

LiFE

Literature for ENYGO

Reviews covering publications from March 31, 2021 – September 30, 2021

Zoia Razumova
Kristina Lindemann
Michael J. Halaska
Kamil Zalewski
Stamatios Petousis
Anna Maria Schütz

Supported by ESGO

Issue No. 2 (14) February 2022





Dear LiFE readers,

Happy New Year!

We thank you for staying with us in 2022 and beyond. With your help and interest, we can continue our project despite all the challenges related to the pandemic.

LiFE 14 includes reviews of the most important publications in the field of gynaecological oncology published between March 31, 2021, and September 30, 2021. LiFE is an initiative of ENYGO supported by ESGO. Moreover, collaboration with the *International Journal of Gynecological Cancer* helps us be even more visible to the professional community, which we are really thankful for.

In this issue, we want to give a warm welcome to our new contributors: Houssein El Hajj (France), Paul Kubelac (Romania), and Catarina Parda (Portugal). With them joining the LiFE team, we are currently professionals from 20 countries worldwide who are doing our best to make up-to-date knowledge in the field more accessible.

Besides, we express our sincere gratitude to the exiting ESGO team member Helena Opolecka who has been the heart of the project since its start.

The LiFE editors also remind you not forget to submit your abstracts to the 23rd ESGO Congress, which becomes annual starting this year. The event will be held October 27–30, 2022, in Berlin, Germany.

We once again thank all ENYGO members for being a part of this great project and sharing each issue's content with their colleagues or on social media.

If you are interested in becoming one of the LiFE authors, please email enygo.life.project@esgomail.org.

We hope that you will find LiFE 14 informative and enjoy reading it.

Yours,

The LiFE Editors

Zoia Razumova
Kristina Lindemann
Michael J. Halaska
Kamil Zalewski
Stamatios Petousis
Anna Maria Schütz

Creative Commons licence

LiFE reports are freely available to read, download and share from the time of publication. Reports are published under the terms of the Creative Commons Licence Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0), which allows readers to disseminate and reuse the article, as well as share and reuse of the scientific material. It does not permit commercial exploitation or the creation of derivative works without specific permission. To view a copy of this licence visit: <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Ovarian cancer

Screening of gynaecological cancer (Catarina Parda)	4
Medical treatment of primary ovarian cancer (Ilker Selçuk)	5
Surgical treatment of primary and recurrent ovarian cancer (Ilker Kahramanoglu and Patriciu Achimas-Cadariu)	6
Medical treatment of recurrent ovarian cancer (Seda Şahin Aker)	7
Borderline ovarian tumours (Anton Ilin)	9
Treatment of ovarian sex cord stromal and germ cell tumours (Paul Kubelac)	10
Emerging molecular-targeted therapies or early preclinical trials in ovarian cancer (Anna-Maria Schütz)	11

Uterine cancer

Medical (chemo- and radiotherapy) treatment of primary uterine cancer (Kamil Zalewski)	12
Medical (chemo and radiotherapy) treatment of recurrent uterine cancer (Stamatios Petousis)	13
Emerging molecular-targeted therapies or early preclinical trials in endometrial cancer (Zoya Razumova)	14
Uterine sarcoma (Marcin Bobiński)	15
Surgical treatment of primary and recurrent endometrial cancer (Houssein El Hajj)	16

Cervical cancer

Surgical treatment of primary and recurrent cervical cancer (Bojana Gutic and Chrysoula Margioulas-Siarkou)	17
Radiotherapy of primary and recurrent cervical cancer (Erbil Karaman and Paweł Bartnik)	18
Medical treatment of primary and recurrent cervical cancer (Kristina Lindemann)	19
Emerging molecular-targeted therapies or early preclinical trials in cervical cancer (Khayal Gasimli)	20

Vulvar and vaginal cancer

Primary and recurrent vulvar cancer treatment (María de los Reyes Oliver and Rubén M. Betoret)	21
--	----

Miscellaneous

Follow-up after gynaecological malignancies (Sunaina Wadhwa)	22
Prevention and management of surgical complications (Anastasia Prodromidou)	23
Fertility-sparing treatment in gynaecological malignancies (Charalampos Theofanakis)	24
Cancer in pregnancy (Michael J. Halaska)	25
Hereditary gynaecological cancer (Sara Giovannoni and Ariel Glickman)	26
Treatment of pre-invasive gynaecological malignancies (Elko Gliozheni)	27
Pathology of gynaecological cancers (Nicolas Samartzis and Dimitrios Rafail Kalaitzopoulos)	28
Gestational trophoblastic disease management (pathology, diagnosis, follow-up, pregnancies) (Joanna Kacperczyk-Bartnik)	29
Nutrition and perioperative care (Begoña Díaz de la Noval)	30
Quality of life in gynaecological cancers/palliative care (Nadja Taumberger and Engin Çelik)	31
Treatment of elderly patients with gynaecological cancers (Alex Mutombo)	32
COVID-19 and gynaecological cancers (Jakub Dobroch and Patrick Maguire)	33

List of contributors, acknowledgments	34
---------------------------------------	----

Screening of gynaecological cancer

Catarina Pardal

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), a randomised, controlled trial, investigated if ovarian cancer (OC) screening could reduce cancer-related deaths and reported OC mortality after a long-term follow-up. Altogether, 202,638 postmenopausal women aged 50–74 were recruited in 13 centres in the UK and were randomly assigned to either annual transvaginal ultrasound screening (USS), multimodal screening including longitudinal CA125 and second line transvaginal ultrasound (MMS), or no screening, in a 1:1:2 ratio. At a median follow-up of 16.3 years for all groups, 2,055 women were confirmed to have OC. The incidence per 100,000 women-years was 67.7 (522 cases of cancer) in the MMS group, 68.2 (517) in the USS group, and 65.4 (1,016) in the no-screening group. When comparing the MMS to the no-screening group, an increase of 39.2% in stage I or II and a decrease of 10.2% in stage III or IV OC was seen. There was no

significant difference in incidence at any stage when comparing the USS with the no-screening group. In total, 1,206 women died of OC, with no significant reduction in cancer-related deaths in the MMS ($p = 0.58$) or USS ($p = 0.36$) group compared with the no-screening group. Based on this data, general population screening for OC cannot be recommended. Limitations of this trial included the long interval from the end of screening in 2011 to censorship in 2020 and the fact that most patients included were diagnosed and treated more than a decade ago while major advances in OC treatments have been made that might have altered the prognosis. [1]

The HPV FOCAL Trial is a randomised, controlled trial that compared the efficacy of primary HPV testing with reflex cytology to primary liquid-base cytology among women in the population-based Cervix Screening Program in British Columbia, Canada. In

this paper, cost-effectiveness of these screening methods was evaluated by comparing costs of any CIN2+ detection. A total of 19,009 women aged 25 to 65 were randomised, with both groups receiving co-testing at the 48-month screening exit. Primary HPV testing was less costly than the primary liquid-base cytology testing, with a difference of -773 USD. In summary, HPV-based screening every four years was associated with lower overall costs and superior rates of CIN2+ detection. [2]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial	Menon U et al.	Lancet	https://pubmed.ncbi.nlm.nih.gov/33991479/
2	Cost-effectiveness analysis of primary human papillomavirus testing in cervical cancer screening: Results from the HPV FOCAL Trial	Cromwell I et al.	Cancer Med	https://pubmed.ncbi.nlm.nih.gov/33811457/



Medical treatment of primary ovarian cancer

Ilker Selçuk

JAVELIN Ovarian 100 was an open-label, randomised, phase III study that evaluated the role of avelumab, an anti-PD-L1 monoclonal antibody, in previously untreated ovarian cancer (OC). In all, 998 stage III–IV epithelial OC patients were randomly (1:1:1) assigned to chemotherapy followed by avelumab (maintenance group, n = 332), chemotherapy + avelumab followed by avelumab maintenance (combination group, n = 331), and chemotherapy alone (control group, n = 335) after either receiving upfront surgery or neoadjuvant chemotherapy (NACT) + interval debulking. Randomisation was stratified by paclitaxel regimen (q1wk vs q3wk) and resection status. Avelumab was administered 10mg/kg iv q3wk during chemotherapy and q2wk during the maintenance. The median duration of follow-up for progression-free survival (PFS) was 10.8m. At the time of interim analysis cut-off, disease progression or death occurred in 30%, 27%, and 21% of patients in the maintenance, combination, and control groups, respectively. Median PFS was 16.8m (95% CI: 13.5—not estimable) for the maintenance group, 18.1m (14.8—not estimable) for the combination group and could not be estimated for the control group (18.2m—not estimable). The stratified hazard ratio for PFS was 1.43 (95% CI: 1.05–1.95, p = 0.99) and 1.14 (0.83–1.56, p = 0.79) for the maintenance and combination group versus the control group. Immune-related adverse events (AEs) of any grade occurred in 16%, 28%, and 0% in the respective groups. AEs which led to discontinuation

occurred in 11%, 16%, and 6%, respectively. The addition of avelumab to frontline chemotherapy as maintenance or in combination did not improve PFS when compared to chemotherapy alone. In addition, PD-L1 positivity was not associated with better survival outcomes in either avelumab group, which is in contrast with findings from the JAVELIN Ovarian 200 trial (see *Medical treatment of recurrent ovarian cancer*). However, there is no obvious explanation for the unexpected results of this study. Limitations included missing information on BRCA and homologous recombination deficiency status and no information about predictive biomarkers to help with the selection of patients. [1]

Another anti PD-L1 antibody, atezolizumab, was assessed in addition to standard platinum-based chemotherapy regimen + bevacizumab in newly diagnosed untreated stage III or IV epithelial OC patients who had either undergone primary cytoreductive surgery resulting in gross residual disease or NACT followed by interval surgery in a multicentre, placebo-controlled, double-blind, randomised phase III trial. Randomisation occurred (1:1) to either atezolizumab 1,200mg (n = 650) or placebo (n = 651) q3wks (cycles 1–22), both in combination with paclitaxel-carboplatin + bevacizumab. Median duration of follow-up was 19m. Median PFS was 19.5m (95% CI: 18.1–20.8) and 18.4m (17.2–19.8) in the atezolizumab and placebo groups, respectively. The hazard ratio for PFS was 0.92 (95% CI: 0.79–1.07,

p = 0.28) in the intention-to-treat population. PD-L1 positive tumours (60%) had a median PFS of 20.8m (95% CI: 19.1–24.2) and 18.5m (16.6–21.4) in the atezolizumab and placebo groups, respectively. The hazard ratio for PFS was 0.80 (95% CI: 0.65–0.99, p = 0.038). In patients with a high PD-L1 expression of ≥ 5%, the median PFS was not reached versus 20.2m (95% CI: 17.1–21.9) for atezolizumab versus placebo. The median PFS was 16.6m versus 17.2m in the NACT arm (HR 1.12, 0.85–1.47). For the primary surgery cohort with ≤ 1cm residual tumour burden, the median PFS was 21.1m versus 18.3m (HR 0.78, 0.60–1.01) and 18.6m versus 17.1m with > 1cm residual tumour (HR 0.80, 0.61–1.05) for the respective groups of atezolizumab and placebo. Interim OS analysis showed no benefit for atezolizumab. The incidence of grade 3 or 4 adverse events was higher for atezolizumab (79% vs 73%), with neutropenia, hypertension, and anaemia being reported most commonly. In this trial, the addition of atezolizumab to chemotherapy + bevacizumab did not improve PFS either in the intention to treat population nor in the PD-L1 positive group. BRCA and homologous recombination deficiency status were unknown, potentially leading to an imbalance between the two arms. [2]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): an open-label, randomised, phase 3 trial	Monk BJ et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/34363762/
2	Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39)	Moore KN et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/33891472/

Surgical treatment of primary and recurrent ovarian cancer

Ilker Kahramanoglu and Patriciu Achimas-Cadariu

Surgical treatment of primary ovarian cancer

A prospective multicentre phase II (CILOVE) study analysed the feasibility and surgical safety of performing interval cytoreductive surgery via laparoscopic approach in 44 patients with advanced ovarian carcinoma who received a minimum of three cycles of platinum-based neoadjuvant chemotherapy (NACT). After laparoscopic exploration, cytoreductive surgery was performed if there was no extensive macroscopic disease outside the pelvis. If complete cytoreduction could not be achieved laparoscopically, it was converted to laparotomy. Forty-one of 44 patients were eligible for cytoreductive surgery, 32 underwent laparoscopy, and nine laparotomy. Successful laparoscopic cytoreduction was achieved in 29/32 (91%). The median operative time was 267 min (range 146–415) with a median blood loss of 150mL. Reasons for conversion included multiple surgical adhesions (n = 1), miliary carcinomatosis, adhesion to the intraperitoneal mesh (n=1), and poor laparoscopic evaluation of transverse colon (n = 1). All except for one patient (97%) had complete cytoreduction with no grade 3–4 postoperative complications. Regarding oncological safety, no port metastases were reported; however, 34% had peritoneal metastases at recurrence. [1]

Surgical treatment of recurrent ovarian cancer

A retrospective, single-institution study of 114 patients analysed clinicopathologic and surgical factors associated with oncologic outcomes in patients with ovarian cancer (OC) undergoing tertiary

cytoreduction from 1990–2019. Complete gross resection (CGR), treatment-free interval, and platinum sensitivity were significantly associated with disease-specific survival (HR 3.71, 95% CI: 1.59–8.70; HR 0.49, 95% CI: 0.28–0.85; and HR 2.94, 95% CI:1.22–7.07). Ninety per cent of patients selected for tertiary surgery achieved CGR. Thirty-three per cent of all patients experienced postoperative complications, 14% of them being grade 3 and 0.9% grade 4. Limitations of the study included the fact that the selection of which patients would undergo tertiary surgery was solely based on the surgeon's decision and the long study timespan of over three decades. Patients with high-grade serous OC and a single-site recurrence after ≥2 years from secondary cytoreduction had the best survival outcome. [2]

A prospective, single-institution, non-randomised study analysed the recurrence patterns and outcomes of 92 women with advanced (56.5%) or recurrent (43.5%) OC after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The recurrence pattern was the following for interval versus recurrent CRS+HIPEC: pelvic in 50.0% (n = 15) versus 22.5% (n = 9); upper abdomen (UA) in 23.3% (n = 7) versus 5.0% (n = 2); extraperitoneal (EP) in 56.7% (n = 17) versus 60.0% (n =24); and in 40.0% (n = 12) versus 66.7% (n = 20) EP-only recurrence. The median PFS was 10.5 versus 13.0 months for peritoneal versus EP-only recurrences (p = 0.02) for both interval and recurrent CRS+HIPEC. For recurrent CRS+HIPEC, EP recurrence was associated with significantly im-

proved PFS (18.1 vs 10 months, p = 0.03) and OS (not reached vs 33.6 months, p = 0.02) compared with peritoneal recurrence. This might suggest that HIPEC changes the recurrence pattern of advanced OC by reducing peritoneal-based recurrences, which have been associated with worse survival. Limitations include the non-randomised character of the study, implicating a potential selection and treatment bias, and the limited follow-up duration of 20 months. [3]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Laparoscopic management of advanced epithelial ovarian cancer after neoadjuvant chemotherapy: a phase II prospective multicenter non-randomized trial (the CILOVE study)	Pomel C et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34670829/
2	Tertiary cytoreduction for recurrent ovarian carcinoma: An updated and expanded analysis	Manning-Geist BL et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34045053/
3	Patterns of recurrence in women with advanced and recurrent epithelial ovarian cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	Chambers LM et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33551202/



Medical treatment of recurrent ovarian cancer

Seda Şahin Aker

The JAVELIN Ovarian 200, a randomised, open label, phase 3 trial evaluated avelumab alone or avelumab + pegylated liposomal doxorubicin (PLD) compared with PLD alone in patients with platinum-resistant or platinum-refractory ovarian cancer (OC) across 149 cancer centres. In all, 566 patients were randomised in a 1:1:1 ratio. Randomisation was stratified by platinum status, number of previous anticancer regimens (1, 2, or 3), and bulky disease (tumour size ≥ 5 cm vs < 5 cm). Patients received avelumab 10mg/kg iv q2wk and/or PLD 40mg/m² iv q4wk. The median progression-free survival (PFS) was 3.7 months (95% CI: 3.3–5.1) in the combination group, 3.5 months (2.1–4.0) in the PLD group, and 1.9 months (1.8–1.9) in the avelumab group. Median OS was 15.7 (95% CI: 12.7–18.7), 13.1 (11.8–15.5), and 11.8 months (8.9–14.1), in the respective groups. Grade 3–5 adverse events (AE) were reported in 125 (69%), 105 (59%), and 93 (50%) patients in the combination, PLD, and avelumab groups, respectively. The most common AEs were palmar-plantar erythrodysesthesia syndrome, rash, fatigue, stomatitis, anaemia, and neutropenia. Two patients died related to AEs; one from sepsis in the PLD group and one from intestinal obstruction in the avelumab group. The trial's unmet primary objectives of improved PFS or overall survival were not expected. Of interest, in the subgroup analysis, the combination vs PLD treatment showed greater benefit for PD-L1 and CD8 positive tumours, and HR was even lower for tumours which were both PD-L1 and CD8 positive. This might be of interest for future studies. However, this needs to be interpreted with caution as the trial was not designed to show statistically significant differences in the small biomarker subgroups. [1]

The NIMES-ROC trial, a prospective, non-interventional, international, multicentre, phase IV study, evaluated trabectedin + PLD in platinum-sensitive recurrent ovarian cancer (OC). In total, 218 patients were included and the primary endpoint was PFS. Patients received PLD 30 mg/m² followed by trabectedin 1.1mg/m² iv q3wk. The median treatment duration was 21.1 weeks. Median PFS was 9.5 months (95% CI: 7.9–10.9) and median OS 23.6 months (95% CI: 18.1–34.1). Platinum sensitivity and BRCA status showed no statistically significant differences in PFS ($p = 0.62$, $p = 0.58$). Patients who received ≥ 6 cycles obtained a significantly better response ($p < 0.001$) than those who received < 6 cycles. Grade 3–4 AEs were reported in 115 patients (52.7%). The

most common were neutropenia, anaemia, thrombocytopenia, and asthenia. PLD plus trabectedin showed an alternative for pre-treated OC patients at an acceptable safety profile. Limitations of the study included the heterogenous study population. [2]

The final analysis of OS from the SOLO2/EN-GOT-Ov21 trial, a double-blind, randomised, placebo-controlled, multicentre, phase III study which reported on the efficacy of olaparib tablets as maintenance therapy in platinum-sensitive relapsed high-grade serous or endometrioid OC with BRCA 1 and/or 2 mutation was published. In total, 295 patients were randomised (2:1) to receive olaparib or placebo. The median follow-up was 65.7 versus 64.5 months with olaparib and placebo. The median OS was 51.7 (95% CI: 41.5–59.1) versus 38.8 months (31.4–48.6; HR 0.74 [95% CI: 0.54–1.00]; $p = 0.054$). Germline BRCA1/2 mutation was present in 97% of patients in both groups. In BRCA1/2 positive patients, median OS was 52.4 (95% CI: 41.5–61.4) versus 37.4 months (29.8–44.2) (HR 0.71, 95% CI: 0.52–0.97; $p = 0.031$). The most common AEs were anaemia, acute myeloid leukaemia, myelodysplastic syndrome, neutropenia, and thrombocytopenia. Treatment-emergent AEs with an outcome of death occurred in eight (4%) patients in the olaparib group; due to myelodysplastic syndrome ($n = 3$), acute myeloid leukaemia ($n = 3$), gastric adenocarcinoma ($n = 1$), and plasma cell myeloma. Of note, although somatic BRCA1/2 mutation were eligible for randomisation, only germline BRCA1/2 mutations were included. In summary, the use of olaparib as maintenance therapy showed a clinically meaningful, albeit not statistically significant, benefit in OS of 12.9 months. [3]

Clamp et al. further analysed the data of the ARIEL 3 trial on rucaparib as maintenance in recurrent OC in subgroups based on progression-free interval following penultimate platinum-based regimen, the number of prior chemotherapies, and prior use of bevacizumab. In total, 564 patients were randomised 2:1 to rucaparib or placebo. Patients received rucaparib 600mg twice daily or placebo in continuous 28-day cycles until disease progression. Subgroups were further divided into BRCA-mutant, HRD-positive, and the intention-to-treat population. In the intent-to-treat population, median PFS was 8.2 versus 4.1 months for rucaparib versus placebo (HR 0.33, 95% CI: 0.24 to 0.46, $p < 0.0001$) for patients with PFI six to ≤ 12 months; 13.6 versus 5.6 months (HR

0.39, 95% CI: 0.30–0.52, $p < 0.0001$) for the PFI > 12 months group; 10.4 versus 5.4 months (HR 0.42, 95% CI: 0.32–0.54, $p < 0.0001$) for patients with two prior chemotherapies; and 11.1 versus 5.3 months (HR 0.28, 95% CI: 0.19–0.41, $p < 0.0001$) for patients with ≥ 3 prior chemotherapies; 10.3 versus 5.4 months (HR 0.42, 95% CI: 0.26–0.68, $p = 0.0004$) for prior bevacizumab treatment; and 10.9 versus 5.4 months (HR 0.35, 95% CI: 0.28–0.45, $p < 0.0001$) for no prior bevacizumab treatment for the rucaparib versus placebo group. Rucaparib showed significantly better results across all subgroups in the BRCA-mutant and HRD cohort as well. The safety profile was similar among all subgroups. The analysis of the subgroup 'number of prior chemotherapies' and 'prior bevacizumab treatment' were post-hoc in nature and some subgroups consisted of a small number of patients, which might limit the conclusions that can be drawn. This paper showed a significant benefit in PFS for maintenance rucaparib across all above-mentioned subgroups. [4]

ICON6, an international, double-blind, randomised trial, evaluated the efficacy of cediranib, an anti-angiogenic VEGFR 1-3 inhibitor, in recurrent OC across 62 centres. In total, 456 women were randomised, using stratification, to receive chemotherapy with either placebo throughout (arm A), with concurrent cediranib followed by maintenance placebo (arm B), or with concurrent cediranib followed by maintenance cediranib (arm C). Results on the primary endpoint PFS have already been published and show a positive effect of cediranib + maintenance cediranib (11.0m vs 8.7m for arm C and arm A). In this paper, the results on final OS, which was the secondary endpoint, were reported. Median follow-up was 25.6 months. Ninety per cent of the patients have died and there was a 7.4-month difference in median OS for arm A vs arm C (19.9m vs 27.3m; HR 0.86, 95% CI: 0.67–1.11). Cediranib as maintenance treatment prolonged the median time to first subsequent treatment compared with maintenance placebo by 5.2 months (13.2m vs 18.5m). Initially, ICON6 was designed as a larger study with OS as primary endpoint, a restriction of the drug supply was leading to a smaller sample size and a change of primary endpoint from OS to PFS. Demonstrating OS advantage in a small trial where 90% have post-progression treatment and a median post-progression survival of 14.4m is very unlikely. This has to be considered when interpreting the non-significant improvement in OS. [5]

Medical treatment of recurrent ovarian cancer

Seda Şahin Aker

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study	Pujade-Lauraine E et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/34143970/
2	A European, observational, prospective trial of trabectedin plus pegylated liposomal doxorubicin in patients with platinum-sensitive ovarian cancer	Pignata S et al.	Oncologist	https://pubmed.ncbi.nlm.nih.gov/33289956/
3	Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial	Poveda A et al.	Lancet Onc	https://pubmed.ncbi.nlm.nih.gov/33743851/
4	Rucaparib maintenance treatment for recurrent ovarian carcinoma: the effects of progression-free interval and prior therapies on efficacy and safety in the randomized phase III trial ARIEL3	Clamp AR et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34103386/
5	Cediranib in addition to chemotherapy for women with relapsed platinum-sensitive ovarian cancer (ICON6): overall survival results of a phase III randomised trial	Ledermann JA et al.	ESMO Open	https://pubmed.ncbi.nlm.nih.gov/33610123/

Borderline ovarian tumours

Anton Ilin

Lymph node involvement (LNI) is one of the main prognostic factors that define staging, treatment, and survival. However, it is still unclear whether LNI has an impact on prognosis in patients with borderline ovarian tumours (BOTs). Fan et al. performed a systematic review and meta-analysis of 25 studies with 12,503 patients. The authors found that LNI is associated with a higher risk of recurrence (OR 2.23, 95% CI: 1.13–4.40), but did not decrease survival rates (HR 1.73, 95% CI: 0.99–3.02) or disease-free interval (HR 1.48, 95% CI: 0.56–3.92). Also, lymphadenectomy did not reduce the risk of recurrence (OR 0.91, 95% CI 0.57–1.46), overall survival (HR 0.90, 95% CI: 0.58–1.40), and disease-free survival (HR 0.95, 95% CI 0.61–1.50). It is concluded that lymphadenectomy should not be considered in all patients with BOT since it does not appear to influence prognosis. At the same time, it could be considered in those patients suspected of having positive lymph nodes according to imaging or surgical exploration. [1]

BOTs, in comparison with ovarian cancer, mainly affect the younger population. Therefore, the question of fertility-sparing surgery (FSS) rises quite often in patients diagnosed with BOT. It is also known that FSS is standard management of young patients with BOT limited to one or both ovaries, but the data concerning such an approach for extensive disease is still limited primarily due to the low frequency of the disease. The MITO group conducted a multi-institutional retrospective study to evaluate oncological and reproductive outcomes in women undergoing FSS due to stage II–III serous BOTs. Ninety-one patients were included. Median disease-free survival was 96 months (95% CI: 24.6–167.3); 2.2% of patients relapsed with invasive carcinoma. The only independent predictors of recurrence were the size of extra-ovarian lesions and the presence of invasive implants. Twenty-nine patients (31.8%) attempted to conceive: 20 (68.9%) had at least one pregnancy, and 18 (62%) delivered a healthy child. At the end of the observation period, 88 patients (96.7%) showed

no evidence of disease, two (2.2%) were alive with disease, and one patient (1.1%) died because of BOT. To conclude, patients with serous BOTs can safely undergo fertility-preservation management. Despite the high recurrence rate, FSS gives good chances of reproductive success without negatively impacting overall survival. [2]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Influence of lymph node involvement or lymphadenectomy on prognosis of patients with borderline ovarian tumors: A systematic review and meta-analysis	Fan Y et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34119365/
2	Fertility-sparing treatment in advanced-stage serous borderline ovarian tumors. An analysis from the MITO14 study database	Falcone F et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33781554/



Treatment of ovarian sex cord stromal and germ cell tumours

Paul Kubelac

Portuesi et al. analysed serial inhibin B measurements and related imaging examinations using data from 47 postmenopausal women that were followed up for the detection of recurrent adult-type granulosa cell tumours of the ovary in a retrospective, single-centre study. At a cut-off of 7pg/mL, inhibin B levels were significantly correlated with the presence/absence of disease, with a sensitivity of 98.8% and a specificity of 88.9%. Inhibin B levels were significantly higher in patients with larger lesions. The authors correlated inhibin B levels to the probability of showing macroscopic disease in the CT scan with a risk of having an abnormal scan of 25%, 50%, and 75% for inhibin B levels of 15.6pg/mL, 44.6pg/mL, and 73.6pg/mL, respectively. Limitations of the study included the small sample size, the retrospective design, as well as the interval between initial inhibin B increase and clinical recurrence. In summary, inhibin B might be a useful tumour marker for the follow-up of adult-type granulosa cell tumours of the ovary. [1]

The role of adjuvant chemotherapy in stage I malignant ovarian germ cell tumours is still controversial. Mangili et al. published preliminary data on 45 patients with stage I malignant ovarian germ cell tumours that were included in MITO-9, a prospective observational study. After a median follow-up of 46.2 months, there was only one (successfully treated) relapse reported among the 31 patients who underwent only surveillance, advocating that close surveillance alone could represent an option in properly staged IA–C dysgerminomas, IA–C G1–3 immature teratomas, or IA mixed malignant germ cell tumours. Given the short follow-up, results have to be considered preliminary until further validation. [2]

A National Cancer Database analysis of 497 patients with stage IA/IB grade 2 or 3 immature teratoma, yolk sac, or mixed germ cell tumours diagnosed between 2004 and 2014 was performed, with 68% patients receiving adjuvant chemotherapy. Median follow-up for the chemotherapy and surveil-

lance-only group was 61.7 versus 63.8 months. No difference in OS was seen for adjuvant chemotherapy versus surveillance for grade 2–3 immature teratoma (p = 0.35, p = 0.47, respectively) or mixed germ cell tumours (p = 0.55). However, patients with yolk sac tumours who received chemotherapy had better survival outcomes compared with those who did not (5-year OS of 92.7% and 79.6%, p = 0.019). Several limitations of the study, such as the lack of a central pathology review, missing information on staging procedures, surveillance strategies, tumour relapse, cause of death, and factors influencing the physician’s decision for adjuvant chemotherapy should be noted. [3]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Role of inhibin B in detecting recurrence of granulosa cell tumors of the ovary in postmenopausal patients	Portuesi R et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33893147/
2	Surveillance alone in stage I malignant ovarian germ cell tumors: a MITO (Multicenter Italian Trials in Ovarian cancer) prospective observational study	Mangili G et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34035080/
3	Surveillance only for high-risk FIGO stage IA/IB malignant ovarian germ cell tumors: results from a national cancer database	Nasioudis D et al.	Am J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/33710136/



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

Anna-Maria Schütz

Phase I

Fuh et al. investigated the safety and efficacy of AVB-500 in combination with paclitaxel (PAC) or pegylated liposomal doxorubicin (PLD) in platinum-resistant ovarian cancer (OC) in a phase Ib, open-label, multicentre trial. AVB-500, a high affinity fusion protein, binds GAS6 and thereby prevents AXL signalling. GAS6 and AXL are expressed in high-grade serous OC but not in normal ovarian tissue. Patients were either given AVB-500 at 10, 15, or 20mg/kg iv q2wk combined with PAC (n = 23) or PLD (n = 30). Adverse advents (AEs) were observed in 78% and 63% for the PAC and PLD groups and were similar regardless of dose level. Most common AEs were fatigue, infusion-related reactions, anaemia, nausea, and headache. No dose discontinuation and no grade 5 AE were reported. Serum GAS6 levels were evaluated and were completely suppressed to below the level of quantitation at each dose level. The recommended phase 2 dose (RP2D) was defined as 15mg/kg AVB-500. The overall response rate (ORR) was 10.7% versus 34.8%, median duration of response (mDoR) was 4.2 versus 7.0, while pro-

gression-free survival (PFS) was 3.6 versus 3.1, and overall survival (OS) was 11.2 versus 10.3 months for AVB-500+PLD and AVB-500+PAC, respectively. Clinical activity was greater at 10 and 15mg/kg in both groups. Subgroup analysis showed best clinical activity for AVB-500+PAC patients who had never received bevacizumab and for those whose AVB-500 trough levels were >13.8mg/L. The combination of AVB-500+PAC will be further investigated along with further analysis on prior bevacizumab treatment in a phase III trial. [1]

Phase II

A multicentric, open-label, single-arm phase II study investigated the efficacy and safety of fluzoparib, a PARP inhibitor, in platinum-sensitive recurrent OC with germline BRCA1/2 mutation. One hundred and thirteen patients who had previously received 2–4 lines of platinum-based chemotherapy were enrolled and were given fluzoparib 150mg orally twice daily. The median follow-up was 15.9 months. Tumour response was assessed by an independent review committee (IRC) and the investigator. ORR

was 69.9% and 70.8% by IRC and the investigator, respectively, and was consistent across all sub-groups (BRCA mutation status, time from last platinum-based chemotherapy to progression/relapse, lines of previous chemotherapy, lines of previous platinum-based chemotherapy, age). Median IRC and investigator-assessed PFS were 12.0 and 10.3 months, respectively. The 12-month survival rate was 93.7%. Regarding CA-125 level, a reduction of ≥ 50% in baseline was reported in 90.9%. Grade ≥ 3 AEs were reported in 63.7%, with anaemia being the most common. Treatment interruption and dose reduction occurred in 39.8% and 34.5%, respectively. One patient discontinued treatment due to AEs. One treatment-related death has been reported. Limitations of this study include the open-label character and the lack of a control arm. [2]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Phase 1b study of AVB-500 in combination with paclitaxel or pegylated liposomal doxorubicin platinum-resistant recurrent ovarian cancer	Fuh KC et al .	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34474927/
2	An open-label, multicenter, single-arm, phase II study of fluzoparib in patients with germline BRCA1/2 mutation and platinum-sensitive recurrent ovarian cancer	Li N et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/33558426/



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

Kamil Zalewski

Radiotherapy choice and dosing different from drug therapy are mostly standardised based only on the cancer type and location. A study published in Lancet Oncology with data derived from 11 previously published studies on radiation therapy in different cancers showed that adding individual patients' genomic information to optimise radiotherapy doses significantly affected two endpoints: time to the first recurrence (95% CI: 0.97–0.99, $p = 0.0017$) and overall survival (95% CI: 0.95–0.99, $p = 0.0007$). Within 1,615 analysed patients, 204 were diagnosed with endometrial cancer. The authors created an algorithm based on a genomic-adjusted radiation dose that enables the personalised dose of the radiotherapy based on its biological effect. It involves changes in expression levels of ten genes (AR, cJun [JUN], STAT1, PKC- β [PRKCB], RelA [RELA], cABL [ABL], SUMO1, PAK2, HDAC1, and IRF1) that were shown to correlate with radiosensitivity. Despite the fact that the study is based on already published data and needs to be validated prospectively, the authors suggest that genomic-adjusted radiation dose can already serve as a tool to modulate prescribed radiation doses in clinical practice individually. [1]

In their multicentre, phase II non-comparative prospective trial, Antill et al. demonstrated that treatment with a single-agent anti-PD-L1 antibody (durvalumab) has encouraging activity (objective tumour response, OTRR) and tolerability in women with dMMR advanced or recurrent endometrial cancer not

eligible for surgical resection. The authors assessed durvalumab activity in 71 women who were divided into two groups of patients: one characterised by the expression of four mismatch mutation repair (pMMR group with 36pts, 57% with endometrioid histology) proteins (MLH1, MSH2, MSH6 and PMS2) and the second group presenting a loss of at least one of these proteins (dMMR group with 35 pts, 94% with). The small group of studied women and the lack of randomisation could be considered limitations of this study. Contrary to the dMMR group, in which OTRR was observed in 47% of patients (17/36, 95% CI: 32–63; 6 complete responses), in the pMMR group, this parameter was only 3%. The majority of patients (58%) in the dMMR cohort received this treatment as first-line therapy (OTRR 57%). Durvalumab was well tolerated, and only one patient needed to stop its treatment due to the toxicity. The authors suggested that a single-agent anti-PD-L1 antibody could be compared in further prospective trials with chemotherapy. [2]

Pathological complete response (pCR) to intrauterine levonorgestrel (LNG-IUD) inserted into the uterine cavity was accessed in a phase II trial in which 165 obese patients (a body mass index $> 30 \text{ kg/m}^2$) with stage I FIGO (less than 50% of the depth of myometrial invasion on preoperative MRI) grade 1 endometrial adenocarcinoma (EAC) and endometrial hyperplasia with atypia (EHA) were randomised to one of the three groups: LNG-IUD and only observa-

tion, LNG-IUD and weight-loss intervention, or LNG-IUD and 500mg of metformin orally given twice daily. The feMMe trial showed pCR were 43% and 82% for EAC and EHA, respectively. The most encouraging response was observed in groups with LNG-IUD with observation and weight-loss intervention, 61% and 67%, respectively. Only 57% of patients receiving metformin had pCR on endometrial sampling. The authors concluded that a phase III trial is needed to provide powered results formally, allowing for comparison of the outcomes, and that molecular predictors of response should be looked into. [3]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Pan-cancer prediction of radiotherapy benefit using genomic-adjusted radiation dose (GARD): a cohort-based pooled analysis	Scott JG et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/34363761/
2	Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer. A nonrandomized phase 2 clinical trial	Antill Y al.	J Immunother Cancer	https://pubmed.ncbi.nlm.nih.gov/34103352/
3	Complete pathological response following levonorgestrel intrauterine device in clinically stage 1 endometrial adenocarcinoma: Results of a randomized clinical trial	Janda M et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33762086/



Medical (chemo and radiotherapy) treatment of recurrent uterine cancer

Stamatios Petousis

Hori et al. published a phase II, open-label, single-arm study to determine the safety and efficacy of paclitaxel and carboplatin in treating advanced or recurrent endometrial cancer. Overall, 48 women enrolled, of whom 46 were eligible to participate. Patients of stage III disease with some residual tumour, FIGO stage IV disease, recurrence after front-line curative treatment, or recurrence after second-line chemotherapy or radiotherapy were enrolled. The authors observed a satisfying tolerance rate as 63% of participants managed to receive over six cycles of chemotherapy. The observed response rate was 71.3%, with a complete response in 13 and partial in 20 cases. The authors concluded that PTX with CBCDA is feasible as a treatment option for advanced or recurrent endometrial cancer. The study is characterised by prospective design, enrolling a dose-dense schema. However, there is a mixture of

both advanced and recurrent uterine endometrial cancer cases, while most of the participants supposedly received post-treatments that were neither defined nor followed up. [1]

Alban et al. published a retrospective study evaluating clinical outcomes and toxicity in patients with vaginal recurrence of early-stage endometrial cancer treated with definitive radiotherapy. There were 62 patients enrolled. Patients had been diagnosed with stage I–II endometrial cancer and vaginal recurrence, having previously received external-beam radiotherapy and image-guided brachytherapy. The authors reported that three- and five-year rates of vaginal control, recurrence-free survival, and overall survival were 86% and 82%, 69% and 55%, and 80% and 61%, respectively. In the subset of patients with known mismatch repair status, recurrence rates were significantly higher for those with mismatch

repair-deficient tumours (3-year recurrence-free survival 52% vs 100% for mismatch repair-proficient disease). Late severe toxicity was reported to be under 3%. The authors concluded that definitive radiotherapy with image-guided brachytherapy is safe and effective for treatment of vaginal recurrence of early-stage endometrial cancer. This seems to be a well-designed study, also reporting on the prognostic impact of various clinical and histopathological parameters and, despite its retrospective character, may contribute to assessing the therapeutic value of definitive radiotherapy. [2]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	A phase II, open-labeled, single-arm study of dose-dense paclitaxel plus carboplatin in advanced or recurrent uterine endometrial cancer treatment: a KCOG-G1303, DOENCA trial	Hori K et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34085798/
2	Definitive radiotherapy for vaginal recurrence of early-stage endometrial cancer: survival outcomes and effect of mismatch repair status	Alban G et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33858956/



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

Zoia Razumova

Dasatinib is a small molecule inhibitor of multiple tyrosine kinases, including EphA2. Overexpression of this transmembrane receptor tyrosine kinase is found in 50%–90% of human cancers, including endometrial cancer (EC), where it predicts poor outcomes.

Coleman et al. conducted a pilot study to investigate the role of dasatinib in EphA2 signalling. Eighteen patients with advanced-stage, chemo-naïve primary or recurrent EC in the lead-in phase of the study received single-agent dasatinib (150mg/14 days). After biopsy samples had been taken, patients were initiated on the triplet combination of paclitaxel and

carboplatin (standard of care) plus dasatinib taken daily for six 21-day cycles.

The response rate was 45% (95% CI: 17–77%), with a median progression-free survival of 10.5 months and overall survival of 30.4 months. A reverse-phase protein array and proximity ligation assay showed that CRAF/BRAF dimerization, caveolin-1 level, and Notch pathway signalling were predictive in dasatinib treatment. Neutropenia (76%), thrombocytopenia (53%), anaemia (53%), and fatigue (12%) were the primary grade 3–4 adverse events.

The hypothesis-generating nature of this study had its limitations, such as a small group of enrolled pa-

tients and a smaller than expected group of patients that were able to complete the planned six cycles of therapy, primarily due to its toxicity. Besides, most biomarkers measured before and after dasatinib treatment were not significantly different.

The authors concluded that the combination of paclitaxel, carboplatin, and dasatinib showed clinical activity in EC with tolerable toxicity. The authors supposed that pretreatment with dasatinib may reduce toxicity due to the drug combination. [1]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Dasatinib, paclitaxel, and carboplatin in women with advanced-stage or recurrent endometrial cancer: A pilot clinical and translational study	Coleman RL et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33551196/



Uterine sarcoma

Marcin Bobiński

The French Sarcoma Group published the long-term follow-up of results of the LMS-02 trial, in which 108 enrolled patients with primary leiomyosarcoma were treated with doxorubicin combined with trabectedin. In this single-arm prospective study, 61 patients with soft tissue leiomyosarcoma (ST-LMS) and 47 with uterine leiomyosarcoma (U-LMS) received 60mg/m² doxorubicin followed by trabectedin 1.1mg/m². With the median follow-up of 7.2 years, the overall survival (OS) was 34.4 months in the ST-LMS group and 27.5 months in the U-LMS group, whereas median progression-free survival (PFS) was 12.9 and 8.3 months for ST-LMS and U-LMS, respectively. A significant extension of median PFS (18.2 vs 8.2 months) was noted in an oligometastatic patient subgroup that underwent interval debulking surgery after six cycles of chemotherapy when compared with surgery-free patients. Overall survival in the non-operated group was 31.6 months and was not reached in the group of patients after secondary surgery. Even if the results obtained in this study are encouraging, there are major limitations in the study, including its phase II

status and lack of consistent criteria of qualifications for interval debulking surgery, and conclusions should be made carefully. The authors have initiated a phase III randomised trial to further investigate (LMS04 trial (NCT02997358)). [1]

Wang et al. studied the performance of a computer-aided diagnostic tool (CAD) in distinguishing between malignant and benign mesenchymal uterine tumours. Their model used both radiomics features based on hyperintense T2-weighted image (T2WI) of MRI scans, as well as clinical features, including symptoms, patient demographics, clinical characteristics, etc. All results were retrospectively compared with the opinion of two blinded, experienced radiologists. The authors concluded that when combining the results from both clinical and radiomics, the accuracy of differentiation between malignant and benign tumours performed by the CAD is better than the results achieved by professional radiologists. The study was limited because the authors included only T2WI-based radiomics while ignoring other functional

MR sequence images as well as including stromal tumours of uncertain malignant potential in the malignant group instead of analysing them separately. [2]

Chiappa et al. assessed the utility of radiomics algorithms built on the data retrieved from ultrasound scans to differentiate the type of myometrial tumours. The total number of retrospectively enrolled cases was 70 (50 benign tumours and 20 malignant) and 390 radiomics parameters were analysed. The system achieved accuracy 0.85±0.01, sensitivity 0.80±0.01, specificity 0.87±0.01, and AUC 0.86±0.03. The authors concluded that such a method might be a useful tool supporting clinical decisions, but results need to be confirmed in a prospective study with a higher number of cases. Despite the fact that this study is novel and multicentre, the low number of retrospectively enrolled cases is a limitation. [3]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	A single-arm multicentre phase II trial of doxorubicin in combination with trabectedin in the first-line treatment for leiomyosarcoma with long-term follow-up and impact of cytoreductive surgery	Pautier P et al.	ESMO Open	https://pubmed.ncbi.nlm.nih.gov/34325109/
2	A combined radiomics and clinical variables model for prediction of malignancy in T2 hyperintense uterine mesenchymal tumors on MRI	Wang T et al.	Eur Radiol	https://pubmed.ncbi.nlm.nih.gov/33486606/
3	Using rADioMics and machine learning with ultrasonography for the differential diagnosis of myometrial tumors (the ADMIRAL pilot study). Radiomics and differential diagnosis of myometrial tumors	Chiappa V et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33867144/



Surgical treatment of primary and recurrent endometrial cancer

Houssein El Hajj

In their randomised trial (RHOMANY), Gueli Aletti et al. evaluated the impact of uterine manipulator usage on the lymph vascular space invasion (LVSI) rate in patients treated for early-stage endometrial carcinoma (EC) via minimally invasive surgery (MIS). A total of 154 patients with low-grade, early-stage EC were randomised 1:1 to either use a UM or not. After a median follow-up of 38.7 months, no difference was found concerning overall survival (OS) ($p = 0.996$) and disease-free survival (DFS) ($p = 0.480$), nor the recurrence rate ($p = 0.486$). The study's main limitation is that it was not designed to reveal definite differences in oncologic outcomes. [1]

Angeles et al. prospectively evaluated 102 patients with intermediate or high-risk EC who underwent sentinel lymph node (SLN) mapping using transvaginal ultrasound-guided myometrial injection of the radiotracer. The rate of intraoperative SLN detection was 79.4% (81/102). The overall sensitivity and negative predictive value (NPV) for detecting LNM in women with intermediate and high-risk EC were 87.5% and 97.0%, respectively, and 83.3% and 96.9% for paraaortic metastases. However, after applying the Memorial Sloan Kettering Cancer Center mapping algorithm, the sensitivity and NPV were 93.8% and 98.5%, respectively. Ultra-staging increased the technique's sensitivity (37.5% to

detect overall LN and 16.6% to detect paraaortic LN involvement). The authors concluded that ultra-staging should be mandatory in SLNs, as detecting low-volume metastases might provide important prognostic value. The strength of this study relies on its prospective aspect and its homogeneous design. However, the relatively low number of patients included only one radiotracer, and the monocentric aspect constituted its main limitations. [2]

Moukarzel et al. retrospectively compared the different treatment modalities for 376 patients with recurrent EC. Sixty-one patients (16.2%) were treated with secondary cytoreduction (SCS), 257 (68.4%) with medical management, 32 (8.5%) received hormonal therapy, and 26 (6.9%) received no further treatment. Patients treated with SCS presented significantly longer median PFS2 (14.9 months) and a median OS of 57.6 months compared to other treatment modalities ($p < 0.001$). On multivariate analysis, SCS was an independent predictor of improved survival even when it is non-exenterative. This study presents one of the largest cohorts of recurrent EC. However, limitations are its retrospective design and the resultant selection bias, absence of standardised perioperative care protocols, follow-up and screening protocols, as well as the difference in the size of the compared groups. [3]

Feigenberg et al. retrospectively reviewed 758 patients with high-grade EC carcinoma treated with MIS. They characterised all 157 recurrences into either intraabdominal or extra-abdominal recurrences. Multivariable analysis showed that stage and uterine weight ($>75\%$ percentile) were the only factors significantly associated with intraabdominal or vaginal recurrence (OR 2.207, CI: 1.123–4.337) with no increase in extra-abdominal or intraparenchymal recurrence. This highlights the potential local tumour spillage and the tumour spillage through the fallopian tubes during uterine extraction through the vagina. This study concludes that extracting a large uterus after MIS is associated with an increased risk of intraabdominal and vaginal recurrence; however, limitations are its retrospective aspect with data collection bias and the absence of standardised protocols dictating which surgical technique to choose. [4]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	A multicentric randomized trial to evaluate the ROle of Uterine MANipulator on Laparoscopic/Robotic HYsterectomy for the Treatment of Early-Stage Endometrial Cancer: The ROMANHY Trial	Gueli Aletti S et al.	Front Oncol	https://pubmed.ncbi.nlm.nih.gov/34568050/
2	Paraortic sentinel lymph node detection in intermediate and high-risk endometrial cancer by transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR)	Angeles MA et al.	J Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33908710/
3	Non-exenterative surgical management of recurrent endometrial carcinoma	Moukarzel LA et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34090704/
4	Factors associated with an increased risk of recurrence in patients diagnosed with high-grade endometrial cancer undergoing minimally invasive surgery: A study of the society of gynecologic oncology of Canada (GOC) community of practice (CoP)	Feigenberg T et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34183164/



Surgical treatment of primary and recurrent cervical cancer

Bojana Gutic and Chrysoula Margioulas-Siarkou

Ohta et al. retrospectively reviewed records of 929 patients with FIGO stage IB1 and IIA cervical cancer treated in 2015 in Japan. The majority of patients had stage IB1 disease (94.4%), while more than half of patients (59.5%) had squamous histological tumours. Open surgery was used in 91.2% and minimally invasive surgery (MIS) in 8.8% patients who underwent radical surgery. The authors indicated that age (≥ 47), adenocarcinoma, tumour size (≥ 2 cm), parametrial invasion, and positive lymph node metastasis were independent prognostic factors for DFS. Furthermore, adenocarcinoma or rare histological sub-types and positive lymph node metastasis were independent prognostic factors for OS. Comparing the open surgery and MIS groups, the authors indicated that the median operation time was significantly longer while blood loss was significantly lower in the MIS group. [1]

Hiraoka et al. analysed the outcomes of 25 patients with recurrence after definitive radiotherapy/chemo-radiotherapy. Recurrence status was confirmed with fluorodeoxyglucose-positron emission tomography (FDG-PET) and biopsy except for lesions unavailable for biopsy. Thirteen patients had isolated extra-pelvic LN (EPLN) recurrence, eight patients were with recurrence in para-aortic LN, two in para-aortic + axially LN, three with mediastinum metastasis, and

12 had other patterns of recurrence. Chemotherapy was selected for patients who were unfit for local salvage therapy but could receive chemotherapy. Patients who underwent surgery or radiotherapy for palliative purpose were excluded. Overall survival after first recurrence (OSr) was 59.5%. The two-year OSr for patients who underwent local salvage therapy was 75.2%, and for patients who did not undergo local salvage therapy 41.6% ($p = 0.04$). The two-year OSr for patients with isolated EPLN recurrence was 83.1% and 31.2% for patients with other patterns of recurrence ($p < 0.001$). The median progression-free survival after first recurrence (PFSr) in the group that received local salvage therapy was 18.9 months, while it was 4.7 months for patients who received only chemotherapy alone. The authors concluded that indications of local salvage therapy should be considered, especially for patients with isolated EPLN recurrence with favourable prognosis. [2]

Kavallaris et al. retrospectively studied the impact of laparoscopic nerve-sparing radical hysterectomy without uterine manipulator for cervical cancer stage IB. They analysed 27 patients with FIGO (2009) stage IB1 and five with stage IB2. The mean PFS was 79.3 months for IB1 and 34.8 months for IB2. The three-year PFS was 93.7%

for the overall population and 96.1% for IB1 stage. They reported two recurrences overall, one central (initial-stage IB1) and the other in the lateral pelvic wall (initial-stage IB2). Both were retreated and had no disease recurrence. The authors concluded that oncological outcome was superior in laparoscopic nerve-sparing radical hysterectomy without uterine manipulator compared with outcomes reported by studies in which a uterine manipulator was routinely used with the absence of vaginal sealing of the tumour. [3]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Surveillance of radical hysterectomy for early-stage cervical cancer in the early experienced period of minimally invasive surgery in Japan	Ohta T et al.	Int J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/34435284/
2	Efficacy of local salvage therapy for recurrent uterine cervical cancer after definitive radiotherapy	Hiraoka S et al.	Int J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/34165659/
3	Laparoscopic nerve-sparing radical hysterectomy without uterine manipulator for cervical cancer stage IB: description of the technique, our experience and results after the era of LACC trial	Kavallaris A et al.	Arch Gynecol Obstet	https://pubmed.ncbi.nlm.nih.gov/33068159/



Radiotherapy of primary and recurrent cervical cancer

Erbil Karaman and Paweł Bartnik

The Postoperative Adjuvant Radiation in Cervical Cancer (PARCER) study is a phase III randomised trial performed by Chopra et al. on a group of 300 patients with cervical cancer who underwent postoperative adjuvant radiotherapy. Patients were randomly assigned to image-guided intensity-modulated radiotherapy (IG-IMRT) or three-dimensional conformal radiation therapy (3D-RCT). The authors set a primary endpoint as a three-year grade ≥ 2 late gastrointestinal toxicity. Secondary endpoints included acute toxicity; health-related quality of life; and pelvic relapse-free, disease-free, and overall survival. As a result, the three-year cumulative incidence of grade ≥ 2 late gastrointestinal toxicity in the IG-IMRT and 3D-CRT arms was 21.1% versus 42.4% (HR 0.46; 95% CI: 0.29–0.73; $p < 0.001$). At the same time, cumulative incidence of grade ≥ 2 any late toxicity was 28.1% versus 48.9% (HR 0.50; 95% CI: 0.33–0.76; $p < 0.001$), respectively. Despite reduced toxicity in the IG-IMRT arm, no difference in the three-year survival rates was observed. [1]

EMBRACE-I is a prospective, observational, multicentre cohort study that evaluated local tumour control and morbidity after chemoradiotherapy and MRI-based image-guided adaptive brachytherapy (IGABT). Pötter et al. analysed 1,341 patients with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix, FIGO stage IB–IVA disease or FIGO stage IVB disease restricted to paraaortic lymph metastasis below the L1–L2 interspace, suitable for curative treatment. Treatment included chemoradiotherapy (weekly intravenous cisplatin 40 mg/m², 5–6 cycles, one day per cycle, plus 4–50 Gy external-beam radiotherapy delivered in 1.8–2 Gy fractions) followed by MRI-based IGABT. It was shown that chemoradiotherapy and MRI-based IGABT effectively achieved long-term local control and had limited severe morbidity in locally advanced cervical cancer. [2]

Grover et al. conducted a prospective cohort study to evaluate the benefits of chemoradiation versus radiation alone in women diagnosed with FIGO IIIB cervical

cancer with concurrent HIV infection. One hundred eighty-seven patients were enrolled, among whom 118 (63%) were HIV seropositive. Also, the multivariable Cox regression receipt of chemoradiation (HR 0.63, $p = 0.04$) and total radiation dose ≥ 80 Gy (HR 0.57, $p = 0.02$) was associated with two-year overall survival, regardless of HIV status. The authors concluded that chemoradiotherapy improved overall survival, regardless of HIV status, and was even more essential in women who could not receive full doses of radiation. [3]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Late toxicity after adjuvant conventional radiation versus image-guided intensity-modulated radiotherapy for cervical cancer (PARCER): A randomized controlled trial	Chopra S et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/34506246/
2	MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study	Pötter R et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/33794207/
3	Chemoradiation versus radiation alone in stage IIIB cervical cancer patients with or without human immunodeficiency virus	Grover S et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34312220/



Medical treatment of primary and recurrent cervical cancer

Kristina Lindemann

Colombo et al. published the practice-changing randomised phase III KEYNOTE-826 study. In all, 617 patients with persistent, recurrent, or metastatic cervical cancer were randomised to paclitaxel (175mg/m²) and the investigator's choice of cisplatin (50mg/m²) or carboplatin (AUC = 5) every three weeks and pembrolizumab (200mg) or placebo every three weeks for up to 35 cycles. The administration of bevacizumab was optional. Treatment was continued until progressive disease, unacceptable toxic effects, or the maximum number of cycles. PD-L1 expression was centrally assessed as a combined positive score. Most patients had squamous carcinoma, and only 18.8% and 20.7% of patients in pembrolizumab and placebo arm respectively had primary metastatic disease. Notably, about 63% of the patients in both

arms received bevacizumab and approximately 11% were PDL-1 negative. During a median follow-up of 22 months, both progression-free (10.4 months vs 8.2 months) and 24-month overall survival estimate (50.4% vs 40.4%) were significantly longer in the pembrolizumab arm. These results were observed in patients with PD-L1 combined positive scores of one or more and ten or more. No new safety signals emerged in the pembrolizumab group. [1]

The Japan Clinical Oncology Group designed the JCOG1311 study, a new phase II/III trial based on the results of JCOG0505. In all, 122 patients with metastatic or recurrent cervical cancer were randomised to dose-dense weekly paclitaxel plus carboplatin (ddTC) with or without bevacizumab

compared to conventional, tri-weekly paclitaxel plus carboplatin (cTC) with or without bevacizumab. The primary endpoint was response rates, which for patients on cTC+bevacizumab was 67.9%, for patients on ddTC+bevacizumab: 60.7%, cTC: 55.2%, and ddTC: 50.0%. As a result, the study did not meet its primary endpoint, which was to observe a 5% improved response rate in the dose-dense arm. [2]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Pembrolizumab for persistent, recurrent, or metastatic cervical cancer	Colombo N et al.	N Engl J Med	https://pubmed.ncbi.nlm.nih.gov/34534429/
2	A randomized phase II/III trial of conventional paclitaxel and carboplatin with or without bevacizumab versus dose-dense paclitaxel and carboplatin with or without bevacizumab, in stage IVB, recurrent, or persistent cervical carcinoma (JCOG1311): Primary analysis	Ishkawa M et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34016453/



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

Khayal Gasimli

Phase II

Tisotumab vedotin is an antibody-drug conjugate that binds to tissue factors on cervical cancer cells and releases monomethyl auristatin E intracellularly, which induces apoptotic cell death through microtubule disruption. In the frame of a multicentre, open-label, single-arm innovaTV 204/ GOG-3023/ ENGOT-cx6 study, Coleman et al. investigated the efficacy and safety of tisotumab vedotin in 102 patients with recurrent or metastatic cervical cancer. All included patients were applied at most two

previous chemotherapies, 63% already with doublet chemotherapy and bevacizumab. The drug was administrated intravenously once every three weeks until disease progression or intolerable toxicity. The RECIST criterion was used to evaluate response rate after at least one dose administration in each patient. The results showed that disease control could be achieved in 72 (95% CI: 63–81) cases; of them, seven (7%) patients had a complete response and 17 (17%) patients—a partial response. In addition, a six-month progression-free survival rate could be registered in 30% (95% CI: 21–40) cases.

In addition, alopecia, epistaxis, nausea, conjunctivitis, fatigue, and dry eye were observed in order as the most common treatment-related grade 1–2 adverse events. The most common treatment-related severe adverse events (\geq grade 3) were peripheral sensorimotor neuropathy (2%), pyrexia (2%), and one death due to septic shock. [1]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study	Coleman RL et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/33845034/



Primary and recurrent vulvar cancer treatment

María de los Reyes Oliver and Rubén M. Betoret

The long-awaited results of the Groningen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-V-II) were published. They were first presented by Dr Maaïke Oonk at ESGO 2019 in Athens, Greece [abstract A-1025-0028-01830]. This was a prospective multicentre phase II single-arm treatment trial aiming to establish whether inguinofemoral radiotherapy is a safe alternative to inguinofemoral lymphadenectomy (IFL) in vulvar cancer (VC) patients with metastases in sentinel lymph node (SLN). The secondary aim was to establish the treatment-related morbidity for this management strategy.

A total of 322 patients with early-stage VC, who had primary surgical treatment (local excision with SLN biopsy) and in whom SLNs were involved were included. Inguinofemoral radiotherapy (50Gy) was administered after surgery in all patients. The primary endpoint was isolated groin recurrence rate at 24 months. After 54 months of follow-up and enrolling 91 patients, interim analysis revealed that in the group of patients with macrometastases in SLNs (>2 mm), radiotherapy was not a safe alternative to IFL and increased the risk of groin recurrence. The previously defined stopping rule was immediately applied, and the protocol was amended. In the following part of the study, patients with macrometastases in SLNs and/or extra-nodal extension received standard of care, which is IFL (with radiotherapy if >1 metastasis or extra-nodal extension), while those with micrometastases in SLNs (<= 2mm)

continued to receive inguinofemoral radiotherapy. Among 160 patients with micrometastases in SLNs, 126 received inguinofemoral radiotherapy, with an ipsilateral isolated groin recurrence rate at two years of 1.6%. Among 162 patients with macrometastases in SLNs, the isolated groin recurrence rate at two years was higher in those who underwent radiotherapy compared to IFL (22% vs 6.9%, $p = 0.011$). The combination of SLN biopsy with subsequent radiotherapy to the groin was mostly associated with low-grade toxicities, whereas the patients who underwent IFL experienced the highest incidence of lymphoedema (32.0% vs 22.9%, $p < 0.001$). The number of enrolled patients is definitely one of the main strengths of the GROINSS-V-II study, while the lack of pretreatment radiotherapy contouring and planning quality control might be mentioned as its limitations. The authors concluded that inguinofemoral radiotherapy for VC patients with micrometastases in SLNs appears to be a safe alternative for IFL characterised by minimal morbidity. For patients with SLNs with macrometastases, radiotherapy with a total dose of 50 Gy resulted in a higher number of isolated groin recurrences compared with IFL. For them, radiotherapy dose escalation in combination with chemotherapy will be further investigated. [1]

In their Swedish nationwide population-based cohort study, Zach et al. retrospectively examined the patterns of recurrence and their association with survival in a group of 489 women diagnosed with VC. The overall recurrence rate was 22.3%. Local

recurrence was observed in 61.0%, while the groin was affected in 30.0% of patients. Surgical groin staging was omitted in 23.7% of FIGO stages IB–II and was significantly associated with poor survival. This was the largest population-based study on recurrence and post-recurrence survival in VC and was obviously limited, including by the lack of a central pathology review and information on further lines of treatment. In line with other reports, the authors concluded that surgical groin staging is a crucial part of primary treatment and should not be omitted. [2]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Radiotherapy versus inguinofemoral lymphadenectomy as treatment for vulvar cancer patients with micrometastases in the sentinel node: Results of GROINSS-V II	Oonk MHM et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/34432481/
2	Patterns of recurrence and survival in vulvar cancer: A nationwide population-based study	Zach D et al.	Gynecol oncol	https://pubmed.ncbi.nlm.nih.gov/33736857/



Follow-up after gynaecological malignancies

Sunaina Wadhwa

The standard style of follow-up care is primarily focused on diagnosing recurring disease but not identifying and handling psychosocial difficulties. Campbell et al. developed and validated MOST-S26, a patient-reported symptom index, for the follow-up of patients with ovarian cancer after first-line chemotherapy. It is a prospective analysis of 726 women who received more than three rounds of chemotherapy and did not have progression in three months. MOST-S26 includes 26 items and five multi-item indexes: peripheral neuropathy (MOST-NTx), disease or treatment-related (MOST-DorT), abdominal (MOST-Abdo), and psychological symptoms (MOST-Psych), as well as nine individual items. The construct's validity was confirmed (r range = 0.43–0.88). Discriminative validity demonstrated the expected group differences. The study has shown that MOST-S26 accurately detects improvement in peripheral neuropathy symptoms, psychological distress, and relapse symptoms. [1]

Skorstad et al. assessed the compliance and adherence to follow-up guidelines in gynaecological cancer survivors in a multicentre cross-sectional study. Participants were labelled as adherent if they attended the requisite number of follow-up visits,

non-adherent if they attended fewer visits than indicated, or over-users if they attended more appointments than suggested—the study comprised 911 of the 4,455 survivors who were invited. Information on follow-up visits, healthcare utilisation, self-management, clinical characteristics, and demographics were collected using validated questionnaires. Survivors with a high level of self-control were more likely to follow through with the indicated follow-up. Non-adherent survivors showed lower self-management (OR 1.54, 95% CI: 1.03–2.32) than adherent survivors in the health-directed activities area (OR 1.54, 95% CI: 1.03–2.32). As a result, the authors showed that low self-management appears to lower the likelihood of adhering to national gynaecological cancer follow-up guidelines. [2]

In a national multicentre observational study, Kargo et al. assessed the role of actively employing the patient-reported outcome measures (PROMs) model throughout an 18-month follow-up. There were 223 patients registered, with 168 (75.3%) using PROMs actively at five sites and 53 (23.8%) passively using it at three sites. No statistically significant difference between the two groups was shown regarding decision-making, satisfaction with care, unmet needs,

or quality of life. Therefore, active PROM use is not beneficial in improving patients' sense of involvement in follow-up care compared to passive use. [3]

The National Comprehensive Cancer Network Electronic Health Record Oncology Advisory Group developed a working group to review oncologists' thoughts on telemedicine's current and future responsibilities for cancer patients using a 20-question survey. In all, 1,038 providers from 26 institutions answered, and 766 clinical cases were compared to in-person visits. For evaluating benign follow-up data, 88% said video and 80% said phone was as good as or better than office visits. For building a personal connection with patients, 24% and 7% said video and telephone were as good as or better than office visits, respectively. Ninety-three per cent reported no bad effects from telemedicine visits. It was concluded that telemedicine could be helpful in a wide range of clinical settings. [4]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Development and validation of the measure of ovarian symptoms and treatment concerns for surveillance (MOST-S26): An instrument to complement the clinical follow-up of women with ovarian cancer after completion of first-line treatment	Campbell R et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34481610/
2	Self-management and adherence to recommended follow-up after gynaecological cancer: results from the international InCHARGE study	Skorstad M et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33858949/
3	The PROMova study comparing active and passive use of patient-reported outcome measures in ovarian cancer follow-up: effect on patient-perceived involvement, satisfaction with care, and usefulness	Kargo AS et al.	Acta Oncol	https://pubmed.ncbi.nlm.nih.gov/33651647/
4	Oncologist perspectives on telemedicine for patients with cancer: A national comprehensive cancer network survey	Tevaarwerk AJ et al.	JCO Oncol Pract	https://pubmed.ncbi.nlm.nih.gov/34264741/



Prevention and management of surgical complications

Anastasia Prodromidou

Chambers et al. evaluated the effect of the frailty index on the postoperative course of patients with advanced gynaecological cancer who underwent cytoreductive procedures with hyperthermic intra-peritoneal chemotherapy (HIPEC). Patients with a modified Frailty Index (mFI) of 0–1 ($n = 115$) were considered non-frail, while patients with $mFI \geq 2$ comprised the frail group ($n = 26$). Analysis of postoperative outcomes revealed significantly increased re-operation rates ($p < 0.001$), incidence of respiratory failure ($p < 0.001$), intensive care unit admission ($p = 0.018$), and acute kidney injury ($p = 0.001$) in frail patients compared to non-frail. A similar effect was also observed in the length of hospital stay and time to chemotherapy, which were both significantly prolonged ($p = 0.004$ and $p = 0.024$, respectively). A mFI score ≥ 2 was independently associated with an increased risk of postoperative complications (Accordion grade ≥ 2) in a multivariate analysis. [1]

The efficacy of implementation of a venous thromboembolism (VTE) prophylaxis quality improvement (QI) initiative was assessed by Gonzalez et al. in gynaecological oncology surgical patients during three retrospective cancer-enriched cohorts (2016–2017/pre-intervention era, 2018, 2019). The intervention algorithm included implementation of modalities to

improve heparin protocols and education on sequential compression device compliance for patients and care providers. A significantly improved adherence to evidence-based peri-operative thromboprophylaxis guidelines was observed (31% in 2016–2017, 69.1% in 2018, and 82.4% in 2019, $p < 0.001$) over time. Heparin administration was also significantly increased (34.8% in 2016–2017, 83.3% in 2018, and 92.5% in 2019, $p < 0.001$). Concerning VTE rates within 30 days of surgery, despite the observed reduction from 5% in 2016–2017 to 3.6% and 1% in 2018 and 2019, respectively, the difference did not reach significance ($p = 0.255$). This was also observed in case of adverse events and blood transfusion rates. [2]

A prospective non-randomised comparative study by Iltar et al. ($n = 208$ patients) evaluated the efficacy of the application of prophylactic subcutaneous retention sutures in patients who underwent surgery due to confirmed or suspected gynaecologic malignancy through midline laparotomy. Superficial wound site dehiscence rates were significantly elevated in patients without the sutures compared to those with retention sutures (23.9% vs 12.6%, $p = 0.038$). Furthermore, the presence of retention sutures and high body mass index were independently associated with the risk of superficial wound separation on

multivariate analysis (OR 0.31, 95% CI: 0.11–0.83, $p = 0.019$, OR 1.12, 95% CI: 1.09–1.28, $p < 0.001$, respectively). [3]

In their randomised controlled trial, Perutelli et al. compared patients who had primary major surgical procedures due to ovarian cancer and were randomised to those managed with the intraoperative use of a nylon bag for bowel isolation ($n = 48$) or not ($n = 44$). Time to first flatus was significantly protracted in the no-isolation bag group (3.09 ± 1.07 vs 2.2 ± 0.77 , $p < 0.001$) and the rates of first/continued passage of flatus within three days were also significantly increased (79.2% vs 34.3%, $p < 0.001$). However, this was not reflected in main surgical outcomes, including operative time, blood loss, and transfusion rates. Hospital stay was significantly shorter in the isolation bag group. For procedures that lasted more than 220min, the advantages of isolation bag application were more prominent (OR 0.02, 95% CI: 0.001–0.57, $p < 0.001$). [4]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Modified frailty index predicts postoperative complications in women with gynecologic cancer undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	Chambers LM et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/34083027/
2	A quality improvement initiative to reduce venous thromboembolism on a gynecologic oncology service	Gonzalez R et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33994013/
3	Prophylactic subcutaneous retention sutures in the prevention of superficial wound separation of midline laparotomy	Iltar E et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34290046/
4	Modified intestinal isolation bag as promising tool in promoting bowel resumption after ovarian cancer cytoreductive surgery: a randomized clinical trial	Perutelli A et al.	Arch Gynecol Obstet	https://pubmed.ncbi.nlm.nih.gov/33555430/

Fertility-sparing treatment in gynaecological malignancies

Charalampos Theofanakis

Endometrial cancer

A study by Chung et al. attempted to evaluate the prognostic significance of Proactive Molecular Risk Classifier in young patients with endometrial cancer. Fifty-seven specimens were obtained through endometrial biopsies before the initiation of progesterone therapy. The primary endpoint was the response rate after hormone therapy, while secondary endpoints were the recurrence rate after the complete response, hysterectomy rate owing to treatment failure, and upstaged diagnosis rate after hysterectomy. Results showed that patients with mismatch repair deficiency had significantly lower complete or partial response rates than those with wild-type p53 (44.4% vs 82.2%, $p = 0.018$). The authors concluded that the Proactive Molecular Risk Classifier serves as an important prognostic factor in young patients with endometrial cancer. [1]

A retrospective study by Chen et al. evaluated the re-treatment of patients with recurrent endometrial cancer and atypical endometrial hyperplasia after complete remission. The study included 80 patients that wished to preserve their fertility after recurrence, of whom 71 achieved complete response, 96% and 75.8% in atypical hyperplasia and endometrial cancer, respectively. A second relapse was reported in 22 patients with a median recurrence time of 12 months, 10 of whom received a third course of hormone treatment. The authors stated

that re-treatment could be considered for patients with recurrent endometrial cancer and atypical hyperplasia. [2]

Cervical cancer

A prospective, single-arm, multicentre study by Schmeler et al. evaluated conservative surgery in 100 patients with FIGO 2009 stage IA2–IB1 cervical cancer. Surgical approach included conisation and pelvic lymphadenectomy in 44 patients, conisation followed by simple hysterectomy with lymph node assessment in 40 women, and inadvertent simple hysterectomy, followed by lymph node dissection in 16 women. Positive lymph nodes were found in five patients (5%). Residual disease in the post-conisation hysterectomy specimen was noted in 1/40 patients, presenting an immediate failure rate of 2.5%, while three patients developed a recurrence two years after surgery. The authors stated that conservative surgery could be an option for a selected group of patients with early-stage cervical cancer. [3]

A retrospective study by Tamauchi et al. evaluated the outcomes of ovarian stimulation after radical trachelectomy. Thirty cycles in 14 patients were compared to 54 cycles in 30 controls. Compared with the control group, the radical trachelectomy group had significantly lower mean estradiol concentration ($p = 0.029$) during controlled ovarian stimulation cycle and a smaller median number of

retrieved oocytes ($p = 0.007$), despite the higher use of gonadotropin ($p = 0.001$). The authors showed that the response to ovarian stimulation decreases after radical trachelectomy. [4]

A pilot study by Russo et al. assessed the role of MRI in evaluating the response to neoadjuvant chemotherapy, followed by conisation, in 13 patients with tumour size 2–4 cm. MRI was accurate in 11 cases, according to RECIST 1.1, compared to histopathology, with the authors suggesting MRI as a useful tool in the assessment of treatment response in patients with FIGO stage IB2–IIA1 cervical cancer. [5]

Ovarian cancer

A retrospective study by Nitecki et al. evaluated the outcome of the first pregnancy after fertility-sparing surgery for 153 patients with early-stage ovarian cancer, compared to 306 controls. Histologic types included epithelial (55%), germ-cell (37%), and sex-cord stromal (7%). Treatment for ovarian cancer was not associated with preterm birth before 37 weeks of gestation (13.7% vs 11.4%), SGA neonates (11.8% vs 12.7%), severe maternal morbidity (2.6% vs 1.3%), or neonatal morbidity (both 5.9%). The authors concluded that patients who conceived at least three months after surgery for early-stage ovarian cancer did not have an increased risk of adverse obstetric outcomes. [6]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Mismatch repair status influences response to fertility-sparing treatment of endometrial cancer	Chung YS et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/33039397/
2	Management of recurrent endometrial cancer or atypical endometrial hyperplasia patients after primary fertility-sparing therapy	Chen J et al.	Front Oncol	https://pubmed.ncbi.nlm.nih.gov/34568074/
3	ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer	Schmeler KM et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34493587/
4	Reduced response to controlled ovarian stimulation after radical trachelectomy: A pitfall of fertility-sparing surgery for cervical cancer	Tamauchi S et al.	Int J Gynaecol Obstet	https://pubmed.ncbi.nlm.nih.gov/33438209/
5	The role of MRI in cervical cancer > 2 cm (FIGO stage IB2–IIA1) conservatively treated with neoadjuvant chemotherapy followed by conization: a pilot study	Russo L et al.	Radiol Med	https://pubmed.ncbi.nlm.nih.gov/34060027/
6	Outcomes of the first pregnancy after fertility-sparing Surgery for early-stage ovarian cancer	Nitecki R et al.	Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/33957660/

Cancer in pregnancy

Michael J. Halaska

Breast cancer diagnosed during pregnancy belongs to the most common cancer types in the majority of populations. Chemotherapy and surgery have been already well described. As breast tumours in pregnancy are usually diagnosed at an advanced stage disease, modified radical mastectomy and/or neoadjuvant chemotherapy are usually chosen. Breast-conserving surgery (BCS) could be chosen in selected patients but the issue is when it is performed during the first trimester as it should be followed by adjuvant radiotherapy. Blunda et al. evaluated the risk of a delay of radiotherapy in patients operated during the first trimester by BCS. The set of 67 patients was divided into 30 who underwent BCS, while the others underwent radical surgery. The rate of local recurrences as well as dissemination was found to be similar in both groups. Even though it is a non-randomised study it provides information on safety of BCS during the first trimester.

Wu et al. have performed an in-house comparison of 43,132,097 delivery complications between three groups of patients: patients with cancer during pregnancy, with a history of cancer, and without any relation to cancer. Preterm birth was the most common complication, especially in patients with haematologic malignancy (aOR = 1.48, 95% CI: 1.35–1.62); cervical cancer (aOR = 1.47, 95% CI: 1.32–1.63), and breast cancer (aOR = 1.93, 95% CI: 1.72–2.16). Some were related to iatrogenic prematurity. Current haematologic cancer was associated with the risk of peripartum cardiomyopathy (aOR = 12.19, 95% CI: 7.75–19.19), arrhythmia (aOR, 3.82, 95% CI: 2.04–7.15) and postpartum haemorrhage (aOR = 1.31, 95% CI: 1.11–1.54). History of cancer, without current recurrence, was not related with an increased perinatal risks.

Johansson et al. searched the Swedish cancer and birth registry to identify women diagnosed with

cancer at age 15–49 between 1970 and 2018. They identified 121,382 women, from whom 5,079 women had a diagnosis of pregnancy-associated cancer (diagnosed during or within one year after the delivery). The most common cancer types found in Sweden were: malignant melanoma, breast, cervical, thyroid, and central nervous system neoplasms. Increased mortality was found for breast, upper digestive cancer during pregnancy and colon cancer diagnosed within one year after the delivery. In recent years, most survival improved over time.

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Early breast cancers during pregnancy treated with breast-conserving surgery in the first trimester of gestation: A feasibility study	Blundo C et al.	Front Oncol	https://pubmed.ncbi.nlm.nih.gov/34504801/
2	In-hospital complications in pregnant women with current or historical cancer diagnoses	Wu P et al.	Mayo Clin Proc	https://pubmed.ncbi.nlm.nih.gov/34272068/
3	Cancer survival in women diagnosed with pregnancy-associated cancer: An overview using nationwide registry data in Sweden 1970-2018	Johansson ALV et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/34371441/



Hereditary gynaecological cancer

Sara Giovannoni and Ariel Glickman

Schrijver et al. investigated the association between oral contraceptive use and ovarian cancer (OC) risk in an international retrospective study, including 3989 BRCA1 and 2445 mutation BRCA2 carriers. Oral contraceptives were less often used by BRCA carriers with a diagnosis of OC than by unaffected carriers (58.6% vs 88.9% for BRCA1 and 53.5% vs 80.7% for BRCA2). Median duration of use was seven years for BRCA1/2 carriers who developed OC and nine and eight years for unaffected BRCA1 and BRCA2 carriers. For BRCA1 carriers, ever oral contraceptive use was associated with an OC risk reduction (HR 0.51); the reduction increased after a longer duration of use. Duration was found to be a more prominent protective factor than recency of use or starting age (5–9 years of treatment HR 0.54; > 10 years HR 0.32 $p = < 0.001$). The association between duration of use and reduced OC risk persisted for more than 15 years. With BRCA2 carriers, the findings were similar; however, due to the limited study size, the data were less conclusive. Limitations of the study included the potential testing (over-sampling of women with a history of OC and breast cancer) and survival bias. This study confirmed, in a large cohort, the protective role of oral contraceptive use for BRCA1 carriers. [1]

Dominguez-Valentin et al. described the impact of risk-reducing hysterectomy (RRH) and bilateral salpingo-oophorectomy (BSO) on endometrial cancer (EC) and OC in 15,800 women carrying Lynch Syndrome by using the Prospective Lynch Syndrome Database (PLSD). Lynch Syndrome is caused by pathogenic variants of four DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6, PMS2, and risk-reducing hysterectomy and BSO before the age of 40 is recommended for these patients. Women from the PLS database were included in a prospective follow-up. RRH performed at 25 years showed to prevent EC before 50 years in 15%, 18%,

13%, and 0%, respectively, for MLH1, MSH2, MSH6, PMS2 carriers and cancer related death in 2%, 2%, 15, and 0%, respectively. BSO at the age of 25 prevented OC before 50 years in 6%, 11%, 2%, and 0%, respectively, while RRH with 40 years prevented EC by 50 years in 13%, 16%, 11%, and 0%, and OC in 4% ,8%, 0%, and 0%. Risk-reducing surgery performed < 40 years achieved a small benefit related to EC/OC risk and mortality. For pathogenic PMS2 carriers, no demonstrable risk for pre- and postmenopausal EC or OC has been described; therefore, the recommendation for BSO might be the same as for the general population. Limitations of this study include the low numbers of path_MSH6 and path_PMS2 variants which may reflect that they are infrequently identified and referred to genetic testing as well as a potential time bias (elder women might not have had the same option for risk-reducing surgery as offered today). [2]

De Jonge et al. retrospectively investigated 5,980 BRCA1/2 and 8,451 non-BRCA1/2 mutation carriers from the Dutch cohort of the Hereditary Breast and Ovarian cancer study (HEBON) to quantify the risk of EC in BRCA1/2 mutation carriers. EC risk was compared with 1) the general population based on Dutch population-based incidence rates; and 2) non-BRCA1/2 mutation carriers, using Cox-regression analyses, expressed as hazard ratio. Follow-up either started in 1989 or at the age of 25 years (whichever came last) and ended at date of EC diagnosis, last follow-up, or death (whichever came first). Median follow-up was 22.5 years. Overall EC risk in BRCA1/2 mutation carriers was 2.83-fold increased compared with the Dutch EC incidence rates. BRCA1 mutation was associated with a higher relative EC risk (HR 2.91) compared with BRCA2 mutation (HR 1.45). Subgroup analysis showed strongly increased risks for EC with serous-like histology, BRCA1 showing higher HR of 10.48 than BRCA2 (HR 4.13).

The highest HR was observed for p53-abnormal EC in BRCA1 mutation carriers (HR 15.71). Risk for endometrioid EC in BRCA1 mutation carriers was increased twofold (HR 2.01), unlike BRCA2 (HR 0.93). The main limitation of this study was the possibility of a cancer-related testing bias as EC is not an indication for BRCA1/2 testing. Apart from that, if patients included have ever received hormone therapy no information on the type of HT (tamoxifen vs aromatase inhibitor) was given. Overall, this study showed that BRCA1/2 mutation carriers have a two- to threefold increased risk for EC, with highest risk observed for the rare subgroups of serous-like and p53-abnormal EC in BRCA1 mutation carriers. [3]

Graf et al. used the Cancer Genome Atlas Ovarian Cancer database to assess whether copy number variations (CNV) have an impact on prognosis in OC. OC has a wide spectrum and diversity of CNV. A risk score was built based on CNV. In all, 564 patients with serous OC (stages I–IV) diagnosed from 1992 to 2013 were included. Thirteen genome regions with 14 alterations were identified as significantly risk-associated. High-, standard-, and low-risk groups with respective median OS estimates of 2.9, 4.1, and 5.7 years ($p < 0.001$) were defined. Associated five-year survival estimates were 15%, 36%, and 53% for the respective risk groups. The risk score had more discriminatory ability to prognosticate OS than age, clinical stage, grade, and race combined and was strongly additive to significant clinical features ($p < 0.001$). The main limitations of this study were the lack of validation with external data sets and the fact that there have been substantial advancements in therapy since the study period. This trial found that a CNV-based risk score might be superior to OC genomic biomarkers for the prognosis of OS. [4]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Oral contraceptive use and ovarian cancer risk for BRCA1/2 mutation carriers: an international cohort study	Schrijver LH et al.	Am J Obstet Gynecol .	https://pubmed.ncbi.nlm.nih.gov/33493488/
2	Risk-reducing hysterectomy and bilateral salpingo-oophorectomy in female heterozygotes of pathogenic mismatch repair variants: a prospective Lynch Syndrome Database report	Dominguez-Valentin M, Crosbie EJ et al.	Genet Med.	https://pubmed.ncbi.nlm.nih.gov/33257847/
3	Endometrial cancer risk in women with germline BRCA1 or BRCA2 mutations: multicenter cohort study	de Jonge MM et al.	J Natl Cancer Inst.	https://pubmed.ncbi.nlm.nih.gov/33710348/
4	Association of copy number variation signature and survival in patients with serous ovarian cancer	Graf RP et al.	JAMA Netw Open.	https://pubmed.ncbi.nlm.nih.gov/34181012/



Treatment of pre-invasive gynaecological malignancies

Elko Gliozheni

Di Donato et al. conducted a meta-analysis on the impact of adjuvant human papillomavirus (HPV) vaccination to prevent recurrent cervical dysplasia after surgical treatment. They analysed 11 studies that met the inclusion criteria. There were 21,310 patients included, of whom 19% had received a peri-operational adjuvant HPV vaccine while the remaining 81% received surgery alone. They found that the recurrence rate was significantly lower in the vaccinated group for CIN2+ (OR 0.35) and for CIN1+ (OR 0.51) than the only-surgery group, thus concluding that adjuvant HPV vaccination is beneficial. No difference in the HPV persistence rate was observed between the groups. This is a well-designed meta-analysis, representing a level-I evidence leading to a clinically important observation. [1]

Firnhaber et al. aimed to assess whether HPV vaccination prior to Loop electroexcision procedure (LEEP) prevents recurrent high-grade squamous intraepithelial lesions (HSIL) in HIV-positive women. Therefore, they performed a randomized double-blind placebo-controlled trial. They enrolled 180 HIV positive patients diagnosed with HSIL by biopsy, of which 50% received an HPV vaccine (week 0, 4,

26) and the rest a placebo. Colposcopy and cytology were performed at weeks 26 and 52. They found no significant difference between study groups. HSIL recurrence was associated with detection of HSIL at the margins of the LEEP sample. This study concluded that HPV vaccination does not prevent the recurrence of HSIL after LEEP in HIV-positive women. Despite the fact that the study concerns only the group of HIV-positive women, it is a well-designed prospective study amongst few to examine the relative research question. [2]

Chung et al. performed a secondary analysis of a randomised clinical trial to evaluate whether cryotherapy or LEEP is more effective at clearing high-risk HPV (hrHPV) and whether persistent hr-HPV is associated with CIN2+ recurrence among HIV-positive women. Cervical samples were collected and analysed from 354 HIV-positive women with CIN2+ before and after cryotherapy or LEEP. Clearance of hr-HPV was significantly higher amongst the patients who underwent LEEP compared with cryotherapy (OR 1.4) after 24 months. Hr-HPV persistence was also significantly associated with CIN2+ recurrence (OR 4.7) after 12-24 months. Authors concluded

that LEEP was more likely to clear hrHPV than cryotherapy and therefore prevent CIN2+ recurrence in HIV-positive women. Study results are in line with previous studies, including, however, a relatively greater sample size. [3]

Ikeda et al. performed a placebo-controlled, double-blind randomised trial to evaluate the efficacy of HPV16 E7-expressing lactobacillus GBL101c for the treatment of CIN2. They randomised 40 patients with HPV16-positive CIN2 in a group receiving GBL101c for five days at one, two, four, and eight weeks and a group receiving placebo. No statistically significant differences were noted regarding the primary endpoint which was pathological regression after 16 weeks of the first dose. However, only in the GBL101c group, two patients had complete regression within 16 weeks. In these two cases, E7 specific Th1 immune responses were observed at week 16, thus concluding that a novel lactobacillus-based vaccine with stronger immunogenicity than GBL101c should be developed. This is a well-designed trial, highlighting the potential for a novel treatment of CIN2. [4]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Adjuvant HPV vaccination to prevent recurrent cervical dysplasia after surgical treatment: A meta-analysis	Di Donato V et al.	Vaccines (Basel)	https://pubmed.ncbi.nlm.nih.gov/33919003/
2	Human papillomavirus vaccination prior to Loop electroexcision procedure does not prevent recurrent cervical high-grade squamous intraepithelial lesions in women living with human immunodeficiency virus: A randomized, double-blind, placebo-controlled trial	Firnhaber C et al.	Clin Infect Dis	https://pubmed.ncbi.nlm.nih.gov/32975556/
3	Human papillomavirus persistence and association with recurrent cervical intraepithelial neoplasia after cryotherapy vs Loop electrosurgical excision procedure among HIV-positive Women: A secondary analysis of a randomized clinical trial	Chung MH et al.	JAMA Once	https://pubmed.ncbi.nlm.nih.gov/34351377/
4	A placebo-controlled, double-blind randomized (Phase IIB) trial of oral administration with HPV16 E7-expressing lactobacillus, GBL101c, for the treatment of cervical intraepithelial neoplasia grade 2 (CIN2)	Ikeda Y et al.	Vaccines (Basel)	https://pubmed.ncbi.nlm.nih.gov/33915901/

Pathology of gynaecological cancers

Nicolas Samartzis and Dimitrios Rafail Kalaitzopoulos

Based on a prospective analysis of the intestinal microbiome of 55 patients with cervical cancer undergoing chemoradiation, Sims et al. demonstrated that the diversity of gut microbiota is an independent factor in favourable treatment response. Flow cytometry analysis of immune cells from cervical tumours revealed a correlation between high microbial diversity, increased tumour infiltration of CD4+ lymphocytes, and activation of CD4 cells during the course of radiotherapy. While the limitations of the study that can be indicated are the small sample size and lack of patient lifestyle characteristics, the strength of a solid methodology used to assess bacterial community compositional changes should be noted. Based on the statistically significant differences, the authors hypothesised that gut microbiota may modulate radiation response through immunological mechanisms and that optimising the microbiome before radiotherapy might improve treatment efficacy. [1]

The study group of Shi et al. proposed a novel scoring system of endocervical adenocarcinomas. The authors evaluated a tumour budding/nest size grading system (TBNS) for 398 consecutive cases of primary endocervical adenocarcinoma to assess its prognostic value. In the cohort of 94 surgically treated cases, both high tumours budding and small nest size were each associated with reduced

overall survival, disease-specific survival, and disease-free survival. The grading system presented by the authors is stratified into three grades and is independent of patient age, pathologic stage, and lymph node status. Further validation studies are warranted to assess whether the TBNS classification system should be routinely incorporated into clinical decision-making. [2]

Circulating tumour cells have been shown to have prognostic value in various human cancers. Yousefi et al. took advantage of this finding in ovarian cancer. They studied a multi-marker gene panel consisting of EpCAM, MUC1, CEA, HE4, and CA125 mRNAs as surrogate markers for circulating tumour cells in 51 patients with epithelial ovarian cancer measured before and after adjuvant chemotherapy. CEA was the only marker that decreased after chemotherapy. Its expression correlated with tumour stage before chemotherapy ($r = 0.594$, $p = 0.000$), while after chemotherapy it correlated with CA125 antigen ($r = 0.658$, $p = 0.000$), making it the most important indicator of therapy response. The persistence of HE4 mRNA showed the highest sensitivity for advanced stages. Despite the small sample size, these results should be taken into account in future studies targeting non-invasive assays to assess cancer progression and therapeutic efficacy. [3]

Response to rucaparib, an oral PARP inhibitor (PARPi), was evaluated by Swisher et al. in the second part of the international multicentre single-arm, open-label phase II (ARIEL2) study (relapsed, platinum-sensitive/platinum-resistant/refractory high-grade ovarian carcinoma) among heavily pretreated patients. Post hoc exploratory biomarker analyses of patients having 3–4 prior lines of chemotherapy have shown that RAD51C and RAD51D mutations and high-level BRCA1 promoter methylation were predictive of response to rucaparib, similar to BRCA1/BRCA2 mutations. BRCA reversion mutations, as well as described for the first-time loss of BRCA1 methylation were presented as a major cross-resistance mechanism to platinum and PARPi. Accumulation of genomic scarring (as evidence of homologous recombination deficiency in later lines of treatment) was shown to be an irreversible process, persisting even as platinum resistance develops. Therefore, it should be considered a predictive factor of rucaparib response only in platinum-sensitive disease. The authors concluded that introduction of rucaparib, as active treatment, should be considered in earlier lines of therapy, before the emergence of platinum resistance. [4]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Gut microbiome diversity is an independent predictor of survival in cervical cancer patients receiving chemoradiation	Sims TT et al.	Commun Biol	https://pubmed.ncbi.nlm.nih.gov/33619320/
2	Grading of endocervical adenocarcinoma: a novel prognostic system based on tumor budding and cell cluster size	Shi H et al.	Mod Pathol	https://pubmed.ncbi.nlm.nih.gov/34593968/
3	Clinical significance of circulating tumor cell related markers in patients with epithelial ovarian cancer before and after adjuvant chemotherapy	Yousefi M et al.	Sci Rep	https://pubmed.ncbi.nlm.nih.gov/34006887/
4	Molecular and clinical determinants of response and resistance to rucaparib for recurrent ovarian cancer treatment in ARIEL2 (Parts 1 and 2)	Swisher EM, Kwan TT et al.	Nat Commun	https://pubmed.ncbi.nlm.nih.gov/33941784/

Nutrition and perioperative care

Begoña Díaz de la Noval

Matsuo et al. analysed the Laparoscopic Approach to Cervical Cancer (LACC) trial influence on U.S. surgeons. In the post-LACC period, since March 2018, the likelihood of minimally invasive surgery (MIS) decreased by 63% (adjusted OR 0.37, 95% CI: 0.33–0.42) as the perioperative complications increased by 23% (adjusted OR 1.23; 95% CI: 1.08–1.40). By December 2018, radical hysterectomy by laparotomy was used in most surgeries (> 80%) as the Society of Gynecologic Oncology and National Comprehensive Cancer Network practise guidelines have endorsed abdominal radical hysterectomy for early-stage cervical cancer. The main study limitations included the lack of surgical performance, tumour characteristics, use of an ERAS programme, surgeon experience, hospital surgical volume, oncologic outcomes, re-admission, long-term complications, and patient quality of life. [1]

The European Society of Gynaecological Oncology published the guideline for the peri-operative management of advanced ovarian cancer patients undergoing debulking surgery. The guide includes the best evidence and expert agreement on key aspects of peri-operative care and management of complications. [2]

Joshi et al. performed a retrospective analysis of narcotic use after the implementation of an enhanced recovery after surgery (ERAS) protocol in patients undergoing exploratory laparotomy for primary gynaecological cancers (360 patients in the pre-ERAS cohort 2011–2013 and 364 patients in the ERAS cohort 2014–2016). Patients who underwent bowel resections were excluded. Narcotic use was quantified during hospitalisation and 72h postoperatively using oral morphine milligram

equivalents (MME) with standard conversion tables. Compared to the non-ERAS population, the ERAS cohort was more likely to reduce: almost half of postoperative narcotic use ($p < 0.001$), one day in the length of hospital stay ($p < 0.001$), one day earlier return of bowel function ($p < 0.001$), intraoperative use of blood transfusions ($p = 0.008$). The use of a TAP block for multimodal pain control. The rate of 30-day readmissions and postoperative complications did not differ. [3]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Decreasing utilization of minimally invasive hysterectomy for cervical cancer in the United States	Matsuo K et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33992450/
2	European Society of Gynaecological Oncology guidelines for the peri-operative management of advanced ovarian cancer patients undergoing debulking surgery	Fotopoulou C et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34407962/
3	Implementation of an enhanced recovery protocol in gynecologic oncology	Joshi TV et al.	Gynecol Oncol Rep	https://pubmed.ncbi.nlm.nih.gov/34036136/



Quality of life in gynaecological cancers/palliative care

Nadja Taumberger and Engin Çelik

Kiuchi et al. investigated prognostic factors for palliative chemotherapy in recurrent ovarian cancer patients. Thirty-six ovarian cancer patients who died at Dokkyo Medical University from 2014 to 2019 were included. Clinical and laboratory data were obtained before the last chemotherapy. Eight patients (22%) died within 30 days after the chemotherapy regimen. In univariate analysis, neutrophil to lymphocyte ratio (NLR) above median (10.5) represented a hazard ratio of 2.56 (95% CI: 1.27–51.4, $p = 0.008$); modified Glasgow Score above two represented a hazard ratio of 6.90 (95% CI: 1.59–29.94, $p = 0.01$); and prognostic palliative score above median (4.5) represented a hazard ratio of 2.91 (95% CI: 1.41–6.00, $p = 0.004$). In multivariate analysis, no factors were independent prognostic factors for survival. [1]

Mathevet et al. conducted an open-label study in which they included patients with early cervical carcinoma (FIGO 2009 stage IA2–IIA1) who were randomised to SN resection alone (SN arm) or SN and pelvic lymph node dissection (SN + PLND arm).

followed by either a radical hysterectomy or radical trachelectomy. The primary endpoint was defined as morbidity related to the lymph node dissection and the three-year recurrence-free survival was defined as a secondary endpoint. Two hundred and six patients were randomly assigned to the SN arm (105) or SN + PLND arm (101). The lymphatic morbidity was significantly lower in the SN arm (31.4%) than in the SN + PLND arm (51.5%, $p = 0.0046$) as well as postoperative neurological symptoms (7.8% vs 20.6%, $p = 0.01$), although the difference decreased after six months. There was no difference in the three-year recurrence-free survival. [2]

Perrone et al. performed a multicentre prospective observational study including 55 patients with vulvar cancer undergoing palliative electrochemotherapy (ECT) with bleomycin and investigated the impact of ECT on the quality of life using validated questionnaires: visual analogue pain scale, EuroQol 5-Dimension 5-Level (EQ-5D-L5), and Functional Assessment Of Cancer Therapy–Vulva cancer

(FACT-V). Compared to the baseline (6.1 ± 2.1), VAS was significantly reduced at early (4.3 ± 2.5) and late follow-up (4.6 ± 2.8) ($p < 0.0001$) and also the FACT-V score improved significantly at early (9.6 ± 4.0) ($p < 0.0001$) and late follow-up (8.9 ± 4.1) ($p < 0.0054$) as compared to the baseline (7.1 ± 3.6). The authors concluded that ECT in VC is a feasible option based on the favourable outcomes both in terms of response and QoL. [3]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Clinical indicators useful in decision-making about palliative chemotherapy for end-of-life ovarian cancer patients	Kiuchi K et al.	Arch Gynecol Obstet	https://pubmed.ncbi.nlm.nih.gov/34347151/
2	Sentinel lymph node biopsy and morbidity outcomes in early cervical cancer: Results of a multicentre randomised trial (SENTICOL-2)	Mathevet P et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/33773275/
3	Quality of life with vulvar carcinoma treated with palliative electrochemotherapy: The ELECHTRA (ELECTroCHemoTherapy vulvaR cAnCer) study	Perrone AM et al.	Cancers (Basel)	https://pubmed.ncbi.nlm.nih.gov/33915692/



Treatment of elderly patients with gynaecological cancers

Alex Mutombo

In order to identify comorbid conditions and treatment-related factors for poor outcomes in older women with advanced high-grade epithelial ovarian cancer, Mallen et al. conducted a retrospective review which identified 351 patients who underwent cytoreductive surgery (CRS). Patients ≥ 70 years old had higher cumulative Illness rating scale-geriatric (CIRS-G) score (5.9 vs 4.3; $p = 0.0001$), less completion of adjuvant chemotherapy (24% vs 15.1%; $p = 0.049$), less intraperitoneal therapy (18.2% vs 35.5%; $p = 0.002$), less clinical trial participation (16% vs 26.3%; $p = 0.040$), and decreased platinum sensitivity (60% vs 73.7%; $p = 0.012$). They were less likely to have optimal CRS (75% vs 86.9%; $p = 0.007$) and had significantly

worse PFS and OS. The main limitation of this study was its retrospective design which can lead to bias in data collection. Moreover, the study population was predominantly Caucasian (93%) and so not representative of diverse populations. [1]

Wenzel et al. found no improvement in the survival of older women with cervical cancer. In fact, among 21,644 patients diagnosed with cervical cancer between 1989 and 2018, the relative survival for cervical cancer increased over the last three decades. In early cervical cancer, surgery remains the preferred treatment for ages 15–74. Overall, it was applied more often in younger than in older patients (92% in 15–44; 64% in 65–74). Survival remained stable in

75+ (38%–34%; 0.82 [0.66–1.02]). A limitation of this study lies in a disparity between the FIGO and TNM classification on suspected para-aortic lymph nodes. The TNM defines these as non-regional lymph nodes and, therefore, as distant metastasis. This has resulted in a higher metastasis rate than studies using the FIGO classification. [2]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Impact of age, comorbidity, and treatment characteristics on survival in older women with advanced high grade epithelial ovarian cancer	Mallen A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/33812698
2	No improvement in survival of older women with cervical cancer-A nationwide study	Wenzel HHB et al.	Eur J Cancer	https://www.ncbi.nlm.nih.gov/pubmed/33993062



COVID-19 and gynaecological cancers

Jakub Dobroch and Patrick Maguire

Coiffi et al. reported on a survey of the impact of COVID-19 on medical treatment (focusing on chemotherapy and PARP inhibitors) of gynaecological cancer undertaken between November 2020–January 2021, with responses from clinicians affiliated with the MITO group in 49 Italian cancer centres. Screening tests for SARS-CoV-2 were performed at least once a month by 83%. For patients with asymptomatic SARS-CoV-2 infection, mild symptoms, and moderate symptoms, planned chemotherapy was suspended by 83.5%, 83.7%, and 92% of respondents, respectively. [1]

Picardo et al. examined the perception of telemedicine among women undergoing cancer follow-up in an Italian cancer centre, including 78 women with gynaecological cancer, using a 27-question survey. Telemedicine was generally accepted by all women, with younger women and those with higher educational attainment levels having the most positive perception of telemedicine. Women who required 'intensive' follow-up, defined by the authors as those who had received adjuvant chemotherapy or radiotherapy, also found telemedicine acceptable. [2]

Gaba et al. assessed the impact of the pandemic on both training and mental well-being of surgical gynaecological trainees with a questionnaire circulated by national and international organisations May–November 2020. There were 127 responses from 34 countries. A fall in household income was

experienced by 28%. The perception that additional time would be required to complete training was more common among trainees in countries with no national training programme (49% vs 32%). Compared to pre-pandemic mental well-being scores, post-pandemic scores were significantly lower (8.3 vs 7.0, $p < 0.01$). [3]

Knoll et al. reported a 45% decline in newly diagnosed gynaecological cancer patients in a tertiary centre in Austria during the national lockdown compared with the corresponding period of 2019. Analysis of FIGO stage at presentation revealed no significant differences between the two periods. Kaltofen et al. conducted a similar study in a German academic centre which showed a 10% decrease in newly diagnosed gynaecological cancers from January–July 2020 when compared to the first six months of 2019. In contrast to Knoll's study, a tendency towards higher FIGO stage at presentation was observed. [4-5]

Goenka et al. conducted a retrospective study examining ovarian cancer treatment delay and patients' compliance during the pandemic in India. The study found that the time from diagnosis to treatment onset was significantly longer among patients who were admitted during the national lockdown in 2020. Moreover, among 38 patients suitable for upfront surgery, almost half of them did not undergo the procedure due to organisational issues related to the pandemic,

including operating theatre closure or patients' transportation difficulties. During the pandemic, only a minority of patients completed the recommended six cycles of adjuvant chemotherapy. [6]

A comprehensive, prospective analysis performed by the international COVIDSurg Collaborative found a correlation between the degree of COVID-related national restrictions and a tendency toward surgery delay or cancellation. In some types of tumours, including gynaecological malignancies, an increased use of neoadjuvant chemotherapy instead of primary surgery was observed, with pandemic-related issues cited as one of the reasons for this change in practice. [7]

Relevant articles retrieved March 31, 2021 – September 30, 2021

No	Title	Authors	Journal	Link to abstract
1	Impact of COVID-19 on medical treatment patterns in gynecologic oncology: a MITO group survey	Cioffi R et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34426526/
2	Oncophone20 study: Patients' perception of telemedicine in the COVID-19 pandemic during follow-up visits for gynecological and breast cancers	Picardo E et al.	Int J Gynaecol Obstet	https://pubmed.ncbi.nlm.nih.gov/34258764/
3	Impact of SARS-CoV-2 on training and mental well-being of surgical gynecological oncology trainees	Gaba F et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/34326158/
4	The impact of COVID-19 pandemic on the rate of newly diagnosed gynecological and breast cancers: a tertiary center perspective	Knoll K et al.	Arch Gynecol Obstet	https://pubmed.ncbi.nlm.nih.gov/34559295/
5	Changes in gynecologic and breast cancer diagnoses during the first wave of the COVID-19 pandemic: analysis from a tertiary academic gynecologic center in Germany	Kaltofen T et al.	Arch Gynecol Obstet	https://pubmed.ncbi.nlm.nih.gov/34491417/
6	The "collateral damage" of the war on COVID-19: impact of the pandemic on the care of epithelial ovarian cancer	Goenka L et al.	Med Oncol	https://pubmed.ncbi.nlm.nih.gov/34581889/
7	Effect of COVID-19 pandemic lockdowns on planned cancer surgery for 15 tumour types in 61 countries: an international, prospective, cohort study	COVIDSurg Collaborative	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/34624250/

List of contributors, acknowledgements

Achimas-Cadariu, Patrick	University Of Medicine And Pharmacy Iuliu Hatieganu Cluj, Ion Chiricuta Cancer Center, Cluj-Napoca, Romania
Bartnik, Pawel	2 nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland
Betoret, Rubén	Hospital Universitario del Vinalopó, Elche, Spain
Bobirski, Marcin	1 st Chair and Department of Gynaecolgical Oncology and Gynaecology, Medical University of Lublin, Lublin, Poland
Çelik, Engin	Faculty of Medicine, Istanbul University, Istanbul, Turkey
Díaz de la Noval, Begoña	Gynaecology and Obstetrics Department Hospital Universitario Central de Asturias, Oviedo, Spain
Dobroch, Jakub	Department of Gynecology and Gynecologic Oncology, University Oncology Center, Medical University of Bialystok, Bialystok, Poland
El Hajj, Houssein	Oscar Lambret Institute, Lille, France
Gasimli, Khayal	Goethe University Frankfurt, Department of Gyneacology and Gyneacological Oncology, Frankfurt am Main, Germany
Giovannoni, Sara	Policlinico Sant'Orsola Malpighi, Bologna, Italy
Glickman, Ariel	Hospital Clínic Barcelona, Barcelona, Spain
Gliozheni, Elko	Materniteti Koco Gliozheni, Tirana, Albania
Gutic, Bojana	Oncology Institut of Vojvodina and Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
Halaska, Michael	3 rd Medical Faculty, Charles University in Prague and Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic
Ilin, Anton	Hadassah Medical Moscow, Moscow, Russian Federation
Kacperczyk-Bartnik, Joanna	2 nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland
Kahramanoglu, Ilker	Emsey Hospital, Department of Gynecologic Oncology, Istanbul, Turkey
Kalaitzopoulos, Dimitrios Rafail	University Hospital of Zurich, Zurich, Switzerland
Karaman, Erbil	Yuzuncu yil University, Medical faculty, Department of Obstetrics and Gynaecology, Division of Gynaecologic Oncology, Van, Turkey
Kubelac, Paul	Department of Medical Oncology, the Oncology Institute „Prof. Dr. Ion Chiricuță”, Cluj-Napoca, Romania
Lindemann, Kristina	Department of Gynaecological Cancer, Division of Cancer Medicine, Oslo University Hospital, Norway and Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
Maguire, Patrick J	St James's Hospital, Dept Gynaecological oncology, Dublin, Ireland
Margioula-Siarkou, Chrysoula	2 nd Department of Obstetrics and Gynaecology, Ippokrateion General Hospital of Thessaloniki, Thessaloniki, Greece
Mutombo, Alex	Kinshasa University Hospital, Department of Obstetrics and Gynecology, Kinshasa, Democratic Republic of Congo
Oliver, Maria de los Reyes	Hospital Universitario 12 de Octubre, Madrid, Spain
Pardal, Catarina	Hospital de Braga, Braga, Portugal
Petousis, Stamatis	2 nd Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Thessaloniki, Greece

