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LiFE report
Literature for ENYGO

LiFE | Literature for ENYGO

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

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Preface

Dear colleagues,

We're happy to present LiFE 6 to you, with reviews of publications in gynaecological oncology from February 15, 2017–August 15, 2017. LiFE is an initiative of ENYGO supported by ESGO.

Some of the topics have found new authors. We welcome Eleftherios G Klonos (Greece), Charalampos Theofanakis (Greece), Joel Laufer (Uruguay), Florian Drews (UK) and Kemal Güngördük (Turkey) to the LiFE team.

We enjoy the close and continuing work with individual authors and are very proud of this international collaboration. In order to further improve the scientific value of LiFE, we are looking forward to our workshop for the LiFE authors at the upcoming ESGO meeting in Vienna. It will be dedicated to the search for literature and the critical appraisal of scientific papers. Prof. Christina Fotopoulou and Prof. Sean Kehoe will support this event with their lectures and expertise. We are looking forward to meeting the authors there and discussing their work on LiFE.

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

We hope you will enjoy LiFE 6 and find it interesting! Please let us know if you have any feedback for us, as we constantly strive to improve.

Are you interested in becoming an author? Please send an email to enygo.life.project@esgomail.org to find out how to become a part of our team.

Yours,

The LiFE team

Kristina Lindemann
Kamil Zalewski
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Miscellaneous

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Pathology/pathogenesis of malignant ovarian tumours

Editor Dogan Vatansever

Descriptive summary

In the period covered by this LiFE report, four original research articles and one review article considered relevant were published.

Original Research Articles

Poly (ADP-ribose) polymerase (PARP) inhibitors are especially effective in patients with BRCA1/2 mutations. However, there are no approved biomarkers for olaparib in high-grade serous ovarian cancer (HGSOC) and long-term responses to the poly (ADP-ribose) polymerase inhibitor olaparib have been observed also in patients without BRCA1/2 mutations. Lheureux et al. performed integrated exome, low-pass genome, and RNA sequence analysis of HGSOC tumours from three patients without germline BRCA1/2 mutations who experienced exceptional responses to olaparib. They observed somatic disruption of BRCA1/2 in all three patients at diagnosis, followed by subsequent BRCA recovery upon progression by copy number gain and/or upregulation of the remaining functional allele in two patients. The third patient with ongoing response (seven years) had a tumour at diagnosis with biallelic somatic deletion and loss-of-function mutation, thereby lacking a functional allele for recovery of BRCA1 activity and indicating a potential cure [1].

There are some emerging studies regarding a novel iron-dependent cell death mechanism called ferroptosis. Basuli et al. showed that ovarian cancer exhibits a targetable alteration in iron metabolism. Ferroportin (FPN), the iron efflux pump, is decreased, and transferrin receptor (TFR1), the iron importer, is increased in tumour tissue from patients with high- grade (but not low- grade) serous ovarian cancer. They also demonstrated that reduction in intracellular iron reduces the proliferation in vitro and inhibits both tumour growth and intraperitoneal dissemination of tumour cells in vivo. As a result, the iron-dependent metabolism of ovarian cancer cells suggests the induction of iron-dependent cell death (ferroptosis) as well as iron chelators as new possible therapeutic options [2].

MicroRNAs (miRNAs) have regulatory roles in various cellular processes, including apoptosis. X-linked inhibitor of apoptosis protein (XIAP) has been reported to be dysregulated in epithelial ovarian cancer (EOC). Li et al. showed that miRNA-137 interacting with luciferase reporter gene fused with XIAP 3'UTR and decreased the levels of XIAP protein which results in increased cisplatin-induced apoptosis [3].

Clear cell ovarian carcinoma (CCOC) is associated with a significantly worse prognosis and the therapeutic options are limited. Howitt et al. demonstrated there is a cohort of CCOCs with MSI (MSI-CCOCs) which are highly immunogenic. A higher number of CD8+ TILs, a higher CD8/CD4 ratio and higher PD-1+TILs are seen in MSI-CCOCs compared to microsatellite stable (MSS) CCOCs and compared to high-grade serous ovarian cancers. This subgroup of ovarian cancer patients is mostly resistant to standard chemotherapy and should be considered for alternative therapeutic options, potentially susceptible for immunotherapy [4].

Review

Although our understanding of cancer genome evolution and the dynamic interplay between tumour cells and the microenvironment has dramatically increased, the field of cancer evolutionary therapeutics is still in its infancy. As we attempt to forecast evolution and proactively manage a dynamic tumour genome and its microenvironment, it is worth remembering that Darwin recognised such challenges "throw up a handful of feathers, and all fall to the ground according to definite laws; but how simple is the problem where each shall fall compared to that of the action and reaction of innumerable plants and animals which have determined, in the course of centuries, the proportional numbers and kinds of trees now growing." (Darwin, 1859). The beginning to the conclusion of a great review [5]. Although it is not directly related to ovarian cancer, it covers cancer in general and is strongly recommended.

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Somatic BRCA1/2 recovery as a resistance mechanism after exceptional response to poly (ADP-ribose) polymerase inhibition	Lheureux S et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28221868
2	Iron addiction: a novel therapeutic target in ovarian cancer	Basuli D et al.	Oncogene	https://www.ncbi.nlm.nih.gov/pubmed/28319068
3	microRNA-137 promotes apoptosis in ovarian cancer cells via the regulation of XIAP	Li X et al.	BJC	https://www.ncbi.nlm.nih.gov/pubmed/27875524
4	Clear cell ovarian cancers with microsatellite instability: a unique subset of ovarian cancers with increased tumour infiltrating lymphocytes and PD-1/PD-L1 expression	Howitt BE et al.	Oncoimmunology	https://www.ncbi.nlm.nih.gov/pubmed/28344892
5	Clonal heterogeneity and tumour evolution: past, present, and the future	McGranahan N et al.	Cell	https://www.ncbi.nlm.nih.gov/pubmed/28187284

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Screening for ovarian and fallopian tube cancer

Editor Lucas Minig

Descriptive summary

UK FOCSS phase II results

The phase II results of the United Kingdom Familial Ovarian Cancer Screening Study (UK FOCSS) were published. It aimed to establish screening performance with serum cancer antigen 125 (CA-125), utilising the risk of ovarian cancer algorithm (ROCA), and transvaginal ultrasound (TVUS) for women at high risk of ovarian cancer (OC) or fallopian tube cancer (FTC). High-risk patients were defined as: a) BRCA mutation carriers (n= 804) or b) having an estimated lifetime risk of ovarian cancer of more than 10% based on personal and family history (n=3.544). CA-125 was measured every four months to calculate the ROCA score. TVUS was performed annually if ROCA results were normal or within two months in cases with an abnormal result. A total of 19 cancers were diagnosed using this algorithm (n = 13 in the "high-risk group"; and n = 6 in BRCA mutation carriers after risk-reducing salpingo-oophorectomy). After more than 13 years of screening, patients were followed up for a median time of 4.8 years. Cancer was diagnosed at stage IIIb–IIIc in 37% of patients (n = 7). However, when excluding BRCA carriers, 54% (n = 7) of the 13 cancer patients were diagnosed at stage IIIb–IIIc. The authors concluded ROCA-based screening is an option in women at high ovarian cancer risk because only two deaths occurred among the 13 screened women who developed cancer. Although women enrolled in the UK FOCSS who did not have a known BRCA1/2 mutation were calculated to have greater than 10% lifetime risk, only 13 cancers developed in the 3,544 women; this translated to an annual incidence of one in 4,761 (0.021%). Notably, this risk is not appreciably different than that of the general population [1].

UKCTOCS cost effectiveness

An analysis of the cost-effectiveness of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was published. The study suggested that screening is potentially cost effective when only the costs of CA-125 and TVUS are included [2]. However, it is important to note that the additional costs of the proprietary ROCA algorithm were not considered in the analysis.

Kentucky Ovarian Cancer Screening Program, complications after surgery

The incidence of complications of surgical intervention for participants in the Kentucky Ovarian Cancer Screening Program was recently reported. A total of 657 patients underwent surgery for a positive screen from 1988–2014. Complete information was available for 548 patients. Complications were graded using the Clavien-Dindo classification. Complications were recorded in 54/548 (10%) subjects and they were mostly minor (93%) and were more common in cancer versus non-cancer surgery. For women with malignancy, 17/90 (19%) had complications compared to 37/458 (8%) with benign pathology ($p < 0.003$) [3].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom familial ovarian cancer screening study	Rosenthal AN et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28240969
2	The cost-effectiveness of screening for ovarian cancer: results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)	Menon U et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28742794
3	Complications from surgeries related to ovarian cancer screening	Baldwin LA et al.	Diagnostics (Basel)	https://www.ncbi.nlm.nih.gov/pubmed/28282907

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Surgical treatment of primary ovarian cancer

Editor Sileny Han

Descriptive summary

Pre-operative staging

Van de Vrie et al. evaluated the cost-effectiveness of diagnostic laparoscopy prior to primary debulking surgery (to prevent operations leaving > 1cm residual disease), based on direct medical costs. Laparoscopy reduced the number of futile laparotomies from 39% to 10%, while its costs were 1,400 per intervention, making the overall costs of both strategies comparable (difference: 80 per patient [95% CI: -470–300]) [1].

PDS vs. neoadjuvant chemotherapy (NAC)

Seagle et al. found PDS was associated with increased overall survival (OS) among women with stage III ovarian cancer in a cohort from the National Cancer Database treated with PDS or NAC between 1998–2011. Overall, 44,907 women (85.9%) underwent PDS, and 7,348 women (14.1%) received NAC. Among women with stage III disease, PDS was associated with increased OS compared with NAC (median OS, 44.9 [44.2–45.7] vs. 31.4 [30.2–33.0] months; hazard ratio [95% CI], 0.70 [0.66–0.76]; $p < 0.001$). Among women with stage IV disease, there was no OS difference between PDS and NAC cohorts (median OS, 31.2 [30.4–32.3] vs. 28.4 [27.2–30.2] months; hazard ratio [95% CI], 0.93 [0.85–1.02]; $p = 0.12$) [2].

A retrospective review by Nicklin et al. reported the increasing utilisation of NACT. NACT followed by interval debulking surgery (IDS) at the Queensland Centre for Gynaecological Cancer (QCGC) has been associated with increasing rates of optimal cytoreduction and survival rates have continued to rise in excess of those achieved in the trials reported to date. In all, 2,601 patients were treated 1982–2013. No patients received NACT-IDS before 1995. This proportion increased to 55% in 2013. No macroscopic residual disease (R0) was achieved 32% of the time by 2006, rising to 48% in 2009, and 62% in 2013. Despite the increase in utilisation of NAC-IDS, there was a continued rise in OS probability at five years, to 45% [3].

Centralisation of care

Spencer et al. performed a retrospective cohort study using the National Cancer Database of women undergoing ovarian cancer surgery 2004–2012 (n = 24,827 women from 602 hospitals). The primary outcome of the study was mortality rate by hospital volume. Compared with low-volume centres (ten or fewer patients annually), ultra-high-volume centres (31 or more) had significantly lower 30- and 90-day risk-adjusted mortality [4].

Fertility-sparing surgery

Fertility-sparing surgery was not associated with increased risk of death in young women with stage I epithelial ovarian cancer when compared to women who underwent conventional surgery. In a cohort study using the National Cancer Database from the United States, 1,726 women with stage Ia and unilateral Ic epithelial ovarian cancer were treated. In all, 825 (47.8%) of those underwent fertility-sparing surgery. The probability of survival ten years after diagnosis was 88.5% (95% CI: 82.4–92.6) in the fertility-sparing group and 88.9% (95% CI: 84.9–92.0) in the conventional surgery group [5].

Technique

Komiyama et al. describe a surgical technique for dissection of the high paraaortic lymph nodes above the renal vein; with complete mobilisation of the small intestine and right hemicolon followed by externalisation of these viscera in isolation bags. Visualisation of the entire aorta is achieved, from the superior mesenteric artery to the common iliac artery. This enables safe and complete removal of the high para-aortic nodes [6]. This paper is also included in this LiFE issue in Elisa Piovano's report on technical aspects.

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Cost-effectiveness of laparoscopy as diagnostic tool before primary cytoreductive surgery in ovarian cancer	van de Vrie R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28645428
2	Survival after primary debulking surgery compared with neoadjuvant chemotherapy in advanced ovarian cancer: a National Cancer Database Study	Seagle BL et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28763362
3	The shift toward neo-adjuvant chemotherapy and interval debulking surgery for management of advanced ovarian and related cancers in a population-based setting: Impact on clinical outcomes	Nicklin JL et al.	Aust N Z J Obstet Gynaecol	https://www.ncbi.nlm.nih.gov/pubmed/28718942
4	Ninety-day mortality as a reporting parameter for high-grade serous ovarian cancer cytoreduction surgery	Spencer RJ et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28697111
5	All-cause mortality after fertility-sparing surgery for stage I epithelial ovarian cancer	Melamed A et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28594773
6	Safe dissection of high paraaortic lymph nodes superior to the renal vein in ovarian, primary peritoneal, or fallopian tube cancer by the "Komiyama's manoeuvre", a modification of Kocher's manoeuvre	Komiyama S et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28237617

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Surgical treatment of recurrent ovarian cancer

Editor Patriciu Achimas-Cadariu

Descriptive summary

Secondary cytoreductive surgery

A number of studies assessing the role of secondary cytoreductive surgery (SCS) have been published to date, but neither of the two randomised trials has so far published OS data. The first trial (GOG 213, NCT00565851) recently reported the results of the bevacizumab component, showing that the addition of bevacizumab to standard chemotherapy (carboplatin/taxol), followed by maintenance therapy until progression might be an important addition to the available therapeutic options in platinum-sensitive relapsed ovarian cancer [1].

The second trial (DESKTOP III, NCT01166737), evaluating SCS in patients with positive AGO-score (PS ECOG 0, ascites ≤500 ml; complete resection at initial surgery) with first relapse after more than six months of platinum-free interval. The authors have now published results of the predetermined interim analysis. Complete resection was achieved in 67% of patients. The analysis demonstrated a longer median PFS in the surgery arm in comparison with the chemotherapy-only arm (14 vs. 19.6 months, HR: 0.66, 95% CI: 0.52–0.83, $p < 0.001$) with acceptable morbidity associated with surgery. The analysis of the primary endpoint OS is still immature [2].

There are different approaches to select patients for SCS. Cowan et al. published a comparative analysis of prediction models for complete gross resection in SCS for ovarian cancer. The MSK criteria (SCS is recommended for patients with a single site of recurrence, regardless of disease-free interval (DFI); patients with multiple sites of recurrence but with no evidence of carcinomatosis and DFI >12 months; and patients with carcinomatosis but DFI > 30 months) had a complete gross resection rate of 86% and had a good concordance rate with the previously published Tian model. This model could be used to further assess if intermediate MSK cases (DFI 6–12 months and multiple sites of recurrence but no carcinomatosis, DFI 12–30 months and carcinomatosis) are suitable for SCS. In the MSK population, the AGO criteria were too strict, precluding 51% of cases from SCS [3].

Tertiary cytoreductive surgery

A retrospective multicentre MITO study evaluated the role of tertiary cytoreductive surgery (TCS) in recurrent epithelial ovarian cancer and assessed predictors of complete cytoreduction in 103 platinum-sensitive patients. The authors reported a 68.9% complete cytoreduction rate which also was the most important predictor of survival followed by FIGO stage I–II at initial diagnosis, exclusive retroperitoneal recurrence, and TCS performed more than three years after primary diagnosis. Complete TCS was associated with a significantly longer OS in comparison with patients that had residual disease (43 vs. 33 months; $p < 0.001$). The only significant predictors of complete TCS were the presence of a single lesion and good (ECOG 0) performance status [4].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/ Gynaecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial	Coleman RL et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/?term=28438473
2	Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20	Du Bois A et al.	J Clin Oncol	http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.5501
3	A comparative analysis of prediction models for complete gross resection in secondary cytoreductive surgery for ovarian cancer	Cowan RA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/?term=28285846
4	Tertiary cytoreductive surgery in recurrent epithelial ovarian cancer: A multicentre MITO retrospective study	Falcone F et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/?term=28716306

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Medical treatment of primary ovarian cancer

Editor Ilker Selcuk and Elefteherios Klonos

Descriptive summary

Progression-free survival (PFS) and overall survival (OS) in clear cell ovarian carcinoma (OCCC) and serous ovarian carcinoma (SOC) patients were compared by Oliver at al. after platinum-based chemotherapy was treated in 12 GOG trials. In total 9,531 eligible, FIGO stage I–IV epithelial ovarian carcinoma (EOC) patients from 12 prospective, randomised GOG studies were reviewed. In all, 544 (6%) had OCCC, 7,054 (74%) had SOC, and 1,933 (20%) had other histologies. Prior to any adjustment, clear cell patients had better PFS and OS; however, this was due to the predominantly favourable prognostic factors (stage, age, and performance status). In early-stage disease, PFS was significantly worse for OCCC than SOC (hazard ratio: PFS was 1.37 (95% CI: 1.20–1.56; $p < 0.001$). The same trend was observed for OS when adjusted for age and stratifying by protocol and treatment arm, stage, performance status, and race, HR 1.58 (95% CI: 1.38–1.82; $p < 0.001$) for OCCC versus SOC patients. In stage I–II patients, PFS was significantly better in OCCC, OS was better but not statistically significant. After adjusting for prognostic factors, PFS and OS for OCCC were significantly shorter than SOC in stage III and IV disease, $p < 0.001$ (however, this effect was reversed after 2–3 years, especially in stage III patients). The authors also tried to assess the differential effect of three vs. six cycles of platinum-based chemotherapy on OCCC vs. SOC. Six cycles of adjuvant carboplatin/paclitaxel revealed statistically significantly ($p = 0.048$) greater treatment effect on PFS for early-stage SOC (HR: 0.42, 95% CI: 0.18–0.99) when compared with the effect for early-stage OCCC (HR: 1.32, 95% CI: 0.62–2.82) [1].

Barber et al. looked for the neoadjuvant chemotherapy usage in stage IIIC and IV EOC among high volume hospitals. Totally 11,574 patients from 55 high volume hospitals (treating >20 stage IIIC/IV patients per year) were reviewed. Hospitals were categorized due to the observed rate of neoadjuvant treatment in comparison with 95% confidence interval of predicted rate. Median neoadjuvant chemotherapy rate was 39% (range 23%-55%) for high utilization hospitals and 10% (range 5%-17%) for low utilization hospitals. After adjusting for clinico-pathologic factors, treatment at an average or high neoadjuvant chemotherapy use hospital had a lower rate of death (HR 0.90, 95% CI 0.83-0.97) than treatment at a low neoadjuvant chemotherapy used hospital (HR 0.85, 95% CI 0.75-0.95) [2].

Von Gruenigen et al. studied the likelihood of chemotherapy completion in elderly patients with baseline Instrumental Activities Daily Living (IADL) score, which is measured by self-care skills that allow independent functioning within the community. Patients 70 years of age (207 evaluable patients) received either carboplatin AUC 5 and paclitaxel 135mg/m2 (n = 148) or carboplatin AUC 5 (n = 59), given every three weeks after upfront surgery or as neoadjuvant chemotherapy. Patients with higher IADL score were more likely to complete four cycles of chemotherapy regardless of dose reduction and delay ($p = 0.008$). Each additional independent activity of the patient had an OR of 1.21 to complete four cycles of chemotherapy (95% CI: 1.05–1.4, $p = 0.008$). Moreover, development of toxicities grade 3 were inversely associated with the IADL score (17% decrease for each additional activity). In patients who received carboplatin and paclitaxel, the completion of four cycles of chemotherapy without a more than seven-day delay or dose reduction was associated with ADL score ($p = 0.002$) and the IADLs was associated with OS ($p = 0.013$) [3].

Gershenson et al. evaluated the role of hormonal maintenance therapy after primary cytoreductive surgery and platinum-based chemotherapy in a retrospective study. In all, 203 women with low-grade serous carcinoma of the ovary and peritoneum stages II–IV were treated with hormonal maintenance therapy (HMT) (n = 70) or observation (OBS) (n = 133). The HMT group had a lower risk of disease progression, HR: 0.44 (95% CI: 0.31–0.64, $p < 0.001$). Although median PFS was significantly longer in the HMT group (64.9 vs. 26.4, $p < 0.001$), OS was not significantly different between the two groups (115.7 vs. 102.7, $p = 0.42$). Median OS was similar for women who had never received HMT and who had received HMT for progression and recurrence (102.7 vs. 106.8, $p = 0.37$). There were more patients with residual tumour in the HMT group (49, 77.8% vs. 68, 66.7%). Despite these differences in baseline characteristics, they performed better [4].

Feng et al. analysed the hormone receptor expression profiles between the paired primary and recurrent high-grade SOC tissue specimens of 107 patients. Discordance rates for oestrogen, progesterone, and androgen receptors were 34.9%, 12.4%, and 41.7%, respectively. However, hormone receptor discordance was not associated with patient survival [5].

Petrillo et al. evaluated the role of BRCA mutation status on initial disease presentation and clinical outcome. BRCA 1/2 germline mutations were detected in 107 newly diagnosed high-grade SOC patients (n = 273). Peritoneal spread without an ovarian mass (25.2% vs. 13.9%, $p = 0.018$), bulky lymph nodes (30.8% vs. 17.5%, $p = 0.010$) and a higher peritoneal tumour load (laparoscopic predictive index value ≥ 8; 42.1% vs. 27.1%, $p = 0.016$) were detected significantly more in patients with BRCA 1/2 mutations. There was no difference in PFS in terms of primary debulking surgery (median 28m) or neoadjuvant chemotherapy (median 23m) for patients with BRCA mutations ($p = 0.268$) [6].

The factors predicting the use of neoadjuvant chemotherapy (n = 6922-11%) compared to primary debulking surgery (n = 31,280-50%) in the National Cancer Database were analysed by Leiserowitz et al. In 38,201 patients (total cohort, $p = 62,727$) with stage IIIc and IV EOC, diagnosed between 2003 and 2011, patients with age > 50 years, higher comorbidity, stage IV disease and high-grade tumours were more likely to have received neoadjuvant chemotherapy, ($p < 0.0005$) [7].

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Medical treatment of primary ovarian cancer

Descriptive summary (cont.)

The role of neoadjuvant chemotherapy cycle number in stage IIIc and IV high-grade SOC patients, was retrospectively evaluated by Altman et al. In total, 403 patients were analysed, and cycle number divided into two groups; < 4 (263p) and ≥ 4 (139p–34.5%). Achievement of complete cytoreduction during interval cytoreductive surgery was 46%. Cycle number 4 showed a worse prognosis than < 4 cycles (p = 0.011). Factors influencing the decision to give three or more cycles prior to surgery were unknown in the study [8].

Karam et al. reviewed first-line interventions during the Fifth Ovarian Cancer Consensus Conference. Trials assessing the survival of elderly or frail patients are lacking. Additionally, ongoing trials assessing the effect of weekly dose dense paclitaxel, intraperitoneal therapy, and bevacizumab in first-line adjuvant treatment should be awaited before these are implemented in daily practice. The standard dosing of three weekly carboplatin/paclitaxel was just recently reaffirmed by the ICON 8 trial, in which weekly taxol was not better than the standard dosing in prolonging PFS [9].

Matsuo et al. analysed the data of 1,322 women aged 50 and younger in whom ovarian conservation for stage I endometrioid endometrial cancer was performed in the Surveillance, Epidemiology and End Results (SEER) Program. The five- and ten- year cumulative index of developing subsequent ovarian cancer was 1.0% and 1.3% (16 women). Most ovarian cancers were detected in the first three years after the surgery (68.8%). The majority of subsequent cases were endometrioid type (81.3%), still stage I disease (75%). No death due to ovarian cancer was observed during 11.6 years of follow-up. Young women after a diagnosis of endometrioid endometrial cancer have an increased risk of developing a subsequent ovarian carcinoma (cumulative risk for women < 40 years: 2.6%, 40–49 years: 0.4%, HR 5.0, 95% CI: 1.60–15.7, p = 0.002). Potentially, this subsequent cancer could be uterine cancer recurrences. This would, however, still relate to the ovarian preservation in these women at the time of diagnosis. The authors underline the importance of germline mutation in young women with endometrial cancer to detect cases of Lynch syndrome [10].

At the most recent ESMO conference, results of ICON8 were presented. ICON8 randomised 1566 patients to receive six cycles of either the standard three-week dosing regimen (carboplatin/paclitaxel), compared to two different regimens that included once-weekly dose-dense paclitaxel (carboplatin+paclitaxel 80 mg/mq weekly, Arm 2; and carboplatin AUC2+paclitaxel 80 mg/mq weekly, Arm 3). There was no significant difference in PFS with 24.4 months with standard dosing, compared to 24.9 and 25.3 months in arms 2 and 3 respectively. Three-week dosing schedule will therefore remain the standard in Europe [11].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	An evaluation of progression free survival and overall survival of ovarian cancer patients with clear cell carcinoma versus serous carcinoma treated with platinum therapy: An NRG Oncology/Gynecologic Oncology Group experience	Oliver KE et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28807367
2	Variation in neoadjuvant chemotherapy utilization for epithelial ovarian cancer at high volume hospitals in the United States and associated survival	Barber EL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28366545
3	Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer—An NRG oncology/Gynecologic Oncology Group study	von Gruenigen VE et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28089376
4	Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum	Gershenson DM et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28221866
5	Hormone receptor expression profiles differ between primary and recurrent high-grade serous ovarian cancers	Feng Z et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/28416763
6	BRCA mutational status, initial disease presentation, and clinical outcome in high-grade serous advanced ovarian cancer: a multicenter study	Petrillo M et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28549976
7	Factors predicting use of neoadjuvant chemotherapy compared with primary debulking surgery in advanced stage ovarian cancer – a National Cancer Database Study	Leiserowitz GS et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28328580
8	Neoadjuvant chemotherapy and chemotherapy cycle number: a national multicentre study	Altman AD et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28800940
9	Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: first-line interventions	Karam A et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28327917
10	Risk of subsequent ovarian cancer after ovarian conservation in young women with stage I endometrioid endometrial cancer	Matsuo K et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28697110
11	A GCIG Phase III randomised trial evaluating weekly dose- dense chemotherapy integration in first-line epithelial ovarian/ fallopian tube/ primary peritoneal carcinoma (EOC) treatment: results of primary progression	Lederman et al.		ESMO Annual Meeting September 2017. Abstract 9290

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Medical treatment of recurrent ovarian cancer

Editor Ilker Selcuk

Descriptive summary

Motolimod

The efficacy and safety of motolimod was evaluated in a phase II, randomised, placebo-controlled trial. Motolimod is a synthetic, selective agonist of Toll-like receptor 8, which is found in the endosomal compartments of monocytes, and stimulates release of inflammatory cytokines and T helper-1 cells. It stimulates natural killer (NK) cell activity and cellular toxicity. TLR8 engagement provides an innate and adaptive anti-tumour activity in combination with the immunomodulatory effect of pegylated liposomal doxorubicin (PLD). With a 1:1 ratio, 296 patients were randomised to PLD 40 mg/m2 i.v. + either 3.0 mg/m2 motolimod or placebo. Stratification factors were the platinum-free interval (≤ 6 months vs. > 6–12 months) and GOG performance status (0 versus 1). Motolimod was well tolerated without any unexpected adverse effects, only injection site reaction and some simple immune reactions were more common than the placebo arm. However, no improvement in the overall survival (OS) (motolimod + PLD 18.1 months, placebo + PLD 18.9 months, HR: 1.22, p = 0.923) and progression-free survival (PFS) (motolimod + PLD 4.8 months, placebo + PLD 5.2 months, HR: 1.21, p = 0.943) was observed [1].

Irinotecan

Shoji et al. evaluated the role of irinotecan, a topoisomerase I inhibitor, in a phase II clinical study with PLD in platinum and taxane-resistant recurrent ovarian cancer patients (31p). PLD i.v. 30mg/m2 + 80mg/m2 irinotecan were administered. However, the results were disappointing, with a response rate of 32.3%, a median PFS of 2m (95% CI: 2–6) and only 12.9% (95% CI: 4.9–29.7) surviving one year [2].

Endocrine treatment

Colon-Otero et al. published the results of a phase II trial, combination of everolimus (10mg daily) and letrozole (2.5mg daily) in patients with relapsed oestrogen receptor positive high-grade ovarian cancer (n = 19). Median PFS was 3.9m (95% CI: 2.8–11.0) and median OS was 13m (95% CI: 8.8–not reached) with 32% (95% CI: 16%–61%) being relapse-free at six months. The potential synergism between letrozole and everolimus is highlighted by this study as single agent aromatase inhibitor has limited clinical activity in ovarian carcinoma (more beneficial for low-grade serous ovarian carcinoma). The largest phase II trial showed 3m PFS for letrozole (Bowman et al. Clin. Cancer Res. 8 (2002) 2233–2239), which is similar to what is reported from the Paragon study (see below) [3].

Anastrozole

Bonaventura et al. studied the aromatase inhibitor anastrozole in women with oestrogen or progesterone receptor positive, platinum-resistant or refractory-recurrent ovarian carcinoma in a phase II basket study (Paragon). In total, 49 patients were studied and clinical benefit was detected in 13 (27%) patients, but no partial or complete responses. Median PFS was 2.7m (95% CI: 2.6–5.7m). Anastrozole was well tolerated, however, 83% of patients had disease progression within six months. Despite a greater benefit in patients with an oestrogen receptor histoscore of more than 200, the difference was not significant, so the challenge remains how to identify a subset most likely to benefit from endocrine treatment [4].

Angiogenesis

Coleman et al. reported the results of a multicentre, open-label, randomised, phase III, GOG-0213 trial in patients with recurrent platinum-sensitive ovarian cancer; 657 patients were assigned to paclitaxel (175 mg/m2)-carboplatin (area under curve=5) or taxol-carboplatin + bevacizumab (bev) combination therapy followed by bevacizumab maintenance. Median follow-up was 49.6 months (40.8–59.3m for chemotherapy alone (CT) and 41.5–62.2m for CT + bev group). Median PFS was significantly longer with bev 13.8 (95% CI: 13.0–14.7) vs. 10.4 (9.7–11.0) months, respectively (HR 0.628, 95% CI: 0.534–0.739, p < 0.0001). Median OS for the CT and CT+bev arm was 37.3m (95% CI: 32.6–39.7) and 42.2m (95% CI: 37.7–46.2), respectively (hazard ratio-HR, 0.829; 95% CI, 0.683–1.005; p = 0.056). Despite a non-significant overall survival period, the addition of bev might be an important therapeutic target; hypertension, fatigue and proteinuria were more common in the bev arm [5].

The AURELIA trial showed that in patients with platinum-resistant ovarian cancer, CT+bev significantly improved PFS: 6.7m versus 3.4m, respectively. However, post-progression use of bev may have confounded OS results. Bamias et al. explored the role of bevacizumab in patients with disease progression. In all, 182 patients were randomised to CT alone, of those, 72 received bev after disease progression and 110 never received bev. Compared to patients who had no bev treatment, the hazard ratio (HR) for OS in the bev prior to progression group was 0.68 (95% CI: 0.52–0.90, p = 0.01) and in patients with bev after disease progression was 0.60 (95% CI: 0.43–0.86, p = 0.01). Bevacizumab showed better OS for platinum-resistant patients both when administered upfront or after progression

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Medical treatment of recurrent ovarian cancer

Descriptive summary (cont.)

(bev after progressive disease on CT alone). The tolerability of bevacizumab after disease progression was similar [6].

The report by Dinkic et al. on pazopanib and cyclophosphamide in patients with platinum-resistant or refractory, recurrent, ovarian cancer patients (PACOVAR trial) is included in the report by Yaznil and Drews on "Emerging molecular-targeted therapies or early clinical trials in ovarian cancer" [7].

Olaparib

Pujade-Lauraine et al. report on SOLO 2, a randomised, double-blind, placebo-controlled, phase III trial of olaparib tablets in maintenance treatment for patients with platinum-sensitive relapsed ovarian BRCA1/2 positive. Patients who received at least two previous lines of platinum-based chemotherapy and were in objective response were included. Patients were randomised 2:1 to olaparib (n = 195) (300mg, twice daily with 150mg tablets) or placebo (n = 99). Patients had their BRCA mutation before enrolment. Olaparib maintenance treatment provided significantly longer median PFS (19.1m [95%CI: 16.3-25.7]) than placebo (5.5m [95%CI: 5.2-5.8]), HR 0.30 (95% CI: 0.22–0.41), p < 0.0001. The most common grade 3 or worse adverse event was anaemia (19% vs. 2%). These results are in line with other maintenance trials on PARP (NOVA study, Ariel 3) [8].

Rose et al. retrospectively evaluated the role of PLD in low-grade serous ovarian carcinoma patients. A limited number of patients (platinum-resistant, n = 10, and platinum-sensitive, n = 8) were analysed and there was one response in each group of patients; however, 12 patients in total had stable disease. For the platinum-resistant and sensitive group, the median PFS length was 13.5m (95% CI: 2.0–31.0) and 19.5m (95% CI: 2.0–not reached), respectively (p = 0.62). PLD is relatively active in recurrent low-grade ovarian cancer patients with a considerable proportion of stable disease [9].

Platinum-free interval

Bookman et al. analysed the impact of platinum-free interval (PFI) and BRCA mutation status on OS in recurrent ovarian cancer patients in a multicentre, retrospective observational cohort study. In total, 750 patients were reviewed and a primary PFI ≥ 6 m showed a significantly longer median OS than PFI < 6m also for OS after second line (26.2m vs. 12.1m, p < 0.0001) and third-line treatment (15.2m vs. 9.7m, p < 0.002). Moreover, patients with BRCA mutations seem to have better survival throughout multiple lines of treatment, however, these results were not statistically significant [10].

Since platinum-free interval (PFI) is prognostic for OS in patients with ovarian carcinoma, the open-label, prospective, randomised, superiority trial MITO-8 reported by Pignata et al. aimed to improve the overall outcome by prolonging PFI by administration of a non-platinum based chemotherapy after disease relapse 6–12 months of the last chemotherapy. Patients were 1:1 randomised to the standard arm (n = 108) with platinum-based chemotherapy (PBC), or non-platinum based chemotherapy (n = 107). The study showed no beneficial effect of non-PBC on OS (median 21.8m vs. 24.5m, HR 1.38; 95% CI: 0.99–1.94, p = 0.06) and also similar results for PFS (median 12.8 vs. 16.4m, HR 1.41, 95% CI: 1.04–1.92). Still, PBC remains the first option for platinum-sensitive or partially sensitive patients after disease relapse [11].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	A phase 2, randomized, double-blind, placebo- controlled study of chemo -immunotherapy combination using motolimod with pegylated liposomal doxorubicin in recurrent or persistent ovarian cancer: a Gynecologic Oncology Group partners study	Monk BJ et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28453702
2	A phase II study of irinotecan and pegylated liposomal doxorubicin in platinum resistant recurrent ovarian cancer (Tohoku Gynecologic Cancer Unit 104 study)	Shoji T et al.	Cancer Chemother Pharmacol	https://www.ncbi.nlm.nih.gov/pubmed/28656383
3	Phase 2 trial of everolimus and letrozole in relapsed estrogen receptor-positive high-grade ovarian cancers	Colon-Otero G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28461031
4	Paragon (ANZGOG-0903) Phase 2 study of anastrozole in women with estrogen or progesterone receptor positive platinum-resistant or -refractory recurrent ovarian cancer	Bonaventura A et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28498256

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5	Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial	Coleman RL et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28438473/?ncbi_mmode=std
6	Bevacizumab with or after chemotherapy for platinum-resistant recurrent ovarian cancer: exploratory analyses of the AURELIA trial	Bamias A et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28481967
7	Pazopanib (GW786034) and cyclophosphamide in patients with platinum-resistant, recurrent, pre-treated ovarian cancer — results of the PACOVAR-trial	Dinkic C et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28528917
8	Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial	Pujade-Lauraine E et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28754483
9	Efficacy of pegylated liposomal doxorubicin in low-grade serous ovarian carcinoma	Rose PG et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28498259
10	Impact of primary platinum-free interval and BRCA1/2 mutation status on treatment and survival in patients with recurrent ovarian cancer	Bookman MA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28454659
11	Randomized controlled trial testing the efficacy of platinum-free interval prolongation in advanced ovarian cancer: the MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study	Pignata S et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28825853

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Treatment of ovarian sex cord stromal and germ cell tumours

Editor Anna Dückelmann

Descriptive summary

Adefris and Fekadu published a case report of a woman with ovarian granulosa cell tumour (GCT) presenting with hirsutism. The authors conclude that in postmenopausal women with new onset hirsutism, severe or rapidly progressive, an androgen-secreting tumour must be suspected and a thorough evaluation is needed before initiating treatment for idiopathic hirsutism [1].

A review of 29 retrospective studies reporting the prognosis of adult-type granulosa cell tumour (AGCT) patients points out that testing for the FOXL2 mutation is crucial for the differential diagnosis in these patients as the histological diagnosis of AGCT of the ovary is challenging. Anti-Müllerian Hormone and Inhibin B are currently the most accurate circulating biomarkers [2].

Bufa et al. described two cases of postmenopausal women with AGCT of the ovary. Interestingly, they observed a correlation between increased levels of urinary steroids and the recurrence of AGCT. They conclude that a urinary steroid profile could be a more effective method for monitoring such patients during follow-up [3].

De Kock et al. investigated the association between mutations and specific morphologic features in a series of 34 ovarian SLCT. All 30 moderately differentiated/poorly differentiated SLCTs contained DICER1 mutations, whereas well-differentiated SLCTs appear to be DICER1-independent. The authors discuss that well differentiated SLCTs may constitute a unique entity with a different pathogenesis from moderately differentiated and poorly differentiated SLCTs [4].

Rathore et al. correlate the diagnostic utility of FOXL2 with inhibin and calretinin in the diagnosis of ovarian SCSTs. In contrast to inhibin and calretinin, FOXL2 had a sensitivity and specificity of 100% in all cases [5].

In their review on genomic studies of ovarian sex cord-stromal tumours (SCST), Fuller et al. report recurrent DICER1 mutations in non-hereditary cases of Sertoli cell and Sertoli-Leydig cell tumours (SLCTs) and recurrent somatic mutations in both the juvenile and adult forms of GCTs [6].

In a retrospective study by Zhao et al., the role of ovarian cystectomy in patients with early-stage immature teratoma was investigated. None of the 14 patients who was treated with cystectomy only relapsed during follow-up. The authors speculate that cystectomy could be considered for patients with apparent early-stage immature teratoma without compromising survival [7].

According to clinical, morphological, and immunohistochemical examination, small-cell carcinoma of the ovary of hypercalcaemic type is a primitive germ-cell neoplasm arising from a teratoma [8].

Na et al. analysed the immunohistochemical p16 expression in the peritumoural stroma of primary and recurrent AGCTs and investigate whether there were significant differences in stromal p16 expression among nonpathological ovaries, benign sex cord-stromal tumours, and adult granulosa cell tumours. Primary AGCTs had significantly higher stromal p16 expression levels than nonpathological ovaries and benign sex cord-stromal tumours. Moreover, recurrent AGCTs showed significantly elevated levels of stromal p16 expression compared to primary AGCTs [9].

Seagle et al. studied prognostic factors in a large cohort of women with GCT. They conclude that incomplete staging (surgery without bilateral salpingo-oophorectomy and hysterectomy) is associated with decreased survival in stage I GCT. There is no evidence of increased survival with use of adjuvant chemotherapy in stages II–IV. The role of lymph node dissection remains controversial, as the rate of lymph node metastasis in early stage disease is low. In more advanced stages, lymph nodes are also more often involved. Lymph node status does still not directly guide adjuvant treatment to an extent that it modifies survival [10].

A retrospective study of 561 women diagnosed with ovarian yolk sac tumours showed early disease stage, younger age, and treatment with adjuvant chemotherapy, but not omentectomy, hysterectomy, and lymph node sampling/dissection were independently associated with better survival [11].

An interesting case report described a case of extraovarian fibroma with minor sex cord elements arising in the left broad ligament. To date, 17 cases of this entity have been reported in the English-language literature. Extraovarian sex cord-stromal tumour may originate from postsurgical implants, postinflammatory implants, an accessory ovary, a supernumerary ovary, or ovary autoamputation [12].

A retrospective study by Park et al. evaluated the oncologic and reproductive outcomes and prognostic factors after fertility-sparing surgery in 171 patients with early and advanced malignant ovarian germ cell tumours. Survival outcomes were excellent. The pregnancy rate was 75%, and live birth rate was 65%. Yolk sac tumour, incomplete surgical staging, and residual tumour were independent prognostic factors of poor survival [13].

Solheim et al. analysed the expression and potential clinical role of epithelial-to-mesenchymal transition (EMT)-related factors in malignant ovarian germ cell tumours (MOGCT). In contrast to ovarian carcinomas, they found no association between EMT-associated markers and clinical parameters in MOGCT [14].

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No	Title	Authors	Journal	Link to abstract
1	Postmenopausal mild hirsutism and hyperandrogenemia due to granulosa cell tumour of the ovary: a case report	Adefris M et al.	J Med Case Rep	https://www.ncbi.nlm.nih.gov/pubmed/28851436
2	Pathogenesis and treatment of adult-type granulosa cell tumour of the ovary	Färkkilä A et al.	Ann Med	https://www.ncbi.nlm.nih.gov/pubmed/28276867
3	Diagnostic relevance of urinary steroid profiles on ovarian granulosa cell tumours: two case reports	Bufa A et al.	J Med Case Rep	https://www.ncbi.nlm.nih.gov/pubmed/28637499
4	DICER1 mutations are consistently present in moderately and poorly differentiated sertoli-leydig cell tumours	de Kock L et al.	Am J Surg Pathol	https://www.ncbi.nlm.nih.gov/pubmed/28654427
5	Correlation of FOXL2 with inhibin and calretinin in the diagnosis of ovarian sex cord stromal tumours	Rathore R et al.	Turk Patoloji Derg	https://www.ncbi.nlm.nih.gov/pubmed/28272677
6	Genetics and genomics of ovarian sex cord-stromal tumours	Fuller PJ et al.	Clin Genet	https://www.ncbi.nlm.nih.gov/pubmed/27813081
7	Ovarian cystectomy in the treatment of apparent early-stage immature teratoma	Zhao T et al.	J Int Med Res	https://www.ncbi.nlm.nih.gov/pubmed/28415950
8	Clinical, morphological and immunohistochemical evidence that small-cell carcinoma of the ovary of hypercalcaemic type (SCCOHT) may be a primitive germ-cell neoplasm	McCluggage WG et al.	Histopathology	https://www.ncbi.nlm.nih.gov/pubmed/28130795
9	Stromal p16 overexpression in adult granulose cell tumours of the ovary	Na K et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28476811
10	Ovarian granulosa cell tumour: a National Cancer Database study	Seagle BL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28532858
11	Management and prognosis of ovarian yolk sac tumours; an analysis of the National Cancer Data Base	Nasioudis D et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28803748
12	Extraovarian fibroma with minor sex cord elements: a case report and literature review	Omori M et al.	Int J Surg Pathol	https://www.ncbi.nlm.nih.gov/labs/articles/28351194/
13	Analysis of outcomes and prognostic factors after fertility-sparing surgery in malignant ovarian germ cell tumours	Park JY et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28372870
14	Epithelial–mesenchymal transition markers in malignant ovarian germ cell tumors	Solheim O et al.	APMIS	https://www.ncbi.nlm.nih.gov/pubmed/28585395

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

Editor Muhammad Rizki Yaznil and Florian Drews

Descriptive summary

Since the last LiFE report, a multitude of papers have been published on new treatment modalities and phase I trials for ovarian cancer.

A phase I study of anti-angiogenic pazopanib (multi TK inhibitor) combined with metronomic oral cyclophosphamide in recurrent platinum-resistant and previously treated advanced ovarian cancer (PACOVAR trial) by Dinkic et al. showed that pazopanib in combination with metronomic cyclophosphamide had a MTD of 600mg per day. The main side effects were elevation of liver enzymes, diarrhoea, and changes in white blood cell count. Notably, quality of life was not reduced. Furthermore, after 12 weeks of treatment, a complete or partial response was observed in 36% of patients. Median time to progression was 9.47 months and median overall survival at 600mg was 25.3 months [1].

Human epithelial growth factor receptor 2 (HER2/ErbB2) plays a significant role in the development and prognosis of multiple human tumours. Menderes et al. evaluated the anti-tumour activity of SYD985 in comparison to T-DM1 in vitro and in vivo against primary EOC cell lines with different levels of HER2/neu expression. SYD985 is a novel HER2-targeting antibody-drug conjugate (ADC) with remarkable activity against EOC with low/moderate and high HER2/neu expression. SYD985 is significantly more potent than T-DM1 (trastuzumab emtansine) and may be active against EOC independent of HER2/neu expression [2].

MELK (maternal embryonic leucine zipper kinase) is a highly conserved serine/threonine kinase highly expressed in several human cancers and is proposed to play a role in cell cycle control, drug resistance, embryogenesis, and oncogenesis. Kohler et al. showed that MELK was elevated in EOC, and correlated with poorer outcome. MELK inhibition/depletion abrogated proliferation and oncogenic growth by interrupting the cell cycle and inducing apoptosis. The MELK-inhibitor OTSSP167 retained its effectivity in paclitaxel-resistant (IGROV1) and cisplatin-resistant (TYK-nu) cells and sensitised OVCAR8 cells to carboplatin. They conclude that elevated MELK in EOC is a possible therapeutic target and that OTSSP167 is a potential novel compound against (drug-resistant) aggressive ovarian cancers (especially epithelial, undifferentiated, and MMMT) [3].

Histone deacetylases (HDAC), especially HDAC10, have been shown to stimulate homologous recombination in HeLa cells. As such, HDAC10 inhibition would be an interesting target to enhance sensitivity of chemotherapy to ovarian cancer. The study from Islam et al. discovered 1) serous ovarian cancers more commonly have HDAC10 deletions than the general population; 2) in ovarian cancers homozygous deletion of HDAC10 correlated with tumour sensitivity to cisplatin; 3) HDAC inhibitors potentiated the cytotoxicity of cisplatin in primary ovarian cancer cell lines derived from tumour ascites; 4) HDAC inhibitors potentiated the inhibition by cisplatin of DNA repair by homologous recombination; and 5) HDAC10 was required for DNA repair and survival in cells damaged by ionising radiation or cisplatin treatment. Their results provide evidence for exploring HDAC10-specific inhibition as an adjuvant therapy to platinum therapies, especially for BRCA1-deficient ovarian carcinoma patients [4].

Neurotensin (NTS) is a neurotransmitter in the CNS and hormone in the GI tract. The complex of NTS and its high affinity receptor 1 (NTSR1) was shown to contribute to cancer progression. NTSR1 was found overexpressed in several types of solid cancers, in association with the dysregulation of the beta-catenin pathway or epigenetic regulation. Liu et al. reported that blocking the NTS/NTSR1 complex improves the effectivity of carboplatin in ovarian cancer by enhancing the drug-to-target ratio [5].

Filamin A interacting protein 1-like (FILIP1L) is a novel regulator of angiogenesis. Overexpression of FILIP1L could lead to induction of tumour cell apoptosis and inhibition of tumour cell proliferation; FILIP1LΔC103 (COOH terminal truncation mutant 1-790 of FILIP1L) is more effective than wild-type FILIP1L in mediating these activities. Xie et al. combined targeted gene FILIP1LΔC103 with low-dose cisplatin in the ovarian carcinoma therapy. This regimen revealed synergistic anti-tumour effects. Biodegradable cationic HPEI nanogels could serve as a competent gene carrier, without perceivable toxicity at the used dosage. Thus, HPEI nanogels loaded with FILIP1LΔC103 amalgamated with DDP might become a novel therapeutic strategy in ovarian cancer treatment [6].

Nakamura et al. investigated non-thermal atmospheric pressure plasma (plasma-activated medium PAM) as a new therapeutic tool for cancer treatment. PAM suppressed ovarian cancer (ES2) cell migration, invasion and adhesion in-vitro and in-vivo, while cell viability remained unaffected. Prolonged survival was demonstrated in in-vivo mouse models, where PAM inhibited peritoneal dissemination of ES2 cells. On a molecular level, PAM decreased MMP-9 secretion, which is critical for cancer cell motility and prevented the activation of the MAPK pathway. The authors' findings suggest that intraperitoneal PAM therapy may be a promising new treatment option for ovarian cancer [7].

Liu et al. investigated the inhibitory effect of the mammalian lignans (phytoestrogens with oestrogen-like biological activity) enterodiol

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

Descriptive summary (cont.)

(END) and enterolactone (ENL) on ovarian cancer. Their inhibitory effect on ovarian cancer ES2 cell lines in-vitro and in-vivo xenografts on nude mice was demonstrated. Compared to END, ENL behaved in a better time-dose dependent manner on cancer cells in-vitro. In vivo, ENL had better anti-cancer activities and caused fewer side effects. In conclusion, both lignans have potent inhibitory effects, with ENL as the better candidate for potential drug development due to its greater inhibitory effect better side effect profile [8].

Moore et al. carried out a phase I dose-escalation study of mirvetuximab soravtansine (IMGN853), which is an antibody-drug conjugate that selectively targets folate-receptor (FR). To determine the maximum tolerated dose, 44 patients received three weekly IMGN853, until they experienced dose-limiting toxicity or progression. The most common treatment-related adverse events were fatigue, blurred vision, and diarrhoea, the majority of which were grade 1 or 2. Hypophosphatemia and punctate keratitis were the only observed grade 3 dose-limiting toxicities. The authors concluded that IMGN853 has a manageable safety profile at a recommended phase-II dosing of 6.0 mg/kg [9].

Novel compounds with combined cytotoxic and anti-angiogenic properties may show significant improvements in treating refractory ovarian cancer. Rickardson et al. evaluated the anti-tumour activity of the novel microtubule-targeting and vascular-disrupting-agent NOV202. In vitro/vivo, NOV202 was found to suppress cancer cell proliferation and showed equal efficacy between OC cell line A2780 and its multidrug-resistant subline A2780/Adr. The in-vivo effect was comparable to paclitaxel at high doses. In conclusion, NOV202 induced significantly more cell death in OC cells overexpressing Pgp/MDR1, warranting further development of the compound for treating refractory tumours [10].

Members of the ErbB family of receptors are over-expressed in EOC and play key roles in chemotherapy resistance and invasiveness. Thus far, single-targeted ErbB inhibitors have demonstrated only limited activity in chemotherapy resistant EOC. Momeny et al. investigated dacomitinib, a pan-inhibitor of ErbB receptors, in therapy-resistant epithelial ovarian carcinoma (EOC) cells. Dacomitinib inhibits the PLK1-FOXM1 signalling pathway and its down-stream targets Aurora kinase B and survivin. This report demonstrated that dacomitinib diminished growth, clonogenic potential, and induced apoptotic cell death. Furthermore, migration and invasion of EOC cells were attenuated and reduced expression of epithelial-to-mesenchymal transition markers was found. The authors concluded that the therapeutic potential of dacomitinib in the treatment of treatment resistant EOC warrants further investigation [11].

Cha et al. investigated BGJ398 (FGFR inhibitor), which inhibits phosphorylation of AKT and STAT3 in sphere-cultured SKOV3ip1 ovarian cancer cell lines. The differential expression of key signalling molecules in cell survival and proliferation were examined between sphere-cultured and monolayer-cultured SKOV3ip1 cells. The hypothesis is that sphere culture better mimics tumour microenvironment compared to monolayer culture. Compared to monolayer-cultured SKOV3ip1 cells, the phosphorylation of AKT and signal transducer and activator of transcription 3 (STAT3) were up-regulated in sphere-cultured SKOV3ip1 cells. The cell viability and phosphorylation of AKT/STAT3 were markedly reduced in sphere-cultured SKOV3ip1 cells following treatment with BGJ398 opposed to the monolayer culture. Interestingly, a synergistic inhibitory effect was demonstrated in combination with paclitaxel. The authors concluded that BGJ398 is a potent anti-tumour agent in ovarian cancer and FGFR is a promising therapeutic target [12].

Kuhn et al. present a 3D-Matrigel culture-based expansion of directed evolution method for the generation of oncolytic virotherapies and two promising ovarian-cancer targeted oncolytic viruses, OvAd1 and OvAd2. Both viruses are potent against a panel of platinum-resistant ovarian cancer cell lines and are attenuated in normal cells. OvAd1 was developed using 3D-Matrigel cell cultures, whereas OvAd2 was developed in a monolayer culture. Matrigel-based cultures caused a more strongly attenuated bioselected pool on normal cells with normal potency against ovarian cancer cells. Furthermore, in an ovarian carcinomatosis model, OvAd1 suppressed all tumour growth, while OvAd2 was only 50% effective. Lastly, no virus stimulated peritoneal adhesion formation, as previously seen for Ad5-based therapies. The authors concluded that both viruses are novel candidates as treatment of aggressive ovarian cancer [13].

Jandial et al. investigated the role of intraperitoneal (IP) chemotherapy in recurrent ovarian cancer and carried out a phase I study on a proteasome inhibitor bortezomib prior to IP carboplatin to increase tumour platinum accumulation. Thirty-three patients received up to six cycles every 21 days. The overall response rate was 19% in patients with measurable disease. Grade 3 and 4 toxicities were infrequent and included abdominal pain, nausea, vomiting and diarrhoea. The authors concluded that this combination treatment was feasible in the treatment of recurrent ovarian cancer [14].

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

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1	Pazopanib (GW786034) and cyclophosphamide in patients with platinum-resistant, recurrent, pre-treated ovarian cancer – results of the PACOVAR-trial	Dinkic C et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28528917
2	SYD985, a novel duocarmycin-based HER2-targeting antibody-drug conjugate, shows promising antitumor activity in epithelial ovarian carcinoma with HER2/Neu expression	Menderes G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28473206
3	MELK expression in ovarian cancer correlates with poor outcome and its inhibition by OTSSP167 abrogates proliferation and viability of ovarian cancer cells	Kohler R et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28214016
4	HDAC10 as a potential therapeutic target in ovarian cancer	Islam MM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28073598
5	Neurotensin receptor 1 antagonist SR48692 improves response to carboplatin by enhancing apoptosis and inhibiting drug efflux in ovarian cancer	Liu J et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28790113
6	Enhanced antitumor effect of biodegradable cationic heparin-polyethyleneimine nanogels delivering FILIP1LΔC103 gene combined with low-dose cisplatin on ovarian cancer	Xie C et al.	OncoTarget	https://www.ncbi.nlm.nih.gov/pubmed/22825572
7	Novel intraperitoneal treatment with non-thermal plasma-activated medium inhibits metastatic potential of ovarian cancer cells	Nakamura K et al.	Sci Rep	https://www.ncbi.nlm.nih.gov/pubmed/28729634
8	Enterolactone has stronger effects than enterodiol on ovarian cancer	Liu H et al.	J Ovarian Res	https://www.ncbi.nlm.nih.gov/pubmed/28738876
9	Phase 1 dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor -targeting antibody-drug conjugate, in patients with solid tumours	Moore KN et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28440955
10	Evaluation of the antitumor activity of NOV202, a novel microtubule targeting and vascular disrupting agent	Rickardson L et al.	Drug Des Devel Ther	https://www.ncbi.nlm.nih.gov/pubmed/28496304
11	Dacomitinib, a pan-inhibitor of ErbB receptors, suppresses growth and invasive capacity of chemoresistant ovarian carcinoma cells	Momeny M et al.	Sci Rep	https://www.ncbi.nlm.nih.gov/pubmed/28646172
12	Selective FGFR inhibitor BGJ398 inhibits phosphorylation of AKT and STAT3 and induces cytotoxicity in sphere-cultured ovarian cancer cells	Cha HJ et al.	Int J Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28350116
13	OvAd1, a novel, potent, and selective chimeric oncolytic virus developed for ovarian cancer by 3D-directed evolution	Kuhn I et al.	Mol Ther Oncolytics	https://www.ncbi.nlm.nih.gov/pubmed/28345024
14	A phase I pharmacokinetic study of intraperitoneal bortezomib and carboplatin in patients with persistent or recurrent ovarian cancer: an NRG Oncology/Gynecologic Oncology Group study	Jandial DA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28341300

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

Editor Sara Giovannoni

Descriptive summary

PARP inhibitors

Niraparib

On March 27, the Food and Drug Administration (FDA) approved niraparib as a maintenance therapy in women with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy [1]. Approval was based on the results of the NOVA trial that randomised 553 patients to either niraparib or matched placebo. Niraparib demonstrated a significant improvement in PFS irrespective of the presence or absence of a germline BRCA mutation or homologous recombinant deficiency (HRD), becoming a new future option in the maintenance treatment of platinum-sensitive patients including women without BRCA mutation or HRD. A recent review summarises the data and the toxicity profile of these drugs [2].

Veliparib

Steffensen et al. published the results of a phase I–II study investigating the effect of veliparib in heavily pretreated patients with BRCA mutations and with a platinum resistant or partially platinum-sensitive ovarian cancer relapse. Treatment with veliparib yielded a PFS of 5.6 months and an OS of 13.7 months [3]. Veliparib, as monotherapy, seems to be promising also in patients with otherwise poor prognosis. This trial is in line with another phase II study on veliparib with a dose of 400mg yielding a median PFS of 8.18 b.i.d. months for patients with gBRCA [4].

Recently a phase I dose escalation trial on veliparib plus carboplatin and weekly paclitaxel in first-line treatment confirmed the safety and tolerability of this PARP inhibitor at a recommended dose of 150 mg b.i.d. [5]. Other trials including veliparib in combination with chemotherapy are ongoing.

Olaparib

Pujade-Lauraine et al. published the final results of the phase III placebo controlled SOLO2 trial evaluating olaparib maintenance in platinum-sensitive relapsed ovarian cancer patients with BRCA1/2 mutations. The study enrolled 295 patients. The trial confirmed the efficacy of olaparib with a PFS of 19.1 months versus 5.5 months (HR 0.30) with placebo, with no detrimental effect on quality of life [6]. This study is also discussed in the chapter on "Medical treatment of relapsed ovarian cancer" by Selcuk. At ASCO 2017, Friedlander presented the health-related quality of life (HRQOL) data with maintenance olaparib of the patients enrolled in the SOLO2 trial through the Functional Assessment of Cancer Therapy-Ovarian trial outcome index (FACT-O TOI) [7]. This analysis showed no significant detrimental effect of olaparib versus placebo in TOI score, but a significant improvement on maintenance olaparib on TWiST (time without symptoms of disease or toxicity).

Dougherty et al. investigated the role of somatic mutations in olaparib response showing a similar clinical outcome for placebo and olaparib in patients with somatic BRCA1/2 mutations and germline mutations [8]. The Ariel 2 trial studied the efficacy of the PARP inhibitor rucaparib in patients with relapsed ovarian cancers with BRCA somatic or germline mutations (median PFS 13 months and RR 72% in both groups). The results support the hypothesis that the majority of somatic BRCA mutated cases have a similar biological phenotype as germline BRCA1/2 mutated tumours, explaining their responsiveness to PARP inhibitors [9].

Clinical and molecule predictors of antitumor response to olaparib

Rafii et al. retrospectively studied baseline clinical predictors of response to olaparib in BRCA1/2 mutated patients [10]. RECIST CR/PR rate was significantly lower in platinum-resistant patients compared to those with platinum-sensitive disease (13% vs. 35%, $p = 0.02$), but response rates of 15% in patients deemed platinum-resistant suggests that platinum response status is not an absolute predictor of response to olaparib. No association was found between other clinical factors such as FIGO staging, debulking surgery or prior history of breast history and the response to olaparib. The results also demonstrated the impact of the interval between the end of the most recent platinum chemotherapy and olaparib as a predictive factor for response to olaparib. Patients with > 24 weeks between platinum-CT and commencement of PARP had significantly higher response rates than patients with an interval of < 24 weeks (34.5% vs. 10%, $p = 0.04$). These findings were independent of the platinum response status [10].

Risk-reducing strategies and quality of life in BRCA1/2 mutation carriers

The systematic review by Tschernichovsky et al. summarises the current evidence on risk-reducing surgery in BRCA mutation carriers. Risk-reducing salpingo-oophorectomy (RRSO) is currently the most effective method for reducing the risk of ovarian cancer in BRCA mutation carrier women as supported by international guidelines. RRSO is associated with significant short- and long-term morbidity,

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

Descriptive summary (cont.)

stemming from reduced circulating oestrogen. Also, a significant proportion of cancers identified at RRSO are localised to the fallopian tube rather than the ovary. Salpingectomy with delayed oophorectomy could be an adequate risk reducing approach in selected patients, however, further studies are needed [11].

The quality of life after RRSO has been explored in an interesting recent review on the role of a short-term hormonal therapy as a valid strategy to improve quality of life leading to an improvement in sexual function, vasomotor symptoms, vaginal atrophy, and bone loss [12].

The beneficial effects of hormonal therapy administered after RRSO has been also confirmed in a recent prospective study by Vermeulen et al. However, the positive effect of endocrine and sexual symptoms in HRT users persisted in the first year only, with no significant differences thereafter [13].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Niraparib: first global approval	Scott LJ	Drugs	https://www.ncbi.nlm.nih.gov/pubmed/28474297
2	Niraparib for the treatment of ovarian cancer	Kanjanapan Y et al.	Expert Opin Pharmacother	https://www.ncbi.nlm.nih.gov/pubmed/28299955
3	Veliparib monotherapy to patients with BRCA germ line mutation and platinum resistant or partially platinum sensitive relapse of epithelial ovarian cancer: a phase I/II study	Steffensen KD et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28763368
4	A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation—An NRG Oncology/Gynecologic Oncology Group study	Coleman RL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/25818403
5	A phase 1 study of veliparib with carboplatin and weekly paclitaxel in Japanese patients with newly diagnosed ovarian cancer	Nishio S et al.	Cancer Sci	https://www.ncbi.nlm.nih.gov/pubmed/28837250
6	Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial	Pujade-Lauraine E et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28754483
7	Health-related quality of life (HRQOL) and patient-centered outcomes with maintenance olaparib compared with placebo following chemotherapy in patients with germline (g) BRCA-mutated (m) platinum-sensitive relapsed serous ovarian cancer (PSR SOC): SOLO2 phase III trial	Friedlander M et al.		http://meetinglibrary.asco.org/record/153171/abstract
8	Biological and clinical evidence for somatic mutations in BRCA1 and BRCA2 as predictive markers for olaparib response in high-grade serous ovarian cancers in the maintenance setting	Dougherty BA et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/28525389
9	Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2.	Oza AM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28882436
10	Baseline clinical predictors of antitumor response to the PARP inhibitor olaparib in germline BRCA1/2 mutated patients with advanced ovarian cancer	Rafii S et al.	Oncotarget. 2017	https://www.ncbi.nlm.nih.gov/pubmed/28454085
11	A risk-reducing strategy for ovarian cancer in BRCA mutations carriers: a balancing act	Tschernichovsky R et al.	The Oncologist	https://www.ncbi.nlm.nih.gov/pubmed/28314837
12	The effect of hormone therapy on quality of life and breast cancer risk after risk-reducing salpingo-oophorectomy: asystematic review	Siyam T et al.	BMC Women's Health	https://www.ncbi.nlm.nih.gov/pubmed/28320467
13	Hormone replacement therapy after risk-reducing salpingo-oophorectomy minimises endocrine and sexual problems: a prospective study	Vermeulen RFM et al.	Eur J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28818705

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

Editor Santiago Scasso and Joel Laufer

Descriptive summary

Agopiantz et al. evaluated the contribution of neurotensin (NTS) to endometrial carcinogenesis. They analysed NTS receptor 1 (NTSR1) expression and NTSR1 promoter methylation in 385 cases of endometrial cancer (EC) from The Cancer Genome Atlas. The expression of NTSR1 was an independent poor prognostic factor in EC ($p = 0.004$). The authors highlighted the contribution of NTS in EC progression and its potential use as a prognostic marker [1].

Mancebo et al. analysed the prognostic impact of CD133 expression in EC. CD133+ tumours were less likely to have vascular invasion ($p=0.010$) and more likely to be well differentiated ($p=0.034$). C133+ tumours predicted favourable OS and PFS of EC patients, with a hazard ratio of 4.731. The authors support that CD133 tumour status emerges as a useful biomarker of low-risk EC and could be viewed as a complementary tool in the planning of primary treatment for EC as it provides a more accurate assessment of prognosis and adjuvant treatment [2].

Tomica et al. studied the status of hormone receptors in the myometrium of patients with EC. Patients with negative oestrogen receptors (ER) and progesterone receptor (PR) expression had a shorter period until recurrence ($p=0.013$ and 0.043) and shorter OS ($p= 0.011$ and 0.066). Their results showed that loss of hormone receptors in the myometrium indicate poor prognosis. Likewise, they postulate these results support the theory that stromal and myometrial cells contribute to tumorigenesis in EC [3].

Tangen et al. investigated L1CAM as a predictive marker for lymph node metastases and its prognostic impact in curettage specimens and preoperative plasma samples. Both in curettage and preoperative plasma samples, L1CAM upregulation was significantly associated with features of aggressive disease and poor outcome ($p < 0.001$). They demonstrate that preoperative evaluation of L1CAM levels (curettage and plasma) predicts lymph node metastases and adds valuable information on patient prognosis [4].

Cymbaluk-Ploska et al. explored the diagnostic potential of the serum levels of HE4 and MMP2 in patients with EC and benign endometrial diseases. They observed statistically significant differences in mean serum levels between the group of EC patients and the group of patients without EC ($p = 0.002/0.003$). HE4 and MMP2 are characterised by high specificity and may be useful as biomarkers in the diagnostics of endometrial cancer [5]. When determined preoperatively, HE4 is correlated with the prognostic factors of EC and may be helpful in the planning of individual treatment of EC patients.

Piulats et al. reviewed the usefulness of molecular techniques in classifying EC. Although histological classification is the current gold standard for patient stratification, molecular studies have obtained promising results providing important information about prognosis and predictive response to novel therapies. Topics included correlation between genotype and phenotype, the value of molecular pathology, including interobserver variation in pathologic interpretation, the importance of applying TCGA concepts to clinical practice, and its usefulness in tailoring immunotherapy. They suggested improving assessment and combining pathologic and a surrogate TCGA molecular classification for an optimal and prognostic classification [6].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Expression of neurotensin receptor 1 in endometrial adenocarcinoma is correlated with histological grade and clinical outcome	Agopiantz M et al.	Virchows Arch	http://www.ncbi.nlm.nih.gov/pubmed/28836043
2	Prognostic impact of CD133 expression in Endometrial Cancer Patients	Mancebo G et al.	Sci Rep	http://www.ncbi.nlm.nih.gov/pubmed/28794448
3	Impact of oestrogen and progesterone receptor expression in the cancer cells and myometrium on survival of patients with endometrial cancer	Tomica D et al.	J Obstet Gynaecol	http://www.ncbi.nlm.nih.gov/pubmed/28764605
4	Expression of L1CAM in curettage or high L1CAM level in preoperative blood samples predicts lymph node metastases and poor outcome in endometrial cancer patients	Tangen IL et al.	Br J Cancer	http://www.ncbi.nlm.nih.gov/pubmed/28751757
5	Clinical importance of serum HE4 and MMP2 levels in endometrial cancer patients	Cymbaluk-Płoska A et al.	Onco Targets Ther	http://www.ncbi.nlm.nih.gov/pubmed/28721066
6	Molecular approaches for classifying endometrial carcinoma	Piulats JM et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/28040204

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Screening for uterine cancer/hereditary uterine cancer

Editor María de los Reyes Oliver Pérez

Descriptive summary

Uterine cancer screening

The current American Cancer Society Guidelines in cancer screening have been reviewed. Regarding endometrial carcinoma (EC), universal screening is still not recommended but should be considered for women at very high risk. The following criteria are established for the EC: 1) known Lynch syndrome (LS) genetic mutation carrier status, 2) the substantial likelihood of being a mutation carrier or 3) the absence of genetic testing results in families with suspected autosomal-dominant predisposition. The annual endometrial biopsy from age 35 is still the standard for determining any pathology of the endometrium [1].

Hereditary uterine cancer (HUC)

Two literature reviews, two prospective and one retrospective study of LS have been published in the period covered by this LIFE report and selected for discussion [2–6].

LS-associated cancers are amenable to surveillance strategies that may improve survival. The age at which surveillance should start is still disputed [2,3,5,6]. Moller et al. have published two reports from the prospective LS database [2,3]. The first was based on follow-up of 1,942 mutation carriers without previous cancer [2]; it estimated the risk of cancer and the effects of surveillance were analysed by age, sex, and mutated gene. The cumulative incidence at 70 years for endometrial cancer was 34%, 51%, 49%, and 24% for MLH1, MSH2, MSH6, and PMS2 mutation carriers, respectively. The second report included 3,119 patients [3] and aimed to determine prospectively observed incidences of cancers and survival in path_MMR carriers up to 75 years of age. Cumulative incidences at age 75 for endometrial cancer were 43%, 57%, and 46% in path_MLH1, path_MSH2, and path_MSH6 carriers, respectively. Ryan et al. [4] published a retrospective cohort study of 1,063 individuals with proven LS associated colorectal, endometrial, and/or ovarian cancers. In women with EC, the incidence of MMR variant mutation was 27% for MLH1, 30% for MSH2 30%, and less prevalent for MSH6. Also, MSH6 mutation carriers presented EC at later ages than carriers of mutations in MSH2 or MLH1. In the three selected studies, the authors conclude that carriers of different path_MMR variants exhibit distinct patterns of cancer risk and survival. Therefore risk estimates for counselling and planning surveillance and treatment should be tailored to each patient's age and path_MMR variant.

Regarding universal screening for LS in EC, Watkins et al. [7] have published a prospective study in which 242 EC were screened for MLH1, PMS2, MSH2, and MSH6 deficiencies using IHC, followed by MLH1 promoter methylation testing when appropriate. They obtained an unmethylated MMR-deficient incidence of 4.5%. The LS incidence confirmed by 1 germline testing was 1.7%. The authors consider universal IHC screening a reasonable option.

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Cancer screening in the United States, 2017: 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/28170086
2	Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database	Moller P et al.	Gut	https://www.ncbi.nlm.nih.gov/pubmed/26657901
3	Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database	Moller P et al.	Gut	https://www.ncbi.nlm.nih.gov/pubmed/28754778
4	Association of mismatch repair mutation with age at cancer onset in Lynch syndrome implications for stratified surveillance strategies	Ryan NAJ et al.	JAMA Oncology	https://www.ncbi.nlm.nih.gov/pubmed/28772289
5	Current and future role of genetic screening in gynecologic malignancies	Ring KL et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28411145
6	Genetics of gynaecological cancers	Constantinou P et al.	Best Pract Res Clin Obstet Gynaecol	https://www.ncbi.nlm.nih.gov/pubmed/28202331
7	Universal screening for mismatch-repair deficiency in endometrial cancers to identify patients with Lynch syndrome and Lynch-like syndrome	Watkins JC et al.	Int J Gynecol Pathol	https://www.ncbi.nlm.nih.gov/pubmed/27556954

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

Editor Kastriot Dallaku and Elko Gliozheni

Descriptive summary

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

In their review, Sanderson et al. discussed current endometrial hyperplasia (EH) classification systems used to stratify women at risk of malignant progression to endometrial cancer (EC) and highlighted several potential immunohistochemical biomarkers that have been described as both diagnostic tools for EH and markers of progression to EC [1]. Van der Putten et al. analysed the presence of KRAS, PIK3CA, AKT1, CTNNB1, BRAF, EGFR, and NRAS mutations in the endometrium, and found no mutations in the included cases with benign endometrium, and only one mutation in the cases with simple hyperplasia [2]. Complex hyperplasia without atypia and complex atypical hyperplasia appear to be important steps in endometrial carcinogenesis, as most mutations were found in these cases. Bone morphogenetic protein (BMP) expression was found to be altered in women with abnormal uterine bleeding [3]. It was significantly decreased in EC compared to EH. Gupta et al. reported that evaluation of morphometric parameters of the endometrial cells in liquid-based cytology samples might be helpful to differentiate between benign and malignant endometrial lesions [4]. In Japan, endometrial cytology has been used as a screening tool in routine clinical practice. Munakata et al. validated the criteria of the New Terminology in Endometrial Cytology (NTEMC). Samples categorised as "suspicious" by endometrial cytology in 106 patients were re-evaluated according to the NTEMC criteria. Despite low inter-observer reproducibility (kappa value 0.14 +/- 0.019), the authors concluded the new system NTEMC system works well in clinical practice and properly reflects the atypical squamous cells categories in the Bethesda reporting system for cervical cytology [5]. The OSCAR-Endo protocol consisting of a fast-track protocol with hysteroscopy, dilation, and curettage [6] and liquid-based endometrial [7] were reported with very good results in daily clinical screening for endometrial malignancies.

Conservative and definitive treatment for patients with endometrial hyperplasia

Authors of the meta-analysis comparing the levonorgestrel-releasing intrauterine system (LNG-IUS) with oral cyclic medroxyprogesterone acetate (MPA) in EH [8] reported that the LNG-IUS treatment has a higher regression rate than cyclic MPA (RR 1.41; 95% CI: 1.23–1.62; four trials, 265 patients; I2 = 0%).

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Abnormal glucose metabolism and insulin resistance was highly prevalent in patients with atypical EH and EC in a population-based, case-control study with EH/ EC women and with gestational diabetes in the past (n = 256 EH/ EC patients) [9, 10]. Vitamin D supplementation was evaluated by Tabassi et al. in a randomised, double-blind, placebo-controlled trial conducted among 60 women diagnosed with EH (30 pt 50,000 IU of vitamin D3, two-week intervention). Vitamin D administration was associated with significant decreases in fasting plasma glucose (FPG) (-1.6 ± 7.0 vs. +2.1 ± 6.1 mg/dL, p = 0.03), serum insulin levels (-0.8 ± 1.9 vs. +1.1 ± 3.5 µIU/mL, p = 0.01), homeostasis model of assessment-insulin resistance (HOMA-IR) (-0.2 ± 0.6 vs. +0.3 ± 0.8, p = 0.01), and a significant increase in the quantitative insulin sensitivity check index (QUICKI) (+0.003 ± 0.01 vs. -0.01 ± 0.02, p = 0.02) compared with the placebo. The authors concluded that vitamin D3 supplementation for 12 weeks among women with EH had beneficial effects on glucose metabolism by improving glycaemic control [11]. In a randomised controlled trial of 50 participants, Moradan et al. compared the therapeutic effects of oral megestrol acetate (40mg daily for two weeks/month for a total period of two months) and letrozole (2.5mg daily for 2 months total) in the treatment of simple EH; both treatments appeared to have similar effects while letrozole had fewer side effects [12]. Uysal et al. compared the effectiveness of dienogest, MPA, and micronised progesterone for treatment of simple EH, confirming that DIE was an effective treatment in these cases [13]. In postmenopausal women with atypical EH or EC who are poor candidates for surgical intervention, LNG-IUS was recommended as a suitable treatment [14]. Risk of disease relapse was evaluated in series of 57 women with ES receiving LNG-IUS or oral progestin using clinical and biological markers [15]. The authors found a significant correlation with relapse of increased expression of progesterone receptor B and reduced expression of progesterone receptor A.

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

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	New concepts for an old problem: the diagnosis of endometrial hyperplasia	Sanderson PA et al.	Hum Reprod Update	https://www.ncbi.nlm.nih.gov/pubmed/27920066
2	Molecular profiles of benign and (pre)malignant endometrial lesions	van der Putten LJM et al.	Carcinogenesis	https://www.ncbi.nlm.nih.gov/pubmed/28203752
3	Abnormal uterine bleeding is associated with increased BMP7 expression in human endometrium	Richards EG et al.	Reprod Sci	https://www.ncbi.nlm.nih.gov/pubmed/28142396
4	Morphometric analysis of endometrial cells in liquid-based cervical cytology samples	Gupta P et al.	Cytopathology	https://www.ncbi.nlm.nih.gov/pubmed/27510614
5	Practical usefulness of atypical endometrial cell categories within the new classification of endometrial cytology when applied to conventional smears	Munakata S et al.	Cytopathology	https://www.ncbi.nlm.nih.gov/pubmed/27859783
6	One-stop clinical assessment of risk for endometrial hyperplasia (OSCAR-Endo): a fast-track protocol for evaluating endometrial pathologies	Hefler-Frischmuth K et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/28265757
7	Liquid-based endometrial cytology using SurePath™ is not inferior to suction endometrial tissue biopsy in clinical performance for detecting endometrial cancer including atypical endometrial hyperplasia	Yanaki F et al.	Acta Cytol	https://www.ncbi.nlm.nih.gov/pubmed/28324882
8	Levonorgestrel-releasing intrauterine systems versus oral cyclic medroxyprogesterone acetate in endometrial hyperplasia therapy: a meta-analysis	Yuk JS et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27896507
9	Prospective evaluation of abnormal glucose metabolism and insulin resistance in patients with atypical endometrial hyperplasia and endometrial cancer	Mitsuhashi A et al.	Supportive Care in Cancer	https://www.ncbi.nlm.nih.gov/labs/articles/28028620/
10	Association of endometrial hyperplasia and cancer with a history of gestational diabetes	Wartko PD et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/28577154
11	Clinical and metabolic response to vitamin D supplementation in endometrial hyperplasia: a randomized, double-blind, placebo-controlled trial	Tabassi Z et al.	Horm Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28283863
12	Comparing the administration of letrozole and megestrol acetate in the treatment of women with simple endometrial hyperplasia without atypia: a randomized clinical trial	Moradan S et al.	Adv Ther	https://www.ncbi.nlm.nih.gov/pubmed/28353144
13	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
14	Nonoperative management of atypical endometrial hyperplasia and grade 1 endometrial cancer with the levonorgestrel intrauterine device in medically ill post-menopausal women	Baker WD et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28427775
15	Prediction of relapse after therapy withdrawal in women with endometrial hyperplasia: a long-term follow-up study	Sletten ET et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28476823

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Surgical treatment of primary uterine cancer

Editor Piotr Lepka

Descriptive summary

Nodal involvement

Based on prospectively maintained multicentre database data of 181 patients with high-to-intermediate-risk endometrial cancer (EC) (according to the ESMO/ESGO/ESTRO classification), Ouldamer et al. tried to establish whether systematic nodal staging should be part of surgical staging. Patients with endometrioid type 1, grade 1–2 tumours with deep (≥ 50%) myometrial invasion and unequivocally positive LVSI, and those with grade 3 tumours with < 50% myometrial invasion regardless of LVSI status were enrolled. Overall, 145 patients (80.1%) underwent at least pelvic lymphadenectomy and 62 (43.7%) had lymph node (LN) metastases. Five-year overall survival (OS) rates according to the LN status were 85% (95% CI: 76.5–91.4) in patients with negative LN, 71.8% (95% CI: 61.9–80.4) positive LN and 36% (95% CI: 26.6–46.2) in unstaged women. The authors concluded nodal staging should be considered part of surgical staging in that group of women, as it may result in a better tailoring of adjuvant therapies [1].

Rossi et al. reported the results of the largest multicentre, prospective cohort study published to date (FIRES trial), which evaluated sentinel lymph node (SLN) biopsy in patients with clinically determined stage I EC. Patients received a standardised cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy (LAD). From 340 patients who had LAD, 86% (n = 293) had successful mapping of at least one SLN. Positive nodes occurred in 12% (n = 41) and 36 of these had at least one mapped SLN. Nodal metastasis were identified in 97% (n = 35) of these 36 patients. The sensitivity to detect node-positive disease was 97.2% (95% CI: 85.0–100) and negative predictive value was 99.6% (97.9–100). Results shown that SLN biopsy is equivalent to LAD in the staging of EC. Patients with SLN negative for metastatic disease can be reassured that this result is accurate in more than 99% of cases, and only approximately 3% of patients with nodal metastases will have their disease unrecognised by sentinel lymph node biopsy [2].

In their retrospective study based on 1,052 patients with stage I–III endometrioid EC, Tuomi et al. compared three risk-stratification models: Mayo (the low-risk group comprised of tumours with grade 1–2, endometrioid histology, myometrial invasion ≤ 50%, and diameter ≤ 2cm), Helsinki (thrombocytosis, elevated serum CA125, preoperative high-risk histology, and tumour size ≥ 3cm as significant predictors for an advanced disease), and Milwaukee (depth of myometrial invasion and tumour size as parameters for identifying patients at low-risk for lymph node involvement, with low-risk criteria being satisfied with depth of invasion is ≤ 33% and tumourdiameter ≤ 50mm, regardless of grade) in prediction of lymphatic dissemination. The results showed similar accuracy in predicting lymphatic dissemination in the studied models, although the lowest LAD rate was associated with the Milwaukee model [3].

Lefringhouse et al. prospectively validated an intraoperative surgical algorithm to stratify patients with early EC by risk of lymph node metastasis. Study participants were divided into a low-risk (LR) group based on the Mayo Clinic Criteria (endometrioid cell type with confined to the uterine corpus, any grade without myometrial invasion, grade 1 or 2 tumours with myometrial invasion less than or equal to 50% and primary tumour ≤ 2cm). The remaining subjects were classified as high-risk (HR) and were surgically staged with pelvic and para-aortic lymph node dissection. From 136 HR subjects, 126 had LAD performed, with 14 (11%) positive for nodal metastases. Of the 62 LR cancers, two patients developed disease recurrence, as did five in the HR group. The suggested algorithm using targeted frozen section for women with early endometrial cancer showed 90% sensitivity but may not be suitable to appropriately tailor surgery due to the low specificity of 36% specificity [4].

Surgery related to age

In their multicentre retrospective study, Bourgin et al. compared different surgical approaches, perioperative morbidity, and surgical staging in patients with EC according to age. The study enrolled 270 patients under age 75 and 74 patients older than 75. Minimal invasive surgery was performed less often in the elderly group compared to younger group (58.2% vs. 74.8%; p = 0.006). The rate of pelvic and para-aortic lymphadenectomy was lower in women older than 75 years old than in their younger counterparts (52.7% vs. 74.2% and 8.1% vs. 21.8%, respectively). Surgical understaging was also more frequent in the older group than in the younger one (37% vs. 15.2%). The authors concluded that, although elderly women with EC should benefit from minimally invasive surgery and optimal surgical staging to the same extent as younger women, they are often surgically understaged despite the absence of evidence of greater perioperative complications in the elderly [5].

Continued on the next page ➲

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Surgical treatment of primary uterine cancer

- Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Call for surgical nodal staging in women with ESMO/ESGO/ESTRO high-intermediate risk endometrial cancer: a multicentre cohort analysis from the FRANCOGYN study group	Ouldamer L et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28058558
2	A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study	Rossi EC et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28159465
3	Prediction of lymphatic dissemination in endometrioid endometrial cancer: comparison of three risk-stratification models in a single-institution cohort	Tuomi T et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28069268
4	Prospective validation of an intraoperative algorithm to guide surgical staging in early endometrial cancer	Lefringhouse JR et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28190648
5	Impact of age on surgical staging and approaches (laparotomy, laparoscopy and robotic surgery) in endometrial cancer management	Bourgin C et al.	Europ J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27955835

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Medical (chemo- and radiotherapy) treatment of primary uterine cancer

Editor David Lindquist

Descriptive summary

In the largest study during this review period, the SEER program identified more than 100,000 women with surgically treated stage I–II endometrial cancer (EC). The study investigated temporal trends of adjuvant intracavitary brachytherapy, adjuvant whole pelvic radiotherapy, pelvic lymphadenectomy, and sampled node counts. The authors suggest that radiation oncologists consider the extent of pelvic lymphadenectomy when counselling these women for adjuvant radiotherapy [1] and more often offer adjuvant RT when nodes have not been removed.

Several studies focused on different aspects of adjuvant treatment for women with early-stage disease with high-risk type. Boothe et al. analysed more than 10,000 women with high-risk EC and concluded that the best survival is achieved when women receive both adjuvant chemotherapy and radiotherapy [2]. Wong et al. focused on uterine carcinosarcomas in their study, including almost 5,000 women, and concluded that both chemotherapy and radiotherapy in the adjuvant setting significantly improved overall survival [3]. In the study by Hong et al., more than 5,000 women with stage I clear cell or papillary serous carcinoma were studied and the highest survival rate was reported for women receiving combined adjuvant treatment [4].

Three additional studies reported improved survival for women with high-risk histology receiving different types of adjuvant treatment [5–7]. Thus, there is some evidence for a beneficial effect of adjuvant treatment for women with high-risk EC; however, none of the reports were randomised clinical trials. Regarding adjuvant treatment of uterine leiomyosarcoma, Seagle et al. identified more than 7,000 women and investigated factors believed to predict survival. Regarding chemotherapy, increased survival was only observed in women with metastatic disease [8]. Finally, Reynaers et al. compared two different treatment strategies from two different centres for patients with stage Ib and II high-grade endometrioid EC. Results showed a survival benefit for combining chemotherapy and radiotherapy compared with radiotherapy alone, however, this study was also retrospective and included only 116 women [9]. In summary, there is still a need for more randomised clinical trials as evidence for adjuvant treatment of primary EC. On the other hand, the retrospective studies on adjuvant treatment in women with high-risk histology, although with some differences in methodology, are all suggesting that adjuvant treatment, including both chemotherapy and radiotherapy, may be beneficial to this patient group.

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Extent of pelvic lymphadenectomy and use of adjuvant vaginal brachytherapy for early-stage endometrial cancer	Matsuo K et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28017306
2	The addition of adjuvant chemotherapy to radiation in early-stage high-risk endometrial cancer: survival outcomes and patterns of care	Boothe D et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28498257
3	Use of adjuvant chemotherapy, radiation therapy or combined modality therapy and the impact on survival for uterine carcinosarcoma limited to the pelvis	Wong AT et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28574930
4	Impact of chemotherapy and radiotherapy on management of early stage clear cell and papillary serous carcinoma of the uterus	Hong JC et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28375927
5	Impact of adjuvant therapy on recurrence patterns in stage I uterine carcinosarcoma	Matsuo K et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28215838
6	Stage I uterine carcinosarcoma: matched cohort analyses for lymphadenectomy, chemotherapy, and brachytherapy	Seagle BL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28317560
7	Utility of radiation therapy for early-stage uterine papillary serous carcinoma	Cham S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28343693
8	Prognosis and treatment of uterine leiomyosarcoma: a national cancer database study	Seagle BL et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28317559
9	Improved outcome of high-grade, early 1-stage endometrioid endometrial carcinoma with adjuvant chemotherapy and radiotherapy: comparison of 2 treatment strategies	Reynaers EA et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28129237

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Surgical treatment of recurrent uterine cancer

Editor Arun Kalpdev

Descriptive summary

The role of surgery in recurrent endometrial cancer (REC) is still a topic of debate pending strong recommendations. The latest database search has a very limited number of studies on the role of surgical approach in REC.

Campos et al. reviewed the role of surgery for REC. The authors presented a limited number of indications for surgical treatment in REC. Women who develop recurrence and are amenable for surgical resection mainly fall in two categories: 1) isolated vaginal recurrence and 2) recurrence limited to the pelvic structures (vagina, lower urinary tract, rectosigmoid colon, pelvic sidewall). Although surgery may be in option In both situations, the authors conclude it is not the preferred approach. For women with recurrence who did not previously receive radiotherapy, surgery 'alone' can be a curative and reasonable alternative to radiotherapy for very selective patients (declining radiotherapy or with contraindications to radiotherapy). For women with isolated vaginal recurrence and recurrence limited to the pelvic structures that were previously treated with radiotherapy, surgery should only be considered for patients who can tolerate the procedure and in whom complete resection is technically feasible. Pelvic exenteration or radical resection of locally recurrent disease are deemed to be potential surgical approaches. After the surgical resection of pelvic recurrence, patients should be offered adjuvant chemotherapy in view of the high chance of relapse. Moreover, the option of surgical treatment should be weighed against quality of life of the patient at that particular stage [1].

The role of surgery in REC has also been evaluated based on the multicentre, retrospective database review. Ozkan et al. have published their experience with 67 women with REC after initial diagnosis and treatment for low-risk endometrial cancer. In their study, 25 out of 78 women received surgical resection either alone, with chemotherapy, with radiation or with chemo-radiation. Though the study doesn't elaborate the indications for surgery, it gives an insight that surgical approach is considered for recurrences in endometrial cancer treatment, that too, as per institutional policy [2].

A study by Shim et al. evaluated prognostic factors for OS after recurrence in endometrioid EC patients and is also mentioned in this LiFE report by Surynt. Out of 108 patients with REC, 29 patients (27%) with solitary or a limited number of recurrent lesions underwent salvage surgery. The specific sites of recurrence which were managed with surgery included recurrences at the lung (n = 9), pelvis (n = 6), retroperitoneal lymph node (n = 5), vagina (n = 4), intra-abdominal (n = 3), and brain (n = 2). This shows that the role of surgery in recurrent EC remains intact and preferred in combination with adjuvant therapies [3].

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

No	Title	Authors	Journal	Link to abstract
1	Treatment of recurrent or metastatic endometrial cancer	Campos SM et al.	www.uptodate.com	https://csn.cancer.org/node/308552
2	Factors associated with survival after relapse in patients with low-risk endometrial cancer treated with surgery alone	Ozkan N et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28657226
3	Stratification of risk groups according to survival after recurrence in endometrial cancer patients	Shim SH et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/28538383

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Medical treatment of recurrent endometrial cancer

Editor Ewa Surynt

Descriptive summary

PI3K inhibitors

Heudel et al. report the negative results of a phase II study from the GINECO group of the PI3K inhibitor BKM120 in patients with advanced or recurrent endometrial carcinoma (EC) (18 and 22 patients, respectively). Due to the high rate of grade 3/4 toxicities (cutaneous rash in 54%, depressive events in 47%, and anxiety in 40% of patients), authors stopped recruitment at the 100mg dose and reduced the dose to 60mg per day. No objective response was reported. Six patients (25%) received fewer than three months of treatment because of a rapid progressive disease, whereas four patients were not evaluable for efficacy because of a very early medical withdrawal due to toxicity. The trial was stopped due to the high toxicity of the drug [1].

In a randomised phase II non-comparative study, Del Campo et al. evaluated the safety and efficacy of two PI3K/mTOR inhibitors, PF-04691502 (orally on a daily basis) and gedatolisib (intravenously weekly), in 58 patients with recurrent endometrial cancer. The authors demonstrated that PF-04691502 daily oral dosing was not well tolerated and its clinical benefit response was assessed as low. Gedatolisib had a manageable toxicity profile and was active as a single agent in patients with advanced endometrial cancer. Gedatolisib appeared to have activity in stathmin-low cancers but an appropriate biomarker to direct gedatolisib therapy was not confirmed in this study [2].

Stathmin and GOG-177

Reyes et al used patient specimens from GOG-177 to study the prognostic role of stathmin expression in the two treatment arms. GOG-177 was a phase III randomised controlled trial that enrolled patients with advanced or recurrent endometrial cancer between two treatment arms: adriamycin (doxorubicin)/cisplatin (AP) versus adriamycin/cisplatin/paclitaxel with G-CSF (TAP). Results from this trial showed that patients treated with the three-drug regimen TAP had a better overall response rate (57% vs. 34%), median PFS (8.3 vs. 5.3 months), and median OS (15.3% vs. 12.3%). High stathmin expression correlated with poor PFS and OS, particularly in patients who received adriamycin/cisplatin only, and should be considered a poor prognostic marker in EC. Paclitaxel may help to negate the impact of stathmin overexpression when treating high-risk EC patients [3].

Modelling survival and decision-making in recurrent disease

Based on a retrospective cohort of 108 patients, Shim et al. aimed to develop a prediction model incorporating the prognostic factors for survival after recurrence in endometrioid EC patients and stratify the patients into subgroups according to survival outcomes. Multivariate regression analysis revealed that time to relapse after initial treatment, CA-125 level at recurrence, and the number of recurrent lesions were independent predictors of OS. When authors stratified patients into three subgroups considering these factors, their OS differed among groups. They concluded that after external validation, this model could be valuable in terms of predicting outcomes and planning clinical trials [4]. This study is also mentioned by Kalpdev in this LiFE issue.

The Expert Panel on Radiation Oncology–Gynaecology presented American College of Radiology Appropriateness Criteria for the management of recurrent EC. As there are no randomised controlled trials that have been published to determine optimal management in this group of patients, management was divided into two main categories: women who had previous adjuvant RT and those who had no adjuvant RT after hysterectomy. The authors developed five clinical variants to address common scenarios in the management of women with recurrent EC that may guide clinical decision-making [5].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Phase II study of the PI3K inhibitor BKM120 in patients with advanced or recurrent endometrial carcinoma: a stratified type I-type II study from the GINECO group	Heudel PE et al.	Br J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28072765
2	A randomized phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer	Del Campo JM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27103175
3	High stathmin expression is a marker for poor clinical outcome in endometrial cancer: An NRG oncology group/gynecologic oncology group study	Reyes HD et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28532857
4	Stratification of risk groups according to survival after recurrence in endometrial cancer patients	Shim SH et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pubmed/28538383
5	ACR Appropriateness Criteria® Management of Recurrent Endometrial Cancer	Elshaikh MA et al.	Am J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27400117

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Novel therapies in endometrial cancer (EC)

Editor Ines Vasconcelos

Descriptive summary

There were no new studies published this period that included only patients with endometrial cancer (EC), but there were basket trials on solid tumor that also included EC patients. A phase I trial of ridaforolimus combined with paclitaxel and carboplatin included five EC patients. It had no unanticipated toxicities and was deemed safe while showing anti-tumour activity [1]. A phase I dose escalation trial of pilaralisib in combination with carboplatin and paclitaxel included 19 patients with EC. It showed a good safety profile but it did not enhance the anti-tumour activity of the chemotherapeutic agents [2].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Phase I study of oral ridaforolimus in combination with paclitaxel and carboplatin in patients with solid tumour cancers	Chon HS et al.	BMC Cancer	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5465458/
2	Phase I dose escalation study of pilaralisib (SAR245408, XL147) in combination with paclitaxel and carboplatin in patients with solid tumors	Wheler J et al.	The Oncologist	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5388374/

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Uterine sarcoma

Editor Marcin Bobiński

Descriptive summary

Incidence, treatment, and follow-up

Although the overall risks of leiomyosarcoma (LMS) and occult malignancy and procedure-related mortality are low in general, the elevated risk of LMS in older patients should be incorporated into patient-centered risk-benefit discussions regarding surgery for fibroids, according to Siedhoff et al. The authors presented a decision-tree model comparing published clinical outcomes of laparoscopic hysterectomy (LH) and abdominal hysterectomy (AH) [1]. Meanwhile, Nasioudis et al. concluded that ovarian preservation is not associated with worse oncologic outcomes and it could be considered for women with LMS, sparing them from the morbidity associated with iatrogenic menopause. This was based on the National Cancer Institute's Surveillance, Epidemiology, and End Results database and evaluated the risk of ovarian preservation in 418 women with LMS limited to the uterus [2]. Other analyses published this period included one by Ruengkhachorn et al. that presented 11,258 hysterectomies in which they found 22 cases of uterine sarcoma; incidence 0.2%. Among these patients, 60% experienced recurrence and the median OS was less than five years [3]. Ricci et al. published an article regarding treatment of uterine sarcomas, including contemporary surgical and medical management of uterine LMS. The role of targeted therapies and the implications of uterine morcellation on gynaecologic surgical practice were discussed [4].

The recent randomzied GeDDis trial compared doxorubicine and gemcitabine plus docetaxel in the treatment of soft-tissue sarcomas. There was no significant differences in survival outcomes. More adverse events with impact on quality of life were noted in the combination arm. Authors concluded that either schedule can be used according to patients or clinicians preferences [5]. The article is accompanied by a comment by Tap et al. with noteworthy comments on the relatively low dose of gemcitabine and the number of cycles used in the trial.

Molecular research

Davidson et al. published the results of an immunochemical study revealing that expression levels of two proteins, cyclin D2 neuron navigator-2(NAV2), could serve as novel candidate prognostic markers in patients with LMS and low-grade endometrial stromal sarcoma (LG-ESS) [6]. Using an IHC screening approach, Cuppens et al. aimed to investigate the expression of potential therapeutic targets in a large cohort of different human uterine sarcomas, encompassing all the main subtypes. The authors observed that p-S6S240, reflecting mTOR pathway activity, is mainly expressed in high-grade sarcomas and that its presence correlates with shorter progression-free survival in leiomyosarcomas. Based on the patient-derived LMS xenograft models, the authors also provided preclinical evidence for the efficacy of dual PI3K/mTOR inhibition in uterine LMS patients and suggested p-S6S240 could be a predictive marker for response [7]. PTEN loss was introduced as associated with anti-PD-1 checkpoint blockade therapy resistance in metastatic uterine LMS by George et al. [8].

Ferrero et al. presented a review on the tyrosine kinase inhibitor pazopanib pharmacokinetics, pharmacodynamics, clinical efficacy, and safety, in the treatment of LMS. They emphasised that, although preliminary results both in terms of efficacy and safety are promising, uterine LMS are not only a very heterogeneous class of tumours with at least 40 different histotypes, but also different from LMS originating in other soft tissue. Future trials should take into account not only the histotype but also the site of origin [9]. Davidson and Micci published a review regarding molecular characteristics of uterine sarcomas including wide range of genetic and proteomic markers. They listed and described multiple molecules that are potential therapeutic targets as well as those with potential predictive value [9].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Laparoscopic hysterectomy with morcellation versus abdominal hysterectomy for presumed fibroids: an updated decision analysis following the 2014 FDA Safety Communications	Siedhoff MT et al.	AJOG	https://www.ncbi.nlm.nih.gov/pubmed/27890646
2	Safety of ovarian preservation in premenopausal women with stage I uterine sarcoma	Nasioudis D et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28541635
3	Undiagnosed uterine sarcomas identified during surgery for presumed leiomyoma at a national tertiary hospital in Thailand: a 10-year review	Ruengkhachorn I et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28498251
4	Uterine leiomyosarcoma: epidemiology, contemporary treatment strategies and the impact of uterine morcellation	Ricci S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28209496

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Uterine sarcoma

- Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
5	Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial	Seddon B et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28882536
	GeDDiS: insight into frontline therapy in soft tissue sarcoma. Comment	Tap W et al.	Lancet Oncol	
6	Neuron navigator-2 and cyclin D2 are new candidate prognostic markers in uterine sarcoma	Davidson et al.	Virchows Arch	https://www.ncbi.nlm.nih.gov/pubmed/28643014
7	Potential targets' analysis reveals dual PI3K/mTOR pathway inhibition as a promising therapeutic strategy for uterine leiomyosarcomas—an ENITEC Group initiative	Cuppens et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28232476
8	Loss of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapy in metastatic uterine leiomyosarcoma	George et al.	Immunity	https://www.ncbi.nlm.nih.gov/pubmed/28228279
9	Molecular characteristics of uterine sarcomas	Davidson B and Micci F	Expert Rev Mol Diagn	https://www.ncbi.nlm.nih.gov/pubmed/28335657

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Cervical pre-invasive disease

Editor Geanina Dragnea

Descriptive summary

Vaccination efficacy

A two-centre observational study including 361 vaccinated and unvaccinated women aged 20–25, attending colposcopy following an abnormal cervical cytology result at routine cervical screening, found that the prevalence of HPV 16 was significantly lower in the vaccinated group (8.6%) compared with the unvaccinated group (46.7%) ($p = 0.001$). The number of cases of CIN2+ was significantly lower in women who had been vaccinated ($p = 0.006$). HPV vaccine did not have a statistically significant effect on commonly recognised colposcopic features [1].

HPV screening

An analysis of HPV distribution in 3,393 patients with CIN revealed that the rate of HPV negative tests in CIN positive women was 17.42%, which may be clinically significant [2].

E6/E7 mRNA assay had higher specificity than HPV DNA assays for the detection of CIN 2+ in two studies, which may be useful for clinical risk stratification. In the first study, E6/E7 mRNA assay (Aptima HPV testing) demonstrated significantly higher specificity (41% vs. 13%; $p < 0.0001$) and positive predictive value (25% vs. 16%; $p < 0.03$) than HPV DNA assays (Cobas) for the identification of biopsy-confirmed CIN 2+ cases. The sensitivity was high: 97% for both tests [3]. In the second study on women with ASCUS, E6/E7 mRNA assay had also higher specificity than HPV DNA assays (36.4% vs. 24.3%, $p = 0.006$), with similar sensibility (88.2% vs. 90.7%, $p = 0.636$) [4].

Treatment

A study of 80 women with a diagnosis of CIN 1 obtained by colposcopy-guided biopsy and subsequently submitted (up to 45 days) to large loop excision of the transformation zone, detected CIN 2+ in 19% of cases and three cases of CIN3 and one case of sclerosing adenocarcinoma stage Ia [5]. Therefore, women undergoing expectant management must have an adequate follow-up.

Endocervical curettage (ECC) at the time of conisation is of limited benefit in predicting endocervical lesions, having low sensitivity (25.0%); ECC has also low sensitivity (42.9%) in predicting residual endocervical lesions identified in the subgroup of patients who subsequently underwent hysterectomy [6].

Risk factors for recurrence

A retrospective, population-based study of 360 women treated by cold knife cone biopsy or loop electrosurgical excision procedure for adenocarcinoma-in-situ (AIS) between 2001 and 2012, with negative histopathological margins, and a median follow-up time 3.9 years (range six months to 12.2 years) observed a low but significant risk of persistent or recurrent cervical neoplasia: seven (1.9%) women were diagnosed with CIN 2/3, ten (2.8%) with AIS, and one (0.3%) with cervical adenocarcinoma [7].

The subsequent risk for other HPV-related neoplasia

A population-based cohort study on 89,018 women identified from the Dutch nationwide registry of histopathology and cytopathology with a diagnosis of CIN3 between 1990 and 2010 and 89,018 matched control subjects without a history of CIN3 found that, between 1990 and 2015, women in the first group had increased risk of HPV-related carcinomas and premalignancies, with incidence rate ratios of 3.85 for anal cancer, 6.68 for anal intraepithelial neoplasia grade 3, 4.97 for vulvar cancer, 13.6 for vulvar intraepithelial neoplasia grade 3, 86.08 for vaginal cancer, 25.65 for vaginal intraepithelial neoplasia grade 3, and 5.51 for oropharyngeal cancer. This risk remained significantly increased even after long-term follow-up of up to 20 years [8].

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Cervical pre-invasive disease

- Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	The impact of human papillomavirus type on colposcopy performance in women offered HPV immunisation in a catch-up vaccine programme: a two-centre observational study	Munro A et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/28102931
2	Analysis of HPV distribution in patients with cervical precancerous lesions in Western China	Li K et al.	Medicine (Baltimore)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5521883/
3	Performance of Aptima and Cobas HPV testing platforms in detecting high-grade cervical dysplasia and cancer	Ge Y et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28574670
4	Detection of cervical intraepithelial neoplasia with HPVE6/E7 mRNA among women with atypical squamous cells of unknown significance	Li Y et al.	Int J Gynaecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/28170083
5	Underdiagnosis of cervical intraepithelial neoplasia (CIN) 2 or worse lesion in women with a previous colposcopy-guided biopsy showing CIN 1	Souza CA et al.	Rev Bras Ginecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/28264203
6	Evaluation of endocervical curettage with conisation in diagnosis of endo-cervical lesions	Suzuki Y et al.	J Obstet Gynaecol Res	https://www.ncbi.nlm.nih.gov/pubmed/28168772
7	Risk of persistent or recurrent neoplasia in conservatively treated women with cervical adenocarcinoma in situ with negative histological margins	Munro A et al.	Acta Obstet Gynecol Scand	https://www.ncbi.nlm.nih.gov/pubmed/28181670
8	Long-lasting increased risk of human papillomavirus-related carcinomas and premalignancies after cervical intraepithelial neoplasia grade 3: a population-based cohort study	Ebisch RMF et al.	J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28541790

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Surgical treatment of primary and recurrent cervical cancer

Editor Aljosa Mandic and Matteo Morotti

Descriptive summary

Extended mesometrial resection

Extended mesometrial resection (EMMR) is a novel treatment for locally advanced cervical cancer. Wolf et al. conducted a prospective single-centre study to evaluate the feasibility of EMMR and therapeutic lymph node dissection as a surgical treatment approach for patients with cervical cancer fixed to the urinary bladder and/or its mesenteries as determined by intraoperative evaluation. None of the patients received postoperative adjuvant radiotherapy. Forty-eight consecutive patients were accrued into the trial. Median tumour size was 5cm, and 85% of all patients were found to have lymph node metastases. Complete tumour resection (R0) was achieved in all cases. Recurrence-free survival at five years was 54.1% (95% CI: 38.3–69.9). The overall survival rate was 62.6% (95% CI: 45.6–79.6) at five years. Perioperative morbidity represented by grade 2 and 3 complications (determined by the Franco- Italian glossary) occurred in 25% and 15% of patients, respectively. In conclusion, the authors demonstrate the feasibility of EMMR as a surgical treatment approach for patients with locally advanced cervical cancer and regional lymph node invasion without the necessity for postoperative adjuvant radiation [1].

Sentinel lymph node mapping

Especially in early stage patients, sentinel lymph node mapping (SLNM) has recently gained more interest. Salvo et al. retrospectively reviewed women with early-stage cervical cancer who underwent SLN mapping followed by complete pelvic lymphadenectomy as part of initial surgical management from August 1997 through October 2015. Lymphatic mapping was performed using blue dye, technetium-99msulfur colloid (Tc-99), and/or indocyanine green (ICG). They determined SLN detection rates, sensitivity, and negative predictive value. In all, 188 patients were included, and 35 (19%) had lymph node metastases. At least one SLN was identified in 170 patients (90%), and bilateral SLNs were identified in 117 patients (62%). The majority of SLNs (83%) were found in the pelvis. There was no difference in detection rates between mapping agents, surgical approach, patients with and without prior conisation or between patients with tumours < 2cm and ≥ 2cm. Metastatic disease in sentinel nodes was detected by H&E staining in 78% of cases and required ultrastaging/immunohistochemistry in 22% of cases. Only one patient had a false-negative result, yielding in a sensitivity of 96.4% (95% CI: 79.8%–99.8%) and negative predictive value of 99.3% (95% CI: 95.6%–100%). The false-negative rate was 3.6%. The authors concluded that SLN biopsy had very high sensitivity and negative predictive value in these women with early-stage cervical cancer [2]. This paper is also included in the report on "Minimal invasive surgery" by Borja Otero.

Microinvasive cancer

The current FIGO definition differentiates microinvasive cancer as one that is identified only microscopically, with a maximum stromal invasion of 5.0mm in depth and 7.0mm in width (stage Ia). Bena et al. published an interesting observation for microinvasive adenocarcinoma of the cervix. Among 1,567 patients with cervical adenocarcinoma, five-year survival was 97.3% for stage Ia1 disease and 98.3% for stage Ia2. For comparison, five-year survival rates for 5,749 patients with stage Ia1 or Ia2 squamous cell carcinoma were 96.7% and 95.6%, respectively. There was no statistical difference in survival between patients having either cell type undergoing local excision ($p = 0.26$), simple hysterectomy ($p = 0.08$), or radical hysterectomy ($p = 0.87$). There was no statistically significant difference in survival among patients with adenocarcinoma compared by treatment type (local excision compared with simple hysterectomy [$p = 0.64$]; local excision compared with radical hysterectomy [$p = 0.82$]; or simple hysterectomy compared with radical hysterectomy [$p = 0.70$]). Among patients with adenocarcinoma, 0.97% had positive pelvic lymph nodes, none had positive aortic lymph nodes, and 91.85% had confirmed negative lymph nodes. For squamous cell carcinoma, 0.72% of patients had positive pelvic lymph nodes and 0.10% had positive aortic lymph nodes. There was no significant difference in survival when patients were compared by cell type or procedure. Also, the authors discuss that survival of patients with microinvasive adenocarcinoma is not improved by more invasive surgery. Regardless of histology, the frequency of nodal involvement was low in both groups, supporting an overall excellent prognosis for all patients with microinvasive disease [3].

Blood transfusions

Bogani et al. published an interesting article about the impact of blood transfusions on the survival of locally advanced cervical cancer patients undergoing neoadjuvant chemotherapy followed by radical surgery. The study included 275 patients. Overall, 170 (62%) patients had a blood transfusion. Via univariate analysis, the authors observed transfusion correlated with an increased risk of developing recurrence (HR 2.2; $p = 0.02$). Other factors associated with five-year disease-free

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Surgical treatment of primary and recurrent cervical cancer

Descriptive summary (cont.)

survival were noncomplete clinical response after neoadjuvant chemotherapy (HR, 2.99; p = 0.06) and pathological (p = 0.03) response at neoadjuvant chemotherapy as well as parametrial (p = 0.004), vaginal (p < 0.001), and lymph node (p = 0.002) involvements. However, in multivariate analysis, only vaginal and lymph node involvements correlate with worse disease-free survival. No association with worse outcomes was observed for patients undergoing blood transfusion (HR 2.71; p = 0.07). Looking at factors influencing overall survival, the authors observed that lymph node status (p = 0.01) and vaginal involvement (p = 0.06) were independently associated with survival. The authors concluded that the role of blood transfusions in increasing the risk of developing recurrence in LAAC patients treated by neoadjuvant chemotherapy plus radical surgery remains unclear so further prospective studies are warranted [4].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Extended mesometrial resection (EMMR): Surgical approach to the treatment of locally advanced cervical cancer based on the theory of ontogenetic cancer fields.	Wolf B et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28526168
2	Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer	Salvo G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28188015
3	Survival of women with microinvasive adenocarcinoma of the cervix is not improved by radical surgery	Bean LM et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28522318
4	Impact of blood transfusions on survival of locally advanced cervical cancer patients undergoing neoadjuvant chemotherapy plus radical surgery	Bogani G et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28129238

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Medical treatment of primary and recurrent cervical cancer

Editor Kristina Lindemann

Descriptive summary

Primary treatment

Salihi et al. have published the paper that was presented at ESGO and discussed in LiFE 2. They studied dose-dense carboplatin/paclixatel as an alternative to TIP in the neoadjuvant setting of Ib1 to IIb cervical cancer. In all, 36 patients were included in this prospective phase II study. Half of the patients operated on showed optimal pathological response. However, the study also included 13 patients with suspect lymph nodes. Two patients progressed on treatment; six patients were not operable. Twelve patients were candidates for further adjuvant treatment after surgery; 11 of those received radiation [1]. Despite the favourable safety profile and the equivalent response rates compared to TIP, it is noteworthy that a considerable proportion had three modality treatments (neoadjuvant chemotherapy (NACT), surgery, chemoradiation), and some two (NACT+chemoradiation). One could argue that some patients potentially could have been treated by one modality only (chemoradiation).

Treatment of recurrent disease

At ESMO, Vergote et al. just presented a first-in-human study of tisotumab vedotin, an antibody specific for tissue factor, which is aberrantly expressed in cervical cancer. Thirty-four cervical cancer patients were included in the expansion cohort. A response rate of 32% was achieved, with a median duration of response of 8.3 months. The most common grade 3 toxicities were: vomiting, abdominal pain, fatigue, and nausea. Ocular events of any grade were reported in 53% of the patients, mainly conjunctivitis [2].

Tewari et al. reported the final overall survival results of GOG240. The benefit in OS was also evident with prolonged follow-up. The chemotherapy plus bevacizumab groups continued to show significant improvement in OS compared with the chemotherapy-alone groups: OS was 16.8 months in chemotherapy+bevacizumab groups versus 13.3 months in the chemotherapy-alone groups (hazard ratio 0.77 [95% CI: 0.62–0.95]; p = 0.007) [3].

The role of adding NACT to current treatment strategies was explored in another phase II trial. The addition of NACT (two cycles of cisplatin+gemcitabine) did not result into a clinically meaningful improvement of response rate, but 20% of patients experienced Grade 3-4 toxicity on NACT [4].

Chan et al. reported on a phase II study with brivanib which is an oral inhibitor of VEGFR-2, FGFR-1, and FGFR-2. Seven percent of the patients responded and 25% survived longer than six months. The activity of oral brivanib was comparable to other biologic agents in recurrent cervical cancer patients. Adverse events associated with brivanib included hypertension, hypothyroidism, proteinuria, but also hyponatremia [5].

Immunotherapy in cervical cancer

Two reviews focused on the role of immunotherapy in cervical cancer [6, 7]. They are also discussed by Zoltan in this issue of the LiFE report. Borcoman and Le Tourneau review the evidence of pembolizumab in cervical cancer. Keynote 028 included 24 patients with cervical cancer in the expansion cohort. ORR was 17%, including long-lasting responses (mean duration of response, 26 weeks). Although median PFS was modest, median OS reached nine months, which is substantial in this heavily pretreated patient population. Ipilimumab has been reported to reach a response rate of 9% with the median PFS 2.5 months. In several ongoing trials, immunotherapy was studied in conjunction with chemoradiation (ClinicalTrials.gov identifier: NCT02635360 or bevacicumab (ClinicalTrials gov identifier: NCT02921269). Another approach lies in the development of anticancer therapeutic vaccines that rely on cell-mediated immunity against HPV-infected cells, with the HPV-produced oncoproteins E6 and E7 used as the selected antigens. ADXS11-001, which is a bacterial-vector vaccine targeting the oncoprotein E7, showed an overall disease control rate of 43%. Adoptive T-cell therapy is also currently explored in several early trials.

At the most recent ASCO meeting, Hollebecque et al. reported on 19 patients treated with nivolumab: ORR, 26.3% with responses regardless of PD-L1 or HPV status [8].

Neuroendocrine tumour

Sharabi et al. published a case report of a metastatic neuroendocrine cervical cancer. The tumour showed a high tumour mutational burden as a consequence of a mismatch repair gene defect and MSI-H. The patients were effectively treated with nivolumab and stereotactic body radiation therapy (SBRT). The patients also received sandostatin after a positive octreotid scan [9].

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- Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Neoadjuvant weekly paclitaxel-carboplatin Is effective in stage I–II cervical cancer	Sahili R et al.	Int J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28574931
2	A phase IIa study of tisotumab vedotin (HuMax®-TF-ADC) in patients with relapsed, recurrent and/or metastatic cervical cancer	Vergote I et al.	ESMO Annual Meeting 2017 Abstract #931	http://files.shareholder.com/downloads/AMDA-KPIBN/3986123675x0x956188/A61B9EC8-0EEE-446F-AA80-66145D-0CA5E8/2017_ESMO_Phase_IIA_Study_of_Tisotumab_Vedotin_in_Patients_with_Relapsed_Recurrent_and_or_metastatic_cervical_cancer.pdf
3	Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240)	Tewari KS et al.	Lancet	https://www.ncbi.nlm.nih.gov/pubmed/28756902
4	Phase II trial of neoadjuvant chemotherapy followed by chemoradiation in locally advanced cervical cancer	de Azevedo CRAS et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28709705
5	A phase II evaluation of brivanib in the treatment of persistent or recurrent carcinoma of the cervix: An NRG Oncology/Gynecologic Oncology Group study	Chan JK et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/28728751
6	Pembrolizumab in cervical cancer: latest evidence and clinical usefulness	Borcoman E et al.	Ther Adv Med Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28607581
7	Immunotherapy in ovarian, endometrial and cervical cancer: State of the art and future perspectives	Ventriglia J et al.	Cancer Treatment reviews	https://www.ncbi.nlm.nih.gov/pubmed/28800469
8	An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers	Hollebecque A et al.	J Clin Oncol	http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.5504
9	Exceptional response to nivolumab and Stereotactic Body Radiation Therapy (SBRT) in neuroendocrine cervical carcinoma with high tumor mutational burden: management considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center	Sharabi A et al.	Oncologist	https://www.ncbi.nlm.nih.gov/pubmed/28550027

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Radiotherapy in the management of primary cervical cancer

Editor Vishal Bahall

Descriptive summary

Between 1986 and 1991, Landoni et al. randomised 343 patients with stage Ib to IIa cervical carcinoma to treatment with radical surgery or radiotherapy (RT). Now they report a 20-year update to assess the long-term survival, morbidity and patterns of relapse between the two modalities. They reported a survival in surgery and RT group of 72% and 77%, respectively ($p = 0.280$). Overall, 94 recurrences were reported with a median time to relapse of 13.5 and 11.5 months in the surgery and RT group, respectively. Risk factors for survival are histological subtype ($p = 0.020$), tumour diameter (0.008), and lymph node status ($p < 0.001$) [1].

Jhawar et al. reviewed the national cancer database (US) for 3,051 patients with cervical cancer to determine the effects of overall treatment time (OTT) during chemo-radiotherapy in the adjuvant setting on overall survival (OS). They found that prolongation of adjuvant chemo-radiotherapy (duration over seven weeks) was associated with poorer prognosis (HR 1.33; $P < 0.001$). Interval time from surgery to radiotherapy should be less than eight weeks if clinically feasible [2].

To determine the long-term global health status of women who survived more than four years after curative radiotherapy for cervical cancer, Sung et al. reviewed medical records of 562 women. Disease status and morbidity were evaluated in 303 women after 259 were excluded (died and lost to follow up). Quality-of-life assessments were performed on 168 of these women and compared to an age-matched healthy population. New recurrences occurred in 5% of women with a median time to recurrence of 6.0 years. Grade ≥ 2 treatment-related morbidities were found in 33% of women with a higher rate in women aged ≥ 51 [3].

Romano et al. reported the clinical outcomes (OS, local control and toxicity) at one year of high-dose rate (HDR) compared to low-dose rate (LDR) brachytherapy (BT) for 258 women. They were not able to demonstrate any significant difference in OS and local control (LC) between the 184 LDR women and the 74 HDR women. There was more toxicity (acute and chronic) in the HDR group (24%) vs. LDR group (10%) ($p = 0.04$) [4].

Kamran et al. compared 56 women with locally advanced cervical cancer who were treated with MR-guided ($n = 29$) versus CT-guided ($n = 27$) brachytherapy to determine LC, OS and dose to organs at risk (OAR). At two years, there was no significant difference in OAR, LC (96% vs. 87%) and toxicities between MR- and CT-BT, respectively. The two-year OS was significantly better with MR-BT (84% vs. 56%, $p = 0.036$) [5].

To determine the efficacy of concurrent chemoradiotherapy (CCRT) over radiotherapy in locally advanced cervical cancer (LACC), Datta et al. conducted a systematic review and meta-analysis. CTRT improved the complete response (CR) (+10.2%, $p = 0.027$), locoregional control (+8.4%, $p = 0.001$) and OS (+7.5%, $p < 0.001$) over RT alone in the 2,445 evaluated women. Late toxicities were equivalent in both groups [6].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Randomized study between radical surgery and radiotherapy for the treatment of stage IB-IIA cervical cancer: 20-year update	Landoni F et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28382797
2	Adjuvant chemoradiation therapy for cervical cancer and effect of timing and duration on treatment outcome	Jhawar S et al.	Int J Radiat Oncol Biol Phys.	https://www.ncbi.nlm.nih.gov/pubmed/28721897
3	General health status of long-term cervical cancer survivors after radiotherapy	Sung Uk L et al.	Strahlenther Onkol	https://www.ncbi.nlm.nih.gov/pubmed/28492995
4	Transition from LDR to HDR brachytherapy for cervical cancer: evaluation of tumour control, survival, and toxicity	Romano KD et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/28139420
5	Comparison of outcomes for MR-guided versus CT-guided high-dose-rate interstitial brachytherapy in women with locally advanced carcinoma of the cervix	Kamran SC et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28318644
6	Concurrent chemoradiotherapy vs. radiotherapy alone in locally advanced cervix cancer: a systematic review and meta-analysis	Datta NR et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28188016

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Radiotherapy in management of recurrent cervical cancer

Editor Erbil Karaman

Descriptive summary

In this period, only two papers were published on radiotherapy (RT) in management of recurrent cervical cancer.

Kim et al. evaluated the data of 33 patients who had salvage radiotherapy for recurrent cervical cancer confined to the pelvic cavity after hysterectomy alone for early-stage uterine cervical cancer. The median interval between initial hysterectomy and recurrence was 26 months. The median follow-up period was 53 months for surviving patients. Most patients (97.0%) completed salvage RT of ≥ 45Gy. Complete response (CR) was achieved in 23 patients (69.7%). Pelvic sidewall involvement and evaluation with positron-emission tomography-computed tomography were significantly associated with CR. The five-year progression-free survival (PFS), local control (LC), distant metastasis-free survival (DMFS), and overall survival (OS) rates were 62.7%, 79.5%, 72.5%, and 60.1%, respectively. The incidence of severe acute and late toxicities (≥ grade 3) was 12.1% and 3.0%, respectively. They concluded that aggressive salvage RT with or without concurrent chemotherapy for recurrent cervical cancer confined to the pelvic cavity was feasible, with promising treatment outcomes and acceptable toxicities [1].

Damato et al. conducted a study on cadavers using injection of a novel hydrogel (TraceIT; Augmenix Waltham, MA) between the cervix, rectum, and bladder during cervical cancer brachytherapy with comparison to standard gauze packing. In this study, five cadavers were used and evaluated by CT and MRI. They found that the use of hydrogel in addition to packing resulted in a 22% decrease in rectum D2cc dose, a 10% decrease in bladder D2cc, and no change in sigmoid D2cc dose. They stated that a significant clinically meaningful decrease in rectal D2cc is associated with the use of hydrogel in addition to gauze packing. TraceIT hydrogel holds promise as a spacer in cervical cancer therapy [2].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Salvage radiotherapy with or without concurrent chemotherapy for pelvic recurrence after hysterectomy alone for early-stage uterine cervical cancer	Kim SW et al.	Strahlenther Onkol	https://www.ncbi.nlm.nih.gov/pubmed/28357468
2	Rectum and bladder spacing in cervical cancer brachytherapy using a novel injectable hydrogel compound	Damato AL et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/28619385

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

Editor Marcin Mardas

Descriptive summary

The synergistic cytotoxic effects of Pinellia pedatisecta (PE) and cis-dichlorodiammineplatinum-II (CDDP) against human cervical cancer were evaluated. Combination therapy of PE with CDDP exhibited synergistic cytotoxicity towards CaSki cell growth in mouse xenograft tumours. When mice were co-treated with PE and CDDP, the inhibitory ratio was higher than that of mice treated with CDDP alone (50.8% vs. 68.4%, respectively). In the combined PE and CDDP treatment group, E6 protein expression was significantly decreased and p53 was increased. Upregulation of p53-dependent apoptosis-associated proteins, including Bcl-2-associated X protein and cleaved caspases-9 and -3, was observed in the combined PE and CDDP treatment group [1].

TAK1 inhibitor 5Z-7-oxozeaenol significantly augmented the cytotoxic effects of Dox in a panel of cervical cancer cell lines. Treatment with 5Z-7-oxozeaenol hindered Dox-induced NF- B activation and promoted Dox-induced apoptosis in cervical cancer cells. Moreover, 5Z-7-oxozeaenol showed similar effects in both positive and negative human papillomavirus-infected cervical cancer cells [2].

Ursolic acid nanoparticles significantly suppress cervical cancer cell proliferation, invasion, and migration compared to the control group, Wang et al. showed. Also, apoptosis was induced by ursolic acid nanoparticles in cervical cancer cells through activating caspases, p53 and suppressing anti-apoptosis-related signals. Furthermore, tumour size was reduced by treatment of ursolic acid nanoparticles in in vivo experiments. They concluded that ursolic acid nanoparticles inhibited cervical cancer cell proliferation via apoptosis induction, which could be a potential target for future therapeutic strategy clinically [3].

Xie et al. studied NVP-BEZ235, a novel dual PI3K/mTOR inhibitor that has showed efficacy in other solid tumours, but unknown effects on cervical carcinoma. In human cervical carcinoma cell lines, this molecule effectively and specifically blocked dysfunctional PI3K/mTOR pathway activation, suppressed cell growth in a time- and concentration-dependent manner, led to G1 cell cycle arrest, and induced apoptosis. NVP-BEZ235 suppressed HeLa cell invasiveness and metastasis by inhibiting the PI3K/Akt/MMP-2 pathway. Further, they demonstrated that NVP-BEZ235 treatment in combination with cisplatin or carboplatin induced a synergistic anti-tumoural response in cervical carcinoma cells [4].

Live lactobacilli [multiplicity of infection (MOI) of 1,000:1] significantly possessed inhibitory effects on cell migration ability of cervical cancer cells, Li et al. showed. Lactobacilli (MOI: 1,000:1) significantly upregulated E-cadherin expressions in HeLa and U14 cells ($p < 0.05$). Similar to the western blot assay, immunohistochemistry results also indicated that lactobacilli treatment significantly upregulated E-cadherin in tumour tissues ($p < 0.05$) [5].

Ueda et al. investigated whether itraconazole exerts an anticancer effect on cervical cancer cells. Transcription and protein expression were assessed by cDNA microarray analysis and immunoblotting, respectively. Itraconazole suppressed proliferation of CaSki and HeLa cells in a dose- and time-dependent manner. Furthermore, CaSki cells were more significantly affected by itraconazole than HeLa cells. The microarray analysis showed an eight-fold down-regulation in the expression of GLI1, WNT4, and WNT10A among itraconazole-treated CaSki cells. Moreover, the transcription of sterol carrier protein-2 and ATP-binding cassette transporter-1 was unaffected by itraconazole. Immunoblots showed suppression in -catenin expression and Akt phosphorylation [6].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Synergistic cytotoxic effects of a combined treatment of a Pinellia pedatisecta lipid-soluble extract and cisplatin on human cervical carcinoma in vivo	Zhang M et al.	Oncol Lett	https://www.ncbi.nlm.nih.gov/pubmed/28588727
2	TAK1 inhibitor 5Z-7-oxozeaenol sensitizes cervical cancer to doxorubicin-induced apoptosis	Guan S et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/28430599
3	Ursolic acid nanoparticles inhibit cervical cancer growth in vitro and in vivo via apoptosis induction.	Wang S et al.	Int J Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28259944
4	Dual blocking of PI3K and mTOR signalling by NVP-BEZ235 inhibits proliferation in cervical carcinoma cells and enhances therapeutic response	Xie G et al.	Cancer Lett	https://www.ncbi.nlm.nih.gov/pubmed/27894954
5	Lactobacilli inhibit cervical cancer cell migration in vitro and reduce tumour burden in vivo through upregulation of E-cadherin	Li X et al.	Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/28713905
6	Itraconazole modulates hedgehog, WNT/ -catenin, as well as Akt signalling, and inhibits proliferation of cervical cancer cells	Ueda T et al.	Anticancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28668841

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

Editor Kamil Zalewski

Descriptive summary

In their systematic review and meta-analysis, Faber et al. estimated that the prevalence of HPV in vulval cancer (VC) was 39.7% (95% CI: 35.1%–44.4%) and in vulvar intraepithelial neoplasia (VIN) was 76.3% (95% CI: 70.1%–82.1%). In the new subcategories of VIN (uVIN and dVIN) it was 86.2% (95% CI: 73.5%–95.5%) and 2.0% (95% CI: 0%–10.0%), respectively [1].

Halec et al. focused on obtaining evidence of HPV transcriptional activity. Their study identified the presence of HPV mRNA in 87% of 447 HPV DNA+ VC tissue samples. From the 433 cases with both HPV mRNA and p16INK4a data available, 83% were concordant pairs of HPV mRNA+ and p16INK4a+. A proportion of HPV DNA+ cases (9%) didn't express an additional marker of HPV activity, therefore the authors concluded HPV attribution in that subset is questionable [2].

Hou et al. reported the results from a comparative molecular analysis of 51 vulvar and vaginal melanomas (VVMs) and 2253 nongynaecologic melanomas (NGMs). VVMs harboured distinct mutation rates in the c-KIT, BRAF, and NRAS genes compared with NGMs (22% vs. 3%, 26% vs. 8.3%, 4% vs. 25.9%, respectively). As the PD-L1 (56%) and PD-1 (75%) were among the most frequently expressed molecular markers in VVMs, the authors highlighted the potential use of immunotherapy alone or in combination with targeted therapy for this disease [3]. Palisoul et al. analysed 149 cases of VC and described molecular alterations [EGFR, MRP1, TOP2A, programmed death-1 receptor (PD-1), loss of PTEN; the most common concurrent alteration was EGFR and PD-1, occurring in 57% of cases] that contribute to the pathogenesis of that disease. The authors also identified specific molecular drug targets (cMET, PDL1, PTEN loss, HER2, and hormone receptors) for this rare disease [4]. Kashofer et al. investigated 72 samples of VC and focused on frequency and type of TP53 gene mutations, analysing the entire coding region of the TP53 gene. The authors demonstrated a high frequency of patients with TP53 mutated cancers (40/45) had either disruptive mutations and/or mutations at hot spot locations and at splice site regions (89% of mutated SCC and 64% of all HPV-negative SCC) which have been already linked to chemo- and radioresistance [5]. SOX2 (SRY-related HMG-box 2) belongs to the SOX gene family of high-mobility transcription factors indispensably involved in gene regulation in pluripotent stem cells and neural differentiation. Gut et al. showed that SOX2 is variably amplified in vulvar cancers and is related to HPV-driven carcinogenesis in vulvar carcinomas [6]. Sznurkowski et al. presented that p16Ink4a-status impacts local immune surveillance in VC and suggested that p16INK4a-status could stratify patients for separate immunotherapeutic approaches in VC [7].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Prevalence and type distribution of human papillomavirus in squamous cell carcinoma and intraepithelial neoplasia of the vulva	Faber MT et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28577297
2	Biological relevance of human papillomaviruses in vulvar cancer	Halec et al.	Mod Pathol	https://www.ncbi.nlm.nih.gov/pubmed/28059099
3	Vulvar and vaginal melanoma: a unique subclass of mucosal melanoma based on a comprehensive molecular analysis of 51 cases compared with 2253 cases of nongynecologic melanoma	Hou JY et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28026870
4	Identification of molecular targets in vulvar cancers	Palisoul ML et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28536037
5	Analysis of full coding sequence of the TP53 gene in invasive vulvar cancers: Implications for therapy	Kashofer K et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28527674
6	SOX2 gene amplification and overexpression is linked to HPV-positive vulvar carcinomas	Gut A et al.	Int J Gynecol Pathol	https://www.ncbi.nlm.nih.gov/pubmed/28700423
7	Local immune response depends on p16INK4a status of primary tumour in vulvar squamous cell carcinoma	Sznurkowski JJ et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/28515351

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

Editor Kamil Zalewski

Descriptive summary

In this period, a number of clinical studies focused on the aetiology and treatment of vulvar intraepithelial neoplasia (VIN) have been published.

Based on a RT3VIN clinical trial in which 180 patients with histologically confirmed VIN 3 were randomised to receive topically administered cidofovir or imiquimod, Jones et al. quantified HPV DNA methylation in 167 pretreatment biopsies and assessed its association with response to topical treatment. They found that pretreatment DNA methylation of the HPV E2 gene significantly correlated with response to treatment with cidofovir ($P \leq 0.0001$). E2 methylation > 4% predicted response with 88.2% sensitivity and 84.6% specificity. There was weaker evidence of association between E2 DNA methylation and response to treatment with imiquimod ($p = 0.03$). E2 methylation < 4% predicted response with 70.6% sensitivity and 62.5% specificity. The authors suggested that these data indicate cidofovir and imiquimod may be effective in two biologically distinct patient groups. They concluded that a high proportion of patients could be successfully treated using a nonsurgical approach if, after further prospective validation, HPV DNA methylation was used as a predictive biomarker [1].

Samuels et al. conducted a phase I clinical trial to evaluate the safety and immunogenicity of the TTFCE7SH vaccine (encoding the fusion protein of Tetanus Toxin Fragment C and a shuffled variant of HPV16 E7), applied via DNA tattooing, for the treatment of 12 patients with HPV16-positive uVIN lesions. Patients were vaccinated with a fixed dose of TTFC-E7SH on days zero, three, and six and received a boost vaccination scheduled at week four (days 28, 31, and 34). The TTFC-E-7SH was administered using a novel intradermal application strategy using a permanent make-up device. Although the treatment was well tolerated by all patients, only limited CD4+ and CD8+ T-cell vaccine-induced immune responses and no clinical responses were observed [2].

Raphaelis et al. proved the superiority of information provided orally over written form in terms of clinically important improvement of symptom prevalence in a multicentre randomised controlled parallel-group phase II trial. The trial studied two interventions (written information concerning wound care vs. a set of leaflets plus five nurse consultations) provided to 49 patients after the initial diagnosis of VIN and surgical treatment [3].

A study by Brinton et al. demonstrated risk factors consistent with an HPV-related aetiology and confirmed an increased risk of VIN3 for white compared to non-white women. The authors evaluated aetiologic factors for rare vulvar neoplasms (198 patients with VIN3) based on data collected within the NIH-AARP Diet and Health Study, a prospective investigation of dietary and lifestyle factors in older individuals [4]. [4]. This study is also mentioned in the chapter on "Epidemiology of gynaecological cancers" by Güngördük.

In their systematic review and meta-analysis, Faber et al. estimated the prevalence of HPV in VIN lesions for 76.3% (95% CI: 70.1%–82.1%) while the HPV prevalence in new subcategories of VIN and uVIN and dVIN was 86.2% (95% CI: 73.5%–95.5%) and 2.0% (95% CI: 0%–10.0%), respectively [5].

No relevant articles concerning vaginal intraepithelial neoplasia (VAIN) have been identified.

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Human papillomavirus DNA methylation predicts response to treatment using cidofovir and imiquimod in vulval intraepithelial neoplasia 3	Jones SEF et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28600473
2	HPV16 E7 DNA tattooing: safety, immunogenicity, and clinical response in patients with HPV-positive vulvar intraepithelial neoplasia	Samuels S et al.	Cancer Immunol Immunother	https://www.ncbi.nlm.nih.gov/pubmed/28451790
3	The impact of written information and counseling (WOMAN-PRO II Program) on symptom outcomes in women with vulvar neoplasia: a multicenter randomized controlled phase II study	Raphaelis S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28483270
4	Epidemiology of vulvar neoplasia in the NIH-AARP Study	Brinton LA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28236455
5	Prevalence and type distribution of human papillomavirus in squamous cell carcinoma and intraepithelial neoplasia of the vulva	Faber MT et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28577297

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Primary vulvar cancer treatment

Editor Rubén M. Betoret

Descriptive summary

Vulvar cancer incidence in high-income countries has increased in the last 20 years [1]. This depicts an increasing five-yearly average percent change of 4.6% in women of all ages, rising to 11.6% in those younger than 60, probably consistent with changing sexual behaviours and elevated HPV exposure in cohorts born around or after 1950.

Sentinel lymph node mapping (SLNM)

Surgery remains a cornerstone in the treatment of primary vulvar malignancies, with many efforts being made to tailor therapies, mostly by groin SLNM. Brincat et al. summarised the evidence available on SLNM-guided management and conclude its feasibility and oncological safety in FIGO Ib–II cases, on unifocal tumours smaller than 4cm and without clinical/radiological suspicion of nodal involvement (cN0) [2]. Garganese et al. in GroSNaPET study prospectively recruited 47 patients from a subset of cN0 women who were candidates for radical inguinal surgery according to current guidelines (most due to large tumour size or multifocality) and tried to assess the utility of SLNM and preoperative PET/CT evaluation. From a total of 73 groins, histopathology revealed 12 metastatic sentinel nodes in nine groins, with a negative predictive value (NPV) of 100%. Preoperative PET/CT showed a 93% NPV, suggesting security and accuracy in carefully selected patients currently excluded for SLNM in guidelines [3].

In those patients treated with inguinal lymph node (LN) resection, Polterauer et al. estimated the value of lymph node ratio (LNR) in a retrospective multicentre study on 745 patients (292 of them with positive LNs) that showed its utility both as prognostic factor (five-year overall survival (OS) rates of 90.9%, 70.7%, and 61.8% in the groups with LNR of 0%, <20%, and >20%, respectively, as well as association with local and distance recurrence-free survival) and as a useful tool to select high-risk candidates for adjuvant radiation [4].

Postoperative care evidence

Pouwer et al. highlighted a frequent clinical concern in the postoperative setting in a Dutch nationwide prospective study: Utilisation of postoperative drainage. A significantly lower estimated incidence of complications (46% vs. 75%) was observed in patients with volume-controlled drainage compared to those with short drainage after groin lymph node resection [5].

Adjuvant therapies

Rao et al. reviewed the American national cancer database identifying 1,352 patients with vulvar squamous cell cancer (SCC) and find on multivariate analysis a significantly reduced hazard of death among patients receiving definitive chemoradiation compared to those receiving definitive radiation alone. As by the design of the study, the groups were not comparable in terms of age and FIGO staging [6].

Molecular

Kashofer et al. mapped the different TP53 gene mutations in vulvar SCC, and discussed its implication in prognosis (31% of patients with TP53-mutated SCC died of disease within 12 months, vs. 0% of HPV-induced or TP53 wild-type SCC) as well as prediction of the response on future promising pharmacological therapies [7].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Vulvar cancer in high-income countries: increasing burden of disease	Kang YJ et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28730615
2	Sentinel lymph node biopsy in the management of vulvar carcinoma: an evidence-based insight	Brincat MR et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28763369
3	Groin sentinel node biopsy and 18-FDG PET/CT-supported preoperative lymph node assessment in cN0 patients with vulvar cancer currently unfit for minimally invasive inguinal surgery: The GroSNaPET study	Garganese G et al.	Eur J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28751058
4	Prognostic value of lymph node ratio and number of positive inguinal nodes in patients with vulvar cancer (VULCAN study collaborative group)	Polterauer S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28797698
5	Volume-controlled versus short drainage after inguinofemoral lymphadenectomy in vulvar cancer patients: a Dutch nationwide prospective study	Pouwer AW et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28687171
6	Improved survival with definitive chemoradiation compared to definitive radiation alone in squamous cell carcinoma of the vulva: a review of the national cancer database	Rao YJ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28662775
7	Analysis of full coding sequence of the TP53 gene in invasive vulvar cancer: implications for therapy	Kashofer K et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28527674

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Treatment of recurrent vulvar cancer

Editor María de los Reyes Oliver Pérez

Descriptive summary

Squamous cell carcinoma of the vulva (VSCC)

The newly published European Society of Gynaecological Oncology (ESGO) guidelines cover diagnosis, preoperative study, surgical treatment, radiotherapy, chemoradiation, systemic treatment, follow-up, and treatment of recurrent disease (local recurrence, groin recurrence, distant metastasis). Regarding local recurrence, surgical treatment is advised. The recommendation is wide local excision, with inguinofemoral lymphadenectomy in case of depth of invasion of more than 1mm and not previously performed groin dissection. The indications for postoperative radiotherapy are comparable to those for the treatment of primary disease. For groin recurrence, recommended treatment is radical excision when possible, followed by postoperative radiation in radiotherapy-naive patients. Definitive chemoradiation is recommended when surgical treatment is not possible. Finally, systemic (palliative) therapy should be considered individually in the treatment of distant metastases [1].

Yap et al. published a detailed literature review on the aetiology, pathobiology, and management of VSCC local recurrence. They summarised the current evidence on immune-based therapies for management of locally advanced and recurrent VSCC [2]. Pembrolizumab, which targets the programmed cell death protein-1 (PD-1) on tumour-infiltrating lymphocytes (TILs), has recently been licensed by the US Food and Drug Administration (FDA) for this purpose.

Brown et al. published an interesting review on the evolution of radical surgical techniques for advanced and recurrent pelvic malignancy [3].

Jafri et al. reported an anecdotal case and review of literature of a recurrent vulvar carcinoma with cardiac metastasis [4].

Non-squamous cell vulvar cancer

No reports with scientific relevance were published in this period.

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	European Society of Gynaecological Oncology Guidelines for the Management of Patients with Vulvar Cancer	Oonk MHM et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28441255
2	Current insights into the aetiology, pathobiology, and management of local disease recurrence in squamous cell carcinoma of the vulva	Yap J et al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/28081287
3	Pelvic exenteration surgery: the evolution of radical surgical techniques for advanced and recurrent pelvic malignancy	Brown KGM et al.	Dis Colon Rectum	https://www.ncbi.nlm.nih.gov/pubmed/28594725
4	The tell-tale heart: a case of recurrent vulvar carcinoma with cardiac metastasis and review of literature	Jafri SIM et al.	Gynecol Oncol Rep	https://www.ncbi.nlm.nih.gov/pubmed/28664179

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Vulvovaginal adenocarcinoma/melanoma/sarcoma

Editor Anna Dückelmann

Descriptive summary

The diagnosis and classification of vulvar adenocarcinomas (VAC) is a complicated and understudied area, as this is a rare histologic subtype of vulvar cancers. The differential diagnoses include mammary-like adenocarcinoma of the vulva (MLAV), adenocarcinoma arising from extramammary Paget disease (EMPD), mucinous carcinoma, Bartholin gland adenocarcinomas, and metastatic adenocarcinomas from various sites. Grewal et al. report a patient initially diagnosed with poorly differentiated VAC. Analysis of the transcriptome led to reclassification of the tumour as a primary HER2+MLAV [1].

Another study on MLAV, showed breast cancer subtyping by immunohistochemistry can be applied to MLAV. All four intrinsic molecular subtypes were seen with frequencies similar to those in breast carcinoma. The authors discuss the potential use of breast cancer molecular profiling algorithms to guide treatment for these types of cancers [2].

Intestinal type is a rare variant of primary AC of the vulva or vagina, also known as AC of cloacogenic origin, enteric type AC or cloacogenic AC. Two reviews [3, 4] present 26 cases published in the literature so far. The suggested treatment is radical local excision without adjuvant therapy, the need for ipsilateral or bilateral inguinal lymph node dissection is under discussion, seeing the apparent low risk of metastasis.

Konstantinova et al. showed that a small subset of primary EMPD may originate in anogenital mammary-like glands, analogous to breast carcinoma [5].

According to a retrospective, multicentre analysis of 144 cases of rhabdomyosarcoma of the lower female genital tract, prepubertal girls and adolescents primarily affected by this disease have excellent survival rates. Older age, advanced stage of disease, and non-embryonal histologic subtypes are associated with inferior outcomes. Wide local tumour excision and chemotherapy are the recommended treatment [6].

Nguyen et al. presented 54 patients affected by vulvar dermatofibrosarcoma protuberans (VDFSP). VDFSP most commonly presents as a slowly enlarging tender or asymptomatic mass on the labia majora, with histological findings of classic DFSP. Most patients were treated with wide local excision. The authors recommend Mohs micrographic surgery as the best treatment option which may decrease local recurrence and seems well suited for use especially in vulvar DFSP [7].

Yuan et al. reported nine cases of early-stage embryonal rhabdomyosarcoma of the female genital tract; three originated from the vagina and six from the cervix. The standard therapeutic modality is the combination of surgery and chemotherapy (vincristine, dactinomycin, and cyclophosphamide). For the surgical treatment of vaginal rhabdomyosarcoma, extended local resection has shown better outcome [8].

Skovsted et al. presented 17 patients, Udager et al. presented 59 patients, and Tasaka et al. presented five cases diagnosed with malignant melanoma of the vagina or vulva, respectively [9,10, 11]. Early diagnosis and staging of these aggressive tumours with poor prognosis is important. The main complaint of patients with vaginal melanoma is abnormal genital bleeding. Positron emission tomography-computed tomography should be the standard method for staging the disease. The aggressive clinical behaviour of non-vulvar tumours (vagina and/or cervix) is independent of advanced clinical stage and lymph node metastasis. Targeted molecular analysis confirms an overall low rate of oncogenic mutations (BRAF, KIT, NRAS, and CTNNB1). The primary treatment is resection of the tumour, but future treatment might be a combination of resection and immunotherapy.

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Detection and genomic characterization of a mammary-like adenocarcinoma	Grewal JK et al.	Cold Spring Harb Mol Case Stud	https://www.ncbi.nlm.nih.gov/pubmed/28877932
2	Molecular subtyping of mammary-like adenocarcinoma of the vulva shows molecular similarity to breast carcinomas	Tessier-Cloutier B et al.	Histopathology	https://www.ncbi.nlm.nih.gov/pubmed/28418164
3	Primary mucinous adenocarcinoma of the vulva, intestinal type	Lee IH et al.	Obstet Gynecol Sci	https://www.ncbi.nlm.nih.gov/pubmed/28791269
4	Primary villoglandular mucinous adenocarcinoma of the vulva	Matsuzaki A et al.	Case Rep Pathol	https://www.ncbi.nlm.nih.gov/pubmed/28503335

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Vulvovaginal adenocarcinoma/melanoma/sarcoma

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

No	Title	Authors	Journal	Link to abstract
5	Spectrum of changes in anogenital mammary-like glands in primary extramammary (anogenital) Paget disease and their possible role in the pathogenesis of the disease	Konstantinova AM et al	Am J Surg Pathol	https://www.ncbi.nlm.nih.gov/pubmed/28614205
6	Rhabdomyosarcoma of the lower female genital tract: an analysis of 144 cases	Nasioudis D et al	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/28634755
7	Clinical features and treatment of dermatofibrosarcoma protuberans affecting the vulva: a literature review	Nguyen AH et al	Dermatol Surg	https://www.ncbi.nlm.nih.gov/pubmed/28323651
8	Stage 1 embryonal rhabdomyosarcoma of the female genital tract: a retrospective clinical study of nine cases	Yuan G et al	World J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28173865
9	Melanomas of the vulva and vagina.	Skovsted S et al.	Dan Med J	https://www.ncbi.nlm.nih.gov/pubmed/28260594
10	A retrospective clinical analysis of 5 cases of vaginal melanoma	Tasaka R et al	Mol Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28451415
11	Gynecologic melanomas: a clinicopathologic and molecular analysis	Udager AM et al	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28844540

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Minimally invasive surgery

Editor Borja Otero

Descriptive summary

Cervical cancer

The MD Anderson Cancer Center group has published its results regarding the sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer. They performed a retrospective study of 188 women with stage Ia1–Ib1 and stage IIa1 cervical cancer who underwent sentinel lymph node biopsy and complete pelvic lymphadenectomy. Lymphatic mapping was performed using either technetium 99m sulphur colloid, patent blue dye, indocyanine green or a combination of tracers. At least one SLN was identified in 170 patients (90%) and bilateral SLN were found in 117 patients (62%). After complete pelvic lymphadenectomy, the sensitivity of SLN biopsy was 96.4% (95% CI: 79.8%–99.8%) and the negative predictive value was 99.3% (95% CI: 95.6%–100.0%) [1]. This study is also included in the report on "Surgical management of cervical cancer" by Mandic Aljosa and Matteo Morotti.

Endometrial cancer

The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial published its results regarding disease-free survival and overall survival among women with stage I endometrial cancer. In an international multi-centric setting, 760 patients were randomised to undergo either total laparoscopic hysterectomy (n = 353) or total abdominal hysterectomy (n = 407). After a median follow-up of 4.5 years, there was no statistically significant difference in recurrence of endometrial cancer (28/353 in TAH group [7.9%] vs. 33/407 in TLH group [8.1%]; risk difference, 0.2% [95% CI: -3.7%–4.0%]; p=0.93) or in overall survival (24/353 in TAH group [6.8%] vs. 30/407 in TLH group [7.4%]; risk difference, 0.6% [95% CI: -3.0%–4.2%]; P=.76). The only relevant between-group difference was the percentage of patients on which pelvic or aortic lymph node dissection was performed (58.4% in TAH group and 39.6% in TLH group) and although that did not mean a difference in the percentage of patients with stage IIIc cancer, this bias should be considered [2].

Although there is an increasing trend towards robotic surgery, a retrospective study compared the outcomes and costs of vaginal and robotic hysterectomy for patients with endometrial cancer. After an adequate selection of patients with low risk of needing the performance of a subsequent lymphadenectomy, similar surgical and oncologic outcomes and lower costs were obtained in patients undergoing vaginal hysterectomy [3].

Ovarian cancer

The role of minimally invasive surgery (MIS) in ovarian cancer after chemotherapy has been explored in two recent papers.

Leitao et al. described how MIS plays a role in secondary surgical cytoreduction (SSCR) in patients with recurrent ovarian carcinoma. They retrospectively identified 170 patients with platinum-sensitive epithelial ovarian cancer who had undergone SSCR. Of these, 39 had undergone MIS (both robotic and conventional laparoscopy). After exhaustive preoperative evaluation and selection, patients undergoing MIS had better operative outcomes including less estimated blood loss, shorter hospital stay, and similar complete gross resection and complication rates compared to patients undergoing laparotomy. Regarding oncologic outcomes, both groups had similar two-year progression-free survival and overall survival [4].

Another study analysed data from the National Cancer Database to assess the role of MIS compared with laparotomy for debulking ovarian cancer after neoadjuvant chemotherapy. In all, 3,484 patients receiving neoadjuvant chemotherapy and interval debunking surgery were detected, of whom 450 (14.7%) underwent MIS and 2,621 (85.3%) underwent laparotomy. Patients in the cohort undergoing MIS had three-year survival rates similar to women who underwent interval debulking surgery by laparotomy with a modestly shorter post-operative hospitalisation and similar readmission rates and risk of perioperative death [5].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Sensitivity and negative predictive value for sentinel lymph node biopsy in women with early-stage cervical cancer	Salvo G et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28188015
2	Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer: a randomized clinical trial	Janda M et al.	JAMA	https://www.ncbi.nlm.nih.gov/pubmed/28350928
3	Vaginal vs. robotic hysterectomy for patients with endometrial cancer: a comparison of outcomes and cost of care	Nitschmann CC et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28392125
4	Minimal access surgery compared to laparotomy for secondary surgical cytoreduction in patients with recurrent ovarian carcinoma: perioperative and oncologic outcomes	Eriksson AGZ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28527673
5	Laparoscopy compared with laparotomy for debulking ovarian cancer after neoadjuvant chemotherapy	Melamed A et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28383367

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Sentinel node mapping in gynaecological malignancies

Editor Anton Ilin

Descriptive summary

Endometrial cancer

Bilateral SLN detection rate varies between 50% and 88% according to literature and seems to be one of main characteristics of a successful procedure. Persson et al. are the first to present an algorithm aiming for bilateral identification of both the upper paracervical pathway (UPP) and the lower paracervical pathway (LPP) with a bilateral detection rate of 96% [1].

One of the largest studies published recently on this topic evaluated the impact of SLN mapping compared to standard lymphadenectomy on recurrence patterns and recurrence-free survival (RFS). In all, 472 patients underwent either SLN mapping (SLN cohort, n = 275) or systematic lymphadenectomy (LND cohort, n = 197). No significant difference in overall RFS could be identified between the cohorts at 48 months but pelvic sidewall recurrences accounted for 30% of recurrences in the SLN cohort compared to 71.4% in the LND cohort. This paper suggests that appropriate use of SLN biopsy technique may reduce the risk of relapses at the pelvic side wall [2].

Part of SLN procedure implies pathological ultrastaging of the SLN, which has led to the detection of more low-volume metastasis (LVM), such as micrometastasis and isolated tumour cells (ITC). Up to 8% more LVM have been detected by submitting SLN to ultrastaging. On an example of 31 patients with ITC in SLN, Plante et al. demonstrated that during the 29-month follow-up period there was no significant difference in RFS comparing to node-negative patients, which meant that use of adjuvant treatment in this group should be tailored to uterine factors and histology and not solely based on the presence of ITCs [3].

In a systematic review, Bodurtha Smith et al. evaluated the sustained the efficacy of SLN mapping procedure in 55 eligible studies that included 4,915 women. The overall detection rate of SLN mapping was 81% with a 50% bilateral pelvic node detection rate and 17% paraaortic detection rate. The sensitivity to detect metastases was 96%. Cervical injection was associated with significantly higher rates of bilateral SLN detection (56% vs. 33%) compared with uterine injection. However, cervical injection was associated with a significantly lower rate of paraaortic SLN detection than uterine injection (7% vs. 27%). In cases with positive SLNs, these were macrometastases in 29%, micrometastases in 39%, and isolated tumour cells in 32% of cases. As paraaortic metastases are a poor prognostic indicator, the incidence of paraaortic metastases in the absence of pelvic metastases is exceedingly low (1%–5%), especially in women with low-grade endometrial cancer. If paraaortic SLN mapping fails, pelvic SLN mapping is likely sufficient in most patients, given the low likelihood of isolated paraaortic metastases in this setting [4].

Other data were obtained by Martinelli et al., who published the largest series (202 procedures) of SLN mapping following hysteroscopic injection of combined tracers (ICG and Tc-99). Bilateral pelvic mapping was found in 59.7% of cases. In 50.8% of cases (91/179), SLNs were mapped both in pelvic and aortic nodes, and in five cases (2.8%) only in the aortic area. Authors linked the high rate of paraaortic SLNs identification with usage of ICG, which probably permits the visual following of lymphatic channels. Similarly, high bilateral detection was associated with two factors: first of all, ICG allows the following of lymphatics up to the SLN, adding the visual identification to just the acoustic one; secondly, gamma probe is not 100% reliable in detecting nodes, especially the laparoscopic one, due to the operating angles available. Furthermore, radiation background, even after uterus removal, was present in the pelvis, partially masking SLNs radiation [5].

The FIRES study, a multicentre prospective cohort study on SLN mapping in early stage endometrial cancer is included in the report by Piotr Lepka on "Surgical treatment of primary uterine cancer".

Cervical cancer

The hybrid tracer ICG-Tc-99 combines the advantages of both tracers, and its value has been reported in other pelvic malignancies, such as vulvar and urological neoplasms with high SLN detection rates (98% for vulvar cancer and 97% for penile cancer). Paredes et al. presented results of the first study in which combined tracer was used for SLN mapping procedure for patients with Ia1–Ib1 cervical cancer. Sixteen patients were included, and patent blue was additionally injected in 14 patients. Of the 69 SLN defined during surgery, 66 (95.65%) were identified by their radioactivity signal, 67 (97.1%) by their fluorescence signal, and 35 (50.7%) by their blue coloration. The technique seems to be feasible and safe but further studies are needed to clarify the value of combined tracers [6].

Using PET/CT for determining lymph node metastasis is controversial

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Sentinel node mapping in gynaecological malignancies

Descriptive summary (cont.)

mostly because small metastatic lesions may remain undetected and more widely have been described for endometrial cancer patients. Papadia et al. evaluated a clinical staging protocol combining preoperative PET/CT and SLN mapping in patients with early-stage cervical cancer. Sixty patients with FIGO IA1-IIA met inclusion criteria. The advantage of combination of PET/CT and SLN mapping was shown only for tumours > 2cm in diameter (sensitivity 100%, specificity 76%, PPV of 72%, and NPV 100%) [7].

Vulvar cancer

A combination of ICG, Tc, and patent blue was evaluated in 27 patients with vulvar cancer smaller than 4cm. ICG showed higher detection rates than Tc-guided SLNM [8]. Results of a retrospective AGO-CaRE-1 study on 772 patients comparing SLNM and LND were also published; both PFS and OS were statistically similar between the cohorts [9].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Description of a reproducible anatomically based surgical algorithm for detection of pelvic sentinel lymph nodes in endometrial cancer.	Persson J et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28751118
2	Impact of sentinel lymph node mapping on recurrence patterns in endometrial cancer	How J et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28104296
3	Isolated tumour cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter?	Plante M et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28577885
4	Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis	Bodurtha Smith A J et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27871836
5	Sentinel node mapping in endometrial cancer following hysteroscopic injection of tracers: A single centre evaluation over 200 cases	Martinelli F et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28625394
6	Role of ICG-99mTc-nanocolloid for sentinel lymph node detection in cervical cancer: a pilot study	Paredes P et al.	Eur J Nucl Med Mol Imaging	https://www.ncbi.nlm.nih.gov/pubmed/28492965
7	The combination of preoperative PET/CT and sentinel lymph node biopsy in the surgical management of early-stage cervical cancer	Papadia A et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28669052
8	Sentinel lymphadenectomy in vulvar cancer using near-infrared fluorescence from indocyanine green compared with Technetium 99m nanocolloid	Soergel P et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28399034
9	Outcome after sentinel lymph node dissection in vulvar cancer: a subgroup analysis of the AGO-CaRE-1 study	Klapdor R et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27896515

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

Editor Elisa Piovano

Descriptive summary

Lower limb lymphoedema (LLL)

Kuroda et al. retrospectively analysed timing and risk factors for LLL in 264 patients submitted to pelvic (PLA) or pelvic and para-aortic lymphadenectomy (PALA) for gynaecological malignancies. LLL developed after a median of 13.5 months, and cumulative incidence rates were 23.1% at one year, 32.8% at three years, and 47.7% at five years. Independent risk factors for LLL were BMI≥25, PLA+PALA, lymphocyst formation, and postoperative radiotherapy [1].

Hayes et al. prospectively analysed timing and risk factors for LLL in 408 patients surgically treated for gynaecological cancer. They collected both self-reported measures (swelling in one/both legs) and objectively measured lymphoedema (by bioimpedance spectroscopy). Three-quarter of the LLL cases presented by 12 months after surgery. The two-year incidence of LLL was 45%, according to self-reported data; 37% according to bioimpedance spectroscopy. They confirmed similar risk factors as reported in the study by Kuroda et al., adding insufficient level of physical activity and a presence of pre-treatment lymphoedema. A comprehensive preoperative assessment should probably focus on these aspects [2].

Charoenkwan et al. conducted an update of a previously published Cochrane review about the effect of retroperitoneal pelvic drainage (active or passive suction drains) versus no drainage on lymphocyst formation after pelvic lymphadenectomy for gynaecological cancer. They included four RCT with a total of 571 women. Regarding short-term outcomes, placement of retroperitoneal tube drains had no benefit in the prevention of lymphocyst formation. In patients where the pelvic peritoneum was left open, tube drain placement was associated with a higher risk of short- and long-term symptomatic lymphocyst formation (respectively, RR 3.25, 95% CI: 1.26–8.37 and RR 7.12, 95% CI: 0.89–56.97) [3].

Venous thromboembolic disease

Greco et al. retrospectively analysed timing and incidence for venous thromboembolic events (VTE) in 125 patients with ovarian cancer submitted to neoadjuvant chemotherapy (NACT) + interval debulking surgery (IDS). Thirteen patients were excluded because they had VTE at diagnosis. VTE developed in 30/112 patients (26.8%): 13 during NACT, six after IDS, 11 during adjuvant chemotherapy. The authors suggested additional attention to VTE prophylaxis especially during chemotherapy [4].

Surgical site infections (SSI)

Kuroki et al. present their RCT randomising 163 patients to staples or subcuticular 4–0 monofilament suture for midline vertical skin closure in obese women to compare wound complication rates. This study was not focused on oncologic patients, but the results are interesting. Women with staples reported worse cosmetic outcomes, but there were no differences in wound complications rates (33% vs. 32%, RR 1–05, 95% CI: 0.68–1.64). Smoking strongly correlated with wound complications (OR 4.96, 95% CI: 1.32–18.71) [5].

Hopkins et al. evaluated the frequency of SSI before and after implementation of a multidisciplinary perioperative glycaemic control initiative (preoperative triage for diabetes/prediabetes, standardisation of intraoperative insulin choices, rigorous perioperative glucose monitoring with control targets set to maintain BG ≤10mmol/L (180mg/dL), and communication with primary care providers). The initiative provided over two-fold reduction in SSI compared to pre-implementation group (5.7% vs.14.6%; p = 0.001, RR: 0.45, 95% CI: 0.25–0.81) [6].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Risk factors and a prediction model for lower limb lymphedema following lymphadenectomy in gynecologic cancer: a hospital-based retrospective cohort study	Kuroda K et al.	BMC Womens Health	https://www.ncbi.nlm.nih.gov/pubmed/28743274
2	Lymphedema following gynecological cancer: results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors	Hayes SC et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28624154
3	Retroperitoneal drainage versus no drainage after pelvic lymphadenectomy for the prevention of lymphocyst formation in women with gynaecological malignancies	Charoenkwan K et al.	Cochrane Database Syst Rev	https://www.ncbi.nlm.nih.gov/pubmed/28660687
4	Incidence and timing of thromboembolic events in patients with ovarian cancer undergoing neoadjuvant chemotherapy	Greco PS et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28486358
5	Wound complication rates after staples or suture for midline vertical skin closure in obese women: a randomized controlled trial	Kuroki LM et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28594761
6	Implementation of a referral to discharge glycemic control initiative for reduction of surgical site infections in gynecologic oncology patients	Hopkins L et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28532856

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

Technical aspects/tricks of surgery in management of gynaecological malignancies

Editor Elisa Piovano

Descriptive summary

During the period covered, only two interesting papers dealing with gynaecological oncology surgery technical aspects were published.

Komiyama et al. describe "Komiyama's manoeuvre", a modification of Kocher's manoeuvre to perform dissection of high paraaortic lymph nodes, superior to the renal vein in ovarian cancer. An educational surgical video is provided [1]. This technique is also mentioned in this issue of LiFE in Han's report on primary surgical treatment.

Kim et al. describe their experience with ileal ureter replacement for complex ureteral loss as a result of various aetiology (single and bilateral replacement). The surgical technique is described. Among the 31 patients included in the study, 24 were affected by ureteral defects after gynaecological surgery/radiation. The mean operation time was 370 minutes and the hospital stay was 25 days. Despite a high rate of short- and long-term complications (33.3% and 87.1%), all cases but one were relieved by conservative care and only one case needed surgical intervention. After a mean follow-up of 23.6 months, apart from two patients who died due to the progression of cervical cancer, all patients had stent-free status [2].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Safe dissection of high paraaortic lymph nodes superior to the renal vein in ovarian, primary peritoneal, or fallopian tube cancer by the "Komiyama's maneuver", a modification of Kocher's maneuver	Komiyama S et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28237617
2	Use of the ileum for ureteral stricture and obstruction in bilateral, unilateral, and single-kidney cases	Kim A et al.	Urology	https://www.ncbi.nlm.nih.gov/pubmed/28818535

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Fertility-sparing treatment in gynaecological malignancies

Editor Charalampos Theofanakis and Dimitris Papatheodorou

Descriptive summary

Endometrial cancer

A retrospective study assessed the oncologic and pregnancy outcomes of combined oral medroxyprogesterone acetate (MPA)/levonorgestrel-intrauterine system (LNG-IUS) treatment in young women with grade 2 stage Ia endometrial adenocarcinoma who wished to preserve fertility. The study included five patients with a mean age of 30.4 ± 5.3 years (range 25–39 years). Mean treatment duration was 11.0 ± 6.2 months (range 6–18 months) and complete response (CR) was recorded in three of the five patients, with partial response (PR) in the other two. The authors concluded that combined oral MPA/LNG-IUS treatment is considered to be a reasonably effective fertility-sparing treatment for grade 2 stage Ia endometrial cancer [1]. Park et al. conducted a multicentre retrospective study, which included 154 young patients with grade 1 stage Ia endometrioid adenocarcinoma who received progestin therapy. The authors assessed the significance of body weight change during the treatment. A pretreatment BMI of ≥ 25 kg/m2 was significantly associated with a lower complete response rate to progestin therapy (p = 0.003) and a high recurrence rate (p = 0.049) [2]. Corzo et al. reviewed the available methods for fertility-sparing treatment in young patients with grade 1 stage Ia endometrial cancer. The authors concluded that uterine preservation is a safe and feasible option in selected young women interested in future fertility, but also emphasized that only patients with complex atypical hyperplasia or grade 1 endometrioid adenocarcinoma are candidates for a conservative approach [3].

Cervical cancer

A retrospective analysis assessed the pattern of recurrence after conisation and pelvic lymphadenectomy in 54 patients with early-stage cervical cancer (CC). Relapse was recorded in seven patients (13%), while in six cases (86%) the recurrence was local. The authors recorded a local pattern of recurrence (on the cervix) up to 4%. However, the pattern of recurrence and recurrence rates after conisation and pelvic lymphadenectomy for early-stage CC are still unclear [4]. A meta-analysis evaluated the recurrence rates, survival, and pregnancy outcomes of early-stage cervical cancer patients treated with cervical conisation (CON) and radical trachelectomy (RT) with or without pelvic lymphadenectomy. A total number of 2,854 patients from 60 observational studies were included and the authors found that NOC procedures seems to result in better pregnancy outcomes then RT with similar rates of recurrence and mortality [5].

Ovarian cancer

A retrospective study assessed the oncologic and obstetric outcome in young patients with stage I epithelial ovarian cancer (EOC) treated with fertility-sparing surgery. A total of 108 premenopausal patients were included, of which 48.1% underwent fertility-sparing surgery (FSS) while 51.9% underwent a radical surgery (RS). After a follow-up period of 83 months, the authors concluded that grade 3 or clear cell histologic type were the only independent risk factors for disease-free survival. Thirty-four out of 52 (65.4%) FSS patients attempted to get pregnant and 28 (82.4%) achieved a successful pregnancy with a full-term delivery. The authors stated that FSS could be safely performed on patients of reproductive age with grade 1–2 stage I EOC, while grade 3 and clear-cell carcinoma warrants further evaluation [6]. A cohort study compared all-cause mortality between women who underwent fertility-sparing surgery and conventional surgery for stage I epithelial ovarian cancer. The study enrolled 1,726 women under 40 years old with stage Ia and unilateral Ic epithelial ovarian cancer. Fertility-sparing surgery was not associated with hazard of death and the probability of survival ten years after diagnosis was 88.5% in the fertility-sparing group and 88.9% in the conventional surgery group. In patients with high-risk features such as clear cell histology, grade 3, or stage Ic, ten-year survival was 80.5% among women who underwent fertility-sparing surgery and 83.4% among those who had conventional surgery. The authors concluded that, compared with conventional surgery, fertility-sparing surgery was not associated with increased risk of death in young women with stage I epithelial ovarian cancer [7].

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Fertility-sparing treatment in gynaecological malignancies

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Combined oral medroxyprogesterone/levonorgestrel-intrauterine system treatment for women with grade 2 stage Ia endometrial cancer	Hwang JY et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28346240
2	Significance of body weight change during fertility-sparing progestin therapy in young women with early endometrial cancer	Park JY et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28526167
3	Updates on conservative management of endometrial cancer	Corzo C et al.	J Minim Invasive Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28782618
4	Conization in early stage cervical cancer: pattern of recurrence in a 10-year single-institution experience	Tomao F et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28486242
5	Oncologic and obstetrical outcomes with fertility-sparing treatment of cervical cancer: a systematic review and meta-analysis	Zhang J et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/28418849
6	Oncofertility in patients with stage I epithelial ovarian cancer: fertility-sparing surgery in young women of reproductive age	Jiang Q et al.	World J Surg Oncol	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5557507/
7	All-cause mortality after fertility-sparing surgery for stage I epithelial ovarian cancer	Melamed A et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28594773

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Gestational Trophoblastic Disease

Editor Manuela Undurraga Malinverno

Descriptive summary

Diagnosis and prediction

Quite a few articles focused on the diagnosis and prediction of GTN outcomes in this period covered by LiFE 6.

Khashaba et al. confirmed that immunohistochemical staining of p57Kip2 helps in the differential diagnosis of complete and partial moles, as well as molar and non-molar pregnancies. They found that criteria such as villous shape and outline, trophoblast hyperplasia, cistern formation, and trophoblastic inclusion were helpful in this differentiation [1].

Asmar et al. analysed the utility of uterine artery Doppler flow velocimetry in the prediction of GTN after complete mole. In this prospective cohort study, they found that the pre-and post-evacuation pulsatility indices were significantly lower in patients who developed GTN compared to those who had spontaneous remission. They also found that a pre-evacuation index of ≤ 1.38 and post-evacuation index of ≤ 1.77 were predictive of GTN development [2].

De Souza et al. compared two hCG essays, and found them equivalent for the diagnosis of low levels of hCG (+- 100 mIU/mL). If additional studies compare different commercially available essays, this could be important from a cost perspective [3].

Zhao et al. created a new daily hCG regression rate curve and compared it to the actual weekly hCG regression rate curve, and found that with their daily curve GTN was diagnosed an average of 15.3 days earlier compared to the weekly curves were used. They state, however, that this is preliminary information and that further studies should be done before changing the actual curves [4].

Kong et al. evaluated the characteristics and prognosis of ultra-high-risk gestational trophoblastic neoplasia patients. In their retrospective cohort study, they confirmed the lower overall survival compared to other GTN groups (68%). Risk factors are previous non-molar pregnancies, brain metastasis, and previous failure to respond to multi-agent chemotherapy. Most interestingly, they found a survival benefit in patients who had had salvage surgery [5].

Two studies concentrated on the predictor of live births during pregnancies with coexisting moles with live foetuses. Suksai et al. confirmed the 35% rate of live births, and found that a sub-group of patients without history of pregnancy-induced hypertension, hyperparathyroidism, and hyperemesis gravidarum had favourable obstetrical outcomes if the initial serum hCG level was less than 400.000 mIU/mL [6]. On the other hand, Lin et al. had higher live birth rates (60%) when comparing both Brazilian and American trophoblastic centres, though they also found that elevated hCG levels and medical co-morbidities were predictive factors of negative foetal outcomes [7].

Sefibdakht et al. found that diffusion-weighted imaging was not useful in the prediction of progression of molar pregnancy to GTN [8].

Eysbouts et al. did a retrospective analysis to see if the actual FIGO scoring system could be simplified. Only three of the eight factors currently present were predictive of single-agent resistance in low-grade disease. The factors were levels of pre-treatment hCG, interval exciding seven months since last pregnancy, and tumour size. They state that new research is needed to further validate their findings [9].

Treatment modalities

Four retrospective articles evaluated different treatment modalities during this period.

An interesting study by Wang et al. evaluated the efficacy of embolisation in patients with massive haemorrhage due to GTD and if the embolisation had an effect on the outcome of patients after chemotherapy. They found that not only was embolisation able to control haemorrhage in more than 90% of patients, but this treatment did not affect the outcome of chemotherapy. Two other articles addressed the role of surgery in the treatment of GTD [10]. Girgione et al. analysed the role of surgery in patients over age 40 with GTD, and found that hysterectomy did not reduce the incidence of GTN or the amount of chemotherapy [11]. However, Eysbouts et al. report that in patients with localised disease primary hysterectomy led to significant shorter chemotherapy duration with a lower number of administered cycles [12].

Essel et al. confirmed the utility of certain salvage chemotherapy regimens in patients treated for high-risk or recurrent GTN. They state that the use of either methotrexate or dactinomycin immediately after failure of other single-agent chemotherapy has a complete response rate of up to 56%, so it is reasonable to use these therapies as second line before passing on to multi-regimen chemotherapy. In the case of multi-regimens, EMA-CO had the greatest activity in patients who fail initial chemotherapy. Other regimens identified as active in GTN were MAC, BEP, ICE, and other platinum- and etoposide-based combination therapies [13].

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Gestational Trophoblastic Disease

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Morphological features and immunohistochemical expression of p57Kip2 in early molar pregnancies and their relations to the progression to persistent trophoblastic disease	Khashaba M et al.	J Pathol Transl Med	https://www.ncbi.nlm.nih.gov/pubmed/28607326
2	Uterine artery Doppler flow velocimetry parameters for predicting gestational trophoblastic neoplasia after complete hydatidiform mole, a prospective cohort study	Asmar FTC et al.	Clinics (Sao Paulo)	https://www.ncbi.nlm.nih.gov/pubmed/28591340
3	Comparison of 2 human chorionic gonadotropin immunoassays commercially available for monitoring patients with gestational trophoblastic disease	de Souza JMQ et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28692637
4	A novel prediction model for postmolar gestational trophoblastic neoplasia and comparison with existing models	Zhao P et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28498254
5	Clinical characteristics and prognosis of ultra high-risk gestational trophoblastic neoplasia patients: a retrospective cohort study	Kong Y et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28461032
6	Complete hydatidiform mole with co-existing fetus: predictors of live birth	Suksai M et al.	Eur J Obstet Gynecol Reprod Biol	https://www.ncbi.nlm.nih.gov/pubmed/28301807
7	Multiple pregnancies with complete mole and coexisting normal fetus in North and South America: a retrospective multicentre cohort and literature review	Lin LH et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28132722
8	Qualitative and quantitative analysis of diffusion-weighted imaging of gestational trophoblastic disease: can it predict progression of molar pregnancy to persistent form of disease?	Sefidbakht S et al.	Eur J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/28189211
9	Can the FIGO 2000 scoring system for gestational trophoblastic neoplasia be simplified? A new retrospective analysis from a nationwide dataset	Eysbouts YK et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28459944
10	Bleeding from gestational trophoblastic neoplasia: embolotherapy efficacy and tumour response to chemotherapy	Wang Z et al.	Clinic Radiol	https://www.ncbi.nlm.nih.gov/pubmed/28673447
11	Role of surgery in the management of hydatidiform mole in elderly patients: a single-center clinical experience	Giorgione V et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28129241
12	The added value of hysterectomy in the management of gestational trophoblastic neoplasia	Eysbouts YK et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28390821
13	Salvage chemotherapy for gestational trophoblastic neoplasia: utility or futility?	Essel KG et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28473205

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Cancer in pregnancy

Editor Michael J. Halaska

Descriptive summary

A number of original articles and several reviews have been published recently on cancer in pregnancy. Most commonly, they dealt with melanoma, breast cancer, thyroid cancer, hematologic malignancies, and cervical cancer.

Two interesting studies focused on imaging techniques during pregnancy. Peccatori et al. used whole-body MRI during pregnancy for staging purposes in 14 patients with breast cancer. Without using a contrast agent, the technique is safe for foetus and mother after the first trimester [1]. Myers et al. evaluated preoperative breast MRI in 53 pregnancy-associated breast cancer patients and compared it to mammography or ultrasonography. MRI changed a surgical procedure in 28% of patients (larger or smaller tumourectomy, bilateral procedure, etc.) [2].

An issue of timing planned pregnancy after the treatment of breast cancer was described by Iqbal et al. by evaluating the survival of 7,553 women. Survival was lower if the patient became pregnant less than six months after the treatment. Historically, the proposed delay was 24 months, therefore the finding is of high importance for clinical practice [3].

Breast feeding after chemotherapy was evaluated by Stopenski et al. in a prospective study. A statistically significant difference in breastfeeding difficulties was found in patients exposed to chemotherapy (63.5% vs. 9%, $p < 0.001$). A lower gestational age and a higher number of cycles of chemotherapy were associated with breastfeeding difficulties. A pathological examination of biopsies before and after chemotherapy showed clear lobular atrophy of the breast gland [4].

Epidemiologic studies are always important, as they can show precise figures of malignancies not confounded by single institution bias. A population-based study on the incidence of pregnancy-related cancer in Lombardy, Italy, was presented by Parazzini et al. There are large differences between different regions. Here, the most common cancers were breast, thyroid, lymphomas, and skin carcinomas. Contrary to other reports, there were no changes in time [5].

The largest set of patients with melanoma was reported by the INCIP group by de Haan et al. A demographic and therapeutic description of 60 patients showed that melanoma diagnosed during pregnancy is more often found at higher stages. Due to new systemic treatment advances in metastatic melanoma, the option to terminate pregnancy prematurely has to be considered. In early-stage disease, surgery can be safely performed with preservation of pregnancy [6].

A set of 28 cervical cancer patients has been described by Bigelow et al. The patients were matched by age and stage. Prognosis was similar for both groups, even though 25% of patients had a termination. Women undergoing radical hysterectomy peripartally had similar rate of complications as non-pregnant women [7].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Whole body MRI for systemic staging of breast cancer in pregnant women	Peccatori FA et al.	Breast	https://www.ncbi.nlm.nih.gov/pubmed/28756339
2	Imaging appearance and clinical impact of preoperative breast MRI in pregnancy-associated breast cancer	Myers KS et al.	AJR Am J Roentgenol	https://www.ncbi.nlm.nih.gov/pubmed/28609163
3	Association of the timing of pregnancy with survival in women with breast cancer	Iqbal J et al.	JAMA Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28278319
4	After chemotherapy treatment for maternal cancer during pregnancy, is breastfeeding possible?	Stopenski S et al.	Breastfeed Med	https://www.ncbi.nlm.nih.gov/pubmed/28170295
5	Frequency of pregnancy related cancer: a population based linkage study in Lombardy, Italy	Parazzini F et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28107260
6	Melanoma during pregnancy: a report of 60 pregnancies complicated by melanoma	de Haan J et al.	Melanoma Res	https://www.ncbi.nlm.nih.gov/pubmed/28099365
7	Management and outcome of cervical cancer diagnosed in pregnancy	Bigelow CA et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27810552

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Immunotherapy in gynaecological cancers

Editor Zoltan Novak

Descriptive summary

Published clinical immunotherapy trials

A phase II, randomised, placebo-controlled trial was conducted in women with recurrent epithelial ovarian carcinoma to evaluate the efficacy and safety of a Toll-like receptor 8 agonist, motolimod associated with pegylated liposomal doxorubicin (PLD). The addition of motolimod to PLD did not significantly improve overall survival or progression-free survival; however, in a subset of patients experiencing injection site reactions, the risk of death was significantly lower [1]. Also see the report by Ilker Selcuk on "Medical treatment of recurrent ovarian cancer".

An interim analysis of a phase I/IIa trial of E39 +GM-CSF vaccine to prevent recurrences in disease-free EC and OC patients was published. Folate binding protein is an immunogenic protein over-expressed in endometrial and ovarian cancer and the E39 is a folate binding protein vaccine. This vaccine was well-tolerated and elicited a strong, dose-dependent in vivo immune response. With 12 months median follow-up, in the small group of patients receiving higher dose of the vaccine, the risk of recurrence was 13.3% vs. 55% in the control group ($p = 0.01$), showing promising results for further trials [2].

A small phase II study evaluated albumin-bound paclitaxel followed by GM-CSF to prolong remissions in ovarian cancer patients. The combination demonstrated short-lived biochemical responses in a majority of patients; however, it did not demonstrate an advantage in overall survival over prior studies of albumin-bound paclitaxel monotherapy [3].

Samuels et al. published the results of a phase I trial testing the safety and immunogenicity of a HPV E7 DNA vaccine administered by a new method, called DNA tattooing, in patients with usual type vulvar intraepithelial neoplasia. The vaccine proved to be safe but low immune response was induced and no clinical responses were detected. Therefore, this vaccine needs to be improved for further studies [4].

Checkpoint inhibitor treatment in gynaecological cancers

Sharabi et al. report on a chemotherapy refractory advanced neuroendocrine cervical cancer patient treated by nivolumab and stereotactic body radiation therapy. Tissue sequencing confirmed a high tumour mutational burden as a consequence of a mismatch repair gene defect. The patient showed a dramatic durable clinical response [5]. A similar case report was published recently (reviewed in the previous LiFE report) suggesting a possible therapeutic modality in this rare devastating condition. Another case report presents a case of a heavily pretreated advanced cervical cancer patient who showed a striking response to the immune checkpoint inhibitor pembrolizumab [6].

A paper reports an adverse event associated with programmed death-1 inhibitor treatment: pneumonitis in an endometrial cancer patient. This report focuses on the computed tomography diagnostic features of nivolumab-related pneumonitis and the appropriate corticosteroid therapy [7].

Immune microenvironment in endometrial cancer

There are few data on the immune microenvironment of endometrial cancers, therefore we cite here the paper by Pakish et al. who investigated the association of microsatellite instability and immune microenvironment in endometrial cancer patients. They concluded that endometrial tumours with high microsatellite instability has increased immune cell infiltration compared to microsatellite-stable tumours and the hereditary or sporadic origin impacts immune response [8].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	A phase 2, randomized, double-blind, placebo- controlled study of chemo-immunotherapy combination using motolimod with pegylated liposomal doxorubicin in recurrent or persistent ovarian cancer: a Gynecologic Oncology Group partners study	Monk BJ et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28327944
2	Interim analysis of a phase I/IIa trial assessing E39+GM-CSF, a folate binding protein vaccine, to prevent recurrence in ovarian and endometrial cancer patients	Jackson DO et al.	Oncotarget	https://www.ncbi.nlm.nih.gov/pubmed/27852036
3	Phase II trial of albumin-bound paclitaxel and granulocyte macrophage colony-stimulating factor as an immune modulator in recurrent platinum resistant ovarian cancer	Liao JB et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28089377

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Immunotherapy in gynaecological cancers

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

No	Title	Authors	Journal	Link to abstract
4	HPV16 E7 DNA tattooing: safety, immunogenicity, and clinical response in patients with HPV-positive vulvar intraepithelial neoplasia	Samuels S et al.	Cancer Immunol Immunother	https://www.ncbi.nlm.nih.gov/pubmed/28451790
5	Exceptional response to nivolumab and Stereotactic Body Radiation Therapy (SBRT) in neuroendocrine cervical carcinoma with high tumor mutational burden: management considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center	Sharabi A et al.	Oncologist	https://www.ncbi.nlm.nih.gov/pubmed/28550027
6	Pembrolizumab in recurrent advanced cervical squamous carcinoma	Martinez P et al.	Immunotherapy	https://www.ncbi.nlm.nih.gov/pubmed/28399693
7	Case report of nivolumab-related pneumonitis	Tada K et al.	Immunotherapy	https://www.ncbi.nlm.nih.gov/pubmed/28303763
8	Immune microenvironment in microsatellite-instable endometrial cancers: hereditary or sporadic origin matters	Pakish JB et al.	Clin Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28264871

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Imaging in gynaecologic malignancies

Editor Tanja Nikolova and Natasha Nikolova

Descriptive summary

^{18}F-FDG PET CT showed significant improvement in staging in gynaecological malignancy, patient selection for treatment and detecting of early recurrent disease [1]. MRI is superior for local staging and ^{18}F-FDG PET for distant metastases [2].

Endometrial cancer (EC)

In the combination of T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast enhancement, MRI provides a "one-stop shop" approach for patient-specific accurate staging in EC [3].

Sentinel lymph nodes (SLN) assessments with indocyanine green plus isosulfan blue and near-infrared imaging had excellent sensitivity for metastasis detection in EC [4].

Combined with conventional subjective MRI, calculating exponential ADC of the peri-endometrial zone could improve the accuracy of preoperative assessment of myometrial invasion in EC [5].

In the FIRES multicentre study, SLN identified with indocyanine green showed to have a high diagnostic accuracy of 97.2% and NPV of 99.6% [6]. Please also see the report by Piotr Lepka on "Surgical treatment of primary uterine cancer".

Integration of MRI and hysteroscopic excisional biopsy showed sensitivity of 85.0%, specificity of 88.5%, NPV of 91.9%, and PPV of 79.0% in preoperatively identifying low-risk EC patients [7].

Compared with diagnostic CT alone, the addition of PET significantly increased sensitivity in both the abdomen and pelvis, maintaining high specificity [8].

The current data favour the use of cervical injection techniques with indocyanine green in SLN mapping [9].

Cervical cancer (CC)

In a systematic review, 1,028 patients were analysed and MRI showed good performance for detection of parametrial invasion in CC [10].

Ovarian cancer (OC)

Prolactin ligand receptor and human placental lactogen fused to gadolinium and near-infrared fluorescence imaging agents improve the detection of OC [11].

PET/CT and PET/MRI combinations give more accurate staging and recurrence detection in OC. The added accuracy of these ionising modalities involvement needs to be justified by improved survival of OC patients [12].

Transvaginal ultrasound-based International Ovarian Tumour Analysis (IOTA) strategies and subjective assessment for the diagnosis of early stage OC. Simple Rules (SRs), Simple Rules Risk (SRR), Assessment of Different NEoplasias in the adneXa (ADNEX) model and subjective assessment to discriminate between stage I–II OC and benign disease. Sensitivity and specificity of SRs were 94.3% and 73.4%, of subjective assessment 90.0% and 86.7%, respectively. AUC of SRR and ADNEX were 0.917 and 0.905, respectively. IOTA has good ability to discriminate between stage I–II OC and benign disease [13].

Breast cancer (BC)

Three screening mammography recommendations (benefits and risks) were assessed. Mean mortality reduction was greatest with annual screening at ages 40–84 (39.6%) [14].

Automated breast ultrasound (ABUS) and hand-held traditional ultrasound (HHUS) were compared in the BIRADS characterisation of lesions. In all, 1,886 women with breast density category C or D were examined. Overall agreement between HHUS and ABUS was 99.8 %. ABUS could be successfully used in the characterisation of breast lesions [15].

It was investigated whether adjunctive breast-specific gamma imaging (BSGI) has incremental value for detecting cancer in women with suspicious calcifications detected by mammography, and compared BSGI with adjunctive ultrasonography (US). For detecting BC using mammography plus BSGI, sensitivity, specificity, PPV, NPV, and AUC were 94%, 90%, 91%, 94%, and 0.92, respectively. For mammography plus US, the respective values were 97%, 51%, 68%, 94%, and 0.74, respectively. Adjunctive BSGI had higher specificity than adjunctive US without loss of sensitivity. BSGI may be a useful complementary initial imaging method in women with calcifications at mammography [16].

Surveillance mammography in BC survivors showed that it may reduce breast cancer-specific mortality through early/asymptomatic detection (HR for those without/with symptoms: 0.64, 95% CI: 0.55–0.74). Organised screening programs should consider including women with a previous BC [17].

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Imaging in gynaecologic malignancies

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	The role of (18)F-FDG PET CT in common gynaecological malignancies	Narayanan P et al.	Br J Radiol	https://www.ncbi.nlm.nih.gov/pubmed/28830238
2	PET/MR imaging in gynecologic oncology	Ohliger MA et al.	Magn Reson Imaging Clin N Am	https://www.ncbi.nlm.nih.gov/pubmed/28668166
3	From staging to prognostication: achievements and challenges of MR imaging in the assessment of endometrial cancer	Nougaret S et al.	Magn Reson Imaging Clin N Am	https://www.ncbi.nlm.nih.gov/pubmed/28668163
4	A prospective cohort study comparing colorimetric and fluorescent imaging for sentinel lymph node mapping in endometrial cancer	Holloway RW et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28265777
5	Combined subjective and quantitative analysis of magnetic resonance images could improve the diagnostic performance of deep myometrial invasion in endometrial cancer	Deng L et al.	Clin Imaging	https://www.ncbi.nlm.nih.gov/pubmed/28232207
6	A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study	Rossi EC et al.	Lancet Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28159465
7	Preoperative work-up for definition of lymph node risk involvement in early stage endometrial cancer: 5-year follow-up	Cignini P et al.	Updat Surg	https://www.ncbi.nlm.nih.gov/pubmed/28108938
8	Utility of PET/CT to evaluate retroperitoneal lymph node metastasis in high-risk endometrial cancer: results of ACRIN 6671/GOG 0233 trial	Atri M et al.	Radiology	https://www.ncbi.nlm.nih.gov/pubmed/27178725
9	Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis	Bodurtha Smith AJ et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/27871836
10	Magnetic resonance imaging for detection of parametrial invasion in cervical cancer: an updated systematic review and meta-analysis of the literature between 2012 and 2016	Woo S et al.	Eur Radiol	https://www.ncbi.nlm.nih.gov/pubmed/28726120
11	Prolactin receptor-mediated internalization of imaging agents detects epithelial ovarian cancer with enhanced sensitivity and specificity	Sundaram KM et al.	Cancer Res	https://www.ncbi.nlm.nih.gov/pubmed/28202518
12	Systematic review on the accuracy of positron emission tomography/computed tomography and positron emission tomography/magnetic resonance imaging in the management of ovarian cancer: is functional information really needed?	Suppiah S et al.	World J Nucl Med	https://www.ncbi.nlm.nih.gov/pubmed/28670174
13	Validation of the performance of International Ovarian Tumor Analysis (IOTA) methods in the diagnosis of early stage ovarian cancer in a non-screening population	Froyman W et al.	Diagn Basel Switz	https://www.ncbi.nlm.nih.gov/pubmed/28574444
14	Comparison of recommendations for screening mammography using CISNET models	Arleo EK et al.	Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28832983
15	The performance of 3D ABUS versus HHUS in the visualisation and BI-RADS characterisation of breast lesions in a large cohort of 1,886 women	Vourtsis A et al.	Eur Radiol	https://www.ncbi.nlm.nih.gov/pubmed/28828640
16	Adjunctive breast-specific gamma imaging for detecting cancer in women with calcifications at mammography	Chung HW et al.	Ann Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28819909
17	Breast screening for survivors of breast cancer: a systematic review	Muradali D et al.	Prev Med	https://www.ncbi.nlm.nih.gov/pubmed/28765083

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Treatment of elderly patients with gynaecological cancers

Editor Alex Mutombo

Descriptive summary

Most of the studies published in this period involved endometrial and ovarian cancers. This may be explained by the fact that most of these publications originate from northern countries where those gynaecological malignancies are the most frequent compared to cervical cancer, which is common in low- and middle-income countries. Reliable data on these tumor groups in elderly patients may therefore be underreported.

Many studies evaluated if older age alone negatively impacts survival endpoints in women with endometrial cancer (EC) and epithelial ovarian cancer (EOC) or if their reported prognostic impact is due to an interaction with other well-known adverse factors and comorbidities. Increasing age has been associated with shorter survival in ovarian cancer patients, a finding attributed to diminished tolerance of standard therapy even though inherent tumour biology may be a significant contributor [1]. Grossly, elderly women are often surgically understaged whereas there is no evidence of greater perioperative complications compared to their younger counterparts. They should benefit from minimally invasive surgery and optimal surgical staging to the same extent as younger women. Moreover, intraperitoneal chemotherapy appears well tolerated and effective among select older patients and is likely under-utilised outside of clinical trials [2]. Nonetheless, some authors suggest that a frailty measure was a more robust predictor of survival than patient age, tumour characteristics, and comorbidities in older women with very good functional status [3, 4].

In a cervical cancer study comparing outcomes of definitive chemoradiation in elderly and younger patients, vaginal infiltration, lymph node metastasis, concomitant chemotherapy were predictive of overall survival, disease-free survival, and local recurrence, and larger tumour (> 4cm) was a significant prognostic factor for local recurrence. Although age limited the delivery of aggressive treatment, concurrent chemoradiotherapy in elderly patients was associated with improved outcomes similar as in younger counterparts without increasing serious acute and late toxicities, according to one study [5].

Some studies reported novel therapeutic approaches; recently, a SEER-Medicare analysis demonstrates improvement in overall survival with lipophilic statin use after surgery in elderly patients with epithelial ovarian cancer. Yoshida et al. reported that nedaplatin (NDP), a second-generation platinum analogue, has been developed to reduce the toxicity of cisplatin. Although NDP is a useful therapeutic option for Ovarian Cancer, careful consideration of the adverse effect should be given for patients 70 years and older [6, 7].

Bishop et al. compared clinical data and surgicopathologic results of 715 patients ≥ 70 years with patients <70 years (enrolled in the Gynecologic Oncology Group Study LAP2 randomizing endometrial cancer patients to laparotomy versus laparoscopy). The study showed that in a healthy, clinically early stage EC population, patients ≥ 70 years have worse PFS and OS than patients < 70 years despite the comparable surgical management and similar rates of adjuvant therapy [9]. A systematic review provides guidance on the efficacy of radiation treatment in elderly patients with medically inoperable EC. Dutta SW et al. reported that definitive radiation therapy is an effective treatment in this patient population [10]. Eggemann H et al. investigated reasons associated with less aggressive treatment of elderly women with EC in comparison with their younger counterparts in a large retrospective cohort register study. Rather than patient's refusal, indicated treatment options are often not offered to the patients based on performance status and comorbidities [11]. Swanick CW et al. used SEER-Medicare linked data of 444 elderly women (age ≥66 years) with node-positive vulvar cancer to assess the delivery and effectiveness of adjuvant radiotherapy after primary surgery. Adjuvant radiotherapy was associated with improved OS and cause-specific survival. However, for optimal benefit maximizing radiation delivery metrics is important, but among elderly patients only just over half actually achieved RT that met basic delivery metrics [11].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Contribution of age to clinical trial enrollment and tolerance with ovarian cancer	Gillen J et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28087143
2	Evaluation of the efficacy and toxicity profile associated with intraperitoneal chemotherapy use in older women	Crim A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28583323
3	Frailty measure is more predictive of outcomes after curative therapy for endometrial cancer than traditional risk factors in women 60 and older	Driver JA and Viswanathan AN	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28359689
4	Ovarian cancer in elderly patients: patterns of care and treatment outcomes according to age and modified frailty index	Ferrero A et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28763363

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Immunotherapy in gynaecological cancers

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

No	Title	Authors	Journal	Link to abstract
5	Definitive chemoradiotherapy in elderly cervical cancer patients: a multiinstitutional analysis	Guler OC et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28604459
6	Statin treatment is associated with survival in a nationally representative population of elderly women with epithelial ovarian cancer	Vogel TJ et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28596017
7	Feasibility and response to nedaplatin monotherapy in older patients with ovarian cancer	Yoshida H et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/28803267
8	Pathologic and treatment outcomes among a geriatric population of endometrial cancer patients: an NRG Oncology/Gynecologic Oncology Group ancillary data analysis of LAP2	Bishop EA et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28399028
9	Management of elderly patients with early-stage medically inoperable endometrial cancer: systematic review and National Cancer Database analysis	Dutta SW et al.	Brachytherapy	https://www.ncbi.nlm.nih.gov/pubmed/28262518
10	Management of elderly women with endometrial cancer	Eggemann H et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28666541
11	Challenges to delivery and effectiveness of adjuvant radiation therapy in elderly patients with node-positive vulvar cancer	Swanick CW et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28506563

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Nutritional support/status in gynaecological cancer

Editor Fernanda Santos

Descriptive summary

Cancers are a main cause of malnutrition due to the physical and metabolic effects and also due to anticancer treatments. Prolonged undernutrition can lead to cachexia, a complex syndrome not fully reversed by conventional nutritional support. According to research, malnutrition is a highly prevalent problem among gynaecological cancer patients (20%–53%). The specific risk varies among cancer types, stage, previous anticancer treatments, patient age, and individual comorbidities. Cancer-associated malnutrition can also lead to higher incidence of post-operative complications such as infection, impaired response to cytotoxics, and death. About 20% of all gynaecological cancer deaths are due to malnutrition [1].

Since malnutrition is an increasingly important issue in the setting of cancer, several groups have published recommendations and guidelines for including nutritional management in the global management of this disease. For example, the European Society for Clinical Nutrition and Metabolism (ESPEN) advocates systematic nutritional assessment before and during all exclusive chemotherapy procedures, in order to identify early nutritional deficits and plan intervention. The French Health Authority recommends that nutritional status should be evaluated by the combined measurement of age, body mass index, weight loss, and albumin levels [2].

Salas et al. analysed 102 oncological patients, all submitted to chemotherapy, and concluded that the presence of anorexia, the palliative nature of the chemotherapy, and an elevated C-reactive protein (CRP) dosage were independent predictive factors of lower quality of life. Based on that, they argued that this information should be evaluated in order to identify which patients will be more vulnerable to chemotherapy [2]. Recently, Kumar et al. also evaluated nutrition status and inflammatory markers that predict perioperative outcomes in patient with ovarian cancer (stage III/IV). They analysed 48 patients, and concluded low serum albumin (< 3g/dl) and elevated CRP (≥70mg/dl) were predictors of death within six months and that elevated IL6 (≥24pg/ml) was a predictor of surgical complications. Therefore, they concluded that these markers should be used to select patients for neoadjuvant chemotherapy at high risk of short survival [3]. Bobin-Dubigeon et al. analysed other biomarkers and concluded that low levels of leptin are independently related to undernutrition. No relation was attributed to adiponectin [4].

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

In conclusion, given the importance of nutritional evaluation on oncological patients, larger randomised clinical trials are urgently needed in order to corroborate findings that have already been published.

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Nutrition interventions in patients with gynaecological cancers requiring surgery	Obermair A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28173966
2	Nutritional status and quality of life of cancer patients needing exclusive chemotherapy: a longitudinal study	Salas S et al.	Health Qual Life Outcomes	https://www.ncbi.nlm.nih.gov/pubmed/28173966
3	Inflammatory and nutritional serum markers as predictors of peri-operative morbidity and survival in ovarian cancer	Kumar A et al.	Anticancer Research	https://www.ncbi.nlm.nih.gov/pubmed/28668859
4	Leptin and adiponectin as new markers of undernutrition in cancer	Bobin-Dubigeon C et al.	Clin Chem	http://www.sciencedirect.com/science/article/pii/S0009912016303745

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Epidemiology of gynaecological cancers

Editor Kemal Güngördük

Descriptive summary

Endometrial cancer (EC)

A Norwegian cohort of 1,353,724 individuals followed up for 12,354,392 person years reported that the risk of EC was elevated in women treated with clomiphene citrate (HR, 2.19; 95% CI: 1.87–4.53) and risk was highest for nulliparous women (HR, 4.49; 95% CI: 2.66–7.60) and among parous women with more than six cycles (HR, 4.68; 95% CI: 1.74–12.6) [1].

Borch et al. reported that the lowest physical activity level, based on patients' Norwegian Women and Cancer (NOWAC) questionnaires, was associated with a high risk for EC (HR, 1.60; 95% CI: 1.16–2.20) [2].

A case-control study carried out in the USA, including 593 cases and 5,743 controls, reported that a history of gestational diabetes, particularly in younger women, is associated with a high risk for EC (OR, 1.80; 95% CI: 1.22–2.65) [3].

A recent meta-analysis by Jordan et al. included more than 8,500 patients with EC from 14 case-control and three cohort studies. The authors reported that breastfeeding was associated with an 11% reduced risk of EC (OR, 0.89; 95% CI: 0.81–0.98) [4].

A meta-analysis of 11 studies including a total of 766,929 participants showed that using metformin was associated with a 13% reduction in EC among patients with diabetes (OR, 0.87, 95% CI: 0.80–0.98) [5].

A large population based study that included 47,555 African-American women demonstrated that, consistent with previous results in Caucasian populations, reproductive factors such as age at menarche < 11 years, age at menopause > 55 years, history of infertility or diagnosis of polycystic ovary syndrome were associated with risk of EC among African-American women [6].

A meta-analysis of 19 case-control and six cohort studies reported hypertension as a strong risk factor for EC with a 61% increase in relative risk [7].

A large prospective cohort study from the USA showed that endometriosis confirmed by laparoscopy is not strongly linked to EC (OR 0.76; 95% CI: 0.35–1.64) [8].

Ovarian cancer (OC)

A study of 59,000 women, including African-American women, demonstrated that, similar to Caucasian women, oral contraceptive use was inversely associated with OC (HR 0.50; 95% CI: 0.30–0.98) [9]. In addition, the greatest reduction in risk was seen when it was used for more than ten years (HR 0.38; 95% CI: 0.17–0.83). In contrast to premenopausal women, using hormonal drugs such as oestrogen and progestin (HR 1.37; 95% CI: 0.73–2.55) or only oestrogen (HR 0.66; 95% CI: 0.90–3.07) was significantly associated with OC [9].

A population-based case control study was carried out in Montreal from 2011 to 2016, including 496 cases and 908 controls and showed a non-significant increased risk (OR 1.34; 95% CI: 0.98–1.83) with late menarche, but there was no strong pattern of association with age at menopause for OC. Furthermore, a history of endometriosis was strongly associated with an increased risk for type I tumours (OR 2.96; 95% CI: 1.54–5.67), but not type II tumours. A history of uterine fibroids was positively associated with type II tumours. In addition, an inverse association was observed for an increased number of pregnancies and OC [10].

Terry et al. reported that higher intake of supplemental selenium (5.71 mg/d) may be inversely associated with a risk for OC in African-American women [11].

In a prospective case-control study, Yang et al. demonstrated that longer circulating leukocyte telomere length may be associated with lower OC risk (OR 0.89; 95% CI: 0.78–1.01), especially for non-serous and rapidly fatal cases [12]. In another case-control study that included 834 patients, 11 single nucleotide polymorphisms for two genes (TEP1 and TERT) showed significant associations with an overall risk of OC [13].

A meta-analysis of 13 studies including a total of 766,929 participants showed that pelvic inflammatory disease was associated with an increased risk of OC (OR 1.24; 95% CI: 1.06–1.44) [14].

A case control trial from the USA demonstrated that premenopausal hysterectomy was inversely associated with an increased risk for OC (OR 0.75; 95% CI 0.56–1.01). However, if these women used oestrogen-only hormone therapy after the hysterectomy, it may negate the protective effects of hysterectomy on OC, creating the appearance of a slightly increased risk (OR 1.71; 95% CI: 0.76–3.84) [15].

A population-based case control study including 3,210 women showed that smoking is associated with an increased risk of serous OC (OR 1.46; 95% CI: 1.11–1.92) [16].

A recent meta-analysis by Song et al., including more than 490,000 participants from 15 studies, reported that dietary calcium and dairy calcium may reduce the risk of OC (OR 0.78; 95% CI: 0.69–0.88).

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Epidemiology of gynaecological cancers

Descriptive summary (cont.)

However, dietary plus supplemental calcium was not associated with a decreased risk of OC [17].

A meta-analysis of 15 cohort studies suggested a moderate relative increase in the risk of OC among patients with diabetes mellitus (DM) [(OR 1.24; 95% CI: 1.06–1.44; for type I DM) and (OR 1.32; 95% CI: 1.14–1.52 for type II DM)] [18].

Cervical cancer (CC)

A recent meta-analysis including 15,619 participants (7,433 cases and 8,186 controls) from 16 studies demonstrated that women who use oral contraceptives did not have an increased risk for cervical cancer (OR, 1.12; 95% CI: 0.90–1.38). In subgroup analyses, no significant associations were found for the different durations of OC use (< 5 years: OR, 0.84; 95% CI: 0.68–1.04; 5–10 years: OR, 1.06; 95% CI: 0.66–1.71; > 10 years: OR, 1.25; 95% CI: 0.76–2.06). Moreover, using oral contraceptives did not increase the risk of cervical cancer among women with human papillomavirus infections (OR, 1.09; 95% CI: 0.80–1.49) [19].

Vulvar and vaginal cancer

A large cohort study including 201,469 women from the USA demonstrated that obesity (OR for BMI ≥ 30 vs. <25 = 1.62, 95% CI: 1.10–2.40) and current smoker status (OR 1.86, 95% CI: 1.21–2.87) were associated with an increased risk for squamous cell vulvar cancer [20]. This study is also mentioned in the chapter on "Preinvasive disease of vulva and vagina (aetiology, diagnosis, management, follow-up)" by Zalewski.

A recent population-based trial containing 7,616 patients with lichen sclerosus (LS) showed LS was associated with an increased risk of vulvar (OR 33.6, 95% CI: 28.9–38.6) and vaginal cancer (OR 3.69, 95% CI: 1.01–9.44) [21].

Relevant articles retrieved Feb 2017 – Aug 2017

No	Title	Authors	Journal	Link to abstract
1	Cancer risk in women treated with fertility drugs according to parity statu – a registry-based cohort study	Reigstad MM et al.	Cancer Epidemiol Biomarkers Prev	https://www.ncbi.nlm.nih.gov/pubmed/28108444
2	Physical activity and risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) study	Borch KB et al.	Int J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28108996
3	Association of endometrial hyperplasia and cancer with a history of gestational diabetes	Wartko PD et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/28577154
4	Breastfeeding and endometrial cancer risk: an analysis from the epidemiology of endometrial cancer consortium	Jordan SJ et al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/28486362
5	Metformin use is associated with reduced incidence and improved survival of endometrial cancer: a meta-analysis.	Tang YL et al.	Biomed Res Int	https://www.ncbi.nlm.nih.gov/pubmed/28409158
6	Reproductive factors and incidence of endometrial cancer in U.S. black women	Sponholtz TR et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/28361447
7	Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies	Aune D et al.	Sci Rep	https://www.ncbi.nlm.nih.gov/pubmed/28387226
8	Endometriosis and risk of ovarian and endometrial cancers in a large prospective cohort of U.S. nurses	Poole EM et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/28299512
9	A prospective study of reproductive factors and exogenous hormone use in relation to ovarian cancer risk among Black women	Bethea TN et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/28025764
10	Hormonal and reproductive factors and the risk of ovarian cancer	Koushik A. et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/28102526
11	Supplemental selenium may decrease ovarian cancer risk in African-American women	Terry PD et al.	J Nutr	https://www.ncbi.nlm.nih.gov/pubmed/28202637
12	Prediagnosis leukocyte telomere length and risk of ovarian cancer	Yang M et al.	Cancer Epidemiol Biomarkers Prev	https://www.ncbi.nlm.nih.gov/pubmed/28209595

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

No	Title	Authors	Journal	Link to abstract
13	Genetic variants in telomere-maintenance genes are associated with ovarian cancer risk and outcome	Sun Y et al.	J Cell Mol Med	https://www.ncbi.nlm.nih.gov/pubmed/28233473
14	Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis	Zhou Z et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/28342087
15	Premenopausal hysterectomy and risk of ovarian cancer in African-American women	Peres LC et al.	Am J Epidemiol	https://www.ncbi.nlm.nih.gov/pubmed/28444120
16	Cigarette smoking and the association with serous ovarian cancer in African American women: African American Cancer Epidemiology Study (AACES)	Kelemen LE et al.	Cancer Causes Control	https://www.ncbi.nlm.nih.gov/pubmed/28466107
17	Calcium intake and the risk of ovarian cancer: a meta-analysis	Song X et al.	Nutrients	https://www.ncbi.nlm.nih.gov/pubmed/28665326
18	Diabetes mellitus and risk of ovarian cancer. A systematic review and meta -analysis of 15 cohort studies	Zhang D et al.	Diabetes Res Clin Pract	https://www.ncbi.nlm.nih.gov/pubmed/28554142
19	Is oral contraceptive use associated with an increased risk of cervical cancer? An evidence-based meta-analysis	Peng Y et al.	J Obstet Gynaecol Res	https://www.ncbi.nlm.nih.gov/pubmed/28759170
20	Epidemiology of vulvar neoplasia in the NIH-AARP Study	Brinton LA et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/28236455
21	Lichen sclerosus and risk of cancer	Halonen P et al.	nt J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/28124469

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