2-38.7) and 32.1m (30.8-34.1, $p<.001$) respectively. The higher proportion of women with poor performance status may explain these results.

Dimitrova et al.11 evaluated BRCA 1 gene exon 11 to measure the related clinical outcomes. BRCA 1 exon 11 mutations were detected in 18/263 (6.8%) women. All of them were Type 2 tumours and they were generally younger ($p=0.01$). Moreover, it is not an independent predictive factor of optimal cytoreduction, platinum response and survival. For these tumours, outcomes are similar to sporadic epithelial ovarian cancers. For these tumours, outcomes are similar to sporadic epithelial ovarian cancers, but the study is limited by its retrospective design and the fact that only mutations on one single exon were considered.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Assessment of PARP protein expression in epithelial ovarian cancer by ELISA pharmacodynamic assay and immunohistochemistry	Veskimae K et al.	Tumour Biol	https://www.ncbi.nlm.nih.gov/pubmed/27155850
3	Bevacizumab in ovarian cancer: state of the art and unanswered questions	Musella A et al.	Chemotherapy	https://www.ncbi.nlm.nih.gov/pubmed/27794568
4	Do ovarian cancer patients with a family history of cancer (suspected BRCA1 or BRCA2 mutation) suffer greater chemotherapy toxicity?	Egloff H et al.	Cancer Invest	https://www.ncbi.nlm.nih.gov/pubmed/27791391
5	Does the number of neoadjuvant chemotherapy cycles before interval debulking surgery influence survival in advanced ovarian cancer?	Akladios C et al.	Oncology	https://www.ncbi.nlm.nih.gov/pubmed/27784027
6	Effect of neoadjuvant chemotherapy on platinum resistance in stage IIIC and IV epithelial ovarian cancer	Luo Y et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5023911/
7	Use of CA-125 Tests and Computed Tomographic Scans for Surveillance in Ovarian Cancer	Esselen KM et al.	JAMA Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27442965
8	Toxicities of different first-line chemotherapy regimens in the treatment of advanced ovarian cancer: A network meta-analysis	Qu CP et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5266167/
9	The Glasgow Prognostic Score (GPS) is a novel prognostic indicator in advanced epithelial ovarian cancer: a multicenter retrospective study	Zhu J et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27566683
10	Serum HE4 superior to CA125 in predicting poorer surgical outcome of epithelial ovarian cancer	Shen Y, Li Li	Tumour Biol	https://www.ncbi.nlm.nih.gov/pubmed/27629144
11	Overall survival following neoadjuvant chemotherapy vs primary cytoreductive surgery in women with epithelial ovarian cancer: analysis of the National Cancer Database	Rauh-Hain JA et al.	JAMA Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27892998

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Medical treatment of recurrent ovarian cancer

Editor Ilker Selcuk

Descriptive summary

Schram et al. raised concerns about niraparib for inducing cross-resistance to chemotherapy, making recurrent ovarian cancer more refractory and potentially diminishing the benefit of overall survival. Mirza et al. replied that each patient's initial progression-free survival was subtracted from the progression-free survival 2 interval (the time from randomisation until assessment of progression during receipt of the next anticancer therapy after the study treatment or until death) to emphasise niraparib had no effect on the effectiveness of subsequent chemotherapy.

Dalton et al. evaluated the effect of bevacizumab in both recurrent low-grade serous ovarian or peritoneal cancers retrospectively. The median number of prior regimens was four (range 1–15), and the average duration of bevacizumab treatment was four months (m) (range 0.7–43.9m). In total, 45 patient regimens were administered; ten (22.2%) were platinum-sensitive and 35 (77.8%) were platinum-resistant. Complete response (CR) was seen in 7.5%, however, 40% and 30% of patients had partial response (PR) and stable disease (SD), respectively. Disease progression was seen in nine (22.5%) patients.

Marth et al. analysed the activity of trebananib, a peptide-Fc fusion protein, which inhibits angiogenesis via angiopoietin-1/2 and tyrosine kinase receptor Tie2. Women with recurrent ovarian cancer (223 patients) were randomised to iv pegylated liposomal doxorubicin (PLD) 50 mg/m2 once every four weeks plus weekly iv trebananib 15 mg/kg or placebo (ENGOT-ov-6/TRINOVA-2). Objective response rates (ORR) were 46% versus 21% for the trebananib and placebo arms, respectively, but there was no difference in median progression-free survival (PFS) (7.6 m; 95% CI: 7.2–9.0 vs. 7.2 m; 95% CI: 4.8–8.2 in the trebananib and placebo arms, respectively). The most commonly observed adverse events were oedema, vomiting, and ascites.

Rucaparib, an oral PARP inhibitor, was evaluated by Swisher et al. in the ARIEL2 Part 1 study (relapsed, platinum sensitive high-grade ovarian carcinoma) including a BRCA mutant (n=40), BRCA wild type loss of heterozygosity (LOH) high (n=82) and low (n=70) subgroup. Median PFS after rucaparib (median 5.7m treatment) was 12.8m (95% CI 9.0–14.7) in the BRCA mutant subgroup, 5.7m (5.3–7.6) in the LOH high, and 5.2m (3.6–5.5) in the LOH low subgroup. PFS was significantly longer for the BRCA mutant (hazard ratio 0.27, 95% CI 0.16¬0.44, p<0.0001) and LOH high (HR 0.62, 95% CI 0.42¬0.90, p=0.11) subgroups than the LOH low subgroup.

Sorio et al. evaluated the safety and efficacy of bevacizumab in elderly patients (subgroup analysis of randomised phase III AURELIA trial). Although the PFS was similar for both >65 and <65 years of age, older patients had more grade 2 and 3 hypertension independent of baseline hypertension.

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Sehouli et al. found no PFS or overall survival (OS) benefit of topotecan and carboplatin when compared to standard platinum-based combinations in a randomised phase III trial of platinum-sensitive recurrent ovarian cancer.

Nakayama et al. found no difference in the effectivity of PLD for 40 mg/m^2 and 50 mg/m^2. However, the incidence and severity of palmar-plantar erythrodysesthesia and stomatitis were lower in PLD 40 mg/m^2 arm. These data support the use of 40 mg/m2 in clinical practice.

Ledermann et al. assessed the role of olaparib on overall survival in patients with platinum-sensitive, recurrent serous ovarian cancer. A total of 265 patients were randomly assigned to oral olaparib (400 mg, twice a day) maintenance or placebo after two or more courses of platinum-based chemotherapy. BRCA mutation was positive in 136 patients. Median OS was 29.8 m (95% CI 26.9 – 35.7) for patients treated with olaparib and 27.8 m for patients treated with placebo (24.9 – 33.7) (p<0.0095); however, in patients with BRCA mutation, the median OS was 34.9 m (95% CI 29.2¬54.6) vs. 30.2 m (23.1 – 40.7) for olaparib and placebo, respectively.

Harter et al. published a critical appraisal of the article by Spilliotis et al. published in Annals of Surgical Oncology in 2015. Spilliotis et al. reported on the first prospective randomised trial on HIPEC in recurrent epithelial ovarian cancer and reported a significantly improved overall survival in the HIPEC arm, both in platinum-sensitive and -resistant patients (60 patients HIPEC+, 60 patients HIPEC-). In platinum-sensitive patients, OS was 26.8 m vs. 15.2 m for HIPEC+ and HIPEC- patients, respectively. In platinum-resistant patients; OS was 26.6 vs. 10.2 m for HIPEC+ and HIPEC- patients, respectively). Harter et al. focussed on the methodological and scientific shortcomings of the article. They also raise doubt about the validity of the findings due to these limitations and express their concerns that such questionable data could potentially change current practices.

Lindemann et al. compared the effect of endocrine therapy, tamoxifen, with single-agent chemotherapy in platinum-resistant ovarian cancer patients. In this randomised phase III study, the primary endpoint was health-related quality of life (HLQoL), and patients on tamoxifen had less toxicity and fewer patients experienced a worsening in social functioning. Meanwhile, median PFS on tamoxifen was 8.3 weeks (95% CI, 8.0 – 10.4), compared with 12.7 weeks (95% CI, 9.0 – 16.3) on chemotherapy (HR, 1.54; 95% CI, 1.16 – 2.05; log-rank P=0.003). There was no difference in overall survival. With the caveat of a secondary analysis, this study questions the palliative benefit of single-agent chemotherapy in resistant ovarian cancer patients and underlines the importance of including HLQoL end points in clinical trials end points.

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Medical treatment of recurrent ovarian cancer

Descriptive summary (cont.)

Monk et al. report on a randomised phase II trial of iv bevacicumab (15 mg/kg) vs or the combination of bevacizumab plus the vascular disruptive agent fosbretabulin (60 mg/m^2). The rationale is that VDAs target existing tumour vascularity rather than preventing neovascularisation and thereby may be an ideal combination with antiangionetic agents like bevacizumab. The population was heterogenous and included both platinum–sesntiv and –resistant patients. The study of 107 patients met its primary endpoint showing a median PFS of 4.8 months for bevacizumab and 7.3 months for bevacizumab plus fosbretabulin; HR, 0.69; two-sided 90% CI, 0.47 to 1.00; one-sided, P = .05. Response rates of patients with measurable disease who were treated with bevacizumab plus fosbretabulin responded to treatment (28.2% for bevacizumab [90%CI, 16.7%to 42.3%] were not statistically different from the combination (response rate 35.7% [90% CI, 23.5% to 49.5%]). The combination increased the risk of hypertension, and the study was not placebo-controlled. As the reported PFS is shorter than previously reported, especially for patients with platinum-sensitive disease, a combination with chemotherapy may be needed to achieve better clinical outcomes.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Niraparib in recurrent ovarian cancer	Schram AM et al.	N Engl J Med	https://www.ncbi.nlm.nih.gov/pubmed/28229583
3	Activity of bevacizumab-containing regimens in recur-rent low-grade serous ovarian or peritoneal cancer: A single institution experience	Dalton HJ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28139261
4	ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partial-ly platinum-sensitive or resistant ovarian cancer	Marth C et al.	Eur J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27914241
5	Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial	Swisher EM et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27908594
6	Safety and efficacy of single-agent bevacizumab-containing therapy in elderly patients with platinum-resistant recurrent ovarian cancer: Subgroup analysis of the randomised phase III AURELIA trial	Sorio R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27871723
7	Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabine plus carboplatin (GC) or pegylated liposomal doxorubicin plus carboplatin (PLDC): a randomized phase III trial of the NOG-GO-AGO-Study Group-AGO Austria and GEI-CO-ENGOT-GCIG intergroup study (HECTOR)	Sehouli J et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27789470
8	A comparison of overall survival with 40 and 50 mg/m2 pegylated liposomal doxorubicin treatment in patients with recurrent epithelial ovarian cancer: Propensity score-matched analysis of real-world data	Nakayama M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27612976
9	Overall survival in patients with platinum-sensitive re-current serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial	Ledermann JA et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27617661
10	Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study	Spiliotis J et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/25391263
11	Brief report about the role of hyperthermic intraperi-toneal chemotherapy in a prospective randomized phase 3 study in recurrent ovarian cancer from Spiliotis et al.	Harter P et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28114231
12	Chemotherapy vs. tamoxifen in platinum-resistant ovarian cancer: a phase III, randomised, multicentre trial (Ovaresist)	Lindemann K et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28118323
12	Randomized phase II evaluation of bevacizumab versus bevacizumab plus fosbretabulin in recurrent ovarian, tubal, or peritoneal carcinoma: An NRG Oncology/Gynecologic Oncology Group Study	Monk et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27217446

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Treatment of ovarian sex cord stromal and germ cell tumours

Editor Anna Dückelmann

Descriptive summary

Goudeli et al. presented the rare case of an ovarian mature cystic teratoma (MCT) evolving in squamous cell carcinoma (SCC). SCC arising from MCT is a rare, albeit potentially lethal, disease. Malignant transformation of MCTs occurs in 1 – 2% of cases. The most common type of malignant transformation consists of SCC, arising from the ectoderm, which accounts for > 80% of cases. The patient's age is a risk factor for malignancy, as SCC in MTC typically occurs in postmenopausal women. Tumour size and certain tumour markers (SCC antigen, CA125, CA19-9, and CEA) are potential indicators. Due to the poor prognosis and high recurrence rates, chemotherapy based on alkylating agents is the recommended adjuvant treatment in patients with teratoma-related SCC.

In a good overview of ovarian sex cord-stromal tumours by Schulz et al., the association between Sertoli-Leydig cell tumours and gynandroblastomas and DICER1 mutations was pointed out. Testing for DICER1 mutations may have important implications for individuals and familial tumour risk and may facilitate diagnosis of associated conditions (e.g., pleuropulmonary blastoma). Patients with Sertoli-Leydig cell tumour should be enrolled in the "International ovarian and testicular stromal tumour registry". The on-going GOG 264 trial compares primary treatment with carboplatin and paclitaxel versus cisplatin, etoposide, and bleomycin in randomly assigned women with newly diagnosed and recurrent chemo-naïve ovarian sex cord-stromal tumours. In another on-going trial, the combined treatment with taxanes and bevacizumab is being investigated.

A retrospective study from Chen et al. confirmed the typical sonographic features of ovarian thecoma-fibroma groups (OTFG), such as adnexal hypoechoic masses with clear border and acoustic attenuation as well as minimal Doppler flow signals. OTFG neoplasms often occur in postmenopausal women with no obvious clinical symptoms. Most of them are unilateral with a diameter smaller than 5 cm, benign, and have a good prognosis.

The cytological features of primary adult granulose cell tumours are monotonous cells, microfollicular pattern, and nuclear grooves. Fine needle aspiration with corroborating immunohistochemistry and cytohistologic correlation with prior biopsies may be sufficient for diagnosis of recurrent and metastatic granulosa cell tumour, according to a retrospective analysis of eight cases of metastatic granulosa cell tumours [Harbhajanka et al.], thus avoiding unnecessary surgical interventions for diagnostic purposes.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Ovarian thecoma-fibroma groups: clinical and sonographic features with pathological comparison	Chen et al.	J Ovarian Res	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5120502/
2	Ovarian sex cord-stromal tumours	Schultz et al.	J Oncol Pract	https://www.ncbi.nlm.nih.gov/pubmed/27858560
3	An ovarian mature cystic teratoma evolving in squamous cell carcinoma: A case report and review of the literature	Goudeli et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5192096/
4	Cytomorphology and clinicopathologic correlation of the recurrent and metastatic adult granulosa cell tumor of the ovary: a retrospective review	Harbhajanka et al.	Diagn Cytopathol	https://www.ncbi.nlm.nih.gov/pubmed/27493080

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Emerging molecular-targeted therapies or early preclinical trials in ovarian cancer

Editor Muhammad Rizki Yaznil

Descriptive summary

Bergamini et al. [1] produced a review about folate receptor alpha antagonists. FR alpha is an ideal target for anticancer therapy since it is highly expressed in tumour cells and its expression is not affected by chemotherapy and has been found to correlate with tumour stage and grade. Two categories of therapeutics are included in this class: FRalpha targeted mAbs and FRalpha-binding-ADC (antibody drug conjugates); both share the interesting possibility of selecting patients via a biomarker that is already available. In the first category, farletuzumab has reached the most advanced stage in clinical evaluation and results of a phase II randomised trial are awaited to assess its efficacy in a specific patient setting. MOv18 IgE represents a novel strategy for targeting FRalpha expressing cells, which has shown encouraging results in preclinical studies. Further evaluation is needed in the clinical setting. In the second category, IMGN 853 is an innovative FRalpha-binding ADC under development, with only preliminary results of a phase I trial available.

USP7 (ubiquitin-specific enzyme) has been found to be critical in cancer progression because of its influence on the stability of the tumour suppressor p53. USP7 has a higher binding affinity for MDM2, thereby causing MDM2 stabilisation via the antagonisation of its autoubiquitination and the consequent induction of p53 degradation. Qin et al. [2], identified CDDO-Me as a novel inhibitor of USP7. Intraperitoneal injection of CDDO-Me inhibited HO8910 and SKOV3 tumour growth. CDDO-Me increased p53 protein levels in HO8910 cells but decreased UHRF1 in HO8910 and SKOV3 cells, indicating the inhibition of USP7 activity. The development of novel USP7 selective compounds based on the CDDO-Me-scaffold warrants further investigation.

Integrins, a family of heterodimeric adhesion receptors for diverse extracellular matrices, have consistently been implicated as crucial drivers of ovarian cancer development and progression and are strongly dependent on the activation of focal adhesion kinase (FAK) and its downstream signalling, including the PI3K/Akt- and Ras/MAPK-dependent pathways. TAE-226 and VS-6063, two of most potent inhibitors against active FAK, are highly effective in inhibiting ovarian tumour growth and metastatic potential. Owing to the potential off-target effects of FAK inhibitors, disruption of the integrin signalling axis remains a challenge. Xu et al. [3] screened inhibitors for being functionally cooperative with small-molecule VS-6063, a phase II FAK inhibitor. From this screening, JQ1, a potent inhibitor of the Myc oncogenic network, emerged as the most robust collaborator. Treatment with a combination of VS-6063 and JQ1 synergistically caused an arrest of tumour cells at the G2/M phase and a decrease in the XIAP-linked cell survival; this functional cooperation was strongly associated with the concomitant disruption of activation or expression of FAK and c-Myc as well as their downstream signalling through the PI3K/Akt pathway.

Pereles-Puchalt et al. [4] tried to define the safety and effectiveness of T-cells re-directed against FSH Receptor (FSHR)-expressing ovarian cancer cells. In recent years, transferring autologous T-cells engineered to express chimeric antigen receptors (CARs) has shown impressive cures for patients with chemo-resistant haematologic malignancies; however, this is not the case for solid tumours. The most challenging obstacle in developing CAR therapies is the identification of specific targets expressed on the surface of tumour cells that are not shared with healthy tissues. The follicle-stimulating hormone receptor (FSHR) is thought to be selectively expressed in women in ovarian granulosa cells. Most importantly, this surface antigen is expressed in 50 – 70% of serous ovarian carcinomas. T-cells expressing full-length FSHR-re-directed chimeric receptors mediate significant therapeutic effects (including tumour rejection) against a panel of patient-derived tumours in vivo. In immunocompetent mice growing syngeneic, orthotopic, and aggressive ovarian tumours, fully murine FSHR-targeted T-cells also increased survival without any measurable toxicity. Interestingly, FSHR-targeted T-cells persisted as memory lymphocytes without noticeable PD-1-dependent exhaustion during end-stage disease, in the absence of tumour cell immunoediting. However, exosomes in advanced tumour ascites diverted the effector activity of this and other chimeric receptor-transduced T-cells away from targeted tumour cells.

Overexpression of the hepatocyte nuclear factor 1b (HNF1b) transcription factor is ubiquitously overexpressed in ovarian clear cell carcinoma. However, to date, drugs targeting HNF1b have not been developed, due to the high content of intrinsically disordered regions in transcription factors. Human HNF1b is made up of three domains: the dimerisation domain, the transactivation domain, and the DNA-binding domain (DBD). In addition, the existence of a nuclear localisation signal (NLS) has recently been confirmed within the DBD

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Emerging molecular-targeted therapies or early preclinical trials in ovarian cancer

Descriptive summary (cont.)

of HNF1b, which directs the nuclear import of the protein. Therapeutic targeting of the nuclear import of transcription factors provides a strategy for inhibiting their function since activity depends on successful localisation to the nucleus for transcription to take place. Wiedmann et al. [5] developed constrained peptide-based inhibitors that target the HNF1b–importin, a protein–protein interaction (PPI), and inhibit the activity of HNF1b. This work provides the first example of using constrained peptides that mimic the ordered state of NLSs to target the nuclear import of transcription factors.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Folate receptor alpha antagonists in preclinical and early stage clinical development for the treatment of epithelial ovarian cancer	Bergamini A et al.	Expert opinion on investigational drugs	http://www.ncbi.nlm.nih.gov/pubmed/27797594
2	CDDO-Me reveals USP7 as a novel target in ovarian cancer cells	Qin D et al.	Oncotarget	http://www.ncbi.nlm.nih.gov/pubmed/27780924
3	Inhibition of the integrin/FAK signaling axis and c-Myc synergistically disrupts ovarian cancer malignancy	Xu B et al.	Oncogenesis	http://www.ncbi.nlm.nih.gov/pubmed/28134933
4	Follicle-stimulating hormone receptor Is expressed by most ovarian cancer subtypes and Is a safe and effective immunotherapeutic target	Perales-Puchalt A et al.	Clinical cancer research	http://www.ncbi.nlm.nih.gov/pubmed/27435394
5	Development of cell-permeable, non-helical constrained peptides to target a key protein-protein Interaction in ovarian cancer	Wiedmann MM et al.	Angewandte Chemie	http://www.ncbi.nlm.nih.gov/pubmed/27918136

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

Editor Sara Giovannoni

Descriptive summary

Prevention and screening

- Based on the ESMO clinical practice guidelines for cancer prevention and screening in BRCA mutation carriers and other hereditary cancer syndromes, published on September 2016: the use of the oral contraceptive pill has been demonstrated to have a significant risk-reducing effect on the development of ovarian cancer by 40–60%; however, there are conflicts concerning breast cancer risk in these patients. There are no data proving that screening for ovarian cancer is able to reduce mortality, and several trials are still on going. Nowadays, the most effective measure for preventing ovarian cancer is the risk-reducing salpingo-oophorectomy (RRSO), which has consistently been shown to reduce the risk by 80–90%, reducing mortality as well. Based on ESMO guidelines, the RRSO should be carried out at age 35–40. In patients with RAD51 or BRIP1 mutations, RRSO may be considered, but after 45 years of age. Finally, based on several pieces of evidence suggesting that ovarian cancer originates in the fimbria or fallopian tubes, there is a growing interest in risk-reducing salpingectomy. However, this procedure alone cannot yet be recommended, outside the setting of a clinical trial [1].
- In the NCCN guidelines, RRSO or TAH are options that may be considered for risk reduction in women with ML-H1,MSH2,MSH6,PMS2,EPCAM mutation. For RAD51 and BRIP1 mutations, the panel recommends RRSO between ages 45 and 50; however, large trials are needed to recommend a specific age [2].

PARP inhibitors

- The FDA approved the PARP inhibitor rucaparib to treat women with advanced ovarian cancer who have already been treated with at least two lines of chemotherapy and have a BRCA1 or BRCA2 gene mutation [3]. Futhermore, FDA approved the FoundationFocus CDxBRCA test (Foundation Medicine Inc.), the first FDA-approved next-generation sequencing (NGS)-based companion diagnostic to identify patients with advanced ovarian cancer eligible for treatment with rucaparib. Approval of rucaparib and the FoundationFocus CDxBRCA test was based on data from two multicentre, single-arm, open label clinical trials that evaluated the efficacy of rucaparib in 106 patients with advanced ovarian cancer who had progressed after treatment with two or more prior treatments. All 106 patients received rucaparib 600 mg orally twice daily. The results showed that 54% (57/106; 95% CI: 44-64%). of patients attained a complete or partial response to rucaparib (ORR), and the responses persisted for a median duration of 9.2 months. (95% CI: 6.6, 11.6) [10]. In Europe, rucaparib is not yet approved; however, the updated results of ARIEL2, confirming the efficacy and the safety of rucaparib, have allowed the start of new trials ARIEL3 and ARIEL4 – both ongoing.
- In their review, Incorvaia et al. summarised the biology and trials with PARP inhibitors focusing on the mechanism of the primary and acquired resistance including PTEN mutations, ATM dysfunction, and NHEJ defection. Although new data are needed, these may become predictive markers of response/resistance to PARP inhibitors [4].
- The role of NHEJ was investigated by McCormick et al., demonstrating that NHEJ is defective in 40% of ovarian cancers, which is independent of HR function and associated with resistance to PARP inhibitors in ex vivo primary cultures [5].
- Ledermann et al. published the updated results of the overall survival (OS) of the Study 19 trial, a phase II trial comparing olaparib maintenance versus placebo in platinum sensitive recurrent serous ovarian cancer patients including those with BRCA1 and BRCA2 mutations. The results suggest an overall survival advantage for patients with platinum-sensitive recurrent ovarian cancer who received olaparib maintenance compared with placebo (HR 0.73). Patients with BRCA mutation had the greatest overall survival benefit from olaparib, despite not reaching a statistical significance. (34.9 months vs. 30.2 months – HR 0.62 p=0.025H0 0.62). The Kaplan Meier survival curves for the two treatments groups begin to separate from about 42 months after randomisation, likely due to a result of the heterogeneous nature of the overall population and the different treatment effect in patients with BRCAm or BRCAwt. These data support the previously published results from study 19, showing that PFS, time to first and second subsequent therapy or death are significantly prolonged with olaparib, especially in patients with BRCAm [6].
- Konecny et al. discussed in an editorial recently published online [7], the response to PARP inhibitors in sporadic ovarian cancer. Up

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

Descriptive summary (cont.)

to 50% of all high grade serous ovarian cancers had a BRCA-like phenotype and this could be the explanation of this finding. Furthermore, 20-25% of patients may have epigenetic silencing of BRCA or mutations involved in HR DNA repair. The authors underlined the role of the measurement of the LOH (loss of heterozygosity) as a surrogate marker for HR deficiency in ovarian cancer. LOH may represent a good predictive marker of PARP inhibitor responsiveness/resistance. However, further improvements in the assessment of LOH are needed such as the definition of a standard cut-off for tumour genomic LOH.

Finally, three interesting reviews has been published: One by McLachan et al. [8] reviewing the current evidence for PARP inhibitors and discussing the ongoing clinical trials with new PARP inhibitors including rucaparib, niraparib, veliparib, and talezoparib. The reviews by Gonzalez Martin et al. and by Miller et al. discuss the role of PARP inhibitors beyond BRCA mutations [9,11].

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Prevention and screening in BRCA mutation carriers and other breast/ovarin hereditary cancer syndromes : ESMO clinical practice guidelines	Paluch-Shimon S et al.	Ann Oncol	https://academic.oup.com/annonc/article/27/suppl_5/v103/2237157/Prevention-and-screening-in-BRCA-mutation-carriers
2	NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017	Daly MB et al.	J Natl Compr Canc Netw	http://www.jnccn.org/content/15/1/9.full
3	Rucaparib approved for ovarian cancer		Cancer Discov	https://www.ncbi.nlm.nih.gov/pubmed/28057616
4	"Back to a false normality": new intriguing mechanisms of resistance to PARP inhibitors	Incorvaia L et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/28055979
5	Ovarian cancers harbor defects in nonhomologous end joining resulting in resistance to rucaparib	McCormick A et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/27702817
6	Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial	Ledermann JA et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27617661
7	Understanding exceptional responses to Poly (ADP-ribose) Polymerase Inhibition in sporadic ovarian cancer	Konecny GE	JCO	http://ascopubs.org/doi/pdf/10.1200/JCO.2016.72.0052
8	The current status of PARP inhibitors in ovarian cancer.	McLachlan J et al.	Tumori	https://www.ncbi.nlm.nih.gov/pubmed/27716873
9	Progress in PARP inhibitors beyond BRCA mutant recurrent ovarian cancer?	González Martín A et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27908593
10	The status of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in ovarian cancer, part 2: extending the scope beyond olaparib and BRCA1/2 mutations	Miller RE et al.	Clin Adv Hematol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27673289
11	Factors associated with deciding between risk-reducing salpingo-oophorectomy and ovarian cancer screening among high-risk women enrolled in GOG-0199: An NRG Oncology/Gynecologic Oncology Group study	Mai PL ET AL.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28190649
12	Mainstreaming cancer genetics: A model integrating germline BRCA testing into routine ovarian cancer clinics	Kentwell M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28162234

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

- Relevant articles retrieved Aug 2016 – Feb 2017 (cont.)

No	Title	Authors	Journal	Link to abstract
13	New perspective on maintenance therapies for platinum- sensitive recurrent ovarian cancer in women with germline and somatic mutations in BRCA1 and BRCA2 genes	Vergote I et al.	Facts Views Vis Obgyn	https://www.ncbi.nlm.nih.gov/pubmed/28003870
14	Targeting the ATR/CHK1 axis with PARP inhibition results in tumor regression in BRCA mutant ovarian cancer models.	Kim H et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/27993965
15	Practical guidance on the use of olaparib capsules as maintenance therapy for women with BRCA mutations and platinum-sensitive recurrent ovarian cancer.	Friedlander M et al.	Asia Pac J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27917619
16	Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients.	Vergote I et al.	Eur J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27821315
17	Trabectedin as a chemotherapy option for patients with BRCA deficiency.	Monk BJ et al.	Cancer Treat Rev	https://www.ncbi.nlm.nih.gov/pubmed/27710871
18	In vivo anti-tumor activity of the PARP inhibitor niraparib in homologous recombination deficient and proficient ovarian carcinoma.	AlHilli MM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27614696
19	Trabectedin as a chemotherapy option for patients with BRCA deficiency	Friedlander M et al.	Asia Pac J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27917619
20	In vivo anti-tumor activity of the PARP inhibitor niraparib in homologous recombination deficient and proficient ovarian carcinoma	Vergote I et al.	Eur J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27821315

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

Editor Santiago Scasso

Descriptive summary

Suarez et al. described the "historical perspective" from Bokhman dualistic concepts to the nowadays complex and heterogeneous disease from epidemiologic, clinical, pathological, and molecular points of view as the recent molecular classification of endometrial cancer (EC) based on the Cancer Genome Atlas (TCGA).

Piulats et al. reviewed the usefulness of molecular techniques to classify EC. Although histological classification is the current gold standard for patient stratification, molecular studies have obtained promising results providing important information about prognosis and predictive response to novel therapies. Topics included: correlation between genotype and phenotype, the value of molecular pathology, including interobserver variation in pathologic interpretation, the importance of applying TCGA concepts to clinical practice, and its usefulness in tailoring immunotherapy. They suggested improving assessment and combining pathologic and a surrogate TCGA molecular classification.

Talhouk et al. in, assessed whether PROMISE (Proactive Molecular Risk classification tool for Endometrial cancers) could be performed on diagnostic endometrial specimens prior to staging surgery and its concordance on hysterectomy specimen. In all, 60 cases had a complete molecular and pathologic categorisation. Concordance metrics for pre- versus. post-staging categorised by PROMISE were highly favourable (with sensitivity 0.9 and specificity 0.96, PPV 0.9, NPV 0.96) with an excellent agreement rate (kappa 0.86). The highest level of concordance was to "p53 abn"' tumours, a group associated with the worst prognosis. In contrast, grade and histotype assignment from original pathology reports pre- vs. post-staging showed only moderate levels of agreement (kappa 0.55 and 0.44, respectively), even with subspecialty pathology.

Capriglione et al., in their systematic review, assessed the value of HE4 as a prognostic factor in EC and its potential role in clinical practice. Fifteen studies met the eligibility criteria and compared the value of HE4 with the pathology tumour's features. Despite the fact that, to date, no good markers are routinely used in clinical practice, an increasing interest in literature on HE4 has been growing due to its good performance in the prognosis and monitoring of the disease. The authors support the opinion that HE4 may have potential as an additional information tool for the decision-making process. However, these findings require further validation.

Shen et al. analysed the positivity of ER/PR in 1,054 women with EC in a retrospective study taking into account cancer types and menopausal status. HR positive were associated with better EC prognosis. The positivity of ER or PR (>90%) was significantly higher in type 1 compared to type 2 EC (71% or 64%) in both pre- and postmenopausal women. No differences in the positivity of ER or PR in type 1 EC according to menopausal status was found. However, in type 2, the positivity of ER or PR in premenopausal women was significantly higher compared with postmenopausal women.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Bokhman Redux: Endometrial cancer "types" in the 21st century	Suarez AA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27993480
2	Molecular approaches for classifying endometrial carcinoma	Piulats JM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28040204
3	Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: Earlier prognostic information to guide treatment	Talhouk A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27421752
4	Further insight into prognostic factors in endometrial cancer: the new serum biomarker HE4	Capriglione S et al.	Expert Rev Anticancer Ther	https://www.ncbi.nlm.nih.gov/pubmed/27892774
5	Is the positivity of estrogen receptor or progesterone receptor different between type 1 and type 2 endometrial cancer?	Shen F et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/27888807

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Screening for uterine cancer/hereditary uterine cancer

Editor María de los Reyes Oliver Pérez

Descriptive summary

Screening for uterine cancer

In the period covered by the fifth edition of the LiFE report, one literature review and two clinical trials on the screening of uterine cancer have been selected. Bagaria et al. published a literature review on novel approaches to the early detection of endometrial cancer [1]. The authors focused on biomarkers that can be identified in biospecimens collected by minimally invasive and non-invasive approaches, including self-collected lower genital tract biospecimens. The four clinical trials reviewed are focused on endometrial cytology. Margari et al. proposed a classification scheme of endometrial pathology using liquid-based endometrial cytology [2]. This classification has six categories from no diagnostic/unsatisfactory to malignant. Each diagnostic category is linked to an implied risk of malignancy. Ma et al. investigated the diagnostic accuracy of liquid endometrial cytology in postmenopausal women in comparison with histology [3]. The diagnostic accuracy of the liquid-based endometrial cytology was 81.5%, with a sensitivity of 75.9%, specificity of 83.3%, a positive predictive value of 59.1% and negative predictive value of 91.6%. In their opinion, this method can be considered useful in the detection of endometrial cancer.

Hereditary uterine cancer (HUC)

Regarding universal screening for Lynch syndrome (LS), Bruegl et al. prospectively identified the incidence of LS when universal tissue testing is applied to patients with endometrial carcinoma [4]. In total, 213 endometrial carcinoma patients underwent microsatellite instability and immunohistochemical (IHC) testing for expression of DNA mismatch repair (MMR) proteins. Patients with low (MSI-L) or high (MSI-H) levels of tumour MSI or immunohistochemical loss of MLH1, MSH2, MSH6 or PMS2 were referred to a genetic counsellor for consideration of germ line testing. Authors identified seven germ line LS mutations in this cohort (3.4%). Overall concordance between IHC and MSI was 96.9%. Goverde et al. assessed the cost-effectiveness of routine screening for LS in endometrial cancer patients up to 70 years of age [5]. Screenings for LS in 179 endometrial cancer patients identified seven LS carriers. The authors concluded that routine LS screening in these patients is a cost-effective strategy, allowing colorectal cancer prevention in endometrial cancer patients and their relatives. Finally, Aissaoui et al. evaluated if the prediction model PREMM (available for free at http: //premm. Dfci.harvard.edu/) can be used to select patients to undergo genetic testing for LS [6].

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Novel approaches to early detection of endometrial cancer	Bagaria M et al.	Curr Opin Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27861202
2	A reporting system for endometrial cytology	Margari et al.	Diagn Cyto-pathol	https://www.ncbi.nlm.nih.gov/pubmed/27653446
3	Liquid-based endometrial cytology associated with curettage in the investigation of endometrial carcinoma in postmenopausal women	Ma K et al.	Taiwan J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28040118
4	Clinical challenges associated with universal screen-ing for Lynch Syndrome-associated endometrial can-cer	Bruegl A et al.	Cancer Prev Res	https://www.ncbi.nlm.nih.gov/labs/articles/27965287/
5	Cost-effectiveness of routine screening for Lynch syndrome in endometrial cancer patients up to 70 years of age	Goverde A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27789085
6	Genetic mutation risk calculation in Lynch syndrome inheritance: evaluating the utility of the PREMM model in Lyon: the first French study	Aissaoui et al.	Bulcan	https://www.ncbi.nlm.nih.gov/pubmed/28038733

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

Editor Kastriot Dallaku and Elko Gliozheni

Descriptive summary

Diagnosis, biology, and follow-up for patients with endometrial hyperplasia

A new structured diagnostic set-up, including imaging techniques, endometrial sampling, and hysteroscopy was proposed by Dueholm et al. to identify uterine bleeding causes [1]. The imaging techniques for structured evaluation of endometrial abnormalities included contract sonography, three-dimensional ultrasonography, and magnetic resonance. Patel et al. examined the correlation between the histopathological diagnosis and endometrial thickness measured with transvaginal ultrasound in women with postmenopausal bleeding [2]. They concluded that an endometrial thickness threshold of 3 to 4 mm can be used to maximise sensitivity for endometrial biopsy. Contrast-enhanced ultrasonography (CEUS) was studied by Liu et al. to screen between benign and malignant endometrial lesions [3]. The authors concluded that CEUS seems to indirectly reflect vascular changes inside the endometrial lesions. Shitano et al. used magnetic resonance imaging (MRI) to differentiate between benign and malignant endometrial lesions [4]. They concluded that it is difficult to differentiate normal and endometrial lesions based on thickness, but a low signal intensity of MRI may be helpful. Bakir et al. used diffusion weighted imaging using contrast-enhanced MRI to compare the differences between benign and malignant endometrial lesions, the result of which was statistically significant [5]. The expression of human epididymis-specific protein 4 (HE4) was evaluated by Orbo et al. in patients with endometrial hyperplasia receiving progestin therapy (levonorgestrel-releasing intrauterine system LNG-IUS or oral progestins) in order to predict therapy response and disease relapse [6]. Another study found that pre-operative HE4 plasmatic levels are more increased in patients with endometrial cancer than those with endometrial hyperplasia and recommended that HE4 may be used as an additional marker, combined with clinical and histopathology findings, for planning treatment [7]. The expression of paired boxed gene 1 (PAX1) was evaluated in patients with endometrial hyperplasia and endometrial carcinoma (EC) [8]. The results of this study showed that PAX1 protein expression is a potential biomarker for the differential diagnosis of endometrial hyperplasia and EC, and it is also a prognostic biomarker in cases of EC. Another marker of endometrial malignancies is PAX2, which in EC tissues has shown an increased expression compared to endometrial hyperplasia and normal endometrial cells [9]. The investigation of hypoxia marker HIF-1 in EC found that high stromal HIF-1 expression was significantly associated with reduced survival in EC and with increased tumour metabolism at PET/CT [10]. Pennant et al. conducted a systematic literature review to evaluate the risk of atypical endometrial hyperplasia and EC in premenopausal patients with abnormal uterine bleeding [11]. The authors inferred that among these patients, the risk for EC is low, except in cases with medical treatment failure, inter-menstrual bleeding and older age, which may need further investigation.

Conservative and definitive treatment for patients with endometrial hyperplasia

Marnach et al. retrospectively evaluated the effectiveness of oral progestin (OP) versus the LNG IUS, in the medical management of endometrial intraepithelial neoplasia ((296 women initially treated with OP and 94 with LNG IUS) [12]. Based on the results authors concluded that LNG IUS was easy to use, had minimal adverse effects, lower relapse rate, and long-term endometrial protection. A systematic review by Yuk et al. found that management with LNG-IUS has a higher regression rate than cyclic medroxyprogesterone acetate in simple and complex endometrial hyperplasia [13]. Metformin and megestrol were compared for their treatment effects in women with endometrial hyperplasia. The result showed that metformin had similar effects with megestrol for the treatment of simple endometrial hyperplasia [14]. Clement et al. emphasised that metformin can reverse the endometrial hyperplasia and can, therefore, decrease endometrial cancer, without consequences to fertility and other side effects [15]. Another treatment modality of bariatric surgery was proposed by Charalampakis et al. for patients with polycystic ovary syndrome and endometrial hyperplasia which are known to be associated with increased risk of endometrial carcinoma [16]. A study by Flannery et al. investigated an alternative to progestin in menopausal hormone therapy; bazedoxifene (BZA) reduces endometrial hyperplasia induced by oestrogens, through inhibiting fibroblast growth factor (FGF18) [17].

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

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Structured imaging technique in the gynecologic office for the diagnosis of abnormal uterine bleeding	Dueholm et al.	Best Pract Res ClinObstetGynaecol	https://www.ncbi.nlm.nih.gov/pubmed/27818130
2	Endometrial thickness as measured by transvaginal ultrasound and the correspondinghistopathologic diagnosis in women with postmenopausal bleeding	Patel et al.	Int J Gynecol Pathol	https://www.ncbi.nlm.nih.gov/pubmed/27801761
3	Quantitative contrast-enhanced ultrasonography for the differential diagnosis of endometrial hyperplasia and endometrial neoplasms	Liu et al.	OncolLett	https://www.ncbi.nlm.nih.gov/pubmed/27895728
4	MR appearance of normal uterine endometrium considering menstrual cycle: differentiation with benign and malignant endometrial lesions	Shitano et al.	ActaRadiol	https://www.ncbi.nlm.nih.gov/pubmed/26787675
5	Role of diffusion weighted MRI in the differential diagnosis of endometrial cancer, polyp, hyperplasia, and physiological thickening	Bakir et al.	Clin Imaging	https://www.ncbi.nlm.nih.gov/pubmed/27829198
6	HE4 is a novel tissue marker for therapy response and progestin resistance in medium- and low-risk endometrial hyperplasia	Ørbo et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27711084
7	The role of human epididymis secretory protein E4 in patients with endometrial cancer and premalignant endometrial lesions	Yılmaz et al.	J Obstet Gynaecol	https://www.ncbi.nlm.nih.gov/pubmed/28006994
8	Paired boxed gene 1 expression: A single potential biomarker for differentiating endometrial lesions associated with favorable outcomes in patients with endometrial carcinoma	Liu et al.	J Obstet Gynaecol Res	https://www.ncbi.nlm.nih.gov/pubmed/27226215
9	DNA methylation promotes paired box 2 expression via myeloid zinc finger 1 in endometrial cancer	Jia et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/27764784
10	Tissue and imaging biomarkers for hypoxia predict poor outcome in endometrial cancer	Berg et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/27634881
11	Premenopausal abnormal uterine bleeding and risk of endometrial cancer	Pennant et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/27766759
12	Oral progestogens versus levonorgestrel-releasing intrauterine system for treatment of endometrial intraepithelial neoplasia	Marnach et al.	J Womens Health (Larchmt)	https://www.ncbi.nlm.nih.gov/pubmed/27901412
13	Levonorgestrel-releasing intrauterine systems versus oral cyclic medroxyprogesterone acetate in endometrial hyperplasia therapy: a meta-analysis	Yuk et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27896507
14	A comparison between the effects of metformin and megestrol on sim-ple endometrial hyperplasia	Sharifzadeh et al.	Gynecol Endocrinol	https://www.ncbi.nlm.nih.gov/pubmed/27690687
15	Metformin for endometrial hyperplasia: a Cochrane protocol	Clement et al.	BMJ Open	https://www.ncbi.nlm.nih.gov/pubmed/27531741
16	Polycystic ovary syndrome and endometrial hyperplasia: an overview of the role of bariatric surgery in female fertility	Charalampakis et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/27773356
17	Endometrial cancer-associated FGF18 expression is reduced by Bazedoxifene in human endometrial stromal cells in vitro and in murine endometrium	Flannery et al.	Endocrinology	https://www.ncbi.nlm.nih.gov/pubmed/27267714

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Surgical treatment of primary uterine cancer

Editor Piotr Lepka

Descriptive summary

Guidelines

In the period covered by the fifth LiFE report, the Korean Society of Gynaecologic Oncology Consensus Statement on the management of endometrial cancer (EC) was published [1]. The main recommendations regarding surgical treatment of EC were:

- Lymphadenectomy was recommended as an integral part of the surgical staging. However, pelvic lymphadenectomy may be omitted in patients who are predicted to have a very low risk of lymph node metastasis (and low-grade tumour with endometrioid histologic type confined to the endometrium or superficial myometrium).
- Para-aortic lymphadenectomy was recommended if deep myometrial invasion or high-grade lesions (including serous or clear cell carcinoma) are identified.
- Laparoscopic staging surgery was recommended for the surgical staging of early endometrial cancer.
- Ovarian preservation was recommended at the time of hysterectomy for young women with early-stage endometrial cancer that is confined to the uterus without evidence of extrauterine spread.
- If clinically suspected, cervical biopsy before surgery was recommended to determine infiltration. In patients with uterine cervical invasion confirmed by cervical biopsy preoperative radiotherapy followed by hysterectomy, bilateral salpingoopherectomy and pelvic and para-aortic lymph node dissection can be considered.

Use of the uterine manipulator

Uccella et al. retrospectively compared the results of treatment of 579 patients with early-stage EC who underwent laparoscopic hysterectomy with a uterine manipulator to the 372 operated without an intrauterine device. At the median time of follow- up (46 months), the rate of recurrence was 13.5% and 11.6%, respectively, and did not reach statistical significance. Also, disease-free, disease-specific, and overall survival did not differ between the groups. The type of uterine manipulator, as well as the presence or not of the balloon, were not significantly associated with the risk of recurrence.

Nodal metastasis

Boyraz et al. retrospectively evaluated 191 patients with EC grade 1 or 2 with less than 50% of myometrial invasion. Patients were divided into groups with tumour sizes of more than 2 cm and less than 2 cm. Lymph node metastasis was detected in 12 patients only in the group with tumour sizes bigger than 2 cm. None of the 67 patients with tumour sizes of 2 cm or less was found to have lymphatic involvement. In that group of patients with low risk-EC, lymph vascular space invasion and tumour size were found to be significant predictors for lymph node metastasis. Teixeira et al. based their retrospective study on 329 patients and developed a scoring system for the prediction of lymph node metastasis. On multivariate logistic regression analysis, tumour grade, tumour extension and location in the lower uterine segment were significantly associated with lymph node metastasis. Papadia et al. retrospectively analysed patients with preoperative diagnosis of a complex atypical hyperplasia and grade 1 and 2 EC who underwent laparoscopic hysterectomy. Indocyanine green fluorescence for the detection of sentinel lymph node mapping was performed, and the decision to perform pelvic (PLND) and/or paraaortic (PPALND) lymphadenectomy was based on an intraoperative frozen section of the uterus and evaluation of the risk factors (grade 3 and deep myometrial invasion). After frozen section, 23 (36.5%) and 14 (22.2%) patients underwent a PLND and PPALND, respectively. Five patients with stage IIIC disease were identified with a false negative rate of 16.7% and a negative predictive value and positive predictive value of 97.6 and 27.3%, respectively.

Ovarian preservation

In their meta-analysis, Wang et al. included 5,299 young patients with early EC. The effect of preservation of the ovaries was determined amongst a group of 916 patients. There was no significant difference in five-year overall survival and five-year recurrence rates between the groups.

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Surgical treatment of primary uterine cancer

- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Practice guidelines for management of uterine corpus cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement	Lee et al.	J.Gynecol. Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27894165
2	The effect of a uterine manipulator on the recurrence and mortality of endometrial cancer: a multi-centric study by the Italian Society of Gynecological Endoscopy	Uccella et al.	American Journal of Obstetrics and Gynecology	https://www.ncbi.nlm.nih.gov/pubmed/28147240
3	Incidence of lymph node metastasis in surgically staged FIGO IA G1/G2 endometrial cancer with a tumor size of more than 2 cm	Boyraz et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28187095
4	A preoperative and intraoperative scoring system to predict nodal metastasis in endometrial cancer	Teixeira et al.	Int J Gynaecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/28093726
5	FIGO stage IIIC endometrial cancer identification among patients with complex atypical hyperplasia, grade 1 and 2 endometrioid endometrial cancer: laparoscopic indocyanine green sentinel lymph node mapping versus frozen section of the uterus, why get around the problem?	Papadia et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27834005
6	[Meta-analysis of prognosis of ovarian preserving in young patients with early endometrial cancer]	Wang et al.	Zhonghua Fu Chan Ke Za Zhi	https://www.ncbi.nlm.nih.gov/pubmed/27561940

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Medical (chemo and radiotherapy) treatment of primary uterine cancer

Editor David Lindquist

Descriptive summary

One of the more important studies during this review period includes a meta-analysis including more than 9,000 patients investigating the possible value of adding radiontherapy to chemotherapy in the adjuvant treatment of endometrial cancer. The pooled results demonstrated higher overall survival in patients receiving both treatment regimens in combination [1]. This is further supported by a National Cancer Data Base Analysis [2] including 2,500 women, mainly for patients with advanced disease. In addition, another population-based analysis including only clear cell carcinomas concluded that survival was higher in patients with advanced disease, including chemotherapy as well as combined therapy [3]. Another study including a series of 64 patients with endometroid, serous, and clear cell carcinomas evaluated the use of docetaxel and cisplatin as adjuvant treatment. PFS and OS were feasible but grade 3 and 4 toxicities were found in 80-95% of patients. It is a small series of patients with very high toxicities and this combination of treatment needs further evaluation and is probably only feasible for a selected group of patients [4].

Another study retrospectively assessed survival in type two endometrial cancer and carcinosarcomas at stages I-II [5]. All patients underwent comprehensive surgical staging and the group of patients receiving both chemotherapy and radiotherapy had the best recurrence rate at 12.5%. However, the study is retrospective in nature and should not affect guidelines, but offering this treatment to patients with high-risk histology is probably already standard at some institutions.

The Taiwanese Gynaecology Oncology Group published retrospective data on a large cohort including 541 patients with stage III and IV endometroid adenocarcinomas [6]. Several known risk factors were confirmed to have prognostic significance. Most patients were treated with surgery including paraaortal and pelvic lymphadenectomy and adjuvant chemotherapy. The whole group had a PFS of 43 months and OS of 52 months which is in line with previously published data. One study retrospectively compared stage I and II type I endometrial cancer with regard to whether patients had received adjuvant radiotherapy or when relapsed received salvage radiotherapy in a matched setting [7]. The groups were well balanced and the group receiving adjuvant radiotherapy had five-year DSS of 95% as compared to the group receiving salvage radiotherapy with five-year DSS of 77%, which would suggest that adjuvant radiotherapy is feasible in a subset of these patients.

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Another single-center study investigated recurrences and toxicity after adjuvant vaginal brachytherapy [8]. The authors reported 16% acute vaginal toxicity, 55.4% chronic toxicity, and survival rates were around 95% depending on stage and grade. The value of adjuvant external beam radiotherapy was evaluated retrospectively in one study including 84 women with serous or clear cell carcinomas where all women had received adjuvant chemotherapy and vaginal brachytherapy after staging surgery [9]. A subset had received additional external radiotherapy and the authors conclude that external radiotherapy adds only toxicity for these stage I patients. Some additional smaller studies were published during this period as well [10-15].

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Medical (chemo and radiotherapy) treatment of primary uterine cancer

- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Comparison of survival benefits of combined chemotherapy and radiotherapy versus chemotherapy alone for uterine serous carcinoma: a meta-analysis	Lin Y et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5181126/
2	Utilization and role of adjuvant radiotherapy and chemotherapy for uterine clear cell carcinoma: a national cancer data base analysis	Xu KM et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/?term=26825837
3	Patterns of care, predictors, and outcomes of adjuvant therapy for early- and advanced-stage uterine clear cell carcinoma: a population-based analysis	Gockley AA et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/?term=26825834
4	Safety and anti-tumor effects of docetaxel plus cisplatin in intermediate- and high-risk endometrial cancer	Mivahara D et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/?term=27354646
5	Combination of adjuvant chemotherapy and radiotherapy is associated with improved survival at early stage type II endometrial cancer and carcinosarcoma	Sozen H et al.	Aust N Z J Obstet Gynaecol	https://www.ncbi.nlm.nih.gov/pubmed/26890292
6	Outcomes of patients with surgically and pathologically staged iiia-ivb pure endometrioid-type endometrial cancer: a taiwanese gynecology oncology group (tgog-2005) retrospective cohort study (a strobe-compliant article)	Chen JR et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/?term=27082583
7	Salvage versus adjuvant radiation treatment for women with early-stage endometrial carcinoma: A matched analysis	Bance S et al.	Int J Gynecol. Cancer	https://www.ncbi.nlm.nih.gov/pubmed/?term=26745700
8	Recurrences and toxicity after adjuvant vaginal brachytherapy in Stage I-II endometrial cancer: A monoinstitutional experience	Perrucci E et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/26727332
9	Adjuvant Chemotherapy and Vaginal Vault Brachytherapy With or Without Pelvic Radiotherapy for Stage 1 Papillary Serous or Clear Cell Endometrial Cancer	Tétreault-Laflamme A	Int J Gynecol. Cancer	https://www.ncbi.nlm.nih.gov/pubmed/?term=26745699
10	Uterine clear cell carcinoma: does adjuvant chemotherapy improves outcomes	Nguyen JMV et al.	Int J Gynecol Cancer	http://journals.lww.com/ijgc/Abstract/2017/01000/Uterine_Clear_Cell_Carcinoma__Does_Adjuvant.12.aspx
11	Statin use significantly improves overall survival in high-grade endometrial cancer	Feng CH et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/?term=27654261
12	Extrauterine spread, adjuvant treatment, and prognosis in noninvasive uterine papillary serous carcinoma of the endometrium: A retrospecitve multicenter study	Boyraz G et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27668395
13	Gemcitabine and docetaxel compared with observation, radiation, or other chemotherapy regimens as adjuvant treatment for stage I-to-IV uterine leiomyosarcoma	Roque DR et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/?term=26807641
14	The impact of combined radiation and chemotherapy on outcome in uterine papillary serous carcinoma compared to chemotherapy alone	Mahdi H et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/26463437
15	Role of adjuvant therapy for stage IA serous and clear cell uterine cancer: Is observation a valid strategy?	Velker V et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/?term=26825823

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Surgical treatment of recurrent uterine cancer

Editor Arun Kalpdev

Descriptive summary

Margolis et al. reported a case report with long-term survival after anterior pelvic exenteration and total vaginectomy for recurrent endometrial carcinoma (REC) with metastatic inguinal nodes at the time of surgery. Based on their experience, authors have suggested that historically strict selection criteria of patients appropriate for pelvic exenteration need not exclude select patients who, on an individual basis, may benefit from the procedure. In some cases, it can also be used in patients with multifocal recurrence, although the ability to achieve negative margins remains a necessity for that procedure. The authors have underlined the benefit of individualised treatment planning in patients with that recurrent gynaecologic malignancy [1]. The Korean Society of Gynaecologic Oncology has given a viewpoint on the role of surgery in REC [2]. In the consensus statement, it has been described that, in the solitary metastasis of endometrial cancer, surgical removal of the relapsed lesion with or without radiotherapy should be considered. In patients who did not previously undergo radiotherapy, this method should also be discussed. Based on the literature review, Krengli et al. concluded that intraoperative radiotherapy (IORT) after surgical resection could increase the probability of local control of locally advanced and REC [3]. The addition of IORT to surgery could be proposed in patients with isolated REC, especially when margins might be close to negative or microscopically positive. Although scarce data comes from retrospective single-institutional studies, it can be estimated that patients with limited loco-regional REC have a relatively high control rate of about 60% at five years, either with pelvic exenteration or local EBRT (in non-previously irradiated patients).

Relevant articles retrieved Aug 2016 – Feb 2017 (cont.)

No	Title	Authors	Journal	Link to abstract
1	Long-term survival after anterior pelvic exenteration and total vaginectomy for recurrent endometrial carcinoma with metastatic inguinal nodes at the time of surgery	Margolis B et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/28070552
2	Practice guidelines for management of uterine corpus cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement	Lee SW et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27894165
3	Intraoperative radiotherapy in gynaecological and genitourinary malignancies: focus on endometrial, cervical, renal, bladder and prostate cancers	Krengli M et al.	Radiat Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28100242

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Medical treatment of recurrent endometrial cancer

Editor Ewa Surynt

Descriptive summary

In the period covered by the fifth edition of the LiFE project, two publications focused on and discussed the problem of recurrent endometrial cancer (REC).

McCourt et al. presented the response rate and safety profile of ixabepilone in women with recurrent or persistent uterine carcinosarcoma [1]. In total, 42 patients received ixabepilone 40mg/m^2 as a three-hour IV infusion on day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity occurred. Stable disease for at least eight weeks was achieved in eight patients (23.5%). Median PFS and OS were 1.7 and 7.7 months, respectively, with a median follow-up of 37 months. Authors concluded that, as a single agent, ixabepilone had modest but insufficient clinical activity.

In their statement on uterine cancer management (see report on "Surgical treatment of primary uterine cancer" by Dr. Lepka), the Korean Society of Gynaecologic Oncology also discussed the topic of REC [2]. The combination of paclitaxel and carboplatin is advised in this group of patients, as supported by the preliminary results of a randomised trial showing similar efficacy and less toxicity compared with cisplatin, doxorubicin, and paclitaxel.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	A phase II evaluation of ixabepilone in the treatment of recurrent/persistent carcinosarcoma of the uterus, an NRG Oncology/Gynecologic Oncology Group study	McCourt CK et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28029447
2	Practice guidelines for management of uterine corpus cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement	Lee SW et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27894165

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Novel experimental therapies in endometrial cancer

Editor Ines Vasconcelos

Descriptive summary

During this period, three negative and two positive trials were published.

Negative trials

A single-arm, multicentre, phase II trial on apitolisib (a dual PI3K/mTOR inhibitor) was limited by tolerability, especially in diabetic patients. Grade 3/4 apitolisib-related adverse events were hyperglycaemia (46%), rash (30%), colitis (5%), and pneumonitis (4%), requiring doses in 31% of diabetic and 42% of nondiabetic patients [1]. A phase II, randomised trial on irosustat (a steroid sulphatase inhibitor) monotherapy did not attain a level of activity sufficient for further development, with a median progression-free survival of 16 weeks [2]. The third study was a phase II trial on the PIK3 inhibitor BKM120 and was associated with an unfavourable safety profile and minimal antitumour activity when given in monotherapy. It was associated with cutaneous rash (54%), depressive events (47%), and anxiety (40%), resulting in a median progression-free survival for all patients of 4.5 months [3].

Positive trials

A phase I study of azacitidine priming (a hypomethylating agent) and nanoparticle albumin bound paclitaxel was well tolerated and resulted in responses in pre-treated cancer patients. Clinical activity included four partial responses in endometrial cancer patients [4]. The last study, a phase I/IIa trial of E39 (GALE 301)+GM-CS, an HLA-A2-restricted, folate binding protein (FBP)-derived peptide vaccine to prevent recurrences in disease-free endometrial and ovarian cancer patients, was well tolerated regardless of dose. With 12 months median follow-up, among the patients receiving a dose of 1000 mcg the recurrence rate was 13.3% in the vaccinated group vs. 55% in the control group, p = 0.01. The estimated two-year DFS was 85.7% in the 1,000 mcg group vs. 33.6% in the control group (p = 0.021). It revealed that E39+GM-CSF was well tolerated and elicited a strong, dose-dependent in vivo immune response. Early efficacy results were promising in the 1,000 mcg dose cohort, and a larger prospective trial is likely to be undertaken [5].

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	A multicenter, single-arm, open-label, phase 2 study of apitolisib (GDC-0980) for the treatment of recurrent or persistent endometrial carcinoma (MAGGIE study)	Makker et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27603005
2	A phase 2, randomized, open-label study of irosustat versus megestrol acetate in advanced endometrial cancer	Pautier et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27870712
3	Phase II study of the PI3K inhibitor BKM120 in patients with advanced or recurrent endometrial carcinoma: a stratified type I-type II study from the GINECO group	Heudel et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28072765
4	A phase I trial of azacitidine and nanoparticle albumin bound paclitaxel in patients with advanced or metastatic solid tumors	Cohen et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/28039455
5	Interim analysis of a phase I/IIa trial assessing E39+GM-CSF, a folate binding protein vaccine, to prevent recur-rence in ovarian and endometrial cancer patients	Jackson et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/27852036

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Uterine sarcoma

Editor Marcin Bobiński

Descriptive summary

Problem of morcellation and uterus-preserving surgery

The most significant publication regarding uterine sarcoma in the period covered by the fifth issue of LiFE is the ESGO statement on fibroid and uterine morcellation [1]. The conclusion of this article is that "eliminating the technique of morcellation could lead to an increased morbidity in low-risk patients; therefore, after preoperative evaluation and discussion with patients, morcellation still has its place in the gynaecologic surgery".

Lee et al. presented an evaluation that aimed to assess the impact of initial uterus-preserving surgery, such as myomectomy or subtotal hysterectomy, on the recurrence rates of patients with uterine sarcoma found incidentally. They stated that uterus-preserving surgery does not appear to be associated with an adverse impact on survival outcomes in cases when surgical re-exploration was performed immediately [2].

Molecular research

Miller et al. presented wide review of potential molecular targets in leiomyosarcomas (LMS) and potential new therapeutic options (i.e., tyrosine kinase inhibitors, antihormonal agents, mTOR inhibitors) [3]. The original research analysing the amplification and presence of multiple copies of the BCL2 gene in STUMP tumours was published by Conconi et al. The authors considered both factors (amplification and multiple copies of BCL2 gene) as potential markers of STUMP malignancy potential and recurrence [4]. Miolo et al. presented the case of a patient with such mutation who experienced a complete remission after three courses of trabectedin. This observation supports the hypothesis that the response to trabectedin may be positively conditioned by the different DNA repair defects present in the neoplasm [5]. The molecular pathology of LMS was analysed by Hayashi et al., who reported the presence of mutation in three genes: JAK1, STAT1 and, PSMB9/ 1i. Furthermore, they proposed these genes as potential targets for therapeutic interventions [6].

Role of lymphadenectomy (LAD) in uterine sarcoma treatment

The meta-analysis of the impact of LAD on patient outcome was performed by Si et al. They concluded that it bears little prognostic or therapeutic benefit in patients with uterine sarcoma. Systematic LAD may not be recommended in patients with LMS or ESS unless the patient has obvious extra-uterine involvement, clinically suspicious enlarged nodes, or advanced sarcomas [7].

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Management of uterine sarcoma—guidelines

Recently, several guidelines regarding management of uterine sarcoma were published:

- British guidelines cover all soft tissue sarcomas but a significant part of the guidelines is devoted to the various kinds of uterine sarcoma [8].
- The Taiwan Society of Gynaecology Systematic Review Group published the review of recent knowledge about uterine sarcoma, including its pathology, diagnostics, and treatment [9].
- A very clear update of recommendations was released by the Korean Society of Gynaecologic Oncology [10].

Varia

Gauthé et al. presented an interesting case report of LMS metastases to the thyroid gland. They discuss the role of 18F-FDG PET/CT in the diagnostic of patients with metastatic LMS [11]. Artioli et al. presented the case of cardiac metastasis of uterine leiomyosarcoma [12].

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Uterine sarcoma

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	European society of gynecological oncology statement on fibroid and uterine morcellation	Halaska et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28002210
2	Outcomes of uterine sarcoma found incidentally after uterus-preserving surgery for presumed benign disease	Lee et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4995644/
3	Molecular targets and emerging therapeutic options for uterine leiomyosarcoma	Miller et al.	Sarcoma	https://www.ncbi.nlm.nih.gov/pubmed/27721667
4	Potential role of BCL2 in the recurrence of uterine smooth muscle tumours of uncertain malignant potential	Conconi et al.	Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/28004108
5	Association of the germline BRCA2 missense variation Glu2663Lys with high sensitivity to trabectedin-based treatment in soft tissue sarcoma	Miolo et al.	Cancer Biol Ther	https://www.ncbi.nlm.nih.gov/pubmed/27561088
6	Molecular pathology and novel clinical therapy for uterine leiomyosarcoma	Hayashi et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/27798858
7	Role of lymphadenectomy for uterine sarcoma: A meta-analysis	Si et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27668397
8	UK guidelines for the management of soft tissue sarcomas	Dangoor et al.	Clin Sarcoma Res	https://www.ncbi.nlm.nih.gov/pubmed/27891213
9	Uterine sarcoma part I-uterine leiomyosarcoma: the topic advisory group systematic review	Wen et al.	Taiwan J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27590365
10	Practice guidelines for management of uterine corpus cancer in Korea: a Korean Society of Gynecologic Oncology Consensus Statement	Lee et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27894165
11	Uterine leiomyosarcoma metastatic to thyroid shown by 18F-FDG PET/CT imaging	Gauthé et al.	Rev Esp Med Nucl Imagen Mol	https://www.ncbi.nlm.nih.gov/pubmed/27777040
12	Unusual cardiac metastasis of uterine leiomyosarcoma: case report and literature review	Artioli et al.	Tumori	https://www.ncbi.nlm.nih.gov/pubmed/27079906

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Cervical pre-invasive disease

Editor Geanina Dragnea

Descriptive summary

Pathogenesis

A study about HPV integration status performed on 13 HPV16-infected patients concluded that this virus probably contributes to oncogenesis not only by disrupting tumour suppressor genes, but also by inducing chromosome instability [1].

HPV screening

A population-based randomised trial on 43,339 women aged 29 – 61 years with a negative HPV and/or negative cytology, followed-up for 14 years with three screening rounds every five years, suggested the extension of the HPV-based cervical screening interval beyond five years for women HPV negative, aged 40 years and older [2] .

Vaccination efficacy

In a post-hoc analysis of the PATRICIA trial, the efficacy of the HPV-16/18 AS04-adjuvanted vaccine (received at zero, one and six months) was evaluated in a subset of patients who underwent excisional procedure after the vaccination regarding the prevention of developing a subsequent CIN lesions. Efficacy was 88.2% against CIN2+, suggesting a benefit from vaccination [3].

HPV genotyping

The 12 non-16/18 high risk (HR)-HPV genotypes can be further categorised (HPV31/33/35/45/52/58 vs. HPV39/51/56/59/66/68) by risk stratification for developing CIN2+. In a retrospective study, the age-adjusted odds ratios for CIN2+ of the HPV31/33/35/45/52/58 and HPV39/51/56/59/66/68 positive groups compared with an HR-HPV negative group were 11.9 and 2.4, respectively, while the ratio of the HPV-16/18 positive group was 18.1 [4].

Viral load

- Viral load at the first HR-HPV (non-16/18) positive visit for women with a cytologic diagnosis of within normal limits, ASC-US, or LSIL was found to be associated with a statistically significant risk of CIN2/3 in a follow-up period of two years, mainly for HPV types related to HPV16 (31, 33, 35, 52, 58) [5].
- Re-analysing the data from a trial of 8,556 patients showed a relationship between the viral load and the severity of the lesion: The mean RLU/CO values for negative, CIN 1, CIN 2, CIN 3, and cancer were 6.86, 119.43, 410.90, 449.39, and 853.26, respectively. The algorithm using ≥10 RLU/CO as cut-off value for immediate colposcopy and triage cytology for the other HPV positive women (≥1 < 10 RLU/CO) had a sensitivity of 93.13% vs. 96.45% and specificity of 92.32% vs. 91.44% for CIN 2+ and the colposcopy referral rate was 10% [6].
- In a case-cohort natural history study, HPV-specific slopes (suggestive of progression, regression, serial transient, and transient infection) were calculated using serial type-specific viral-load measurements (≥3). In CIN3+ cases, at least one of the HPV types had a clonal progressive course. This result suggests that, in women with multiple HPV types, serial type-specific viral-load measurements predict the natural history of the different HPV types and elucidates HPV-genotype attribution [7].

HPV clearance

Two studies, a longitudinal one on 650 HR-HPV-positive women and a double-blind, randomised clinical trial on 195 women, observed that HR-HPV persistence in women with normal cervix or low-grade lesion was associated with a significant higher risk of developing CIN 2+ lesions when compared with women who cleared the infection [8, 9]. Almost all CIN2+ cases occurred within six years [9]. The risk of viral persistence in women aged 50 – 60 years was higher compared to those aged 30 – 49 years. Higher viral load at baseline increased the probability of having persistent infection and increasing viral load at follow-up had a significant higher risk of developing CIN2+ lesions compared to those with decreasing load (20.9% vs 4.8%; $p<0.001$) [8].

Atypical glandular cells (AGC) and HPV test

In a retrospective study on women with various types of AGC on cytology who had histological follow-up results within one year, HR-HPV testing was found to have an important role in the management of these individuals. The overall rate of HR-HPV positivity was 27.7% and the risk of high-grade cervical lesions in the HR-HPV+ group was significantly higher compared with the HR-HPV- group (16.8% vs. 0.6% with CIN2/3, 5.7% vs. 0.2% with adenocarcinoma in situ/adenocarcinoma) [9].

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Cervical pre-invasive disease

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No	Title	Authors	Journal	Link to abstract
1	HPV16 integration probably contributes to cervical oncogenesis through interrupting tumor suppressor genes and inducing chromosome instability	Zhao JW et al.	J Exp Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/27884161
2	Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands	Dijkstra MG et al.	BMJ	https://www.ncbi.nlm.nih.gov/pubmed/27702796
3	Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: Post-hoc analysis from a randomized controlled trial	Garland SM et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27541373
4	Can human papillomavirus (HPV) genotyping classify non-16/18 high-risk HPV infection by risk stratification?	Sung YE et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27550402
5	Type-dependent association between risk of cervical intraepithelial neoplasia and viral load of oncogenic human papillomavirus types other than types 16 and 18	Fu Xi L et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28052328
6	Evaluation of viral load as a triage strategy with primary high-risk human papillomaviruscervical cancer screening	Luo H et al.	J Low Genit Tract Dis	https://www.ncbi.nlm.nih.gov/pubmed/27851695
7	Linear viral load increase of a single HPV-type in women with multiple HPV infections predicts progression to cervical cancer	Depuydt CE et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27339821
8	Risk of high-grade precancerous lesions and invasive cancers in high-risk HPV-positive women with normal cervix or CIN 1 at baseline-A population-based cohort study	Mittal S t al	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28108997
9	Management of women with human papillomavirus persistence: long-term follow-up of a randomized clinical trial	Elfgren K et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27825977
10	Significance of high-risk HPV detection in women with atypical glandular cells on Pap testing: Analysis of 1857 cases from an academic institution	Patadji S et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28060456

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Surgical treatment of primary and recurrent cervical cancer

Editor Mandic Aljosa and Matteo Morotti

Descriptive summary

Derks et al. compared urinary, bowel symptoms, and quality of life (QoL) scores amongst women treated with Wertheim-Meigs (WM, type III) or Wertheim-Okabayashi (WO, type IV) radical hysterectomy technique and pelvic lymphadenectomy for early-stage cervical cancer. Variables were assessed with the EORTC QLQ-C30, EORTC QLQ-CX24, and Leiden Questionnaire. Two hundred sixty-eight women were included (152 WO and 116 WM). Quality of life and bowel symptoms were not significantly different in patients treated by WO or WM. Urinary symptoms were more often reported by patients in the WO group compared to the WM group: Multivariate analysis showed that surgical technique was an independent factor that can explain differences between groups in urinary symptoms after surgery [1].

Lee et al. investigated the risk factors for distant recurrence in node-positive cervical cancer patients who had undergone radical hysterectomy and pelvic lymphnodes (PLND) and/or para-aortic (PALND) dissection or para-aortic sampling (PALNS). A total of 299 patients with lymph node metastasis after radical surgery were included. Of these, 72 (24.1%) patients underwent PLND only and 227 (75.9%) underwent PLND with PALNS or PALND. Among 223 patients, the mean number of positive lymph nodes was 4.46. Multivariate analyses using the Cox proportional hazards model showed that histologic types (HR=3.031, P≤0.001 for adenocarcinoma, HR=2.302, P=0.066 for adenosquamous carcinoma), number of positive lymph nodes (HR=1.077, P≤0.001), and surgical stage (HR=1.264, P=0.022) were independent risk factors for distant recurrence. A scoring system including these parameters (histology, stage, number of nodes) for the prediction of distant recurrence was generated and validated in an internal cohort. The authors concluded that this scoring system could be used to identify a group of patients who required systemic control of distant micrometastasis. This group of patients could be an appropriate target for consolidation chemotherapy after concurrent chemoradiation therapy [2].

There is discrepancy in the literature regarding the appropriate timing of definitive surgery after an excision procedure for cervical cancer. In a retrospective cohort, Sullivan at al. evaluated the risk of surgical complications between patients who underwent a cervical excision procedure followed by definitive minimally invasive surgery (MIS) within six weeks (early group) or between six weeks to three months (delayed group). The primary outcome were 30-day complications. Overall, 138 patients met the inclusion criteria. Of these, 33% (n = 46) had early definitive surgery and 67% (n = 92) had delayed definitive surgery. When adjusting for relevant demographic and surgical factors, patients in the early group were twice as likely to have 30-day complication (RR 2.6, 95% CI 1.14–5.76, p = 0.02). Evaluating only women who underwent a radical procedure, 30-day complications remained higher in the early surgery group (RR 2.56; 95%CI 1.22–5.38, p=0.01) [6]. The Authors concluded that performing definitive MIS for cervical cancer within six weeks after cervical excision is associated with increased risk for 30-day complications. Providers should consider delaying definitive surgical procedures for at least six weeks following excision to reduce surgical complications.

No randomised trial has yet demonstrated the benefit of a preoperative brachytherapy in patients with early-stage cervical cancer, but retrospective reports have examined the clinical outcome of patients treated according to this radiosurgical modality and shown high local control rates and a satisfactory toxicity profile. Escande et al. published a report on preoperative brachytherapy as part of a multimodal strategy. Patterns of relapse, long-term sequelae, and clinical prognostic factors were examined. Consecutive patients with early-stage IB1-IIA1 invasive cervical cancer with risk factors (emboli and/or tumour >2 cm) were included. The treatment consisted of preoperative low dose or pulse dose-rate uterovaginal brachytherapy followed, six to eight weeks later, by a radical hysterectomy/bilateral salpingo-oophorectomy plus pelvic ± para-aortic lymph node dissection. Postoperative chemoradiation was delivered in patients with histological evidence of lymph nodes metastases (n=26, 14.3%). In total,182 patients were identified. A tumour residuum at histological examination of the uterus was showed in 55 patients (30.2%). The five-year disease-free survival (DFS) rate was 93.6% (95%CI: 91.6–95.6%). In log-rank analysis, the presence of pelvic nodal metastases at the time of lymphadenectomy (p=0.001) and tumour size ≥3 cm (p=0.003) correlated with a poorer DFS. The presence of a tumour residuum on a hysterectomy specimen correlated with a higher risk of pelvic or para-aortic failure (p=0.035). A time interval >10 weeks between brachytherapy and surgery correlated with a higher risk of failure outside the pelvis (p = 0.003). Significant postoperative complications were reported in 16 patients (8.8%). All delayed toxicities were mild to moderate [4].

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Surgical treatment of primary and recurrent cervical cancer

- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Long-term pelvic floor function and quality of life after radical surgery for cervical cancer: A multicenter comparison between different techniques for radical hysterectomy with pelvic lymphadenectomy	Derks M et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27465892
2	A postoperative scoring system for distant recurrence in node-positive cervical cancer patients after radical hysterectomy and pelvic lymph node dissection with para-aortic lymph node sampling or dissection	Lee Y-J et al	Gynecol Oncol	http://dx.doi.org/10.1016/j.ygyno.2017.01.001
3	Association between timing of cervical excision procedure to minimally invasive hysterectomy and surgical complications	Sullivan S et al.	Gynecol Oncol	http://dx.doi.org/10.1016/j.ygyno.2016.11.037
4	Outcome of early stage cervical cancer patients treated according to a radiosurgical approach: Clinical results and prognostic factors	Escande A et al.	Gynecol Oncol	http://dx.doi.org/10.1016/j.ygyno.2016.12.026

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Medical treatment of primary and recurrent cervical cancer

Editor Kristina Lindemann

Descriptive summary

Neuroendocrine tumours

Frumovitz et al. assessed the clinical activity and safety of the three-drug combination topotecan, paclitaxel, and bevacizumab (TPB) in a retrospective study of 13 patients with small-cell cervix cancer and compared them with patients treated with a variety of other regimens (n=21). On TPB, ten (77%) of the patients remained without progression at the first assessment (after two–three cycles). Response rates for the other regimen were not reported, but the median PFS in TBP patients was 7.8 months (95% CI 4.5–21.8), compared to patients in the non-TBP group of 4.0 months (95% CI 2.5–5.7), (HR 0.21, 95% CI 0.09–0.54, P = 0.001). There was an 8% discontinuation rate, but toxicities were not reported in detail. The advantage in PFS did not result in a difference in OS. Two patients developed new brain metastases while in complete response in the thorax and abdomen with metastatic disease in the chest and abdomen. The authors discuss the role of whole brain irradiation of patients with relapsed disease. Gaducci et al. provided a review on the histopathology, prognosis, and available evidence of treatment of these rare tumours and suggested a treatment algorithm.

Primary treatment

Di Donato et al. reported on the clinical outcome of 52 stage III cervical cancer cases treated with platinum-based chemotherapy followed by radical surgery. In total, 76.9% were offered radical surgery, while the others had progressive disease, poor performance status, or were intra-operatively assessed as non-resectable. The majority of patients received further adjuvant treatment after surgery. The relapse rate in all patients was high and the five-year OS poor at 29.5%, but median OS in patients successfully treated with surgery was 60 months and 43 months for stage IIIA and B, respectively.

Luvero et al. reported on the long-term survival of patients with IB2-IIB cervical cancer treated with neoadjuvant chemotherapy+radical surgery+adjuvant chemotherapy. The prognostic role of lymph node involvement was confirmed after long-term follow-up with an OS of 63% in the subgroup of patients with positive nodes, and of 75% with negative nodes. The article is accompanied by a letter by Ali et al. and the author's reply.

Treatment of recurrent disease

The retrospective report from the Royal Marsden Hospital by McLachlan et al. included 75 patients who had received chemotherapy for recurrent or metastatic disease. The study underlines the fact there is no standard treatment in second-line chemotherapy, but there are poor response rates and unmet needs of these patients.

Thaker et al. reported on a phase I trial of cisplatin/paclitaxel and the PARP inhibitor veliparib in persistent or recurrent cervical cancer. The dose of veliparib could safely be escalated to 400 mg twice daily on days one–seven.

For the cohort with veliparib at 400 mg with concurrent chemotherapy, the RR was 60% (3/5) (95% CI.23%–88%). The median PFS was 6.2 months (95% CI .2.9–10.1), and the median OS was 14.5 months (95% CI.8.2–19.4) for the entire cohort. Anaemia, neutropenia, and hypersensitivity reactions were the main adverse events observed.

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Medical treatment of primary and recurrent cervical cancer

- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Combination therapy with topotecan, paclitaxel, and bevacizumab improves progression-free survival in recurrent small cell neuroendocrine carcinoma of the cervix	Frumovitz M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27823771
2	Neuroendrocrine tumors of the uterine cervix: A therapeutic challenge for gynecologic oncologists	Gaducci A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/labs/articles/28057354/
2	Effects of neoadjuvant chemotherapy plus radical surgery as front line treatment strategy in patients affected by FIGO Stage III cervical cancer	Di Donato et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/labs/articles/27678502/
3	The impact of systemic therapy beyond first-line treatment for advanced cervical cancer	McLachlan J et al.	Clinical Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27838135
4	A phase I trial of paclitaxel, cisplatin, and veliparib in the treatment of persistent or recurrent carcinoma of the cervix: an NRG Oncology Study (NCT#01281852)	Thaker PH et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27998970

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Radiotherapy in the management of primary cervical cancer

Editor Vishal Bahall

Descriptive summary

Lan et al. reported on the clinical outcomes and toxicity of 115 women who were given pelvic intensity-modulated therapy (IMRT) and three dimensional conformal radiation therapy (3D-CRT) after radical hysterectomy and pelvic lymph node dissection (PLND). They reported two-year disease-free survival (DFS) of 88.8% and 86.0% in 3D-CRT and IMRT groups, respectively. Overall survival (OS) was 90.3% in 3D-CRT and 91.6% in IMRT. The IMRT group showed less grade 1/2 GI (19.2%) and GU (50.2%) toxicities compared to 3D-CRT which showed grade 1/2 GU and GI toxicities of 50.1 and 80.9%, respectively.

Fallon et al. published a review on long-term outcomes in primary cervical cancer treated with external beam and high dose rate (HDR) interstitial brachytherapy (IBT) in a group of 315 women who were not eligible for intra-cavitary brachytherapy (ICBT) alone. The ten-year actuarial local control was 87%, DFS was 54%, and OS was 40%. The rates of late-grade GU and GI toxicities were 4.8% (G3) and 5.4% (G4), respectively.

Cho et al. investigated whether high HDR ICBT dose ratios (>0.43) can predict treatment outcomes when compared to low HDR ICBT ratio (≤0.43) in 93 patients with stage IIB cervical cancer. They found that a high HDR ICBT dose ratio improves disease-specific survival (DSS) and PFS.

Chang et al. reported on a randomised controlled trial of 67 patients to investigate the radiation effects and acute damage in inoperable cervical cancer patients irradiated at different times during the day. Sixty-seven women were randomised to a morning group (MG, 9:00 - 11:00 AM) and an evening group (EG, 9:00 - 11:00 PM). Women were given both external beam radiotherapy (EBRT) and BT. There were similar efficacy between MG and EG but significantly lower rates of Grade 3-4 diarrhoea in MG were found, while severe hematotoxicity was significantly higher in EG.

Yoshizawa et al. reported OS and PFS of 32 women who were treated with radiotherapy with no boost irradiation to pelvic lymph node (PLN) metastases for primary cervical cancer. The authors showed a two-year cumulative OS and PFS of 74% and 31%, respectively.

Lee et al. reported on the prognostic significance of changes in primary tumour volume (pTV) and serum squamous cell cancer antigen (SCC-ag) during radiotherapy (RT) for women with cervical cancer. They reviewed 40 women treated from November 2009 to August 2015. The authors concluded that there was a significant correlation between pTV reduction rate (pTVRR) and SCC-ag reduction rate (SCCRR). They also found that tumour parameters such as pre-RT pTV, mid-RT tumour size, and pTVRR were associated with PFS in women with cervical cancer. Multivariate analysis, however, did not show any relation between these factors and OS/PFS.

Zhou et al. evaluated the clinical outcomes in patients with International Federation of Gynecology and Obstetrics (FIGO) stage I to IVA squamous cell carcinoma (SCC), adenocarcinoma (AC), and adeno-squamous carcinoma (ASC) of the uterine cervix after definitive radiotherapy. They evaluated 8,751 women over 25 years and concluded that AC and ASC subtypes are associated with poorer survival outcomes compared to SCC subtype. Interestingly, this finding was not affected by FIGO stage.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Clinical outcomes and toxicity of postoperative intensity-modulated versus three-dimensional conformal radiation therapy in patients with cervical cancer	Lan et al.	Asia-Pac J Clin Oncol	http://onlinelibrary.wiley.com/doi/10.1111/ajco.12476/abstract
2	Clinical impact of escalating relative high-dose-rate intracavitary brachytherapy dose in stage IIB cervical cancer	Cho et al.	Anticancer Res.	http://ar.iiarjournals.org/content/37/1/327.abstract
3	Research on radiotherapy at different times of the day for inoperable cervical cancer	Chang et al.	Int J. Clin Pharmacol Ther	https://www.ncbi.nlm.nih.gov/pubmed/27615005
4	Outcomes of uterine cervical cancer patients with pelvic lymph node metastases after radiotherapy without boost irradiation of metastases.	Yoshizawa et al.	J. Obstet Gynaecol Res	https://www.ncbi.nlm.nih.gov/pubmed/28127834
5	The predictive value of tumor size, volume, and markers during radiation therapy in patients with cervical cancer	Lee et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27668394
6	Comparison of clinical outcomes of squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma of the uterine cervix after definitive radiotherapy: a population-based analysis	Zhou et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27646608
7	Long term results from a prospective database on high dose rate (HDR) interstitial brachytherapy for primary cervical carcinoma	Fallon et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28029448

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Radiotherapy in management of recurrent cervical cancer

Editor Erbil Karaman

Descriptive summary

During the period covered by the fifth edition of the LiFE report, three out of ten papers dealing with radiotherapy in the management of recurrent cervical cancer were published and rated as relevant for the update.

Liu et al. described a new therapeutic technique in brachytherapy (BT) and reported the data of sixteen patients with recurrent cervical cancer after radical surgery and adjuvant radiation therapy who were treated with salvage interstitial brachytherapy guided by real-time three-dimensional computed tomography. These patients underwent high dose rate (HDR) interstitial brachytherapy with free-hand placement of metal needles guided by 3D tomography. Initial response, defined as complete remission (CR) and partial remission (PR), was found in 13 (81.3%) patients, according to pelvic MRI findings and clinical gynaecological examination at three months after interstitial BT. Of all the patients with initial responses, six (37.5%) exhibited CR and seven (43.8%) PR. The remaining three (18.7%) patients showed stable disease (SD) at three months after interstitial BT. No patient experienced progressive disease (PD). The authors concluded that this technique results in good dose-volume histogram parameters and may be clinically feasible. However, the long-term clinical outcomes should be further investigated.

Krengli et al. published a review regarding the use of intraoperative radiotherapy (IORT) in gynaecologic and genito-urinary malignancies including cervical cancer. Intraoperative radiotherapy refers to the delivery of a single radiation dose to a limited volume of tissue during a surgical procedure. The use of IORT was reported mainly in retrospective studies. The review concluded that literature data supports the use of IORT in recurrent cervical cancer to improve local control whereas its use appears more controversial in primary locally advanced disease. In the review, up to 15% of side effects related to IORT were pointed out. And also, the potential benefit of this approach should be further verified by prospective, possibly randomised trials investigating the potential advantage compared to EBRT alone.

Pontoriero et al. evaluated the role of stereotactic body radiation therapy (SBRT) in the retreatment of locally recurrent cervical cancers. This was the first study that reports the use of endovaginal device such as "fiducials" for tracking in an image-guided radiation therapy modality. Five patients with recurrent cervical cancer, previously submitted to radiotherapy, were treated with stereotactic body radiation therapy using a CyberKnife system (Accuray Incorporated, Sunnyvale, California) with a fiducial tracking system. The median follow-up was 12 months. six months after treatment, three patients showed complete response and two patients showed partial response. No severe (>grade 3) acute/late genitourinary or low gastrointestinal toxicity was observed. The authors concluded that stereotactic body radiation therapy "simulating" high dose rate for recurrent cervical cancers confirms a minimal toxicity and an optimal outcome. The stereotactic body radiation therapy is an alternative to high dose rate brachytherapy for gynaecologic tumours.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Salvage interstitial brachytherapy based on computed tomography for recurrent cervical cancer after radical hysterectomy and adjuvant radiation therapy: case presentations and introduction of the technique	Liu ZS et al.	J Contemp Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/27895683
2	Intraoperative radiotherapy in gynaecological and genito-urinary malignancies: focus on endometrial, cervical, renal, bladder and prostate cancers	Krengli M et al.	Radiat Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28100242
3	Stereotactic radiotherapy in the retreatment of recurrent cervical cancers, assessment of toxicity, and treatment response: initial results and literature review	Pontoriero A et al.	Technol Cancer Res Treat	https://www.ncbi.nlm.nih.gov/pubmed/26424502

ENYGO ESGO European Network of Young Gynae Oncologists | LiFE report Literature for ENYGO

Emerging molecular-targeted therapies or early preclinical trials in cervical cancer

Editor Marcin Mardas

Descriptive summary

Zhang et al. showed that hyaluronic acid binding protein 1 (HABP1) expression was found to be positively higher in CC than in CIN2/3 cases (P = 0.020), and overexpression was associated with advanced FIGO stage (P = 0.001), poor histologic grade (P = 0.013), large tumour size (P = 0.025), LVSI (P = 0.024), deep stromal infiltration (P = 0.001), and lymph node metastasis (P = 0.023). Multivariate analysis suggested that HABP1 overexpression was an independent factor for disease-free survival (HR 3.082; 95%CI 1.372-7.501; P = 0.007).

Santos et al. reported that turmeric (CEO, Curcuma longa L.), and ginger (GEO, Zingiber officinale R.) exhibited potent cytotoxic activity against HeLa cells. The morphology of HeLa cells showed condensation of chromatin, loss of cell membrane integrity with protrusions (blebs), and cell content leakage for cells treated with CEO and GEO.

Mane et al. suggested that ascorbyl stearate (fatty acid ester derivative of ascorbic acid) has an apoptotic effect against HeLa cells by inducing change in mitochondrial membrane permeability, cytochrome c release and subsequent activation of caspase-3 and NF-B.

Sakai et al. demonstrated that AZD1152-hQPA had an antagonistic effect on the cytotoxicity of cisplatin, etoposide, and doxorubicin, but had a synergistic effect on that of all-trans-retinoic acid (ATRA), Am80 and TAC-101, when tested on HeLa cells. Cisplatin, etoposide, and doxorubicin increased the cellular expression of aurora kinase B (AURKB), while ATRA, Am80 and TAC-101 downregulated its expression. Results suggested that AURKB expression is regulated by these anticancer agents at the transcriptional level, and that the level of expression of AURKB may influence the cytotoxic effect of AZD1152-hQPA.

Tai et al. tested the combination of dihydroartemisinin (DHA) and doxorubicin (DOX) in the HeLa, OVCAR-3, MCF-7, PC-3 and A549 cells. The HeLa cells treated with the combination of DHA and DOX showed up to a 91.5% decrease in viability, which was higher than that of the same cells treated with DHA or DOX alone at the same concentration, respectively (P<0.01). In a mouse model, the tumour volume was markedly reduced with no significant toxicity.

Lukhele and Motadi compared the anti-proliferative effects of crude extract of Cannabis sativa and its main compound cannabidiol on different cervical cancer cell lines. Both cannabidiol and Cannabis sativa extracts were able to halt cell proliferation, however, apoptosis was induced by cannabidiol as shown by increased subG0/G1 and annexin V and confirmed by overexpression of p53, caspase 3, and bax.

Sikander et al. reported that novel analogue of cucurbitacin (cucurbitacin D) inhibited viability and growth of cervical cancer cells (CaSki and SiHa) in a dose-dependent manner. Cucurbitacin D treatment of CC cells arrested the cell cycle in G1/S phase, inhibited constitutive expression of E6, Cyclin D1, CDK4, pRb, and Rb and induced the protein levels of p21 and p27. In a mouse model cucurbitacin D treatment effectively inhibited growth of CC cells.

Cheng et al. indicated that sulforaphane may delay the development of cancer by arresting cell growth in the G /M phase via down-regulation of Cyclin B1 gene expression, dissociation of the cyclin B1/CDC2 complex, and up-regulation of GADD45 proteins.

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Emerging molecular-targeted therapies or early preclinical trials in cervical cancer

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Hyaluronic acid binding protein 1 overexpression is an indicator for disease -free survival in cervical cancer	Zhang M et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28039537
2	Assessment of Cytotoxic Activity of Rosemary (Rosmarinus officinalis L.), Turmeric (Curcuma longa L.), and Ginger (Zingiber officinale R.) Essential Oils in Cervical Cancer Cells (HeLa)	Santos PA et al.	ScientificWorldJournal	https://www.ncbi.nlm.nih.gov/pubmed/28042599
3	Ascorbyl Stearate Promotes Apoptosis Through Intrinsic Mitochondrial Pathway in HeLa Cancer Cells	Mane SD et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/27919962
4	In vitro evaluation of a combination treatment involving anticancer agents and an aurora kinase B inhibitor	Sakai S et al.	Oncol Lett	https://www.ncbi.nlm.nih.gov/pubmed/27895801
5	In vitro and in vivo inhibition of tumor cell viability by combined dihydroartemisinin and doxorubicin treatment, and the underlying mechanism	Tai X et al.	Oncol Lett	https://www.ncbi.nlm.nih.gov/pubmed/27900057
6	Cannabidiol rather than Cannabis sativa extracts inhibit cell growth and induce apoptosis in cervical cancer cells	Lukhele ST et al.	BMC Complement Altern Med	https://www.ncbi.nlm.nih.gov/pubmed/27586579
7	Cucurbitacin D exhibits potent anti-cancer activity in cervical cancer	Sikander M et al.	Sci Rep	https://www.ncbi.nlm.nih.gov/pubmed/27824155
8	Sulforaphane, a Dietary Isothiocyanate, Induces G /M Arrest in Cervical Cancer Cells through CyclinB1 Downregulation and GADD45 /CDC2 Association	Cheng YM et al.	Int J Mol Sci	https://www.ncbi.nlm.nih.gov/pubmed/27824155

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

Editor Kamil Zalewski

Descriptive summary

DNA methylation is a covalent modification of DNA tightly regulated by a group of three enzymes known as the DNA methyltransferases (DNMT). Leonard et al. compared the expression of DNMT1, DNMT3A, and DNMT3B in the invasive component and in the normal adjacent epithelium of vulvar squamous cancer (VSCC) [1]. They found that DNMT3A over-expression was associated with a significantly increased risk of local recurrence and inversely related to the expression of CDKN2A in VSCC and may be used as a biomarker to identify HPV-negative VSCC patients at risk of developing local vulval recurrence. Sha et al., based on the few VSCC samples, suggested that several long non-coding RNAs (MEG3 and MALAT1) could serve potentially important biomarkers in VSCC [2]. In their retrospective study, Napoletano et al. evaluated the immunological and clinical impact of CD133-expressing cancer stem cells in 43 patients with VSCC [3]. They showed that CD133 expression was present in 16.6% of patients and that over 90% of tumour samples expressing this marker exhibited a strong tumour infiltration of Tregs, indicating the presence of a significant immunosuppressive microenvironment. In addition, CD133 expression correlated with younger age at diagnosis, lymph-node metastasis, and larger tumour diameter. Holthoff et al. identified not only an association between the development of epithelial-mesenchymal transition (EMT) and an increased risk for poor clinical outcomes in VSCC but also presented data supporting the idea that its development correlates with the aggressive behaviour of the tumours [4]. The authors suggested that the identification of EMT should be reported, as it could affect treatment planning and overall outcomes for VSCC patients. Halec et al. gave evidence of HPV transcriptional activity and identified viral mRNA in 87% of 447 tissue samples from HPV DNA+ VSCC cases [5]. Among the 433 cases with both HPV mRNA and p16 INK4a data available, 83% were concordant pairs of HPV mRNA+ and p16 INK4a+. Most HPV DNA+ vulvar cancers were associated with HPV16 (85%).

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Over-expression of DNMT3A predicts the risk of recurrent vulvar squamous cell carcinomas	Leonard S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27623253
2	Long non-coding RNA expression profile in vulvar squamous cell carcinoma and its clinical significance	Sha N et al.	Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/27633334
3	Immunological and Clinical Impact of Cancer Stem Cells in Vulvar Cancer: Role of CD133/CD24/ABCG2-Expressing Cells	Napoletano C et al	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/27798870
4	Pathologic features of aggressive vulvar carcinoma are associated with epithelial-mesenchymal transition	Holthoff ER et al.	Hum Pathol	https://www.ncbi.nlm.nih.gov/pubmed/27327194
5	Biological relevance of human papillomaviruses in vulvar cancer	Halec G et al.	Mod Pathol	https://www.ncbi.nlm.nih.gov/pubmed/28059099

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

Editor Kamil Zalewski

Descriptive summary

Vulvar intraepithelial neoplasia (VIN)

The European Academy of Dermatology and Venereology and the American Society for Colposcopy and Cervical Pathology Committee, together with the American College of Obstetricians and Gynaecologists, issued their guidelines for vulvar intraepithelial neoplasia management. Surgery as the first choice of treatment is underlined in both documents [1,2]. Toby et al. described a course of usual VIN in a unique series of HIV-positive patients, suggesting that treating them with imiquimod is effective and well tolerated [3]. Regauer et al. reported on the rare frequency of HPV-induced squamous intraepithelial lesion (1.2%) in patients with vulvar lichen planus (LP). This was a less frequent event than the development of d-VIN or HP-negative squamous vulvar cancers (VSCC) in LP (3%) [4]. Riviero et al. proposed to assess p53 expression as an alternative when the differential diagnosis on haematoxylin and eosin stain includes differentiated VIN in the setting of lichen sclerosus or HPV-independent VSCC [5]. Nooij et al. determined that stathmin expression with a sensitivity of 100% (exceeding p16 and Ki67) and a specificity of 80% can improve the diagnosis and correct grading of vulvar LSILs and HSILs. The authors suggested it can be used in addition to p16 and Ki67 staining when differentiation between vulvar LSILs and HSILs is difficult.

Vaginal intraepithelial neoplasia (VAIN)

Lamos et al., in their series of VAIN patients, described HPV 16 as the main virus type to be associated with the development of the disease. Also, repeated HPV 16 infection, VIN, or condylomata acuminata in past medical history seemed to be significant risk factors for relapse.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	2016 European guideline for the management of vulval conditions	van der Meijden WI et al.	J Eur Acad Dermatol Venereol.	https://www.ncbi.nlm.nih.gov/pubmed/28164373
2	Committee Opinion No.675: Management of Vulvar Intraepithelial Neoplasia	Goje O et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27661656
3	Usual vulval intraepithelial neoplasia in HIV-positive women – a case series	Toby M et al.	J STD AIDS	https://www.ncbi.nlm.nih.gov/pubmed/26472432
4	Human papillomavirus-induced squamous intraepithelial lesions in vulvar lichen planus	Regauer S et al.	J Low Genit Tract Dis	https://www.ncbi.nlm.nih.gov/pubmed/27490079
5	Carcinogenesis of vulvar lesions: morphology and immunohistochemistry evaluation	Rivero RC et al.	J Low Genit Tract Dis	https://www.ncbi.nlm.nih.gov/pubmed/28027121
6	Stathmin is a highly sensitive and specific biomarker for vulvar high-grade squamous intraepithelial lesions	Nooij LS et al.	J Clin Pathol	https://www.ncbi.nlm.nih.gov/pubmed/27226646
7	Detection of Human Papillomavirus Infection in Patients with Vaginal Intraepithelial Neoplasia	Lamos C et al.	PLoS One	https://www.ncbi.nlm.nih.gov/pubmed/27907089

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Treatment of primary vulvar cancer

Editor Rubén M. Betoret

Descriptive summary

Primary vulvar cancer is an uncommon malignancy affecting mostly elderly women with predominance of squamous-cell histology and who are usually surgically treated in different extents of radicality; whereas chemoradiation, as well as sentinel lymph node dissection, stand as invaluable tools for selected patients.

Surgical approach

After the release of clarifying ESGO Guidelines on squamous-cell vulvar cancer in 2016, feedback from other international societies was expected. A review article by Dellinger et al.[1], under the auspices of the National Comprehensive Cancer Network, aims to serve as a guideline for surgical management of vulvar cancer (no substantial differences show in the management, but it includes a worthwhile, very detailed table with treatment according to stage).

Two other interesting views on surgical approach include the paper by Klapdor et al. [2] on groin recurrence in 30 node-negative vulvar cancer patients after sole sentinel lymph node dissection (stating a fatal groin recurrence of 6.6% [95% Confidence Interval (CI) of 1.9% – 21.3%], especially in midline tumours larger than two centimetres) and the meta-analysis of Nooij et al. [3] assess the risk of local recurrence associated with the tumour-free margin width (pooled risk ratio of 1.99 [95% CI of 1.13-3.51], p=0.02 in the group with a tumour-free margin of less than eight millimetres).

Adjuvant therapies

An American group contributes two publications on adjuvant therapies. Natesan et al.[4] designed a retrospective study in a single-institutional setup, recruiting 25 advanced vulvar cancer patients treated with definitive chemoradiation and obtaining a three-year overall survival (OS) of 71% [95% CI of 49% – 93%], and freedom from local recurrence of 65% [95% CI of 43% – 87%], with a rate of late G3 skin toxicity of 45% [95% IC of 20% – 69%], and lymphoedema of 25% [95% IC of 5% – 44%].

Encouraging results about the effectiveness and tolerability of this approach led to a large nationwide analysis [5], comparing OS in 2,046 women with locally advanced vulvar cancer treated either with primary radiation therapy (RT)/chemoradiation (CRT) or with preoperative RT/CRT plus surgery. A compromised OS was detected at three years in the primary RT/CRT group [41.7% vs. 57.1%; p<0.001].

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Less relevant but yet inspiring is the phase I trial of Kunos et al. [6] on the combination of cisplatin chemotherapy with endovenous triapine (a small-molecule RNR inhibitor) on solid tumours. Based on its results, a phase I trial on oral bioavailability of triapine in vulvar cancer patients is underway.

Non-squamous tumours

And finally, there is a remarkable increase in papers referring to non-squamous vulvar cancer, eventually pointing out a publicational bias towards these even-rarer malignancies without specific and comprehensive guidelines for their proper management: Van der Linden et al.[7] provide information about incidence and survival of glandular vulvar malignancies in a large nation-wide cancer registry research. Onaiwu el al.[8] retrospectively review clinical characteristics and outcomes of 89 patients with Paget´s disease of the vulva, focusing in the lack of association between positive margins and recurrence. Ferraioli et al.[9] present the experience of two French comprehensive cancer centers on vulvar melanoma, its prognosis factors, and treatment modalities.

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Treatment of primary vulvar cancer

- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Surgical management of vulvar cancer	Dellinger TH. et al.	J Natl Compr Canc Netw	https://www.ncbi.nlm.nih.gov/pubmed/28040722
2	Groin recurrences in node negative vulvar cancer patients after sole sentinel lymph node dissection	Klapdor R. et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27870709
3	Tumour-free margins in vulvar squamous cell carcinoma: Does distance really matter?	Nooij LS. et al.	Eur J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27497345
4	Definitive chemoradiotherapy for vulvar cancer	Natesan D. et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27575629
5	Primary versus preoperative radiation for locally advanced vulvar cancer	Natesan D. et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28333840
6	Phase I trial of daily triapine in combination with cisplatin chemotherapy for advanced-stage malignancies	Kunos CA. et al.	Cancer Chemother Pharmacol	https://www.ncbi.nlm.nih.gov/pubmed/27878356
7	Incidence and survival of glandular vulvar malignancies in the Netherlands	Van der Linden M. et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28129884
8	Paget´s disease of the vulva: A review of 89 cases	Onaiwu CO. et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/28124023
9	Genital melanoma: prognosis factors and treatment modality	Ferraioli D. et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/27365105

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Treatment of recurrent vulvar cancer

Editor María de los Reyes Oliver Pérez

Descriptive summary

In the period covered by the fifth edition of the LiFE report, two literature reviews and practice guidelines from the National Comprehensive Cancer Network (NCCN) discussing the problem of recurrent vulvar cancer (VSCC) were published.

In their review, Nooij et al. [1] focused not only on epidemiology, risk, and prognostic factors but also discussed the treatment of recurrent VSSC. Based on 24 articles that met their inclusion criteria, authors recommended surgical resection of recurrent disease and, if needed, combining it with reconstructive and/or groin surgery. Concurrent chemo-radiotherapy can be considered if primary resection does not seem to be feasible, either preoperatively for downsizing of a bulky groin recurrence or as definitive or palliative treatment. The treatment of distant recurrences is only palliative. Clancy et al. [2] reviewed molecular targeted agents that have therapeutic relevance to both HPV-independent and HPV-associated VSCC.

Treatment of the recurrent VSCC was also discussed in details in the NCCN guidelines [3]. In the case of disease clinically limited to the vulva with clinically negative nodes and lack of prior radiotherapy (RT), surgical treatment and further RT is recommended. Pelvic exenteration can be considered for selected patients with a central recurrence. Additional therapy is indicated according to the margins and nodal status. Nonsurgical treatment includes external beam radiotherapy with or without brachytherapy and/or concurrent chemotherapy. For nodal recurrence or distant metastasis, palliative chemotherapy and best supportive care, or clinical trial enrolment is recommended. Resection followed by systemic therapy can be considered only for select patients with isolated groin or pelvic recurrences that were previously irradiated.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Risk factors and treatment for recurrent vulvar squamous cell carcinoma	Nooij et al.	Crit Rev Oncol Hematol	https://www.ncbi.nlm.nih.gov/pubmed/27637349
2	The forgotten womans´s cancer: vulvar squamous cell carcinoma (VSCC) and a targeted approach to therapy	Clancy et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27329249
3	Vulvar Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology	Koh WJ et al.	J Natl Compr Canc Netw	https://www.ncbi.nlm.nih.gov/pubmed/28040721

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Vulvovaginal adenocarcinoma/melanoma/sarcoma

Editor Anna Dückelmann

Descriptive summary

Agarwal and Kaushal report an unusual case of a primary vaginal melanoma diagnosed by fine needle aspiration [1]. Noguchi et al. presented a case of malignant melanoma of the uterine cervix with disseminated metastases throughout the vaginal wall, diagnosed by cervical Pap smear cytology [2]. Although the patient was treated by radical hysterectomy, pelvic lymphadenectomy, and total vaginectomy, and received adjuvant chemotherapy with six courses of dacarbazine, she died of the disease 13 months after surgery.

Schoolmeester et al. presented ten cases of alveolar soft part sarcoma (ASPS) of the female genital tract [3]. ASPS is characterised by an immunohistochemical profile (TFE3 nuclear expression and lack of muscle and melanocytic markers) and demonstration of ASPSCR1-TFE3 gene fusion. Separating ASPS from its morphologic mimics, particularly PEComa, is of clinical value due to targeted agents such as MET (mesenchymal epithelial transition factor)-selective and VEGF signalling inhibitors in ASPS.

Yang et al. presented a retrospective case series of eight girls with genital tract rhabdomyosarcoma who received a combined therapy with local excision and chemotherapy [4]. The prognosis is highly correlated with tumour site and histologic type.

Van der Linden et al. presented 197 patients with a glandular vulvar malignancy [5]. Vulvar glandular tumours are rare, with an incidence of 0.9 to 2.5 per 1,000,000 women per year. Adenocarcinomas and invasive vulvar Paget disease are the most common diagnoses. About half of the cases are primary vulvar glandular malignancies; the other half is secondary to other malignancies, mainly (ano-) rectal. Five-year survival of patients with a primary glandular vulvar malignancy is around 70%.

According to an analysis of 178 lesions from 146 patients by Konstantinova et al., adnexal involvement in primary extramammary Paget disease (EMPD) is a very common feature occurring in more than 90% of cases [6]. Hair follicles and eccrine ducts are the most commonly affected adnexa by Paget cells, with a maximal depth of involvement of as much as 3.6 mm. Considering this fact, common topical therapy seems to be insufficient.

Wide surgical excision is the standard therapeutic approach of primary EMPD of the vulva. Postoperative radiotherapy may be considered in the presence of cases with a positive surgical margin, lymph node metastasis, multifocal disease, or associated adnexal adenocarcinomas. Radiotherapy alone is an alternative therapeutic approach for patients with extensive inoperable disease or medical contraindications. According to a review by Tolia et al., there is still no consensus on doses, fields, techniques and fractionation of radiotherapy, nor is there data on disease-free survival [7].

Dogan et al. presented a case and the literature about the successful use of imiquimod as an adjuvant treatment option for women with EMPD and involved resection margins after surgery [8].

Aoyama et al. presented a case of an apocrine adenocarcinoma of the vulva with inguinal lymph node metastases, treated by surgery alone. Because of inguinal recurrence, the patient received reresection and adjuvant radiotherapy [9].

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Vulvovaginal adenocarcinoma/melanoma/sarcoma

- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Cytology of primary vaginal melanoma: An unusual report on fine needle aspiration	Agarwal and Kaushal	Diagn Cytopathol	https://www.ncbi.nlm.nih.gov/pubmed/27863187
2	A case of malignant melanoma of the uterine cervix with disseminated metastases throughout the vaginal wall	Noguchi et al.	Case Rep Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28197351
3	Alveolar soft part sarcoma of the female genital tract	Schoolmeester et al.	Am J Surg Pathol	https://www.ncbi.nlm.nih.gov/pubmed/28009610
4	Clinical study on female genital tract rhabdomyosarcoma in childhood: changes during 20 years in one center	Yang et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27870705
5	Depth and patterns of adnexal involvement in primary extramammary (anogenital) paget disease: A study of 178 lesions from 146 patients	Konstantinova et al.	Am J Dermatopathol	https://www.ncbi.nlm.nih.gov/pubmed/26863064
6	Primary extramammary invasive Paget's vulvar disease: what is the standard, what are the challenges and what is the future for radiotherapy?	Tolia et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4966592/
7	Incidence and survival of glandular vulvar malignancies in the Netherlands	Van der Linden et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28129884
8	Paget's disease of the vulva treated with imiquimod: case report and systematic review of the literature	Dogan et al.	Gynecol Obstet Invest	https://www.ncbi.nlm.nih.gov/pubmed/27655036
9	Apocrine adenocarcinoma of the vulva: A case report and review of the literature	Aoyama	Case Rep Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27668109

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Treatment of vaginal cancer

Editor Elis Ismail

Descriptive summary

Primary vaginal melanoma (VM) accounts for 1% of all cancers, and only 3% to 7% of these tumours occur in the female genital tract. Lee et al. presented two patients with VM and discussed their treatment [1]. In their literature review, Cozzolino et al. focused on the exceedingly rare diagnosed primary vaginal cancer (VC) arising from endometriosis. A total of 23 eligible studies were identified providing information about 37 patients. The most common histological subtype was endometrioid adenocarcinoma (17 cases), followed by endometrial stromal sarcoma (six cases). The majority of patients received cancer-directed surgery while adjuvant treatment was commonly employed for patients with sarcomas [2]. Yang et al. described eight women with rhabdomyosarcoma (RMS) of the female genital tract,five tumours originated in the vagina. Except for the patient with pelvic RMS, who was diagnosed after acute abdominal pain, all the other patients presented with polypoid masses protruding from the vagina. All RMS were embryonal tumours with three botryoid variants. Patients were treated with surgery and adjuvant chemotherapy, and many achieved complete remission. Two patients with vaginal RMS experienced tumour relapse and died [3]. Heller et al. described the case of a 31-year-old woman with a fibroepithelial polyp diagnosed during a postpartum visit. These are benign lesions that can affect the lower female genital tract, including the vulva, cervix, and vagina. The potential pitfall of overdiagnosing malignancy based on increased or atypical mitoses, stromal hypercellularity, and cytological atypia was discussed [4]. Brătilă et al. reported the case of a 22-year-old woman initially diagnosed with a condyloma-like tumour of the left vaginal wall, which at immunostaining turned out positive for epithelioid angiosarcoma [5]. Damast et al., in their retrospective series, reported on ten patients with small volume, early-stage, primary VC treated with pelvic radiotherapy (RT) and MRI-based intracavitary brachytherapy (ICBT). The authors concluded that those with small tumours with volume < 10 cm^3, and those with initial tumour thickness measuring ≤ 2 cm from the surface of the cylinder to the lateral/apical margin of tumour, may be appropriate candidates for an ICBT boost [6].

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Primary malignant melanoma of cervix and vagina	Lee JH et.al.	Obstet Gynecol Sci	https://www.ncbi.nlm.nih.gov/pubmed/27668208
2	Malignant transformation of vaginal endometriosis - a review of literature	Cozzolino M et al.	Gynecol Obstet Invest	https://www.ncbi.nlm.nih.gov/pubmed/27618565
3	Clinical study on female genital tract rhabdomyosarcoma in childhood: Changes during 20 years in one center	Yang J et.al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27870705
4	Pseudosarcomatous vaginal polyp	Heller A et.al.	Int J Surg Pathol	https://www.ncbi.nlm.nih.gov/pubmed/?term=Heller+A+Pseudosarcomatous
5	Vaginal epithelioid angiosarcoma: a rare case	Brătilă E et.al.	Rom J Morphol Embryol	https://www.ncbi.nlm.nih.gov/pubmed/28002534
6	Treatment of early stage vaginal cancer with EBRT and MRI-based intracavitary brachytherapy: A retrospective case review	Damast S et.al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/27536721

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Minimal invasive surgery in gynaecological cancer (laparoscopy, robotics)

Editor Borja Otero

Descriptive summary

Cervical cancer

While waiting for the results of the Laparoscopic Approach to Cervical Cancer (LACC) trial, a recent retrospective cohort study carried out in two academic medical institutions in the United States, with data of 383 patients, has confirmed the feasibility of minimally invasive radical hysterectomy for cervical cancer with no significant differences on overall survival, recurrence rate, positive surgical margins or need for adjuvant treatment compared to laparotomy [1]. However, the laparoscopic approach has demonstrated a significantly larger number of harvested lymph nodes, lower rate of perioperative blood transfusion and shorter postoperative hospital stay both in this study and a systematic review of minimally invasive lymphadenectomy in cervical cancer [2].

In order to reduce surgical complications after minimally invasive hysterectomy, it seems that time between excision procedure and definitive surgery could be important. A retrospective cohort study involving 138 patients concludes that patients undergoing definitive MIS within six weeks after cervical excision having an increased risk for 30-day complications [3].

Finally, quality of life and sexuality in disease-free survivors of cervical cancer after radical hysterectomy has been retrospectively analysed in a cohort study carried out on 58 patients. It found insignificant differences between women treated by laparoscopy and laparotomy [4].

Endometrial cancer

A recent sub-analysis of the GOG LAP-2 randomised trial focused on the results of 753 patients with apparent early-stage high-grade uterine cancer and demonstrated that patients with uterine serous carcinomas and carcinosarcomas have poorer prognosis than patients with endometrioid or clear cell carcinomas regardless the surgical approach (laparoscopy or laparotomy) [5].

In this kind of surgery, uterine mobilisation has remained a controversial aspect of this technique despite reports suggesting the safety of the use of uterine manipulators. However, this point has been analysed again in a multi-institutional cohort study recruiting 951 patients and after a median follow-up of 46 months no significant differences have been found either in the risk of recurrence nor in disease-free and overall survival [6].

Moreover, this MIS could also be performed using a single site robotic approach as demonstrated in a multi-institutional cohort study including 125 patients [7].

Ovarian cancer

Five recent papers have evaluated the role of MIS in the management of ovarian cancer.

Regarding advanced epithelial ovarian cancer, a retrospective case-control study has compared a minimal invasive approach versus standard laparotomy for treatment completion after neoadjuvant chemotherapy. A survival analysis was attempted comparing progression-free survival but not overall survival between groups. With 30 and 65 patients respectively in each arm, no significant difference was found [8].

Regarding early stage epithelial ovarian cancer, two papers have retrospectively compared MIS to laparotomy for the treatment of these neoplasms. One of them, collecting data of 4,798 patients from the US National Cancer Data Base, found non significant difference in the overall survival between patients who underwent staging by laparoscopy and laparotomy in favor of laparotomy (hazard ratio, 0.77, 95% confidence interval, 0.54-1.09; P = .13) [9]. Another study was also conducted in an Italian tertiary centre analysing 100 patients undergoing either laparoscopic staging or open surgical staging. In this study, no difference in survival outcomes was observed [10].

If opting for a MIS approach, both robotic and laparoscopic staging are feasible and comparable options as demostrated by a retrospective cohort study performed by Gallota et al.. With data on 32 patients undergoing the robotic approach and 64 patients undergoing a laparoscopic approach, no relevant differences have been found regarding number of retrieved nodes, estimated blood loss and early and postoperative complications [11].

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Minimal invasive surgery in gynaecological cancer (laparoscopy, robotics)

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Minimally Invasive Radical Hysterectomy for Cervical Cancer Is Associated With Reduced Morbidity and Similar Survival Outcomes Compared With Laparotomy	Diver E et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28011096
2	Minimally Invasive Lymphadenectomy in Uterine Cervical Cancer: A Systematic Review	Rizou N et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28011511
3	Association between timing of cervical excision procedure to minimally invasive hysterectomy and surgical complications	Sullivan SA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27894753
4	Quality of life and sexuality in disease-free survivors of cervical cancer after radical hysterectomy alone: A comparison between total laparoscopy and laparotomy	Xiao M et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/27603383
5	Impact of histology and surgical approach on survival among women with early-stage, high-grade uterine cancer: An NRG Oncology/Gynecologic Oncology Group ancillary analysis	Fader AN et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27743738
6	The effect of a uterine manipulator on the recurrence and mortality of endometrial cancer: a multi-centric study by the Italian Society of Gynecological Endoscopy	Uccella S et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28147240
7	Robotic single site staging in endometrial cancer: A multi-institution study	Corrado G et al.	Eur J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27612413
8	Minimally invasive versus standard laparotomic interval debulking surgery in ovarian neoplasm: A single-institution retrospective case-control study	Gueli Alletti S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27769526
9	Laparoscopic staging for apparent stage I epithelial ovarian cancer	Melamed A et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27567562
10	Minimally invasive surgical staging for ovarian carcinoma: A propensity-matched comparison with traditional open surgery	Ditto A et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27702704
11	Robotic versus laparoscopic staging for early ovarian cancer: A case-matched control study	Gallotta V et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27856387

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Sentinel node mapping in gynaecological malignancies

Editor Anton Ilin

Descriptive summary

Sentinel lymph node (SLN) mapping for gynaecological cancers seems to be a promising procedure in terms of cost and side-effects compared to traditional treatment options. In recent studies more often techniques, tracers, sensitivity, and negative predictive values are discussed. One of the largest the FIRES study, included 385 patients with endometrial cancer (EC). In all, 293 (86%) patients had successful mapping of at least one sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97.2% (95% CI 85·0–100), and a negative predictive value of 99.6% [1]. Results are going in line with previous data.

Indocyanine green (ICG) seems to be a safe, feasible and effective tracer. Ruscito et al. published results of meta-analysis where authors compared ICG with other conventional dyes (99Tc, blue dyes) for SLN mapping procedure among patients with cervical (CC) and endometrial cancer. Six studies including 538 patients met selection criteria. Compared with blue dyes, ICG had higher overall (OR 0.27; 95 % CI 0.15–0.50; $p < 0.0001$) and bilateral detection rates (OR 0.27; 95 % CI 0.19–0.40; $p < 0.00001$). No differences were found between ICG and 99TC (alone or in combination with blue dye) [2].

At the same time, Tanaka et al. showed a higher detection rate of 99TC compared to ICG. A total of 119 patients with cervical cancer underwent SLN biopsy and radical hysterectomy using three types of tracers (99TC, indigo carmine, ICG). Detection rates were 85.8%, 20.2%, and 61.6%, respectively [3].

In a systematic review, Rocha et al. showed effectiveness of ICG SLN mapping for patients with EC and CC. In all, 422 patients were included in ten studies. The detection rate in SLN mapping using ICG ranged from 78% to 100% for cervical injection and from 33% to 100% for hysteroscopic injection. Sensitivity and negative predictive value (NPV) varied from 50% to 100% and 88% to 100%, respectively. The cervical submucosal and stromal injections were the most frequent sites used [4]. Cervical injection is commonly used because it is a most accessible way of tracer administration. Sahbai et al., in an analysis of 106 patients with endometrial cancer, achieved higher detection rates after cervical versus hysteroscopic peritumoural injection (83% vs 69%) [5]. Taking into account less invasivity, the cervical approach seems to be an attractive tool but further studies are required to understand whether it may substitute hysteroscopic way or not.

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Different pelvic pathways were firstly described in 1904 by Delamere et al. Since then, many studies have failed to include lower paracervical pathway in the SLN concept. Geppert et al. conducted prospective consecutive study of 90 women with EC to describe the anatomy of uterine lymphatic drainage following cervical or fundal tracer injection. Two consistent lymphatic pathways with pelvic SLNs were identified irrespective of injection site; an upper paracervical pathway (UPP) with draining medial external and/or obturator lymph nodes and a lower paracervical pathway (LPP) with draining internal iliac and/or presacral lymph nodes. Bilateral display of at least one pelvic pathway following cervical and fundal injection occurred in 98% and 80%, respectively ($p = 0.005$). Bilateral display of both pelvic pathways occurred in 30% and 20%, respectively ($p = 0.6$) as the LPP was less often displayed. Nearly one-third of the 19% node-positive patients had metastases along the LPP [6]. The authors concluded that bilateral detection of at least one SLN in both the UPP and LPP should be aimed for. It is a good point to think about standardisation of a pelvic SLN concept in EC.

The 2015 National Comprehensive Cancer Network (NCCN) cervix cancer guidelines states that radial trachelectomy and pelvic lymph node dissection, with or without para-aortic lymph node sampling, is an option for patients with stage IB1 disease who want to sustain their fertility. The tumour size of 2 cm is a borderline to fertility-preserving surgery. Nowadays it is a point of debate if lymph node dissection could be safely replaced by SLN biopsy or not.

Lennox et al. compared recurrence-free survival (RFS) of 1,188 node-negative patients with stage IA/IB CC. In 1,078 bilateral lymph node dissection was performed and in 110 – SLN biopsy only was performed. There was no difference in two and five year RFS (95% vs. 97% and 92% vs. 93%, respectively) as well as in intraoperative complications and short-term morbidity but stage, age, date. and LVSI were different between the groups [7].

Salvo et al. showed similar data when they included 188 patients with early-stage CC in retrospective analysis. At least one SLN was identified in 170 patients (90%). Only one patient had a false-negative result, yielding to a sensitivity of 96.4% (95% CI 79.8%–99.8%) and negative predictive value of 99.3% (95% CI 95.6%– 100%). The false-negative rate was 3.6% [8].

Not much data exists about SLN mapping for patients with ovarian cancer (OC). Injection in tumour is unfavourable because of unpre-

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Sentinel node mapping in gynaecological malignancies

Descriptive summary

dictable tracer dissemination and high risk of cancer cells extension. Most promising seems to be the injection in ovarian ligaments, which is possible in early-stage disease. Angelucci et al. published the result of five cases of SLN mapping for patients with OC FIGO I-II. In three patients, the first detected SN was found in the area of the common iliac artery; in two patients at paracaval region. The biopsies of all of 6 SNs were negative: the remaining 22 non-sentinel nodes were negative too [9]. Obviously, more studies are needed to standardise SLN technique for this group of patients.

SLN mapping is especially valuable for vulvar cancer patients. It helps to reduce the number of treatment complications such as lymphorrhea, cellulitis or nerve injuries. High specificity and sensitivity were demonstrated by different studies. Analysis of the AGO-CaRE-1 Study evaluated the influence of SLND alone on progression-free survival (PFS) and overall survival (OS). In 487 (63.1%) of 772 included patients with tumours smaller than 4 cm, an LND was performed and no metastatic lymph nodes were detected (LN0). Another 69/772 (8.9%) women underwent SLND alone, showing a negative SLN (SLN0). After a median follow-up of 33 months (0–156), no significant differences in relation to isolated groin recurrence rates (SLN0 3.0% vs. LN0 3.4%, p = 0.845) were detected. Similarly, univariate three-year PFS analysis showed no significant differences between both groups (SLN0 82.7% vs. LN0 77.6%, p = 0.230) [10].

Similar results were shown by Klapdor et al. on a series of 30 patients [11].

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): A multicentre, prospective, cohort study	Rossi EC et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28159465
2	Sentinel Node Mapping in Cervical and Endometrial Cancer: Indocyanine Green Versus Other Conventional Dyes—A Meta-Analysis	Ruscito I et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27160526
3	The detection of sentinel lymph nodes in laparoscopic surgery for uterine cervical cancer using 99m-technetium-tin colloid, indocyanine green, and blue dye	Tanaka T et al.	Journal of Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/27894166
4	Indocyanine green and infrared fluorescence in detection of sentinel lymph nodes in endometrial and cervical cancer staging – a systematic review	Rocha A et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/27750179
5	Pericervical injection of 99mTc-nanocolloid is superior to peritumoral injection for sentinel lymph node detection of endometrial cancer in SPECT/CT	Sahbai S et al.	Clin Nucl Med	https://www.ncbi.nlm.nih.gov/pubmed/27749429
6	A study on uterine lymphatic anatomy for standardization of pelvic sentinel lymph node detection in endometrial cancer	Geppert B et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/28196672
7	Can sentinel lymph node biopsy replace pelvic lymphadenectomy for early cervical cancer?	Lennox GK et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/27742472
8	Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer	Salvo G et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/28188015
9	Laparoscopic indocyanine green sentinel lymph node mapping in early ovarian cancer. A pilot study and review of the literature	Angelucci M et al.	Ital J of Gynecol and Obst	http://www.italianjog.com/numeri/dec-vol28-n5/Corrado-Angelucci.pdf
10	Outcome After Sentinel Lymph Node Dissection in Vulvar Cancer: A Subgroup Analysis of the AGO-CaRE-1 Study	Klapdor R et al.	Ann Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27896515
11	Groin Recurrences in Node Negative Vulvar Cancer Patients after Sole Sentinel Lymph Node Dissection	Klapdor R et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27870709

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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, seven papers were considered important for the LIFE report.

Surgical site infection (SSI)

Desale et al. investigated the impact of fluid status on perioperative outcomes of patients undergoing cytoreductive surgery for advanced epithelial ovarian cancer (using the perioperative weight change as a surrogate for fluid status). The perioperative fluid excess was common and was independently associated with SSI: OR 1.22, p=0.017.

Thomas et al. evaluated the effectiveness of a cyanoacrylate microbial sealant (CMS) to reduce post-operative SSI following laparotomy for suspected gynaecologic malignancy (randomised trial: standard skin preparation vs preparation with CMS): unfortunately, the addition of CMS alone did not appear to reduce risk of overall SSI.

Anastomotic leak

Kalogera et al. investigated whether a standardised protocol for temporary bowel diversion after recto-sigmoid resection (RSR) for gynaecologic malignancies can reduce the rate of anastomotic leak (AL). Patients with any of the following underwent temporary diversion: preoperative albumin ≤3.0g/dL, prior pelvic radiation, RSR plus additional large bowel resection, anastomosis ≤6cm from the anal verge, failed leak test, or contamination of the pelvis with stool. Comparing the AL rate to the historic AL rate, they found a significative AL rate reduction: 1.3% vs. 7.8%, p=0.039.

Bowel obstruction

Milek et al. present a self-developed, nickel titanium alloy (nitinol), self-expanding enteral stent, to be used in patients with an ovarian cancer induced obstruction of the left half of the colon. The implantation was performed in 13 women and the decompression of the enteric obstruction was obtained in 11 patients (85%), with one stent migration. They propose this palliative stenting as an alternative to palliative surgical treatment.

Lower extremity lymphedema (LEL)

Kim et al. analysed preoperative and postoperative 1-year CT scans as a screening tool for identifying risk factors of occult LEL after lymphadenectomy for gynaecologic cancer. In addition to a high number of lymph nodes retrieved and adjuvant pelvic radiotherapy, open surgery, long operation time, and no use of intermittent pneumatic compression were independent risk factors for greater increases in subcutaneous layer thickness of the thigh.

Predicting complications

Martin et al. analysed retrospectively whether preoperative hyponatremia is associated with postoperative complications in women with ovarian/tubal/peritoneal cancer: hyponatremia was associated with an increased risk of hospital stay of >14 days (OR 1.69; 95% CI 1.11-2.57) and 30 day postoperative mortality (OR 2.37; 95% CI 1.13-4.98). Additional work is needed to determine if correction of hyponatremia in the preoperative period alters outcomes.

Mendivil et al. retrospectively evaluated the impact of total parenteral nutrition (TPN) in ovarian cancer patients who underwent debulking surgery and a bowel resection. When compared to patients receiving a conservative management (n = 78), patients with TPN (n = 69) demonstrated a longer time until restoration of bowel function (5.77 vs. 4.70 days; $p < 0.001$), lower pre-operative albumin levels (2.22 vs. 2.97 g/dl; $p < 0.001$), and significantly longer hospital stay (11.46 vs. 7.14 days; $p < 0.001$). Therefore, postoperative TPN in ovarian cancer patients may be inadvisable because of the increased risk for complications.

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

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Perioperative fluid status and surgical outcomes in patients undergoing cytoreductive surgery for advanced epithelial ovarian cancer	Desale MG et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28029449
2	Effectiveness of cyanoacrylate microbial sealant in the reduction of surgical site infection in gynecologic oncology procedures: A phase III single institution prospective randomized trial	Thomas ED et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27836205
3	A prospective algorithm to reduce anastomotic leaks after rectosigmoid resection for gynecologic malignancies	Kalogera E et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27919575
4	Using our own developed stent in the palliative treatment of obstruction in the left half of the colon due to ovarian cancer	Milek T et al.	Ginekol Pol	https://www.ncbi.nlm.nih.gov/pubmed/28157254
5	Identifying risk factors for occult lower extremity lymphedema using computed tomography in patients undergoing lymphadenectomy for gynecologic cancers	Kim M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28094037
6	Preoperative hyponatremia in women with ovarian cancer: An additional cause for concern?	Martin JY et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27388697
7	The impact of total parenteral nutrition on postoperative recovery in patients treated for advanced stage ovarian cancer	Mendivil AA et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/27832350

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Technical aspects/tricks of surgery in the management of gynaecological malignancies

Editor Elisa Piovano

Descriptive summary

During the period covered by the fifth edition of the LiFE report, two interesting papers dealing with technical aspects in gyne onc surgery were published.

Cordeiro Vidal et al. present a surgical film about the ovarian cancer debulking using PlasmaJet™ (electrically neutral argon plasma) technology, describing a case history and operative technique. In all, 51 women underwent primary debulking surgery or interval debulking surgery for a stage IIIC-IV ovarian cancer in their hospital and were operated with systematic use of the PlasmaJet device. Of these, 78.4% (n=40) of the 51 patients had a complete cytoreduction. In addition, 15.7% (n=8) of patients undergoing diaphragmatic stripping with the PlasmaJet required a pleural drain. As already reported in the paper by Panuccio et al. 2016 (see LiFE report 4), PlasmaJet™ seems to help the surgeon to perform a peritoneal stripping of the upper abdominal areas, without increased morbidity.

Kawamura et al. usually perform transureteroureterostomy (TUU) in cases of unilateral lower ureteral cancerous involvement. They describe their technique and report the outcomes in 11 patients treated with TUU (for primary or recurrent colon cancer, rectal cancer, uterine/cervical cancer and ovarian cancer). All patients had a ureteral stent in the donor ureter. The stent was removed in all patients postoperatively. Early postoperative complications relevant to TUU occurred in four patients; three patients were managed conservatively and recovered quickly (urine leakage, hydronephrosis with or without urinary tract infection). Only one patient developed ureteral obstruction, which resulted from anastomotic hematoma at the ureteral opening after stent removal. She underwent percutaneous nephrostomy and subsequent ureteral stenting. No patients experienced worsening of their renal function or recurrent urinary tract infection. They conclude TUU is considered a feasible and reasonable technique for ureteral reconstruction for primary or recurrent non-urothelial pelvic malignancy.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Primary debulking surgery of the upper abdomen and the diaphragm, with a plasma device surgery system, for advanced ovarian cancer	Cordeiro Vidal G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27836207
2	The use of transureteroureterostomy during ureteral reconstruction for advanced primary or recurrent pelvic malignancy in the era of multimodal therapy	Kawamura J et al.	Int J Colorectal Dis	https://www.ncbi.nlm.nih.gov/pubmed/27714520

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Fertility-sparing treatment in gynaecological malignancies

Editor Dimitris Papatheodorou

Descriptive summary

In this literature, we retrieved articles on fertility-sparing treatment in gynaecological malignancies. They are classified according to the cancer site:

Endometrial cancer

A prospective study by Falcone et al. reported the fertility-sparing treatment in young patients with early endometrial cancer (EC) treated by combined hysteroscopic resection and progestin therapy. The study enrolled 28 patients aged 18 to 40 years with stage IA, G1 and 2 endometrioid EC. After three months from the progestin start date, 25 patients (89.3%) showed a complete regression, two (7.1%) showed persistent disease, while one patient (3.6%) presented with progressive disease and underwent definitive surgery (stage IA, G3 endometrioid). Two recurrences were observed (7.7%), both involving the endometrium and synchronous ovarian cancer. A review study by Vitale et al. concluded that fertility-sparing surgery for stage IA type I and G2 endometrial cancer in reproductive-aged patients is a valid option. A prospective study by Laurelli et al. assessed the long-term oncologic and reproductive outcomes in fertility-sparing treatment of young women with endometrial cancer. The authors concluded that after a long follow-up, combined HR and LNG-IUD would seem to improve the efficacy of progestin alone. A review published by Carneiro et al. that assessed the safety of fertility-preservation in endometrial cancer stated that conservative treatment should only be offered to patients with G1 well-differentiated tumours, absence of lymph vascular space invasion, no evidence of myometrial invasion, metastatic disease or suspicious adnexal masses, and expression of progesterone receptors in the endometrium. It was also stated that the presence of co-existing ovarian metastatic or synchronous cancer should be investigated and ruled out before the decision to preserve the ovaries. Gamete, embryo, or ovarian tissue cryopreservation techniques can be employed, although the latter remains experimental.

Cervical cancer

A review study by Willows et al. assessed the oncologic and reproductive outcomes of fertility-sparing management in cervical cancer patients. Outcomes after non-radical surgery (simple trachelectomy or cervical conisation) are similar, although only applicable among a highly selected patient population. For patients ineligible for fertility-preserving surgery or who require adjuvant radiation therapy, current options include ovarian transposition and cryopreservation of oocytes or embryos but other techniques are under investigation. A retrospective review study by Okugawa et al. assessed the oncologic and obstetric outcomes and complications during pregnancy in 151 patients after fertility-sparing abdominal trachelectomy for cervical cancer. The authors declare an excellent oncologic outcome, but infertility treatment was necessary to achieve the majority of conceptions.

Ovarian cancer

A retrospective analysis by Fruscio et al. assessed the long-term results of fertility-sparing treatment for early-stage epithelial ovarian cancer. Analysis showed that tumour grade was associated with a shorter relapse-free interval ($p<0.001$) and shorter cancer-specific survival ($p<0.001$), while the type of treatment did not influence either of the above factors. In a systematic review conducted by Bentivegna et al., it was stated that conservative treatment can be safely carried out for stage IA and IC grade 1 and 2 disease and stage IC1 according to the new FIGO staging system. However, the number of patients with grade 2 disease reported in this study was too small to definitively confirm whether fertility-sparing surgery is safe in this subgroup.

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Fertility-sparing treatment in gynaecological malignancies

- Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer	Falcone F et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27670256
2	Fertility sparing surgery for stage IA type I and G2 endometrial cancer in reproductive-aged patients: evidence-based approach and future perspectives	Vitale SG et al.	Updates Surg	https://www.ncbi.nlm.nih.gov/pubmed/28188573
3	Long-term oncologic and reproductive outcomes in young women with early endometrial cancer conservatively treated: A prospective study and literature update	Laurelli G et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27654262
4	Fertility-preservation in endometrial cancer: is it safe? Review of the literature	Carneiro MM et al.	JBRA Assist Reprod	https://www.ncbi.nlm.nih.gov/pubmed/28050959
5	Fertility-sparing management in cervical cancer: balancing oncologic outcomes with reproductive success	Willows K et al.	Gynecol Oncol Res Prect	https://www.ncbi.nlm.nih.gov/pubmed/27795832
6	Oncologic and obstetric outcomes and complications during pregnancy after fertility-sparing abdominal trachelectomy for cervical cancer: a retrospective review	Okugawa K et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27804040
7	Long-term results of fertility-sparing treatment compared with standard radical surgery for early-stage epithelial ovarian cancer	Fruscio R et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27537385
8	Fertility-sparing surgery in epithelial ovarian cancer: a systematic review of oncological issues	Bentivegna E et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27502723

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Gestational Trophoblastic Disease

Editor Manuela Undurraga

Descriptive summary

Most articles retrieved for this period were retrospective studies, with a few prospective studies. There were no RCT. Of note, quite a few good quality reviews were published on gestational trophoblastic disease during this period on placental site trophoblastic tumours (PSTT) and epithelioid trophoblastic tumours (ETT) [1, 2], the genetic bases of hydatidiform moles [3] and a general review [4].

Pathology

In pathology, certain morphologic features were found to help in the distinction between molar and triploid pregnancies. As such, there is a significant difference in the presence of trophoblast proliferation, lacelike trophoblast, large trophoblastic inclusions, small round villous inclusions, apoptosis and fibrillary collagen, with the latter being more common in trisomy specimens while all the others are more frequent in partial molar pregnancies [5].

Diagnosis

Much research was published in this period concerning genetic diagnosis. For example, genomic profiling of choriocarcinomas (CC) was performed, with the discovery of significant genomic alterations such as the absence of two tumour suppressor genes TRIM32 (9q33.1) and CDH19 (18q22.1)[6]. Another study found that miR-21 is upregulated in molar tissue, but more importantly, it can promote proliferation, migration, and invasion of CC cells, as well as negatively regulate PDCD4 and PTEN in CC cells [7]. Two novel mutations in the KHDC3L gene were found in Asian patients with recurrent moles [8]. In PSTT and ETT, molecular genotyping found that most antecedent pregnancies are female but of normal (and not molar) origin [9]. Genetic analysis was also used to predict the failure of treatment in low-risk gestational trophoblastic neoplasia (GTN): the presence of the MTHFR 677T allele in molar tissue was significantly related to methotrexate (MTX) resistance. It is interesting to note that the same presence in patients' blood DNA was not related to MTX treatment outcome [10].

Treatment

An interesting phase II study evaluated the use of a second curettage in lieu of chemotherapy in the treatment of low-risk non-metastatic GTN and found that 40% of patients that had a second curettage avoided chemotherapy. Second curettage is likely to benefit patients aged 20–40 years, with a risk score of <5 [11]. Concerning chemotherapy, second line carboplatin was used instead of combination chemotherapy in patients with low-risk GTN following methotrexate-resistance, with an overall complete hCG response rate of 81% and overall survival of 100%, in absence of alopecia, but with 71% of patients resulting in treatment delay because of grade 3–4 myelotoxicity [12]. Another team reported their experience with floxuridine, dactinomycin, etoposide, and vincristine for stage IV GTN, and found a primary remission rate of 80% and an overall disease-free survival rate of 93%. 26.7% had grade 4 neutropenia. two patients (6.7%) had grade 4 thrombocytopenia. Three patients (10%) had grades 3–4 anaemia and received packed cells. Two patients discontinued treatment during consolidation treatment due to neutropenia. This myelotoxicity is higher that what have been reported for EMA-CO [13].

Follow-up

MRI and diffusion coefficient values are not useful for the prediction of progression or persistent disease [14].

Other

A retrospective comparison between the Dutch classification system and the FIGO 2000 score for patients with GTN was performed. In the study, both systems turned out to be equivalent, with similar risk classification in more than 93% of cases [15].

Continued on the next page ➲

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Gestational Trophoblastic Disease

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Placental site trophoblastic tumors and epithelioid trophoblastic tumors: Biology, natural history, and treatment modalities	Neil S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27789086
2	Historical, morphological and clinical overview of placental site trophoblastic tumors: from bench to bedside	Santoro G et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/27549089
3	Hydatidiform moles: Genetic basis and precision diagnosis	Pei Hui et al.	Annu Rev Pathol	https://www.ncbi.nlm.nih.gov/pubmed/28135560
4	15 years of progress in gestational trophoblastic disease: Scoring, standardization and salvage	Brown J et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27743739
5	Histological comparison of partial hydatidiform mole and trisomy gestation specimens	Wilson Y et al.	Pathology	https://www.ncbi.nlm.nih.gov/pubmed/27575970
6	Genomic profile in gestational and non-gestational choriocarcinomas	Bette J et al.	Placenta	https://www.ncbi.nlm.nih.gov/pubmed/28161066
7	miR-21 is overexpressed in hydatidiform mole tissues and promotes proliferation, migration, and invasion in choriocarcinoma cells	Wang Y-X et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27922982
8	Two novel mutations in the KHDC3L gene in Asian patients with recurrent hydatidiform mole	Rezaei M et al.	Hum Genome Var	https://www.ncbi.nlm.nih.gov/pubmed/27621838
9	Molecular genotyping of placental site and epithelioid trophoblastic tumours; female predominance	Zhao S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27246306
10	Presence of the methylenetetrahydrofolate reductase gene polymorphism MTHFR C677T in molar tissue but not maternal blood predicts failure of methotrexate treatment for low-risk gestational trophoblastic neoplasia	Qu J et al.	Eur J Pharmacol	https://www.ncbi.nlm.nih.gov/pubmed/27840191
11	Second curettage for low-risk nonmetastatic gestational trophoblastic neoplasia	Osborne RJ et al.	Obstetrics & Gynecology	https://www.ncbi.nlm.nih.gov/pubmed/27500329
12	Risk adapted single-agent dactinomycin or carboplatin for second-line treatment of methotrexate resistant low-risk gestational trophoblastic neoplasia	Winter MC et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27756557
13	Primary treatment of stage IV gestational trophoblastic neoplasia with floxuridine, dactinomycin, etoposide and vincristine (FAEV): A report based on our 10-year clinical experiences	Yang J et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27426306
14	Qualitative and quantitative analysis of diffusion-weighted imaging of gestational trophoblastic disease: Can it predict progression of molar pregnancy to persistent form of disease?	Sefidbakhta S et al.	Eur J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/28189211
15	Dutch risk classification and FIGO 2000 for gestational trophoblastic neoplasia compared	Eysbouts YK et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27654257

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Cancer in pregnancy

Editor Michael J. Halaska

Descriptive summary

Excepting several comprehensive reviews, 13 original articles have been retrieved in this period. Breast cancer is discussed in two important articles.

In Stopenski et al., the authors have evaluated the impact of chemotherapy on the ability to breastfeed and the psychological impact on the mothers. Interestingly, the authors found a significantly decrease in the production of milk (63.5 vs. 9%) in patients after chemotherapy during pregnancy. There was no difference in maternal age, type or stage of cancer. Pathological specimens were evaluated and found significant lobular atrophy in patients after chemotherapy. Depression occurrence was not different between groups. Another work evaluated post-partum pregnancy-associated breast cancer (PABC) in 317 patients. When comparing to non-PABC patients, the authors found a lower risk of incidence in primiparous, younger (under age 35) women who delivered spontaneously. A bias of the influence of older women on the risk factors is of note.

Several reports described gastric cancer in patients diagnosed during pregnancy and possible treatment options. Two of them referred to a successful laparoscopic gastrectomy with lymph node dissection.

An evaluation of 27 cases with choroidal melanoma diagnosed during pregnancy described no impact of pregnancy on the prognosis of patients. Treatment using proton beam was safely used in 85% of cases already during pregnancy without any impaired effect.

Italian authors described four women with locally advanced cervical cancer treated by neoadjuvant chemotherapy during pregnancy. Chemotherapy used combined cisplatin 70–75 mg/m^2 and paclitaxel 135 mg/m^2 given every three weeks without any negative impact on the newborns.

Other minor reports were also published on lymphomas and pancreatic cancer. This did not come to any significant conclusions but added to the increasing number of case reports.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	After chemotherapy treatment for maternal cancer during pregnancy, is breastfeeding possible?	Stopenski S et al.	Breastfeed Med	https://www.ncbi.nlm.nih.gov/pubmed/28170295
2	Pregnancy-associated risk factors of postpartum breast cancer in korea: A nationwide health insurance database study	Kang EJ et al.	PLoS One	https://www.ncbi.nlm.nih.gov/pubmed/27977789
3	Gastric cancer in pregnancy: is laparoscopic gastrectomy with lymph node dissection feasible and safe?	Alshahrani AS et al.	Ann Surg Treat Res	https://www.ncbi.nlm.nih.gov/pubmed/28090507
4	Laparoscopic gastrectomy followed by chemotherapy for advanced gastric cancer diagnosed during pregnancy: a case report	Kim EY et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/27630333
5	Locally advanced cervical cancer in pregnancy overcoming the challenge. A case series and review of the literature	Ricci C et al.	Int J Gynaecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27575627

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Immunotherapy in gynaecological cancers

Editor Zoltan Novak

Descriptive summary

Human immunotherapy trials

An interim analysis of a phase I/IIa trial investigated a protein vaccine to prevent recurrence in endometrial and ovarian cancer patients. The vaccination with a high dose (1000 mcg) E39 (GALE 301)+GM-CSF an HLA-A2-restricted, folate binding protein-derived peptide vaccine not only induces strong immune response, but could successfully decrease the recurrence rate: the two-year disease-free survival was 85.7% in the vaccinated group vs. 33.6% in the control group (p = 0.021) [1]. In another phase II trial, a glypican-3 peptide vaccine was tested on refractory clear-cell ovarian cancer patients. Although just partial responses could be observed, the prognosis of palliative care patients in the control group was significantly poorer than that of those with glypican-3 peptide vaccinations [2]. Another phase II study investigated the clinical efficacy of a GMCSF/bi-shRNA furin DNA engineered autologous tumour cell in stage III/IV epithelial ovarian cancer patients with clinical complete response following primary treatment. Inhibition of the furin enzyme in the patient's cancer cells results in nearly complete reduction in the expression of TGF 1 and TGF 2. While inducing strong antitumour immunity in all 31 patients, the recurrence-free survival also improved: mean 826 days and 481 days in the vigil arm and in the control arm, respectively, (p=0.033) [3]. A new integrative approach including healthy human volunteers, non-human primates, mice reconstituted with human CD34+ cells, and patients with cancer to assess the combination of a novel Toll-like receptor 8 agonist, motolimod with pegylated liposomal doxorubicin PLD for the treatment of ovarian cancer. The mouse model helped elucidate the mechanism of action of the combination, while there were favourable clinical responses in ovarian cancer patients: two subjects (15%) had complete response and seven subjects (53%) had disease stabilisation [4].

An interesting paper reported the successful treatment of a patient with recurrent, metastatic PD-L1-negative small cell neuroendocrine carcinoma of the cervix. The patient with this very aggressive tumour showed complete response following nivolumab checkpoint inhibitor treatment, and she continues to have no evidence of disease. The treatment choice was extrapolated from experiences with checkpoint inhibitor treatment in small cell lung cancer patients [5]. The next reported paper studied if the tumour-draining lymph nodes of patients with cervical cancer could be used as a source for adoptive cell transfer therapy. The isolated lymphocytes were expanded and tested for HPV specificity. The authors concluded that pelvic lymph nodes represent a rich source of polyclonal HPV16 E6- and E7-specific T cells, which can be expanded for adoptive immunotherapy in patients with cervical cancer [6].

Review papers

The first recommended review paper from this period focused on microsatellite instability as a predictive biomarker of response to immune checkpoint inhibition in different cancer types [7]. The other paper summarises the current scientific data on the role of therapeutic vaccines in HPV-associated premalignant and invasive cervical diseases [8].

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Interim analysis of a phase I/IIa trial assessing E39+GM-CSF, a folate binding protein vaccine, to prevent recurrence in ovarian and endometrial cancer patients	Jackson DO et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/27852036
2	Efficacy of glypican-3-derived peptide vaccine therapy on the survival of patients with refractory ovarian clear cell carcinoma	Suzuki S et al.	Oncoimmunology	https://www.ncbi.nlm.nih.gov/pubmed/27999758
3	Phase II study of Vigil® DNA engineered immunotherapy as maintenance in advanced stage ovarian cancer	Oh J et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27678295
4	Integrative development of a TLR8 agonist for ovarian cancer chemoimmunotherapy	Mon BJ et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/27702821
5	Metastatic small cell neuroendocrine carcinoma of the cervix treated with the PD-1 inhibitor, nivolumab: a case report	Paraghamian SE et al.	Gynecol Oncol Res Pract	https://www.ncbi.nlm.nih.gov/pubmed/28174665
6	Potential use of lymph node-derived HPV-specific T cells for adoptive cell therapy of cervical cancer	van Poelgeest MI et al.	Cancer Immunol Immunother	https://www.ncbi.nlm.nih.gov/pubmed/27619514
7	Immunotherapy and patients treated for cancer with microsatellite instability	Colle R et al.	Bull Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27979364
8	Targeting immune response with therapeutic vaccines in premalignant lesions and cervical cancer: hope or reality from clinical studies	Vici P et al.	Expert Rev Vaccines	https://www.ncbi.nlm.nih.gov/pubmed/27063030

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Imaging in gynaecologic malignancies

Editor Tanja Nikolova and Natasha Nikolova

Descriptive summary

Endometrial cancer

Kang et al., using strict preoperative criteria, identified low-risk patients for LNs metastases in a group with histologically confirmed endometrial cancer. Sensitivity, specificity, and NPV were: 84.9%, 55.5%, and 97.1%, respectively. These criteria are accurate in identification of low risk patients for LNs metastasis [1].

Bakir et al. [2] compared diffusion-weighted imaging (DWI) and contrast-enhanced MRI in the diagnosis of endometrial pathologies. Differences of the apparent diffusion coefficient, b1000q, and Cq values between various common benign and malignant lesions were statistically significant ($p < 0.001$).

Cervical cancer

Kim et al. [3] analysed patients with stage IB1 to IIA2 cervical cancer; when comparing the preoperative MRI with postoperative histological report, they determined the predictive value of MRI for parametrial invasion (PMI). They found that greater tumour diameter, larger tumour volume, presence of PMI, and vaginal involvement were significantly associated with PMI ($p < 0.001$). Their predictive model seems to be valuable in surgery planning.

Woo et al. [4] investigated the value of MRI after conisation in determining residual tumour in patients with FIGO stage IA–IB1 cervical cancer. Multivariate analysis showed that age, positive conisation margin, and identifiable tumour on MRI were independently predictive of residual tumour.

Liu et al. [5] compared the diagnostic performance of CT, MRI, PET using 2-[18F] fluoro-2-deoxy-D-glucose (FDG) and DW-MRI for LNs metastases in patients with cervical cancer and reported that PET or PET/CT has the highest specificity, and DWI-MRI has the highest sensitivity.

Ovarian cancer

Li et al. [6] investigated the dynamic contrast-enhanced MRI (DCE-MRI) in the differentiation of malignant, borderline, and benign complex ovarian tumours. The patterns (I, II, and III) of time-signal intensity curve (TIC) and three semi-quantitative parameters: enhancement amplitude (EA), maximal slope (MS), and time of half rising (THR) were compared among the groups of tumours. DCE-MRI may aid in characterising complex ovarian tumours. Semi-quantitative parameters perform poorly when distinguishing malignant from borderline tumours.

Michielsen et al. [7] assessed the clinical feasibility of whole-body DWI/MRI for detection of complete tumour resection in patients with suspected recurrent ovarian cancer. Patients were evaluated for detection of tumour recurrence, prediction of tumour extent, and complete resection compared with CT. Tumour presence was confirmed by pathology obtained by surgery or biopsy or by imaging follow-up. Whole body DWI/MRI allowed for better detection of ovarian cancer recurrence and better prediction of complete resection than CT.

Kusunoki et al. [8] determined the diagnostic accuracy of PET/CT using FDG to differentiate between malignant transformation of endometrioma and endometrioma. Age, tumour size, presence of shading on MRI, and maximum standardised uptake values (SUVmax) on PET/CT were significantly different between the two groups. SUVmax could exclude endometriomas with 75% sensitivity and 100% specificity.

Breast cancer

Tsigginou et al. [9] proposed a malignancy potential score (MPS) that incorporated BIRADS and CESM scores. Patients underwent dual-energy contrast-enhanced spectral mammography (CESM) with BIRADS score 2–5. Histology reports were compared with imaging. AUC: 0.843, 0.888, and 0.917 for BIRADS, CESM and MPS, respectively ($p < 0.05$). Sensitivity, specificity, and accuracy: 91.83, 80.47, and 85.40%, respectively. MPS had higher diagnostic performance than digital mammography or CESM alone.

Barco et al. [10] investigated the performance of MRI in either primary or recurrent breast cancer before surgery. MRI sensitivity for tumour size and additional foci together was 74.3%, and 80.3% for additional foci exclusively. MRI specificity for additional foci was 95.3%, PPV 77.4%, and NPV 94.6%. Preoperative MRI discloses additional foci, but core-needle biopsy cannot be neglected in the diagnosis of such additional malignant foci, which could result in a change in surgical treatment.

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Imaging in gynaecologic malignancies

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Preoperative assessment of lymph node metastasis in endometrial cancer: A Korean Gynecologic Oncology Group study	Kang S et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28067948
2	Role of diffusion weighted MRI in the differential diagnosis of endometrial cancer, polyp, hyperplasia, and physiological thickening	Bakir B et al.	Clin Imaging	https://www.ncbi.nlm.nih.gov/pubmed/27829198
3	Magnetic resonance imaging as a valuable tool for predicting parametrial invasion in stage IB1 to IIA2 cervical cancer	Kim M et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28114236
4	Early stage cervical cancer: role of magnetic resonance imaging after conization in determining residual tumor	Woo S et al.	Acta Radiol Stockh Swed	https://www.ncbi.nlm.nih.gov/pubmed/26671305
5	A Comprehensive Comparison of CT, MRI, Positron Emission Tomography or Positron Emission Tomography/CT, and Diffusion Weighted Imaging-MRI for Detecting the Lymph Nodes Metastases in Patients with Cervical Cancer: A Meta-Analysis Based on 67 Studies	Liu B et al.	Gynecol Obstet Invest	https://www.ncbi.nlm.nih.gov/pubmed/28183074
6	The value of dynamic contrast-enhanced MRI in characterizing complex ovarian tumors	Li H-M et al.	J Ovarian Res	https://www.ncbi.nlm.nih.gov/pubmed/28088245
7	Whole-body diffusion-weighted magnetic resonance imaging in the diagnosis of recurrent ovarian cancer: a clinical feasibility study	Michielsen KLM et al.	Br J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/27585490
8	Analysis of positron emission tomography/computed tomography in patients to differentiate between malignant transformation of endometrioma and endometrioma	Kusunoki S et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27380167
9	Adding the power of iodinated contrast media to the credibility of mammography in breast cancer diagnosis	Tsigginou A et al.	Br J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/27452266
10	Magnetic resonance imaging in the preoperative setting for breast cancer patients with undetected additional disease	Barco I et al.	Eur J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/27666617

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Treatment of elderly patients with gynaecological cancers

Editor Alex Mutombo

Descriptive summary

One of the major trends is that older women are more likely to die of gynaecological cancer compared with younger patients. In gynaecological cancers, both mortality rates and survival are age-dependent with a significantly shorter survival in the group of elderly, according to the study conducted by Or Knudsen et al. in Denmark.

This situation could be explained by aggressive tumour biology, less favourable clinicopathological features, more advanced disease, as well as reluctance to offer surgical treatment and increased complications of treatment in older women.

For this reason, Powell et al. reviewed each treatment modality for older women and introduced the components of comprehensive geriatric assessment for older women with cancer in general and those with endometrial cancer specifically.

In this scope, Haley et al. published a study in the International Journal of Gynaecological Oncology, which aimed at evaluating if older age alone negatively impacts survival endpoints in women with early-stage uterine endometrioid carcinoma (EC). They concluded that when older patients with EC are matched with younger patients based on tumour stage, grade, and adjuvant management the prognostic impact of old age disappears.

Moreover, the mainstay of treatment for uterine corpus cancer is surgery, and minimally invasive surgery can now be considered the gold standard. When comparing the perioperative complications and demographics of patients aged 80 or older, Zakhari et al. reported that robotic surgery was associated with a shorter hospital admission and a better complication profile than laparoscopy.

While Gillen et al. studied the contribution of age to clinical trial enrolment and tolerance in women with ovarian cancer and reported shorter survival for older women with ovarian cancer, in a study published in 2016, Muralikrishnan et al. found that elderly women over age 65 who were diagnosed with primary ovarian cancer were able to tolerate standard chemotherapy with relatively few significant adverse effects.

Also in order to predict chemotherapy tolerance in elderly patients, Von Gruenigen et al. prospectively tested the association of the baseline Instrumental Activities of Daily Living (IADL) score with the ability to complete four cycles of first-line chemotherapy without dose reductions or more than seven days' delay in elderly ovarian cancer patients. In their study published in the Gynecologic Oncology journal, they concluded that patients with a higher baseline IADL score were more likely to complete four cycles of chemotherapy and less likely to experience higher toxicity.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Treatment of older women with endometrial cancer: improving outcomes with personalized care	Duska L et al.	Am Soc Clin Oncol Educ Book	https://www.ncbi.nlm.nih.gov/pubmed/27249697
2	Contribution of age to clinical trial enrollment and tolerance with ovarian cancer	Gillen J et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28087143
3	Is older age a real adverse prognostic factor in women with early-stage endometrial carcinoma? A matched analysis	Haley L et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28060139
4	Chemotherapy for elderly ovarian cancer patients	Muralikrishnan S et al.	Gynecol Obstet (Sunnyvale)	https://www.ncbi.nlm.nih.gov/pubmed/27695647
5	Trends in gynecologic cancer among elderly women in Denmark, 1980-2012	Or Knudsen A et al.	Acta Oncol	https://www.ncbi.nlm.nih.gov/pubmed/26784001
6	Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer – An NRG oncology/Gynecologic Oncology Group study	Von Gruenigen VE et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28089376
7	Hysterectomy for uterine cancer in the elderly: a comparison between laparoscopic and robot-assisted techniques	Zakhari A et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27648646

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Treatment of elderly patients with gynaecological cancers

- Relevant articles retrieved Aug 2016 – Feb 2017 (cont.)

No	Title	Authors	Journal	Link to abstract
8	Patterns of care of cervical cancer in the elderly: a qualitative literature review	Venkatesulu BP et al.	I Geriatr Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28169196
9	Impact of age on surgical staging and approaches (laparotomy, laparoscopy and robotic surgery) in endometrial cancer management	Bourgin C et al.	Eur J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27955835
10	Management and survival of elderly and very elderly patients with endometrial cancer: an age-stratified study of 1228 women from the FRANCOGYN group	Poupon C et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28008573
11	Feasibility and benefit of concurrent chemoradiotherapy for elderly patients with uterine cervical cancer	Nosaka K et al.	Tumori	https://www.ncbi.nlm.nih.gov/pubmed/27443893
12	Carcinoma of the cervix in elderly patients treated with radiotherapy: patterns of care and treatment outcomes	Lin MY et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27550405
13	Improving outcomes for older women with gynaecological malignancies	Dumas L et al.	Cancer treat Rev	https://www.ncbi.nlm.nih.gov/pubmed/27664393

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Quality of life and sexual function in gynaecological cancers/palliative care

Editor Cosyns Stef

Descriptive summary

There were two interesting studies covering Quality of Life (QoL) among cancer survivors in Africa and in eight low- and middle-income countries of Southeast Asia. The same known factors as in the high-income countries were reported as negatively affecting the QoL: age, education, employment, income, and residence. Also, illness-related, treatment-related, and psychological factors influence QoL. Patients with advanced cancer stages at diagnosis and in a poor socio-economic position had the highest risk of poor outcomes. Cultural factors, including fatalism and bewitching, may present different influencing factors than in high-income countries.

In addition, a report on long-term morbidity and QoL in cervical cancer survivors with comparison between surgery (radical hysterectomy with pelvic lymphadenectomy) and definitive chemoradiotherapy was published. The FIGO stage and age were higher in the chemoradiotherapy group, as expected. Lymphoedema was only seen in the lymphadenectomy group. The group receiving definitive chemoradiotherapy reported more physical, social, and sexual symptoms. Also noteworthy is the study from Lee et al., which compared QoL and sexuality in cervical cancer survivors (without evidence of disease after primary treatment) and healthy women. Of course, lymphoedema was observed more in the cervical cancer survivors group. Surprisingly, sexual activity, sexual enjoyment, sexual worry, desire, arousal, lubrication, orgasm, satisfaction, and pain were similar between the groups. Finally, Fleming et al. described an immediate postoperative decline in several QoL assessments after radical trachelectomy (in 32 patients) returning back to the baseline after six months. Only emotional well-being showed a significant worsening of symptoms persisting even at four years, which was the endpoint of this study. These findings should be used while counselling our cervical cancer patients about treatment-related (long-term) morbidity and sexuality.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Quality of life among female cancer survivors in africa: An integrative literature review	Muliira RS et al.	Asia Pac J Oncol Nurs.	https://www.ncbi.nlm.nih.gov/pubmed/28217724
2	Health-related quality of life and psychological distress among cancer survivors in Southeast Asia: results from a longitudinal study in eight low- and middle-income countries	ACTION Study Group	BMC Med	https://www.ncbi.nlm.nih.gov/pubmed/28081724
3	Long-term morbidity and quality of life in cervical cancer survivors: A multicenter comparison between surgery and radiotherapy as primary treatment	Derks M et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27984376
4	Comparison of quality of life and sexuality between cervical cancer survivors and healthy women	Lee Y et al.	Cancer Res Treat	https://www.ncbi.nlm.nih.gov/pubmed/26875196
5	Quality of life after radical trachelectomy for early-stage cervical cancer: A 5-year prospective evaluation	Fleming ND et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27742473

ENYGO ESGO European Network of Young Gynae Oncologists | LiFE report Literature for ENYGO

Follow-up after gynaecological malignancies

Editor Jenneke Kasius and Anne van Altena

Descriptive summary

The ENDCAT trial performed by Beaver et al. is the first randomised non-inferiority trial that evaluated the effectiveness of nurse-led telephone follow-up. A total of 259 women treated for stage I endometrial cancer participated. The primary outcomes were psychological morbidity and patient satisfaction. The secondary outcomes were patient satisfaction, quality of life, and time to detection of recurrence. The study was not powered for survival. Ninety-two women declined to participate. The nurse-led telephone follow-up was shown to be non-inferior to the traditional hospital-based follow-up. The patient satisfaction was high and similar between both groups. The conclusion of the authors was that telephone follow-up provides an effective alternative to hospital-based follow-up for patients with stage I endometrial cancer, with no reported physical or psychological detriment.

Esselen et al. assessed the use of CA-125 and CT scans in clinical practice before and after the publication of the randomised controlled trial by Rustin et al. in 2009, and estimated the economic impact of surveillance testing. A prospective cohort of 1,241 women with ovarian cancer in clinical remission after completion of primary cytoreductive surgery and chemotherapy was included. Within the cohort, the use of CA-125 and CT scan performance did not significantly differ before and after 2009. Also, among the women detected with a doubling of CA-125, there was no significant difference in the time to retreatment with chemotherapy. The authors conclude that CA-125 and CT scans are still part of the routine follow-up despite the lack of evidence for their health benefit and their use may have significant quality of life and cost implications.

A population-based cohort was derived from the Danish Gynaecological Cancer database by Jeppesen et al. to select all women diagnosed with early-stage endometrial cancer from 2005–2009. Of the women with a recurrence within three years after treatment, the mode of recurrence detection was retrospectively identified from hospital charts; asymptomatic or symptomatic recurrence and detected at regular or "in between" follow-up. Of the 2,612 women, 183 women had a recurrence, of which 65.5% appeared to be symptomatic. The three-year survival rate was significantly better in the asymptomatic women (80.3% vs. 54.3%, $p < 0.01$). An important comment of the authors is the risk of length-time bias, that is, the effect of aggressive tumour biology in symptomatic recurrences, due to the non-randomised controlled trial design of the study.

Leeson et al. descriptively summarised the available data and an overview of on-going trials on the follow-up of gynaecological cancers. They report that the current follow-up generally consists of a doctor-led hospital-based surveillance for five years, although the evidence for this approach is lacking. In search of an alternative surveillance program following treatment for gynaecological cancer, they provide an overview of the randomised controlled trials currently recruiting in Europe: ENDCAT, ENSURE, OPAL, TOPCAT-G, TOTEM. Most on-going studies include women with endometrial cancer and study qualitative patient related outcomes and/or cost-utility. Finally, Leeson et al. discussed the cost-effectiveness studies, which show conflicting results on the cost-effectiveness of a nurse-led surveillance.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	The future for follow-up of gynaecological cancer in Europe. Summary of available data and overview of on-going trials	Leeson S et al.	EJOG	https://www.ncbi.nlm.nih.gov/pubmed/28157644
2	Detection of recurrence in early stage endometrial cancer - the role of symptoms and routine follow-up	Jeppesen M et al.	ACTA Oncologica	https://www.ncbi.nlm.nih.gov/pubmed/28080157
3	Use of CA-125 Tests and CT Scans for Surveillance in Ovarian Cancer	Esselen K et al.	JAMA Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27442965
4	Comparing hospital and telephone follow-up for patients treated for stage–I endometrial cancer (ENDCAT trial): a randomised, multicentre,non-infer iority trial	Beaver K et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/27062690

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Nutritional support/status in gynaecological cancer

Editor Fernanda Santos

Descriptive summary

Cancers are one of the main causes of malnutrition, which can occur because of physical and metabolic effects, but also due to anticancer treatments. Prolonged malnutrition can lead to cachexia, a complex syndrome not fully reversed by conventional nutritional support [1].

According to research, malnutrition is a highly prevalent problem among gynaecological cancer patients (20–53%). The specific risk varies among cancer types, stage, previous anticancer treatments, patients' ages, and individual comorbidities. Cancer-associated malnutrition can also lead to a higher incidence of post-operative complications such as infection, impaired response to cytotoxics, and death. About 20% of all gynaecological cancer deaths are due to malnutrition [1].

Given the high prevalence of malnutrition, guidelines were established [2,3]. Despite the absence of consensus on how to evaluate nutritional screening and which cut-off should initiate further assessment, the need to regularly evaluate it is generally agreed, ideally when patients are not yet severely malnourished. Some authors prefer the direct evaluation of nutritional intake, weight change, and body mass index or the indirect evaluation via validated nutritional screening tools, for example, the Malnutrition Universal Screening Tool or the Patient Generated Subjective Global Assessment. [2,3,4].

When abnormal screening is detected, it is recommended to make an objective assessment of nutritional intake, muscle mass (e.g. bioimpedance analysis), physical performance, and the degree of systemic inflammation (e.g., serum C-reactive protein).

The initial assessment should start with nutritional counselling, not forgetting individual preferences. According to metabolic studies, patients should follow a high protein diet (1–1.5 g/Kg/day) in order to promote muscle protein anabolism. When there is insulin resistance, fat and carbohydrates ingestion is advised, but the optimal ratio is not yet known. Vitamin and mineral supplements are also recommended in similar amounts to recommended dietary allowances; however, the level of evidence for this recommendation is low. These kinds of interventions are only possible when patients are able to eat. When an oral route is not possible, enteral nutrition is recommended. Parenteral nutrition is indicated in cases of severe colitis, bowel obstruction, short bowel syndrome or carcinosis [3].

Obermair et al. reviewed seven randomised trials; the outcome was early return to oral diet after gynaecological surgery. All studies were performed in developed countries and for different cancer types. They concluded that the following diets were safe: early clear liquid diet, semiliquid diet, regular diet or immune-enhanced enteral diets; furthermore, in five of seven better outcomes in the intervention groups were observed. Regardless of positive outcomes, investigators were not able to identify the best approach, since nutritional interventions varied greatly between trials [1].

Mendivil et al. performed a recent retrospective study, in which they compared the outcomes of advanced ovarian cancer patients who had been submitted to debulking surgery with bowel resection prior to initiating total parenteral nutrition (TPN) or conservative management (no TPN). There was an absence of benefit and, in hypoalbuminaemic patients, TPN not only delayed postoperative recovery but also precipitated manifestation of nosocomial sequelae [5].

In conclusion, although recent guidelines underline the importance of nutritional evaluation on oncological patients, randomised clinical trials are urgently needed because of the absence of high-quality scientific evidence.

Relevant articles retrieved Aug 2016 – Feb 2017

No	Title	Authors	Journal	Link to abstract
1	Nutrition interventions in patients with gynaecological cancers requiring surgery	Obermair et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/28173966
2	Oncology evidence-based nutrition practice guideline for adults	Thompson et al.	J Acad Nutr Diet	http://www.andjrnl.org/article/S2212-2672(16)30265-9/abstract
3	ESPEN guidelines on nutrition in cancer patients	Arends et al.	Clin Nutr	http://www.sciencedirect.com/science/article/pii/S0261561416301819
4	Estado nutricional segundo avaliação subjetiva global produzida pelo paciente de acordo com a localização do tumor	Cagol et al.	Nutr Clín Ciet Hosp	https://www.ncbi.nlm.nih.gov/pubmed/27436529
5	The impact of total parenteral nutrition on postoperative recovery in patients treated for advanced stage ovarian cancer	Mendivil et al.	Archives of Gynecology and Obstetrics	https://www.ncbi.nlm.nih.gov/pubmed/27832350

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