LiFE report
Literature for ENYGO

LiFE | Literature for ENYGO

Reviews covering publications from September 30, 2020 – March 31, 2021

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Dear LiFE readers,

A year and a half after the start of the pandemic, the world appears to be slowly recovering. More and more people are being vaccinated, and the future seems to be bright again. Hopefully, the situation we all must live in will empower us and help us appreciate our daily routines, like having a coffee with a colleague at a conference.

Despite all these challenges, we are happy to announce that our team was able to finalise LiFE 13. This edition includes reviews of the most important publications in the field of gynaecological oncology published between September 30, 2020, and March 31, 2021. LiFE is an initiative of ENYGO supported by ESGO.

This issue has a new temporary chapter entitled "COVID-19 and gynaecological cancers." Jakub Dobroch (Poland) and Patrick Maguire (Ireland), our new contributors, reviewed all articles published on this topic from the start of the pandemic until the end of March this year. Thank you, and welcome to the team.

We also want to express our sincere gratitude to Anna Maria Schütz (Austria) and Stamatios Petousis (Greece), who recently joined the editorial team, as well the people who are usually behind the scenes – Helena Opolecka, Beth Green, and Tomáš Grünwald. Their ongoing effort and enthusiasm have made it possible for this issue to be on the screens of your devices now. We thank all ENYGO members who share the content of each issue with their colleagues. In addition, we acknowledge our continued collaborators – the *International Journal of Gynecological Cancer* – who help us to add visibility to our project.

The LiFE editors also encourage you to attend the upcoming ESGO Congress. This can't-miss event will be held October 23–25, 2021, in Prague, Czech Republic. This year you have a chance to join the event both virtually and onsite.

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

Thank you once again for staying with us and supporting this great project. We also hope you will find LiFE 13 informative.

Yours,

The LiFE Editors

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

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Ilker Selçuk

Neoadjuvant chemotherapy

A post-hoc exploratory analysis of ICON-8, a randomised (1:1:1), phase III, international, multi-centre trial, was published by Morgan et al. ICON-8 evaluated response to neoadjuvant chemotherapy (NACT) using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST) and CA125. They compared three arms of NACT and reported that the use of weekly dose-dense chemotherapy in the first-line setting of primary ovarian cancer did not provide any benefit in progression-free survival (PFS) in European ethnicity and delayed primary surgery was not inferior to primary surgery in terms of PFS. This post-hoc analysis included only women that had received NACT followed by delayed primary surgery and the aim was to evaluate RECIST and / or CA125 responses and compare them with the extent of surgical cytoreduction. All three groups of chemo-therapy were combined. The median follow-up was 29.5 m (IQR 15.5–54.3 m). Of 564 women who had RECIST-evaluable disease after NACT, 62% had a RECIST complete or partial response and 32% had stable disease. The median PFS was 14.4 m for patients with a complete/partial response and 13.3 m for those with stable disease. Complete cytoreduction (R0) was achieved in 56% of women with complete/partial response and in 42% with stable disease, resulting in a significantly lower R0 resection rate ($p = 0.004$) for the second cohort. In all, 727 women were evaluable by CA125 criteria, with 84% reporting a response. The median PFS was 13.8 m for patients with and 9.7 m for those without CA125 response. R0 was achieved in 50% with and 30% without CA125 response. Delayed primary surgery was not performed in 11% with and 40% without CA125 response. It is worth mentioning that PFS was defined differently in the main trial and the post-hoc analysis (starting with the date of first randomisation vs the date of presurgical planning radiological tumour assessment, which occurred during cycle 3 or 4 of NACT). Therefore, survival outcomes using the landmark analysis for the post-hoc analysis are approximately two months shorter than those reported in the intention-to-treat primary efficacy analysis.

The results of this post-hoc analyses showed that 62% had RECIST complete/partial response after NACT, a lower number than often quoted, and that response to RECIST criteria and CA125 level should not preclude DPS. The decision on surgery should be based on the patient's clinical capacity (performance status and comorbidities) and, of course, the surgical feasibility.

Limitations of this study were that only patients with complete data on RECIST and CA125 responses were included, which might lead to a bias regarding PFS; apart from that, the BRCA status of the enrolled patients is unknown, which might be interesting as BRCA mutated tumours are often highly sensitive to platinum-based chemotherapy. [1]

PARP inhibitors

A meta-analysis by Lin et al. evaluated the role of maintenance PARP inhibitors (PARPi) in the setting of newly diagnosed advanced ovarian carcinoma in terms of PFS. Phase III trials that were settled on primary or interval debulking surgery and platinum-based chemotherapy were included. SOLO1; olaparib vs placebo with a median PFS of 49.9 versus 13.8 m, PRIMA; niraparib versus placebo with a median PFS of 13.8 versus 8.2 m in over a period of 13.8 m of follow-up, VELIA; veliparib versus placebo with a median PFS of 23.5 versus 17.3 m in over a 28 m follow-up and PAOLA-1; olaparib + bevacizumab versus placebo + bevacizumab with a median PFS of 22.1 vs 16.6 m in 22.7 m of follow-up. This meta-analysis showed the benefit of PARPi on PFS in BRCA-mutated patients with a hazard ratio of 0.35 (95% CI: 0.29–0.42, $p < 0.00001$, with no heterogeneity), in BRCA non-mutated patients with a hazard ratio of 0.72 (95% CI: 0.63–0.82, $p < 0.00001$, with no heterogeneity), in homologous-recombination-deficiency- (HRD-) positive patients with a hazard ratio of 0.43 (95% CI: 0.32-0.60, $p < 0.00001$, with heterogeneity) and in HRD-negative patients with a hazard ratio of 0.83 (95% CI: 0.70–0.99, $p < 0.04$, with little heterogeneity). Additionally, the hazard ratio was 0.53 (95% CI: 0.40–0.71, $p < 0.0001$, with heterogeneity) in the whole population. Overall, the greatest advantage of PARPi was reported in women with BRCA mutations followed by HRD-positive women during the maintenance setting of newly diagnosed ovarian carcinoma. [2]

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No	Title	Authors	Journal	Link to abstract
1	Objective responses to first-line neoadjuvant carboplatin-paclitaxel regimens for ovarian, fallopian tube, or primary peritoneal carcinoma (ICON8): post-hoc exploratory analysis of a randomised, phase 3 trial	Morgan RD et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/33357510/
2	PARP inhibitors as maintenance therapy in newly diagnosed advanced ovarian cancer: a meta-analysis	Lin Q et al.	BJOG	https://pubmed.ncbi.nlm.nih.gov/32654312/

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Surgical treatment of primary and recurrent ovarian cancer

Ilker Kahramanoglu and Patriciu Achimas-Cadariu

Primary surgery or neoadjuvant chemotherapy in advanced ovarian cancer

Coleridge et al. performed a meta-analysis comparing primary debulking surgery followed by chemotherapy and neoadjuvant chemotherapy (NACT) followed by interval debulking surgery in patients with advanced epithelial ovarian cancer. Five randomised controlled trials were included. There was no significant difference in overall survival (OS) (HR 0.95, 95% CI: 0.84–1.07; I2=0%) and progression-free survival (PFS) (HR 0.97, 95% CI: 0.87–1.07; I2=0%) between these two cohorts. The risk of haemorrhage was similar between both groups (RR 0.99, 95% CI: 0.25–3.89; I2=84%). Fewer events of venous thromboembolism (RR 0.28, 95% CI: 0.09–0.90; I2=15%), infection (RR 0.30, 95% CI: 0.16–0.56; I2=0%), stoma creation (RR 0.43, 95% CI: 0.26–0.72; I2=0%), and bowel resection (RR 0.49, 95% CI: 0.26–0.92; I2=67%) were reported in the NACT group. The risk of peri-/post-operative mortality within a month after surgery was higher in the primary debulking surgery group (RR 0.18, 95% CI: 0.06–0.54; I2=0%). Overall, questions in first-line treatment of advanced ovarian cancer still remain. The results of the TRUST trial are awaited. [1]

Narasimhulu et al. developed a triage algorithm to reduce postoperative morbidity and mortality after primary debulking surgery. According to this algorithm, patients who had one of the following three criteria were regarded as high risk for surgical morbidity and mortality and were offered NACT: 1. albumin < 3.5 g/dL, 2. age ≥ 80, 3. age 75–79 + one of the following: ASA score 3–4, stage IV disease, expectation of complex surgery (multiple liver parenchymal or lung metastasis). Of 334 patients, those with no high risk (232; 69.5%) were triaged to primary debulking surgery and those with high risk (102; 30.5%) received NACT. Complete cytoreduction (62.5% vs 66.7% for the primary debulking surgery vs interval debulking cohort, p = 0.47), postoperative 30-day grade 3–4 morbidity (18.3% vs 12.9%, p = 0.22) and 90-day mortality (2.2% vs 3.8%, p = 0.42) were comparable between both groups. In addition, short-term outcomes such as ICU stay, length of hospitalisation, and timing of adjuvant chemotherapy were similar. This study showed the potential use of an algorithm in order to decide on the timing of cytoreductive surgery. [2]

Secondary surgery in advanced ovarian cancer

Shi et al. presented the results from the SOC-1 trial, a randomised phase III trial comparing secondary debulking surgery followed by chemotherapy versus chemotherapy alone in patients with a first platinum-sensitive relapse. The iMODEL score, which was based on FIGO stage, residual disease after primary debulking, platinum-free interval, ECOG performance status, current CA125 level, and presence of ascites was used together with a PET-CT scan to assess patients eligible for surgery. In all, 357 patients were randomly assigned to no surgery (n = 175) or surgery (n = 182), with a complete cytoreduction being achieved in 77%. Targeted maintenance therapy was allowed, with 10% receiving bevacizumab and 16% PARP inhibitors in subsequent lines. Median follow-up was 36.0 months. Progression-free survival and OS were co-primary endpoints. The surgery group had a longer progression-free period compared to the chemotherapy group (17.4 vs. 11.9 months; HR 0.58; 95% CI: 0.45–0.74; p < 0.001). Data for the OS group was immature, however. The interim analysis revealed no significant difference between the surgery and chemotherapy groups (58.1 vs. 53.9 months; HR 0.82; 95%CI 0.57-1.19). The worst median OS was reported on patients with incomplete resection, highlighting the importance of appropriate patient selection for surgery. [3]

The three currently published randomised clinical trials (DESKTOP III, GOG-0213, SOC-1) on secondary debulking surgery followed by chemotherapy versus chemotherapy alone were compared in a systematic review and meta-analysis. Altogether, 1,250 patients were included. Results showed that secondary cytoreductive surgery resulted in a significant PFS advantage (HR 0.69; 95% CI: 0.61–0.78; p < 0.001). OS was similar among study arms (HR 0.93; 95% CI: 0.78–1.10; p = 0.37); however, a survival advantage was seen in the surgery arm for the subpopulation that had complete resection (HR 0.73; 95% CI: 0.59–0.91; p = 0.004). Of note, the included studies showed heterogeneity regarding the surgical expertise of the included centres and the selection of patients eligible for surgery and maintenance therapy with bevacizumab and PARP inhibitors, all factors that might have an impact on OS data. [4]

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No	Title	Authors	Journal	Link to abstract
1	Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer	Coleridge SL et al.	Cochrane Database Syst Rev	https://pubmed.ncbi.nlm.nih.gov/33543776/
2	Appropriate triage allows aggressive primary debulking surgery with rates of morbidity and mortality comparable to interval surgery after chemotherapy	Narasimhulu DM et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33390326/
3	Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): a multicentre, open-label, randomised, phase 3 trial	Shi T et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/33705695/
4	The role of secondary cytoreductive surgery in recurrent ovarian cancer: a systematic review and meta-analysis	Marchetti C et al.	Ann Surg Oncol	https://pubmed.ncbi.nlm.nih.gov/33067742/

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Medical treatment of recurrent ovarian cancer

Seda Şahin Aker and Mara Mantiero

The ENGOT-OV16/NOVA trial, a double-blind, randomised, placebo-controlled phase III trial on niraparib in 553 patients with recurrent ovarian cancer, published data on long-term safety. Patients were randomly assigned to 300 mg niraparib daily or placebo and were divided into a germline BRCA mutation (n = 203) and non-gBRCAmut (n = 350) cohort. Results from the trial showed a prolonged progression-free survival (PFS) of 21.0 versus 5.5 months for niraparib in the gBRCA-cohort (and 9.3 vs 3.9 months for the non-gBRCAmut group). Approximately 20% of patients received niraparib for ≥ 2 years. For the treatment group, dose reductions were required in 34%, 27%, and 20% in months 1, 2, and 3, respectively. Treatment emergent adverse events were reported in < 5% across all time intervals, occurred early, were well manageable by dose reduction, and decreased over the first three months. Maintenance with niraparib was generally well tolerated, especially with adequate early dose modifications and was safe for long-term use. [1]

The NORA trial evaluated the efficacy and safety of maintenance therapy with niraparib in a randomised, double-blind, phase III study in platinum-sensitive recurrent ovarian cancer in 30 centres in China. Two hundred and sixty-five eligible patients were randomised (2:1) to niraparib (n = 177) or placebo (n = 88) and were stratified by BRCA mutation. Patients with a bodyweight < 77 kg or a platelet count < 150,000/μL received 200 mg/day niraparib instead of 300 mg/day after a protocol amendment (200 mg or matched placebo n = 235; 300 mg or matched placebo before, n = 14; and after the amendment, n = 16). Median PFS was significantly longer for the niraparib cohort with 18.3 vs. 5.4 months (HR 0.32; 95% CI: 0.23–0.45; p < 0.000), regardless of BRCA mutation status (germline BRCA mutation; HR 0.22; 95% CI: 0.12–0.39; no BRCA mutation; HR 0.40; 95% CI: 0.26–0.61). The chemotherapy-free interval was 18.5 vs 9.7 months (HR 0.34; 95% CI: 0.24–0.48; p < 0.0001) and median time to first-subsequent treatment was 16.7 vs 7.7 months (HR 0.35; 95% CI: 0.25–0.49; p < 0.0001) for the niraparib versus placebo cohort. Longer median progression free-survival and lower rates of haematological adverse events were shown in the NORA trial than the NOVA trial (300 mg niraparib vs placebo). The lower rate of adverse events might be related to the better tolerability of the individualised starting dose. The most common adverse events were haematological events and nausea. One treatment-related fatal acute leukaemia was reported in the niraparib group. The limitations of this study were the relatively high rate of germline BRCA mutations in the study group, the change of dosing within the ongoing trial, as well as absent information about homologous recombination deficiency status and quality of life data. [2]

Zsiros et al. evaluated the efficacy of pembrolizumab in combination with bevacizumab and oral metronomic cyclophosphamide in a single-arm, non-randomised, phase II trial in recurrent platinum-sensitive, platinum-resistant, or refractory epithelial ovarian cancer. Forty patients received 200 mg pembrolizumab, 15 mg/kg bevacizumab q3w, and 50 mg oral cyclophosphamide daily during a 21-day cycle. The mean age was 62.2 years. Median PFS was 10.0 months (90% CI: 6.5–17.4). Complete, partial response, and stable disease were reported in three (7.5%), 16 (40.0%), and 19 women (47.5%), respectively, resulting in an overall response rate of 47.5%. Clinical benefit was reported in 38 patients (95.0%). DOR was 5.9 months for patients who achieved clinical benefit and 8.3 months for patients who showed partial/complete response. For platinum-resistant patients, the overall response rate was 43.3% with a median PFS of 7.6 months versus 60.0% and 20.2 months for the platinum-sensitive cohort. BRCA-positive and BRCA-negative patients had an overall response rate of 71.4% versus 30.4% (p = 0.02). Baseline PD-L1 status was measured in 36 patients, with 19 (47.5%) being anti PD-L1 positive and having an overall response rate of 52.6% versus 35.3% for PD-L1–negative patients (p = 0.34), with no difference in PFS (p = 0.13). Patients who received ≤ 3 lines of prior chemotherapy had significantly better progression-free (10.8 vs 6.5 months; p = 0 .03) and overall survival (OS) (26.1 vs. 12.5 months; p = 0.03) compared with those having ≥ 3 prior lines of treatment. In this study, only dose interruption was allowed, not dose reduction. Four patients (10%) discontinued the most common ≥ grade 3 adverse events were lymphocytopenia and bevacizumab-induced hypertension. Limitations of this study included the lack of a comparison arm and the small cohort with a heterogenous tumour histology. [3]

Low-grade serous ovarian carcinomas (LGSOCs), a rare tumour entity which is known for low chemotherapy responses, expresses MAPK pathway alterations (most commonly KRAS/BRAF) in about 30–60% of cases. Monk et al. evaluated the efficacy of binimetinib, an oral potent MEK1/2 inhibitor, in recurrent or persistent LGSOCs (n = 303) who had received ≥ 1 ≤ 3 prior lines of chemotherapy in the MILO/ENGOT ov11 trial. It was a 2:1 randomised, prospective, phase III study of binimetinib (45 mg twice daily) versus physician's choice chemotherapy (PCC). The primary endpoint was PFS, which was not met (median PFS was 9.1 months vs 10.6 for binimetinib and PCC, respectively), resulting in an early study closure. However, a post hoc analysis suggests a possible association between KRAS mutation, present in 33% of the included patients, and response to binimetinib; with a PFS of 17.7 versus 10.8 months for binimetinib. The overall response rate (complete response/partial response) was 16% versus 13%; median DOR was 8.1 months versus 6.7 months and median OS was 25.3 versus 20.8 months for binimetinib and PCC, respectively. The most common grade 3 adverse event was increased blood creatine kinase level.

An important limit of the study was the unselected patient populations in terms of biomarkers for response. Apart from that, response to chemotherapy was better than expected from previous trials. In spite of the early trial closure, binimetinib showed response in patients with KRAS mutation and should therefore be further investigated in this cohort. [4]

Lheureux et al. evaluated the efficacy of adavosertib, a Wee1 inhibitor, in combination with gemcitabine in a double-blind, randomised, placebo-controlled, phase II trial in patients with recurrent platinum-resistant or refractory high-grade serous ovarian cancer. Wee1 kinase is a crucial regulator of the G2/M checkpoint, which is alternated in TP53 mutated tumours as HGSOC. Ninety-nine patients were randomly assigned (2:1) to adavosertib + gemcitabine (n = 65) or placebo + gemcitabine (n = 34). Twenty-five patients with non-high-grade serous ovarian cancer were enrolled in an exploratory cohort. Patients received gemcitabine i.v. (1000 mg/m² on days 1, 8, and 15) with either oral adavosertib (175 mg) or placebo on days 1, 2, 8, 9, 15, and 16, in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was PFS; secondary endpoints were response rate, OS after one year of follow-up, safety, and tolerability. Median age was 62 years. Median PFS was 4.6 months versus 3.0 months for the adavosertib group (HR 0.55; 95% CI: 0.35–0.90; p = 0.015).

Medical treatment of recurrent ovarian cancer

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The exploratory analysis of PFS without censoring patients at the date of treatment discontinuation showed similar results (p = 0.007). Median OS at the time of data cut-off was 11.4 versus 7.2 months (HR 0.56; 95% CI: 0.35–0.91; p = 0.017) and 23% versus 6% (p = 0.038) reported a partial response according to RECIST 1.1 when comparing adavosertib to placebo. All assessed subsets of TP53 mutations derived clinical benefit from the addition of adavosertib to gemcitabine. The most common adverse events were haematological events and fatigue. There were no treatment-related deaths. The limitations of the study include the randomisation approach, the small sample size, resulting potentially in numerical differences in BRCA mutation status between the two cohorts, and missing information on BRCA status in approx. 30% of the study cohort, as well as the absence of quality of life data. Larger confirmatory studies are required. [5]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: Results from the phase III ENGOT-OV16/NOVA trial	Mirza MR et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32981695/
2	Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial	Wu XH et al.	Ann Oncol	https://pubmed.ncbi.nlm.nih.gov/33453391/
3	Efficacy and safety of pembrolizumab in combination with bevacizumab and oral metronomic cyclophosphamide in the treatment of recurrent ovarian cancer: a phase 2 nonrandomized clinical trial	Zsiros E et al.	JAMA oncol	https://pubmed.ncbi.nlm.nih.gov/33211063/
4	MILO/ENGOT-ov11: binimetinib versus physician's choice chemotherapy in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum	Monk BJ et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/32822286/
5	Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial	Lheureux S et al.	Lancet	https://pubmed.ncbi.nlm.nih.gov/33485453/

Borderline ovarian tumours

Anton Ilin

The French National College of Obstetricians and Gynecologists updated its borderline ovarian tumour treatment guidelines. The guidelines are separated into two parts: Part 1 Epidemiology, biopathology, imaging, and biomarkers and Part 2 Surgical management, follow-up, hormone replacement therapy, fertility management, and preservation. The guidelines cover all aspects of borderline ovarian tumour diagnostic and treatment tools and mostly correlate with European and USA recommendations. [1, 2]

Conservative treatment of borderline tumours became a subject of immediate interest in the last decade. Much data is published on the early stages of the disease but information about locally advanced/advanced tumours is insufficient. Gouy et al. presented data about the conservative treatment of patients with stage II–III serous borderline ovarian tumours. Sixty-five cases were analysed. The recurrence rate was 58% (n = 38). The authors concluded that conservative treatment compared with radical treatment has worse results in terms of progression-free survival but without any impact on overall survival. [3]

Spaan et al. analysed the correlation between assisted reproductive technology and ovarian cancer and the incidence of borderline tumours. The national cohort study comprised 30,625 women who received ovarian stimulation for assisted reproductive technology. The median follow-up was 24 years. During this period, 158 ovarian cancer cases and 100 borderline ovarian tumours occurred. It was found that ovarian cancer risk was higher in the assisted reproductive technology group compared with the general population (standardised incidence ratio 1.43, 95% CI: 1.18–1.71). Borderline ovarian tumour risk was also increased in the assisted reproductive technology group (standardised incidence ratio 2.20, 95% CI: 1.66–2.86 vs HR 1.84, 95% CI: 1.08–3.14). Nevertheless, the authors concluded that increased risk was more associated with nulliparity than assisted reproductive technology treatment because no dose-response relationship was observed. [4]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Borderline ovarian tumors: French guidelines from the CNGOF. Part 1. Epidemiology, biopathology, imaging and biomarkers	Huchon C et al	J Gynecol Obstet Hum Reprod	https://pubmed.ncbi.nlm.nih.gov/33160106/
2	Borderline ovarian tumors: French guidelines from the CNGOF. Part 2. Surgical management, follow-up, hormone replacement therapy, fertility management and preservation	Bourdel N et al.	J Gynecol Obstet Hum Reprod	https://pubmed.ncbi.nlm.nih.gov/33144266/
3	Results after conservative surgery of stage II/III serous borderline ovarian tumors	Gouy S et al.	Ann Surg Oncol	https://pubmed.ncbi.nlm.nih.gov/33140251/
4	Long-term risk of ovarian cancer and borderline tumors after assisted reproductive technology	Spaan M et al.	J Natl Cancer Inst	https://pubmed.ncbi.nlm.nih.gov/33769500/

Treatment of ovarian sex cord stromal and germ cell tumours

Natalia Rodriguez Gómez-Hidalgo

A study from Wang et al. evaluated the therapeutic role of lymphadenectomy in patients with malignant ovarian germ cell tumour (MOGCT). Data from a total of 2,424 patients with MOGCT and information on lymph node status were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. In the entire cohort, 70.6% of patients had FIGO stage I disease and 46.2% received lymphadenectomy. As for histology, 10-year overall survival (OS) was 98.0% for dysgerminoma, 95.4% for struma ovarii, 92.4% for teratoma, 89.7% for mixed GCT, 88.7% for endodermal sinus tumour, and 46.0% for embryonal carcinoma. A subgroup analysis on lymphadenectomy showed that in children (0–14 years) OS was not improved ($p > 0.05$), whereas lymphadenectomy was favourable ($p < 0.05$) for adult patients (20–39 years). Patients ≥ 40 years had the best survival rate when having ≥ 21 lymph nodes resected ($p = 0.044$). The role of lymphadenectomy varies regarding histology; with improved survival rates in dysgerminoma and endodermal sinus type. For teratomas, lymphadenectomy (≥ 21 RLNs) had no effect on short-term survival but it tended to benefit long-term survival. Limitations of this study include the accuracy of histopathologic diagnosis and the lack of information on adjuvant chemotherapy after initial surgery. [1]

An international multicentre study that investigated the safety of surveillance versus adjuvant chemotherapy in stage IA–C immature teratomas of any grade was published by Bergamini et al. Of 108 included post-pubertal patients, 61.1%, 2.8%, and 36.1% had FIGO stage IA, IB, and IC, respectively, with 28.7%, 38%, and 33.3% having G1, 2, and 3 disease, respectively. After surgery, 27 patients (25%) received adjuvant chemotherapy and 81 (75%) received surveillance only. The median time to relapse was 17.8 months (range 3–47). None of the patients with recurrence had a G1 tumour at primary diagnosis. There was no significant difference regarding the risk of relapse (G2–3 immature teratoma; 9/81 vs 2/27; $p = 0.72$), progression-free survival, or OS for the surveillance versus the chemotherapy cohort. A lower tumour grade and complete surgical staging were independent prognostic factors for prolonged progression-free survival. The type of surgical approach, surveillance, or stage were not associated with an increased risk of recurrence. Limitations of this study included its retrospective nature, case ascertainment bias, and the comparatively small number of cases in the surveillance cohort. Nevertheless, this study represents one of the largest retrospective data collections of post-pubertal patients with this rare tumour entity. According to these results, appropriate complete surgical staging followed by surveillance, including negative postoperative tumour markers, is recommended for FIGO stage I patients. Systemic treatment should be reserved to treat recurrent disease. [2]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	The individualized significance of lymphadenectomy across all age groups and histologies in malignant ovarian germ cell tumors	Wang J et al.	Arch Gynecol Obstet	https://pubmed.ncbi.nlm.nih.gov/32888090
2	Can we replace adjuvant chemotherapy with surveillance for stage IA-C immature ovarian teratomas of any grade? an international multicenter analysis	Bergamini A et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/32763784

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

Anna-Maria Schütz

Phase I

Rubinstein et al. investigated the safety and tolerability of selinexor, a selective nuclear export inhibitor, in combination with paclitaxel and carboplatin in patients with advanced ovarian or endometrial cancer in an open-label phase I, 3+3 dose-escalation study. Twenty-three patients (5 serous ovarian cancer, 18 endometrial cancer, 6 carcinosarcomas) were administered to one of four regimens (selinexor at 30 mg/m^2 or 60 mg flat dose + carboplatin at AUC 5 and paclitaxel at 175 mg/m^2 or 80 mg/m^2, respectively) for six to 10 cycles followed by selinexor as a maintenance therapy. Ovarian cancer patients had previously received one platinum-based therapy, whereas endometrial cancer patients had either received one prior platinum-based therapy or were chemo-naïve. A 60 mg flat dose of selinexor weekly with either dosing schedule of carboplatin/paclitaxel was established as recommended phase II dose. Treatment-related adverse events (TRAEs) grade 1 to 4 occurred in > 20% of patients, most commonly thrombocytopenia (100%), leukopenia (91%), and hyperglycaemia (87%). The most common grade 3 to 4 TRAEs were leukopenia (70%), neutropenia (70%), lymphopenia (61%), anaemia (57%), and alanine transaminase increase (43%). One treatment-related dose-limiting toxicity occurred, which was a grade 3 syncope. Twelve patients achieved a partial and one achieved a complete response. Overall, this combination appeared safe and tolerable, although attribution of toxicities was challenging as some toxicities were overlapping for carboplatin, paclitaxel, and selinexor. [1]

A multicentric, open-label phase Ib study on safety and clinical activity of atezolizumab, a PD-L1 antibody, combined with bevacizumab in patients with platinum-resistant ovarian cancer was performed by Moroney et al. Twenty patients received 1,200 mg atezolizumab and 15 mg/kg bevacizumab i.v. q3w. The primary endpoint was safety; secondary endpoints were overall response rate, duration of response, progression-free survival (PFS), and overall survival (OS). Apart from that, exploratory biomarkers were evaluated. TRAEs were reported for 19 patients (95%), with seven (35%) having grade 3–4 events, most commonly bowel obstruction, nausea, hypertension, and hyponatremia. No grade 5 events occurred. The safety profile of atezolizumab + bevacizumab was consistent with those of the individual agents. Two patients (10%) discontinued treatment due to pneumonitis and small bowel obstruction. The overall response rate was 15%; three patients had partial responses with a duration of 11.3 to 18.9 months. Stable disease was seen in eight patients (40%) with a disease control rate of 55%. Median duration of response was not reached (95% CI: 11.3–not reached). Median PFS was 4.9 months (range 1.2–20.2) and median OS was 10.2 months (range 1.2–26.6). In this small cohort, no association between treatment response and PD-L1 expression, tumour mutational burden, BRCA 1 or 2 mutation, tumour histology, or the number of prior therapies was seen. In summary, the combination of atezolizumab + bevacizumab showed safety profiles that were consistent with those of each single agent. Despite modest overall response rate and PFS, the disease control rate of 55% and the prolonged duration of response were encouraging for further investigation of the combination of anti-PD-L1 and anti-VEGF therapy in this heavily pre-treated cohort. [2]

Chelariu-Raicu et al. performed a phase Ib/II study on the efficacy and safety of topotecan and gefitinib, an epidermal growth factor receptor- (EGFR-) tyrosine kinase inhibitor, in patients with platinum-resistant ovarian cancer with EGFR positivity. In general, 50–70% of epithelial ovarian cancer express EGFR, which is associated with a poor prognosis. In this study, 19 patients received 250 mg gefitinib orally per day and topotecan intravenously on days 1, 8, and 15 in a 28-day cycle. Topotecan was administered in a dose escalating scheme (dose levels 1–3: 2, 3, and 4 mg/m^2) until the maximum tolerated dose was reached. Phase II included 10 patients with the following histologic ovarian cancer types: serous (74%), mixed (11%), transitional (11%), and clear cell (5%). In phase Ib, each dose level included three patients. The recommended phase II dose was determined as 4.0 mg/m^2 topotecan and 250 mg gefitinib. Progressive disease was reported in 63.2% (n = 12), stable disease in 15.8% (n = 3), and partial response in 10.5% (n = 2). The most common TRAEs of any grade were anaemia (89.4%), neutropenia (68.4%), abdominal pain (84%), constipation (78.9%), and diarrhoea (78.9%). In conclusion, this drug combination did not show sufficient clinical activity, with results not being superior to topotecan therapy alone. [3]

Phase II

Rocconi et al. determined the safety and efficacy of gemogenovatucel-T, an autologous tumour cell vaccine, in ovarian cancer maintenance therapy in a multicentric, randomised, double-blind, placebo-controlled, phase IIb (VITAL) trial. This vaccine reduces the expression of furin and downstreams TGF-β1 and TGF-β2. Ninety-one women with stage III/IV high-grade serous, endometrioid, or clear cell ovarian cancer in clinical complete response after surgery and platin-based chemotherapy were included in the study to receive either gemogenovatucel-T (n = 47) or placebo (n = 44). Intradermal injection was given once a month for a minimum of four and up to 12 doses. The primary endpoint was PFS. For the vaccine and the placebo group, the median follow-up was 40.0 months and 39.8 months, respectively. PFS was 11.5 months (95% CI 7.5–not reached) versus 8.4 months (HR 0.69; 90% CI: 0.44–1.07; one-sided p = 0.078). Gemogenovatucel-T resulted in no grade 3 or 4 toxic effects. Seven patients (4 in the placebo group and 3 in the vaccination group) had 11 serious adverse events. Gemogenovatucel-T immunotherapy did not reach its primary endpoint of a significantly superior PFS; however, in the subgroup analysis, it did show significant improvements in PFS and OS in patients with BRCAWT tumours. These patients might be more sensitive to gemogenovatucel-T. [4]

Phase II

A randomised open-label phase III trial (FORWARD I) on mirvetuximab soravtansine (MIRV), an antibody-drug conjugate comprising a folate receptor (FR) α-binding antibody, versus chemotherapy in patients with platinum-resistant ovarian cancer was carried out by Moore et al. In all, 352 patients with ≥ 1 ≤ 3 prior lines of chemotherapy and FRα positive tumours were randomised to either MIRV (6 mg/kg, adjusted ideal body weight) q3w or chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan) in a 2:1 ratio. The primary endpoint was PFS. A FRα high expression (≥75% of tumour cells with any FRα membrane staining visible at ≤ x 10 microscope objective) population was prespecified. The median PFS was 4.1 versus 4.4 months in the MIRV versus chemotherapy cohort. In the high FRα subgroup analysis, PFS was 4.8 months versus 3.3 months for the MIRV cohort, without statistical

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

Anna-Maria Schütz

significance. Superior outcomes for MIRV were reported for the FRα high expression cohort (n = 218, 59.6%) with an overall response rate of 24% versus 10%, CA-125 responses in 53% versus 25% and patient-reported outcomes in 27% versus 13%. Grade ≥ 3 related adverse events occurred in 25.1% versus 44.0%, events leading to dose reduction in 19.8% versus 30.3% and treatment discontinuation in 4.5% versus 8.3%. In summary, although secondary endpoints did favour MIRV, especially in the FRα high expression cohort, MIRV did not reach its primary endpoint of a superior PFS. [5]

An ESMO round-table discussion on first-line PARP inhibitor maintenance therapy in newly diagnosed ovarian cancer patients, regarding the selection of patients, toxicity management, and treatment after recurrence, was published. HRD-positive patients benefit from adding PARP inhibitors either alone or with bevacizumab. For the HRD-negative cohort, niraparib can be considered as an option; however, there is a recommendation against the addition of PARP inhibitors when already receiving bevacizumab. Non-BRCA mutation-associated histological subtypes (other than HGSOC and high-grade endometroid ovarian cancer) should not routinely be considered for PARP inhibitor therapy. In terms of duration, olaparib should be given for at least two and niraparib for three years after first-line chemotherapy. When toxicities occur, dose reductions and interruptions are recommended; a discontinuation should only be considered when these options have failed. For patients with a recurrence following maintenance therapy, there is no data available proving an efficacy of retreatment. [6]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	A phase I open-label study of selinexor with paclitaxel and carboplatin in patients with advanced ovarian or endometrial cancers	Rubinstein M et al.	Gynaecol Onc	https://pubmed.ncbi.nlm.nih.gov/33139041/
2	Safety and clinical activity of atezolizumab plus bevacizumab in patients with ovarian cancer: A phase Ib study	Moroney J et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/32723836/
3	Phase Ib/II study of weekly topotecan and daily gefitinib in patients with platinum resistant ovarian, peritoneal, or fallopian tube cancer	Chelariu-Raicu A et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33037105/
4	Gemogenovatucel-T (Vigil) immunotherapy as maintenance in frontline stage III/IV ovarian cancer (VITAL): a randomised, double-blind, placebo-controlled, phase 2b trial	Rocconi R et al.	Lancet	https://pubmed.ncbi.nlm.nih.gov/33271095/
5	Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I	Moore K et al.	Ann Oncol	https://pubmed.ncbi.nlm.nih.gov/33667670/
6	First-line PARP inhibitors in ovarian cancer: summary of an ESMO Open - Cancer Horizons round-table discussion	Banerjee S et al.	ESMO open	https://pubmed.ncbi.nlm.nih.gov/33310779/

Surgical treatment of primary and recurrent endometrial cancer

Piotr Lepka

In the multicentre retrospective study SENTIFAIL, Sozzi et al. evaluated patients who underwent laparoscopic hysterectomy with sentinel lymph node mapping with intracervical indocyanine green injection. There were 376 patients included, in whom the bilateral and unilateral detection rates were 76.3% and 20%, respectively. The failed bilateral mapping was associated with lymph vascular space involvement [OR 2.4 (1.04–1.12), p = 0.003], non-endometrioid histology [OR 3.0 (1.43–6.29), p = 0.004], and intraoperative finding of enlarged lymph node [OR 2.3 (1.01–5.31), p = 0.045]. [1]

Padilla-Iserte et al., in a multicentre retrospective study, evaluated the oncological safety of using a uterine manipulator in patients with apparent early-stage endometrial cancer that underwent minimal invasive hysterectomy. In all, 1,756 cases in which a uterine manipulator was used were compared with 905 cases in which it wasn't. Histology, tumour grade, myometrial invasion, FIGO stage, and adjuvant treatment were comparable between the groups. However, the recurrence rate was significantly higher in the manipulator group compared to the no-manipulator group (11.69% vs. 7.4%, respectively; p < 0.001). In addition, the use of a manipulator in FIGO stage I–II endometrial cancer was associated with impaired progression-free survival (p = 0.027) and increased risk or death (p = 0.026). [2]

The new ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma were published in the covered period. The major changes in the surgical treatment compared with the previous version from 2015 were as follows:

Early-stage disease

1. For stage I/II endometrial carcinoma, minimally invasive surgery should be the main surgical approach, including patients with high-risk endometrial carcinoma.
2. Any intraperitoneal tumour spillage, including tumour rupture or morcellation (including in the bag), should be avoided.
3. Tumour with metastases outside the uterus and cervix (excluding lymph node metastases) are relative contraindications for minimally invasive surgery.
4. Surgical restaging can be considered in previously incompletely staged patients with high-intermediate risk and high-risk disease if the outcome might have an implication for adjuvant treatment strategy.

Lymph node staging

1. Sentinel lymph node biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease. It can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended in this group.
2. Surgical lymph node staging should be performed in patients with high- to intermediate- and high-risk disease. Sentinel lymph node biopsy is an acceptable alternative to systematic lymph node dissection in stage I/II.
3. For sentinel lymph node biopsy, indocyanine green is recommended, and re-injection is an option if the sentinel is not visualized up-front.
4. If pelvic lymph node involvement is found intraoperatively, further systematic pelvic lymph node dissection should be omitted. However, debulking of enlarged lymph nodes and paraaortic staging can be considered.

Ovarian preservation

1. Ovarian preservation can be considered in premenopausal patients younger than 45 years old with low-grade endometrioid endometrial carcinoma with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease.
2. Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk (e.g., BRCA mutation, Lynch syndrome).

Medically unfit patients

In rare conditions, for patients with medical contraindications to the standard surgical management by minimally invasive surgery, vaginal hysterectomy with bilateral salpingo-oophorectomy is recommended if feasible. [3]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Laparoscopic sentinel node mapping with intracervical indocyanine green injection for endometrial cancer: the SENTIFAIL study – a multicentric analysis of predictors of failed mapping	Sozzi G et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32868384/
2	Impact of uterine manipulator on oncological outcome in endometrial cancer surgery	Padilla-Iserte P et al.	Am J Obstet Gynecol.	https://pubmed.ncbi.nlm.nih.gov/32693096/
3	ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma	Concin N et al.	Radiother Oncol.	https://pubmed.ncbi.nlm.nih.gov/33712263/

Medical (chemo and radiotherapy) treatment of recurrent uterine cancer

Stamatios Petousis

Lindemann et al. published the results of a multicentre retrospective study to evaluate the clinical outcome after salvage radiotherapy for first pelvic relapse after endometrial cancer. In all, 139 patients were included who had pelvic relapse but no lymph node involvement and had received median EQD2 (Equivalent Dose in 2 Gy fractions) to the clinical target volume of 70.0 Gy. Some 39.6% of patients developed a second relapse. Risk group classification based on histology, grading, and stage were independent prognostic factors for overall survival and progression-free survival. Specifically, five-year OS was 88% for stage I low-risk patients, while relative rates were 72% and 38% for intermediate and high-risk, respectively. In conclusion, the authors stated that the majority of central pelvic recurrences may be successfully salvaged; however, survival remains poor in patients with high-risk disease. The retrospective character of the present study clearly represents a limitation; however, this study is one amongst few to demonstrate that over 60% of pelvic recurrence may be treated with salvage radiotherapy. [1]

Sapienza et al. published an interesting observational study reporting outcomes and toxicity after salvage radiotherapy. Inclusion criteria were pathologically-confirmed recurrence; loco-regional relapse (in the absence of distant metastases); and salvage treatment, including external-beam radiotherapy and/or vaginal brachytherapy. The most common site of recurrence was the vaginal apex. The five-year rate of local control was 89%, regional control was 91.5%, metastasis-free was 75.5%, the disease-free interval was 69%. and overall survival reached 83%. Regarding toxicity, 18% of patients experienced acute grade ≥3 events (most commonly gastrointestinal). The five-year rates of rectal bleeding, small bowel obstruction, and pelvic fracture were 31%, 18%, and 13%, respectively. The authors concluded that salvage radiotherapy imparts excellent loco-regional control for vaginal relapses of endometrial cancer and should entail combination external-beam radiotherapy and vaginal brachytherapy. Patients should be closely monitored for late gastrointestinal toxicity following salvage radiotherapy. Despite the profound drawback of small sample size, the study is one amongst few to conclude that salvage radiotherapy imparts excellent loco-regional control for vaginal relapses. [2]

Liu et al. published a phase II study of the WEE1 inhibitor adavosertib. The primary endpoints of this single-arm two-stage phase II study were objective response rate and rate of progression-free survival at six months. Women with recurrent uterine serous carcinoma were treated with adavosertib monotherapy at a starting dose of 300 mg orally once daily days one through five and eight through 12 of a 21-day cycle until disease progression. In 34 evaluable patients, ten total responses were observed with adavosertib monotherapy, for an overall response rate of 29.4% (95% CI: 15.1–47.5). Frequent treatment-related adverse events included diarrhoea (76.5%), fatigue (64.7%), nausea (61.8%), and hematologic adverse events. Adavosertib monotherapy demonstrated encouraging and durable evidence of activity in women with uterine serous carcinoma, while further investigation of this agent in this cancer and biomarkers of activity are indicated. [3]

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No	Title	Authors	Journal	Link to abstract
1	Salvage radiation for pelvic relapse after surgically treated endometrial cancer	Lindemann K et al.	Cancers (Basel)	https://pubmed.ncbi.nlm.nih.gov/33803531/
2	Outcomes and toxicity after salvage radiotherapy for vaginal relapse of endometrial cancer	Sapienza LG et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32376738/
3	Phase II study of the WEE1 inhibitor adavosertib in recurrent uterine serous carcinoma	Liu JF et al.	J Clin Oncol 2021	https://pubmed.ncbi.nlm.nih.gov/33705205/

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

Zoia Razumova

Sootome et al. examined the preclinical characteristics of futibatinib, a novel irreversible FGFR1-4 inhibitor. Among a panel of 296 human kinases, futibatinib selectively inhibited FGFR1-4. It covalently bound the FGFR kinase domain, inhibiting FGFR phosphorylation and downstream signalling in FGFR-deregulated tumour cell lines. It also exhibited potent, selective growth inhibition of several tumour cell lines, including endometrial cancer, with various FGFR genomic aberrations. Oral administration of the agent led to significant dose-dependent tumour reduction in different FGFR-driven human tumour xenograft models, and it was correlated with sustained FGFR inhibition. Interestingly, it was proportional to the administered dose. The frequency of appearance of drug-resistant clones was lower with futibatinib than a reversible ATP-competitive FGFR inhibitor, and futibatinib inhibited several drug-resistant FGFR2 mutants. In general, the results indicate that futibatinib is a novel orally available, potent, selective, and irreversible inhibitor of FGFR1-4 with a broad spectrum of antitumor activity in preclinical models. These findings provide a strong rationale for testing futibatinib in patients with tumours oncogenically driven by FGFR genomic aberrations, with phase I to III trials ongoing. [1]

The combination of targeted agents and chemotherapy is one of the most important directions in cancer therapy. An NRG Oncology/Gynecologic Oncology Group (GOG) Study GOG-86P was one of the first attempts to combine targeted agents like bevacizumab or temsirolimus with chemotherapy in patients with advanced endometrial cancer. Based on the results of this study, Leslie et al. determined P53 mutational status and correlated it with progression-free survival (PFS) and overall survival (OS) on GOG-86P. As a result, mutations in TP53 were correlated with better PFS and OS in patients on bevacizumab than temsirolimus (PFS: HR 0.48, 95% CI: 0.31, 0.75; OS: HR: 0.61, 95% CI: 0.38, 0.98). But there was no statistically significant difference in PFS or OS between arms for cases with WT TP53. In conclusion, the authors suggested that combining chemotherapy with bevacizumab, but not temsirolimus, may enhance PFS and OS for patients with mutant p53. The results highlight the need for larger clinical studies evaluating the potential of TP53 mutational status as a biomarker to guide treatment choice for endometrial cancer patients. [2]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Futibatinib is a novel irreversible FGFR 1-4 inhibitor that shows selective antitumor activity against FGFR-deregulated tumors	Sootome H et al.	Cancer Res	https://pubmed.ncbi.nlm.nih.gov/32973082/
2	Mutated p53 portends improvement in outcomes when bevacizumab is combined with chemotherapy in advanced/recurrent endometrial cancer: An NRG Oncology study	Leslie KK et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33541735/

Uterine sarcoma

Marcin Bobiński

Friedlander et al. published the results of the PARAGON trial (phase II, single-arm, open-label), which investigated the efficacy of anastrozole in oestrogen and progesterone receptor-positive recurrent low-grade endometrial stromal sarcomas. Patients were treated with anastrozole 1 mg/day; clinical benefit was observed in 73%, both after three and six months of treatment (CR = 6.7%; PR =2.0%; SD = 46.7%; PD = 26.7%). The authors concluded that the most important finding in this trial is that the objective response rates to aromatase inhibitors are much lower than generally believed and appear in most retrospective analyses. The trial results cannot be considered definitive due to the limited number of participants (n = 15). However, they give new insight into this problem and indicate directions to design future clinical trials in the field. [1]

The Turkish Uterine Sarcoma Group released an interesting retrospective study by Ayhan et al., which included 302 cases of uterine leiomyosarcoma patients. A wide range of clinical (type of surgery, FIGO stage, clinical presentation, etc.) and pathological features (nuclear atypia, grading, LVSI, etc.) were analysed, combined with survival data. The obtained results indicated that the presence of LVSI, a higher degree of nuclear atypia, and the absence of lymphadenectomy were negatively correlated with progression-free survival. In contrast, LVSI, mitotic count, higher degree of nuclear atypia, FIGO stage II–IV disease, and suboptimal surgery significantly decreased overall survival. Importantly, lymphadenectomy affects progression-free survival. On the other hand, it is also controversial considering that 77.5% of cases included in this study were at FIGO I stage. Additionally, no correlation between lymphadenectomy and overall survival was observed. The study consists of a significant number of cases. Still, apart from retrospective design, a significant drawback was the lack of biomarker analysis. The addition of even basic biomarkers such as ER, PR, Ki67, P53 could give a new light on the results presented in this paper and increase its cognitive potential as well as practical value. [2]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Phase 2 study of anastrozole in patients with estrogen receptor/progesterone receptor positive recurrent low-grade endometrial stromal sarcomas: The PARAGON trial (ANZGOG 0903)	Friedlander M et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33608144/
2	Prognostic factors and survival outcomes of women with uterine leiomyosarcoma: A Turkish Uterine Sarcoma Group Study-003	Ayhan A et al.	Curr Probl Cancer	https://pubmed.ncbi.nlm.nih.gov/33685725/

Surgical treatment of primary and recurrent cervical cancer

Bojana Gutic and Chrysoula Margioula-Siarkou

Nica et al. analysed both the oncological and fertility impact of a conservative treatment option in early-stage low-risk cervical cancer. The authors retrospectively studied 44 cases of women with FIGO 2009 stage IA1–LVSI+, stage IA2, and stage IB1 with <10 mm stromal invasion, treated with cervical conisation and SLN assessment. In 27 women, the cone specimen had positive margins and an additional conisation was performed, with no residual disease in all cases. LVSI was positive in 41% of patients. SLN biopsy revealed micrometastases in three women, who underwent unilateral lymphadenectomy with a negative outcome. Six patients proceeded to definite further surgical/adjuvant treatment, as they were burdened with high-risk pathology. The median age of patients was 31 years; 45% had no previous pregnancy. Seventeen women became pregnant and 16 delivered at term. The median follow-up was 44 months (range 6–137), with no recurrence mentioned. Conclusively, the authors suggest that conservative management with conisation and SLN mapping may offer an option in early cervical cancer cases, especially where fertility preservation is desired. [1]

Zhang et al. performed a case-matched retrospective single-centre study, in an effort to compare therapeutical outcomes between women with locally advanced cervical cancer (LACC) who received neoadjuvant chemotherapy followed by surgery (NACTS) and those who underwent primary surgery. LACC included cases of FIGO 2009 stage IIB2/IIA2, while neoadjuvant chemotherapy consisted of paclitaxel plus platinum. A propensity score matching was performed between the two groups to equalise pre-treatment characteristics. Each group included 190 cases. The NACTS group had significantly lower tumour diameters ($p < 0.001$) and LVSI (+) ($p < 0.001$). Furthermore, 10.5% of the NACTS patients had ≥ 2 intermediate-risk factors, whereas in the primary surgery patients the relevant rate was 53.2% ($p < 0.001$). Consequently, the need for adjuvant radiotherapy was significantly reduced in the NACTS group (54.2 vs. 70.0%, $p = 0.002$). Rates of overall survival and progression-free survival did not differ between the groups. However, progression-free survival was augmented in the NACTS patients with either tumour size ≥ 5 cm or SCC ≥ 5 ng/mL ($p = 0.016$, $p = 0.007$). The authors concluded that neoadjuvant chemotherapy prior to surgery might be beneficial in cases of LACC, as it seems to decrease pathologic risk factors and rate of adjuvant radiotherapy and may also have a positive impact on survival rates, when tumour size ≥ 5 cm or SCC ≥5 ng/mL. [2]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Cervical conization and lymph node assessment for early stage low-risk cervical cancer	Nica A et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33649012/
2	Paclitaxel plus platinum neoadjuvant chemotherapy followed by surgery versus primary surgery in locally advanced cervical cancer—A propensity score matching analysis	Zhang Y et al.	Front Oncol	https://pubmed.ncbi.nlm.nih.gov/33365272/

Radiotherapy of primary and recurrent cervical cancer

Erbil Karaman and Paweł Bartnik

Kim et al. conducted a retrospective study that investigated the effect of bevacizumab on fistula formation before or after the radiotherapy treatment for stage I–IV cervical cancer. The study included 302 cases. Two hundred forty-nine patients underwent either definitive or adjuvant radiotherapy, and 53 patients were treated with radiotherapy before or after bevacizumab. The median follow-up time was 35.9 months. Three-year cumulative fistula formation was found to be remarkably higher in radiotherapy and bevacizumab cases than in the radiotherapy arm (27.0% vs 3.0%, $p < 0.001$). In subgroup analysis, the authors reported that a 10-month interval between radiotherapy and bevacizumab decreased the fistula occurrence in the radiotherapy and bevacizumab group ($p = 0.032$). In this study, it was concluded that bevacizumab used with pelvic radiotherapy increased the fistula formation in cervical cancer patients and its combination with radiotherapy should be used with caution while close follow-up for fistula formation is mandatory. [1]

Pareek et al. conducted a phase III randomised trial of application of trans-abdominal ultrasound in performing intracavitary brachytherapy to decrease perforation and tissue damage at risk doses. A total of 160 cases were randomised into two groups: Group A (no ultrasound guidance) and Group B (intracavitary brachytherapy with ultrasound use). The study showed that ultrasound guidance significantly decreased the dose applied to the various organs at risk. In the ultrasound guidance group, the procedure time was remarkably shorter (26 min vs 19 min, $p = 0.001$). The uterine perforation rate was significantly lower in ultrasound guidance group [1 case (1.25%) vs 10 case (12.5%), $p = 0.005$]. They concluded that transabdominal ultrasound should be routinely applied for intracavitary brachytherapy, which improves dosimetry and reduction in procedure time. [2]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Use of bevacizumab before or after radiotherapy increases the risk of fistula formation in patients with cervical cancer	Kim N et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33273018/
2	A phase III randomised trial of trans-abdominal ultrasound in improving application quality and dosimetry of intra-cavitary brachytherapy in locally advanced cervical cancer	Pareek V et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33293047/

Medical treatment of primary and recurrent cervical cancer

Kristina Lindemann

Primary treatment of (locally) advanced disease

The STARS 3 trial randomised 1,048 women in an open-label study to adjuvant radiotherapy (total dose, 45–50 Gy), concurrent chemoradiation (weekly cisplatin, 30–40 mg/m^2), or sequential radiotherapy (cisplatin, 60–75 mg/m^2, plus paclitaxel, 135–175 mg/m$^{2)}$ in a 21-day cycle, given two cycles before and two cycles after radiotherapy, respectively. The study reported statistically significant improvement in progression-free survival at three years associated with sequential radiotherapy compared to radiotherapy alone (90.0% vs 82.0%), but no advantage over concurrent chemoradiation. In the concurrent arm, there was significantly more toxicity reported (neutropenia, vomiting, and nausea) leading to a decrease in dose intensity in that arm. The study had few limitations and was nicely presented in an accompanying editorial by Randall et al. Poor tolerability of the concurrent chemoradiation, inclusion of both intermediate- and high-risk patients, and the inclusion of patients with positive lymph nodes may be considered as the main methodological limitations. Several upcoming studies will test intensified treatment in the high-risk population. [1, 2]

Treatment of recurrent/metastatic disease

The phase II single-arm CECILIA study evaluated carboplatin/paclitaxel and bevacizumab in 150 patients with persistent, recurrent, and newly diagnosed metastatic disease. All patients received carboplatin at area under the curve 5, paclitaxel 175 mg/m^2 plus bevacizumab 15 mg/kg, every three weeks. Maintenance bevacizumab was allowed. Overall, 11.3% of patients (n = 17, 95% CI: 6.7–17.5%) experienced at least one perforation/fistula event. Sixty-one percent of patients achieved an objective response, including complete responses in 14%. A further 26% of patients had stable disease, giving a disease control rate of 87%. The median progression-free survival was 10.9 months while median overall survival was 25.0 months. The trial confirms the safety of the triplet bevacizumab with carboplatin-based chemotherapy. Strict inclusion criteria were applied and resulted in a lower frequency of fistula/perforation but comparable efficacy compared to the GOG 240 study. [3]

Oaknin et al. reported the results from the cervical cancer cohort of the SUMMIT phase II basket study investigating the efficacy and safety of neratinib in patients with tumours harbouring activating HER2 somatic mutations. Of the 12 evaluable patients, three patients had a confirmed objective partial response (ORR 25%; 95% CI: 5.5–57.2%) with a duration of 5.6, 5.9, and 12.3 months. Three additional patients had stable disease lasting ≥ 16 weeks (clinical benefit rate 50%; 95% CI: 22.1–78%). Median progression-free survival was 7.0 months) and median OS was 16.8 months. Diarrhoea, nausea, and decreased appetite were the most common adverse events. The study was limited by the small sample size. [4]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Effectiveness of sequential chemoradiation vs concurrent chemoradiation or radiation alone in adjuvant treatment after hysterectomy for cervical cancer the STARS phase 3 randomized clinical trial	Huang H et al.	JAMA Oncol	https://pubmed.ncbi.nlm.nih.gov/33443541/
2	Sequential chemotherapy for early-stage, post-radical hysterectomy cervical cancer Are the STARS aligned?	Randall LM et al.	JAMA Oncol	https://pubmed.ncbi.nlm.nih.gov/33443572/
3	Primary results from CECILIA, a global single-arm phase II study evaluating bevacizumab, carboplatin and paclitaxel for advanced cervical cancer	Redondo A et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32763109/
4	Neratinib in patients with HER2-mutant, metastatic cervical cancer: Findings from the phase 2 SUMMIT basket trial	Oaknin A et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32723675/

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

Khayal Gasimli

Phase I

Rischin et al. investigated the safety, tolerability, and antitumour activity of cemiplimab (PD-1 inhibitor) in a phase I multicentre study in patients with recurrent and advanced cervical cancer. Cemiplimab was administered either as a monotherapy or in combination with hypofractionated radiation therapy to ten patients of each study arm. Only one patient of the monotherapy arm received cemiplimab completely as planned for 48 weeks. For the rest of patients, the administration of cemiplimab was interrupted due to disease progression or recurrence. The majority of patients (> 90%) experienced adverse events of any grade under cemiplimab therapy. Grade ≥3 adverse events were observed in 40% of cases of both therapy arms. The small number of patients with different baseline characteristics of both study arms may be considered the main limitation of this analysis. [1]

Phase II

The multicentre, open-label, single-arm CLAP study examined the antitumour activity and safety of the combinatorial therapy including camrelizumab (as PD1 inhibitor) and apatinib (as tyrosine kinase inhibitor of VEGFR-2). Forty-five metastatic and recurrent cervical cancer patients sustained camrelizumab 200 mg IV biweekly and apatinib 250 mg oral daily as a second-line treatment until 24 weeks, or disease progression, or/and unmanageable toxicity occurred. The disease control rate was 82.2% of the cohort. The median progression-free survival reached 8.8 months. Safety analysis showed a higher incidence rate (>95%) of adverse events among the patients. [2]

Youn et al. reported the interim results of a single-arm and ongoing study regarding antitumour activity of pembrolizumab and GX-188E therapeutic DNA vaccine in HPV 16- and 18 positive metastatic or recurrent cervical cancer. Twenty-six patients underwent preliminary activity assessment using the RECIST criterion. Overall response was observed in 11 (42%) patients, of which 15% was complete and 27% was partial response. The most recorded adverse events were gastrointestinal disorders (17%), followed by hypothyroidism (11%), and skin and subcutaneous tissue disorders (11%). The final results of the study are still expected. [3]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	PD-1 blockade in recurrent or metastatic cervical cancer: Data from cemiplimab phase I expansion cohorts and characterization of PD-L1 expression in cervical cancer	Rischin D et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32917410/
2	Camrelizumab plus apatinib in patients with advanced cervical cancer (CLAP): A multicenter, open-label, single-arm, phase II trial	Lan C et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/33052760/
3	Pembrolizumab plus GX-188E therapeutic DNA vaccine in patients with HPV-16-positive or HPV-18-positive advanced cervical cancer: interim results of a single-arm, phase 2 trial	Youn JW et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/33271094/

Primary and recurrent vulvar cancer treatment

María de los Reyes Oliver and Rubén M. Betoret

Molecular studies have recently become a cornerstone for the development of novel treatment strategies for many types of gynaecological cancers, including vulvar squamous cell cancer (VSCC). Stasenko et al. performed genomic sequencing of 410–468 cancer-related genes (MSK-IMPACT assay) in 26 patients with extramammary Paget's disease of the vulva. The most common mutations were PIK3CA, ERBB2, and TP53, which were found in more than 25% of cases in this real-world clinical cohort. No microsatellite instabilities were reported. Therefore, these mutations may count as potential therapeutic targets for this frequently relapsing entity. [1]

Pors et al. performed a full molecular sequencing of recurrent or multifocal non-HPV VSCC, via a targeted 33-gene next-generation panel (Qiagen QiaAmp FFPE Tissue Kit). They reported 79 mutations on a total series of 54 cases. The most common mutations were TP53 and PIK3CA, and the majority of patients demonstrated a clonal relationship (the same mutations in metachronous or synchronous tumours), while only a small subgroup revealed novel or additional mutations, suggesting that recurrent non-HPV-associated VSCC can arise from these two mechanisms. [2]

Promising therapies targeting the programmed cell death immune checkpoint are on the way; nevertheless, they still fail to succeed in a subset of solid tumours. Dibbern et al. showed clonal or complete loss of major histocompatibility complex (MHC) class I expression in over one-third of a series of 58 HPV-related vulvar and cervical cancers. In this subgroup, treatments with checkpoint inhibitors targeting the PD1/PD-L1 axis may be limited. [3]

Radiotherapy or chemoradiotherapy is an alternative to more aggressive surgical treatments for locally advanced VSCC. Richman et al. assessed the impact of dose-escalated intensity modulated radiotherapy (IMRT) in this locally advanced scenario (similar to three-dimensional radiotherapy dose-escalation, as reported in GOG 205), and concluded that the treatment proved well tolerated, while rates of clinical and pathological complete response (cCR and pCR) were favourable compared with published data. The overall rates of cCR and pCR were 76% and 70%, respectively, while progression-free survival at two years was 65%. [4]

Van der Velden at al. published a retrospective, multicentric cohort of 96 patients treated by radical vulvectomy and uni- or bilateral inguinofemoral lymphadenectomy. In this cohort, no adjuvant treatment was performed in the case of single intracapsular groin metastases. The estimated low risk of recurrence was confirmed: The rate of isolated groin recurrence was only 1%, confirming guidelines' advice of avoiding adjuvant radiotherapy in these cases. The risk of groin recurrence was also indicated to be independent from the size of metastasis and lymph node ratio. [5]

Finally, Prieske et al., based on the AGO-CaRE-1 cohort of 1247 patients, performed a subgroup analysis according to age regarding treatment patterns and prognosis. They concluded that older women (>70 years old) present with advanced tumour stages, larger tumour diameter, more frequent HPV negative tumours, and a higher rate of nodal involvement. Two-year DFS was decreased (59.3%), compared to younger groups (65.8% for age 50–69 and 81.1% for <50.). [6]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Genomic alterations as potential therapeutic targets in extramammary Paget's disease of the vulva	Stasenko M et al.	JCO Precis Oncol	https://pubmed.ncbi.nlm.nih.gov/33015527/
2	Targeted molecular sequencing of recurrent and multifocal non-HPV-associated squamous cell carcinoma of the vulva	Pors J et al.	Int J Gynecol Pathol	https://pubmed.ncbi.nlm.nih.gov/33323855/
3	Loss of MHC class I expression in HPV-associated cervical and vulvar neoplasia	Dibbern M et al.	Am J Surg Pathol	https://pubmed.ncbi.nlm.nih.gov/32496434/
4	Dose-escalated intensity modulated radiation therapy in patients with locally--advanced vulvar cancer- does it increase response rate?	Richman A et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32981696/
5	Radiotherapy is not indicated in patients with vulvar squamous cell carcinoma and only one occult intracapsular groin node metastasis	Van der Velden J et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33067000/
6	Age, treatment and prognosis of patients with squamous cell vulvar cancer (VSCC) – analysis of the AGO-CaRE-1 study	Prieske K et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33648748/

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Follow-up after gynaecological malignancies

Sunaina Wadhwa

There is a dearth of data on the effectiveness of long-term monitoring and follow-up models for cervical cancer survivors, particularly those with low risk. Before implementing new follow-up models, it is critical to consider the perspectives of cervical cancer survivors regarding follow-up care.

In a multicentre retrospective study, Vistad et al. analysed long-term follow-up preferences among relapse-free cervical cancer survivors treated between 2000 and 2007. A questionnaire with items assessing preference for post-treatment, clinical parameters, and a validated questionnaire for anxiety, neuroticism, and depression was formulated and sent to all 974 survivors for response assessment. In all, 546 patients (57% response rate) returned the completed questionnaire. Thirty-five patients were excluded. The patients were stratified into four groups based on their treatment: Group 1, conisation only; Group 2, major surgery (radical hysterectomy with pelvic lymph node dissection with or without bilateral salpingo-oophorectomy); Group 3, chemoradiation only; and Group 4, both surgery and chemo-radiotherapy. Groups 3 and 4 were together labelled as a heavily treated group in the analysis. The median follow-up period was 11 years (range 6–15 years). Fifty-five percent (n = 259) of cervical cancer survivors preferred a follow-up of more than five years. A significant association was found between the preference for five-year follow-up with younger age ($p = 0.035$) and heavily treated patients ($p = 0.001$) in multivariate analyses. Long-term side effects such as sexual problems, bowel problems, urinary tract problems, and lymphoedema were reported by more than 70% of cervical cancer survivors in the heavily treated group. Numerous adverse events were reported in patients in Group 4 compared to other treated groups. However, no significant differences in long-term effects were found between women who self-reported and those who preferred long-term follow-up care. No association was found between preferences for extended follow-up and depression, anxiety, and personality characteristics such as neuroticism. Fear of relapse was a key factor in long-term follow-up, even in patients at low risk.

The authors emphasised the importance of targeted patient education regarding the benefits and drawbacks of follow-up care to keep up with the rising cost of cancer care. Apart from the questionnaire on follow-up preferences, the study's strength was that it was the first of its kind, utilising validated self-assessment tools with established psychometric properties. Cervical cancer survivors should receive follow-up care that is tailored to their unique risk of recurrence and late effects. [1]

Ford et al. conducted an observational cohort study of 7,509 women using the cancer module of the US National Health Interview Survey 2010 to assess differences between black and white women of 18 years of age or above in terms of HPV knowledge, screening behaviour, and follow-up for the abnormal Pap tests. Black women reported higher adherence to early detection of cervical cancer (OR 1.7) but lower rates of being informed about an abnormal Pap test (OR 0.42) and being contacted for follow-up care (OR 0.54). The authors recommended a tiered approach to enable culturally competent education and communication for patients, physicians, clinicians in training, and support staff at the clinic level. [2]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Preferences for follow up in long-term survivors after cervical cancer	Vistad I et al.	Acta Obstet Gynecol Scand	https://pubmed.ncbi.nlm.nih.gov/32232835/
2	Differences in cervical cancer screening and follow-up for black and white women in the United States	Ford S et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33323276/

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Screening of gynaecological cancers

Geanina Hagima

A randomised, double-blind, controlled trial assessed the efficacy of a bivalent HPV vaccine in Costa Rica. In all, 7,466 women aged 18–25 years were randomised 1:1 to receive either an HPV or a hepatitis A vaccine. The follow-up time was four years. After the blinded phase, the control group also received the bivalent HPV vaccination. A group of 2,635 HPV vaccinated women were further enrolled in a long-term follow-up for 11 years and the control group was replaced with new unvaccinated women (n = 2836). Over this 11-year period, the cumulative HPV vaccine efficacy against HPV 16/18-associated CIN2+ and CIN 3+ were 97.4% and 94.9%, respectively. The main limitation of this study was the replacement of the original control group with a new unvaccinated group. [1]

A retrospective cohort study compared the primary high-risk HPV screening (26,171 women) with the replaced cytology-based screening program (19,109 women) in the Netherlands. The new program included the possibility to perform self-sampling. Referral rates, detection of CIN2+, overdiagnosis (defined as ≤ CIN1 in histologic specimen), and overtreatment (≤ CIN1 in treatment specimen) were compared. Referral rates increased by 70.2%, from 2.5% to 4.2%. Detection rates increased to 46.2% for CIN2+, 32.2% for CIN3+, and 31.0% for cervical cancer; overdiagnosis increased to 143.4%. Overtreatment rates were similar with both screening methods. The positive predictive value for the detection of CIN2+ was 34.6% versus 40.2%. Women screened through self-sampling were at higher risk of CIN2+ and receiving treatment (than those screened through physician sampling). The main limitations of the study were the retrospective nature and the inclusion of data only from the first screening round of the high-risk HPV-based screening. This study highlighted the superiority of high-risk HPV-based screening regarding the detection of CIN 2, CIN 3, and cervical cancer with similar overtreatment rates but with higher referral rates compared to cytology-based screening. [2]

Bao et al. published a multicentre, clinical-based, observational study comparing artificial intelligence-(AI-) assisted cytology for the detection of CIN and invasive cervical cancer to liquid-based cytology with manual reading that included 2,145 referral women. The AI system was built on a supervised deep-learning algorithm that was based on a large dataset of 188,542 digital cytological images. Two liquid-based slides were produced for each cervical sample: one random slide that was allocated to AI-assisted reading and one that was read manually by skilled cytologists and cytology doctors. HPV testing and colposcopy-directed biopsy were performed. The histological result was regarded as reference. Detection rates of CIN2 were significantly higher for AI-assisted reading than for skilled cytologist ($p = 0.04$) and cytology doctors ($p < 0.001$). For CIN3+ detection rates of AI were similar to skilled cytologists ($p = 0.75$) and cytologists ($p = 0.54$). This was the first study that compared an AI system to manual reading for the detection of CIN, showing the potential value of AI-assisted cytology in the future. A limitation of the study was that the estimations were made in a referral population, not in the general population. [3]

The effect of pre- or post-conisation HPV vaccination with bi- or quadrivalent vaccine was analysed in a meta-analysis of three retrospective, three prospective studies, three post-hoc analyses of RCTs, and one cancer registry study. The overall study population included 3,939 vaccinations versus 17,150 controls. The results showed a significant relative risk reduction for the development of new HSIL after HPV vaccination (RR 0.41) independent from HPV type. Age-dependent analysis showed no differences between women under 25 years (RR 0.47) and older women (RR 0.52). Results for HPV 16/18-positive CIN2+ showed a recurrence rate of 0.37. Overall, the number of women that would have to be vaccinated before or after conisation to prevent one case of recurrent CIN 2+ is 45.5. This study has some limitations: only one randomised controlled trial with acceptable quality was included, there was significant heterogeneity between the studies, and five of them were connected to and supported by the vaccine manufacturer. [4]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Efficacy of the bivalent HPV vaccine against HPV 16/1 associated precancer: long-term follow-up results from the Costa Rica Vaccine Trial	Porras C et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/33271093/
2	Benefit and burden in the Dutch cytology-based vs high-risk human papillomavirus-based cervical cancer screening program	Loopik DL et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/32800820/
3	Artificial intelligence-assisted cytology for detection of cervical intraepithelial neoplasia or invasive cancer: A multicenter, clinical-based, observational study	Bao H et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32814641/
4	Prophylactic HPV vaccination after conization: A systematic review and meta-analysis.	Jentschke M et al.	Vaccine	https://pubmed.ncbi.nlm.nih.gov/32762871/

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Prevention and management of surgical complications

Anastasia Prodromidou and Anastasios Pandraklakis

The evaluation of The Surveillance, Epidemiology, and End Results (SEER) database by Latif et al., of 15,101 patients who underwent hysterectomy for early-stage endometrial cancer, revealed a significantly increased prevalence of venous thromboembolism in those who had lymphadenectomy compared to those who did not (3.8% vs 2.3%, RR 1.67, $p < 0.0001$). This remained significant even after adjustment for factors including age, stage, grade, Charlson comorbidity index, and surgical approach. Lymphadenectomy was also associated with two-fold higher risk of venous thromboembolism in patients who had minimal invasive surgical approaches, indicating the importance of identifying the appropriate thromboprophylaxis in those patients. [1]

Boitano et al. retrospectively analysed overall complications in high-risk patients with biopsy-proven gynaecologic malignancy. Obese patients (body mass index >30 kg/m^2 and/or those older than 65 years were classified as high risk. Significantly reduced overall complication rates were detected in the group of 259 patients who were managed with enhanced recovery protocols compared to the historical control group of 104 patients (29% vs 53.8%, $p < 0.0001$). This remained unchanged in a separate analysis of obese, morbidly obese, and patients who were older than 65, as well as in a sub-analysis of each complication, including postoperative ileus, pulmonary complications, sepsis, and surgical infections. A shorter hospital stay was found in the enhanced recovery group (3.3 vs 4.2 days, $p < 0.0001$), which was not reflected in a respective increase in 30-day readmission rates 9.6% vs 13.5%, $p = 0.19$). [2]

A prospective randomised trial by Gezer et al. found no difference in rates of both symptomatic and asymptomatic lymphoceles in 36 patients with endometrial cancer in whom thrombin gel matrix (TGM) was applied in the pelvic sidewall after lymphadenectomy when compared to 36 controls. However, in the TGM group, the drainage days were significantly shorter compared to controls (2 vs 3 days, $p = 0.015$), while the amount of drainage, despite not being significant, was also reduced in the TGM group (498 mL vs 650 mL, $p = 0.073$). [3]

In a randomised controlled trial of 505 patients who underwent laparotomy for gynaecological cancer, a total of 254 patients who were randomly allocated to receive prophylactic wound therapy with negative pressure (NPWT) were compared with 251 controls who received standard gauze wound closure. No difference was observed in wound complications among the two groups (17.3% vs 16.3%, risk difference 1%, $p = 0.77$). However, the NPWT group was associated with significantly increased rates of skin blistering compared to controls (13% vs 1.2%, $p < 0.001$). [4]

In the study by Hasselgren et al., a retrospective analysis of 184 women with advanced epithelial ovarian cancer (FIGO stage ≥ III) who underwent surgery, revealed that those with major complications defined as Clavien-Dindo ≥3, were younger, of more advanced stage, and had greater BMI, while they also required more complex surgical procedures, had prolonged surgery, and a higher amount of ascites and blood loss. The authors highlighted the importance of perioperative fluid management as the adjusted odds ratio of major postoperative complications was significantly increased in a perioperative fluid balance of >3,000 mL (OR 4.85, 95% CI: 1.23–19.2, $p = 0.02$), which was further increased as the balance increases at >5,000 mL (OR 33.7, 95% CI: 4.13–275, $p < 0.01$). [5]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Lymphadenectomy is associated with an increased risk of postoperative venous thromboembolism in early stage endometrial cancer	Latif N et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33551203/
2	An enhanced recovery protocol decreases complication rates in high-risk gynecologic oncology patients undergoing non-emergent laparotomy	Boitano TKL et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33495207/
3	Application of thrombin gel matrix for the prevention of lymphocele in patients with endometrial cancer: A prospective randomized trial	Gezer S et al.	J Gynecol Obstet Hum Reprod	https://pubmed.ncbi.nlm.nih.gov/33217600/
4	Prophylactic negative pressure wound therapy after laparotomy for gynecologic surgery: A randomized controlled trial	Leitao MM Jr et al.	Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/33416292/
5	Perioperative fluid balance and major postoperative complications in surgery for advanced epithelial ovarian cancer	Hasselgren et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33715894/

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Fertility-sparing treatment in gynaecological malignancies

Charalampos Theofanakis

Endometrial cancer

A retrospective cohort study by Raffone et al. assessed the accuracy of the progesterone receptor B (PRB) as a predictive marker for patients with atypical endometrial hyperplasia and early endometrial cancer regarding conservative treatment. The study included 36 premenopausal women, 39 with atypical endometrial hyperplasia, and seven with early endometrial cancer. Treatment strategy included hysteroscopic resection of the lesion and insertion of a levonorgestrel-releasing intrauterine device (LNG-IUD) and at least one year of follow-up. The expression of PRB was assessed through immunohistochemistry in the glands and stroma. The predictive accuracy of PRB expression was examined based on sensitivity and specificity regarding treatment failure, no regression, and recurrence. The authors stated that a weak stromal PRB expression is a highly sensitive predictive marker for no response and recurrence of atypical endometrial hyperplasia and early endometrial cancer. [1]

A retrospective study by Novikova et al. compared different therapeutic regimens of hormonal treatment in women with atypical endometrial hyperplasia and early endometrial cancer. Treatment protocols in 418 patients, 228 with atypical endometrial hyperplasia, and 190 with early endometrial cancer, included LNG-IUD, gonadotropin-releasing hormone agonist (aGnRH), or high-dose oral medroxyprogestererone acetate (MPA), separately or combined. The results showed that hormonal therapy with LNG-IUD is superior to MPA-containing regimens but with a high risk of recurrence. Pregnancy rates are acceptable but could be optimised with broader use of assisted reproduction techniques. [2]

Cervical cancer

A retrospective study by Martinelli et al. evaluated the oncological and obstetrical outcomes of 39 patients treated with conisation and laparoscopic lymph node evaluation. Pelvic lymphadenectomy was performed in 29 patients, while ten had sentinel lymph node mapping. Twenty-two patients had squamous histology and 17 adenosquamous carcinoma. Overall, 33 patients retained their childbearing potential, of whom 17 had a second conisation while two experienced a relapse. No deaths were reported, and 13 natural pregnancies resulted in a 76.9% live birth rate. The authors suggested that conisation with laparoscopic nodal evaluation is a safe approach for young patients with early-stage cervical cancer. [3]

Fanfani et al. retrospectively reviewed 42 patients with a median tumour size of 11 mm (range 8–20) and a median age of 32 years (range 19–44) that underwent conisation or simple trachelectomy with pelvic lymph node assessment. With a median follow-up of 54 months (range, 1–185), there was a 7.1% recurrence rate and no deaths. All recurrences were recorded in the pelvis (2 in the cervix and 1 in the lymph nodes), with a three-year-disease-free survival of 91.6%. Eighteen pregnancies resulted in 12 live births and two miscarriages. The authors suggested that this therapeutic approach is feasible in a selected group of patients with 2018 FIGO stage IB1 cervical cancer. [4]

Ovarian cancer

A National Cancer Database search by Nasioudis et al. assessed uterine preservation in patients with stage II epithelial ovarian cancer. Forty-five out of 185 patients managed to preserve their uterus (24.3%). These patients were younger (median 32 vs 37 years, $p < 0.001$) with less chance of having high-grade tumours compared to the hysterectomy group. Subgroup analysis regarding tumour histology, grade, and substage showed no difference in overall survival. [5]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Predictive accuracy of progesterone receptor B in young women with atypical endometrial hyperplasia and early endometrial cancer treated with hysteroscopic resection plus LNG-IUD insertion	Raffone A et al.	J Minim Invasive Gynecol	https://pubmed.ncbi.nlm.nih.gov/33122144/
2	Live births and maintenance with levonorgestrel IUD improve disease-free survival after fertility-sparing treatment of atypical hyperplasia and early endometrial cancer	Novikova OV et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33461741/
3	Conization and lymph node evaluation as a fertility-sparing treatment for early stage cervical cancer	Martinelli F et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33649014/
4	Oncologic and obstetric outcomes after simple conization for fertility-sparing surgery in FIGO 2018 stage IB1 cervical cancer.	Fanfani F et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33649013/
5	Oncologic outcomes of uterine preservation for pre-menopausal patients with stage II epithelial ovarian carcinoma	Nasioudis D et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33649017/

Cancer in pregnancy

Michael J. Halaska

Arakawa et al. reported two cases of vaginal transmission of cancer from mother to the newborn. The coincidence was found when the infants exhibited lung cancer several years after birth. Several reports have already described a transplacental transmission of cancer, but these are the first two cases that reported a direct transmission of cancer cells. [1]

Tumour masses diagnosed during pregnancy are frequent. The majority of them regress spontaneously by the twelfth week of pregnancy. As most patients are young, a higher chance of diagnosing non-epithelial and borderline tumours is described during pregnancy. Zillox et al. reported 14 cases of borderline tumours found during pregnancy. The majority of cases was diagnosed in the first trimester (85.7%). Fifty-seven percent of patients underwent a surgical procedure during pregnancy. The tumour size influenced the surgical approach: 7.5cm was the mean size for primary laparoscopy, while 14cm was the mean size for primary laparotomy. For laparoconversion, 11.9 cm was the mean size. [2]

Another series of 113 patients with a tumour mass in pregnancy evaluated the use of the International Ovarian Tumor Analysis (IOTA) scoring system in pregnancy. The scoring demonstrated similar results to non-pregnant patients. [3]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Vaginal transmission of cancer from mothers with cervical cancer to infants	Arakawa A et al.	N Engl J Med	https://pubmed.ncbi.nlm.nih.gov/33406329/
2	Management of borderline ovarian tumours during pregnancy: Results of a French multi-centre study	Zillox M et al.	Eur J Obstet Gynecol Reprod Biol	https://pubmed.ncbi.nlm.nih.gov/33296755/
3	Management of ovarian masses in pregnancy: patient selection for interventional treatment	Testa AC et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33172924/

Hereditary gynaecological cancer

Sara Giovannoni and Ariel Glickman

Cowan et al. performed a retrospective, single-institution cohort study to analyse the prevalence and outcomes of patients with incidentally detected occult invasive ovarian cancer (OIOC) at the time of risk-reducing salpingo-oophorectomy (RRSO) for BRCA mutation, including 548 patients from 01/2005 to 05/2017. OIOC was detected in 26 women (4.7%), with a median age of 55 years (42–75), all of high-grade serous histology. Mutations in BRCA1, BRCA2, or both were present in 58%, 34%, and 8%, respectively. Some 54% had a history of breast cancer: 38% had stage I, 31% stage II, and 31% stage III disease. BRCA2 mutation was associated with a more advanced stage at diagnosis ($p = 0.03$). All 26 patients with OIOC completed surgical staging and 24 (92%) received adjuvant chemotherapy. With a median follow-up of 67.3 months, five-year progression-free survival (PFS) was 72% and median PFS was 129 months. Five-year PFS was 96%. The main limitation of this study was the retrospective nature of the analysis. This study showed that women with OIOC at RRSO who undergo complete surgical staging have a prognosis consistent with the stage of disease at diagnosis. [1]

Hodan et al. performed an observational cohort study on the prevalence of Lynch Syndrome in mismatch-repair deficient ovarian, fallopian tube, or primary peritoneal cancer including 308 patients between 01/2012 and 12/2019. Until 11/2016, staining by immunohistochemistry was performed for all epithelial ovarian cancers. Afterwards, only non-serous and non-mucinous epithelial ovarian cancers were included, as MMR-D has not been identified in serous and mucinous ovarian cancers. Some 5.2% (16/308) of the tumours were MMR-deficient (MMR-D), and the most common histologic subtypes were endometrioid (68.7%, n = 11), followed by clear cell carcinomas (25%, n = 4) and carcinosarcoma (6.25%, n = 1). Twelve out of 16 MMR-D tumours were suggestive of Lynch Syndrome, showing MMR-D without MLH1 promoter hypermethylation. In eight (66.6%), Lynch Syndrome was confirmed.

There is a controversy about ovarian cancer patients undergoing universal MMR staining. Given the small subset (5.2%) of ovarian cancer patients with MMR-D, these findings do not support universal MMR staining. The main limitation of this study is the relatively small size of the cohort and that germline testing was not performed systematically at any timepoint. [2]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Outcomes of incidentally detected ovarian cancers diagnosed at time of risk-reducing salpingo-oophorectomy in BRCA mutation carriers	Cowan R et al.	Gynecol Oncol.	https://pubmed.ncbi.nlm.nih.gov/33712278/
2	Prevalence of Lynch syndrome in women with mismatch repair-deficient ovarian cancer	Hodan R et al.	Cancer Med.	https://pubmed.ncbi.nlm.nih.gov/33369189/

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Treatment of pre-invasive gynaecological malignancies

Elko Gliozheni

Hunt et al. conducted a prospective evaluation of the diagnostic performance of high-resolution microendoscopy (HRME) to detect cervical intraepithelial neoplasia (CIN) in women with abnormal screening tests. No significant differences were detected in the sensitivity and specificity of HRME with algorithm analysis versus colposcopy for detection of CIN2+ or CIN3+. HRME could provide a low-cost, point-of-care alternative to colposcopy and biopsy in the prevention of cervical cancer, but validation of the technology before providing reliable results could be a limiting factor. [1]

Cao et al. aimed to prospectively assess the value of endocervical curettage during follow-up for patients with CIN2+ after loop electrosurgical excision procedures (LEEP) and to explore risk factors for positive endocervical curettage. In the one-step method group endocervical curettage was routinely performed, with colposcopy, liquid-based cytology, and human papillomavirus (HPV) co-testing. The findings were compared with those from retrospective patients where endocervical curettage was performed depending on colposcopy images according to a two-step method. They found out that the persistent CIN2+ cases were similar between the two groups, but a significantly higher persistence of CIN1 cases was detected in the one-step method group. High-risk factors for positive endocervical curettage included positive endocervical curettage before treatment, involved margins, HPV infection, and abnormal liquid-based cytology. [2]

A prospective cohort was studied by Loopik et al. to evaluate the clinical utility of reflex cytology on positive high-risk human papillomavirus (hrHPV) self-samples for immediate stratification of women according to need for colposcopy. Reflex cytology showed a sensitivity of 26.4% and specificity of 90.5% for detecting abnormal cytology. Of all CIN2+ cases, 29.4% were detected with reflex cytology on self-samples. They concluded that cytology testing is achievable on hrHPV-positive self-samples since, of all hrHPV-positive women, 26.4% could have been directly referred for colposcopy if triage with reflex cytology had been performed. [3]

In a prospective cohort study, Tidy et al. aimed to establish the prevalence of CIN2+ in women referred to colposcopy with persistent hrHPV cytology-negative screening sample according to hrHPV genotype, age at referral, and colposcopic performance. Of 3,107 women referred, the prevalence of CIN2+ was highest for HPV16 infections (10.7%) compared with HPV18 (3.6%) or HPVO (4.7%). The prevalence of CIN2+ declined with age, whereas the percentage of women with an inadequate colposcopic examination increased with age. High-grade colposcopic impression fell over time from 16.1% to 5.1%. The positive predictive value for colposcopic impression of CIN2+ was affected by hrHPV genotype (57.3% for HPV16 vs 32.1% for nonHPV16). They concluded that primary hrHPV cervical screening increases detection of CIN2+; however, low specificity results in more women being referred to colposcopy with a low prevalence of CIN2+ and also that colposcopy performs poorly in women over 50 years of age. [4]

Spinillo et al. aimed to evaluate the association of endocervical gland involvement on histological samples with hrHPV infection and with the persistence/recurrence rate of CIN after treatment. CIN2+ lesions were diagnosed in 40.5% of endocervical-gland-involvement-negative subjects and 86.7% of endocervical-gland-involvement-positive subjects. After a median of 25 months of follow-up of 1,090 treated women, the odds ratio of CIN2+ persistence and or recurrence was higher among endocervical-gland-involvement-positive than negative controls. They concluded that endocervical gland involvement on histological samples is associated with increased rates of HPV16, multiple high-risk HPV infections and CIN2+ lesions, and an increased CIN recurrence/persistence after treatment. [5]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Cervical lesion assessment using real-time microendoscopy image analysis in Brazil: The CLARA study	Hunt B et al.	Int J Cancer	https://pubmed.ncbi.nlm.nih.gov/33811763/
2	Value of endocervical curettage in follow-up for patients with cervical intraepithelial neoplasia stage 2+ after loop electrosurgical excision	Cao D et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32586604/
3	Reflex cytology for triage of high-risk human papillomavirus positive self-sampled material in cervical cancer screening: a prospective cohort study	Loopik DL et al.	BJOG	https://pubmed.ncbi.nlm.nih.gov/32506627/
4	The impact of age and high-risk human papillomavirus (hrHPV) status on the prevalence of high-grade cervical intraepithelial neoplasia (CIN2+) in women with persistent hrHPV-positive, cytology-negative screening samples: a prospective cohort study	Tidy JA et al.	BJOG	https://pubmed.ncbi.nlm.nih.gov/32279427/
5	The relationship of human papillomavirus infection with endocervical glandular involvement on cone specimens in women with cervical intraepithelial neoplasia	Spinillo A et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33041069/

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Pathology of gynaecological cancers

Nicolas Samartzis and Dimitrios Rafail Kalaitzopoulos

A study focussing on a Dutch nationwide registry of 32,419 patients with ovarian cancer diagnosed between 1990 and 2015 investigated the potential correlation of ovarian cancer with endometriosis. In all, 1,979 (6.1%) had histologically proven endometriosis. After adjusting for age, tumour characteristics, and treatment type, they showed significantly longer overall survival compared to patients without endometriosis. A weakness of the study was the lack of clinical information on medical treatment for endometriosis and ovarian cancer and the lack of information on oncological recurrences. [1]

Geistlinger et al. performed single-cell sequencing of 42,000 tumour cells in different localisations of six different high-grade serous ovarian cancers. They were able to demonstrate widespread molecular heterogeneity in the composition of tumour cell types, including mixtures of subclones, accumulation of somatic aberrations, infiltration of immune and stromal cells. This result challenges previous models of discrete subclones in such cancers and indicates a continuous increase of heterogeneity in tumour development. The authors concluded that therapies targeting genomic mutations should therefore focus on events occurring early in tumour evolution. [2]

Krämer et al. proposed an interesting approach using endometrial cancer-inspired molecular subtyping in 511 endometrioid ovarian cancer cases. In total, 3.5% were POLE-mutated, 13.7 MMR-deficient, 9.6% p53-aberrant, and 73.2% had no specific molecular profile class. In multivariable analysis, they were independent of stage, grade, and residual disease and showed in Kaplan-Meier-curve a distinct outcome in overall survival, progression-specific survival, and progression-free survival similar to the result of the ProMisE molecular subtypes. However, the retrospective study design is potential the main flaw of the study. [3]

In a nationwide Korean study, next-generation sequencing testing was applied to 16,458 patients to identify actionable genomic alterations. In all, 779 of these patients had advanced ovarian cancer. Among them, 81.5% had at least one pathogenic mutation (61.5% TP53, 12.2% BRCA1, 10.4% PIK3CA, 10.3% KRAS, 9.6% BRCA2, and 3.7% PTEN). This large study indicates that almost 50% of all ovarian cancers are candidates for genomic medicine. It should be noted, however, that this registry does not report frequencies of histological subtypes of ovarian cancer. [4]

Considine et al. examined circulating plasma proteins in 22,405 patients with epithelial ovarian cancer and 40,941 controls from the Ovarian Cancer Association Consortium. They identified 26 proteins significantly associated with epithelial ovarian cancer that could represent novel biomarkers in circulating plasma. The strength of this study is its large size. Further studies to validate clinical application are warranted. [5]

In a study published by Hagemann et al., 934 serous endometrial cancer patients from a larger group of patients prospectively enrolled in the GOG-0210 study were divided into different subgroups to study the potential correlation of different cancer subtypes with final prognosis (663 pure serous, 138 mixed serous and endometrioid, and 133 indeterminate serous vs endometrioid). Multiple regression analysis of these subtypes showed no significant difference of survival. This result may be helpful in simplifying clinical considerations in the above-mentioned subgroups. [6]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Ovarian cancer prognosis in women with endometriosis: a retrospective nationwide cohort study of 32,419 women	Hermens M et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/32841629/
2	Multiomic analysis of subtype evolution and heterogeneity in high-grade serous ovarian carcinoma	Geistlinger L et al.	Cancer Res	https://pubmed.ncbi.nlm.nih.gov/32747365/
3	Endometrial cancer molecular risk stratification is equally prognostic for endometrioid ovarian carcinoma	Krämer P et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/32737030/
4	Prevalence of pathogenic variants in actionable genes in advanced ovarian cancer: a next-generation sequencing analysis of a nationwide registry study	Kang S et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/33166861/
5	Genetically predicted circulating protein biomarkers and ovarian cancer risk	Considine DPC et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33246661/
6	The presence of an endometrioid component does not alter the clinicopathologic profile or survival of patients with uterine serous cancer: A gynecologic oncology group (GOG/NRG) study of 934 women	Hagemann IS et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33423806/

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

Joanna Kacperczyk-Bartnik

Diagnosis

In a single-institution retrospective cohort study by Aiob et al., the authors examined the incidence of molar pregnancy in their institution between January and October 2020 in comparison to previous years (2010–2019). The authors observed a 0.59% increase in the number of molar pregnancy cases (n = 24) during the COVID-19 pandemic compared to the previous year (n = 9) with no similarly high change in the past. At the same time, the total number of deliveries decreased, with 4,086 births in total (compared to 4,333 in 2019 and 4,501 in 2018). The authors concluded that the delay of early pregnancy complications diagnosis caused by the epidemiological situation could result in clearer sonographic features, higher B-hCG levels, and a lower number of misdiagnoses. [1]

Treatment

The aim of the prospective registration study by Vandewal et al. was to analyse the data of patients with gestational trophoblastic disease treated with a second curettage. Out of the 313 included patients, 37 required second uterine evacuation. It was mostly performed because of elevated hCG (n = 20) and residual molar tissue (n = 15). The authors concluded that for some patients, the second curettage could be an effective treatment with no need of chemotherapy, especially if the hCG level is below 5000 IU/L. [2]

A retrospective study by Sugrue et al. compared the outcomes of 39 gestational trophoblastic disease patients who were treated with hysterectomy between 2009 and 2018, grouped by surgical method. Twenty-two patients underwent minimally invasive hysterectomy and 17 underwent open abdominal hysterectomy. Median follow-up was 67.2 months. The remission rate was similar between the compared groups (81.8% in minimally invasive vs 76.5% in open abdominal hysterectomy; p = 0.68). The difference in five-year survival by mode of surgery was not statistically significant (minimally invasive 90.9%, open abdominal 83.3%; p = 0.40). Minimally invasive surgery was associated with similar oncological results, operative time, uterine size, and demographic characteristics, as well as lower blood loss and shorter hospitalisation compared to open abdominal hysterectomy. [3]

Prognosis

A study by Diver et al. assessed data from the US National Cancer Database in order to identify potential age and racial differences in gestational trophoblastic disease presentation and survival. In total, 1,004 patients were included in the study: 645 white, 233 black, and 83 Asian patients. The disease was more frequent in the younger (10–19 years old) and older (40–54 years old) age groups. The extremes of age were even more emphasised in the cohort of black women. Only 9% of patients were managed in high-volume centres because only six in 448 facilities treated more than one patient with GTD per year. Results of multivariable analysis showed that independent risk factors for worse survival were more advanced age, higher Charlson-Deyo co-morbidity score, and higher disease stage ($p < 0.001$ each). The authors recommend centralisation of care for gestational trophoblastic disease patients in the US for achieving optimal management quality. [4]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	A possible association between hydatidiform mole and the COVID-19 pandemic: a retrospective cohort study	Aiob A et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33712273/
2	Curative effect of second curettage for treatment of gestational trophoblastic disease - results of the Belgian registry for gestational trophoblastic disease	Vandewal A et al.	Eur J Obstet Gynecol Reprod Biol	https://pubmed.ncbi.nlm.nih.gov/33383413/
3	Outcomes of minimally invasive versus open abdominal hysterectomy in patients with gestational trophoblastic disease	Sugrue R et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33272644/
4	Age and racial differences in the presentation of gestational trophoblastic neoplasia	Diver E et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33310882/

Nutrition and perioperative care

Begoña Díaz de la Noval

Wang et al. analysed the perioperative physical function by patient-reported outcomes (PROs) in patients with gynaecological tumours (n = 180). PROs were measured by the MD Anderson Symptom Inventory (MDASI-I) (subjective score) and the Timed Up & Go test (TUGT) (objective score). The MDASI-I measures physical and psychological items on a 0–10 scale. The TUGT indicates the ability to get up from the chair, walk 3 m, turn, walk back, and sit down again, categorized into three groups (normal [<= 10 s], frail, and prolonged [> 20 s]). Scores were collected at three time points: preoperatively, at discharge day, and up to the sixth week of follow-up. All patients received care under the early recovery after surgery (ERAS) protocol. The inability to walk on MDASI-I was significantly associated with a prolonged TUGT score at all three-time points (all $p < 0.01$). Patients with prolonged TUGT had an increased inability to walk ($p = 0.0004$) and severe shortness of breath on the MDASI-I at discharge ($p = 0.0125$). Monitoring of the PROs can facilitate functional recovery and identify the patients most at risk of prolonged recovery. These results strengthened the validity of using PROs; however, it requires further investigation. [1]

Jones et al. performed a prospective study on physical activity levels and change in women with ovarian cancer (n = 110). Physical activity was assessed multiple times from pre-diagnosis to two years post-diagnosis. The activity was estimated as the total metabolic equivalent task according to the frequency, intensity, and duration of physical exercise in the previous week; and categorised as sedentary, insufficiently, or sufficiently active. Physical activity levels increased from baseline through to two years post-diagnosis assessment. However, only 53–57% of women reported being sufficiently active and the overall average remained below the recommended 150 min/week during the entire follow-up. Patients who underwent lymphadenectomy had a better level of physical activity, suggesting that a positive influence (lymphoedema specialist) can improve physical activity. The work is limited by the small sample and the bias of the information given by the patient. The influence of symptoms related to the disease should be considered, as well as appointments, psychological stress, lifestyle, chronic illnesses, chemotherapy side effects, lower income, age, BMI, or a smoking habit. It is necessary to continue the research and establish recommendations for physical activity according to the needs of the ovarian cancer population. [2]

Sánchez-Iglesias et al. performed the PROFAST trial to compare the ERAS protocol and conventional management in women with ovarian cancer who underwent primary or interval cytoreduction surgery by laparotomy (n = 110). Compared to conventional management, patients in the ERAS program had a decreased length of stay (mean 7 vs 9 days; $p = 0.0099$) and a decreased rate of readmission (6% vs 20%; $p = 0.0334$). No statistical differences were detected concerning the incidence and type of intraoperative or postoperative complications. The limitation of randomisation using a sealed envelope, the sample size, and having carried out the study in a single hospital are discussed. Although more studies are required, the study offers evidence in favour of the ERAS program for patients with advanced ovarian cancer. [3]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Assessment of physical function by subjective and objective methods in patients undergoing open gynecologic surgery	Wang XS et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33536127/
2	Physical activity levels among ovarian cancer survivors—a prospective longitudinal cohort study	Jones T et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33462088/
3	PROFAST- A randomised trial implementing enhanced recovery after surgery for high complexity advanced ovarian cancer surgery	Sánchez-Iglesias JL et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/32688208/

Quality of life in gynaecological cancers/Palliative care

Nadja Taumberger and Engin Çelik

Cusimano et al. investigated the acceptability of early palliative care and the feasibility of phase III trials. Twenty-three patients with recurrent ovarian cancer were enrolled in the study at Canadian Kingston Health Sciences Centre. Patients were randomised into two arms, which received early palliative care or standard care. The recruitment rate was 71.8 (95% CI: 53.3–86.3) and the early palliative care adherence rate was 91.7% (95% CI: 61.5–99.8). Patients' reported outcomes were collected from patients at the baseline, and after three and six months. Sixty-five percent of patients (15/23) scored >16 on the Center for Epidemiologic Studies Depression Scale Revised (CESD-R) test. Median survival was 13.3 months after randomisation. None of the early palliative care patients received chemotherapy in their last 30 days of life but 27.3% of standard-care patients (3/23) received a cycle of chemotherapy. [1]

Tigert et al. analysed patients with malignant bowel obstruction caused by gynaecologic cancer between December 2014 to March 2019 at Sunnybrook Health Sciences Centre. They retrospectively investigated management, length of hospital stays, and survival outcome in a group of 107 patients. The majority of patients had ovarian cancer (63%). Conservative management was described as maintaining 'nil by mouth' status, bowel rest, nasogastric decompression, pharmacologic treatment, paracentesis, or a Tenckhoff drain; all other invasive procedures were included in the active management group. Patients who were treated with active management had a longer hospital stay (13 vs 6 days, $p < 0.001$) but had increased survival (9.1 vs 2.9 months, $p = 0.049$). [2]

Post et al. analysed long-term adverse events and health-related quality of life (HRQOL) in patients with high-risk endometrial cancer who were enrolled and treated in the PORTEC-3 trial. The trial compared chemoradiation therapy, consisting of two cycles of cisplatin 50 mg/m^{2}in the first and fourth week of radiation therapy, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 at 3-week intervals versus pelvic radiation alone. Results showed a significant benefit in overall survival and progression-free survival for patients undergoing chemoradiation therapy. For the long-term adverse events and HRQOL, however, the study showed a long-lasting and clinically significant higher toxicity and worse quality of life in patients who received chemoradiation therapy. These results should be discussed with the patient when making an individual decision about the best treatment option. [3]

The effect of hyperthermic intraperitoneal chemotherapy (HIPEC) on the health-related quality of life (HRQOL) measured with the EORTC QLQ-C30, QLQ OV28, and QLQ-CR38 questionnaires was assessed as a secondary endpoint in the OVHIPEC trial by Koole et al. Among 245 patients who had been randomised in this multicentre, open-label, phase III trial, the addition of HIPEC to interval cytoreductive surgery was not significantly associated with worse HRQOL, demonstrated by p-values for linear and non-linear growth: $p > 0.133$ in the QLQ-C30 summary scores. These results underline the importance of HIPEC in the treatment in this patient population because not only does it have no negative effect on the HRQOL, but it also significantly improves overall survival and progression-free survival. [4]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Acceptability and feasibility of early palliative care among women with advanced epithelial ovarian cancer: A randomized controlled pilot study	Cusimano MC et al.	Journal of Obstetrics and Gynaecology Canada	https://pubmed.ncbi.nlm.nih.gov/33731311/
2	Factors impacting length of stay and survival in patients with advanced gynecologic malignancies and malignant bowel obstruction	Tigert M et al.	International Journal of Gynecological Cancer	https://pubmed.ncbi.nlm.nih.gov/33509803/
3	Long-term toxicity and health-related quality of life after adjuvant chemoradiation therapy or radiation therapy alone for high-risk endometrial cancer in the randomized PORTEC-3 trial	Post CCB et al.	International Journal of Radiation Oncology, Biology, Physics	https://pubmed.ncbi.nlm.nih.gov/33129910/
4	Health-related quality of life after interval cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with stage III ovarian cancer	Koole SN et al.	European Journal of Surgical Oncology	https://pubmed.ncbi.nlm.nih.gov/31128948/

Treatment of elderly patients with gynaecological cancers

Alex Mutombo

Filippova et al. conducted a retrospective study to determine whether the Memorial Sloan Kettering Frailty Index (MSK-FI) was associated with decision-making in older women aged 70 years or above surgically treated for advanced-stage ovarian cancer from January 2001 to May 2017. More-frail patients were less likely to have undergone primary debulking surgery (OR for a unit increase of MSK-FI: 0.64, 95% CI: 0.53–0.77; $p < 0.0001$), to delay postoperative chemotherapy (non-linear association $p = 0.009$) and less likely to enroll in research (OR 0.84, 95%CI: 0.70-1.00, $p = 0.049$). Greater frailty was associated with poorer overall survival (OS) (HR 1.16, 95% CI: 1.05–1.30, $p = 0.005$). [1]

To compare feasibility, complication data, and survival of 86 patients under the age of 70 (group A) and 62 patients over the age of 70 (group B) who were managed for endometrial cancer by robot-assisted laparoscopy, Hotton et al. conducted a retrospective comparative single-centre study including patients treated between January 2007 and December 2016. More adhesiolysis was performed in group B ($p < 0.01$). The operating times were significantly longer in group B (220.1 vs 234.4 min, $p = 0.02$). The conversion rate was similar in both groups ($p = 0.7$). There were more tumors at high risk of recurrence after 70 years (33.7 vs 45.2%, $p = 0.04$). No significant difference was found for postoperative complications. There was no difference in OS ($p = 0.7$) or progression-free survival ($p = 0.2$). [2]

Matsuo et al. conducted a retrospective cohort study using the National Cancer Institute's Surveillance, Epidemiology, and End Results database to examine trends and outcomes related to neoadjuvant chemotherapy (NACT) use in women with stage III–IV high-grade serous ovarian carcinoma from 2010 to 2016. Utilization of NACT significantly increased in older women (65 years old or above; 48.4% relative increase), followed by stage IV disease (35.2% relative increase), and stage III disease (25.0% relative increase) (all, p-trend < 0.05). Women who received NACT had OS similar to those who had primary cytoreductive surgery in older women (HR 1.07, 95%CI: 0.95–1.20, $p = 0.284$), stage IV disease (HR 0.96, 95% CI: 0.84–1.10, $p = 0.564$), and more disease extented cases (T3/N1/M1, HR 1.06, 95% CI: 0.84–1.32, $p = 0.640$). [3]

On another note, women aged 65 years or older with epithelial ovarian cancer are thought to have a worse prognosis than younger patients. Zambrano-Vera et al. analysed a prospective database of epithelial ovarian cancer patients to report the outcomes of patients treated with cytoreductive surgery (CRS)/ Hyperthermic Intraperitoneal Chemotherapy (HIPEC) between 1998 and 2019. The median OS after the upfront CRS/HIPEC was 69.2 months for patients under 65 years of age versus 69.3 months for those aged 65 years or above. The median progression-free survival after upfront CRS/HIPEC was 41.3 months for the patients under 65 years of age versus 45.4 months for those aged 65 years or above. The median follow-up period for the entire cohort was 44.6 months (95% CI: 34.7–60.6 months). [4]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	Frailty based on the memorial Sloan Kettering Frailty Index is associated with surgical decision making, clinical trial participation, and overall survival among older women with ovarian cancer	Filippova OT et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33773807/
2	Outcomes of robotic surgery for endometrial cancer in elderly women	Hotton J et al.	Surg Oncol	https://pubmed.ncbi.nlm.nih.gov/32561088/
3	Possible candidate population for neoadjuvant chemotherapy in women with advanced ovarian cancer	Matsuo K et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33196436/
4	Outcomes for elderly ovarian cancer patients treated with cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS/HIPEC)	Zambrano-Vera K et al.	Ann Surg Oncol.	https://pubmed.ncbi.nlm.nih.gov/33393042/

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COVID-19 and gynaecological cancers

Jakub Dobroch and Patrick Maguire

Lara et al. published a retrospective study of outcomes for gynaecological cancer patients with COVID-19. Amongst the 121 included patients there were 17 COVID-19-related deaths. Recent immunotherapy was associated with a relative risk of death of 3.49. No association was found between surgery or cytotoxic chemotherapy and death. [1]

Lee et al. reported their study of 800 patients with cancer and symptomatic SARS-CoV-2 infection: 226 died, with 211 deaths attributed to COVID-19. After controlling for comorbidities and cancer status, recent or current cancer treatment at the time of symptomatic SARS-CoV-2 infection did not impact the prognosis. [2]

Leung et al. published a comparative cohort study that examined the impact of the pandemic on care delivery and perioperative outcomes. There were fewer primary and secondary cytoreduction surgeries performed in 2020 compared to 2019. Fewer laparoscopic surgeries were performed in 2020 with overall higher rates of wound complications and postoperative ileus. There were fewer cases performed by surgical fellows as the primary surgeon in 2020 (15.9% versus 41.9%). [3]

The COVIDSurg Collaborative study examined the optimal duration of a planned delay before surgery for patients with SARS-CoV-2 infection. Of the 140,231 patients, 3,127 had perioperative SARS-CoV-2 infection. Patients having surgery for cancer accounted for 16.7% of the 3,127 patients with perioperative SARS-CoV-2 infection. The overall postoperative mortality rate for all participants was 1.5%. When stratified according to the timing of SARS-CoV-2 infection prior to surgery, 30-day mortality was 9.1% for those diagnosed 0–2 weeks prior, 6.9% for 3–4 weeks prior, 5.5% for 4–6 weeks prior, and 2.0% at ≥7 weeks prior to surgery. [4]

A pan-European survey examined the patients' perspectives on the impact of COVID-19 on oncological management. Participants answered two questionnaires: one COVID related as well as a Hospital Anxiety and Depression Scale (HADS). A total of 1,251 questionnaires were analysed. Some 73.2% of patients stated that they are worried that their treatment could predispose them to COVID-19 infection. Despite that, only 17.5% were afraid more of COVID-19 than cancer. Moreover, 71.0% were afraid of a delay in treatment worsening their prognosis. Some 53.1% were anxious about contracting SARS-CoV-2 in the hospital or clinic. A majority reported no modifications or delay in their treatment and follow-up. Both depression and anxiety scores were on average in the borderline range. [5]

Another study conducted in the USA measured quality of life among 555 ovarian cancer patients during the pandemic. Investigators created a COVID-19 Concern Survey and used validated forms – the Cancer Worry Scale and HADS. One-third of the patients experienced a delay in any type of their care. Some 88.6% reported significant cancer worry. In all, 57.8% of the respondents mentioned the risk of SARS-CoV-2 infection as one of their main concerns. The median anxiety score was similar to the previously discussed European study, while the depression score was lower. [6]

The European Society for Medical Oncology prepared guidelines for the management of gynaecological malignancies in the pandemic. Interventions were divided into three priority groups. High priority was allocated to unstable and symptomatic cases as well as patients newly diagnosed with malignancy. Planned surgeries were allotted to tier 2 interventions. Palliative and prophylactic procedures were considered less urgent. In high-grade ovarian cancer, any postponement of postoperative chemotherapy was not recommended. The extension of periods between chemotherapy cycles was advised as an option. [7]

The American Association for Cancer Research published a statement on vaccinations. The main conclusion was that cancer patients should be considered for vaccination as quickly as possible. The rationale for this recommendation was a higher case fatality rate among patients with cancer and COVID-19. There was no evidence that vaccines interact with cytotoxic or immunomodulatory agents. In addition, oncology patients are often in contact with health care workers, placing them at risk of exposure to SARS-CoV-2. [8]

Relevant articles retrieved September 30, 2020 – March 31, 2021

No	Title	Authors	Journal	Link to abstract
1	COVID-19 outcomes of patients with gynecologic cancer in New York City	Lara OD et al.	Cancer	https://pubmed.ncbi.nlm.nih.gov/32729142/
2	UK Coronavirus Monitoring Project Team, COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study	Lee LY et al.	Lancet	https://pubmed.ncbi.nlm.nih.gov/32473682/
3	Maintaining surgical care delivery during the COVID-19 pandemic: A comparative cohort study at a tertiary gynecological cancer centre	Leung E et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/33358197/
4	Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study	COVIDSurg Collaborative and GlobalSurg Collaborative	Anaesthesia	https://pubmed.ncbi.nlm.nih.gov/33690889/
5	Perspectives, fears and expectations of patients with gynaecological cancers during the COVID-19 pandemic: A Pan-European study of the European Network of Gynaecological Cancer Advocacy Groups (ENGAGe)	Gultekin M et al.	Cancer Med	https://pubmed.ncbi.nlm.nih.gov/33205595/
6	Impact of the coronavirus disease 2019 pandemic on the quality of life for women with ovarian cancer	Frey MK et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/32598911/
7	ESMO management and treatment adapted recommendations in the COVID-19 era: gynaecological malignancies	Colombo I et al.	ESMO Open	https://pubmed.ncbi.nlm.nih.gov/32718919/
8	Priority COVID-19 vaccination for patients with cancer while vaccine supply is limited	Ribas A et al.	Cancer Discov	https://pubmed.ncbi.nlm.nih.gov/33355178/

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