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Reviews covering publications from February 15, 2018 – August 15, 2018

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Dear colleagues,

LiFE 8 is ready! We have included reviews of publications in gynaecological oncology dating from February 15, 2018, through August 15, 2018. LiFE is an initiative of ENYGO supported by ESGO.

We welcome our new authors Zoia Razumova (Sweden), Bojana Gutic (Serbia), Martina Borghese (Italy), and Anna-Maria Schütz (Austria) to the LiFE team.

It has been an interesting year so far, with several landmark papers published in just the last few weeks. The results of the LACC trial, comparing minimally invasive technique with open surgery in the treatment of early-stage cervical cancer, have certainly been discussed within your departments. The published comments and editorials may help to put these data into perspective. This study and other papers on this topic are discussed in the report by Dr. Hasanov on minimally invasive technique. Further, the most impressive results for the adjuvant treatment of patients with BRCA mutated ovarian cancer were presented at ESMO and published in the *New England Journal of Medicine* (Moore et al. NEJM, October 21, 2018). SOLO 1 studied olaparib vs. placebo as maintenance treatment in mBRCA patients with stage III/IV high-grade disease. The risk of progression was 70% lower for patients on olaparib (HR 0.30; 95% CI: 0.23– 0.41; p <0.001) and translated into at least three years longer time to progression compared to placebo (median PFS in the placebo arm 13.8 months). Median PFS in the olaparib group was not reached. Safety data was in line with previous reports. This study underlines the importance of screening patients for BRCA mutations and also the need to implement olaparib in first-line treatment.

We are grateful for our continued collaboration with the *International Journal of Gynecological Cancer*, which adds to the publicity of our work.

And, as there is a constant flow of LiFE authors, please get in touch if you are interested in becoming an author. Send an email to enygo.life.project@esgomail.org.

Stay up to date!

The LiFE team

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Pathology/pathogenesis of malignant ovarian tumours

Dogan Vatansever

Kessous et al. evaluated the expression of homologous recombination genes in high-grade ovarian cancer (HGOC). They extracted RNA from fresh frozen samples of chemotherapy naïve patients (PDS Group) and following neoadjuvant chemotherapy. In the PDS group, three HR genes (NBN, FANCF, RAD50) and in the NACT group one HR gene (RAD51) remained significantly associated with survival when controlled for the extent of debulking in the model. Distinct HR expression profiles may define subgroups associated with overall outcome in patients that are exposed to neoadjuvant chemotherapy and not only chemotherapy-naïve patients.

Mueller et al. investigated the repertoire of somatic genetic alterations focussing on key cancer genes in mucinous ovarian cancers (MOCs) and defined the contribution of massively parallel sequencing to the classification of tumours diagnosed as MOCs based on current clinicopathologic criteria. They performed whole-exome sequencing (n=9) or massively parallel sequencing targeting all exons of 341 key cancer genes (MSK-IMPACT; n=15) on a total of 24 patient samples with a diagnosis of MOCs. The series was compared to a range of other carcinomas, including HGSOCs (high-grade serous ovarian cancers) from The Cancer Genome Atlas (TCGA; n=316) and other gastrointestinal mucinous adenocarcinomas. MOCs were heterogeneous at the genetic level, frequently harbouring TP53 (75%) mutations, KRAS (71%) mutations, and/or CDKN2A/B homozygous deletions/mutations (33%). Although established criteria for diagnosis were employed, four cases harboured mutational and immunohistochemical profiles similar to those of endometrioid carcinomas and one case of colorectal or endometrioid carcinoma. Significant differences in the frequencies of KRAS, TP53, CDKN2A, FBXW7, PIK3CA, and/or APC mutations between the confirmed primary MOCs (n=19) and HGSOCs, mucinous gastric and/or mucinous colorectal carcinomas were found, whereas no differences in the 341 genes studied between MOCs and mucinous pancreatic carcinomas were identified. And interestingly, despite pathologic and clinical re-review, 21% of the cases diagnosed as primary MOCs were, based on their immunohistochemical and mutational profiles, more consistent with a diagnosis of endometrioid ovarian cancers with mucinous differentiation or a mucinous carcinoma of colorectal type.

Ruscito et al. aimed to identify changes occurring from primary to recurrent HGSOC in tumour tissue expression of the angiogenesis-associated biomarkers CD31, applied for detecting microvessel density (MVD) and VEGF-A and correlation of biomarkers expression with patients' clinico-pathological characteristics and survival data. They analysed a large cohort of paired primary (pOCs) and recurrent HGSOC tissue samples (rOCs). High intratumoural MVD and VEGF-A expression were observed in 75.7% (84/111) and 20.7% (23/111) pOCs, respectively. MVDhigh and VEGF (+) samples were detected in 51.4% (57/111) and 20.7% (23/111) rOCs, respectively. There was no significant change in MVD and VEGF-A levels from pOCs to rOCs. MVDhigh pOCs were associated with higher CD3(+) and CD8(+) intratumoural effector TILs, while VEGF (+) samples were most frequently encountered among BRCA-mutated tumours. However, in multivariate analysis, MVD and VEGF were not an independent prognostic factor for OS.

Tsibulak et al. investigated BRCA1/2 mRNA-expression in ovarian cancer (OC) patients compared to non-neoplastic fallopian tubes. OC patients who carry a pathogenic BRCA mutation show better survival rates, possibly due to a better response to platinum-based chemotherapy and PARP inhibitors. In this study, OCs showed higher BRCA1/2 mRNA-expression compared to controls. BRCA1 mutated OCs exhibited lower BRCA1 but higher BRCA2 mRNA-expression. Low BRCA1-expression was associated with favourable overall survival (OS), also in multivariate analysis. Low BRCA2-expression was associated with better progression-free survival (PFS) and OS but was an independent prognostic factor in high-grade serous OCs only. Platinum sensitivity was characterised by lower BRCA1/2 mRNA-expression in BRCA1-wildtype cancers in comparison to platinum refractory OC and BRCA1/2 mRNA levels are suggested as reliable biomarkers to predict responsiveness of cancers to PARP inhibitors.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Distinct homologous recombination gene expression profiles after neoadjuvant chemotherapy associated with clinical outcome in patients with ovarian cancer.	Kessous et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29395310
2	Massively parallel sequencing analysis of mucinous ovarian carcinomas: genomic profiling and differential diagnoses.	Mueller JJ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29793804
3	Characterisation of tumour microvessel density during progression of high-grade serous ovarian cancer: clinico-pathological impact (an OCTIPS Consortium study).	Ruscito I et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29955134
4	BRCA1 and BRCA2 mRNA-expression prove to be of clinical impact in ovarian cancer.	Tsibulak I et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30111871

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Screening for ovarian and fallopian tube cancer

Lucas Minig

No relevant original research articles have been published regarding the screening of ovarian cancer in the covered period. The only relevant article was a review of the American Cancer Society guidelines, which focussed on "Current issues in Cancer Screening". The article confirms that there is still no effective screening strategy for ovarian cancer. Even though the multimodal screening strategy (MMS), which includes annual CA 125 screening using a risk of ovarian cancer algorithm and transvaginal ultrasound as a second-line test, has shown promising results, a longer follow-up is needed before a decision can be made regarding its implementation into clinical practice.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening.	Smith R et al.	CA Cancer J Clin	https://www.ncbi.nlm.nih.gov/pubmed/29846940

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Surgical treatment of primary ovarian cancer

Sileny Han

Complications

Ross et al. performed a single-centre retrospective review (January 1, 2007, to December 1, 2013, at the University of Pittsburgh Medical Center) to determine perioperative factors that predicted unplanned ICU admission and its impact on outcome after primary debulking surgery (PDS). In this six-year period, they found 108 patients with an unplanned postoperative ICU admission. Higher perioperative blood loss, stage III and IV disease, longer operative time, and failure to achieve optimal (<1 cm) cytoreduction were all predictors of postoperative ICU admission. Patients that were admitted to the ICU after surgery had significantly worse overall survival (OS) (median OS 27.3 vs. 57.9 months; p<0.001; adjusted HR 2.16, 95% CI: 1.53–3.05). Neoadjuvant chemotherapy was not associated with risk for ICU admission on multi-variable analysis [1].

Long-term outcome

In a single-centre retrospective study performed at Mayo Clinic in the United States, Torres et al. investigated factors that influence OS in patients with FIGO stage III–IV high-grade serous ovarian cancer after PDS. Between 1994 and 2011, all women with molecular profiling of the primary tumour available were included (n=334). Patients with a higher initial volume of disease (especially with upper abdominal and/or miliary disease) experienced shorter OS. Patients with mesenchymal subtype were more likely to have upper abdominal disease. Mesenchymal subtype was not an independent predictor of survival. The only variable independently associated with OS was debulking with no residual tumour (p<0.001), also in cases with upper abdominal and/or miliary disease. Residual tumour >1 cm compared to nil residual tumour in multivariate analysis showed a hazard ratio of 2.56 (95% CI: 1.74–3.86). Outcome after neoadjuvant chemotherapy was not evaluated [2].

In a similar retrospective study performed at Brigham and Women's Hospital and Massachusetts General Hospital, patients with FIGO stage III–IV high-grade serous ovarian cancer after PDS were included to evaluate the relationship between amount and distribution of residual disease and oncologic outcome. Among women with ≤1 cm residual tumour, the most common sites of disease were the diaphragm 31.7% and the pelvis 31.7%. Arguably, these disease sites seem accessible to radical surgery. After a median follow-up of 36 months, the authors found a total of 191 recurrences (79.6%). The best prognosis was found in patients after debulking to no residual tumour (39.2% of patients). Survival was similar in all patients with residual disease (1 cm or ≤1 cm residual disease) [3].

Interestingly, patients with ≤1 cm residual disease in a single site had better prognosis than patients with ≤1 cm residual disease in multiple sites (6-month PFS difference). Thus, not all "optimally" debulked patients are equal. Debulking to no residual tumour should be the aim of PDS, and the option of neoadjuvant chemotherapy can be considered in patients at risk of residual tumour after PDS.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Unplanned postoperative intensive care unit admission for ovarian cancer cytoreduction is associated with significant decrease in overall survival.	Ross MS et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/?term=29929924
2	Factors that influence survival in high-grade serous ovarian cancer: A complex relationship between molecular subtype, disease dissemination, and operability.	Torres D et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/?term=29925470
3	Moving beyond "complete surgical resection" and "optimal": is low-volume residual disease another option for primary debulking surgery?	Manning-Geist BL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/?term=29933927

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Surgical treatment of recurrent ovarian cancer

Patriciu Achimas-Cadariu

Although level-A evidence supporting the role of secondary cytoreductive (SCS) surgery in recurrent ovarian cancer (OC) is still not available, preliminary data of the DESKTOP III trial [NCT 01166737] presented at ASCO 2017 suggested that SCS is a valuable option for recurrent OC patients, since it improves PFS. Other trials are ongoing, including the SOC 1 trial [NCT 01611766] and the GOG 213 trial [NCT 00565851]. The SOCceR trial [NTR 3337] was stopped due to low accrual.

In the last six months, four observational studies have been published, all supporting the role of SCS in carefully selected OC patients.

Bickell et al. included 1,635 OC recurrences using the SEER-Medicare database for cases diagnosed between 1997–2007. Of these, 72% were treated with chemotherapy only, 16% with surgery and chemotherapy, and 12% received hospice care. The median survival of women treated with chemotherapy alone, surgery and chemotherapy, or hospice care was 4.1, 5.4, and 2.2 years, respectively ($p<0.001$). Survival among women with recurrence treated with surgery and chemotherapy compared with chemotherapy alone (HR=1.67; 95% CI: 1.13–2.47) [1].

A Norwegian Cancer Registry study analysed 397 patients who underwent primary treatment with R0 resection between 2002–2012 with a treatment-free interval of six or more months after completion of primary platinum-based chemotherapy. Eighty percent of the patients in the SCS plus platinum-based chemotherapy group achieved complete resection. Both progression-free survival (HR=0.45; 95% CI: 0.32–0.62) and overall survival (HR=0.50, 95% CI 0.32–0.70) were improved in the SCS plus platinum-based chemotherapy compared with the platinum-based chemotherapy group, although the survival benefit was seen only in patients with no residuals at SCS [2].

Two other retrospective studies reported improved PFS and OS after SCS, with R0 resection rates of 73–87%. The use of scores like DESKTOP, MSK or Tian criteria was predictive of complete cytoreduction, but there is a considerable proportion of patients with a negative score for whom complete resection can be achieved [3,4].

Although mature data supporting SCS in ROC is still lacking, SCS has become popular due to the growing evidence supporting the beneficial effect of cytoreduction in platinum-sensitive ROC. An important comprehensive review has been recently published, which emphasised that the benefits of surgery need to be weighed against the risks such as morbidity and mortality, hospitalisation and costs [5].

Relevant articles retrieved August 15, 2017 – February 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Secondary surgery versus chemotherapy for recurrent ovarian cancer.	Bickell NA et al.	Am J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/27391357
2	Survival after secondary cytoreductive surgery and chemotherapy compared with chemotherapy alone for first recurrence in patients with platinum-sensitive epithelial ovarian cancer and no residuals after primary treatment. A registry-based study.	Szczesny W et al.	Acta Obstet Gynecol Scand.	https://www.ncbi.nlm.nih.gov/pubmed/29790149
3	Positive DESKTOP and Tian scores systems are adequate to predict optimal (R0) secondary debulking surgery in ovarian cancer, but a negative score does not preclude secondary surgery.	Laga T et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29561300
4	A score system for complete cytoreduction in selected recurrent ovarian cancer patients undergoing secondary cytoreductive surgery: predictors- and nomogram-based analyses.	Bogani G et al.	J Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29533023
5	When should surgery be used for recurrent ovarian carcinoma?	Bommert M et al.	Clin Oncol (R Coll Radiol).	https://www.ncbi.nlm.nih.gov/pubmed/29743148

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Medical treatment of primary ovarian cancer

Ilker Selcuk and Muhammad Rizki Yaznil

Schuurman et al. analysed the treatment strategies for elderly epithelial ovarian cancer (EOC) patients between 2002 and 2013. This Dutch observational nationwide study included 10,440 women with advanced-stage EOC, 41% being 70 years or older. The authors observed a shift of treatment from upfront debulking towards more use of neo-adjuvant chemotherapy (NACT) followed by interval debulking. This change in treatment strategy was associated with an increase in relative survival rates for elderly patients. Subgroup analyses revealed that the 1-year survival rate in 2002–2004 was about 73% and increased to 84% in 2011–2013. Moreover, the 5-year survival rate also increased, from 25% in 2002–2004 to 31% in 2008–2010. Additionally, postoperative mortality in elderly patients decreased over time [1].

Marchetti et al. analysed the pooled data of four randomised controlled trials (RCT) to evaluate the efficacy of dose-dense regimen in OC. Regimen with carboplatin AUC 5-6 plus paclitaxel 175–180 mg/m^2 every 3 weeks was grouped as the control. None of the dose-dense chemotherapy schedules (weekly dose dense: paclitaxel 60–80 mg/m^2 and carboplatin AUC 2 weekly administration, semi-weekly dose dense: weekly paclitaxel 80 mg/m^2 and three weekly carboplatin AUC 5-6) showed any beneficial effect to progression-free survival (PFS) over the standard regimen (HR 1.01, 95% CI: 0.93–1.10 and HR 0.82, 95% CI: 0.63–1.08, respectively). The three-weekly regimen still remains the standard treatment [2].

In ovarian clear cell carcinoma (OCCC), there is no clear evidence of adjuvant chemotherapy in stage I disease. Nasioudis et al. reported a possible survival benefit of adjuvant chemotherapy in patients with stage I OCCC (n=2325). The majority had stage IA/IB disease (55.8%) while 43.3% had stage IC disease, and all patients were considered staged. Chemotherapy was more commonly administered to stage IC patients than stage IA/IB (OR: 1.75, 95% CI: 1.4–2.18, p<0.001). After stratifying by disease sub-stage, stage IC and IB or IA patients who received adjuvant chemotherapy had better 5-year OS than the non-receiving counterparts; however, this was statistically significant only for stage IA/B patients (p<0.001; for stage IC: p=0.116). Patients who received adjuvant chemotherapy (n=1629) had better overall survival (OS) than those who did not (n=443) (5-year OS rate was 89.2% vs. 82.6%, p<0.001). After adjustment for sub-stage, adjuvant chemotherapy was associated with better survival for stage I OCCC, even for stage IA patients (HR: 0.59, 95% CI: 0.45–0.78) [3].

Yalcin et al. retrospectively compared the prognosis of women with ovarian carcinosarcoma (OCS, n=54) after optimal cytoreductive surgery plus lymph node dissection (LND) followed by platinum-based chemotherapy to women with ovarian high-grade serous carcinoma (HGSC, n=108) (case-control study). With a median follow-up of 36 months, there was no difference in median disease-free survival (DFS) between women with OCS (29 months, 95% CI: 0–59) and HGSC (27 months, 95% CI: 22.6–31.3) (p=0.76). Median overall survival (OS) was also similar in both groups (62 months in the OCS group compared to 82 months in the HGSC group) (p =0.53). Additionally, there was no difference in 5-year OS rate between the OCS and HGSC groups (54.6% vs. 59.5%, respectively) [4].

May et al. analysed a total of 852 patients with regard to PDS (n=449, 53%) and NACT+IDS (n=403, 47%). The extent of residual disease and median OS were evaluated for both groups, respective values for each group are: 0 mm disease/73.5–38.2 months, 1–9 mm disease/42.4–23.8 months, 10 mm or more disease/33.6–21.1 months. These results highlight the importance of PDS; however, even if no residual disease is not feasible, 1–9 mm residual disease after PDS provides still better OS than NACT+IDS [5].

The international ROSiA study evaluated the safety of bevacizumab 15 mg/kg single-agent maintenance therapy continuing up to 36 cycles (24 months) after concomitant treatment with carboplatin/taxol three-weekly. Patients younger than 70 (n=900, 88%) were compared with elderly patients (n=121, 12%). Anaemia, low-grade diarrhoea and asthaenia with grade 3 or higher toxicities of hypertension (39.7% vs. 22.0%) and thromboembolic events (5.0% vs. 1.4%) were more common in the elderly group. For older patients, the presence of baseline hypertension was more common (70% vs. 28%), and these patients need a careful evaluation/monitorisation before and during the bevacizumab treatment [6].

Timmermans et al. evaluated the effect of time from surgery to adjuvant chemotherapy (TTC) in ovarian cancer patients after PDS (n=1.612) or NACT+IDS (n=2,485). Age (>65y), postoperative complications, prolonged hospitalisation and complete debulking were independently associated with a delay in administration of adjuvant chemotherapy. Median TTC was 29 days (24–37). A longer TTC period (>37 days) was inversely associated with OS after both PDS (HR 1.43, 95% CI: 1.09–1.88) and NACT+IDS (HR 1.22, 95% CI: 1.02–1.47), but only in patients with no residual disease after surgery. The authors advised starting adjuvant chemotherapy within three to six weeks after the surgery [7].

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Medical treatment of primary ovarian cancer

Ilker Selcuk

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Treatment and outcome of elderly patients with advanced stage ovarian cancer: A nationwide analysis.	Schuurman MS et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29514738
2	Dose-dense weekly chemotherapy in advanced ovarian cancer: An update meta-analysis of randomized controlled trials.	Marchetti C et al.	Crit Rev Oncol Hematol	https://www.ncbi.nlm.nih.gov/pubmed/29650273
3	Adjuvant chemotherapy for stage I ovarian clear cell carcinoma: Patterns of use and outcomes.	Nasioudis D et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29751993
4	Carcinosarcoma of the ovary compared to ovarian high-grade serous carcinoma: impact of optimal cytoreduction and standard adjuvant treatment.	Yalcin I et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29143144
5	Examining survival outcomes of 852 women with advanced ovarian cancer A multi-institutional cohort study.	May T et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29621126
6	Safety and efficacy of extended bevacizumab therapy in elderly (Q70 years) versus younger patients treated for newly diagnosed ovarian cancer in the international ROSiA study .	Selle F et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29498983
7	Interval between debulking surgery and adjuvant chemotherapy is associated with overall survival in patients with advanced ovarian cancer.	Timmermans M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30001834

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Medical treatment of recurrent ovarian cancer

Ilker Selcuk

Lindemann et al. re-evaluated patients' response to re-challenge with platinum dependent on the platinum-free interval. A total of 341 traditionally classified platinum-resistant ovarian cancer patients were identified in the prospectively registered Australian Ovarian Cancer Study Group (AOCS). Of these patients, 190 (55.7%) had a platinum-free interval (PFI) of 3≤6 months and 151 (44.3%) had a PFI of 0≤3 months. 51% of these patients responded to platinum. Survival after treatment for first progression (OS2) was significantly longer within the platinum-receiving group compared to the non-platinum-receiving group when the PFI is 3–≤6 months (median 17.6m, 95% CI: 14.7–20.7 vs. median 10.6m, 95% CI: 8.0–12.7). In patients with PFI of 0–≤3 months, the type of second-line chemotherapy, whether platinum-based or not, was not statistically associated with response or survival. There is a need for further studies to evaluate the true sensitivity to platinum in patients with short PFI [1].

The TRIAS trial with sorafenib (400 mg 2x1) showed promising results (median PFS for sorafenib 6.7 m, 95% CI: 5.8–7.6 vs. 4.4 m 95% CI: 3.7–5.0 m for placebo, respectively) with acceptable morbidity rates (the most common grade 3–4 adverse event was leukopenia, 69% vs. 53%, respectively) when administered in combination with topotecan (1.25 mg/m^2 iv) to platinum-resistant ovarian cancer patients [2].

The review article by Mirza et al. summarises the efficacy of PARP inhibitors in platinum-sensitive recurrent ovarian cancer patients. Even though BRCA mutation status is the most important factor in predicting response to the treatment, FDA-approved PARP inhibitors irrespective of BRCA mutation status. Maintenance therapy with PARP inhibitors prolongs the period without disease symptoms (NOVA, SOLO2, ARIEL3); additionally, they provide an anti-tumour activity in patients with a measurable disease with tolerable side effects which can be controlled by dose tailoring [3].

Niraparib, a PARP inhibitor, was evaluated with regard to safety by Berek et al. In the ENGOT-OV16/NOVA study, 73% of patients underwent a dose reduction; however, after three months of treatment, the incidence of grade ≥3 side effects decreased. Baseline body weight and baseline platelet count were the identified risk factors to predict dose modification for niraparib. Patients with a body weight <77 kg or baseline platelet count <150 000 /µl will benefit from the starting dose of 200 mg/day [4].

Functional Assessment of Cancer Therapy-Ovarian Symptoms Index (FOSI) and the European QOL Scale Five Dimension Five Level (EQ-5D-5L) were used to assess patient-reported outcomes in the NOVA trial with niraparib maintenance treatment. The most common adverse events during the baseline analysis were lack of energy, pain, and nausea. Except nausea, all symptoms remained stable or improved. The most common grade 3 and 4 events were haematological toxicities. Pre-progression changes from the baseline were minimal or similar between the niraparib and placebo group [5].

Health-related quality of life (HRQOL) and patient-reported outcomes of the SOLO2 trial (olaparib, 300 mg maintenance therapy vs. placebo) confirmed the favourable toxicity profile of olaparib [6]. There were no differences in the pre-specified HRQOL outcome measure by Trial Outcome Index (TOI) between the groups, p=0.98. Additionally, patient-reported outcomes of QAPFS (incorporates PFS and health state) and QTWIST (incorporates both the quality and quantity of life by the time without significant symptoms of toxicity) showed a longer duration in favour of olaparib (QAPFS: 13.96 vs. 7.28, 95% CI: 4.98–8.54, p<0.0001; QTWIST: 15.03 vs. 7.70 95% CI: 4.70–8.96, p<0.0001).

Hypersensitivity reactions (HSR) are commonly seen with carboplatin administration. Lavigne et al. evaluated the role of extended carboplatin administration (3 hours vs. 30 minutes) with a randomised non-blinded trial on recurrent ovarian cancer patients. Extended infusion did not reduce the incidence of hypersensitivity reactions [7].

Friedlander et al. reported the quality-of-life analysis of AGO+OVAR 16 with pazopanib/placebo in maintenance after first-line chemotherapy for advanced epithelial ovarian cancer. There were no significant differences in terms of patient-centred QoL results despite the higher toxicity reported. PFS (time to second-line chemotherapy) was increased with 19.7 m vs. 15 m in pazopanib and placebo arms respectively, HR: 0.72, p=0.0001 [8].

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No	Title	Authors	Journal	Link to abstract
1	Response rates to second-line platinum-based therapy in ovarian cancer patients challenge the clinical definition of platinum resistance.	Lindemann K et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29807697
2	Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (TRIAS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial.	Chekerov R et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30100379
3	Latest clinical evidence and further development of PARP inhibitors in ovarian cancer.	Mirza MR et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29750420
4	Safety and dose modification for patients receiving niraparib.	Berek JS et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29767688
5	Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial.	Oza AM et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30026000
6	Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial.	Friedlander M et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30026002
7	A randomized trial of prophylactic extended carboplatin infusion to reduce hypersensitivity reactions in recurrent ovarian cancer.	Lavigne K et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29757876
8	Quality of life in patients with advanced epithelial ovarian cancer (EOC) randomized to maintenance pazopanib or placebo after first-line chemotherapy in the AGO-OVAR 16 trial. Measuring what matters-patient-centered end points in trials of maintenance therapy.	Friedlander M et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29267856

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Treatment of ovarian sex cord stromal and germ cell tumours

Anna Dückelmann

Dysgerminoma

Chen et al. presented a case of a pregnant woman complaining about abdominal pain. She was diagnosed with a large ovarian dysgerminoma, associated simultaneously with an abdominal desmoid tumour. The long-term outcome of patients with ovarian dysgerminoma during pregnancy is excellent. Fertility-preserving surgery can be done safely with a favourable outcome in early pregnancy. If chemotherapy is necessary, a platinum-based regimen seems to be the best choice after the first trimester [1].

Shah et al. studied treatment of advanced-stage dysgerminoma in children, adolescents, and young adults based on six GCT trials (3 paediatric, 3 adult). Survival outcomes were comparable between carboplatin-(5 years overall survival (OS5)=0.96 (95% CI, 0.85–0.99)) and cisplatin-(OS5=0.96 (95% CI, 0.87–0.99)) based regimens [2].

Ovarian germ cell tumours

Tamauchi et al. retrospectively analysed the reproductive outcomes of 105 malignant ovarian germ cell tumour (MOGCT) survivors. Regular menstruation recovered in 57 of 72 patients who received adjuvant chemotherapy. Three cases of premature menopause before the age of 40 were recorded. More than 90% of the 45 survivors who attempted to become pregnant achieved pregnancy (n=42); 40 patients delivered [3].

OGCTs are characterised by a low mutation rate and very few recurrent somatic mutations. The first whole exome sequencing on OGCT tumour samples and the analysis of somatic copy number aberration profiles showed that 12p gain is the most frequent copy number aberration, except in immature teratomas. Further, an enrichment in the PI3K/AKT/PTEN pathway in yolk sac tumours was detected [4].

Mature cystic teratoma

Gadducci et al. presented the first case of a type 2 papillary renal carcinoma within a mature cystic teratoma (MCT) of the ovary, diagnosed by histological examination after salpingo-oophorectomy. Malignant transformation occurs in 1.5–2% of MCTs of the ovary and usually consists of squamous cell carcinoma [5].

Adult granulosa cell tumours

A retrospective analysis (MITO-9) was published on the impact on surgical technique on the oncological outcome of stage I adult granulosa cell tumours (AGCTs) of the ovary. Survival outcomes were comparable between laparoscopic and open approaches [6].

Ciucci et al. described the hormone receptor profile of AGCTs. AGCTs express low oestrogen receptor (ER)α, and high ERβ1, ERβ2, ERβ5, progesterone, and androgen receptor levels. The authors show that cytoplasmic ERβ2 localises in mitochondria of granulosa cancer cells, exerting an anti-apoptotic role. ERβ may play a role in the pathogenesis of AGCT and, thus, may be a potential target for therapy according to the authors (e.g., oligonucleotide-based therapy and targeted protein degradation) [7].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Ovarian dysgerminoma in pregnancy: A case report and literature review.	Chen Y et al.	Cancer Biol. Ther.	https://www.ncbi.nlm.nih.gov/pubmed/29580145
2	Is carboplatin-based chemotherapy as effective as cisplatin-based chemotherapy in the treatment of advanced-stage dysgerminoma in children, adolescents and young adults?	Shah R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29884437
3	Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors: a multicenter study.	Tamauchi S et al.	AJOG	https://www.ncbi.nlm.nih.gov/pubmed/30086295
4	The genetic landscape of 87 ovarian germ cell tumors.	Nieuwenhuysen E V et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30170975
5	Malignant transformation in mature cystic teratomas of the ovary: Case reports and review of the literature.	Gadducci A et al.	Anticancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/29848726
6	Laparoscopic surgery in the treatment of stage I adult granulosa cells tumors of the ovary: Results from the MITO-9 study.	Bergamini A et al.	EJSO	https://www.ncbi.nlm.nih.gov/pubmed/29576462
7	Estrogen receptor β: Potential target for therapy in adult granulosa cell tumors?	Ciucci A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29786517

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

Florian Drews and Anna-Maria Schütz

In the six months since the last LiFE review, several phase I (veliparib, vistusertib) and phase II (sorafenib, apatinib, linsitinib, dalantercept, sunitinib) chemotherapy trials for ovarian cancers have been published. The authors attempted to include relevant studies covering the wide field of novel approaches to ovarian cancer treatment.

Phase I

Gray et al. investigated veliparib (a PARP inhibitor) plus carboplatin (AUC 4) and gemcitabine (800 g/m^2) in advanced ovarian cancer and other non-haematological malignancies in a phase I study to evaluate safety, tolerability, and efficacy. Veliparib was given twice daily continuously starting at cycle 2. Of 75 enrolled patients, 54 had ovarian cancer (67% BRCA germline mutation) and 12 breast cancer. The most common treatment-related adverse events were thrombocytopenia, neutropenia, nausea, and anaemia and the dose-limiting toxicities were thrombocytopenia and neutropenia. The MTD/RP2D was established at veliparib 250 mg with carboplatin AUC4 plus gemcitabine 800 mg/m^2. Responses were observed in 69% of patients with BRCA-deficient ovarian cancer. In conclusion, combination therapy demonstrated promising anti-tumour activity in platinum-sensitive ovarian cancer patients with germline BRCA mutations [1].

Basu et al. reported on outcomes of vistusertib (a dual m-TORC1/2 inhibitor) in combination with paclitaxel in the treatment of patients with high-grade serous ovarian and squamous non-small cell lung cancer. Elevated p-S6K levels correlate with resistance to chemotherapy in ovarian cancer and the authors hypothesised that inhibiting p-S6K with the dual m-TORC1/2 inhibitor could improve outcomes in patients receiving paclitaxel. Weekly paclitaxel (80 mg/m^2) was given 6/7 weeks in combination with an escalation dose of vistusertib for either 3 or 2 consecutive days per week. The experienced dose-limiting toxicities were fatigue, mucositis, and rash. A RECIST response rate of 52% was reported in the ovarian cancer cohort, with progression-free survival of 5.8 months [2].

Phase II

Lan et al. investigated apatinip, an oral tyrosine kinase inhibitor selectively inhibiting VEGF receptor-2, in a phase II trial combined with oral etoposide in platinum resistant/refractory ovarian cancer. In 35 patients, the combination of apatinib (initial dose 500 mg once daily) and oral etoposide (50 mg once daily given for a maximum of 6 cycles) showed promising efficacy and manageable toxicities, warranting phase III trials. Objective responses were achieved in 54% of patients. The most common grade 3 or 4 adverse events were neutropenia (50%), fatigue (32%), anaemia (29%), and mucositis (24%). Serious adverse events included anaemia with anorexia and increased ascites due to disease progression [3].

Oza et al. reported on outcomes of a phase II study evaluating linsitinib (either intermittent as 600 mg once daily on days 1–3, or continuous 150 mg twice daily), an oral dual inhibitor of insulin-like growth factor-1 receptor and insulin receptor, and weekly paclitaxel (80 mg/m^2) in recurrent platinum-resistant ovarian cancer. In 152 women, neither intermittent nor continuous linsitinib (PFS 4.2 months/5.6 months) significantly improved PFS over paclitaxel alone (5.6 months). Adverse event rates were higher among patients receiving intermittent linsitinib compared with the other treatment arms [4].

The NRG Oncology/Gynecologic Oncology Group published two phase II trials. First, Burger et al. reported on dalantercept, a soluble ALK1 inhibitor receptor fusion protein. Thirty patients received 1.2 mg/kg subcutaneously every three weeks until disease progression or unacceptable toxicity [5]. However, due to a lack of clinical responses, the trial was closed. In the second phase II trial, Chan et al. evaluated the efficiency of sunitinib in the treatment of persistent or recurrent clear cell ovarian carcinoma. Thirty patients received 50 mg sunitinib per day for four weeks, and the treatment was repeated in 6-week cycles until disease progression or prohibitive toxicity. The median PFS was 2.7 months; the median overall survival 12.8 months. In summary, sunitinib demonstrated only minimal activity in second- and third-line treatment [6].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Phase I combination study of the PARP inhibitor veliparib plus carboplatin and gemcitabine in patients with advanced ovarian cancer and other solid malignancies.	Gray HJ et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29352572
2	Vistusertib (dual m-TORC1/2 inhibitor) in combination with paclitaxel in patients with high-grade serous ovarian and squamous non-small-cell lung cancer.	Basu B et al.	Ann Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30016392
3	Apatinib combined with oral etoposide in patients with platinum-resistant or platinum-refractory ovarian cancer (AEROC): a phase 2, single-arm, prospective study.	Lan CY et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30082170
4	Phase 2 study evaluating intermittent and continuous linsitinib and weekly paclitaxel in patients with recurrent platinum resistant ovarian epithelial cancer.	Oza A et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29454514
5	Phase II evaluation of dalantercept in the treatment of persistent or recurrent epithelial ovarian cancer: An NRG Oncology/Gynecologic Oncology Group study.	Burger RA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30041929
6	A phase II evaluation of sunitinib in the treatment of persistent or recurrent clear cell ovarian carcinoma: An NRG Oncology/Gynecologic Oncology Group Study (GOG-254).	Chan JK et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29921512

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

Sara Giovannoni

Nivolumab

Nivolumab, a human-programmed death receptor-1 (PD-1) blocking antibody, has been investigated in recurrent ovarian cancer patients with BRCA gene mutation. The retrospective trial, published by Matsuo et al., enrolled six pre-treated patients who received nivolumab (3 mg/kg d 1,15 every 4 weeks) as salvage therapy [1]. The majority had platinum-resistant disease. There were three complete responses, one partial response, and two cases of progressive disease. The study confirms the higher susceptibility to immune checkpoint inhibitors in tumours with deficiency in DNA-repair mechanism, including BRCA mutation. The results are limited due to the small number of patients. Further trials are needed.

Genetic counselling

Tea et al. assessed the possibility of improving genetic counselling through the use of tools that combine complex medical information with pictures, diagrams, and tablets (new genetic counselling tool NGCT) as compared to conventional oral genetic counselling (CGC). Seventy women were randomised to receive oral-only oral genetic counselling (conventional) or the new genetic counselling (NGCT). Questionnaires were used to evaluate the comprehension of the medical information. Correct responses were significantly higher in the NGCT group compared to the CGC group (p=0.012). So, the use of counselling tools leads to an overall better understanding of the content of a genetic counselling session than CGC alone [2]. Also, Vogel et al. studied the barriers to genetic counselling in 14 women, testing a new strategy to promote counselling through mobile technology that may in future be useful in developing an interventional trial [3].

The prospective, observational Evaluating a Streamlined Onco-genetic BRCA Testing and Counselling Model Among Patients with Ovarian Cancer (ENGAGE) study evaluated a streamlined, oncologist-led BRCAm testing pathway in order to facilitate more widespread BRCA testing in ovarian cancer [4]. A genetic counsellor was not involved in the counselling. Seven hundred ovarian cancer patients were included. The aims of the ENGAGE study were to assess turnaround time and satisfaction among patients and physicians. The median overall turnaround time was 9.1 weeks (range 0.9 to 37.1 weeks). Patient satisfaction with the oncologist-led BRCAm testing pathway was high, with >99% of patients expressing satisfaction; in addition, the oncologist satisfaction rate was consistent with these results (>80% agreeing). The ENGAGE study demonstrates that an oncologist-led BRCAm testing process is feasible in ovarian cancer.

In a prospective, non-randomised pilot study, Nebgen et al. enrolled 43 pre-menopausal BRCA1/2 mutations carriers aged 30 to 47. The patients chose between screening, bilateral salpingo-oophorectomy (RRSO) or bilateral salpingectomy with delayed oophorectomy (at 40 years for BRCA1 and at 45 years for BRCA2 patients) for ovarian cancer risk reduction. One case of STIC was found in a woman undergoing RRSO. A significant decrease in worry and anxiety was found in patients who underwent salpingectomy with delayed oophorectomy. Bilateral salpingectomy as a risk-reducing strategy to avoid early premenopausal symptoms can still not be considered a standard for ovarian cancer risk reduction due to the lack of prospective data [5].

A prospective cohort study of 872 BRCA1 mutation carriers, who had no history of cancer, was studied in order to evaluate the risk of developing breast cancer with hormone-replacement therapy after RRSO. Ninety-two women (10.6%) had a diagnosis of breast cancer. The hormone-replacement therapy was not associated with an increased risk of breast cancer overall (HR 0.97 for ever use of any of hormone replacement therapy vs. no use). However, the use of oestrogen plus progesterone increased the cumulative incidence of breast cancer compared with oestrogen alone (22% versus 12%). The use of oestrogen after RRSO seems to be safe in BRCA1 mutation carriers [6].

Girardi et al. estimated the risk of breast and ovarian cancer in a large prospective cohort of 1,895 unaffected women, without BRCA1/2 predictive mutation, who have been tested for a specific BRCA mutation found in a biological relative (EMBRACE study). The results didn't provide evidence for elevated risks of breast or ovarian cancer in BRCA1/BRCA2 predictive test negatives with a standardised incidence ratio (SIR) of 0.93 for invasive breast cancer (95% CI: 0.62–1.40) in the overall cohort, 0.85 (95% CI: 0.48–1.50) in non-carriers from BRCA1 families and 1.03 (95% CI: 0.57–1.87) in non-carriers from BRCA2 families. The SIR for ovarian cancer was 0.79 (95% CI: 0.20–3.17) overall [7].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Nivolumab use for BRCA gene mutation carriers with recurrent epithelial ovarian cancer: A case series.	Matsuo K et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/29998185
2	Improving comprehension of genetic counselling for hereditary breast and ovarian cancer clients with a visual tool.	Tea MM et al.	PLoS One.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6042777/
3	A qualitative study of barriers to genetic counselling and potential for mobile technology education among women with ovarian cancer.	Vogel RI et al.	Hered Cancer Clin Pract	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6031189/
4	Evaluation of a streamlined oncologist-led BRCA mutation testing and counselling model for patients with ovarian cancer.	Colombo N et al.	J Clin Onco.	https://www.ncbi.nlm.nih.gov/pubmed/29558274
5	Bilateral salpingectomy with delayed oophorectomy for ovarian cancer risk reduction: A pilot study in women with BRCA1/2 mutations.	Nebgen DR et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29735278
6	Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers.	Kotsopoulos J et al.	JAMA	https://www.ncbi.nlm.nih.gov/pubmed/29710224
7	Risks of breast or ovarian cancer in BRCA1 or BRCA2 predictive test negatives: findings from the EMBRACE study.	Girardi F et al.	Genet Med	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6033314/

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

Aleksandra Strojna

Appendectomy

Song et al. conducted the largest retrospective analysis to determine the frequency of appendiceal involvement and the role of appendectomy in patients undergoing surgery for mucinous borderline ovarian tumours (mBOTs). The analysis included 473 patients who underwent adnexal surgery and were finally diagnosed with mBOTs from hospital databases, 201 (42.5%) of whom underwent appendectomy, 247 (52.2%) did not undergo appendectomy at the time of initial surgery, and 25 (5.3%) had previously undergone appendectomy. Laparotomy (60.7% vs. 48.6%) and radical surgery (47.3% vs. 20.2%) were more frequently performed in patients who underwent appendectomy than in patients who did not undergo appendectomy ($p=0.011$ and $p<0.001$, respectively). The method of surgical approach (laparoscopy vs. laparotomy) was decided based on size of the ovarian tumour, patient requirement, preference of the operating surgeon, and general medical condition. Radical or conservative surgical treatment was dependent on the age of the patient, extent of the disease, and the desire to preserve fertility. No significant difference in the postoperative residual tumour volume or disease prognosis was found between the groups. The rate of operative complications did not differ between groups with or without appendectomy (8.5% vs. 4.5%, $p=0.082$). Among the 201 patients who underwent appendectomy, primary and metastatic appendiceal mucinous neoplasms occurred in one patient each (0.5%), who both showed a macroscopically abnormal appendix. The appendectomy itself did not increase the surgical morbidity and did not influence the recurrence risk ($p=0.964$) or survival ($p=0.219$) of patients with mBOTs. The data suggest that appendectomy at the time of primary surgery for mBOTs is not warranted in the absence of a grossly abnormal appendix or evidence of metastatic disease. The study highlights the need for a careful intra-operative exploration of the appendix [1].

Frozen section/risk of over-treatment

Ratnavelu et al. revealed that BOT diagnosed at frozen section have 21% chance of finally being reported as ovarian cancer. This is significant as BOT rarely metastasize, and long-term survival is significantly better than ovarian cancer. One-third of the women diagnosed with borderline ovarian tumours are younger than 40 years of age, which adds to the complexity of management as one must consider fertility-sparing approaches. The risk of overtreatment in these cases is as great as the risk of under-treatment.

This retrospective multicentre case-control study compared the accuracy of frozen section diagnosis of borderline ovarian tumours among three distinct types of hospital—an academic hospital with gynaecologic pathologists, an academic hospital with non-gynaecologic pathologists, and a community hospital with non-gynaecologic pathologists. On frozen section analysis, the most common diagnosis was serous borderline ovarian tumour (167 patients; 78.8%), followed by mucinous borderline ovarian tumour (39 patients; 18.5%). On final pathologic analysis, 154 patients (72.7%) had serous borderline ovarian tumours and 27 patients (12.7%) had mucinous borderline ovarian tumours. Overall, the frozen section diagnosis of borderline ovarian tumour correlated with the final pathologic diagnosis in 192 of 212 cases (90.6%). The accuracy of frozen section diagnosis did not differ by hospital type. Of the 192 patients with borderline ovarian tumour confirmed on final pathologic analysis, 158 (82.3%) had stage I disease. The stage distribution did not differ between hospital types. Mucinous and endometrioid borderline ovarian tumours are more likely to be upgraded to an invasive carcinoma. Providers should understand the limitations of a frozen section diagnosis of such a tumour [2].

Patients treated at the academic hospital with gynaecologic pathologists were more likely to have radical procedures performed (hysterectomy and bilateral salpingo-oophorectomy) than patients treated at the hospital without gynaecologic pathologists. However, the median age of patients treated at an academic hospital with gynaecologic pathologists was 55 years, higher than the median age of patients in other groups (41 years). They were also more likely to have a personal or family history of cancer, which may also have altered surgical management. Practice patterns and surgical staging may vary at different hospital settings, but overall survival was not affected. The surgeon should use the frozen section diagnosis and results from assessment of the abdominal cavity to decide what components of surgical staging to perform. However, a frozen section diagnosis of borderline ovarian tumour correlates with the final pathologic diagnosis independent of the type of hospital.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	The role of appendectomy in patients with mucinous borderline ovarian tumors.	Song T et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/30145525
2	Accuracy of intraoperative frozen section diagnosis of borderline ovarian tumors by hospital type.	Shah SJ et al.	J Minim Invasive Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/29680231

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

Santiago Scasso and Joel Laufer

The identification of novel and more reliable markers to accurately predict the prognosis of patients with endometrial cancer (EC) are clearly needed until molecular classification platforms are implemented in clinical practice.

In the period covered by LiFE 8 , Liu et al. published a systematic review and a meta-analysis exploring the clinical significance of matrix metalloproteinase-2 (MMP-2) expression in EC and its association with clinicopathologic characteristics (including FIGO stages, degree of differentiation, depth of myometrial invasion, and lymph node metastasis). The results showed that MMP-2 was expressed in a high percentage of endometrial cancer cases and its expression may be associated closely with clinical stage, tumour invasion, and metastasis, indicating that MMP-2 overexpression may serve as a predictive factor for poor prognosis in endometrial cancer [1].

Gómez-Macías et al. retrospectively analysed MMP11 gene expression using the reverse transcription-polymerase chain reaction in 68 cases of type I EC. The rate of proliferation was determined using Ki67 staining, in which an increased rate of proliferation was identified to be associated with adverse histopathological parameters, increased levels of MMP11 expression (p=0.04), vascular invasion and pathological staging. This supports the hypothesis that MMPs are associated with the level of invasion and progression in endometrioid-type carcinoma [2].

As mentioned in the LiFE 6 report, the cell adhesion molecule L1CAM is highly expressed in several human carcinomas and more recently has been described as a new important marker for EC. Corrado et al. retrospectively analysed, by immunhistochemnistry and RT-qPRC, the expression of L1CAM in a cohort of 113 ECs at different stages, of which 50% have relapsed. The authors were able to show that L1CAM is highly expressed in recurrent compared to non-recurrent EC and identified two groups of patients with different prognosis: high L1CAM expression and G3 with poor prognosis, low L1CAM expression and age lower than 67 years with good prognosis [3].

Felix et al. explored the hypothesis that women who have had a tubal ligation for sterilisation have improved EC survival, secondary to lower stage at presentation, suggesting that transtubal spread may represent an important route of metastasis. The authors evaluated the detection of intraluminal tumour cells (ILTCs) as a putative histological marker of transtubal spread and its relation to tumour characteristics and survival. Using a logistic regression model based on the retrospective results of 295 EC patients, the authors conducted a retrospective pathologist analysis. Their findings suggest that ILTCs are associated with adverse EC prognostic features and reduced survival in patients with early stage EC [4].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Clinical significance of matrix metalloproteinase-2 in endometrial cancer: A systematic review and meta-analysis.	Liu C et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/30024495
2	Overexpression of the matrix metalloproteinase 11 gene is a potential biomarker for type 1 endometrial cancers	Gómez-Macías GS et al.	Oncol Lett.	https://www.ncbi.nlm.nih.gov/pubmed/29963184
3	Endometrial cancer prognosis correlates with the expression of L1CAM and miR34a biomarkers.	Corrado G al.	J Exp Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29980240
4	Detection of endometrial cancer cells in the fallopian tube lumen is associated with adverse prognostic factors and reduced survival.	Felix AS et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29754740

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Screening for uterine cancer/Hereditary uterine cancer

María de los Reyes Oliver Pérez

In the period covered by the eighth edition of the LIFE report, two prospective studies [1,3] and two literature reviews [3,4] were selected for discussion.

Screening for uterine cancer

In postmenopausal women without postmenopausal bleeding, the threshold that separates normal from a pathologically thickened endometrium (ET) has not been standardised. Ghoubara et al. prospectively collected the data of 81 consecutive asymptomatic women with ET>4 mm on a transvaginal ultrasound scan. The prevalence of endometrial atypical hyperplasia (EAH) and endometrial cancer (EC) was 4.9%, and polyp was 24.7%. An ET threshold of ≥10 mm had a sensitivity of 100% (95% CI: 40–100%), a specificity of 60% (95% CI: 48–71%) with AUC = 0.8 (95% CI: 0.66–0.93), and p=0.04 for diagnosis of EAH and EC. The authors propose this cut-off point as an indicator of histological study in these patients [1].

Universal screening for Lynch Syndrome (LS) in endometrial cancer

Universal screening for LS in EC has been increasingly implemented in the past five to ten years. However, despite the rapidly expanding use of immunohistochemistry for LS screening, testing protocols vary considerably between institutions. Some institutions screen pre-surgical diagnostic specimens, while others defer screening to the hysterectomy specimen. Chapel et al. report a systematic evaluation of mismatch repair proteins (MMRP) expression in paired pre-surgical samplings (endometrial biopsy or curettage (EMB/C)) and hysterectomy specimens from 99 patients diagnosed with endometrial cancer. The concordance of MMRP expression pattern between EMB/C and paired hysterectomy specimen was 100% [2].

In addition, there are several barriers to genetic counselling and testing follow-up after universal tumour testing for LS in patients with EC. Also, uninformative genetic test results present a management challenge.

Hereditary uterine cancer

Tanakaya published an extensive review of current clinical topics related to LS screening, diagnosis, surveillance, and therapy [3].

Joehlin-Price et al. published a review about two hereditary syndromes related to uterine mesenchymal tumours: hereditary leiomyomatosis and renal cell carcinoma syndrome and the tuberous sclerosis complex. The authors described the current literature on these syndromes, summarising their clinical, morphologic, immunophenotypic, and genetic data [4].

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No	Title	Authors	Journal	Link to abstract
1	Thickened endometrium in asymptomatic postmenopausal women - determining an optimum threshold for prediction of atypical hyperplasia and cancer.	Ghoubara A et al.	J Obstet Gynaecol.	https://www.ncbi.nlm.nih.gov/pubmed/29862866
2	Immunohistochemistry for mismatch repair protein deficiency in endometrioid endometrial carcinoma yields equivalent results when performed on endometrial biopsy/curettage or hysterectomy specimens.	Chapel DB et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29656794
3	Current clinical topics of Lynch syndrome.	Tanakaya K.	Int J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29744602
4	Uterine mesenchymal tumours: hereditary aspects.	Joehlin-Price AS, Garg K.	Adv Anat Pathol.	https://www.ncbi.nlm.nih.gov/pubmed/28945610

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Treatment of endometrial hyperplasia

Elko Gliozheni

Sletten et al. prospectively analysed the efficacy of low-dose levonorgestrel impregnated intrauterine system (LNG-IUS) 13.5 mg, releasing average 6 µg levonorgestrel/24 hours, as therapy for endometrial hyperplasia (EH). Therapy duration was six months (n=16) or 3–6 weeks (n=5), depending on individual risk (low- and medium-risk vs. high-risk) for co-existent or future endometrial carcinoma (EC). The authors found the low-dose LNG-IUS to be an effective therapy option for low- and medium-risk EH; for patients with high-risk EH, only 40% obtained a therapy response [1].

Tamauchi et al. retrospectively analysed the efficacy of medroxyprogesteroneacetate (MPA) treatment and retreatment for atypical endometrial hyperplasia (AEH) and well-differentiated EC (G1EC) without myometrial invasion in 39 women. Complete response rates were 89% of the G1EA group and 93% for the AEH group with recurrence rates being of 88% for the G1EA patients and 50% for the AEH patients. Amongst the recurrent patients who received MPA retreatment, complete response was achieved in 100% of the G1EA group and 92% of the AEH group, thus concluding that MPA can be effective for the treatment of G1EA and AEH even when they recur [2]. Uysal et al., in their prospectively randomised study, compared the effectiveness of dienogest (DIE) depo medroxyprogesterone 17-acetate (MPA) and micronized progesterone (MP) regimens for the treatment of simple endometrial hyperplasia (EH) without atypia. They found that the efficacy of the progestins was similar between the groups, although the highest response rate was in the DIE group (complete response rate of 93.5% in the MP, 88.5% in the MPA, and 96.9% in the DIE group) [3].

Giampaolino et al. retrospectively evaluated the safety and effectiveness of the combination of endometrial focal resection with a levonorgestrel-releasing intrauterine device (LNG-IUD) in 55 young women with AEH and 14 patients with G1EC wishing to preserve their fertility. The authors found that the combination of hysteroscopic resection with LNG-IUD gave a similar response, and live birth rates were comparable to those reported in the literature for progestins alone, though with considerably lower relapse rate [4].

Graul et al. analysed the EH and EC regression rates with levonorgestrel intrauterine system (LNG-IUS) by body mass index (BMI). Morbidly obese patients with EH, AEH, and EC were found to be more likely to progress. Despite the addition of oral progesterone to LNG-IUS, morbid obesity was found to increase the odds of progression by 22.2% for EH, 21.4% for EHA, and 25% for EC in the BMI>40 kg/m² group [5].

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No	Title	Authors	Journal	Link to abstract
1	Low-dose LNG-IUS as therapy for endometrial hyperplasia. A prospective cohort pilot study.	Sletten ET et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29715112
2	Efficacy of medroxyprogesterone acetate treatment and retreatment for atypical endometrial hyperplasia and endometrial cancer.	Tamauchi S et al.	J Obstet Gynaecol Res	https://www.ncbi.nlm.nih.gov/pubmed/29121428
3	The efficacy of dienogest in the treatment of simple endometrial hyperplasia without atypia.	Uysal G et al.	Gynecol Obstet Invest	https://www.ncbi.nlm.nih.gov/pubmed/28715800
4	Hysteroscopic endometrial focal resection followed by Levonorgestrel Intrauterine Device insertion as a fertility-sparing treatment of atypical endometrial hyperplasia and early endometrial cancer: A retrospective study.	Giampaolino P et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/30017893
5	Conservative management of endometrial hyperplasia or carcinoma with the levonorgestrel intrauterine system may be less effective in morbidly obese patients.	Graul A et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/30255125

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Surgical treatment of primary uterine cancer

Piotr Lepka

Lymphadenectomy (LND) in endometrial cancer (EC)

Venigalla et al. retrospectively evaluated survival implications of staging lymphadenectomy for non-endometrioid carcinoma in 7,250 patients with clinical stage I serous carcinoma, clear cell carcinoma or carcinosarcoma. The hazard ratio (HR) for death was assessed based on propensity core-weighted multivariable Cox regression models. The results showed that pelvic LND was associated with decreased risk of death (HP=0.65, 95% CI: 0.59–0.71) compared to no LND. The addition of para-aortic LND to pelvic LND may be most beneficial for patients with serous carcinoma (HR=0.85, 95% CI: 0.79–0.91) compared to pelvic LND alone [1]. Buda et al. retrospectively analysed 171 patients with high-risk EC. Sixty-six women were staged with the sentinel lymph node procedure (SLN) and 105 with SLN plus selective lymphadenectomy (S-LND). The results did not show a difference in the 5-year disease-free survival between staging algorithms [2]. Ayhan et al. proposed a lymph node ratio value as an independent prognostic factor in progression-free survival (PFS) and overall survival (OS) in patients with stage IIIC EC. Lymph node ratio (LNR) was defined as the percentage of positive lymph nodes to total nodes recovered and was stratified into two groups: LNR1(≤0.15) and LNR2 (>0.15). The results showed the 5-year PFS rates for LNR≤0.15 and LNR>0.15 were 76.1% and 58.5%, respectively (p=0.045). An increased LNR was associated with a decrease in 5-year OS from 87% for LNR ≤ 0.15 to 62.3% for LNR>0.15 (p=0.005) [3].

Treatment related to age

Lindfors et al. studied women older than 70 diagnosed with EC who had been operated with the open technique and using robotic surgery in terms of costs, survival, surgical outcome, and operating time. Cohorts of 137 and 141 women was evaluated in open and robotic surgery, respectively. The results showed that the robotic approach was a feasible technique for this group of patients and could be beneficial due to the shorter hospital stay, and decreased blood loss and postoperative complications [4].

Postoperative outcomes

Ferguson et al. prospectively evaluated patient-reported outcomes (PROs) among women treated by laparoscopic, robotic, and open approaches for EC. The results were analysed at baseline, short- (1 and 3 weeks), and long-term (12–24 weeks) follow-up. The results of 468 patients showed no significant differences between the laparoscopy and robotic groups for any PRO (p>0.05). At short-term follow-up, the minimal invasive subgroup had a significantly higher quality of life in the Functional Assessment of Cancer Therapy (FACT-G) scores (p<0.0001) and Euro Qol Five Dimensions scores (EQ-5D) (p<0.0001), less pain (p=0.02) and improved pain interference (p=0.0008) compared to laparotomy group. A long-term follow-up showed improvements in the FACT-G (p=0.035) and EQ-5D visual analogue scale (p=0.022). Sexual health was not associated with surgical approach [5].

Time and surgery

In a prospective double-blind, randomised controlled trial, Fiascone et al. analysed whether preoperative injection with depot medroxyprogesterone acetate (DMPA) decreases tumour glandular cellularity when compared to a placebo injection in women awaiting hysterectomy for endometrial intraepithelial neoplasia or type I EC. Thirty-eight women enrolled to each arm were evaluated. The DMPA group experienced a larger decrease in tumour glandular cellularity. The effect was most pronounced in women waiting three weeks or longer for the surgery. The authors concluded that this strategy may represent a meaningful bridge to surgery in women who can expect a long wait [6].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Survival implications of staging lymphadenectomy for non-endometrioid endometrial cancers.	Venigalla S et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29559170
2	Lymph node evaluation in high-risk early stage endometrial cancer: A multi--institutional retrospective analysis comparing the sentinel lymph node (SLN) algorithm and SLN with selective lymphadenectomy.	Buda A et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29887483
3	Impact of lymph node ratio on survival in stage IIIC endometrioid endometrial cancer: a Turkish Gynecologic Oncology Group study.	Ayhan A et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29770619
4	Robotic vs. open surgery for endometrial cancer in elderly patients: Surgical outcome, survival, and cost analysis.	Lindfors A et al.	Jpn J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29557825
5	Prospective cohort study comparing quality of life and sexual health outcomes between women undergoing robotic, laparoscopic and open surgery for endometrial cancer.	Ferguson SE et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29681461
6	While women await surgery for type I endometrial cancer, depot medroxyprogesterone acetate reduces tumor glandular cellularity.	Fiascone S et al.	Am J Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/30063901

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Medical (chemo and radiotherapy) treatment of primary uterine cancer

David Lindquist

One systematic review studied the benefits of adjuvant chemoradiotherapy and radiotherapy alone in high-risk stage I–III endometrial cancer. Six trials and more than 2,000 patients were studied. There was a statistically significant improvement of progression-free survival and cancer-specific survival, but no difference in overall survival, local recurrence rate, or distant metastasis rate [1]. The value of adjuvant vaginal brachytherapy (VBT) was compared with external beam pelvic radiotherapy and no radiotherapy in a multicentre retrospective study. VBT was found to improve survival in intermediate and high-risk patients, but no benefit was found for adding external beam radiotherapy [2]. In a phase II study, three different experimental arms, paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, and ixabepilone/carboplatin/bevacizumab were evaluated in advanced and recurrent endometrial cancer, but no improved survival could be found when comparing with historical data [3]. In stage IV carcinosarcoma, neoadjuvant chemotherapy with paclitaxel/carboplatin was evaluated in a retrospective cohort of 1,192 women, but no statistically significant difference was found [4]. In contrast, another study from the Netherlands reported a benefit of adjuvant treatment in women with carcinosarcoma when no lymphadenectomy was performed [5]. These two cohorts are, however, not comparable since they differ in several parameters. In serous uterine carcinoma, the efficacy of platinum-based adjuvant chemotherapy (+/- radiotherapy) was evaluated in 409 women. The authors concluded that the effect of platinum-based chemotherapy is short lived and that recurrences within the first two years in patients with R0 are clinically platinum resistant. More effective treatment options are obviously warranted in patients with advanced/relapsed serous uterine cancer [6]. Finally, one multi-institution study addressed the benefit of combined adjuvant chemo and radiotherapy in 414 women with stage IA serous or clear cell carcinomas. The authors conclude that there is a benefit from adjuvant therapy, but observation may be an option for patients undergoing adequate surgical staging [7].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: A systematic review and meta-analysis.	Yi et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29530332
2	Vaginal brachytherapy for endometrial cancer.	Hass et al.	J Cancer Res Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29730776
3	A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer.	Aghajanian et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29804638
4	Survival outcome of women with stage IV uterine carcinosarcoma who received neoadjuvant chemotherapy followed by surgery.	Matsuo et al.	J Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29044542
5	Lymphadenectomy and adjuvant therapy improve survival with uterine carcinosarcoma: A large retrospective cohort study.	Versluis et al.	Oncology.	https://www.ncbi.nlm.nih.gov/pubmed/29791913
6	Uterine serous carcinoma: Reassessing effectiveness of platinum-based adjuvant therapy.	Tortorella et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29550183
7	The role of adjuvant therapy in stage IA serous and clear cell uterine cancer: A multi-institutional pooled analysis.	Qu et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29544706

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Surgical treatment of recurrent endometrial cancer

Arun Kalpdev

The incidence of endometrial cancer is increasing. The clinical outcome of patients suffering from this cancer has not improved in recent decades because this malignancy is primarily driven by high-grade histopathology that is more likely to present at an advanced stage and ultimately is more likely to recur. Generally, the prognosis after recurrent endometrial cancer is poor, especially for the 50% of these women that present with extra pelvic disease recurrence [1].

De Rooij et al. assessed the longitudinal impact of a recurrence of gynaecological cancer (endometrial and ovarian cancers included) on satisfaction with information provision and care. The impact of a recurrence on illness perceptions, anxiety, and depression and health-related quality of life was also assessed. It was concluded that after diagnosis of recurrent disease, patients reported lower health-related quality of life, more anxiety and depression, and more threatening illness perceptions. Additionally, patients were less satisfied with care compared with patients without a recurrence. This perspective shows that we should carefully counsel patients on treatment approach in such cases [2].

Kanao et al. reported a case of recurrent low-grade endometrial stromal sarcoma which developed after 20 years of total abdominal hysterectomy and bilateral salpingo-oophorectomy. Recurrent lesion presented at the vaginal stump, and the patient received multiple cycles of chemotherapy and hormonal therapy. The lesion progressed despite treatment and involved the bladder, left ureter, and left pelvic sidewall. Finally, laparoscopic anterior pelvic exenteration with radical parametrectomy was performed. R0 resection was achieved without any perioperative. No adjuvant treatment was given to the patient, who was free of recurrence 12 months after surgery [3].

Díaz-Montes et al., shared a retrospective case series of recurrent uterine sarcomas, where cytoreductive surgery has a significant positive outcome when supplemented with hyperthermic intraperitoneal chemotherapy (HIPEC). The authors conducted a retrospective analysis of 26 patients with recurrent uterine sarcomas at a single institution over an 11-year study period. The histopathologic subtypes included were leiomyosarcoma, adenosarcoma, endometrial stromal sarcoma, or undifferentiated uterine sarcomas. Out of 26 patients, five patients received chemotherapy and/or radiotherapy without surgical intervention, 14 patients underwent surgery alone or a combination of surgery and adjuvant systemic chemotherapy, and seven patients received cytoreductive surgery with HIPEC. Median disease-free survival was 2.4 months for patients with nonsurgical treatments, 5.3 months for patients treated with conventional surgery, and 11.3 months for patients treated with HIPEC. Median overall survival was 35.9 months for patients treated with conventional surgery and 43.8 months for patients treated with HIPEC [4].

The heterogeneity of histologies included, the retrospective design and the small number of cases included do not allow definite conclusions regarding the role of HIPEC in these patients.

The reviewed literature support a role of surgery in recurrent endometrial cancers.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Management strategies for recurrent endometrial cancer.	Connor EV, Rose PG	Expert Rev Anticancer Ther	https://www.ncbi.nlm.nih.gov/pubmed/29972650
2	Recurrent cancer is associated with dissatisfaction with care-A longitudinal analysis among ovarian and endometrial cancer patients.	de Rooij BH et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29466257
3	Laparoscopic anterior pelvic exenteration with super radical parametrectomy for a recurrent low-grade endometrial sarcoma that is resistant to hormone therapy and chemotherapy.	Kanao H et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29621612
4	Efficacy of hyperthermic intraperitoneal chemotherapy and cytoreductive surgery in the treatment of recurrent uterine sarcoma.	Díaz-Montes TP et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29975291
5	Secondary debulking surgery for para-aortic nodal recurrence in endometrial cancer requiring circumferential resection of the inferior vena cava.	Kato K et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29395305

Medical treatment of recurrent endometrial cancer

Ewa Surynt

A search for medical treatment of recurrent endometrial cancer (EC) retrieved two articles.

Aghajanian et al. presented the results of the efficacy and tolerability of incorporating three novel agents (paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab) into initial therapy in advanced/recurrent endometrial cancer. In this randomised phase II trial, patients with chemotherapy-naïve recurrent (with or without measurable disease) endometrial cancer were randomly assigned to treatment in the following arms: with paclitaxel and carboplatin (PC) plus bevacizumab; PC plus temsirolimus; or ixabepilone and carboplatin (IC) plus bevacizumab. The primary endpoint was progression-free survival (PFS). Comparable patients on the PC arm of the GOG209 trial were used as historical controls. Secondary endpoints were response rate, overall survival (OS), and safety. Response rate and PFS were not significantly increased in any trial arm. OS was significantly increased in the PC plus bevacizumab arm when compared to historical controls treated with PC. The lack of contemporaneous control, the lack of improvement in response rate and PFS, and the imbalance of histotypes necessitate interpreting the OS results with caution.

Gockley et al. described a case report of a 42-year-old woman with a germline BRCA2 mutation and recurrent low-grade endometrioid endometrial adenocarcinoma who experienced clinical and radiographic response to the poly (ADP ribose) polymerase (PARP) inhibitor, olaparib.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer.	Aghajanian C et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29804638
2	Durable response in a woman with recurrent low-grade endometrioid endometrial cancer and a germline BRCA2 mutation treated with a PARP inhibitor.	Gockley AA et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29937315

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Uterine sarcoma

Marcin Bobiński

Treatment and follow-up

Two series reports regarding intraperitoneal chemotherapy in hyperthermia in uterine sarcomas were recently released. Díaz-Montes et al. presented the first report suggesting outcome benefits compared to conventional therapies (n=11) [2]. Sardi et al. published a safety analysis based on a series of seven patients [2]. Xia et al. revealed a novel treatment option: TP53 gene therapy followed by chemotherapy, after which they observed a promising response rate of over 90% [3]. The results of a phase I/II clinical trial with bevacizumab combined with chemotherapy and histone deacetylase inhibitor (VPA) among patients with advanced soft-tissue sarcoma were published by Monga et al. [4]. A retrospective analysis of the impact of oophorectomy on survival among patients suffering from low-grade endometrial stromal sarcoma was released by Stewart et al. The results suggested that oophorectomy prolongs overall survival but, taking into consideration the study limitations, prospective research in this field is indicated [5]. The results of a small series analysis including patients with recurrent uterine sarcomas treated with secondary cytoreductive surgery were presented by Nakamura et al. [6].

Diagnostic tools

Tsuyoshi et al. presented a review of biomarkers in uterine sarcomas; the authors based their review on recent genetic analysis [7]. Nishigaya et al. discussed the potential role of lactate dehydrogenase, D-dimer, and C-reactive protein serum levels in preoperative differentiation between leiomyosarcomas and atypical leiomyoma [8]. Insulin-like growth factor II messenger RNA-binding protein-3 (IMP3) was successfully investigated as a potential prognostic marker in uterine leiomyosarcoma by Yasutake et al. In the research based on a series of 60 cases, its expression was strongly related with poor prognosis [9].

Molecular and basic research

Investigation of the antitumour effects of the hexane fraction of adlay testa ethanolic extracts (ATE-Hex) on the human uterine sarcoma cancer cell line MES-SA and MES-SA/Dx was published by Chang et al. The results suggested that ATE-Hex can inhibit human uterine sarcoma cancer cells and the combination of ATE-Hex and doxorubicin could decrease multidrug resistance and increase the synergistic effect [10]. Przybyl et al. revealed a novel activation of multiple genes implicated in Wnt signalling in low-grade endometrial stromal, that, in the authors' judgment, may be useful for designing future targeted therapeutic options [11].

Varia

A large series of patients suffering from uterine sarcomas was analysed by Bretthauer et al. They compared the survival outcome of patients who underwent morcellation and those treated without using this tool; the 10-year survival rates were 32% vs. 57%, respectively. The data obtained underlined the impact of morcellation on survival among uterine sarcoma patients [12]. Rousseau et al. presented a detrimental review of recent literature regarding laparoscopic morcellation of myometrial lesions. They encouraged the use of in-bag-morcellation; furthermore they suggested the problem of the risk-to-benefit ratio between microinvasive surgery and laparotomy should also be discussed with the patient before the operation [13]. An interesting review of publications about uterine sarcomas published in 2017 was released by Gantzer et al. [14].

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No	Title	Authors	Journal	Link to abstract
1	Efficacy of hyperthermic intraperitoneal chemotherapy and cytoreductive surgery in the treatment of recurrent uterine sarcoma.	Díaz-Montes TP et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29975291
2	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in seven patients with peritoneal sarcomatosis from uterine sarcoma.	Sardi A et al.	Clin Case Rep.	https://www.ncbi.nlm.nih.gov/pubmed/29881584
3	Treatment of uterine sarcoma with rAd-p53 (gendicine) followed by chemotherapy: Clinical study of TP53 gene therapy.	Xia Y et al.	Hum Gene Ther.	https://www.ncbi.nlm.nih.gov/pubmed/29281902
4	A phase I/II study targeting angiogenesis using bevacizumab combined with chemotherapy and a histone deacetylase inhibitor (valproic acid) in advanced sarcomas.	Monga V et al.	Cancers (Basel).	https://www.ncbi.nlm.nih.gov/pubmed/29462961
5	Impact of oophorectomy and hormone suppression in low grade endometrial stromal sarcoma: A multicenter review.	Stewart LE et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29534832
6	Secondary cytoreductive surgery potentially improves the oncological outcomes of patients with recurrent uterine sarcomas.	Nakamura K et al.	Mol Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29556383
7	Molecular biomarkers for uterine leiomyosarcoma and endometrial stromal sarcoma.	Tsuyoshi H, Yoshida Y	Cancer Sci.	https://www.ncbi.nlm.nih.gov/pubmed/29660202
8	Diagnostic value of combination serum assay of lactate dehydrogenase, D-dimer, and C-reactive protein for uterine leiomyosarcoma.	Nishigaya Y et al.	J Obstet Gynaecol Res.	https://www.ncbi.nlm.nih.gov/pubmed/30152048
9	Insulin-like growth factor II messenger RNA-binding protein-3 is an independent prognostic factor in uterine leiomyosarcoma.	Yasutake N et al.	Histopathology.	https://www.ncbi.nlm.nih.gov/pubmed/29077232
10	Hexane fraction of adlay (Coix lachryma-jobi L.) testa ethanolic extract inhibits human uterine sarcoma cancer cells growth and chemosensitizes human uterine sarcoma cells to doxorubicin.	Chang CC et al.	Phytomedicine.	https://www.ncbi.nlm.nih.gov/pubmed/30166110

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Uterine sarcoma

Marcin Bobiński

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
11	Gene expression profiling of low-grade endometrial stromal sarcoma indicates fusion protein-mediated activation of the Wnt signaling pathway.	Przybyl J et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29544705
12	Uterine morcellation and survival in uterine sarcomas.	Bretthauer M et al.	Eur J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30025231
13	Can the risks associated with uterine sarcoma morcellation really be prevented? Overview of the role of uterine morcellation in 2018.	Rousseau M et al.	J Gynecol Obstet Hum Reprod.	https://www.ncbi.nlm.nih.gov/pubmed/29879489
14	Gynecological sarcomas: What's new in 2018, a brief review of published literature.	Gantzer J, Ray-Coquard I	Curr Opin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29846243

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

Zoia Razumova

Insulin-like growth factor-1 pathway

Yahya et al. investigated the role of insulin-like growth factor-1 receptor (IGF1R) targeting in endometrial cancer (EC). IGF1R-targeting with monoclonal antibodies and specific IGF1R tyrosine kinase inhibitors suppressed IGF-induced proliferation. Also, cixutumumab inhibited IGF1-mediated actions and cell signalling. IGF1R targeting jointly with immunotherapy may become a novel approach, the authors concluded [1].

Wnt signalling pathway

Henry et al. investigated the Wnt signalling pathway and the ROR receptors in EC. Immunohistochemistry for ROR1 and ROR2 was done in a group of patients. High ROR1 expression correlated with worse OS; ROR2 expression correlated with better OS [2]. Therefore, ROR1 may promote tumour progression, while ROR2 could act as a tumour suppressor. The study suggests those receptors as therapeutic targets in endometrioid EC.

POLE mutations

Van Gool et al. examined recurrence-free survival (RFS) of women with EC in the PORTEC-1 trial. Sensitivity to radiotherapy and chemotherapy was compared between POLE-mutant stem cells and wild-type cell lines. Women with POLE-mutant EC had an improved RFS. And, POLE-mutant cells had an increased sensitivity to cytarabine and fludarabine. The results support the review of current strategies of adjuvant therapy for early-stage POLE-mutant EC as well as the use of these compounds as a prospectively effective treatment in advanced-stage POLE-mutant EC [3].

PHLDA1 protein

Fearon AE et al. proved that pleckstrin homology-like domain-containing protein, family A, member 1 (PHLDA1) downregulation is important in drug resistance of receptor tyrosine kinase (RTK) - driven cancer. They found that downregulation of PHLDA1 supports an Akt-driven mechanism of compensation. Knockdown of PHLDA1 caused resistance to RTK inhibitors. Induction of PHLDA1 sensitised drug-resistant cancer cells to targeted therapy again. Therefore, PHLDA1 could be a biomarker for drug response [4].

Oxanthroquinone and RAS proteins

Tan et al. explored the mechanism of oxanthroquinone G01 (G01). It delocalised KRAS and HRAS from the plasma membrane and disrupted the spatial organisation of RAS proteins remaining on the membrane. G01 inhibited recycling of epidermal growth factor receptor and transferrin receptor and selectively inhibited the proliferation of KRAS-modified EC cells [5]. Hence, G01 could be a potential anti-RAS therapeutic.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	The role of the insulin-like growth factor 1 pathway in immune tumor microenvironment and its clinical ramifications in gynecologic malignancies.	Yahya MA et al.	Front Endocrinol (Lausanne)	https://www.ncbi.nlm.nih.gov/pubmed/29922232
2	ROR1 and ROR2 play distinct and opposing roles in endometrial cancer.	Henry CE et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29395309
3	Adjuvant treatment for POLE proofreading domain-mutant cancers: Sensitivity to radiotherapy, chemotherapy, and nucleoside analogues.	Van Gool IC et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29559562
4	PHLDA1 mediates drug resistance in receptor tyrosine kinase-driven cancer.	Fearon AE et al.	Cell Rep	https://www.ncbi.nlm.nih.gov/pubmed/29490281
5	An oxanthroquinone derivative that disrupts RAS plasma membrane localization inhibits cancer cell growth.	Tan L et al.	J Biol Chem	https://www.ncbi.nlm.nih.gov/pubmed/29970615

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Cervical pre-invasive disease

Geanina Dragnea

Screening

In a study of 2,376 women, cytology interpreted with prior knowledge of HPV status provides higher sensitivity for CIN 2+ lesions, compared with HP-status-blinded cytology (86.7% vs. 60.0%) [1].

HPV vaccination

A retrospective study evaluated the impact of a quadrivalent HPV vaccination program on HPV prevalence among women aged 18–35 in 2015 in Australia. This program targeting females aged 12–13 commenced in Australia in 2007, with catch-up vaccination of 14–26-year olds through 2009. For the 2015 sample, the Vaccination Register-confirmed three-dose coverage was 53.3% (65.0% and 40.3% aged 18–24 and 25–35, respectively). Prevalence of vaccine HPV types decreased from 22.7% (2005–2007) and 7.3% (2010–2012), to 1.5% (2015) ($p<0.001$) among women aged 18–24, and from 11.8% (2005–2007) to 1.1% (2015) ($p=0.001$) among those aged 25–35. This is the longest surveillance follow-up to date and shows the continued decline in the prevalence of vaccine-targeted HPV types. A substantial decrease also occurred in women aged 25–35, despite lower coverage. Strong herd protection and effectiveness of less than three vaccine doses likely contributed to these reductions [2].

A Cochrane review of 26 randomised controlled trials (73,428 participants) was performed to rate the certainty of evidence for vaccine protection against CIN2+, CIN3+, and AIS, and the associated harms. There is high-certainty evidence that HPV vaccines protect against CIN in adolescent girls and young women aged 15–26. The effect is higher for lesions associated with HPV16/18 than for lesions irrespective of HPV type. The effect is greater in those who are negative for hrHPV or HPV16/18 DNA at enrolment than those unselected for HPV DNA status. There is moderate-certainty evidence that HPV vaccines reduce CIN2+ in older women who are HPV16/18 negative, but not when they are unselected by HPV DNA status. There was no increased risk of serious adverse effects. Increased risk of adverse pregnancy outcomes after HPV vaccination cannot be excluded, although the risk of miscarriage and termination are similar between trial arms. The long-term of follow-up is needed to monitor the impact on cervical cancer, occurrence of rare harms, and pregnancy outcomes [3].

CIN2 evolution

A meta-analysis of 36 studies that included 3,160 women estimated the regression, persistence, and progression of untreated CIN2 lesions managed conservatively. At 24 months, the pooled rates were 50% for regression, 32% for persistence, and 18% for progression. In a subgroup analysis including 1,069 women aged less than 30 years, the rates were 60%, 23%, and 11%, respectively. Active surveillance is therefore justified, especially among young women who are likely to adhere to monitoring [4].

Residual/recurrent CIN

In a retrospective study, 4.7% (6/128) of 128 women with histologically verified CIN2+ who had a conisation developed recurrent disease during a three-year follow-up period. HPV tests at six months control post-conisation gave an NPV of 98.8% and can be used as a solitary test to identify women at risk for recurrent disease. Using both resection margins and an HPV test had a sensitivity of 100% and NPV 100%. Adding cytology did not increase the predictive value [5].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Influence of prior knowledge of human papillomavirus status on the performance of cytology screening.	Martins TR et al.	Am J Clin Pathol	https://www.ncbi.nlm.nih.gov/pubmed/29471316
2	Very low prevalence of vaccine human papillomavirus types among 18- to 35-year old Australian women 9 years following implementation of vaccination.	Machalek DA et al.	J Infect Dis	https://www.ncbi.nlm.nih.gov/pubmed/29425358
3	Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors.	Arbyn M et al.	Cochrane Database Syst Rev	https://www.ncbi.nlm.nih.gov/pubmed/29740819
4	Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis.	Tainio K et al.	BMJ	https://www.ncbi.nlm.nih.gov/pubmed/29487049
5	HPV-testing versus HPV-cytology co-testing to predict the outcome after conization.	Bruhn LV et al.	Acta Obstet Gynecol Scand	https://www.ncbi.nlm.nih.gov/pubmed/29430635

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Surgical treatment of primary and recurrent cervical cancer

Bojana Gutic and Matteo Morotti

A thorough overview of the current debate regarding the use of minimally invasive techniques in the treatment of early-stage cervical cancer is provided in the report by Mir Fuad Hasanov (See surgical management). Tseng et al. analysed 2,571 patients with cervical cancer FIGO stage IB1 who underwent less (LRS—conisation, trachelectomy, simple hysterectomy) and more radical surgery (MRS—modified radical, radical hysterectomy) between 1998 and 2012, inclusive. All patients had lymph node assessment. In all, 807 patients underwent LRS and 1,764 underwent MRS. They found that LRS compared to MRS does not compromise disease-specific survivals (DSS) (93.5% vs. 92.3) and LRS did not have a higher risk of death. There was no difference in 10-year DFS when stratified by tumour size ≤2 cm and >2 cm in two groups (LRS, MRS). Factors independently associated with increased risk of death included adenosquamous histology (HR 2.37), G3 disease (HR 2.86), tumours >2 cm (HR 1.82), and LN positivity (HR 2.42).

Yoshihara et al. compared oncologic outcomes of 38 cervical cancer patients stage IB1. Ten patients underwent abdominal radical trachelectomy (ART), six abdominal radical trachelectomy during pregnancy (ARTDP), and 22 radical hysterectomy (RH) in a four-year period. There was more blood loss and prolonged surgery in the ARTDP group compared with the RH group. The number of lymph nodes was also lower in the ARTDP group. However, there was no significant difference between the ARTDP and ART groups. There were no significant differences in progression-free and overall survival times among the three groups. There was no abortion nor recurrence observed in the ART-DP group. Although this analysis indicates that abdominal radical trachelectomy could be a treatment option for pregnant women with early-stage cervical cancer who strongly desire to keep a pregnancy, more cases and longer follow-up are needed to confirm it.

Pareja et al. reviewed 30 patients with simple 'cut through' hysterectomy, stage IA2 or IB1 tumours, squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma, with defined depth of tumour invasion, and tumour size less than 2 cm. After they were diagnosed with cervical cancer, they underwent radical parametrectomy with the upper third vaginal resection, parametrial tissue, and bilateral pelvic lymphadenectomy. Surgical approach was laparotomy in 20 patients (66.7%), robotic-assisted laparoscopy in 8 patients (26.7%), and laparoscopy in 2 patients (6.7%). The overall complication rate was 56.6% (17/30). No radical parametrectomy specimen had residual tumour, involvement of the parametrium, vaginal tissue, or lymph node metastasis regardless of tumour size. Median follow-up was 99 months (range; 7–160) and there was one recurrence, diagnosed 14 months after surgery. This patient had no residual disease in parametrectomy specimen, 13 negative lymph nodes, and negative LVI. After a pelvic exenteration, this patient was reported free of disease during four years of follow-up. Pareja et al. concluded that pelvic lymphadenectomy is sufficient for patients with free margins, tumour diameter <2 cm, and depth of invasion <10 mm.

Minig et al. evaluated the incidence of lymph node involvement in low-risk cervical cancer, including 271 cervical cancer patients with stage IA2 (8.1%) and IB1 (91.9%). They concluded that patients with negative LVSI and stage IA2 (any grade and histology) or G1 cervical cancer <2 cm (stage IB1) had no lymph node metastasis and may not need lymphadenectomy. BMI was an independent risk factor of lymph node metastasis. The mechanism could be a high expression of insulin-like growth factor 1 receptor with increased BMI. Due to this study risk for leaving microscopic metastatic nodes could potentially occur in 4.3% of G2 and G3 disease, but almost 95% of patients would undergo unnecessary lymphadenectomy.

A retrospective study from Tomita et al. showed that more extensive lymphadenectomy significantly improves the outcome of patients with positive pelvic lymph node even if it is followed by adjuvant radiotherapy. More extensive lymphadenectomy was defined as greater than 40 dissected pelvic lymph nodes (DPLN). DFS was significantly higher in the group with more than 40 DPLN (86% vs. 74%), while overall survival (OS) was similar.

Wei et al. analysed circulating tumour cells (CTCs) of cytokeratin 19 (CK19), cytokeratin 20 (CK20), and a squamous cell carcinoma antigen (SCC-Ag) mRNA of patients who had radical hysterectomy by laparotomy or laparoscopy. There were 78 patients with cervical cancer stage IA2–IIA1 and two control groups: a positive control group with 34 patients with fibroids, and a negative control group composed of 32 healthy subjects. CK 19, CK 20, and SCC-Ag were measured before surgery and 24h and 30 days after surgery. The experimental group had significantly higher levels than controls before surgery. In the experimental group, there was a significant increase of CTCs 24 hours after surgery and no significant difference between the laparotomy and laparoscopy groups. Thirty days after surgery, values had returned to baseline before surgery or lower, and again, with no significant differences between the laparotomy and laparoscopy groups. During the follow-up, two patients recurred. Both had positive CTCs 30 days after surgery. One of those was in the laparotomy group and had a supraclavicular lymph node metastasis at 10 months after surgery. The other was in the laparoscopy group with local recurrence at 15 months postoperatively. CTC´s could be new biomarkers for the detection of micrometastasis.

Kwon et al. analysed 249 patients with early-stage cervical cancer and found no significant difference in DFS between patients with no lymph node metastasis (pN0) and those with 1–3 metastatic lymph nodes (mPLN). They found a significant influence of mPLN>3 on DFS. Two other variables, non-squamous cell carcinoma (non-SqCC) histology and LVSI also affected DFS. Using those three variables, they developed a prognostic nomogram for DFS to estimate individual prognosis, with the largest impact of non-SqCC.

Shimamoto et al. retrospectively analysed 959 patients with stage IB–IV cervical cancer treated between 1997 and 2014. Age groups were <65 years and ≥65 years. Even though overall survival was statistically shorter in elderly patients, disease-specific survival was not significantly different. They concluded that age was not an independent prognostic factor and that treatment modality should be chosen due to the patient's general condition and medical history.

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Surgical treatment of primary and recurrent cervical cancer

Bojana Gutic and Matteo Morotti

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Less versus more radical surgery in stage IB1 cervical cancer: A population--based study of long-term survival.	Tseng JH et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29776598
2	The safety and effectiveness of abdominal radical trachelectomy for early-stage cervical cancer during pregnancy.	Yoshihara K et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29498982
3	Radical parametrectomy after 'cut-through' hysterectomy in low-risk early-stage cervical cancer: Time to consider this procedure obsolete.	Pareja R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29482838
4	Incidence of lymph node metastases in women with low-risk early cervical cancer (<2 cm) without lymph-vascular invasion.	Minig L et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29538254
5	Role of extensive lymphadenectomy in early-stage cervical cancer patients with radical hysterectomy followed by adjuvant radiotherapy.	Tomita N et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29727352
6	Laparoscopic surgery for early cervical squamous cell carcinoma and its effect on the micrometastasis of cancer cells.	Wei XQ et al.	Medicine	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6112876/
7	The prognostic impact of the number of metastatic lymph nodes and a new prognostic scoring system for recurrence in early-stage cervical cancer with high risk factors: A multicenter cohort study (KROG 15-04).	Kwon J et al.	Cancer Res Treat	https://www.ncbi.nlm.nih.gov/pubmed/29081219
8	A study of treatments and outcomes in elderly women with cervical cancer.	Shimamoto K et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/29960201

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Medical treatment of primary and recurrent cervical cancer

Kristina Lindemann

Survey of current practice

Along with the publication of treatment guidelines for cervical cancer, ESGO conducted an online survey on current disease management [1]. There were striking differences in practice. The degree of radicality in very early stage disease, where patients with stages T1a1, LVSI-positive and T1a2 LVSI-negative have approximately 50% chance of receiving parametrectomy and LN dissection are especially alarming. Also, management of stage IB2 varied, with still 41% of the respondents favouring surgery and 14% NACT followed by surgery. According to ESGO/ESTRO/ESP guidelines, concomitant chemoradiation should be the preferred treatment, especially with adequate brachytherapy in place. The survey was limited by the low response rates and selection bias.

Treatment of locally advanced disease

The variety in treatment practice was also illustrated by several papers on the treatment of locally advanced disease. Lorusso et al. published their results of a retrospective study on patients with stage IIA to IIIA disease [2]. After surgery including LAD (pelvic and para-aortic), patients were treated with chemoradiation. Patients with positive lymph nodes further received four cycles of carboplatin/paclitaxel. Matoda et al. presented a multicentre phase II trial of stage IB–IIA squamous cervical cancer treated with chemotherapy only after surgery for node-positive disease [3]. The study suggests that chemotherapy only may be an option for patients with only a few involved lymph nodes, but the small sample size (n=62) and the single-arm design are limitations of this study. Ferrandina et al. reported on a phase II study on NACT, followed by radical surgery and chemoradiation for patients with stage IB2–IVA disease [4]. The heterogeneity in patient population and follow-up make a direct comparison to studies utilising chemoradiation difficult. Trimodality treatment produces encouraging response rates, but these may not translate into better survival. Seventy percent of the patients had postoperative complications, all of them G1 and 2.

A retrospective Italian study reported on 82 patients with locally advanced adenocarcinoma of the cervix treated with various regimen of NACT before radical hysterectomy [5]. More than half of the patients further needed (chemo-)radiation. Response was associated with better survival, but only 12% of the patients showed complete or optimal partial pathological response (with <3 mm stromal invasion). The variety of chemotherapy regimen and the lack of a control group do not allow definite conclusions regarding the role of NACT in these patients.

Oncology Grand Rounds in the *Journal of Clinical Oncology* dealt with the question of which patients may benefit from NACT and discussed critically why current studies have so far failed to show a benefit in survival after NACT [6]. They suggested a treatment algorithm for patients who are candidates for NACT and concluded that there may be a role for NACT before surgery, especially in regions with limited external-beam RT and/or brachytherapy capabilities.

Treatment of advanced/recurrent disease

A randomised phase III study reported on 375 patients with recurrent, persistent or stage IVB disease. Patients were treated with cisplatin -/+ S1 (oral fluoropyrimidine-based anticancer agent) [6]. The significant increase in median PFs by 2.4 months did not lead to an OS benefit, and patients experienced more toxicity with the combination. The role of S1 in an era when combination treatment has become standard treatment for these patients remained uncertain.

Review

Two reviews reported on the changing landscape of treatment of cervical cancer. Leath and Monk summarised the past and ongoing design and findings of GOG studies in patients with cervical cancer [8]. Minion and Tewari focussed on the recent introduction of immune-oncology in the treatment of these patients [9].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	ESGO survey on current practice in the management of cervical cancer.	Dostalek L et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29958236
2	Locally advanced cervical cancer: Is a trimodality treatment a safe and effective approach?	Lorusso D et al.	Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29920481
3	Postoperative chemotherapy for node-positive cervical cancer: Results of a multicenter phase II trial (JGOG1067).	Matoda M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29661497
4	Neo-adjuvant platinum-based chemotherapy followed by chemoradiation and radical surgery in locally advanced cervical cancer (Lacc) patients: A phase II study.	Ferrandina G. et al.	Eur J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29753611
5	Neoadjuvant platinum-based chemotherapy followed by radical hysterectomy for stage Ib2-IIb adenocarcinoma of the uterine cervix - An Italian multicenter retrospective study.	Gadducci A et al.	Anticancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/29848719
6	Which patients with cervical squamous cell carcinoma might benefit from neoadjuvant chemotherapy?	Mahmoud O, Einstein MH	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29668367
7	Phase III study of cisplatin with or without S-1 in patients with stage IVB, recurrent, or persistent cervical cancer.	Aoki Y et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30072745
8	Twenty-first century cervical cancer management: A historical perspective of the gynecologic oncology group/NRG oncology over the past twenty years.	Leath CA and Monk BJ	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29954593
9	Cervical cancer - State of the science: From angiogenesis blockade to checkpoint inhibition.	Minion LE and Tewari KS	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29666026

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Radiotherapy in management of recurrent cervical cancer

Erbil Karaman

Umezawa et al. investigated the efficacy and safety of image-guided high-dose rate (HDR) interstitial brachytherapy (ISBT) for re-irradiation of locally recurrent uterine cervical cancer [1]. The authors included 18 patients in the analysis with a median follow-up of 18.1 months. All patients received re-irradiation using HDR-ISBT for local gross recurrence of uterine cervical cancer after definitive or post-operative radiotherapy. The prescription doses per fraction spanned 2.5–6.0 Gy, while the cumulative EQD2 ranged between 48.6–82.5 Gy. A tumour response was obtained in all patients, with radiological and pathological complete remission seen in 12 (66.7%) patients. The 2-year LC, progression-free survival, and overall survival rates for all patients were 51.3%, 20.0%, and 60.8%, respectively. Haemoglobin level and maximum tumour diameter were found to be prognostic factors for LC. Late ≥ grade 2 adverse events were observed in five patients (27.8%). The authors concluded that image-guided HDR-ISBT for re-irradiation of locally recurrent uterine cervical cancer may play an important role for local tumour control in a subgroup of patients.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Image-guided interstitial high-dose-rate brachytherapy for locally recurrent uterine cervical cancer: A single-institution study.	Umezawa R et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/29275869

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

Marcin Mardas

Tang et al. investigated the effects of rucaparib on the proliferation of cervical cancer cells and sensitivity to radiotherapy [1]. They used the Hela and Siha cells. Animal experiments were also performed. Rucaparib suppressed proliferation, induced G2/M phase arrest, and reduced the expression of cyclin D1 and CDK4 in cervical cancer cells. When rucaparib was combined with radiotherapy in cervical cancer cells, clone formation decreased significantly, and G2/M phase arrest was accentuated. The expression of the DNA-damage marker γ-H2AX was increased significantly, and rucaparib suppressed tumour growth in vivo.

Qiu et al. investigated apatinib—a novel tyrosine kinase inhibitor that targets VEGFR2 signal and exhibits potent anti-tumour effects in human cancers [2]. Both the immortalised cell lines and primary cultured tissues were used to investigate the synergy between apatinib and chemotherapeutic drugs. The in vivo effects of apatinib were validated in a nude mouse model. Compared to normal cervix tissue, VEGFR2 protein was significantly upregulated in cervical cancer tissues ($p<0.001$). Upregulation was positively correlated with advanced tumour stage, lymph node metastasis, and a poor prognosis. In vitro, apatinib markedly induced apoptosis and G1-phase arrest, suppressed cell growth, and decreased colony formation ability. Further, the authors proved that apatinib significantly increased the sensitivity to paclitaxel in cervical cancer cells and the mouse model.

Meng et al. studied PD-L1, PD-1, CD8, and HPV expression in cervical cancer and normal cervix by immunohistochemical staining [3]. PD-L1, PD-1, and CD8 were more frequently expressed in cervical cancer tissues compared to normal tissues, especially those strongly stained with HPV. Additionally, PD-L1, PD-1, and CD8 were more frequently stained in tissues from advanced tumours and tumours with lymphoid nodes or vascular space invasion, respectively. Tissues from patients after chemotherapy showed over-expression of PD-L1 in tumour cells and more PD-1 and CD8 in stromal mononuclear cells, which were identified as tumour-infiltrated lymphocytes (TILs).

Zhao et al. investigate the cytotoxic effect and potential molecular mechanisms of vosaroxin— a quinolone-derivative anticancer agent with inhibitory activity on type II DNA topoisomerases (TOP2) in HeLa cells [4]. Vosaroxin decreased cell viability and increased lactate dehydrogenase (LDH) release in a dose- and time-dependent manner in HeLa cells, but not in normal cervical epithelial cells. Vosaroxin also induced apoptosis and increased caspase-3 activity in HeLa cells. Vosaroxin inhibited the synthesis of HIF-1α protein and interfered with the dimerisation of HIF-1α and aryl hydrocarbon receptor nuclear translocator (ARNT). More importantly, vosaroxin-induced inhibition on HIF-1α and its cytotoxic effects, as measured by cell viability, LDH release and apoptosis, were partially prevented by Sirt3 knockdown or the AMP-activated protein kinase (AMPK) inhibitor compound C.

Bognar et al. studied the effect of desethylamiodarone (DEA) on HeLa cells [5]. They showed that DEA significantly inhibited the proliferation and viability of HeLa cells and induced apoptosis in vitro in dose-dependent and also in a cell cycle-dependent manner because DEA induced G0/G1 phase arrest in the HeLa cell line. They report that DEA treatment downregulated the expression of phospho-Akt and phospho-Bad. In addition, DEA could downregulate expression of Bcl-2, upregulate Bax, and induce cytochrome c release.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	The poly (ADP-ribose) polymerase inhibitor rucaparib suppresses proliferation and serves as an effective radiosensitizer in cervical cancer.	Tang M et al.	Invest New Drugs.	https://www.ncbi.nlm.nih.gov/pubmed/29872938
2	Apatinib, a novel tyrosine kinase inhibitor, suppresses tumor growth in cervical cancer and synergizes with Paclitaxel.	Qiu H et al.	Cell Cycle.	https://www.ncbi.nlm.nih.gov/pubmed/29886786
3	PD-L1 expression correlates with tumor infiltrating lymphocytes and response to neoadjuvant chemotherapy in cervical cancer.	Meng Y et al.	J Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/30123362
4	Vosaroxin induces mitochondrial dysfunction and apoptosis in cervical cancer HeLa cells: Involvement of AMPK/Sirt3/HIF-1 pathway.	Zhao XL, Yu CZ	Chem Biol Interact.	https://www.ncbi.nlm.nih.gov/pubmed/29800573
5	Amiodarone's major metabolite, desethylamiodarone, induces apoptosis in human cervical cancer cells.	Bognar Z et al.	Can J Physiol Pharmacol.	https://www.ncbi.nlm.nih.gov/pubmed/29847733

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

Kamil Zalewski

Location and prognosis of HPV-related and non-HPV-related vulvar squamous cell carcinomas (SCCs)

Hinten et al., based on a retrospective cohort of 318 patients, investigated the predilection site of HPV-related compared to non-HPV-related SCC as well as assessed the disease-specific survival (DSS), disease-free survival (DFS) and overall survival (OS) in patients with HPV-related and non-HPV related vulvar SCC [1]. HPV-related disease was defined as either >25% p16INK4a expression and HPV positivity or >25% p16INK4a expression and high-grade squamous intraepithelial lesion (HSIL) next to the tumour without HPV positivity. The authors showed that there are two distinctly different pathways in vulvar SCC with significantly different survival rates and localisations. HPV-related vulvar SCCs were more often located on the perineum, and patients with HPV-related vulvar SCC have a better prognosis. Both the perineal localisation and the HPV infection seems to be the explanation for a more favourable prognosis.

Contribution of mTOR protein to vulvar cancer progression

Zięba et al. aimed to identify pathogenic mutations implicated in the two pathways of VSCC development in high-risk HPV-positive (hrHPV (+)) and high-risk HPV-negative (hrHPV(–)) VSCC tumours using the next-generation sequencing method (NGS) [2]. Based on 81 fresh frozen VSCC tumour samples, including 52 containing hrHPV DNA and 29 HPV-independent, genetic changes (pathogenic mutations and polymorphisms) were identified in 19 out of the 50 genes examined. Similar rates of pathogenic mutations were detected in hrHPV(+) VSCC tumours and the hrHPV independent tumours (65% and 59%). Mutations of TP53 (46% and 41%, of hrHPV(+) and hrHPV(–) cases respectively) and CDKN2A (p16) (25% and 21%, of hrHPV(+) and hrHPV(–) cases respectively) were the most common genetic alterations identified in VSCC tumours. Further mutations were identified in PIK3CA, FBXW7, HRAS, FGFR3, STK11, AKT1, SMAD4, FLT3, JAK3, GNAQ, and PTEN, albeit at low frequencies. Some of the identified mutations may activate the PI3K/AKT/mTOR pathway; thus, authors concluded that these data provide a rationale for new anti-VSCC therapies targeting the PI3K/AKT/mTOR pathway.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Vulvar cancer: Two pathways with different localization and prognosis.	Hinten F et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29555332
2	Somatic mutation profiling of vulvar cancer: Exploring therapeutic targets.	Zięba S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29980281

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

Kamil Zalewski

Since the last LiFE report, three studies focused on diagnosis and treatment of vulvar intraepithelial neoplasia (VIN) have been published.

Diagnosis

Current evidence supports a dichotomous classification of high- and low-grade squamous intraepithelial lesions (HSIL and LSIL), which subsumes the older three-tiered system (intraepithelial neoplasia grade 1, 2, and 3: –IN1, –IN2, –IN3), correlating with the presence of dysplasia in the bottom third only, extending into the middle third, or extending into the top third of the epithelium. In 2012, the "Lower Anogenital Squamous Terminology (LAST)" recommendations called for "recommended" use of ancillary p16 IHC when a diagnosis of –IN2 is being considered, based on the rationale that –IN2 diagnoses have poor reproducibility, and that the use of p16 IHC has been shown to reduce interobserver variability. In their study, Sun et al. tested the utility of routine IHC in supporting morphologic diagnoses of –IN2 in a practice employing consensus review by specialist gynaecologic pathologists. They showed that that diagnoses of –IN2 can be made reliably on squamous specimens of the lower female genital tract using H&E alone in many cases, at least in practice settings where subspecialty expertise is available. The authors also identified a group of patients for whom a diagnosis of –IN2 was made after an initial differential of –IN2/3; 100% of these cases were p16 positive and this is a population for which ruling out a lower diagnosis is not medically necessary and p16 can be spared. The authors concluded that the LAST recommendation to use p16 IHC to support all diagnoses of -IN2 might result in performing the immunostain in many circumstances where it is not medically necessary [1].

In their multicentre retrospective case series, Sopracordevole et al. evaluated the colposcopic patterns observed in women with a histopathological diagnosis of vaginal intraepithelial neoplasia (ValN). The abnormal colposcopic and vascular patterns were more commonly found in women with ValN3 rather than with ValN1 or ValN2, whereas the micropapillary pattern should be considered an expression of a less severe disease (ValN1 and ValN2) [2].

Treatment

Bogani et al. investigated the long-term effectiveness of carbon dioxide laser treatment for histological-proven high-grade vaginal intraepithelial neoplasia between (HG-ValN) 1998 and 2015. The authors observed that patients affected by HG-ValN are at high risk of recurrence; but the risk of developing invasive genital cancer is quite low (about 3–4%). The type of surgical approach (ablative vs. excisional) does not influence risk of recurrence, and the only factor that independently correlates with recurrence was HPV persistence after treatment.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	p16 Immunohistochemistry is not always required for accurate diagnosis of grade 2 squamous intraepithelial lesions.	Sun L et al.	J Low Genit Tract Dis	https://www.ncbi.nlm.nih.gov/pubmed/29570565
2	Colposcopic patterns of vaginal intraepithelial neoplasia: a study from the Italian Society of Colposcopy and Cervico-Vaginal Pathology.	Sopracordevole F et al.	Eur J Cancer Prev	https://www.ncbi.nlm.nih.gov/pubmed/27428398
3	LASER treatment for women with high-grade vaginal intraepithelial neoplasia: A propensity-matched analysis on the efficacy of ablative versus excisional procedures.	Bogani G et al.	Lasers Surg Med	https://www.ncbi.nlm.nih.gov/pubmed/29756652

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Primary vulvar cancer treatment

Rubén M. Betoret

Adjuvant therapies

Inguinal lymph node involvement is considered the most important prognostic risk factor for survival in vulvar squamous cell cancer (VSCC). Rydzewski et al. highlighted the importance of adding chemotherapy to external beam radiotherapy (EBRT) in patients with two or more positive nodes, finding an incremental improvement of survival for this group (hazard ratio (HR)=0.79, p=0.022) in a cohort of 2,779 patients, whereas no benefit in women with just one positive node was shown (HR=0.93, p=0.605) [1]. van der Velden and Fons in their letter to the editor criticised the conclusions made by Rydzewski et al. that "all patients with node positive disease benefited from adjuvant radiotherapy". They underlined that, although the authors included a large number of patients, significant flaws in the study were the lack of details about clinical (no information about whether the nodes were clinically suspect), surgical (no information if lymphadenectomy was deep or superficial) and pathological variables (lack of information about the status of the capsule in the tumour-positive lymph node) in the group of patients with a single positive lymph node [2]. Another series by Xanthopoulos et al. on 694 node positive patients, treated with or without adjuvant radiotherapy, obtained an overall cause-specific survival benefit in the group with adjuvant radiation (p<0.02), including those with one positive node, thus encouraging health providers to perform EBRT on all node-positive patients [3].

Surgical management

Micheletti et al. published a retrospective study on 114 patients with early-stage (IB/II) VSCC, on the impact of surgical margins, stating a significantly reduced long-term survival in the subgroup with less than 5 mm tumour-free margin, and recommending further surgical or adjuvant treatment in these patients [4]. Opposed to this "metrical approach" was an original work by Höckel et al., based on their own previously published ontogenetic anatomic theories, proposing that locoregional spread of VSCC occurs within tissue domains previously defined by stepwise embryonic and foetal development. They proposed that clinical translation of these principles could improve outcomes of surgical treatment and published their series of 97 consecutive patients treated with vulvar field resection and inguinopelvic node dissection, without adjuvant radiotherapy, with three-year recurrence-free survival of 85.1% (95% CI: 76.9–93.3) [5]. An interesting triple flap technique for vulvar reconstruction was depicted by Mercut et al. on patients undergoing large local vulvar excisions for VSCC. It is feasible, does not require changing the position of the patient after resection, and avoids the need for delicate perforator dissection, with minimal donor site morbidity [6].

Complications

Use of hyperbaric oxygen therapy as adjuvant for treating wound complications proved effective in a subset of 16 patients: included in the retrospective study by Lopes et al., infection control and satisfactory healing were achieved using 10 to 61 daily 90-minute sessions at 2.2 atmospheres absolute pressure, with partial oxygen pressure of 1672 mbar [7].

Research

Perrone et al. reported on neoadjuvant treatment with electrochemotherapy in nine patients treated for primary VSCC, confirming tumour response according to RECIST criteria in 77.8%, thus leading to more conservative surgical approach in 66.7% of their patients [8].

Finally, an original communication by Hiratsuka et al. about boron neutron capture therapy (BNCT) in one case of vulvar melanoma and three cases of genital extramammary Paget´s disease, with complete local tumour control and avoidance of surgical treatment. BNCT is based on a nuclear reaction between the non-radioactive isotope boron-10 (introduced in tumoural cells via para-boronophenylalanine) and low-energy thermal neutrons, resulting in the production of alfa particles with high linear energy transfer and very short path lengths, which selectively kill these malignant cells, sparing the surrounding tissues [9].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Role of adjuvant external beam radiotherapy and chemotherapy in one versus two or more node-positive vulvar cancer: A National Cancer Database study.	Rydzewski NR et al.	Radiother Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29631932
2	In response to Rydzewski NR et al. "Role of adjuvant external beam radiotherapy and chemotherapy in one versus two or more node-positive vulvar cancer: A National Cancer Database study".	van der Velden J, Fons G	Radiother Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/30241790
3	Survival benefit of adjuvant radiation therapy in node-positive vulvar cancer.	Xanthopoulos EP et al.	Am J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30134287
4	Prognostic impact of reduced tumor-free margin distance on long-term survival in FIGO stage IB/II vulvar squamous cell carcinoma.	Micheletti L et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/30022627
5	Vulvar field resection based on ontogenetic cancer field theory for surgical treatment of vulvar carcinoma: a single-centre, single-group, prospective trial.	Höckel M et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29530664
6	Triple flap technique for vulvar reconstruction.	Mercut R et al.	Ann Chir Plast Esthet	https://www.ncbi.nlm.nih.gov/pubmed/29650262
7	Hyperbaric oxygen therapy as adjuvant for treating wound complications after extensive resection for vulvar malignancy.	Lopes A et al.	Undersea Hyperb Med.	https://www.ncbi.nlm.nih.gov/pubmed/29571229
8	Electrochemotherapy pre-treatment in primary squamous vulvar cancer. Our preliminary experience.	Perrone AM et al.	J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29878356
9	Boron neutron capture therapy for vulvar melanoma and genital extramammary Paget´s disease with curative responses.	Hiratsuka J et al.	Cancer Commun	https://www.ncbi.nlm.nih.gov/pubmed/29914570

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Vulvovaginal adenocarcinoma/melanoma/sarcoma

Anna Dückelmann

In a letter to the editor of the *NEJM*, Huo et al. presented the data of the follow-up of 695 patients with clear-cell adenocarcinoma of the vagina and cervix. The 5-year probability of survival differed between the patients with prenatal diethylstilbestrol (DES) exposure (86.1%) and patients without documentation of DES exposure (81.2%), but the 20-year probability of survival was similar between the two groups. This differential effect of DES according to time suggested, according to the authors, that clear-cell adenocarcinoma associated with DES exposure and idiopathic clear-cell adenocarcinoma may have different tumour biologic features. Idiopathic clear-cell adenocarcinoma may be more likely to progress quickly or recur earlier, whereas clear-cell adenocarcinoma associated with DES exposure may be more likely to recur later.

Hiratsuka et al. described four patients with genital malignancies (one vulvar melanoma and three extramammary Paget's disease (EMPD)) who were treated with boron neutron capture therapy (BNCT) as an alternative treatment because the patients had refused wide surgical excision. BNCT is a promising treatment modality which resulted in complete local tumour control in all four patients.

Another interesting case report described a new treatment option in primary malignant melanoma. Inoue et al. reported a clinical response achieved by itraconazole treatment in primary malignant melanoma of the vagina evaluated by PET-CT. The biopsied specimens were analysed by cDNA microarray, providing information on changes in gene expression in response to itraconazole treatment.

Nitecki et al. presented a retrospective case series to evaluate patients with pathologically confirmed vulvar EMPD (extramammary Paget disease of the vulva). The authors proposed an algorithm for treatment of EMPD which reserves radical surgery for invasive disease and focusses on symptom management after thoroughly excluding malignancy.

Yamada et al. reported the seventh published case of neovaginal adenocarcinoma involving the colon, which was constructed 53 years ago for congenital vaginal agenesis. The tumour was immunohistochemically negative for p16. Although rare, clinicians should be aware of cancer arising in the ectopic intestine when anastomosed with other organs, given the persistent risk of malignant transformation.

Wong et al. described a spectrum of vaginal glandular lesions exhibiting gastric differentiation, ranging from benign and atypical adenosis to adenocarcinoma. The five vaginal adenocarcinomas exhibited morphologic features identical to gastric-type adenocarcinoma of the cervix; the six cases of pure vaginal adenosis all contained gastric-type mucinous glands. The authors proposed that gastric-type adenocarcinoma be recognised as a distinct histologic subtype of vaginal adenocarcinoma, and they suggested that gastric-type adenocarcinoma may arise from vaginal adenosis.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Follow-up of patients with clear-cell adenocarcinoma of the vagina and cervix.	Huo D et al.	NEJM	https://www.ncbi.nlm.nih.gov/pubmed/29719188
2	Boron neutron capture therapy for vulvar melanoma and genital extramammary Paget's disease with curative responses.	Hiratsuka J et al.	Cancer Commun	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6006671/
3	Itraconazole treatment of primary malignant melanoma of the vagina evaluated using positron emission tomography and tissue cDNA microarray: a case report.	Inoue K et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987480/
4	Extramammary Paget disease of the vulva.	Nitecki R et al.	IJGC	https://www.ncbi.nlm.nih.gov/pubmed/29324542
5	Adenocarcinoma arising in sigmoid colon neovagina 53 years after construction.	Yamada K et al.	World Journal of Surgical Oncology	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5924482/
6	Primary vaginal gastric-type adenocarcinoma and vaginal adenosis exhibiting gastric differentiation.	Wong R W-C et al.	Am J Surg Pathol	https://www.ncbi.nlm.nih.gov/pubmed/29664741

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Treatment of vaginal cancer

Elis Ismail

Guerri al. focussed on the role of definitive radiotherapy (RT) in the management of vaginal cancer (VC) and presented comprehensive data on clinical outcomes and toxicity. The majority of the patients were treated with a combination of external beam RT and brachytherapy (74.2%). Acute and late grade ≥3 toxicity rates ranged from 0.0% to 24.4% (median, 8.7%) and from 0.0% to 22.5% (median, 12.8%), respectively. The 5-year local control rates ranged between 39% and 79%. The 5-year overall survival ranged between 34% and 71.0% (median, 63.5%). Early disease stage, small tumour size, previous hysterectomy, high pre-treatment/treatment haemoglobin levels, and patients' age were correlated with a better clinical outcome. The authors concluded that a brachytherapy boost should be delivered, especially in patients with higher-stage disease, concurrent weekly cisplatin should be considered in most patients, and transfusion should be used to maintain high haemoglobin levels [1]. Brachytherapy is integral to VC treatment and is typically delivered using an intracavitary single-channel vaginal cylinder (SCVC) or an interstitial brachytherapy (ISBT) applicator. Multi-channel vaginal cylinder (MCVC) applicators allow for improved organ-at-risk (OAR) sparing compared to SCVC while maintaining target coverage. Gebhardt et al. presented clinical outcomes of 60 patients with VC (27% primary vaginal and 73% recurrence from other primaries) who were treated with image-based high-dose rate brachytherapy (HDR BT) using a MCVC. Clinical outcomes of patients with VC and recurrent disease treated definitively in a systematic manner with combination EBRT with image-guided HDR BT utilising a MCVC applicator demonstrate high rates of local control and low rates of severe morbidity. The MCVC technique allows interstitial implantation to be avoided in selected patients with ≤7 mm residual disease thickness following EBRT while maintaining excellent clinical outcomes with extended 4-year follow-up in this rare malignancy [2].

Yuan et al. described the presentation, diagnosis, treatment, and outcomes of 16 children diagnosed below 3 years of age with vaginal yolk sac tumours (YSTs). All patients were treated with bleomycin, etoposide, and cisplatin (PEB) combination chemotherapy alone. Complete remission (CR) was defined by a normal serum α-fetoprotein (AFP) level, no tumour detected on computed tomography, and negative pathology results. Biochemical CR (bCR) was defined by a normal serum AFP level. The results showed that the median age of the patients at diagnosis was 10 months (range, 5–44 months), and all patients presented with abnormal vaginal bleeding and/or vaginal discharge. Serum αAFP is a sensitive tumour marker, and it was markedly elevated in all patients (median 4848 ng/mL). Thirteen patients completed a chemotherapy regimen consisting of PEB alone without surgery. Importantly, all patients achieved CR. Patients received additional cycles of consolidation chemotherapy after bCR, and there were no cases of recurrence [3].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Definitive radiotherapy in invasive vaginal carcinoma: A systematic review.	Guerri S et al.	Oncologist	https://www.ncbi.nlm.nih.gov/pubmed/30139838
2	Image-based multichannel vaginal cylinder brachytherapy for the definitive treatment of gynecologic malignancies in the vagina.	Gebhardt BJ et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/29929925
3	Vaginal yolk sac tumors: Our experiences and results.	Yuan Z et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/29538246

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Sentinel node mapping in gynaecological malignancies

Anton Ilin

The feasibility of SLN procedure in patients with high-grade endometrial cancer seems to be one of the most debated questions recently.

In a retrospective study, Buda et al. determined the impact of the sentinel lymph node mapping algorithm (SLN-A) on staging in high-risk endometrial cancer (EC) compared to SLN plus selective lymphadenectomy (S-LND). In all, 171 patients were divided into two groups: sentinel lymph node mapping and SLN plus selective lymphadenectomy. The five-year comparison did not show a significant difference in disease-free survival (DFS) [HR: 0.82; 95% CI: 0.53–1.28; p=0.390] [1].

Papadia et al. evaluated sensitivity, negative predictive value (NPV) and the false-negative (FN) rate of near-infrared (NIR) indocyanine green (ICG) sentinel lymph node (SLN) mapping in patients with poorly differentiated endometrial cancer who have undergone full pelvic and para-aortic lymphadenectomy after SLN mapping. Forty-two patients were included. The FN rate, sensitivity, and NPV were 10, 90, and 97.1%, respectively. For the SLN mapping algorithm, FN rate, sensitivity, and NPV were 0, 100, and 100%, respectively [2].

Neither the SENTI-ENDO nor the FIRES trial, which are among the largest prospective trials on this topic, focussed entirely on the high-risk population; their conclusions are generalised to all histologies. Obviously, further prospective studies are required.

Obtaining correct results depends totally on the "quality" of SLN procedure, the surgeon's experience, and patient factors. Even small deviations can cause false findings. Body et al. evaluated the factors associated with poor mapping or false negative data. FIGO stage III or IV was the only factor which significantly correlated with failure of bilateral detection (p<0.01). Failed dye migration occurred in 36% of failed mapping instances. It is usually a consequence of technical problems with the cervical injection such as spillage, injection too lateral or in the cervical os, presence of nabothian cysts, bulky cervix or tiny atrophic cervix, bleeding, distorted cervical anatomy, and inexperience. Diffuse smearing precluding accurate identification of an SLN and leading to failed mapping occurred in four hemipelvis. In general, this phenomenon is due to either too much dye injected, dye injected too deeply or more frequently, or it is due to excessive manipulation or dissection of the retroperitoneal space while looking for the SLN. The phenomenon of "swollen" lymphatics or an "empty specimen" when no nodal tissue found on final pathology was the main reason for detection failure and occurred in 40%. One possible explanation for this phenomenon is that since ICG is albumin-bound, it possibly draws more interstitial fluid into the lymphatic channels (oncotic pressure), causing the lymphatics to appear "swollen", look bigger and be easily mistaken for a lymph node. The authors suggested several ways to help when distinguishing swollen lymphatics from lymph nodes. First, be aware of the phenomenon and vigilant. Second, look carefully at the "shape" of the colored specimen. If it is too linear, it is probably lymphatics, as lymph nodes have a "rounder" shape; however, they are not easy to differentiate. Looking at the SPY mode (black and white) and the CSF mode (Color Segmented Fluorescence) is helpful. These modes can be activated on the camera head, and one can switch easily back and forth from the different modes. Third, if still uncertain, ex vivo examination and palpation of the specimen can also help distinguish lymphatic vessels from lymph nodes. Fourth, the specimen can be sent for frozen section [3].

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Lymph node evaluation in high-risk early stage endometrial cancer: A multi--institutionalretrospective analysis comparing the sentinel lymph node (SLN) algorithm and SLN with selectivelymphadenectomy.	Buda A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29887483
2	Retrospective validation of the laparoscopic ICG SLN mapping in patients with grade 3 endometrial cancer.	Papadia A et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29691646
3	Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cance.	Body N et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29909967

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Minimal invasive surgery in gynaecological cancer

Mir Fuad Hasanov

Editorial comment: The LACC trial is published in NEJM, Oct 31 2018. We also recommend the commentaries by Kimmig et al. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5981116/) and Leitao MM (https://www.ncbi.nlm.nih.gov/pubmed/30095706)

Cervical cancer

Undoubtedly, the most important data in the field of minimal invasive surgery in gynaecological cancer is not published yet: the prospective randomised, international, multicentre phase III LACC Trial. It is, however, available as an abstract and was already presented at the SGO Annual Meeting 2018. The study investigated whether disease-free survival (DFS) among patients with cervical cancer (stage IA1 to IB1) who underwent laparoscopic or robotic (MIS) was non-inferior compared to standard-of-care open (TARH) radical hysterectomy.

Randomisation was 1:1. In all, 312 patients were randomised to TARH; 319 patients to MIS (83% laparoscopy and 16% robotic surgery). At the time of analysis, the information available at 4.5 years was 60%, with over 80% power for the primary endpoint and median follow-up of 2.5 years. The non-inferiority boundary of −7.2% for DFS at 4.5 years was breached (TARH 97% vs. MIS 86%, difference −10.6%, 95% C: −16.4% to −4.7%, p = 0.87). MIS was found to have over a three-fold increase in DFS events (7/312 vs. 27/319, HR = 3.74, 95% CI: 1.63–8.58, p = 0.002), which was consistent when adjusted for age, BMI, stage of disease, LVSI, lymph node involvement, and ECOG status. MIS was also associated with a decrease in overall survival (3/312 vs. 19/319, HR = 6.00, 95% CI: 1.48–20.3, p = 0.004). There were no differences in rates of intraoperative complications by treatment received (11% in both, p = 0.76).On the other hand, laparoscopic or robotic radical hysterectomy was associated with higher recurrence rates and worse overall survival when compared with the open approach in women with early-stage cervical cancer [1].

In another viewpoint, colleagues from Italy published a multi-institution retrospective comparison study of different surgical approaches for stage IB1 cervical cancer patients. Between January 2001 and December 2016, 341patients were included: 101 patients were submitted to abdominal radical hysterectomy (ARH), 152 to laparoscopic radical hysterectomy, and 88 to robotic radical hysterectomy. In 97% and 11.5% of cases, bilateral pelvic and aortic lymph node dissections were performed, respectively. Clinical characteristics were similar in the three groups. Compared with ARH, the minimally invasive surgery group was safer in terms of estimated blood loss, transfusion rates, and hospital stay. Above all, robotic surgery was equivalent to laparoscopy in terms of intraoperative and postoperative complications, hospital stay, conversions, and reintervention. On the other hand, robotic surgery had better outcomes compared with laparoscopy in terms of transfusion rates.

The median follow-up was 82.1 months in the abdominal group A (range 3–179 months), 41.7 months in the laparoscopic group B (range 2–162 months), and 46.6 months in the robotic group C (range 2–79.6 months). The recurrence rates were 8.7%, 12.7%, and 10.4% in groups A, B, and C, respectively. The estimated 5-year recurrence-free survival (RFS) rates were 91.3%, 87.2%, and 89.5% in groups A, B, and C, respectively, whereas the estimated 5-year OS rates for groups A, B, and C were 88.7%, 89.7%, and 88.8%, respectively. The Kaplan-Meier curves were statistically significant in RFS between groups A and MIS, whereas there were no significant differences in OS between the three groups (p=0.03 and p=0.69, respectively), even if some of the patients were lost to follow-up, particularly in group A (20.8%), unfortunately.

The authors postulate that minimally invasive surgery (laparoscopy or robotics) was as adequate and effective as abdominal surgery in terms of surgical and oncological outcomes in the surgical treatment of EEC FIGO stage IB1 [2].

Relating to the LACC Trial, there is a debate about possible tumour spillage following laparoscopic radical hysterectomy. Boyraz et al. demonstrated an original method of vaginal closure to prevent tumour spillage in a 40-year-old woman with clinical stage 1B1 cervical squamous cell carcinoma. In this method, after completion of the radical hysterectomy steps, the initial 5-mm left lower-quadrant trocar was changed to a 15-mm trocar to allow for the placement of an EndoGIA with a green cartridge. The uterine manipulator was removed, and the uterus was elevated with a myoma screw. Then, the stapler was placed and fired twice to close the vagina. The upper part of the vaginal cuff was excised and sent to pathology as a surgical margin, and the uterus was removed through the vagina. Finally, the vaginal cuff was closed with intracorporeal suturing [3].

Endometrial cancer

Laparoscopic sentinel lymph node mapping is already widespread. In a meta-analysis made by physicians from Shihezi University (China), the overall detection rate of sentinel lymph node mapping was 96% (95% CI: 95–98) in 389 patients across 8 studies. Also, 366 patients were included in bilateral sentinel node, with a detection rate of 73% (95% CI: 69–77). The sensitivity of the overall detection rate of sentinel lymph node mapping was 96.3% with a sensitivity of 73.1% for bilateral sentinel node detection rate. This data confirms that laparoscopy sentinel lymph node localisation is feasible and accurately predicts lymph node status in patients with EC [4].

Due to better survival curves of patients with endometrial cancer, quality of life (QOL) and sexual health outcomes become more and more the object of various studies. A prospective cohort study from Canada showed that minimally invasive approaches result in improved QOL beyond the short-term postoperative period, with benefits noted up to 12 weeks after surgery. This prolonged QOL advantage provides further evidence that MIS should be the standard surgical approach for women with early-stage endometrial cancer [5].

Ovarian cancer

The role of laparoscopy in ovarian cancer treatment is ambiguous. Interesting recent results include those of a systematic review and meta-analysis of minimally invasive interval cytoreductive surgery in ovarian cancer. There were six studies (three prospective, three retrospective) that met the criteria for meta-analysis with a total of 3,231 patients; 567 were in the minimally invasive group and 2,664 in the laparotomy group. Both groups were similar in the distribution of stage and serous histology. Complete cytoreductive surgery was achieved in 74.5% (95% CI: 40.41–97.65%) and 53.1% (95% CI: 4.88–97.75%) of patients in the minimally invasive and laparotomy groups, respectively. There was no statistically significant difference between these two pooled proportions (p=0.52). Three studies compared minimally invasive surgery to laparotomy. No significant difference was observed between the two groups in obtaining complete cytoreduction [OR=0.90 (95% CI: 0.70–1.16; p=0.43)]. The pooled proportion for grade >2 postoperative complications was not significant among the laparoscopy group [3.11% (95% CI: 0.00–10.24%; p = 0.15)]. The authors concluded that complete cytoreductive surgery appears feasible and safe with minimally invasive surgery in selected advanced ovarian cancer patients after neoadjuvant chemotherapy [6].

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Minimal invasive surgery in gynaecological cancer

Mir Fuad Hasanov

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No	Title	Authors	Journal	Link to abstract
1	Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer	Ramirez PT et al.	NEJM	https://www.nejm.org/doi/full/10.1056/NEJMoa1806395
2	Comparison of different surgical approaches for stage IB1 cervical cancer patients: a multi-institution study and a review of the literature.	Corrado G et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29727351
3	Vaginal closure with EndoGIA to prevent tumor spillage in laparoscopic radical hysterectomy for cervical cancer.	Boyraz G et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/30064005
4	Meta-analysis of laparoscopy sentinel lymph node mapping in endometrial cancer.	Wang L et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/30008031
5	Prospective cohort study comparing quality of life and sexual health outcomes between women undergoing robotic, laparoscopic and open surgery for endometrial cancer.	Ferguson SE et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29681461
6	Minimally invasive interval cytoreductive surgery in ovarian cancer: systematic review and meta-analysis.	Cardenas-Goicoechea J et al.	J Robot Surg	https://www.ncbi.nlm.nih.gov/pubmed/29992404

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Prevention and management of complications in the surgical treatment of gynaecological malignancies (i.e., lymphocele, urological, wound, etc.) including technical aspects/tricks of surgery in the management of gynaecological malignancies

Martina Borghese

Prevention and management of complications in the surgical treatment of gynaecological malignancies

Clark et al. pubished a review documenting 30-day readmission rates for ovarian cancer patients ranging from 2.5–19.3%. NACT with interval cytoreductive surgery was associated with lower readmission rates than after primary debulking surgery. The most frequent adverse events for readmission were small bowel obstruction, wound-related complications, and thromboembolic events. Predictors of readmission were comorbidities, re-operation, and major complications after hospital discharge. Strict follow-up may be effective in decreasing re-admission rates [1]. In their case-control study, Ross at el. characterised some pre- and intraoperative characteristics of 324 patients (i.e., FIGO stage, ascites, age, CA125, bowel resection) that could predict unplanned postoperative ICU admission, which was proved to be associated with many postoperative complications and significant decrease in OS (27.3 vs. 57.9 months; p<0.001) [2]. Bergstrom et al. reported the first results one year after ERAS protocol implementation, showing that, despite substantial reduction in narcotics and PCA, the 109 inaugural ERAS patients reported less pain by POD 3 than historical patients, with no differences in length of stay (5 days), complication rates (13.8% vs. 20.3%; p=0.17) or 30-day readmission rate (9.5 vs. 11.9%, p=0.54) [3]. Li et al. conducted a retrospective observational analysis to review the incidence and latency of urological complications in 614 cervical cancer patients (ureteral obstruction, radiocystitis, and vescicovaginal fistula), reporting acceptable rates of complications (3.26%) with no statistical difference in the risk for patients treated with RAH alone or RAH followed by radiotherapy; the onset of such complications can be relatively late so lifetime follow-up is crucial [4]. Okadome et al. analysed long-term renal function changes in 380 women who underwent RAH with/without pelvic RT and/or platinum-based chemotherapy by calculating eGFR: they demonstrated that post-treatment eGFR for women who underwent surgery alone was higher than for those who underwent RAH and radio/chemotherapy (85.0 mL/min/m² vs. 78 mL/min/m²; p<0.01), with eGFR starting to decline at early stage after postoperative chemotherapy and progressing over time. They also investigated serious urological complications (i.e., rupture of the urinary bladder) which were found to be rare (0.6%) but life-threatening [5].

Technical aspects/tricks of surgery in management of gynaecological malignancies

Lago et al. conducted a prospective, observational pilot study, including 26 patients, to propose ghost ileostomy as a safe option to reduce the number of ileostomies in ovarian cancer patients. Ghost ileostomy presents the advantages of diverting ileostomy while avoiding its drawbacks and without increasing the morbimortality or costs of the surgery; it needs a precise, scheduled follow-up (postoperative rectoscopy, CT scan, and blood tests) to create an ileostomy if anastomotic leakage is suspected [6]. In their review comprising 10 RCT, Xu et al. analysed the effect of chewing gum on postoperative gastrointestinal function in women undergoing gynaecological surgery, finding that chewing gum can significantly shorten the period to first aerofluxus, first intestinal sounds, first defecation, and duration of hospitalisation. It also reduces complications—nausea (OR 0.45; 95% CI: 0.29–0.69), vomiting (OR 0.38; 95% CI: 0.22–0.68), and postoperative ileus (OR 0.25; 95% CI: 0.14–0.44) by activating the cephalon-vagal pathway that releases GI hormones [7]. Bruce et al. conducted a cohort study showing that implementation of an abdominal closure bundle (preoperative antibiotic administration, bowel preparation, chlorhexidine body cleansing, changing of gloves, and new sterile instruments for closure) was not associated with a significant reduction in overall SSI rate (10.2% vs. 7.9%; p=0.148), but that multiple subpopulations with advanced gynaecological cancer (FIGO stage III or IV and intraoperative ascites) could benefit from this intervention [8]. A randomised control, open-label trial by Indirayani et al. in 109 participants reported that sodium pentosan polysulfate 50 mg subcutaneous was associated with increased risk of minor bleeding than subcutaneous enoxaparin 40 mg once daily, without sufficient data to conclude its efficacy as a thromboprophylactic agent in gynaecological surgery [9]. Kondrup et al. presented two alternative products for wound closure (Dermabond Prineo Skin Closure System and Stratafix Symmetric PDS Plus Knotless Tissue Control Device) [10].

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No	Title	Authors	Journal	Link to abstract
1	Thirty-day unplanned hospital readmission in ovarian cancer patients undergoing primary or interval cytoreductive surgery: systematic literature review.	Clark RM et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29929923
2	Unplanned postoperative intensive care unit admission for ovarian cancer cytoreduction is associated with significant decrease in overall survival.	Ross MS et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29929924
3	Narcotics reduction, quality and safety in gynecologic oncology surgery in the first year of enhanced recovery after surgery protocol implementation.	Bergstrom JE et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29661495
4	Urological complications after radical hysterectomy with postoperative radiotherapy and radiotherapy alone for cervical cancer.	Li F et al.	Medicine	https://www.ncbi.nlm.nih.gov/pubmed/29595646
5	Renal function and urological complications after radical hysterectomy with postoperative radiotherapy and platinum-based chemotherapy for cervical cancer.	Okadome M et al.	Japanese Journal of Clinical Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29136246

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Prevention and management of complications in the surgical treatment of gynaecological malignancies (i.e., lymphocele, urological, wound, etc.) including technical aspects/tricks of surgery in the management of gynaecological malignancies

Martina Borghese

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No	Title	Authors	Journal	Link to abstract
6	Ghost ileostomy in advanced ovarian cancer: A reliable option.	Lago V et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29923854
7	Effect of chewing gum on gastrointestinal function after gynecological surgery: A systematic literature review and meta-analysis.	Xu C et al.	J. Obstet. Gynaecol. Res.	https://www.ncbi.nlm.nih.gov/pubmed/29442412
8	Implementation of an abdominal closure bundle to reduce surgical site infection in patients on a gynecologic oncology service undergoing exploratory laparotomy.	Bruce SF et al.	Gynecologic Oncology	https://www.ncbi.nlm.nih.gov/pubmed/29548786
9	Sodium pentosan polysulfate efficacy as thromboprophylaxis agent in high-risk women following gynecological surgery.	Indirayani I et al.	J. Obstet. Gynaecol. Res.	https://www.ncbi.nlm.nih.gov/pubmed/29845672
10	Closing the gap: novel abdominal wound closure techniques.	Kondrup JD et al.	Surg Technol int	https://www.ncbi.nlm.nih.gov/pubmed/29791700

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Cancer in pregnancy

Michael J. Halaska

During this period a number of important reports have been published.

Several case reports on breast, pancreatic, renal carcinoma, and pheochromocytoma have been reported.

For preinvasive lesions, colposcopy was found to have a concordance in about 68%. Ciavattini et al. showed better precision before the 20th week of pregnancy [1].

Salvo et al. reported on five cases of cervical cancer in pregnancy treated by lymphadenectomy and simple trachelectomy. The median tumour size was 27 mm, blood loss 100 mL and surgical time 193 minutes. No complications were reported with median gestational age at delivery at 39 weeks [2].

Contrary to this report, Yoshihara et al. presented six cases of cervical cancer operated by lymphadenectomy and radical abdominal trachelectomy. All tumours were smaller than 20 mm, median blood loss was 1250 mL, and operating time 387 min. Median gestational age at delivery was 33 weeks, but no other complications were reported. These results seemed far worse than the simple trachelectomy set of patients [3].

Han et al. collected data from 145 patients undergoing surgery for breast cancer. SLNM was unsuccessful only in 0.7%. Positive SLN were found in 29.7%, showing that SLNM is feasible during pregnancy [4].

Whole-body diffusion-weighted MRI was evaluated by Han et al. in a separate paper, for nodal and distal metastasis detection. Sensitivity and specificity were close to 100% for nodal involvement while sensitivity for distant metastasis differed between the two readers in the study (66.7 vs 100%). It showed that it is an excellent diagnostic tool for primary diagnostic work-up [5].

Kocian et al. collected data on 27 colorectal carcinomas from an INCIP registry. In 73%, an advanced stage disease was found. Twenty-one patients underwent surgery and 12 patients chemotherapy. Two-year survival was 64%, similar to non-pregnant patients [6].

Boucek et al. evaluated 35 cases of thyroid carcinoma treated during pregnancy. In all, 83% of patients underwent surgery during pregnancy without negative impact on the foetus, supporting active management during pregnancy due to the potential negative effect of thyroid cancer on the foetus [7].

de Haan et al. reported data from the INCIP registry on descriptive characteristics of 1,170 patients diagnosed with cancer during pregnancy. Throughout the following period, there was a clear increase in chemotherapeutic treatment. Platinum-based chemotherapy was associated with small for gestational age diagnosis (OR 2,37), while taxanes were related to NICU admission [8].

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No	Title	Authors	Journal	Link to abstract
1	Reliability of colposcopy during pregnancy.	Ciavattini A et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/30118992
2	Simple trachelectomy with pelvic lymphadenectomy as a viable treatment option in pregnant patients with stage IB1 (≥2 cm) cervical cancer: Bridging the gap to fetal viability.	Salvo G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29804639
3	The safety and effectiveness of abdominal radical trachelectomy for early-stage cervical cancer during pregnancy.	Yoshihara K et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29498982
4	Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy.	Han SN et al.	Breast Cancer Res Treat	https://www.ncbi.nlm.nih.gov/pubmed/29235045
5	Feasibility of whole-body diffusion-weighted MRI for detection of primary tumour, nodal and distant metastases in women with cancer during pregnancy: a pilot study.	Han SN et al.	Eur Radiol	https://www.ncbi.nlm.nih.gov/pubmed/29218610
6	Management and outcome of colorectal cancer during pregnancy: report of 41 cases.	Kocian P et al.	Acta Chir Belg	https://www.ncbi.nlm.nih.gov/pubmed/30010511
7	Maternal and obstetrical outcome in 35 cases of well-differentiated thyroid carcinoma during pregnancy.	Boucek J et al.	Laryngoscope	https://www.ncbi.nlm.nih.gov/pubmed/28988434
8	Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients.	de Haan J et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29395867

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Immunotherapy in gynaecological cancers

Zoltan Novak

Clinical trials

A phase I trial of a modified Vaccinia Ankara vaccine delivering wild-type human p53 (p53MVA) in combination with gemcitabine chemotherapy was conducted in patients with platinum-resistant ovarian cancer. Toxicity, immune response, and clinical outcome were evaluated. Tumour shrinkage or disease stabilisation occurred in four patients; immunologic response was seen in five patients. The authors concluded that p53-reactive T cell expansion was associated with significantly longer PFS [1]. A research group in the US team developed a personalised vaccine generated by autologous dendritic cells pulsed with oxidised autologous whole-tumour cell lysate injected intranodally in platinum-treated recurrent ovarian cancer patients. It was administered alone, in combination with bevacizumab, or bevacizumab plus low-dose intravenous cyclophosphamide until disease progression. In all, 30 patients were recruited, and a total of 392 vaccine doses were administered without serious adverse events. Vaccination induced durable T cell responses to autologous tumour antigen, which were associated with significantly prolonged survival. Vaccination even primed T cells against previously unrecognised neoepitopes, indicating the need for further clinical testing [2]. A randomised phase Ib study investigated the role of combining vaccination with folate binding protein-derived peptide vaccine and vaccination with its attenuated version in patients with breast or ovarian cancer who were disease-free after standard therapy. Immune analysis suggests incorporating the attenuated version of the peptide improves immune responses, while the safety profile of the combined vaccination was the same [3]. Another randomised phase I clinical trial tested the safety and immunogenicity of the folate receptor alpha vaccine, enrolling patients with ovarian cancer or breast cancer who completed conventional treatment with complete remission. Vaccination was well tolerated in all patients and elicited an immune response in more than 90% of patients. The median time to maximal immunity was five months, and the response persisted for at least 12 months [4]. A retrospective study was performed in Taiwan about the results of their immunochemotherapeutic technique. A combination of picibanil and interleukin-2 with platinum- and taxol-based chemotherapy was compared to controls treated with chemotherapy alone. The recurrence rate between the immunochemotherapy and traditional chemotherapy groups showed a significant difference (53.8% vs. 88%; p=0.0128). The diagnosis-to-recurrence duration was longer in the IMCT than in the traditional chemotherapy groups (33.21 vs. 25.63 months), although no statistical significance was found (p=0.4668) [5]. A phase II study incorporating 109 patients investigated the safety and efficacy of axalimogene filolisbac, a Listeria monocytogenes immunotherapy administered with or without cisplatin, in patients with recurrent/refractory cervical cancer following prior chemotherapy or radiotherapy. Median progression-free survival was six months, and the overall response rate was 17%. Adverse events were predominantly mild. The authors concluded that the encouraging 12-month 34.9% combined OS rate warrants further investigation of this treatment [6].

Case reports

A retrospective case series reported six BRCA carriers who received the immune checkpoint inhibitor nivolumab monotherapy for recurrent BRCA-mutated epithelial ovarian cancer. All six patients received salvage therapy prior to nivolumab therapy (median 3 lines), including PARP inhibitors, and the majority were platinum resistant. Median follow-up time was 13.4 months, and there were three complete responses, one partial response, and two patients with progressive disease. The objective response rate was 67%. This study suggests that nivolumab monotherapy is well-tolerated and may be an effective salvage therapy for BRCA mutation carriers with recurrent epithelial ovarian cancer [7]. Li et al. reported the case of a patient with platinum-refractory advanced ovarian adenosquamous carcinoma who received poly adenosine diphosphate ribose polymerase and programmed death-1 inhibitors after failure of prior multiple chemotherapies and antiangiogenic agents. The targeted therapy and immunotherapy stabilised the diseases; the patient has survived longer than 15 months and she is taking nivolumab as maintenance treatment [8]. Another paper reported the case of a patient with recurrent uterine serous carcinoma. It described a 74-year-old woman who experienced a dramatic response to sacituzumab govitecan, a novel antibody-drug conjugate targeting human trophoblast-cell-surface antigen, after failing multiple chemotherapy and immunotherapy attempts. They observed a 66% reduction of target lesions with a duration response of over 10 months [9].

Miscellaneous

An interesting paper helps the reader gain a better understanding of adverse events in patients with ovarian cancer on checkpoint inhibitor therapy. The authors describe three hypothetical case vignettes of patients with gynaecologic cancer on checkpoint inhibitor immunotherapy and discuss common immune-related adverse events [10]. In addition, the tenth Breast, Gynaecological and Immunotherapy International Cancer Conference was held in January 2018, in Cairo, Egypt. This paper reviewed the interesting papers presented during the meeting [11]. Furthermore, de Felice et al. provided a comprehensive update on the role of checkpoint inhibitor therapy in cervical cancer patients [12].

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Immunotherapy in gynaecological cancers

Zoltan Novak

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	p53-reactive t cells are associated with clinical benefit in patients with platinum-resistant epithelial ovarian cancer after treatment with a p53 vaccine and gemcitabine chemotherapy.	Hardwick NR et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29301826
2	Personalized cancer vaccine effectively mobilizes antitumor T cell immunity in ovarian cancer	Tanyi JL et al.	Sci Transl Med	https://www.ncbi.nlm.nih.gov/pubmed/29643231
3	Phase Ib trial of folate binding protein (FBP)-derived peptide vaccines, E39 and an attenuated version, E39': An analysis of safety and immune response.	Vreeland TJ et al.	Clin Immunol	https://www.ncbi.nlm.nih.gov/pubmed/29574039
4	Folate receptor alpha peptide vaccine generates immunity in breast and ovarian cancer patients.	Kalli KR et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/29545464
5	Combined immunotherapy (OK-432, IL-2) with chemotherapy decrease the recurrence rate in advanced ovarian cancer	Wang YL et al.	Reprod Sci	https://www.ncbi.nlm.nih.gov/pubmed/29658435
6	A randomized phase 2 study of ADXS11-001 listeria monocytogenes-listeriolysin o immunotherapy with or without cisplatin in treatment of advanced cervical cancer.	Basu P et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29538258
7	Nivolumab use for BRCA gene mutation carriers with recurrent epithelial ovarian cancer: A case series.	Matsuo K et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/29998185
8	Targeted therapy and immunotherapy for platinum-refractory advanced ovarian adenosquamous carcinoma: a case report.	Li A et al.	Onco Targets Ther	https://www.ncbi.nlm.nih.gov/pubmed/29983579
9	Sacituzumab Govitecan (IMMU-132) in treatment-resistant uterine serous carcinoma: A case report.	Han C et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/29977989
10	Diagnosis and management of immune checkpoint inhibitor-related toxicities in ovarian cancer: A series of case vignettes.	Johnson C, Jazaeri AA	Clin Ther	https://www.ncbi.nlm.nih.gov/pubmed/29519715
11	Highlights from the 10th Breast, Gynaecological and Immunotherapy International Cancer Conference (BGICC), 18-19 January 2018, Cairo, Egypt.	El-Ghazaly H et al.	Ecancermedicalscience	https://www.ncbi.nlm.nih.gov/pubmed/29662533
12	Immune check-point in cervical cancer.	De Felice F et al.	Crit Rev Oncol Hematol	https://www.ncbi.nlm.nih.gov/pubmed/30097236

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Imaging in gynaecological malignancies

Tanja Nikolova and Natasha Nikolova

Endometrial cancer

Bonatti et al. reported that deep myometrial invasion at MRI in endometrial cancer (EC) cases was significantly more frequent in G2–G3 lesions than in G1 ones ($p<0.005$). Neoplasm/uterus volume ratio was significantly higher for high-grade neoplasms. A cut-off of 0.13 enabled G1 to be distinguished from G2–G3 lesions with 50% sensitivity and 89% specificity [1].

Cervical Cancer

According to Chen et al., gross tumour volume and the maximum diameter of resectable cervical cancer (CC) at MRI could demonstrate capability in predicting lymph node metastasis and lymphovascular space invasion and were more accurate than FIGO stage [2].

He et al. have developed a predictive model for parametrial involvement in stages IB1 to IIA2 of CC, based on preoperative MRI. The 5-year progression-free survival rate was significantly higher (96.7%) in low-risk patients than in high-risk (90.8%, $p=0.004$) [3].

Ovarian Cancer

Pozzati et al. described clinical and ultrasound characteristics of confirmed pure clear cell carcinoma of the ovary, using IOTA terminology.

The median patient age was 53.5 years. Tumours were FIGO stage I, and 84.2% were unilateral. All tumours contained solid components. The largest diameter was 117 mm. Papillary projections were present in 38.2% of masses and were vascularised in 91.1%. Endometriosis was noted in 41.5%. Ground glass echogenicity of cyst fluid was more common in clear cell cancers arising in endometriosis than in the others [4].

Sadowski et al. found that the presence of an avascular nodular component in an US-detected indeterminate adnexal cyst was a significant predictor of malignancy at stepwise logistic regression analysis ($p\leq0.0001$) [5].

Llueca et al. established a predictive model for suboptimal cytoreductive surgery (SCS) (residual tumour of >1 cm) using preoperative and intraoperative determination of the peritoneal carcinomatosis index (PCI). Preoperative CT and laparoscopy, when both predicted SCS, was associated with the lowest risk of false positives for SCS when detecting a PCI of >20 and can help to determine whether the patients are suitable for primary debulking surgery or neoadjuvant chemotherapy [6].

From the IOTA database, Moro et al. have described that ovarian pure endometrioid carcinoma are large, unilateral, multilocular-solid or solid. Endometrioid carcinomas arising in endometriosis differ, more often being unilateral cysts with papillary projections, and without ascites [7].

Makvandi et al. found a positive correlation between a novel PET standard uptake values and fluorescent immunohistochemistry for PARP-1 ($r2=0.60$) and confirmed the translational potential of a PARP-1 PET imaging agent [8].

Han et al. confirmed that patients with 18F-FDG PET-derived high metabolic tumour volume and total lesion glycolysis have a higher risk of disease progression or death [9].

Breast Cancer

Cheon et al. found that peritumoural oedema in invasive breast cancer cases identified at preoperative MRI is independently associated with disease recurrence [10].

Brück et al. concluded that preoperative MRI in newly diagnosed unifocal stage I invasive ductal carcinoma could be beneficial. In 28% of cases, MRI detected an additional finding and 50% of these were malignant [11].

Song et al. confirmed that supplemental breast US screening increases early-stage second breast cancers with specificity 91.2% and PPV3 22.6% in women with a personal history of breast cancer [12].

Leiomyosarcoma

Ando et al. found that intratumoural hyperintense area on T1 HIA within leiomyoma showed more homogeneity, better demarcation, a smaller occupying rate, and higher signal intensity than within leiomyosarcoma [13].

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No	Title	Authors	Journal	Link to abstract
1	Prediction of histological grade of endometrial cancer by means of MRI.	Bonatti M et al.	Eur J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/29803384
2	Tumor size at magnetic resonance imaging association with lymph node metastasis and lymphovascular space invasion in resectable cervical cancer: A multicenter evaluation of surgical specimens.	Chen XL et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30044321
3	Assessment of parametrial involvement in early stages cervical cancer with preoperative magnetic resonance imaging.	He F et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30153214
4	Imaging in gynecological disease: clinical and ultrasound characteristics of ovarian clear cell carcinoma.	Pozzati F et al.	Ultrasound Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29978567
5	Indeterminate adnexal cysts at US: Prevalence and characteristics of ovarian cancer.	Sadowski EA et al.	Radiology	https://www.ncbi.nlm.nih.gov/pubmed/29480762
6	Prediction of suboptimal cytoreductive surgery in patients with advanced ovarian cancer based on preoperative and intraoperative determination of the peritoneal carcinomatosis index.	Llueca A et al.	World J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29471831

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Imaging in gynaecological malignancies

Tanja Nikolova and Natasha Nikolova

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No	Title	Authors	Journal	Link to abstract
7	Imaging in gynecological disease: clinical and ultrasound characteristics of endometrioid ovarian cancer.	Moro F et al.	Ultrasound Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29418038
8	A PET imaging agent for evaluating PARP-1 expression in ovarian cancer.	Makvandi M et al.	J Clin Invest	https://www.ncbi.nlm.nih.gov/pubmed/29509546
9	Prognostic value of volume-based metabolic parameters of 18F-FDG PET/CT in ovarian cancer: a systematic review and meta-analysis.	Han S et al.	Ann Nucl Med	https://www.ncbi.nlm.nih.gov/pubmed/30101392
10	Invasive breast cancer: Prognostic value of peritumoral edema identified at preoperative MR imaging.	Cheon H et al.	Radiology	https://www.ncbi.nlm.nih.gov/pubmed/29315062
11	Preoperative magnetic resonance imaging in patients with stage I invasive ductal breast cancer: A prospective randomized study.	Brück N et al.	Scand J Surg	https://www.ncbi.nlm.nih.gov/pubmed/28401771
12	Diagnostic performances of supplemental breast ultrasound screening in women with personal history of breast cancer.	Song SE et al.	Acta Radiol	https://www.ncbi.nlm.nih.gov/pubmed/28786298
13	Uterine smooth muscle tumours with hyperintense area on T1 weighted images: differentiation between leiomyosarcomas and leiomyomas.	Ando T et al.	Br J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/29308922

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Treatment of elderly patients with gynaecological cancers

Alex Mutombo

Gynaecological cancers are frequently associated with patients' characteristics. Uterine serous carcinoma is closely associated with advanced age [1]. The incidence of endometrial cancer is increasing due to an aging world population and obesity. Patients with obesity and advanced age are often subject to physician bias regarding surgical choices and assumptions regarding long-term outcomes. Therefore, careful orchestration pre-, intra- and postoperatively is key to successful outcomes in their treatment [2].

In this scope, Ahmed et al. have reported on NRG CC-002, a prospective cooperative group study aiming at the evaluation whether a pre-operative GA-GYN score derived from a predictive model utilising components of an abbreviated geriatric assessment (GA) was associated with major post-operative complications in elderly women undergoing primary open cytoreductive surgery. This score was not predictive of major postoperative complications in elderly patients but rather in a subgroup of patients with advanced malignant disease [3].

In a study on the management of elderly women with cervical cancer, Eggemann et al. found that elderly women aged 61 years and older were undertreated in comparison with their younger counterparts and this was likely because the therapy which was indicated was not administered [4].

In the Netherlands, Schuurman et al. found large treatment differences between younger and elderly patients with epithelial ovarian cancer. More elderly patients were treated with neoadjuvant chemotherapy while fewer patients underwent surgery and simultaneously postoperative mortality decreased. However, the large and increasing number of elderly patients without treatment and the large survival gap warranted further improvements in the care for elderly EOC patients [5]. Meyer et al. also found neoadjuvant chemotherapy to be associated with decreased perioperative morbidity in patients with ovarian cancer [6].

Gallotta et al. conducted a study on the feasibility, safety, and short-term outcomes of robotic surgery for gynaecological oncologic indications in elderly patients, especially women aged 65 to 74 compared with women age >/=75. They arrived at the conclusion that no patient could be considered too old for a minimally invasive robotic approach, but a multidisciplinary approach was the best management pathway [7].

Hami et al. studied the impact of age on the prognosis of vulvar cancer. Three hundred patients were divided into groups aged below or above 50 years. The disease-free survival (DFS) was calculated, and a multivariate discriminant analysis was conducted. The nodal status was the predominant prognostic factor for the DFS regardless of age. In node-free patients, the risk for recurrence was lower for patients older than 50 years [8].

Finally, Ore et al. assessed disparities associated with ovarian cancer treatment in the state of Kentucky and central Appalachia in the United States; they noticed when the treatment of ovarian cancer did not follow NCCN recommendations, patients had a significantly higher risk of death. Women were less likely to receive NCCN-compliant care if they were younger (20–49 years), had early-stage disease, did not have private insurance, or had care provided at a nontertiary care hospital [9].

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No	Title	Authors	Journal	Link to abstract
1	Aging and uterine serous carcinoma.	Hachisuga T et al.	Histol Histopathol	https://www.ncbi.nlm.nih.gov/pubmed/29565096
2	Defining and mitigating the challenges of an older and obese population in minimally invasive gynecologic cancer surgery.	Hagemann AR et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29329881
3	Pre-operative assessment and post-operative outcomes of elderly women with gynecologic cancers, primary analysis of NRG CC-002: An NRG oncology group/gynecologic oncology group study.	Ahmed A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29807694
4	Management of elderly women with cervical cancer.	Eggemann H et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29500704
5	Treatment and outcome of elderly patients with advanced stage ovarian cancer: A nationwide analysis.	Schuurman MS et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29514738
6	Neoadjuvant chemotherapy in elderly women with ovarian cancer: Rates of use and effectiveness.	Meyer LA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29961559
7	Robotic surgery in elderly and very elderly gynecologic cancer patients.	Gallotta V et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/29339300
8	The impact of age on the prognosis of vulvar cancer.	Hami LT	Oncol Res Treat	https://www.ncbi.nlm.nih.gov/pubmed/30041246
9	Population-based analysis of patient age and other disparities in the treatment of ovarian cancer in Central Appalachia and Kentucky.	Ore RM et al.	South Med J	https://www.ncbi.nlm.nih.gov/pubmed/29863220

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Epidemiology of gynaecological cancers

Kemal Güngördük

Ovarian cancer

Desai et al. analysed the association of statin use and risk of ovarian cancer in the Women's Health Initiative (WHI) population, which included 161,808 postmenopausal women [1]. There was an increased risk for OC (mainly for serous adenocarcinoma) especially associated with the hydrophilic statin pravastatin.

A large population-based prospective cohort study that included 255,786 women demonstrated that assisted reproductive technology was associated with increased risk of OC (OR 1.39; 95% CI: 1.26–1.55), both invasive (OR 1.40; 95% CI: 1.24–1.58) and borderline tumor (OR 1.36; 95% CI: 1.15–1.60). However, these increased risks were only limited to women with endometriosis, low parity, or both [2].

A Danish population-based cohort study that included 29,152 women reported that baseline menopausal hormone therapy (MHT) was associated with statistically significantly higher hazard of OC (HR 1.68; 95% CI: 1.26–2.26). The higher risk was only observed among users of MHT at baseline but not for previous users [3].

A meta-analysis of 9 studies showed that coffee intake was not associated with OC risk (OR 1.06; 95% CI: 0.89–1.26) [4].

Artur et al. demonstrated that an increased healthy lifestyle index score (a favourable combination of diet, physical activity, smoking, alcohol consumption, and anthropometric characteristics) was not associated with altered risk of OC (HR 0.96; 95% CI: 0.90–1.02) [5].

Rotman et al. reported that the risk of developing ovarian cancer increases twofold for women consuming chips and crisps several times a week in the amount of 100g, compared to women who rarely consume these products. The OR for this group of women amounts to 2.06; 95% CI: 0.53–7.99. In addition, women consuming white pasta once a week had ovarian cancer risk that was increased 1.2 times. The OR for this group of women amounted to 1.20; 95% CI: 0.78–1.83. OR rates for women consuming other types of pasta were as follows: Whole meal pasta (0.63; 95% CI: 0.40–0.98), soy pasta (OR=0.55; 95% CI 0.19–1.59), spinach pasta (OR=0.42; 95% CI 0.10–1.83), and durum wheat pasta (OR=0.82; 95% CI 0.53–1.27) [6].

In contrast to the Desai et al. trial, a population-based case (n=3,083) control (n=2,203) study demonstrated women who used statins had a 32% lower risk of ovarian cancer compared to non-users (OR 0.68, 95% CI: 0.54–0.85), adjusting for the matching factors and other covariates. The reduced risk was most apparent in women taking a lipophilic statin who began use after age 49, and who had used them 2–4.9 years. Statin use was associated with lower risks for both serous and non-serous histologic subtypes with strongest effect seen for mucinous and mixed epithelial subtypes. The association became apparent about a decade after the introduction of statins and did not appear to be confounded by indications for use of statins or comcomitant medications [7].

A large population-based prospective cohort study consisting of 118,821 women demonstrated that preterm delivery was associated with an increased risk (pregnancy length ≤30 versus 39>41 weeks) with OR of 1.33 (95% CI: 1.06–1.67); the OR increased as pregnancy length decreased. Older age at first and last birth were associated with a decreased risk (first birth: 30>39 vs. <25 years) with OR of 0.76 (95% CI: 0.70–0.83); last birth >39 versus <25 years: adjusted OR 0.76 (95% CI: 0.71–0.82). Multiparity was protective (≥4 births vs. 1); OR 0.63 (95% CI: 0.59–0.68) for all subtypes, and most pronounced for clear-cell tumours (OR 0.30; 95% CI: 0.21–0.44) [8].

Endometrial cancer

Desai et al. showed that statin use at baseline was associated with a statistically significant lower risk of endometrial cancer compared to non-users (HR 0.74; 95% CI: 0.59–0.94) [1].

Williams et al. demonstrated that ART was not associated with overall EC risk (OR 1.12; 95% CI: 0.95–1.30) [2].

A Danish population-based cohort study reported that baseline menopausal hormone therapy (MHT) was associated with statistically significantly higher hazard of EC (HR 1.86; 95% CI: 1.45–2.37). The hazard was higher in oestrogen-alone users (HR 2.38; 95% CI: 1.50–3.76) than among combined therapy users (HR 1.86; 95% CI: 1.42–2.43) [3].

Artur et al. demonstrated that an increased healthy lifestyle index score (a favourable combination of diet, physical activity, smoking, alcohol consumption, and anthropometric characteristics) was related to lower endometrial cancer risk (HR 0.95; 95% CI: 0.90–0.99) [7].

A recent meta-analysis by Chen et al. included 12 case-control and three cohort studies. The authors reported that vegetable fibre intake tended to be negatively associated with endometrial cancer risk (OR 0.76; 95% CI: 0.64–0.91) [8].

Gavrilyuk et al. showed that there was a statistically significant, positive dose-response relationship between lifetime number of years of menstruation (LNYM) and EC, with a 9.1% higher risk for each additional year of LNYM [9].

A meta-analysis of 12 cohort studies and eight case-control studies showed that increased coffee consumption is associated with decreased risk of endometrial cancer (RR 0.74; 95% CI: 0.68–0.81), especially in women with BMI over 30 (RR 0.71; 95% CI: 0.61–0.81) [10].

Yeh et al. reported that women with adenomyosis are at higher risk of EC (RR 2.19; 95% CI: 1.51–3.16) [11].

A large population-based prospective cohort study demonstrated that risk reductions associated with oral contraceptive (OC) use strengthened with duration of use (long-term OC use [≥10 years] HR 0.60; 95% CI: 0.47–0.76) and were similar across modifiable lifestyle factors for OC. Risk reductions for endometrial cancer strengthened with the duration of use (long-term OC use HR, 0.66; 95% CI: 0.56–0.78); the most pronounced reductions were among long-term OC users who were smokers (HR, 0.47; 95% CI: 0.25–0.88), had obese BMIs (HR 0.36; 95% CI: 0.25–0.52), and who exercised rarely (HR 0.40; 95% CI, 0.29–0.56) [12].

A meta-analysis of 14 trials showed endometrial cancer risk decreased by 7% for every six-month increase in the duration of breastfeeding (RR 0.93; 95% CI: 0.88–0.97) [13].

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Epidemiology of gynaecological cancers

Kemal Güngördük

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No	Title	Authors	Journal	Link to abstract
1	An analysis of the association between statin use and risk of endometrial and ovarian cancers in the Women's Health Initiative.	Desai P et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29422345
2	Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: Data linkage study including 2.2 million person years of observation.	Williams CL et al.	BMJ	https://www.ncbi.nlm.nih.gov/pubmed/29997145
3	The influence of menopausal hormone therapy and potential lifestyle Interactions in female cancer development—A population-based prospective study.	Holm M et al.	Horm Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29948971
4	Coffee consumption is not associated with ovarian cancer risk: a dose-response meta-analysis of prospective cohort studies.	Berretta M et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/29755691
5	A healthy lifestyle index and its association with risk of breast, endometrial, and ovarian cancer among Canadian women.	Artur R et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/30075330
6	Modifiable lifestyle factors and ovarian cancer incidence in women.	Rotman PK et al.	Ann Agric Environ Med	https://www.ncbi.nlm.nih.gov/pubmed/29575880
7	Statin therapy and association with ovarian cancer risk in the New England Case Control (NEC) study.	Akinwunmi B et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30006925
8	Preterm delivery is associated with an increased risk of epithelial ovarian cancer among parous women.	Sköld C et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29737528
9	Lifetime number of years of menstruation as a risk index for postmenopausal endometrial cancer in the Norwegian Women and Cancer Study.	Gavrilyuk O et al.	Acta Obstet Gynecol Scand	https://www.ncbi.nlm.nih.gov/pubmed/29782643
10	Coffee drinking and the risk of endometrial cancer: An updated meta-analysis of observational studies.	Lukic M et al.	Nutr Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29708405
11	Women with adenomyosis are at higher risks of endometrial and thyroid cancers: A population-based historical cohort study.	Yeh CC et al.	PLoS One	https://www.ncbi.nlm.nih.gov/pubmed/29522577
12	Exogenous hormone use and endometrial cancer in U.S. black women.	Sponholtz TR et al.	Cancer Epidemiol Biomarkers Prev	https://www.ncbi.nlm.nih.gov/pubmed/29475971
13	Association between breastfeeding and risk of endometrial cancer: a meta-analysis of epidemiological studies.	Ma X et al.	Eur J Cancer Prev	https://www.ncbi.nlm.nih.gov/pubmed/26258808

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

Joanna Kacperczyk-Bartnik

This review covers recent research concerning gestational trophoblastic disease presented in one meta-analysis, two prospective cohort studies, three retrospective cohort studies, and one cross-sectional study.

Diagnosis

A systematic review and meta-analysis by Madi et al. focussed on the accuracy of immunohistochemistry with p57KIP2 evaluation for complete hydatidiform mole (CHM) diagnosis in comparison to molecular genotyping [1]. With 0.984 sensitivity and 0.625 specificity, immunostaining is a useful method of CHM detection, especially in combination with genotyping for difficult clinical cases differentiation.

The prospective cohort analysis of 187 low-risk gestational trophoblastic neoplasia (GTN) patients by Li et al. examined power Doppler ultrasound as a non-invasive assessment enabling distinction between future chemoresistant (n=111) and non-chemoresistant cases (n=76) [2]. The number of colour pixels was the most promising diagnostic indicator as it was higher in resistant patients.

Treatment

Bolze et al. presented in their retrospective cohort study outcome of 74 low-risk GTN patients with fulfilled reproductive plans who underwent first-line hysterectomy instead of chemotherapy in order to avoid chemo adverse effects [3]. Further treatment with chemotherapy was not required by 82.4% of patients. A higher success rate – patients cured with first-line hysterectomy – was characteristic for lower FIGO score (0–IV) and pathological diagnosis other than choriocarcinoma.

Prognosis and follow-up

Braga et al. published a retrospective cohort study of 1,228 patients, including 163 women with hCG levels ≥ 20,000 IU/L four weeks post-CHM uterine evacuation [4]. This level showed high specificity (98.6%) and was highly predictive of the development of postmolar GTN, but delay in treatment until plateau or increase in HCG according to guidelines did not affect the clinical outcome. Also, only 6% of women will have such high values at four weeks.

He et al. analysed the association between circulating tumour cells (CTC) and clinical features of 115 patients with gestational choriocarcinoma [5]. A higher number of CTCs was characteristic for higher FIGO stage, larger tumour size, higher number of metastases, disease progression, and chemotherapy resistance.

The retrospective cohort analysis by Jiang et al. assessed the risk factors proposed in the 2000 FIGO classification for chemotherapy selection and survival outcomes of 1,420 patients with gestational trophoblastic disease [6]. As age, pretreatment serum β-HCG levels, and maximum tumour diameter were not identified as independent prognostic risk factors, the authors suggested an adjustment of FIGO 2000 System in which factors such as the interval from the index pregnancy, the number of metastases and a history of failed chemotherapy treatments weigh more.

Jewell et al. surveyed 51 GTN survivors in order to assess emotional, reproductive, sexual health, and relationship qualities in accordance with ß-hCG surveillance and accompanying distress. Patients were allocated into a 'low-worry group' (n=29) and a 'high-worry group' (n=19) [7]. Women from the high-worry group were more concerned about GTN recurrence, more frequently suffered from depression, experienced lower sexual desire, and presented a lower number of successful pregnancies after GTN treatment.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Accuracy of p57KIP2 compared with genotyping to diagnose complete hydatidiform mole: a systematic review and meta-analysis.	Madi JM et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/29782064
2	Power Doppler quantification in assessing gestational trophoblastic neoplasia.	Li Y et al.	Ultraschall Med	https://www.ncbi.nlm.nih.gov/pubmed/27529457
3	First-line hysterectomy for women with low-risk non-metastatic gestational trophoblastic neoplasia no longer wishing to conceive.	Bolze PA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29887485
4	Does a human chorionic gonadotropin level of over 20,000 IU/L four weeks after uterine evacuation for complete hydatidiform mole constitute an indication for chemotherapy for gestational trophoblastic neoplasia?	Braga A et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/29477553
5	Clinical significance of circulating tumor cells in predicting disease progression and chemotherapy resistance in patients with gestational choriocarcinoma.	He W.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/30070688
6	Evaluation and suggestions for improving the FIGO 2000 staging criteria for gestational trophoblastic neoplasia: A ten-year review of 1420 patients.	Jiang F et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29653688
7	Association of ß-hCG surveillance with emotional, reproductive, and sexual health in women treated for gestational trophoblastic neoplasia.	Jewell EL et al.	J Womens Health	https://www.ncbi.nlm.nih.gov/pubmed/29267150

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Follow-up after gynaecological malignancies

Jenneke Kasius

Making use of questionnaires, two studies investigated patient preferences for follow-up after gynaecological cancer [1,2].

Fidjeland et al. compared the attitudes toward follow-up care between 100 patients who were about to start follow-up to 139 patients who had been under hospital-based follow-up for more than a year in a cross-sectional study in Norway [1]. Two-thirds of the patients were treated for FIGO stage I gynaecological cancer. Overall, patients preferred hospital-based follow-up over follow-up by their general practitioner (GP) (65% vs. 83%), whom they viewed as less competent for this purpose. Patients who had not yet started follow-up were three times more willing to undergo follow-up at their GP. Both groups rated 'detection of recurrence' as the most important aspect of the follow-up visits. Schlumbrecht et al. investigated questionnaires completed by 449 patients registered with the Foundation for Women's Cancer, who were treated for gynaecological cancer and not diagnosed with a recurrence [2]. The time since end of treatment was not reported. Over 50% of the patients did not feel comfortable having follow-up by any other physician but their primary oncologist, independent of the time since diagnosis. Significant variability in preferences between the survivors was detected, indicating that a uniform follow-up approach may not be feasible.

Jeppesen et al. conducted a study with the aim to check [3]. A total of 156 women with FIGO stage I grade 1 and 2 endometrial cancer were randomised for regular outpatient visits versus patient-initiated follow-up after careful instruction about alarm symptoms. After 10 months of follow-up, the fear of cancer recurrence, based on the Fear of Cancer Recurrence Inventory, was significantly lower in the control group. However, the estimated difference was small (-5.9, 95% CI: -10.9– -0.9), questioning the clinical significance. The hospital visits were significantly reduced in the intervention group (0 vs. 2 median visits).

Williamson and Dixon et al. both reported results of the ENDCAT trial [4, 5]. In the ENDCAT trial, 259 women who had completed treatment for endometrial cancer stage I in England were randomised for either hospital-based follow-up or specialist nurse-led telephone-based follow-up.

Williamson et al. performed a qualitative study, based on interviews with 25 randomly selected patients and seven nurse specialists, to explore the experiences of telephone follow-up. Patients reported the telephone follow-up was more convenient and allowed more privacy. They felt reassured by the structure and repetition of the questions during telephone follow-up. The nurses enjoyed the telephone follow-up and judged it a useful tool to provide holistic care. Dixon et al. performed a cost-consequence analysis. Unfortunately, the study was not powered to detect differences in costs. There was no difference in total health service mean per patient costs at 6 months (mean difference £8, 95% CI: - £147 to £141) or 12 months (mean difference: - £77, 95% CI: - £334 to £154). Telephone follow-up appointments were more frequent and longer.

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No	Title	Authors	Journal	Link to abstract
1	Gynecological cancer patients' attitudes toward follow-up care after cancer treatment: Do preferences reflect patients' experience? A cross-sectional questionnaire study.	Fidjeland HL et al.	Acta Obstet Gynecol Scand.	https://www.ncbi.nlm.nih.gov/pubmed/29893058
2	Gynecologic cancer survivor preferences for long-term surveillance.	Schlumbrecht M et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pubmed/29614979
3	Patient-initiated follow up affects fear of recurrence and healthcare use: a randomised trial in early-stage endometrial cancer.	Jeppesen MM et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/29978593
4	Telephone follow-up after treatment for endometrial cancer: A qualitative study of patients' and clinical nurse specialists' experiences in the ENDCAT trial.	Williamson S et al.	Eur J Oncol Nurs	https://www.ncbi.nlm.nih.gov/pubmed/29784140
5	Cost-consequence analysis alongside a randomised controlled trial of hospital versus telephone follow-up after treatment for endometrial cancer.	Dixon P et al.	Appl Health Econ Health Policy	https://www.ncbi.nlm.nih.gov/pubmed/29651778
6	Assessing the utility of a distress screening tool at capturing sexual concerns in a gyne-oncology follow-up clinic.	Walker LM et al.	Support Care Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28986645

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Sexual function in gynaecologic cancer patients and survivors

Stamatios Petousis

Endometrial cancer

An interesting prospective cohort study was published by Ferguson et al. In this study, there were 486 eligible patients included that were compared in terms of quality of life and sexual health measures according to the surgical approach performed (laparoscopic, robotic, and open). Despite the fact that minimally invasive surgery was observed to significantly improve overall quality of life, there was no significant difference observed based on the Female Sexual Function Index (FSFI) and the Sexual Adjustment and Body Image Scale for Gynaecologic Cancer (SABIS-G) among the three categories. Therefore, despite the beneficial impact of minimally invasive surgery on overall quality of life, this study failed to demonstrate any significant impact on sexual dysfunction [1].

Ovarian cancer

Goetsch published an opinion article in which the author reported on the advantage of lidocaine 95% instead of supplemental systemic hormone therapy in women with ovarian cancer after ovarian ablation or removal. Specifically, the author advised on usage according to a RCT performed in breast cancer patients in which usage of 95% lidocaine before sexual contact was observed to diminish dyspareunia in at least 50% of recipients. It seems that such a policy may be an alternative for ovarian cancer patients, even it requires further study [2].

Cervical cancer

Hofsjö et al. performed a matched case-control study in order to study the impact of radiotherapy on the sexual function of patients with cervical cancer. The authors finally concluded that cervical cancer treatment including radiotherapy was associated with vaginal epithelial atrophy and sexual dysfunction. Indeed, they predominantly observed that such patients suffered from insufficient vaginal lubrication (RR 12.6 compared to controls), vaginal inelasticity (RR 6.5), reduced genital swelling when sexually aroused (RR 5.9), and reduction of vaginal length during intercourse (RR 3.9) [3].

General remarks on all gynaecological cancers

In contrary with the aforementioned remarks made by Hofsjö [3], there was an interesting cross-sectional study published by Moroney et al. enrolling 171 patients [4]. This study indicated no significant difference between gynaecologic cancer patients treated with additional radiotherapy (either external beam or intracavitary) compared with those not receiving any radiation in regards to sexual function parameters. However, they also reported that women experiencing decreased sexual function were more likely to be under 50 years old, having received chemotherapy and having cervical cancer.

Finally, a very important systematic review and meta-analysis was published by Ramaseshan et al. There were 31 articles included, demonstrating a significant increase regarding dyspareunia and vaginal dryness before and after surgery in all subgroups of gynaecological cancer patients. Therefore, the authors concluded that generally pelvic floor disorders represent an area of significant clinical concern and future research [5].

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No	Title	Authors	Journal	Link to abstract
1	Prospective cohort study comparing quality of life and sexual health outcomes between women undergoing robotic, laparoscopic and open surgery for endometrial cancer.	Ferguson SE et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29681461
2	Management of sexuality, intimacy, and menopause symptoms after ovarian cancer.	Goetsch MF	AJOG	https://www.ncbi.nlm.nih.gov/pubmed/29307739
3	Radiotherapy for cervical cancer - impact on the vaginal epithelium and sexual function.	Hofsjö A et al.	Acta Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29140150
4	Radiation therapy is not an independent risk factor for decreased sexual function in women with gynecologic cancers.	Moroney MR et al.	Rep Pract Oncol Radiother	https://www.ncbi.nlm.nih.gov/pubmed/30127672
5	Pelvic floor disorders in women with gynecologic malignancies: a systematic review.	Ramaseshan AS et al.	Int Urogynecol J.	https://www.ncbi.nlm.nih.gov/pubmed/28929201

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Fertility-sparing treatment in gynaecological malignancies

Charalampos Theofanakis

Endometrial cancer

A retrospective study by Yamagami et al. attempted to assess the effect of repeated administration of medroxyprogesterone acetate (MPA) on patients with intrauterine recurrence after fertility-sparing treatment for atypical endometrial hyperplasia (AEH) and stage IA, G1 endometrial cancer. Patients were divided into initial and repeated treatment groups (162 and 82 patients, respectively). Complete response rates in the initial and repeated treatment groups among patients with AEH were 98.5% and 96.4%, respectively. Among patients with G1, response rates were 90.7% and 98.1%, respectively, while 5-year recurrence-free survival (RFS) rates were 53.7% and 33.2% among patients with AEH and G1, respectively. The authors concluded that repeated treatment is sufficiently effective for intrauterine recurrence after hormonal therapy for AEH/early G1 [1]. A retrospective study by Giampaolino et al. evaluated the safety and effectiveness of hysteroscopic endometrial focal resection, combined with a levonorgestrel-releasing intrauterine device (LNG-IUD) in stage IA, G1 endometrial cancer (EEC) and atypical endometrial hyperplasia (AEH). Sixty-nine patients had an LNG-IUD inserted after surgery and were followed for 24 months. Of the 14 patients with EEC, 11 (78.6%) achieved a complete response, two (18.2%) of whom had subsequent relapse, one (7.1%) showed partial response, whereas two (14.3%) were non-responders. The study demonstrated that the combination of hysteroscopic resection with an LNG-IUD is a feasible fertility-sparing treatment of EEC and AEH ,however, with the limitations of the retrospective design [2].

Ovarian cancer

A multicentre retrospective study by Tamauchi et al. assessed the reproductive outcomes of malignant ovarian germ cell tumor survivors under 40 years of age who received fertility-sparing treatment. The median follow-up period was 10.4 years. The study included 109 patients. Out of the 45 patients who desired childbirth, 42 became pregnant. The total number of pregnancies was 65, and 55 babies were born to 40 malignant ovarian germ cell tumor survivors. The study demonstrated that the reproductive outcomes of malignant ovarian germ cell tumor survivor are promising with fertility-sparing treatment [3].

Cervical cancer

A meta-analysis by Feng et al. evaluated the safety of fertility preserving treatment in patients with micro-invasive cervical adenocarcinoma. The study showed that this approach surgery had no adverse effect on recurrence or survival (p=0.524 and 0.485, respectively). The authors stated that the prognosis for patients with micro-invasive cervical adenocarcinoma is excellent and that confirmed these patients are eligible for fertility-sparing treatment [4].

An observational study by Alvarez et al. assessed the association between the residual cervix measured on post-operative MRI after radical vaginal trachelectomy (RVT) and adverse obstetric outcomes. Of the 31 MRI scans available, 19 women (65.5%) had <10 mm and 10 (34.5%) had ≥10 mm residual cervix. Among women with <10 mm residual cervix, seven (36.8%) experienced premature rupture of membranes (PROM) and 10 (66.7%) had a preterm birth. No women with ≥10 mm residual cervix had PROM and two (22.2%) had a preterm birth (p=0.028 and p=0.035, respectively). Overall, there were nine (16.7%) first trimester miscarriages, six (11.1%) late foetal losses, twelve (31.6%) preterm births, and 36 (66.7%) live births. The authors concluded that the incidence of PROM and premature delivery is higher when the residual cervix after RVT is less than 10 mm [5].

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No	Title	Authors	Journal	Link to abstract
1	Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility?	Yamagami W et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29400014
2	Hysteroscopic endometrial focal resection followed by levonorgestrel intrauterine device insertion as a fertility-sparing treatment of atypical endometrial hyperplasia and early endometrial cancer: A retrospective study.	Giampaolino P et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/30017893
3	Reproductive outcomes of 105 malignant ovarian germ cell tumor survivors: a multicentre study.	Tamauchi S et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/30086295
4	The safety of fertility preservation for microinvasive cervical adednocarcinoma: a meta-analysis and trial sequential analysis	Feng Y et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/29876746
5	MRI measurement of residual cervical length after radical trachelectomy for cervical cancer and the risk of adverse pregnancy outcomes: a blinded imaging analysis.	Alvarez RM et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/30099822

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Quality of life in gynaecological cancers/Palliative care

Engin Celik and Nadja Taumberger

Nitecki et al. conducted a retrospective chart review of 391 patients diagnosed with ovarian cancer. Only 28% of patients (n=109) were evaluated by a palliative care service, and 38% of referrals occurred within 30 days of death. The outpatient initial consultation cohort, which was 42% of the referrals, was associated with a one-year overall survival benefit (log rank p<0.01). In a multivariable age-adjusted regression model, advanced stage (OR: 1.7; p=0.02), recurrence (OR: 2.0; p=0.002), and hospice referral (OR: 6.0; p<0.001) were shown to be independently associated with palliative care referral. Pain symptom management was the primary indication for referral. The study highlights the need to carefully explore symptoms in end of life care.

Hacker et al. reviewed pain management in gynaecologic oncology. After the Joint Commission released the standards of pain management in 2001, opioid prescriptions in the US increased, and nowadays the opioid crisis has been defined as a public health emergency. NSAIDs and acetaminophen may represent adequate analgaesia with less opioid use. In the treatment of neuropathic pain, gabapentin and pregabalin are used alone as an adjuvant medication or with opioids. Epidural analgaesia should be reserved for short life expectancy with intractable pain or intolerable adverse reaction to systemic medications. Cognitive behavioural therapy, group or individual counseling may improve cancer pain perception. Spinal cord or peripheral nerve stimulation alters nervous system signals and modulates pain and can be used with a low rate of adverse events.

The retrospective study of Mattsson et al. investigated the prevalence of symptoms in women aged 19–39 who survived gynaecological cancer in terms of cancer-related distress. Furthermore, they focused on the needs of psychological support after treatment end. They enrolled 337 patients who received a study-specific questionnaire that showed that over 80% experienced psychological distress, such as fear of recurrence, depression or anxiety, which are all related to their post-treatment disease. This shows the high burden of young women diagnosed with gynaecological cancer and the need for an optimal follow-up and support system that continues past the end of treatment.

Von Grueningen et al. enrolled 102 patients with persistent or recurrent platinum-resistant ovarian cancer with at least six months of life expectancy to evaluate the symptoms during treatment that focussed on reducing symptoms and prolonging progression-free survival. Results showed that over 90% of the patients suffered from fatigue, approximately 70% from sleep disorders, and more than 70% were bothered by treatment side effects such as hair loss and nausea. Furthermore, most of the study population considered themselves religious or spiritual, and communication about unmet spiritual needs showed improved QoL.

Relevant articles retrieved February 15, 2018 – August 15, 2018

No	Title	Authors	Journal	Link to abstract
1	Patterns of palliative care referral in ovarian cancer: A single institution 5 year retrospective analysis.	Nitecki R	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29395315
2	Ongoing strategies and updates on pain management in gynecologic oncology patients.	Hacker KE	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/29409684
3	Women treated for gynaecological cancer during young adulthood – A mixed-methods study of perceived psychological distress and experiences of support from health care following end-of-treatment.	Mattsson E et al.	Gynecol Oncol	https://linkinghub.elsevier.com/retrieve/pii/S009082581830235X
4	Quality of life, symptoms and care needs in patients with persistent or recurrent platinum-resistant ovarian cancer: An NRG Oncology/Gynecologic Oncology Group study.	Von Grueningen et al.	Gynecol Oncol	https://linkinghub.elsevier.com/retrieve/pii/S0090825818309041

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