LiFE report
Literature for ENYGO

LiFE | Literature for ENYGO

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

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Supported by ESGO

Issue No. 2 (12) December 2020

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Dear colleagues,

Even though the world is still caught in the middle of the COVID-19 pandemic, we were able to finalise LiFE 12. This edition includes reviews of publications in gynaecological oncology dating from March 31, 2020, through September 30, 2020. LiFE is an initiative of ENYGO supported by ESGO.

I can see from what we wrote to you in the preface of LiFE 11 that we all thought the pandemic would be over very soon. However, for some countries, conditions have seriously worsened again and Christmas was celebrated in a lockdown or maybe at work in a very difficult situation. We have become used to online meetings, but we miss the personal scientific exchange and networking of our international meetings. We therefore hope that LiFE is an especially relevant resource for you this year, so you can stay up to date and familiarise yourself with the most important publications in gynae-oncology.

This issue was supported by reports from our new authors Sunaina Wadhwa (India), Anastasia Prodromidou (Greece) and Anastasios Pandraklakis (Greece).

Our editorial team will undergo some changes for future issues. I will step down as editor-in-chief, and I am very happy that Zoia Razumova will take on this responsibility in my place. Anna Maria Schütz (Austria) and Stamatios Petousis (Greece) have joined the editorial team, and we are very much looking forward to working with these new members of the team. We also like to thank all of you who participated in our social media campaign, which will get even more attention in 2021. It has been a great journey with all of you to where we are with LiFE today, and I wish to thank you all for your ongoing effort and enthusiasm. It has been a great pleasure to work with you all.

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

We hope you will enjoy LiFE 12 and find it interesting and informative!

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

Stay safe and we wish you all the best for 2021!

Yours,

The LiFE team

Kristina Lindemann
Kamil Zalewski
Michael J. Halaska
Zoia Razumova

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Medical treatment of primary ovarian cancer

Ilker Selçuk

PARP inhibitor–olaparib

This subgroup analysis of the SOLO1 phase III, multicentre, randomised, double-blind study that investigates the role of maintenance with olaparib (300 mg twice daily) against placebo in newly diagnosed stage III or IV high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer patients with BRCA mutation, regardless of the prior surgical status (upfront or interval cytoreductive surgery), residual disease (no gross or residual) and tumour response (complete response or partial response) was published by DiSilvestro et al. The median follow-up period was 41 months, and median treatment duration was 24.6m versus 13.9m in the olaparib and placebo arms, respectively. The percentage of progression-free patients who had undergone upfront surgery and received olaparib were higher than the placebo group in the 1st (91% vs 58%), 2nd (78% vs 40%), and 3rd (69% vs 32%) years. The superiority of olaparib was also shown in the interval cytoreductive surgery group with more patients being progression-free in the third year (47% vs 19%). In the no-gross-residual-disease group, the percentage of progression-free patients at three years was higher in the olaparib arm than the placebo arm (65% vs 29%). The percentage of progression-free patients in residual disease after surgery group at three years was also higher in the olaparib arm (48% vs 24%). The percentage of progression-free patients was higher in the olaparib arm than the placebo arm in the complete response group at three years (65% vs 29%) and also in the partial response group at three years (50% vs 20%). The objective response rate in patients with a radiologic evidence of disease at baseline was 43% for the olaparib arm and 23% for the placebo arm. When BRCA 1 and 2 patients were compared, the percentage of progression-free patients was higher in the BRCA 2 group than the BRCA 1 group, with olaparib maintenance treatment at three years (80% vs 53%). These results showed that olaparib maintenance in newly diagnosed advanced ovarian cancer patients improved outcomes irrespective of the these patient baseline characteristics. [1]

Dose-dense chemotherapy

The results of the ICON-8 randomised, phase III, three-arm (group 1, 522 patients, three-weekly carboplatin AUC 5/6 and three-weekly paclitaxel 175 mg/m^2; group 2, 523 patients, three-weekly carboplatin AUC 5/6 and weekly paclitaxel 80 mg/m^2; and group 3, 521 patients, weekly carboplatin AUC 2 and weekly paclitaxel 80 mg/m^2) trial in newly diagnosed stage IC–IV epithelial ovarian, primary peritoneal, and fallopian tube carcinoma patients showed that a weekly dose-dense paclitaxel-containing regimen provided no progression-free survival benefit compared to the three-weekly standard regimen in patients of European ethnicity. The cross-sectional and longitudinal quality of life (QoL) analyses were published by Blagden et al. and reported on the 828 (65%) of 1,280 patients with completed QoL measurements. The analysis included a cross-sectional analysis at nine months and a longitudinal analysis of the mean QLQ-C30 global health score between baseline and nine months. The cross-sectional analysis showed no significant difference in the QLQ-C30 global health score between the three groups (group 2 vs group 1, mean difference 2.3, 95% CI: -0.4–4.9, p = 0.094; group 3 vs group 1, mean difference -0.8, 95% CI: -3.8–2.2, p = 0.61). The longitudinal analysis showed a lower mean global health score among the patients in the weekly treatment regimen (group 2 vs group 1, mean difference -1.8, 95% CI: -3.6–0.1, p = 0.043; and group 3 vs group 1, mean difference -2.9, 95% CI: -4.7– -1.1, p = 0.018), but differences were of marginal clinical significance. Between the groups, there were not any differences in social and emotional functioning. The cross-sectional analysis showed no difference in fatigue scores between the groups; however, in the longitudinal analysis, patients in the weekly group 2 scored significantly higher for fatigue symptoms but this was not clinically significant. The cross-sectional analysis showed a significantly higher level of peripheral neuropathy in the weekly groups 2 and 3; however, with no difference in the longitudinal analysis. In post-hoc analysis, neuropathy scores still persisted at 18 months in all groups. The study indicates that it takes a longer time for the patients on the weekly regimen to improve the global health score during the treatment period but they returned to a similar level at nine months. The lack of a benefit for progression-free survival in this European population does not justify the routine administration of a weekly chemotherapy regime and is in contrast to the findings from the Japanese JGOG-3016 study. [2]

The national, Australian, prospectively collected cohort data of the Ovarian cancer Prognosis And Lifestyle (OPAL) study evaluated the impact of chemotherapy dose delay and reductions in patients with newly diagnosed epithelial ovarian cancer. Patients received three-weekly carboplatin AUC 5/6 and paclitaxel 175 mg/m^2 (309 patients) or carboplatin AUC 5/6 and weekly paclitaxel 80 mg/m^2 (325 patients) either in an adjuvant or neoadjuvant setting. There was a higher proportion of stage III/IV (83% vs 63%) and high-grade serous (79% vs 62%) disease in the dose-dense arm. Twenty-four percent (n = 72) and 40% (n = 129) of patients received neoadjuvant chemotherapy and no residual disease was achieved in 66% and 62% of patients in the three-weekly and weekly chemotherapy group, respectively. Dose reductions in either carboplatin or paclitaxel were significantly more common in the weekly dose-dense chemotherapy regimen group than the three-weekly group, 49% (95% CI: 43–54) and 29% (95%: CI 24–34), respectively. At least one dose delay was significantly more common in the dose-dense cohort 58% (95% CI: 52–63) compared to the three-weekly cohort 28% (95% CI: 23–33), p < 0.001. Haematological toxicities were significantly more common in the dose-dense group; however, the percentage of moderate or severe neuropathy was similar. The median PFS was 29.2m (22.9–43.8) and 21.5m (19.5–23.3) and the median OS was 69.5m (60.6–not reached) and 62.4m (56.3–74.5) for the three-weekly and dose-dense cohorts, respectively. When adjusted for FIGO stage, histology, and age, there were no differences in the progression-free survival and overall survival between the three-weekly and dose-dense administration, despite the increased rate of dose reductions and dose delays in the dose-dense cohort. [3]

Medical treatment of primary ovarian cancer

Ilker Selçuk

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

No	Title	Authors	Journal	Link to abstract
1	Efficacy of maintenance olaparib for patients with newly diagnosed advanced ovarian cancer with a BRCA mutation: Subgroup analysis findings from the SOLO1 trial	DiSilvestro P et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/32749942/
2	Weekly platinum-based chemotherapy versus 3-weekly platinum-based chemotherapy for newly diagnosed ovarian cancer (ICON8): quality-of-life results of a phase 3, randomised, controlled trial	Blagden SP et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/32615110/
3	Evaluating the impact of dose reductions and delays on progression-free survival in women with ovarian cancer treated with either three-weekly or dose-dense carboplatin and paclitaxel regimens in the national prospective OPAL cohort study	Sivakumaran T et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32381362/

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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

In a single-centre, randomised controlled trial, Fagotti et al. analysed whether neoadjuvant chemotherapy is superior to primary debulking surgery in terms of perioperative complications and progression-free survival in patients with stage IIIC/IV ovarian, tube, and peritoneal cancer. The trial enrolled 171 patients: 84 in the primary debulking surgery group and 87 in the neoadjuvant chemotherapy group. All patients underwent diagnostic laparoscopy to obtain a histologic diagnosis and to assess the tumour load. Patients were randomised at the time of laparoscopy. Two patients were lost to follow-up during treatment and 26 patients did not complete treatment. Finally, 143 patients were included, 71 in the primary debulking surgery arm and 72 in the neoadjuvant chemotherapy arm. Patients in the primary debulking surgery arm received six cycles of paclitaxel (175 mg/m^2) and carboplatin (AUC 6) and those in the neoadjuvant chemotherapy arm received three or four cycles of preoperative chemotherapy and completed up to six cycles after surgery. Carboplatin/paclitaxel was the most common chemotherapy schedule employed (93.3%). Bevacizumab was given in 31 patients in arm A and 42 in arm B ($p = 0.34$). Complete resection was achieved in 47.6% versus 77% of those who underwent primary debulking surgery and neoadjuvant chemotherapy, respectively ($p = 0.001$). The need for upper abdominal surgery was significantly higher in the primary debulking surgery group. Primary debulking surgery was associated with a longer operative time hospital stay compared to neoadjuvant chemotherapy. Major postoperative complications occurred in 26% and 7.6% of the surgery and chemotherapy groups, respectively. Seven of the 84 patients (8.3%) in the primary debulking surgery group died of early or late postoperative complications, which is a high mortality rate in this population. No postoperative death occurred in the chemotherapy group. The median overall survival was 41 and 43 months in the surgery and chemotherapy arms, respectively (HR 1.12, 95% CI: 0.76–1.65, $p = 0.56$). The median progression-free survival, which was the secondary endpoint of the study, was 15 months in the primary debulking surgery and 14 months in the neoadjuvant chemotherapy arm (HR 1.05, 95% CI: 0.77–1.44, $p = 0.73$). The monocentric design limits this study's generalisability, while the lack of statistical power to show significant differences in progression-free survival are the main limitations of the study. The results of TRUST trial, an adequately powered phase III trial which randomised advanced ovarian cancer patients regardless of their tumour load, are awaited. [1]

ERAS for ovarian cancer

A single-centre, randomised clinical trial by Sanches-Iglesias et al. aimed to compare ERAS to conventional care for patients with advanced ovarian cancer undergoing cytoreductive surgery. The ERAS and conventional management groups included 50 and 49 patients, respectively. The ERAS protocol was based on the guidelines of the ERAS society published in 2013. Overall compliance with the ERAS protocol was 92%. Patients in the ERAS group had a statistically significant decreased median length of stay in hospital (7 vs 9 days, $p = 0.009$) and a decreased rate of readmission (6% vs 20%, $p = 0.033$). No significant difference in the incidence of intra- and postoperative complications, severe complications, reoperation, or mortality was observed between groups. The small number of included patients and single-centre design limit the conclusions of the study. [2]

Multimodality triage algorithm

In a retrospective study performed at MSKCC, Straubhar et al. reported on the implementation and outcomes of a multimodal triage algorithm to triage advanced ovarian cancer patients to primary debulking surgery vs neoadjuvant chemotherapy. All patients underwent chemotherapy of the whole abdomen. Eleven predefined sites, including the lesser sac, splenic hilum or splenic ligaments, root of the superior mesenteric artery, small bowel mesentery, retroperitoneal lymph nodes above the renal hilum, supradiaphragmatic lymph nodes, ascites, gastrohepatic ligament or porta hepatis lesions, gallbladder fossa, and stage IV disease. Combining the preoperative ovarian cancer radiologic and clinical assessment, the Resectability Score 1 was calculated and used by the primary surgeon for clinical decision-making. Patients with a Resectability Score 1 (of possible scores 0–6) were recommended to undergo laparotomy, with an option for diagnostic laparoscopy at the surgeon's discretion. Among them, 19% underwent laparoscopy with subsequent triage of 72% primary debulking surgery and 18% neoadjuvant chemotherapy. Those with a score of 7 or more were recommended to undergo laparoscopic evaluation. Seventy percent of patients with a high-risk score underwent laparoscopy, with subsequent triage of 55% primary debulking surgery and 45% neoadjuvant chemotherapy. A total of 299 patients were analysed. While 76% of them had a score of 0–6, the remaining had a score of 7 or more. Overall, 83% underwent primary debulking surgery, with a 75% complete cytoreduction and 94% optimal cytoreduction rates. The retrospective, single-centre design was the study's main limitation. [3]

HIPEC with primary debulking surgery

Lei et al. performed a multicentre, retrospective cohort study of patients with advanced ovarian cancer who underwent primary debulking surgery. HIPEC was administered using the closed technique. Cisplatin at a dose of 50 mg/m^2 was circulated at 41–43ºC for 60 minutes. The HIPEC procedure was recommended to be performed on days 1, 3, and 5. The median follow-up period was 42.2 (range 33.3–51.0) months. Of the 584 patients, 425 underwent HIPEC. The median overall survival time was 49.8 (95% CI: 45.2–60.2) months for patients undergoing primary debulking surgery with HIPEC and 34.0 (95% CI: 28.9–41.5) months for patients undergoing primary debulking surgery alone, and the three-year overall survival rate was 60.3% (95% CI: 55.3%–65.0%) for patients undergoing primary debulking surgery with HIPEC and 49.5% (95% CI: 41.0%–57.4%) for patients undergoing primary debulking surgery alone (HR 0.64, 95% CI: 0.50–0.82, $p < 0.001$). For patients in whom complete primary debulking surgery was reached and HIPEC was performed, the median overall survival for patients with complete resection after primary debulking surgery with HIPEC was associated with the best survival outcomes, with a median overall survival of 53.9 months and a three-year overall survival rate of 65.9%. In patients who received complete primary debulking surgery alone, the median overall survival was 42.3 months ($p = 0.2$), and the three-year overall survival rate was 55.4% ($p = 0.04$). Its retrospective design and the lack of homogeneity in the selection of the patients are the main limitations of the study. [4]

Surgical treatment of primary and recurrent ovarian cancer

Ilker Kahramanoglu and Patriciu Achimas-Cadariu

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

No	Title	Authors	Journal	Link to abstract
1	Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850)	Fagotti A et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33028623/
2	PROFAST: A randomised trial implementing enhanced recovery after surgery for high complexity advanced ovarian cancer surgery	Sanchez-Iglesias JL et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/32688208/
3	A multimodality triage algorithm to improve cytoreductive outcomes in patients undergoing primary debulking surgery for advanced ovarian cancer: A Memorial Sloan Kettering Cancer Center team ovary initiative	Straubhar AM et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32518012/
4	Evaluation of cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for stage III epithelial ovarian cancer	Lei Z et al.	Jama Netw Open	https://pubmed.ncbi.nlm.nih.gov/32840622/

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Medical treatment of recurrent ovarian cancer

Seda Şahin Aker and Mara Mantiero

Sorafenib is a multi-kinase inhibitor of b-Raf and c-Raf and also targets p38, c-Kit, VEGFR2-3, and PDGFR-beta. Lee et al. performed a phase II trial of bevacizumab (5 mg/kg q14) and sorafenib (200 mg every 12 hours on day 1–5 of a 7-day week) in recurrent ovarian cancer patients with or without prior bevacizumab treatment. Fifty-four women were enrolled: 41 bevacizumab-naïve and 13 bevacizumab-prior. All were heavily pre-treated; 83% of the bevacizumab-naïve cohort and all patients in the bevacizumab-prior cohort had platinum-resistant disease. Twenty-six percent of the bevacizumab-naïve patients had a partial response, and 18 had stable disease > 4 months; no responses were seen in the bevacizumab-prior group, and 54% had stable disease. The bevacizumab and sorafenib combination did not meet the pre-specific primary endpoint of response rate. [1]

Tewari et al. performed a post-hoc analysis of the randomised phase II trial GOG01861 of bevacizumab (15 mg/kg q21) plus fosbretabulin (60 mg/m^2 q21) in recurrent ovarian cancer. Fosbretabulin is a tubulin-binding vascular disrupting agent; when it is combined with anti-angiogenesis therapy such as bevacizumab, the ongoing cellular necrosis within the tumour is accompanied by prevention of vessel regrowth. The study enrolled 103 evaluable patients. With an extended follow-up of nearly three years, the median progression-free survival of the experimental arm was 7.6 months compared to 4.8 months with bevacizumab alone (HR 0.74). Overall survival was similar to experimental and control arm (25.2 vs 24.2 months, HR 0.85, p = 0.46). The antivascular chemotherapy-free doublet studied did not impact survival. [2]

The ARIEL3 study evaluated the efficacy of rucaparib maintenance treatment compared with placebo in relapsed platinum-sensitive ovarian cancer. This randomised, double-blinded, multicentre, placebo-controlled, phase III study enrolled 564 patients with platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma. Patients were randomly assigned to rucaparib (n = 375) and placebo (n = 189). Patients were divided into three cohorts: the BRCA mutation group (n = 196), the homologous recombination deficient group (n = 354), and the intention-to-treat group (n = 564). Patients received oral rucaparib 600 mg twice daily or placebo in continuous 28-day cycles until disease progression, death, or other reason for discontinuation. The study gave the results of prespecified exploratory outcomes of chemotherapy-free interval, the time to start of first subsequent therapy (TFST), time to disease progression on subsequent therapy or death (PFS2), and time to start of second subsequent therapy (TSST). Median follow-up was 28·1 months. In the intention-to-treat population, median chemotherapy-free interval was 14.3 months in the rucaparib group versus 8.8 months in the placebo group (HR 0.43, 95% CI: 0.35–0.53, p < 0.0001), median TFST was 12.4 months versus 7.2 months (p< 0.0001), median PFS2 was 21.0 months versus 16.5 months (p =0.0002), and median TSST was 22.4 months versus 17.3 months (p = 0.0007). In the BRCA-mutant and homologous recombination-deficient cohorts, chemotherapy-free interval, TFST, PFS2, TSST were significantly longer in the rucaparib group. The limitation of this study was that it is an ongoing study with continuing follow-up data collection, overall survival data is not mature, and treatment unblinding was permitted upon investigator request if a decision regarding subsequent treatment depended on whether or not a patient had received previous PARP inhibitor therapy. The most common grade 3 or higher adverse events were anaemia or decreased haemoglobin and increased ALT/AST. [3]

The ESMO consensus convened a panel of 16 leading experts who updated recommendations on predictive biomarker testing for homologous recombination deficiency (HRD) and PARP inhibitor benefit in ovarian cancer. The aims of this project were to define the term 'HRD test', provide recommendations on the clinical utility of HRD tests in the clinical management of HGSC, provide an overview of the biological rationale, and the level of evidence supporting currently available HRD tests. The panel recommended evaluating the tumour tissue for assessment of somatic molecular alterations. There is currently insufficient evidence to determine the clinical validity of individual or panels of non-BRCA HRR genes, BRCA1 or RAD51C promoter methylation, whole genome sequencing based mutational signatures for predicting a PARPi response. Further prospectively collected data is required. In the first-line maintenance setting, germline and somatic BRCA mutation testing is routinely recommended and patients testing positive should receive a PARPi. A validated scar-based HRD test to establish the magnitude of benefit conferred by PARPi use in BRCA wild-type HGSC is recommended. The Myriad and myChoice assay were concurrently approved as a companion diagnostic for olaparib. In the platinum-sensitive relapse maintenance setting, BRCA mutation testing and a validated scar-based HRD test are recommended.[4]

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No	Title	Authors	Journal	Link to abstract
1	Phase II trial of bevacizumab and sorafenib in recurrent ovarian cancer patients with or without prior-bevacizumab treatment	Lee JM et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32747013/
2	Bevacizumab plus fosbretabulin in recurrent ovarian cancer: Overall survival and exploratory analyses of a randomized phase II NRG oncology/gynecologic oncology group study	Tewari SK et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32723679/
3	Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial	Ledermann JA et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/32359490/
4	ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer	Miller RE et al.	Ann Oncol	https://pubmed.ncbi.nlm.nih.gov/33004253/

Borderline ovarian tumours

Anton Ilin

The significant effect of lymph-node involvement on survival was demonstrated for selected patients with ovarian cancer. To evaluate similar patterns for patients with borderline ovarian tumours, Nusbaum et al. assessed cause-specific survival depending in the SEER database on the following approaches: any lymph node involvement, multiple involvement (two or more lymph nodes), and lymph node ratio. The authors found that the only independent factor was lymph-node ratio with the largest magnitude of significance ≥ 13% (adjusted HR 2.399, 95% CI: 1.163–4.947, p = 0.018). Fifteen-year rates were 75.7% versus 94.7%, compared to those without pelvic lymph node involvement. The authors highlight the lack of central pathology review as limitation of the study as the risk of misclassification of borderline tumours is high. There was also a lack of information on adjuvant treatment in the study. [1]

A higher recurrence rate has been described after fertility-sparing surgery compared with radical surgery. Taking into account that borderline ovarian tumours are often diagnosed in young patients, the question of surgery planning remains challenging in some cases. Chevrot et al. reported that live birth was observed in 63% of patients (n = 33) after fertility-sparing surgery. At the same time, 33% of the cases after recurrence had a live birth. [2]

A high pregnancy rate was also described in the paper of Plett et al. (82.9%, n = 29). The authors concluded that significant factors for relapse remained FIGO stages II–IV. The recurrence rate was reported to be 13.7% [3].

In this population-based study from Sweden, 213 patients underwent fertility-sparing surgery (86%, n = 183, unilateral salpingo-oophorectomy and 14%, n = 30, cystectomy). Of those who conceived naturally, 84% (n = 42) succeeded. Only 20 (9%) of the women underwent ART treatment. Overall survival was similar in women treated with fertility-sparing surgery and radical surgery. [4]

The reported results encourage consideration that fertility-sparing surgery may be safely performed in the early stages of borderline ovarian tumours. Secondary fertility-preserving cytoreductive surgery may also be applied in selected cases of local relapse after previous fertility-sparing surgery.

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No	Title	Authors	Journal	Link to abstract
1	Significance of lymph node ratio on survival of women with borderline ovarian tumors	Nusbaum DJ et al.	Arch Gynecol Obstet	https://pubmed.ncbi.nlm.nih.gov/32303888/
2	Fertility and prognosis of borderline ovarian tumor after conservative management: Results of the multicentric OPTIBOT study by the GINECO & TMRG group	Chevrot A et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32241341/
3	Fertility-sparing surgery and reproductive-outcomes in patients with borderline ovarian tumors	Plett H et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32115229/
4	Reproductive and obstetrical outcomes with the overall survival of fertile-age women treated with fertility-sparing surgery for borderline ovarian tumors in Sweden: a prospective nationwide population-based study	Johansen G et al.	Fertil Steril	https://pubmed.ncbi.nlm.nih.gov/32977941/

Treatment of ovarian sex cord stromal and germ cell tumours

Natalia Rodriguez Gómez-Hidalgo

Ray-Coquard et al. published an international, open-label, randomised phase II trial (ALIENOR) conducted at 28 referral centres across Europe and Japan in collaboration with the Rare Tumor committee of the Gynecological Cancer InterGroup. A sequential Bayesian design was applied. Sixty women with sex-cord-stromal tumours (predominantly granulosa cell tumours) that had relapsed after ≥ 1 platinum-based chemotherapy were randomised to receive either paclitaxel (n = 32) or paclitaxel + bevacizumab (n = 28). Regarding oncological outcomes, the estimated six-month progression-free rate was 71% (95% credible interval, 55%–84%) with paclitaxel alone and 72% (95% credible interval, 55%–87%) with paclitaxel-bevacizumab. The Bayesian estimate for the probability that the six-month progression-free rate distribution was higher with the combination than with paclitaxel alone was 57%, less than the predefined superiority threshold. This study is the first international randomised trial in sex-cord-stromal tumours and showed that adding bevacizumab to weekly paclitaxel does not improve clinical benefit despite the higher response rates observed in the combination arm (44%, 95% CI: 26%–65% vs 25%, 95% CI: 12%–43%). [1]

Derquin et al. reported on the results of a retrospective analysis to explore long-term outcomes and prognostic parameters in patients with ovarian germ cell tumours. The data were collected from the French reference network for Rare Malignant Gynaecological Tumours (TMRG). A total of 147 patients were included, of which 101 (68.7%) had FIGO stage I disease. Surgery was performed in 140 (95.2%) of the 147 included patients and 106 (72.1%) received first-line chemotherapy. Twenty-two patients with FIGO stage I disease did not receive chemotherapy. Overall, relapse occurred in 24 patients: 13 were exclusively treated with upfront surgery and 11 had received surgery and chemotherapy. The five-year event-free survival was 82% and five-year overall survival) was 92.4%. Five-year event-free survival in stage I patients who received adjuvant chemotherapy was significantly higher than in those who underwent surgery alone (94.4% vs 54.6%, $p < 0.001$). However, chemotherapy did not show an improvement in the five-year overall survival (96.3% vs 97.8%, $p = 0.62$). In conclusion, prospective trials through international collaborations are needed in order to define treatment strategies in such rare cancer subtypes. [2]

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No	Title	Authors	Journal	Link to abstract
1	Effect of weekly paclitaxel with or without bevacizumab on progression-free rate among patients with relapsed ovarian sex cord-stromal tumors: the ALIENOR/ENGOT-ov7 randomized clinical trial	Ray-Coquard I et al.	JAMA Oncol	https://pubmed.ncbi.nlm.nih.gov/33030515/
2	Need for risk-adapted therapy for malignant ovarian germ cell tumors: a large multicenter analysis of germ cell tumors' patients from French TMRG network	Derquin F et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32624235/

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

Anna-Maria Schütz

Several phase-I (demcizumab + paclitaxel, lifastuzumab vedotin + carboplatin ± bevacizumab, ofranergene obadenovec (VB-111) + paclitaxel) and phase-II (gemcitabine + berzosertib, ipilimumab + vivolumab) chemotherapy trials in ovarian cancer have been published recently.

Phase I

Coleman et al. performed an open-label phase IB (SIERRA) trial on demcizumab combined with paclitaxel in platinum-resistant ovarian-, peritoneal- and fallopian tube cancer. Nineteen patients with ≤ 4 prior chemotherapy regimens were enrolled. Demcizumab is a humanised monoclonal antibody that inhibits Delta-like ligand 4 (DLL4) and was administered iv in two cohorts (2.5 mg/kg and 5 mg/kg) on days one and 15, following a 3+3 dose escalation design. An intermediate dose level (3.5 mg/kg) was to be evaluated if the 5 mg/kg dose was not tolerable. Weekly 80 mg/m^2 paclitaxel was administered until unacceptable toxicity or disease progression. No dose limiting toxicity (DLT) was observed and the maximum tolerated dose was not reached; however, referring to previous studies, 3.5 mg/kg was determined to be the recommended phase II dose (RP2D). The most common adverse events were diarrhoea (68%), fatigue (58%), peripheral oedema (53%), and nausea (53%). Demcizumab-related pulmonary hypertension grade 1 or 2 was reported in 3 patients. The overall response rate was 21% (95% CI: 6–45%); clinical benefit rate was 42% (95% CI: 20–66%), median progression-free survival was 2.3 months, and median overall survival (OS) was 12.2 months (95% CI: 5.3–not reached). Keeping in mind the small study population, activity was shown in this heavily pre-treated cohort, with a median of > 3 prior chemotherapy lines. [1]

Moore et al. investigated the safety and tolerability of lifastuzumab vedotin (LIFA), an antibody-drug conjugate, in patients with recurrent platinum-sensitive ovarian cancer in an open-label, multicentre phase Ib study. Forty-one patients were enrolled. LIFA was given iv in dose escalation cohorts in combination with carboplatin (AUC 6) up to six cycles every three weeks. Dose expansion cohorts were enrolled with or without bevacizumab (15 mg/kg once every 3 weeks). Maximum tolerated dose was not reached. The RP2D was LIFA 2.4 mg/kg + carboplatin ± bevacizumab. All patients experienced ≥1 adverse event, most commonly neutropenia (73%), peripheral neuropathy (61%), thrombocytopenia (61%), nausea (49%), fatigue (46%), anaemia (32%), diarrhoea (29%), vomiting (29%), hypomagnesaemia (24%), increase aspartate aminotransferase (22%) and alanine aminotransferase (20%) as well as alopecia (17%). 43 (83%) patients had grade ≥ 3 adverse events like neutropenia or thrombocytopenia. Nine (22%) patients experienced serious adverse events; however, none of them was regarded as relating to LIFA. Median progression-free survival was 10.71 months (95% CI: 8.54, 13.86) with confirmed complete/partial responses in 24 (59%) patients. A CA-125 response was seen in 81%. Overall, this combination therapy has an acceptable safety in platinum-sensitive ovarian cancer; however dose reductions of LIFA as well as of carboplatin were frequent. [2]

Arend et al. performed an open-label phase I/II of ofranergene obadenovec (VB-111) in combination with paclitaxel in patients with platinum-resistant recurrent ovarian cancer. VB-111 has a dual mechanism of action: antiangiogenesis and induction of tumour directed intra-tumour immune response, such as is seen in viral immune-oncology. In phase I, patients were treated with VB-111 given at day 1 of every odd 28-day cycle (Q8W), following a 3+3 dose escalation. All patients received weekly paclitaxel. In phase II, patients received therapeutic doses of VB-111 and 80 mg/m^2 paclitaxel. Twenty-one patients were enrolled. They had a median of three prior lines of therapy and 50% of them had an anti-angiogenic therapy in the past. The most frequent adverse events included fatigue (52%), nausea (52%), fever (48%), anaemia (38%), diarrhoea (33%) and headache (29%). Six patients (29%) reported serious AEs, and nine (43%) reported grade ≥ 3 adverse events. The most common VB-111-related adverse events were transient mild-moderate fever/flu like symptoms. No dose-limiting toxicities were observed. In the therapeutic dose cohort, CA-125 response was seen in 58%. Median overall survival was 16.6 versus 5.8 months for the therapeutic and sub-therapeutic dose cohort, respectively. Thirteen percent of patients showed partial response and 60% had stable disease by RECIST criteria. [3]

Phase II

A randomised, open-label, multicentre phase II trial on berzosertib, a selective ATR inhibitor, in combination with gemcitabine versus gemcitabine alone in recurrent, platinum-resistant high-grade serous ovarian cancer was performed by Konstantinopoulos et al. Seventy patients who had ≤ 1 line of cytotoxic therapy in the platinum-resistant setting were enrolled. Patients received gemcitabine (1000 mg/m^2) iv on day 1 and 8 with (n = 34) or without (n = 36) berzosertib (210 mg/m^2) which was given on days 2 and 9 of a 21-day cycle. Comparing the combination to the gemcitabine alone arm, median progression-free survival was 22.9 versus 14.7 weeks. In patients with a platinum-free interval of ≤ 3 months, median progression-free survival was 27.7 versus 9.0 weeks (HR 0.29, 0.12–0.71; one-sided log rank test p = 0.0087) and in those with a platinum-free interval > 3 months, median progression-free survival was 18.6 versus 15.3 weeks (HR 1.04, 0.51–2.12; one-sided log-rank test p = 0.46). At data cut-off, 71% versus 81% had died. Median overall survival was 59.4 versus 43.0 weeks (HR 0.84, 0.53–1.32; one-sided log-rank test p = 0.26). In patients with a platinum-free interval of ≤ 3 months, median overall survival was 84.4 versus 40.4 weeks (HR 0.42, 0.19–0.94; one-sided log-rank test p = 0.034) and in those with a platinum-free interval of > 3 months it was 39.0 versus 59.9 weeks (HR 1.29, 0.73–2.31; one-sided log-rank test p = 0.23). Twenty-seven percent versus 25% showed a decrease in CA-125 level of more than 50%. The most common treatment-related grade 3 and 4 adverse events were neutropenia (47% vs 39%) and thrombocytopenia (24% vs 6%). Serious adverse events were observed in 26% versus 28%. There was one treatment-related death in the gemcitabine-alone group due to sepsis and one treatment-related death in the combination group due to pneumonitis. This study showed that the addition of the ATR inhibitor berzosertib to gemcitabine resulted in improved progression-free survival, mainly in the cohort with shorter platinum-free interval. This may be explained by the fact that tumours with a shorter platinum-free interval have indicators of greater replicative stress and therefore may be more likely to respond to ATR inhibition. Further investigation in a phase III trial is warranted. [4]

A randomised phase II trial performed by Zamarin et al. evaluated the efficacy of ipilimumab + nivolumab compared with nivolumab alone in patients with persistent or recurrent epithelial ovarian cancer who had a treatment of ≤ 3 prior regimens and a

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

Anna-Maria Schütz

platinum-free interval of <12 months. In total, 100 patients were enrolled. Sixty-two percent had a progression-free interval of < 6 months. They received nivolumab iv every two weeks with or without ipilimumab every three weeks for four doses, followed by a maintenance dose of nivolumab every two weeks for a maximum of 42 doses. Six (12.2%) versus 16 (31.4%) responses were reported within six months in the nivolumab group and the combination group, respectively (OR 3.28, 85% CI: 1.5–infinity; p = 0.034). Comparing the nivolumbab alone arm to the ipilimumab + nivolumab arm, stable disease was reported in 29% versus 39% of patients. The median progression-free survival was 2 versus 3.9 months (HR 0.53, 95% CI: 0.34–0.82, p = 0.004) and the median overall survival was 21.8 versus 28.1 months (HR 0.789, 95% CI: 0.439–1.418, two-sided p = 0.43). Grade ≥ 3 related adverse events occurred in 33% versus 49%, with no treatment-related deaths. Overall, the frequencies of grade 2–3 adverse events between the two treatment groups were not statistically different. PD-L1 expression was not significantly associated with response in either treatment group. The combination of nivolumab and ipilimumab showed a superior response rate and longer, although limited, progression-free survival. However, the majority of patients did not have a durable clinical benefit. [5]

Duska et al. performed a randomised phase II trial on gemcitabine + pazopanib versus gemcitabine alone in patients with persistent or recurrent epithelial ovarian cancer. In all, 148 patients who had ≤ 3 prior lines of chemotherapy were enrolled. Sixty percent of patients were platinum-resistant. Median follow-up was 13 months. There were no complete responses. Partial response rate (20% vs 11%) was higher in the combination arm. A disease control rate of 80% and 60% was observed in the combination and gemcitabine alone group, respectively. Median progression-free survival was longer in the combination arm (5.3 vs 2.9 months). Longer progression-free survival was observed in the platinum-resistant group (5.32 vs 2.2. months, Tarone-Ware p < 0.001). There was no difference in OS between the two arms. ≥ Grade 3 adverse events in the combination group included hypertension (15%), neutropenia (35%), and thrombocytopenia (12%). The addition of pazopanib to gemcitabine was associated with a longer progression-free survival, especially in the platinum-resistant setting; however, there was no significant difference in overall survival reported. [6]

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

No	Title	Authors	Journal	Link to abstract
1	Demcizumab combined with paclitaxel for platinum-resistant ovarian, primary peritoneal, and fallopian tube cancer: The SIERRA open-label phase Ib trial	Coleman R et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32037195/
2	Phase 1b study of anti-NaPi2b antibody-drug conjugate lifastuzumab vedotin (DNIB0600A) in patients with platinum-sensitive recurrent ovarian cancer	Moore K et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32534811/
3	Ofranergene obadenovec (VB-111) in platinum-resistant ovarian cancer; favorable response rates in a phase I/II study are associated with animmunotherapeutic effect	Arend R et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32265057/
4	Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial	Konstantinopoulos P et al.	Lancet Oncology	https://pubmed.ncbi.nlm.nih.gov/32553118/
5	Randomized phase II trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: an NRG oncology study	Zamarin D et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/32275468/
6	A randomized phase II evaluation of weekly gemcitabine plus pazopanib versus weekly gemcitabine alone in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma	Duska L et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32247603/

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

Kamil Zalewski

The total number of somatic mutations per coding area of a tumour genome (known as the tumour mutational burden or TMB) is an emerging clinical biomarker associated with response to immune checkpoint inhibitor therapy. Marabelle et al. published the results of the phase II KEYNOTE-158 study, showing the activity of pembrolizumab (200 mg iv every 3 weeks for up to 35 cycles) in patients with non-colorectal high microsatellite instability (MSI-H)/mismatch repair-deficient (dMMR) solid tumours. Among 40 patients with endometrial cancer, 20 (57.1%) had a response to the therapy, including eight patients with a complete response. Median progression-free survival was 25.7 months. The same group of authors, using the same data, correlated TMB with response to immune checkpoint blockade. The authors used a cut-off of 10 mutations per megabase to define tTMB-high and non-tTMB-high tumours. TMB was assessed in formalin-fixed paraffin-embedded tumour specimens. The authors showed that, although the survival benefits of the tTMB-high status with pembrolizumab treatment were not significant in the overall population, probably due to the inclusion of tumours characterised by poor prognosis and high treatment resistance, a great benefit was shown in some of the tumour-type-specific cohorts. Endometrial cancer patients showed improvement in median overall survival when comparing tTMB-high (22.7 months, 95% CI: 2.5–not assessable) to non-tTMB-high status (10.3 months, 95% CI: 7.6–14.9). Vulvar and cervical cancer were also positive. These results are discussed in the respective chapters of this LiFE report. The authors underlined that the predictive value of tTMB was reached irrespective of high MSI and tumour PD-L1 expression. In conclusion, tTMB-high status might serve as a predictive biomarker for patients with recurrent solid neoplasm after several lines of treatment that could potentially benefit from pembrolizumab monotherapy. [1, 2]

Miller and collaborators from The Gynecologic Oncology Group published the results of a study indicating optimal first-line therapy for advanced endometrial cancer. The phase III, randomised, therapeutic noninferiority, open-label GOG0209 study aimed to assess whether a less toxic regimen, carboplatin plus paclitaxel, is superior to paclitaxel-doxorubicin-cisplatin as first-line treatment in advanced or recurrent endometrial cancer based on noninferior efficacy and improved quality of life or less toxicity. Patients with stage III, stage IV, and recurrent endometrial cancer (n = 1,381) were enrolled 1:1 to arms with carboplatin + paclitaxel and paclitaxel-doxorubicin-cisplatin. The second regimen included a prophylactic granulocyte colony-stimulating factor. The exclusion criteria did not include radiotherapy and/or hormonal therapy, but chemotherapy was not accepted. After a median follow-up of 124 months, carboplatin + paclitaxel proved not to be inferior in terms of overall survival (median, 37 vs 41 months, HR 1.002; 90% CI: 0.9–1.12) and progression-free survival (median, 13 vs 14 months; HR 1.032; 90% CI: 0.93–1.15). The toxicity profile and quality of life were better for carboplatin + paclitaxel. The authors stated that it appears to be an acceptable and less toxic alternative to paclitaxel-doxorubicin-cisplatin. Even if the final results were first published now, carboplatin/paclitaxel has already been implemented as standrad first line treatment for advanced endometrial cancer. [3, 4]

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No	Title	Authors	Journal	Link to abstract
1	Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 Study	Marabelle A et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/31682550/
2	Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study	Marabelle A et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/32919526/
3	Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study	Fleming GF et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/15169803/
4	Carboplatin and paclitaxel for advanced endometrial cancer: Final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG0209)	Miller DS et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/33078978/

Surgical treatment of primary and recurrent endometrial cancer

Piotr Lepka

Mueller et al. retrospectively assessed the incidence of nodal metastasis in patients undergoing primary surgical staging for apparent endometrioid or serous endometrial carcinoma with bilateral sentinel lymph node procedure (SLN) including ultrastaging. The study confirms that patients with no myometrial invasion and endometrioid histology have a very low risk of nodal metastases. No micro- or macrometastases in SLNs were found among 510 patients with grade 1 or 2 tumours. Isolated tumour cells occurred only in two cases with grade 1 tumours. On the contrary, in the group of patients with serous endometrial histology, 5% (2/41) of patients with non-invasive tumours had micro- or macrometastases and 5% (2/41) had isolated tumour cells. In FIGO stage I, regardless of myometrial invasion, micro/macrometastases were present in 15% of cases with serous histology compared to 2% in grade 1, 6% in grade 2, and 9% in grade 3 tumours presenting with endometrioid histology. [1]

Grassi et al. retrospectively compared two different techniques of ultrastaging SLNs: longitudinal versus perpendicular cuts (called "bread loafing"), based on pathology specimens from 159 endometrial and 65 cervical cancer patients. In the endometrial cancer group, nine positive SLNs were found (9/38) with longitudinal cuts and 15 positive SLNs with the perpendicular cuts technique (15/121). In the cervical cancer cohort, four positive SLNs were detected by longitudinal incisions (4/18) and five with "bread loafing" (5/47). The authors did not find a statistically significant difference in the incidence of SLN metastasis detection within the two different types of ultrastaging protocols. [2]

In a multicentre retrospective study, Padilla-Iserte et al. evaluated a potential link between the use of a uterine manipulator and oncological outcomes in surgically treated patients with endometrial cancer. They enrolled 1,756 patients who underwent hysterectomy with uterine manipulator and 905 patients who were operated without it. Both groups were balanced with respect to histology, tumour grade, myometrial invasion, FIGO stage, and adjuvant therapy. In FIGO stage I and II, the recurrence rate was significantly higher in the uterine manipulator group compared to the group without: 11.69% versus 7.4%, respectively. Patients operated with use of a uterine manipulator in FIGO stages I and II had significantly shorter disease-free survival (HR 1.74, 95% CI: 0.57–0.97, p = 0.27) and a higher risk of death (HR 1.74, 95% CI: 1.07–2.83, p = 026). The retrospective design is a limitation of this study. [3]

Goebel et al. retrospectively re-evaluated 474 SLNs from 155 patients with endometrial cancer, which were considered primarily as negative. SLNs were re-evaluated with a immunohistochemistry protocol with cytokeratin staining at 1, 10, 20, and 50 µm levels to search for isolated tumour cells. In 21 SLNs previously reported as negative, isolated tumour cells were found. Among isolated-tumour-cell-positive patients, 61.9% (13/21) received no adjuvant therapy and none of them recurred after a median follow-up of 31.5 months (range 2–84.4). The role of the isolated tumour cell needs to be clarified in prospective studies. [4]

In a multicentre retrospective study (SENTIFAIL), Sozzi et al. assessed factors that may influence the failure of SLN mapping among 376 patients undergoing laparoscopic treatment of endometrial cancer. In the whole cohort, failure in bilateral mapping detection was 23.7%. After multivariate analysis, 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] were identified as independent predictors of failure of bilateral SLN mapping. [5]

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

No	Title	Authors	Journal	Link to abstract
1	Incidence of pelvic lymph node metastasis using modern FIGO staging and sentinel lymph node mapping with ultrastaging in surgically staged patients with endometrioid and serous endometrial carcinoma	Mueller et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32247604/
2	Two ultrastaging protocols for the detection of lymph node metastases in early-stage cervical and endometrial cancers	Grassi et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32376740/
3	Impact of uterine manipulator on oncological outcome in endometrial cancer surgery	Padilla-Iserte et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/32693096/
4	Retrospective detection of isolated tumor cells by immunohistochemistry in sentinel lymph node biopsy performed for endometrial carcinoma: is there clinical significance?	Goebel et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/31818860/
5	Laparoscopic sentinel node mapping with intracervical indocyanine green injection for endometrial cancer: the SENTIFAIL study - a multicentric analysis of predictors of failed mapping	Sozzi et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32868384/

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

Stamatios Petousis

Fader et al. published an updated analysis of a prospective randomised phase II trial of 61 patients comparing carboplatin-paclitaxel with carboplatin-paclitaxel-trastuzumab in advanced or recurrent uterine serous carcinomas overexpressing Her-2/neu. Median progression-free survival was 7.0 months versus 9.2 months among patients with recurrent disease (HR = 0.12, 90% CI: 0.03–0.48; p = 0.004), and 9.3 months versus 17.7 months in patients included with primary stage III and IV disease HR = 0.44, 90% CI: 0.23–0.83, P = 0.015. The study showed an overall benefit for overall survival of 29.6 months versus 24.4 months (HR = 0.58, 90% CI: 0.34–0.99, p = 0.046), again most pronounced in patients with primary advanced disease. Toxicity was not demonstrated to be different between arms. Therefore, the authors concluded that the addition of trastuzumab to standard treatment with carboplatin-paclitaxel was beneficial for recurrent uterine cancer patients who are positive in Her-2/neu. [1]

Vergote et al. performed an international, open-label single-arm, multicentre, phase II trial to assess the efficacy of lenvatinib, a multitargeted tyrosine kinase inhibitor, as second-line therapy in patients with unresectable endometrial cancer. There were 133 patients included in the study, all of whom had histologically confirmed unresectable endometrial cancer that relapsed after one prior systemic platinum-based chemotherapy. The authors reported that durable stable disease was observed in 23.3% of patients and a clinical benefit rate of 37.5% was seen. Median progression-free survival was 5.6 months and median overall survival 10.6 months. The most common treatment-related adverse events were fatigue/asthenia, hypertension, and nausea/vomiting. They concluded that patients with recurrent endometrial cancer treated with second-line lenvatinib experience modest antitumour activity and treatment was generally well tolerated. [2]

Dhani et al. published a phase II trial of cabozantinib in recurrent/mestastatic endometrial cancer. This was a single-arm study evaluating cabozantinib in 102 women with progression after chemotherapy. In serous and endometrioid histology endometrial cancer regimens, it demonstrated response rates of 12% and 14% with a median progression-free survival of 4.8 and 4.0 months, respectively. However, its effectiveness in uncommon histology endometrial cancer (including carcinosarcoma) was demonstrated to be poor. The authors suggested that further evaluation in genomically characterised patient cohorts should be performed in an effort to identify those populations for whom this regimen may present optimal activity. [3]

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No	Title	Authors	Journal	Link to abstract
1	Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis	Fader NA et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/32601075/
2	Second-line lenvatinib in patients with recurrent endometrial cancer	Vergote I et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/31955859/
3	Phase II trial of cabozantinib in recurrent/metastatic endometrial cancer: A study of the Princess Margaret, Chicago, and California Consortia (NCI9322/PHL86)	Neesha C et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/31992589/

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

Zoia Razumova

DNA mismatch repair

Cancer cells with a lot of mutation-induced neoantigens are often widely presented in DNA mismatch repair (MMR)-deficient and microsatellite-unstable (MSI) tumours. MMR deficiency causes indel at coding microsatellites (cMS) and to neoantigen-inducing translational frameshifts. Ballhausen et al. created a method to calculate frameshift mutations in several MSI cancers, including endometrial cancer. The authors found that frameshift mutation frequency and the immunogenicity of the resulting peptides are negatively correlated. However, there was no correlation in tumours with Beta-2-microglobulin mutations and HLA-A*02:01 status, which is related to cMS mutation patterns. Besides, specific outlier mutations are often presented in MSI tumours, not only related to frameshift peptides with functionally confirmed immunogenicity. It suggests a potential leading role in MSI cancer evolution. The authors concluded that neoantigens resulting from shared mutations might be potential vaccines for MSI cancer prevention. [1]

Deficient DNA mismatch repair (dMMR) induces a hypermutator phenotype that might precede carcinogenesis. McGrail et al. demonstrated that dMMR-induced destabilising mutations cause proteome instability in dMMR tumours. It results in a high number of misfolded protein aggregates. Therefore, dMMR cells utilise a Nedd8-mediated degradation pathway to alleviate the clearance of the misfolded proteins. Also, Nedd8 clearance pathway with MLN4924 blockage leads to accumulation of misfolded protein aggregates, inducing immunogenic cancer cell death in dMMR tumours. The authors combined MLN4924 treatment with PD1 inhibition to consolidate immunogenic cell death. They found that the combined treatment significantly improved MLN4924 treatment efficacy over treatment alone. [2]

Sestrin2

Sestrin2 is a stress-inducible protein involved in homeostatic regulation by repressing reactive oxygen species and the mammalian target of rapamycin complex 1 (mTORC1). Shin et al. investigated Sestrin2 expression, mechanisms, and clinical relevance in endometrial cancer. Sestrin2 was upregulated in endometrial cancer in compression with normal endometrial tissues. Sestrin2 expression was also strongly associated with mTORC1 activity. Moreover, Sestrin2 upregulation correlated with shorter survival rates in patients with endometrial cancer. The authors concluded that Sestrin2 has a prognostic significance and might be a potential therapeutic target in endometrial cancer. [3]

Androgen receptor signalling

Androgen receptor signalling might have biological activity in gynaecological cancer, including type I endometrial cancer. Koivisto et al. evaluated the efficacy of enzalutamide (a 3rd generation androgen receptor antagonist) in a genetic mouse model of endometrial cancer. The authors showed that enzalutamide induces apoptosis in endometrial cancer. However, the drug has a low efficacy as a single treatment. Induction of progesterone receptors showed that combining progestin and enzalutamide might further decrease tumour burden and result in a prolonged response. [4]

Sulforaphane

Sulforaphane has an anti-cancer effect in many cancers. Rai et al. evaluated the utility of sulforaphane for endometrial cancer therapy. They showed that the compound induced apoptosis-associated growth inhibition of Ishikawa xenograft tumours better than paclitaxel and without any toxicity. The authors concluded that sulforaphane is a potential non-toxic endometrial cancer treatment. [5]

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

No	Title	Authors	Journal	Link to abstract
1	The shared frameshift mutation landscape of microsatellite-unstable cancers suggests immunoediting during tumor evolution	Ballhausen A et al.	Nat Commun	https://pubmed.ncbi.nlm.nih.gov/32958755/
2	Proteome instability Is a therapeutic vulnerability in mismatch repair-deficient cancer	McGrail DJ et al.	Cancer Cell	https://pubmed.ncbi.nlm.nih.gov/32109374/
3	mTOR-dependent role of Sestrin2 in regulating tumor progression of human endometrial cancer	Shin J et al.	Cancers (Basel)	https://pubmed.ncbi.nlm.nih.gov/32899752/
4	Evaluating the efficacy of enzalutamide and the development of resistance in a preclinical mouse model of type-I endometrial carcinoma	Koivisto CS et al.	Neoplasia	https://pubmed.ncbi.nlm.nih.gov/32818842/
5	Preclinical efficacy and involvement of AKT, mTOR, and ERK kinases in the mechanism of sulforaphane against endometrial cancer	Rai R et al.	Cancers (Basel)	https://pubmed.ncbi.nlm.nih.gov/32443471/

Uterine sarcoma

Marcin Bobiński

Ray-Coquard et al. reported the results of a phase II clinical trial that evaluated the role of maintenance therapy with cabozantinib in high-grade uterine sarcoma after chemotherapy or in primary metastatic cancer. The study analysed the responses of 35 patients treated with cabozantinib versus placebo in a 1:1 randomisation. The authors reported difficulties conducting the trial, including insufficient patient enrolment, a high drop-out rate, and non-compliance in tumour assessment. Further, central pathology review led to a change in diagnosis in one third of the patients. Due to insufficient patient recruitment (54 were planned to be randomised), the study is not yet completed. [1]

A United States-wide report by Nasioudis et al. aimed to assess the impact of bilateral salpingo-oophorectomy on overall survival among premenopausal patients with FIGO stage I, low-grade endometrial stromal sarcoma. The study included patients younger than 50 years old, operated in the United States from 2004–2015. Of the 743 included patients, 541 underwent bilateral salpingo-oophorectomy. The main limitations of the study were the lack of information on patients' menopausal status and differences in the median age of patients in both groups (43 vs 45). The main result of the trial indicated that none of analysed clinical approaches (bilateral salpingo-oophorectomy or ovarian preservation) was associated with survival benefit (5-year survival 96.2% for patients after bilateral salpingo-oophorectomy vs 97.1% for those with preserved ovaries). Furthermore, radiotherapy was used in 9% of patients, which is not standard of care. Although the percentage of patients treated with radiotherapy was higher in the bilateral salpingo-oophorectomy group (10.2% vs 5.9%, $p > 0.05$), but no sensitivity analysis excluding the group of radiated patients was performed. [2]

Hensley et al. presented the genomic profiling of uterine sarcomas based on tumour samples from 107 patients. Forty-five percent of examined cases had an actionable mutation, i.e., BRCA2, and of these patients, only 17% received matched therapy. The study highlights the potential of molecular profiling of rare gynaecological tumours. [3]

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No	Title	Authors	Journal	Link to abstract
1	A randomized double-blind phase II study evaluating the role of maintenance therapy with cabozantinib in high-grade uterine sarcoma after stabilization or response to doxorubicin ± ifosfamide following surgery or in metastatic first line treatment (EORTC62113)	Ray-Coquard I et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32546554/
2	Effect of bilateral salpingo-oophorectomy on the overall survival of premenopausal patients with stage I low-grade endometrial stromal sarcoma; a National Cancer Database analysis	Nasioudis D et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32354469/
3	Genomic landscape of uterine sarcomas defined through prospective clinical sequencing	Hensley ML et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/32299819/

Surgical treatment of primary and recurrent cervical cancer

Bojana Gutic and Chrysoula Margioula-Siarkou

In a retrospective case-matched control study, Chen et al. examined the impact of laparoscopic versus laparotomic approach on survival outcomes in patients with stage IB1 cervical cancer with tumour size ≤ 2cm. The analysis included 1,852 women, half of whom were treated with laparoscopic radical hysterectomy, while abdominal radical hysterectomy was performed in the remaining 50%. The two studied groups had similar outcomes regarding five-year overall survival and disease-free survival rate. Sub-analysis according to histology showed no difference in survival between women treated with laparoscopy and those who underwent laparotomy in case of squamous carcinoma. On the other hand, histological types of adenocarcinoma and adenosquamous carcinoma were associated with a lower disease-free survival rate in the laparoscopic group (89.9% vs 98%, p = 0.006). The results are limited by the retrospective nature of the study, the difference in type of radical hysterectomy (the laparoscopic group had more type-C hysterectomies), and the lack of information on recurrence. [1]

Sakuragi et al. conducted a retrospective cohort study of 121 patients with early- and locally advanced cervical cancer who were treated with Okabayashi-Kobayashi radical hysterectomy in an effort to evaluate the oncological impact of this nerve-sparing surgical method. Two-thirds of the cases had early-stage cervical cancer (stages IB1 and IIA1, FIGO 2008), and one-third had locally advanced cancer (stages IB2, IIA2, IIB). The median follow-up period was 106 months. The five-year overall survival rate was 95% for the early-stage cancer group and 82% for the one with the locally advanced disease, while the rates of five-year local control were 99% and 87%, respectively. There were 18 cases of recurrences, all within the first three years following surgery. Adenocarcinoma, adenosquamous carcinoma, and lymph node metastasis were factors negatively associated with the overall survival rate. [2]

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

No	Title	Authors	Journal	Link to abstract
1	Laparoscopic versus abdominal radical hysterectomy for stage IB1 cervical cancer patients with tumour size ≤ 2 cm: a case-matched control study	Chen C et al.	Int J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/32062731/
2	Oncological outcomes after Okabayashi-Kobayashi radical hysterectomy for early and locally advanced cervical cancer	Sakuragi N et al.	JAMA Netw Open	https://pubmed.ncbi.nlm.nih.gov/32379332/

Radiotherapy of primary and recurrent cervical cancer

Erbil Karaman and Paweł Bartnik

Murofushi et al. conducted a study to investigate pre-brachytherapy magnetic resonance imaging (MRI) in locally advanced cervical cancer and tried to analyse whether the pre-brachytherapy MRI findings could lead to optimised radiation technique technique. This retrospective study included 146 patients. Non-conventional intracavitary brachytherapy was applied to 34 (23.3%) cases in accordance with the examination of pre-brachytherapy MRI results. The MRI examinations showed that brachytherapy was suitable for 133 (91.1%) cases and unsuitable for 13 (8.9%) cases. Multivariate analysis identified that the malignancy features like dimensions, shape, and depth of invasion were not found to be prognostic elements. However, inappropriate brachytherapy was found to be remarkably associated with diminished tumour local control ($p < 0.001$). [1]

A study by Serban et al. analysed the differences between brachytherapy applicators used in the treatment of cervical cancer. The 902 cases initially included in the EMBRACE I study were analysed in terms of EQD210, V85Gy and bladder, rectum, sigmoid, and vaginal 5-mm lateral-point doses (EQD23), depending on whether tandem/ovoids (T&O; 299 patients) or tandem/ring applicators (T&R; 603 patients) were used for brachytherapy. The intracavitary technique or intracavitary/interstitial techniques were separately taken into account. Patients treated with T&R showed a significantly better ratio when evaluating target, bladder/rectum doses, and V85Gy. The main weakness of this study is related to the centre-associated practice analysis in which EMBRACE cases were not treated according to a specific treatment algorithm. Also, the intracavitary or intracavitary /interstitial cases were evaluated within the same group. Therefore, this might have some effect on the interpretation of results. [2]

An international expert consensus published recommendations for radiotherapy in gynaecological cancers during COVID-19 pandemic. They divided the patients with all other gynaecologic cancers into three risk groups, depending on treatment priority. Given the high risk of rapid progression and high cure rates in cervical cancer, this group was only divided in two: group A, which included patients with severe bleeding and highly curable disease, and group B, which included patients whose therapy could safely be delayed up to 12 weeks. The consensus provided specific guidelines for radiotherapy during the COVID-19 pandemic for each group, A or B, and subgroups based mostly on FIGO classification. [3]

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

No	Title	Authors	Journal	Link to abstract
1	Outcomes analysis of pre-brachytherapy MRI in patients with locally advanced cervical cancer	Murofushi K et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32165406/
2	Ring versus ovoids and intracavitary versus intracavitary-interstitial applicators in cervical cancer brachytherapy: Results from the EMBRACE I study	Serban M et al.	Int J Radiat Oncol Biol Phys	https://pubmed.ncbi.nlm.nih.gov/32007365/
3	Radiation therapy for gynecologic malignancies during the COVID-19 pandemic: International expert consensus recommendations	Elledge CR et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32563593/

Medical treatment of primary and recurrent cervical cancer

Kristina Lindemann

The multi-cohort, open-label, non-randomised, phase II KEYNOTE-158 study included patients with histologically or cytologically confirmed advanced incurable solid tumours (anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, or vulvar). Patients were treated with 200 mg (IV) pembrolizumab every three weeks for up to 35 cycles. Patients were defined as TMB (tumour mutational burden) with at least 10 mutations per megabase. The cut-off was chosen in alignment with other clinical trials. This paper reported on the prespecified analysis of the association of TMB with a response to treatment. In all, 805 (76%) of the enrolled 1,073 patients were evaluable for TMB. Thirteen percent were classified as tTMB-high (high tissue TMB). But baseline characteristics were similar between tTMB-high and non-tTMB-high patients. The prevalence of tTMB-high tumours was 21%, 18%, and 15% among patients with cervical, endometrial, and vulvar cancer, respectively. After a median follow-up of 37.1 months, an objective response was recorded in 29% of the tTMB-high patients compared to 6% of the non-tTMB-high patients. A reduction of tumour measurement from baseline was achieved in 58% vs 35% of the patients. Median duration of response has not been reached for the tTMB-high cohort (2.2–34.8 months) but was 331 months (4.0–35.7 months) in the non-tTMB-high group. TMB score was not associated with PD-L1 expression. There was no statistically significant difference in progression-free survival or overall survival. Still, the visual inspection of the curves suggests a difference in favour of the tTMB high group over time. The question remains if TMB is a marker for good prognosis on standard treatment, rather than a predictive marker for response to immunotherapy as we lack data on the survival of these patients after standrad treatment. [1] A comment on this study was published by Bersanelli [2].

Treatment of locally advanced disease

This study is a randomised phase II open-label study of patients with locally advanced cervical cancer (FIGO 2009 IB-IVA cancer). Patients were randomised to pembrolizumab after or concurrent with chemoradiation for three infusions every three weeks. Chemoradiation included external beam radiation therapy or volumetric modulated arc therapy and image-guided brachytherapy. Standard doses were prescribed. Adverse events were determined by the individual treating physicians and reviewed by the overall principal investigator for the study. At the time of the report, 52 of the planned 88 patients had completed treatment. Short term and delayed toxicity were reported: 88% of the patients experienced grade 2 or higher. Eleven patients experienced at least a grade 4 adverse event; 23 at least one grade 3 adverse event. Diarrhoea, a potentially overlapping toxicity between chemoradiation and immunotherapy was reported by two patients at grade 3, six at grade 2, and 26 at grade 1. Two immune-related adverse events were reported, one hyperthyroidism and one colitis. The number of dose-limiting toxicities was found to be below the pre-defined threshold for stopping the study and is still ongoing. The regimen with both concurrent and subsequent pembrolizumab added to chemoradiation is currently explored in an international phase III trial (Keynote-A18/ENGOT-cx11/GOG3047). [3]

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

No	Title	Authors	Journal	Link to abstract
1	Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study	Marabelle A et al.	Lancet	https://pubmed.ncbi.nlm.nih.gov/32919526/
2	Tumour mutational burden as a driver for treatment choice in resistant tumours (and beyond)	Bersanelli M	Lancet	https://thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30433-2/
3	Results of an early safety analysis of a study of the combination of pembrolizumab and pelvic chemoradiation in locally advanced cervical cancer	Duska L et al.	Cancer	https://pubmed.ncbi.nlm.nih.gov/32910478/

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

Khayal Gasimli

In a Gynecologic Oncology Group phase II study, Santin et al. investigated the efficacy and tolerability of nivolumab as a monotherapy in patients with persistent and recurrent cervical cancer. Twenty-five patients with a good ECOG performance status and prior systemic chemotherapy (88% platinum-based) were analysed in this study. The median follow-up time was 32 months. PD-L1 expression was observed in 77.3% of the formalin-fixed paraffin-embedded tumour biopsy specimens. Nivolumab was administrated for two weeks until disease progression or intolerable adverse effects occurs (maximum 46 doses).

Toxicity and treatment-related adverse events (TRAE) were evaluated according to the National Cancer Institute Common Terminology Criteria version 4.0 (CTCAE v4.0). Response to nivolumab was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria until the disease progression.

The majority of patients suffered from TRAEs of different grades: 12% grade 1, 24% grade 2, 48% grade 3, 12% grade 4, 0% grade 5. The most common grade 3 adverse effects were detected as disorders in the blood and lymphatic system (12%), gastrointestinal system (20%), as well as of metabolism, and nutrition (20%). In this study cohort, partial response was observed in one case (4%) with 3.8 months of response. Nine patients (36%) exhibited stable disease with a median duration of 5.7 months. Increased response to nivolumab was noted in the remaining 60% of patients.

The estimated six-month survival rates for progression-free survival and overall survival were 16% and 78.4%, respectively. Despite its tolerable TRAEs, nivolumab monotherapy demonstrated a low response rate of 4% in patients with persistent or recurrent cervical cancer. [1]

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

No	Title	Authors	Journal	Link to abstract
1	Phase II evaluation of nivolumab in the treatment of persistent or recurrent cervical cancer (NCT02257528/NRG-GY002)	Santin AD et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31924334

Primary and recurrent vulvar cancer treatment

María de los Reyes Oliver and Rubén M. Betoret

Zapardiel et al. performed one of the largest international multicentre retrospective studies (the VULCAN study) to analyse the prognostic factors for overall and progression-free survival in patients with vulvar cancer. A total of 1,727 patients were included. In patients with squamous cell vulvar cancer, the most important predictors of recurrence were the number of positive nodes and lack of adjuvant treatment. Factors that impacted overall survival were the case volume at each center (≥9 vs <9 cases per year), number of positive nodes, FIGO stage, treatment with chemotherapy, surgical margins and stromal invasion > 5 mm. Parallel to that, Klaptor et al. evaluated the association between obesity and tumour recurrence in a cohort of 849 patients with vulvar cancer from the AGO-CaRE 1 study. A body mass index (BMI) >= 30 kg/m^2 was associated with a shorter time to recurrence and higher risk of local recurrence (33.3% vs 18.5%, p < 0.001). Understanding the limitations of the retrospective study, the authors discussed why obesity might influence the results of patients with vulvar cancer and pointed to the following mechanisms: increased tumour growth by tumour-promoting cytokines and hormones; lifestyle factors such as poor nutrition and little physical exercise; inadequate cancer screening or delayed detection by patient or doctor; inadequate primary surgery; inadequate adjuvant treatment and follow-up; and, finally, impaired survival is often detected in obese patients with insulin resistance. [1, 2]

Treatment for squamous cell vulvar cancer often leads to substantial and long-term morbidity. Because of this, there is a need to improve the identification of high-risk patients who really benefit from intensive therapies. In this line, Kortekaas et al. retrospectively stratified 413 squamous cell vulvar cancer patients based on p16 and p53 immunohistochemistry into three clinically subtypes: HPV-positive, HPV-negative/p53 mutated, and HPV-negative /p53 wildtype. HPV-negative/p53 mutated squamous cell vulvar cancer had worse overall survival and progression-free survival (HR 3.76, 95% CI: 2.02–7.00). The authors concluded that this classification may be used to guide treatment and follow up in future studies. [3]

Marabelle et al. prospectively explored the association of high tissue tumour mutational burden (tTMB-high) with outcomes in ten tumour-type-specific cohorts from the phase II KEYNOTE-158 study (multi-cohort, open-label, non-randomised study), which assessed the anti-PD-1 monoclonal antibody pembrolizumab in patients with selected previously treated advanced incurable solid tumours. A total of 790 patients were included, of them 71 with vulvar cancer. Despite being a single-arm study across multiple tumour types, which restricts the interpretation of the predictive value of tTMB in each tumour, the authors concluded that tTMB could be a useful biomarker to predict the efficacy of pembrolizumab monotherapy in these patients. The study is also discussed in the chapter on Medical treatment of primary and recurrent cervical cancer by Lindemann. [4]

Tagliaferri et al. analysed their clinical series of locally advanced vulvar cancer patients (35 patients) managed postoperatively with adjuvant treatment within the framework of a formal multidisciplinary tumour board. The authors showed that, for vulvar cancer patients treated according to multidisciplinary team internal recommendations for adjuvant radiotherapy (based on major and minor tumour criteria), after a median follow -up of 32 months, the progression-free survival and overall survival rates were 82.0% and 91.0%, respectively, with low rates of severe acute (12%) and late (3%) toxicities. In conclusion, they supported the benefit of a multidisciplinary personalised approach in the management of vulvar cancer. [5]

Regarding less-frequent histological types, Donizy et al. analysed the association between PARP1, PD-L1, and IDO1 and immunologic response in a total of 192 mucosal melanomas, including 83 vulvar melanomas. Tumours with high PARP1 expression and those with combined PARP 1 and IDO1 high expression correlated with worse overall survival (p = 0.026 and p = 0.015, respectively). Also, high PARP1 was a predictor of worse overall survival, independent of stage. Notwithstanding the limitations of the study (retrospective design and non-uniform treatments due to its multicentre nature), the authors concluded that these results raised the potential of combined targeted immunotherapy. [6]

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

No	Title	Authors	Journal	Link to abstract
1	Prognostic factors in patients with vulvar cancer: the VULCAN study	Zapardiel I et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32571891/
2	Association between obesity and vulvar cancer recurrence: an analysis of the AGO-Care-1 study	Klapdor R et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32467335/
3	Vulvar cancer subclassification by HPV and p53 status results in three clinically distinct subtypes	Kortekaas K et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32972785/
4	Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study	Marabelle A et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/32919526/
5	Multidisciplinary personalized approach in the management of vulvar cancer-the Vul.Can Team experience	Tagliaferri L et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32474446/
6	Up-regulation of PARP1 expression significantly correlated with poor survival in mucosal melanomas	Donizy P et al.	Cells	https://pubmed.ncbi.nlm.nih.gov/32380691/

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Follow-up after gynaecological malignancies

Sunaina Wadhwa

In a prospective cohort study, Luqman et al. compared a patient-initiated follow-up scheme with hospital follow-up amongst 187 women with low-risk endometrial cancer. The cohort was scheduled to attend 1,673 appointments with hospital follow-up, whereas only 69 clinic appointments and 107 telephone contacts were made with a patient-initiated follow-up scheme. The mean patient-related costs were reduced by 95.6% with patient-initiated follow-up. The total mileage travelled by patients for hospital follow-up was 30,891.4 miles, which was associated with a mean travelling time per patient of 7.41 hours and clinic/waiting time of 7.5 hours compared with 1,165.8 miles, 0.46 hours, and 0.5 hours, respectively, for patient-initiated follow-up. [1]

In a similar prospective audit on implementing a patient-initiated follow-up policy on 129 women in a UK-based gynaecological cancer centre, Coleridge and Morrison observed ten recurrence cases after a median follow-up of 60 months (1.4–109.1 months). Among ten recurred cases, four vaginal vault recurrences (all salvaged), three pelvic recurrences (all salvaged), and three patients with distant metastatic diseases (all died) were diagnosed during the follow-up. Five-year disease-specific survival was 97.3%. The cost saving to the health service of patient-initiated follow-up compared with a traditional hospital follow-up regimen was £116,403 (median £988.60 per patient, range £0–£1071), and patients saved an estimated £7122 in transport and parking costs. [2]

Both of the above studies had the limitation of elucidating the true cost, duration, waiting time, and potential of non-recording of patient contact. The introduction of a patient self-management follow-up scheme for low-risk endometrial cancer was associated with financial/time-saving to both the patient and the healthcare economy compared with hospital follow-up.

In a single institutional randomised study, Ngu et al. assessed nurse-led follow-up outcome with conventional oncologist-led follow-up in survivorship care of 385 patients with gynaecological malignancies. No significant difference in the detection of recurrence was observed in both follow-up protocols. However, women in the nurse-led arm scored higher on emotional ($p = 0.023$) and cognitive functioning ($p = 0.012$). In contrast, women in the gynaecologist-led arm scored higher on the HADS-anxiety scale ($p = 0.001$) and were more likely to report symptoms. [3]

A British gynaecological cancer society published the recommendations and guidance regarding the value, indications, and limitations of patient-initiated follow-up in gynaecological cancers to standardise practice and improve patient care. Patient-initiated follow-up could be offered to low-risk endometrial cancer patients, fully staged 1A/B ovarian cancer (of any grade) after treatment completion because of the low risk of relapse. For the follow-up of early-stage cervical cancer, hospital follow-up for the first two years was thought to be preferable to telephone follow-up because of surgery-associated comorbidities. Patient-initiated follow-up was not suitable for vulvar cancer patients, as regular clinical examination was considered necessary for early recurrence detection. [4]

Mancebo et al. proposed a surveillance algorithm for gynaecological cancer during SARS-CoV-2 (COVID-19) era and emphasised the telemedicine-based surveillance strategies protocol to avoid the infection risk. [5]

The extent of follow-up considering the patient preferences and patient-reported outcome measures are not yet clear. The multicentre observational PROMova study trial design was published in view of the lack of high-level evidence of patients' optimal follow-up with ovarian cancer. Results will be published by 2022. [6]

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

No	Title	Authors	Journal	Link to abstract
1	Patient-initiated follow-up for low-risk endometrial cancer: a cost-analysis evaluation	Luqman I et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32522772/
2	Patient-initiated follow-up after treatment for low risk endometrial cancer: a prospective audit of outcomes and cost benefits	Coleridge S and Morrison J	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32376734/
3	Nurse led follow-up in survivor-ship care of gynaecological malignancies. A randomised control trial	Ngu S-F et al.	Eur J Cancer Care (Engl)	https://pubmed.ncbi.nlm.nih.gov/32888339/
4	British Gynaecological Cancer Society recommendations and guidance on patient-initiated follow-up (PIFU)	Newton C et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32312719/
5	Gynecologic cancer surveillance in the era of SARS-CoV-2 (COVID-19)	Mancebo G et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/33020205/
6	Use of PROM during follow-up of patients with ovarian cancer: the PROMova study protocol	Kargo AS et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32586892/

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Screening of gynaecological cancers

Geanina Dragnea

Cervical cancer

The European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC) published a position paper on cervical screening. It was concluded that a HPV test should replace cytology as it provides better protection against cervical cancer and allows longer screening intervals. Given the low specificity of these tests, triage tests are needed to select women for colposcopy. In this setting, reflx cytology is the only test that has been validated. HPV-based screening is more cost-effective than cytology or co-testing and should be performed in the post-vaccination era as well. Personalized screening frequencies according to patient characteristics, such as vaccination status, need to be implemented. Self-sampling might present an option in under-screened women. [1]

EFC and ESGO also released joint advice on the management of cervical cancer screening and prevention during the ongoing COVID-19 pandemic. Cancer prevention and early diagnosis may be postponed, with the aim of balancing between patient care, local COVID-19 trends, and health systems' capacity. In countries that have adopted primary screening for high-risk HPV, HPV samples should be collected simultaneously with liquid-based cytology to reduce the number of consultations. Time until colposcopic evaluation will depend on the severity of cytology, varying between four weeks up to six–12 months. The evaluation for histopathologic diagnosis or symptoms suspicious for lower genital tract cancers should be done within two weeks, the surgical treatment for high-grade lesions within three months; follow-up for CIN 2, VAIN 2, or VIN 2 should be within six months and up to 12 months for low-grade intraepithelial lesions. After treatment for high-grade disease, the high-risk HPV (with or without cytology) should be performed after six months. Elective diagnostic and surgical procedures should be resumed when there is a sustained reduction in the rate of new COVID-19 cases for at least 14 days. Screening centres and colposcopy clinics should implement virtual consultations. HPV self-sampling can be used, being as accurate as that taken by clinicians. Follow-up in those with a HPV-positive self-sample must be assured. Women presenting with COVID-19 should delay colposcopy, unless there is a strong suspicion of invasive pathology. In that case, evaluation should not be deferred, but patients should wear a surgical mask, and all team members should wear appropriate personal protective equipment. [2]

Turkey's cervical cancer screening programme was evaluated based on the first 4 million participants. This call and recall system screening programme for women aged 30–65 consists of HPV-DNA tests at five-year intervals; if HPV positive, extended genotyping and conventional cytology were performed. In all, 4.39% were found to be HPV DNA-positive; the most common HPV types were 16, followed by 51, 31, 52, 56, and 18. The study revealed the importance of other HPV types such as 33, 31, 35, and 45 that had a positive predictive value of more than 10% for ≥ CIN 2. The Turkish screening programme with HPV DNA and referral to colposcopy if tested HPV 16 or 18 positive or having any smear abnormality ≥ ASC-US gives an overall positive predictive value of 24.3% for ≥ CIN 2 while Pap-smear triage of non-genotyped HPV-positive women alone revealed a positive predictive value of 26.4% for ≥ ASC-US. The results showed the feasibility of this screening method with acceptable colposcopy referral rates. Among triage tests, Pap-smear seems to be effective without a need for extended genotyping. [3]

In a European prospective single-centre study, 388 patients with histologically confirmed HSIL and AIS were screened before intervention with both Cobas (HPV-DNA) and Aptima (HPV E6/7 mRNA) tests prior to definite treatment. The CHIPRON HPV 3.5 LCD-array test, which detects 32 HPV types, was used on the cases with negative Cobas and/or Aptima HPV tests. The objective was to correlate p16ink4a-positive cervical precancers with the preceding clinical Cobas and Aptima screening test. The Aptima and the Cobas test failed to detect 2.6% and 1.8% of the HSIL lesions caused by HR-HPV. Both HPV tests were negative in 20 patients with precancers (5.3%). Due to insufficient DNA, four of 20 double-negative cases were not genotyped on histologic specimens. In the remaining cases, two (10%) were positive for HR-HPV subtypes, whereas ten (50%) were associated with possibly carcinogenic and low-risk HPV. The remaining two (10%) were negative with all HPV tests: one had a somatic PIK3CA gene mutation and the other one had a single nucleotide variant in the APC gene. In conclusion, true HPV-negative HSIL are exceedingly rare and the inclusion of more possibly carcinogenic HPV subtypes in HPV testing may further reduce cervical cancer. [4]

Endometrial cancer

Paraskevaidi et al. reported on the feasibility of using blood spectroscopy together with machine learning algorithms as a detection tool for endometrial cancer and atypical hyperplasia in a cross-sectional diagnostic accuracy study. Blood plasma samples of 342 women with endometrial cancer and of 68 women with atypical endometrial hyperplasia lesion were analysed using total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy. The control group included 242 patients. Endometrial cancer was detected with a sensitivity of 87% and a specificity of 78%. The accuracy was highest for Type I endometrial cancer and atypical hyperplasia, with sensitivities of 91% and 100%, and specificities of 81% and 88%, respectively. This test has the potential to diagnose endometrial cancer and atypical hyperplasia, which may allow fertility-sparing management and cancer prevention. A potential limitation of spectroscopy is that the derived peaks are formed by many different biological entities and this limits its utility to detect the exact molecular pathways involved in carcinogenesis. Future studies of asymptomatic women at high risk of endometrial cancer followed up longitudinally are needed to establish whether spectroscopy can predict the development of cancer. [5]

Screening of gynaecological cancers

Geanina Dragnea

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No	Title	Authors	Journal	Link to abstract
1	Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC)	Kyrgiou M et al.	Br J Cancer	https://pubmed.ncbi.nlm.nih.gov/32507855/
2	European Federation for Colposcopy (EFC) and European Society of Gynaecological Oncology (ESGO) joint considerations about human papillomavirus (HPV) vaccination, screening programs, colposcopy, and surgery during and after the COVID-19 pandemic	Ciavattini A et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32487685/
3	How to triage HPV positive cases: Results of four million females	Gultekin M et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32362567/
4	Possibly carcinogenic HPV subtypes are a cause of HSIL and negative clinical HPV tests - A European prospective single center study	Reich O et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32354471/
5	Detecting endometrial cancer by blood spectroscopy: A diagnostic cross-sectional study	Paraskevaidi M et al.	Cancers (Basel)	https://pubmed.ncbi.nlm.nih.gov/32429365/

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Prevention and management of surgical complications

Anastasia Prodromidou and Anastasios Pandraklakis

A retrospective study by Wolf et al., part of the prospective Leipzig School mesometrial resection study, compared 100 cervical cancer patients who underwent mesoureter preservation during total mesometrial resection with 100 historic controls without mesoureter preservation. The authors demonstrated a marginal reduction in ureteral complication rates (3% vs 11%, p = 0.049) and decreased postoperative percutaneous nephrostomy rates (0 vs 7%, p = 0.014). The technique was safe and feasible, potentially relevant in other pelvic surgical procedures. However, this was a retrospective study with limited patient number and historical controls. [1]

Wang et al. presented the outcomes after one-year follow-up in patients with cervical cancer undergoing laparoscopic radical hysterectomy with pelvic lymphadenectomy. Patients were randomised to postoperative lower-limb decongestive physiotherapy (59 patients) versus no physiotherapy (58 controls). Significantly reduced incidences of secondary lower-extremity lymphoedema and decreased ratio of excess limb volume were recorded in patients who received limb physiotherapy when compared to controls (13.6% vs 34.5%, p = 0.008 and 2.38% vs 4.11%, p = 0.042, respectively). The study was limited by the inclusion of high-risk populations with > 20 lymph nodes removed and those in need of postoperative radiotherapy in both arms. [2]

Chambers et al. retrospectively assessed the impact of closed-incision negative-pressure therapy (ciNPT) on surgical-site infection of patients undergoing laparotomy for gynaecologic malignancy. Significantly reduced rates were noted in both superficial and deep incisional surgical-site infection among the 64 patients in ciNPT group and the 192 matched controls with conventional wound dressing (9.4% vs 29.7%, p < 0.001 and 0.0% vs 6.8%, p = 0.04, respectively). However, no difference was observed in skin dehiscence, seroma, and hematoma rates, as well as in re-operation, re-admission, and intensive care unit admission rates. The authors concluded that ASA score is useful in discriminating patients likely to benefit from ciNPT. [3]

Nguyen et al. retrospectively investigated the safety and efficacy of indocyanine green fluorescence angiography (ICG-FA) administration for the intraoperative detection of anastomotic perfusion in 100 bowel anastomoses performed as a part of gynaecologic malignancy surgery. Particularly, abnormal ICG uptake was detected in three cases (3.6%) in which the operative plan was modified towards diverting loop ileostomy, anastomosis revision, and re-resections. The observed anastomotic leak ratio was 1%. [4]

The PROFAST trial evaluation an ERAS protocol in patients undergoing debulking surgery for advanced ovarian cancer is discuss in the chapter on Surgical treatment of primary and recurrent ovarian cancer by Ilker Kahramanoglu and Patriciu Achimas-Cadariu. [5]

A multicentre, phase III randomised clinical trial by Narducci et al. compared 193 patients who underwent conventional laparoscopy for gynaecological malignancy with 176 patients who had robot-assisted laparoscopy. No significant difference was observed in six-month perioperative morbidity, 18-month overall, and disease-free survival but robot-assisted laparoscopy was associated with significantly prolonged operative time (190 vs 145 min, p < 0.001) and increased blood loss (100 vs 50 ml, p = 0.001). [6]

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No	Title	Authors	Journal	Link to abstract
1	Preservation of the mesureter to reduce urinary complications: analysis of data from the observational Leipzig School MMR study	Wolf B et al.	BJOG	https://pubmed.ncbi.nlm.nih.gov/32037645/
2	Effectiveness of modified complex decongestive physiotherapy for preventing lower extremity lymphedema after radical surgery for cervical cancer: a randomized controlled trial	Wang X et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32107315/
3	Use of prophylactic closed incision negative pressure therapy is associated with reduced surgical site infections in gynecologic oncology patients undergoing laparotomy	Chambers LM et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/32417358/
4	The use of indocyanine green fluorescence angiography to assess anastomotic perfusion following bowel resection in surgery for gynecologic malignancies - A report of 100 consecutive anastomoses	Nguyen JMV et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32423604/
5	PROFAST: A randomised trial implementing enhanced recovery after surgery for high complexity advanced ovarian cancer surgery	Sanchez-Iglesias JL et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/32688208/
6	Severe perioperative morbidity after robot-assisted versus conventional laparoscopy in gynecologic oncology: Results of the randomized ROBOGYN-1004 trial	Narducci F et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32467054/

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Fertility-sparing treatment in gynaecological malignancies

Charalampos Theofanakis

Endometrial cancer

A retrospective cohort study by Ayhan et al. included 27 patients with atypical hyperplasia and 30 with endometrial cancer who were treated with hysteroscopic resection of visible lesions and endometrial curettage prior to progestin therapy. There were two (7.4%) and five (16.7%) recurrences, which resulted in one and two staging surgeries, respectively. After the fertility-sparing approach, the atypical hyperplasia group presented with 37.5 % live birth rates, while the endometrial cancer group had 16.6%. The authors stated that hysteroscopy and endometrial curettage before hormonal therapy is a safe approach to patients with endometrial malignancies. [1]

A retrospective study by Falcone et al. reported the oncological and reproductive outcomes of 23 patients with stage IA, grade 2 endometrial cancer. In a median follow-up of 35 months, 17 patients presented with complete response, while six were offered definitive surgery, with one unfavourable outcome. Three out of 10 complete responders who attempted to conceive presented with at least one live birth. The authors concluded that fertility-sparing treatment is a feasible option, even in grade 2 disease, but with extreme caution of possible undegrading or non-endometrioid histology. [2]

Cervical cancer

A retrospective study by Zusterzeel et al. assessed 18 patients with FIGO 2018 stage IB2 cervical cancer, receiving six weekly cycles of neoadjuvant chemotherapy with cisplatin/carboplatin and paclitaxel, followed by vaginal radical trachelectomy and robot-assisted pelvic lymphadenectomy. Complete remission was achieved in seven patients, while four had poor response. Fourteen of the 18 were treated vaginal trachelectomy 3–4 weeks after neoadjuvant chemotherapy. Four recurrences were reported, four women could not preserve their fertility, and three had term pregnancies. Despite promising results with this course of treatment in stage IB2 patients, a histology of adenocarcinoma and lymph-vascular space invasion were risk factors for recurrence. [3]

Gil-Ibañez et al. presented a retrospective study of 38 patients with FIGO stage IA1 with LVSI, IA2, and IB1 cervical cancer, treated with radical vaginal trachelectomy and laparoscopic sentinel lymph node biopsy. Nineteen patients had laparoscopic bilateral pelvic lymphadenectomy performed, immediately after sentinel lymph node biopsy. After a median follow-up time of 73 months, there were four recurrences, all in patients with adenocarcinoma, with no disease-related deaths. Although this therapeutic regime seems oncologically safe, adenocarcinoma histology presents a risk factor for recurrence. [4]

A retrospective study by Wang et al. highlighted uterine artery preservation during abdominal radical trachelectomy. The authors reviewed 31 patients with a median follow-up of 56 months. Abdominal and pelvic computed tomography in 11 patients showed no evidence of uterine artery occlusion. There were two recurrences and five pregnancies among the 15 patients who attempted to conceive. [5]

Ovarian cancer

A multicentre retrospective study by Chen et al. assessed the safety of fertility-sparing surgery in 36 out of 87 young patients with stage I epithelial ovarian cancer. Regarding the fertility-sparing group, seven patients were diagnosed with FIGO stage IA/IB and 29 with stage IC. In the control group, 12 were diagnosed with stage IA/IB and 39 with IC. The results stated that fertility-sparing surgery, together with adjuvant chemotherapy, did not affect prognosis. However, two out of three recurrences and both deaths occurred in the fertility-sparing group and in patients with stage IC disease. Seventeen pregnancies occurred in 16 women who tried to conceive. The authors concluded that fertility-sparing surgery is a safe procedure in young patients with stage IA epithelial ovarian cancer. [6]

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

No	Title	Authors	Journal	Link to abstract
1	Fertility preservation in early-stage endometrial cancer and endometrial intraepithelial neoplasia: A single-centre experience	Ayhan A et al.	Taiwan J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/32416890/
2	Fertility-sparing treatment for intramucous, moderately differentiated, endometrioid endometrial cancer: a Gynecologic Cancer Inter-Group (GCIG) study	Falcone F et al.	J Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32808500/
3	Neoadjuvant chemotherapy followed by vaginal radical trachelectomy as fertility-preserving treatment for patients with FIGO 2018 stage 1B2 cervical cancer	Zusterzeel PLM et al.	Oncologist	https://pubmed.ncbi.nlm.nih.gov/32339376/
4	Vaginal fertility-sparing surgery and laparoscopic sentinel lymph node detection in early cervical cancer. Retrospective study with 15 years of follow-up	Gil-Ibañez B et al.	Eur J Obstet Gynecol Reprod Biol	https://pubmed.ncbi.nlm.nih.gov/32480177/
5	The safety and effectiveness of preserving the ascending uterine artery in a modified fertility-sparing abdominal radical trachelectomy	Wang Y et al.	Eur J Obstet Gynecol Reprod Biol	https://pubmed.ncbi.nlm.nih.gov/32623251/
6	Reproductive outcomes of fertility-sparing surgery in women with early-stage epithelial ovarian carcinoma: A multicenter retrospective study	Chen J et al.	Curr Med Sci	https://pubmed.ncbi.nlm.nih.gov/32862386/

Cancer in pregnancy

Michael J. Halaska

Maggen et al. evaluated 80 patients diagnosed with non-Hodgkin lymphoma during pregnancy. Only 5% of pregnancies were terminated, while all remaining patients received chemotherapy during pregnancy. R-CHOP, CHOP, and EPOCH were the most-used chemotherapy regimens. Two minor congenital anomalies were found after R-CHOP chemotherapy. Of all neonates, 44.4% were diagnosed with low birth weight for their gestational age, regardless of whether or not they were exposed to chemotherapy. Additionally, other complications, such as preterm delivery (52%) and obstetric (41%) and neonatal complications (12.5%) were observed. [1]

Sawyers et al. analysed the decision-making process in the treatment of pregnant patients diagnosed with melanoma. While management of early-stage melanoma patients did not differ from non-pregnant patients, late-stage patients had a significant impact on pregnancy. Termination or preterm delivery were found in all patients. Surgical treatment was the most commonly used modality in melanoma patients. [2]

Vandenbroucke et al. published INCIP data on the psychomotoric development of six-year-old children exposed to different oncological treatment in utero. The study group consisted of 132 patients who were matched with children non exposed to the treatment. Even though the results were within normal ranges, there were statistically significant differences found in mean verbal IQ and long-term visuospatial memory in terms of lower scores in the study versus the control group (98.1, 95% CI: 94.5–101.8 vs 104.4, 95% CI: 100.4–108.4, $p = 0.001$). Another significant difference was observed in diastolic blood pressure, with higher values in chemotherapy-exposed (61.1, 95% CI: 59.0–63.2) versus control children (56.0, 95% CI: 54.1–57.8) ($p < 0.001$). [3]

Placental development and function were tested on an in-vitro culture using different cytostatics. The study analysed various placental transporters. The highest cytotoxic effect on syncytiotrophoblast was found in epirubicin. Epirubicin, docetaxel, and vinblastine inhibited HCGB and PIGF expression while methotrexate and tamoxifen and its two metabolites increased it. [4]

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

No	Title	Authors	Journal	Link to abstract
1	Maternal and neonatal outcomes in 80 patients diagnosed with non-Hodgkin lymphoma during pregnancy: results from the International Network of Cancer, Infertility and Pregnancy	Maggen C et al.	Br J Haematol	https://pubmed.ncbi.nlm.nih.gov/32945547/
2	Management of melanoma during pregnancy: A case series of 11 women treated at NYU Langone Health	Sawyers AE et al.	Oncology	https://pubmed.ncbi.nlm.nih.gov/32894847/
3	Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy	Vandenbroucke T et al.	Eur J Cancer	https://pubmed.ncbi.nlm.nih.gov/32858478/
4	Effects of chemotherapy on placental development and function using in vitro culture of human primary cytotrophoblasts	Depoix CL et al.	Invest New Drugs	https://pubmed.ncbi.nlm.nih.gov/31155684/

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Hereditary gynaecological cancer

Sara Giovannoni and Ariel Glickman

The Ovarian Tumour Tissue Analysis Consortium tried to characterise PTEN expression as a biomarker in ovarian cancer. PTEN is a potent tumour suppressor known for its inhibition of the PI3K pathway. This study evaluated the correlation between PTEN expression and overall survival, age, tumour stage, residual tumour, expression of oestrogen and progesterone receptors and the CD8+ infiltrating lymphocyte count from 5,400 ovarian cancer samples with an average follow up of 5.5 years. The results highlighted the association between downregulation of PTEN and longer overall survival in high-grade serous ovarian cancer ($p = 0.022$). The proportion of PTEN loss or downregulation in this cohort was 75%. Heterogeneous expression of PTEN was more frequent in advanced disease without BRCA1/2 mutation. Furthermore, PTEN expression was associated with oestrogen-, progesterone-receptor expression and higher CD8+ counts. The highest rate of complete loss of PTEN was found in endometrioid and clear cell ovarian cancer in 35% and 32%, respectively. In endometrioid, PTEN loss was more often seen in younger patients (<50 years). Overall, PTEN expression might be used as a biomarker and might help in the provision of tailored therapies for patients with PTEN-loss tumours by using PI3K pathway inhibitors. [1]

Dominguez-Valentin et al. published the results of an international survey in which 31 cancer centres from the prospective Lynch syndrome database were participating. The survey included data regarding policies of risk-reducing hysterectomy, bilateral salpingo-oophorectomy, and hormone replacement. Lynch syndrome carriers have a lifetime risk of up to 50% of developing colorectal and endometrial cancer and of 17% of developing ovarian cancer. While path MSH6 mutation is associated with the highest risk of developing endometrial cancer, a lower risk rate of developing any gynaecological cancer was seen in path PMS2 carriers. Prophylactic hysterectomy and bilateral salpingo-oophorectomy were offered to path-MLH1, MSH2, MSH6 mutation carriers in 95% to 91%; it was discussed in 67% of PMS2 carriers. The most common age in which risk-reducing surgery was offered was > 40 years. Some 71% of the participating cancer centres recommended hormone replacement. The survey showed a wide variation in how, when, and to whom prophylactic surgery was offered. There is a need for more research on this topic in order to provide evidence-based counselling for Lynch syndrome carriers. [2]

Piombino et al. reviewed the available literature and summarised recommended screening strategies for hereditary cancer syndromes other than BRCA mutations. Surveillance recommendations for women with Li–Fraumeni syndrome (mutations in pT53) include clinical breast examination every 6–12 months, starting at the age of 20, combined with annual breast MRI from 20 to 75 years. Risk-reducing bilateral mastectomy should be discussed with these patients. For Cowden Syndrome (mutations in PTEN), endometrial biopsy every 1–2 years may be considered, while hysterectomy should be discussed on a case-by-case basis. Breast examination every six months beginning at 25 years as well as annual mammogram and breast MRI starting at 30–35 years are recommended. In patients with Peutz–Jeghers syndrome (mutation in the STK11 gene), an annual mammogram and breast MRI screening with contrast should be performed starting at age 25. Transvaginal ultrasound, serum CA-125, and pelvic exam with Pap smear should be conducted annually beginning at the age of 18. Women with neurofibromatosis type 1 should receive annual mammography, possibly combined with breast MRI between 30 and 50 years of age (after 50; breast cancer risk in those patients is similar to the general population). PALB2 mutation carriers should be offered breast ultrasound and MRI every year from 25 to 29 years of age, alternating once every six months and changing to annual mammogram and breast MRI screening every six months, starting at 30 and lasting until age 65. For BRIP1, RAD51C, and RAD51D mutation carriers, there is a lack of data regarding screening programs for ovarian and breast cancer. [3]

Kotsopoulos et al. conducted a matched case-control analysis to evaluate the association between breastfeeding history and the risk of developing ovarian cancer in BRCA-mutation carriers. They included 1,650 women with ovarian cancer and BRCA mutation into the study population and 2,702 women without ovarian cancer but BRCA mutation to the control group. A history of ever-breastfeeding was associated with a 23% risk reduction of developing ovarian cancer compared to women who had never breastfed. The protective effect increased with breastfeeding from one month to seven months, after which the association was relatively stable, resulting in a risk reduction of 32% in those who were breastfeeding for ≥ seven months. Furthermore, the combination of breastfeeding and a history of oral contraceptive use showed to be strongly protective against developing ovarian cancer in these patients ($p = 0.47$). Breastfeeding should be encouraged in BRCA carriers in order to significantly reduce ovarian cancer risk. [4]

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

No	Title	Authors	Journal	Link to abstract
1	Clinical and pathological associations of PTEN expression in ovarian cancer: a multicentre study from the Ovarian Tumour Tissue Analysis Consortium	Martins FC et al.	Br J Cancer	doi.org/10.1038/s41416-020-0900-0
2	Risk-reducing gynecological surgery in Lynch syndrome: Results of an international survey from the prospective lynch syndrome database	Dominguez-Valentin M et al.	J. Clin Med	doi.org/10.3390/jcm9072290
3	Secondary prevention in hereditary breast and/or ovarian cancer syndromes other than BRCA	Piombino C et al.	J Oncol	doi.org/10.1155/2020/6384190
4	Breastfeeding and the risk of epithelial ovarian cancer among women with a BRCA1 or BRCA2 mutation	Kotsopoulos J et al.	Gynecol Oncol	doi.org/10.1016/j.ygyno.2020.09.037

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Treatment of pre-invasive gynaecological malignancies

Elko Gliozheni

Most treatment options for CIN2/3 are either excisional or ablative and require sequential visits to healthcare providers. In a first-in-human, proof-of-concept phase I trial, Trimble et al. aimed to assess the safety and efficacy of self-administered artesunate vaginal inserts in biopsy-confirmed cervical intraepithelial neoplasia 2/3 (CIN2/3). Artesunate, a compound that is WHO-approved for the treatment of acute malaria, also has shown cytotoxic effects on squamous cells transformed by the human papillomavirus (HPV). The authors assessed the severity, frequency, and duration of reported adverse events as well as tolerability and efficacy. Reported adverse events were mild and self-limited, while histologic regression was observed in 67.9% of the subjects. Clearance of HPV genotypes detected at baseline occurred in 47.4% of the patients. Although the sample size was small, the findings encouraged the authors to plan a phase II study. [1]

In their phase II prospective randomised multicentre study, Choi et al. aimed to determine the efficacy of the therapeutic DNA vaccine (GX-188E) in CIN 3 lesions. Enrolled patients were positive for HPV type 16/18. The primary endpoint of the study was to determine the histopathologic regression to ≤CIN 1 at visit 7 (20 weeks after receiving the vaccine), and an extension study was pursued until visit 8 (36 weeks after the first injection). The results showed that 52% of the patients at visit 7 and 67% at visit 8 presented histopathologic regression while 73% (visit 7) and 77% (visit 8) of the patients with histologic regression also showed HPV clearance. The authors concluded that GX-188E is an effective therapeutic vaccine in a cohort with CIN3 patients. [2]

Salcedo et al. prospectively evaluated cervical cancer screening based on HPV testing in Mozambique where cervical cancer is the leading cause of cancer-related deaths among women. The objective of the study was to evaluate the implementation of cervical cancer screening with HPV testing, followed by the navigation of women with abnormal results to appropriate diagnostic and treatment services. All enrolled patients had a cervical sample collected and tested for HPV. If positive, they were referred for cryotherapy or a loop electrosurgical excision procedure. Of the participants, 20.3% were women living with HIV. HPV positivity was 23.7%. Women with HIV were twice as likely to be positive for HPV as HIV-negative women (39.2% vs 19.9%). Most HPV-positive women (91.1%) completed all steps of their diagnostic work-up and treatment. Therefore, the authors concluded that cervical-cancer screening with HPV testing is feasible in a low-resource African country. [3]

As there is limited information available about the efficacy of point-of-care thermal ablation among high-risk HPV-positive women in low- and middle-income countries, Zhao et al. evaluated this strategy in China. Enrolled women positive for high-risk HPV and having colposcopically suspected lesions eligible for ablation underwent biopsy and thermal ablation at one visit. Post-treatment follow-up at six months or more with HPV test and cytology, followed by colposcopy and biopsy for HPV- and/or cytology-positive women. Cure was defined as either negative cytology and HPV test or absence of histopathology-proven CIN in any positive women. Cure rates after thermal ablation were 90.3% for CIN1 and 76.2% for ≥ CIN2. The HPV clearance rate was 80.4% in women undergoing thermal ablation, which was lower for HPV16/18 compared to other oncogenic types (67.6% vs 85.7%). [4]

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

No	Title	Authors	Journal	Link to abstract
1	A first-in-human proof-of-concept trial of intravaginal artesunate to treat cervical intraepithelial neoplasia 2/3 (CIN2/3)	Trimble C et al.	Gynecol Oncol	https://www.sciencedirect.com/science/article/abs/pii/S0090825819318657
2	A phase II, prospective, randomized, multicenter, open-label study of GX-188E, an HPV DNA vaccine, in patients with cervical intraepithelial neoplasia 3	Choi Y et al.	Clin Cancer Res	https://pubmed.ncbi.nlm.nih.gov/31727676/
3	The Capulana study: a prospective evaluation of cervical cancer screening using human papillomavirus testing in Mozambique	Salcedo M et al.	Int J Gynecol Cancer	https://ijgc.bmj.com/content/30/9/1292
4	Efficacy of point-of-care thermal ablation among high-risk human papillomavirus positive women in China	Zhao X et al.	Int J Cancer	https://pubmed.ncbi.nlm.nih.gov/32895912/

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Pathology of gynaecological cancers

Nicolas Samartzis and Dimitrios Rafail Kalaitzopoulos

Endometrial cancer

Russo et al. conducted next-generation sequencing in endometrial hyperplasia and compared 15 cases that showed a progression to endometrioid adenocarcinomas with 17 cases, which resolved on repeated tissue sampling or did not have a progression after at least two years of follow-up. Mutation of ARID1A and MYC were seen only in patients with progression to endometrioid adenocarcinomas. ARID1a have been reported in 33%, while MYC amplification was in two cases only. Mutations in PTEN, PIK3CA, and FGFR2 were found more commonly in endometrial hyperplasia with progression to adenocarcinomas but showed an overlap with non-progressing hyperplasia. Despite the small study's sample size, the authors highlighted that the results revealed insights on the biology of endometrial hyperplasia and provided evidence that genomic sequencing may be a possible strategy to assess the risk of malignant progression of endometrial hyperplasia. [1]

Cervical cancer

In the FIGO 2019 updated classification of cervical cancer, horizontal tumour extent was removed as a parameter included in the staging. Zyla et al. analysed 285 patients with a median follow-up of 48 months and showed that horizontal tumour extent was only associated with recurrence-free and disease-specific survival for tumours larger than FIGO IA. In cervical cancer with less than 5 mm invasive depth, horizontal tumour extent did not add prognostic value, supporting the recommendation to remove this parameter from staging. A study limitation was the retrospective setting and the fact that reproducibility of the measurement of horizontal tumour extent in this study was not assessed. [2]

Vetter et al. retrospectively examined the discordance between clinical and pathologic tumour size in women with stage IB1 cervical cancer after radical hysterectomy in a population of 630 women and found that 12% of this population were upstaged after pathologic assessment. The upstaged patients were characterised by higher deep stromal invasion, lymphovascular space invasion, positive margins, positive lymph nodes, receipt of adjuvant therapy. However, they also showed lower preoperative conisation levels and preoperative tumour sizes ≤ 2cm. The recurrence and all-cause death were higher in the population with pathologic upstaging. Although some confounders, such as the type of radical hysterectomy, the vaginal manipulator used, the technique for sentinel node mapping (which could influence the outcome), were not examined, this remains the largest multicentre study published on this topic. [3]

Vulvar cancer

Williams et al. analysed the molecular profiles of 280 vulvar squamous carcinomas and could show that 61% of HPV-positive cases had a pathogenic alteration in the pi3k/mTOR pathway, whereas HPV-negative cases had significant more alterations in DNA damage regulation (TP53), cell-cycle regulation (TERTp, CDKN2A and CCND1), single pass transmembrane receptors (FAT1 and NOTCH1), EGFR amplification, and PD-L1 amplification. The limitation of this study is the lack of information about the history of treatment, such as prior radiation or systemic therapy and outcome at follow-up. This study is of clinical interest, as the identification of the different molecular profiles based on HPV status could help in the prediction for responsiveness to known or future therapeutic targets. [4]

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

No	Title	Authors	Journal	Link to abstract
1	Mutational profile of endometrial hyperplasia and risk of progression to endometrioid adenocarcinoma	Russo M et al.	Cancer	https://pubmed.ncbi.nlm.nih.gov/32187665/
2	The prognostic role of horizontal and circumferential tumor extent in cervical cancer: Implications for the 2019 FIGO staging system	Zyla RE et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32471646/
3	Pathologic and clinical tumor size discordance in early-stage cervical cancer: Does it matter?	Vetter MH et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32888724/
4	Vulvar squamous cell carcinoma: comprehensive genomic profiling of HPV+ versus HPV- forms reveals distinct sets of potentially actionable molecular targets	Williams EA et al.	JCO Precis Oncol	https://pubmed.ncbi.nlm.nih.gov/32923875/

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

Joanna Kacperczyk-Bartnik

Ultrasound examination

An observational study by Tang et al. compared the results of pre-evacuation ultrasound and naked-eye examination of the specimen obtained at the time of uterine evacuation in 577 patients with a missed abortion. Sensitivity detection of hydatidiform moles was 25% with ultrasound and 60% with the naked eye assessment. The study confirms the importance of histology examination in a missed abortion. [1]

The necessity of routine histological examination after uterine evacuation following a missed abortion was also emphasised in a study by Jauniaux et al. Authors analysed the diagnostic process of 198 women with hydatidiform mole and a missed or incomplete miscarriage up to the 13th gestational week. The role of ultrasound examination for the differential diagnosis between complete and partial hydatidiform mole in patients with early pregnancy loss was examined. The diagnosis of a partial hydratidiform mole by ultrasound is challenging also in the hands of experts. [2]

Treatment protocols

In a retrospective study by Jareemit et al., the efficacy and toxicity of two regimens in patients with gestational trophoblastic disease were compared: etoposide, methotrexate, actinomycin-D (EMA) and etoposide, methotrexate, actinomycin-D alternating weekly with cyclophosphamide and vincristine (EMACO). Forty-four patients were treated with the EMA protocol, and 39 women received treatment according to the EMACO regimen. In a multivariate analysis, treatment efficacy and time to remission in EMA and EMACO groups were similar. Greater toxicity was reported in the EMA group. [3]

A phase II multi-centre trial (ClinicalTrials.gov identifier: NCT03135769) by You et al. examined the efficacy of avelumab (anti–PD-L1) in a cohort of patients with chemo-resistant gestational trophoblastic disease (GTD). Fifteen patients were enrolled in the study, with a median follow-up of 25 months. Data showed that avelumab could improve treatment for 50% of the patients with GTD resistant to single-agent chemotherapy regimens. The probability of hCG normalization did not depend on the disease stage, FIGO score, nor baseline hCG levels. [4]

Prognosis

In a group of 1,304 patients treated for GTD in a single centre between 2004 and 2018, 99 were diagnosed with lung metastases. Bouchard-Fortier et al. analysed the outcome of 40 patients with residual lung disease. The difference in relapse rate among patients with residual lung metastases (4/40; 10.0%) compared to patients without residual disease (3/59; 5.1%) was not statistically significant. However, the authors highlight the small number of cases included as a limtation of the study. [5]

Reproductive outcomes

In a retrospective study by Jiang et al., the reproductive outcomes of 464 patients with malignant GTD treated with floxuridine-based protocols were investigated. Median follow-up was 85 months. Pregnancy intentions were reported by 320 of the examined patients. The main factors influencing the desire for pregnancy after GTD treatment were age and parity at disease onset. Fertility outcomes were similar to the general population, with 439 pregnancies and 317 live births during the observation period in a group of 313 patients who intended and managed to conceive. [6]

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No	Title	Authors	Journal	Link to abstract
1	The impact of pre-evacuation ultrasound examination in histologically confirmed hydatidiform mole in missed abortion	Tang Y et al.	BMC Womens Health	https://pubmed.ncbi.nlm.nih.gov/32912152/
2	Ultrasound diagnosis of complete and partial hydatidiform moles in early pregnancy failure: An inter-observer study	Jauniaux E et al.	Placenta	https://pubmed.ncbi.nlm.nih.gov/32792066/
3	EMA vs EMACO in the treatment of gestational trophoblastic neoplasia	Jareemit N et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32404247/
4	Avelumab in patients with gestational trophoblastic tumors with resistance to single-agent chemotherapy: cohort A of the TROPHIMMUN phase II trial	You B et al.	J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/32716740/
5	Following chemotherapy for gestational trophoblastic neoplasia, do residual lung lesions increase the risk of relapse?	Bouchard-Fortier G et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32654764/
6	Reproductive outcomes after floxuridine-based regimens for gestational trophoblastic neoplasia: A retrospective cohort study in a national referral center in China	Jiang F et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32917411/

Epidemiology of gynaecological cancers

Kemal Güngördük and Anik Ghosh

Ovarian cancer

Parity is associated with a decreased risk of ovarian cancer in a dose-dependent manner. Compared to the nulliparous population, women with one birth experience a 24% (95% CI: 12%–34%) decrease, and women with two or more births have an approximate 42% (95% CI: 35%–49%) risk reduction. The association with incomplete pregnancies has never been studied before. In a meta-analysis, Lee et al. studied 15 case-control studies and found that incomplete pregnancies (defined as pregnancy lasting < 6 months) decreased the risk of ovarian cancer. Of note is that the risk further reduces with an increase in the number of incomplete pregnancies, with a 34% decreased risk in the > 4 incomplete pregnancy group as compared to 14% in the single incomplete pregnancy group. The inverse association is strongest with the incidence of clear cell carcinoma and weakest for high-grade serous cancer. Endometriosis is considered a positive risk factor for ovarian cancer. [1]

Hermens et al. analysed 131,450 women with histologically proven endometriosis. The results revealed a crude incidence rate ratio of 4.79 (95% CI: 4.33–5.31) and an age-adjusted incidence rate ratio of 7.18 (95% CI: 6.17–8.36) for ovarian cancer in the entire population. A higher incidence was seen with clear cell and endometrioid ovarian cancer. [2]

Few studies have addressed the differences in risk factors associated with the origin of these cancers. Fortner et al. prospectively analysed 891,731 women from 15 cohorts in the Ovarian Cancer Cohort consortium and found 3,738 ovarian, 337 peritoneal, and 175 fallopian tube cancers. Eighteen putative risk factors were assessed. Higher early-adult BMI was associated with a higher risk of peritoneal but not ovarian or fallopian tube cancer. Associations between first pregnancy (phet = 0.04), tubal ligation (phet = 0.01) and early-adult BMI (age 18–21 years) (phet = 0.02) differed between ovarian and peritoneal cancers. The association between early adult BMI and risk further differed between peritoneal and fallopian tube cancer (phet = 0.03). First pregnancy and tubal ligation were inversely associated with ovarian but not peritoneal cancer. [3]

In a prospective cohort of postmenopausal women enrolled in the PLCO Cancer Screening Trial, it was demonstrated that aspirin use was not significantly associated with ovarian cancer risk regardless of dose or period of use (HR: 0.93, 95% CI: 0.72–1.21) [4].

Endometrial cancer

The Surveillance, Epidemiology, and End Results (SEER) data, including 10,090 patients with endometrial cancer, showed that metabolic syndrome was associated with worse cancer-specific survival in early-stage (stage I and stage II) disease (HR 0.84, 95% CI: 0.72–0.96). For this reason, the management of metabolic syndrome through lifestyle and pharmacologic therapies can build up cancer prognosis in this population. [5]

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

No	Title	Authors	Journal	Link to abstract
1	Expanding our understanding of ovarian cancer risk: the role of incomplete pregnancies	Lee AW et al.	J Natl Cancer Inst	https://pubmed.ncbi.nlm.nih.gov/32766851/
2	Incidence of endometrioid and clear-cell ovarian cancer in histological proven endometriosis: the ENOCA population-based cohort study	Hermens M et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/31981507/
3	Ovarian cancer risk factor associations by primary anatomic site: The ovarian cancer cohort consortium	Fortner RT et al.	Cancer Epidemiol Biomarkers Prev	https://pubmed.ncbi.nlm.nih.gov/32732252/
4	Aspirin use and ovarian cancer risk using extended follow-up of the PLCO Cancer Screening Trial	Hurwitz LM et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32919779/
5	Association between metabolic syndrome and endometrial cancer survival in a SEER-Medicare linked database	Jin J et al.	Am J Clin Oncol	https://pubmed.ncbi.nlm.nih.gov/32205571/

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Nutrition and perioperative care

Begoña Díaz de la Noval

Kalogera et al. retrospectively analysed bowel preparation in 224,687 hysterectomies, of which 38,539 were in patients with malignant disease. Bowel resection was performed in 0.4% of the benign and 2.8% of the malignant cohort. In the subgroup of malignant abdominal hysterectomies, the use of individual types of bowel preparation (mechanical bowel preparation alone, oral antibiotics alone, or mechanical bowel preparation with oral antibiotics, each one compared to no preparation) was not associated with decreased rates of surgical site infection [OR 95%, CI: 1.18 (0.78, 1.77)], anastomotic leaks [OR 95%, CI: 1.79 (0.87, 3.65)], postoperative ileus [OR 95%, CI: 1.64 (0.97, 2.79)], and major morbidity [OR 95%, CI: 1.21 (0.82, 1.79)] compared to no bowel preparation. In conclusion, no individual type of bowel preparation decreased rates of postoperative infectious or major morbidity compared to no bowel preparation following benign or malignant hysterectomies, irrespective of surgical approach or need for bowel surgery. The authors concluded that bowel preparation may be safely omitted, especially in the context of well-established Enhanced Recovery After Surgery pathways. Practices with high baseline rates of surgical site infections may still consider using bowel preparation in the form of oral antibiotics alone or combined with mechanical bowel. [1]

A home-based prehabilitation program developed for patients undergoing neoadjuvant therapy while awaiting surgery during the current COVID-19 pandemic may help promote optimal outcomes during neoadjuvant therapy and better prepare them for surgery. Sell et al. proposed a multimodal intervention that provides an opportunity to improve patients' health by optimising cardiopulmonary reserve, skeletal muscle mass, nutritional status, and mental well-being. The proposed multimodal intervention consists of a standardised fitness program (one hour per session three times a week), nutrition supplementation (protein intake of 30 g in addition to their normal dietary intake), smoking cessation, and mindfulness practice. [2]

Harrison et al. reported that an ERAS program can be implemented safely and feasibly in obese patients undergoing open abdominal surgery for gynaecologic cancer. The authors performed an observational cohort study of 1,225 patients. Neither postoperative length of stay [3 days (IQR 2–4)] nor the rate of grade III–IV complications (10.9% and 6.6%, respectively; $p = 0.06$) differed significantly despite longer operations (218 min vs 192.5 min, $p < 0.001$), greater blood loss (300 mL vs 200 mL, $p < 0.001$), and requiring more opioid ($p = 0.003$) use among obese patients compared to non-obese patients. However, grade I–II complications were more common among obese patients (62.4% vs 48.3%, $p < 0.001$) as they had more wound complications (17.8% vs 4.9%, $p < 0.001$). [3]

Hüber et al. published the ERAS Society Recommendations for perioperative management of patients affected by peritoneal surface malignancies treated with cytoreductive surgery and HIPEC. Part I included the preoperative and intraoperative management and Part II the postoperative management and special considerations. The evidence in this field is yet poor and prospective evaluation of these guidelines are needed. [4, 5]

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

No	Title	Authors	Journal	Link to abstract
1	Use of bowel preparation does not reduce postoperative infectious morbidity following minimally invasive or open hysterectomies	Kalogera et al.	Am J Obstet Gynecol	https://pubmed.ncbi.nlm.nih.gov/32112733/
2	Prehabilitation telemedicine in neoadjuvant surgical oncology patients during the novel COVID-19 coronavirus pandemic	Sell et al.	Ann Surg	https://pubmed.ncbi.nlm.nih.gov/32675505/
3	Enhanced recovery for obese patients undergoing gynecologic cancer surgery	Harrison et al.	Int J Gynecol Cancer	https://pubmed.ncbi.nlm.nih.gov/32848023/
4	Guidelines for perioperative care in Cytoreductive Surgery (CRS) with or without hyperthermic IntraPEritoneal chemotherapy (HIPEC):Enhanced recovery after surgery (ERAS®) Society Recommendations Part I: Preoperative and intraoperative management	Hübner et al.	Eur J Surg Oncol	https://pubmed.ncbi.nlm.nih.gov/32873454/
5	Guidelines for perioperative care in Cytoreductive Surgery (CRS) with or without hyperthermic IntraPEritoneal chemotherapy (HIPEC): Enhanced Recovery After Surgery (ERAS®) Society Recommendations - Part II: Postoperative management and special considerations	Hübner et al.	Eur J Surg Oncol	https://pubmed.ncbi.nlm.nih.gov/32826114/

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

Quality of life in gynaecological cancers/Palliative care

Nadja Taumberger and Engin Çelik

Paiva et al. investigated the usefulness of palliative care referral protocol in an outpatient clinic with advanced-stage breast and gynaecological cancer patients at Barretos Cancer Hospital. The first phase of data was collected prospectively through a study nurse before clinical visits. One hundred and twenty patients were evaluated. Twenty-three (19.2%) patients were referred by an oncologist to the palliative care unit, while the palliative care referral protocol would identify 82 (68.3%) patients. Overall survival was worst in patients who were screened positive by oncologist referral (130 days). After January 2019, the palliative care referral protocol was implemented in the outpatient clinic. The second phase of the study is a retrospective analysis of 251 patients. Ninety-seven patients (38.6%) met at least one criterion in palliative care referral protocol. [1]

Lindemann et al. analysed 3,940 patients who died from gynaecological cancer between 2013 to 2016. They retrospectively investigated the Swedish Register of Palliative Care. Older patients were more likely to spend their last days in nursing homes and were less likely to be cared for by a palliative team. The study showed that information about imminent death was given to 80% of patients, pain assessment was done in 49% of patients, but an oral health investigation was done only in 56% of the patients. For most of these quality indicators defined by the Swedish National Board of Health and Welfare, the goal level was not met. [2]

The LACC trial, a randomised, open-label, phase III, non-inferiority trial which was done in 33 centres worldwide, included women with early-stage cervical cancer who were randomly assigned in a 1:1 ratio to receive open or minimally invasive radical hysterectomy with the primary endpoint of disease-free survival at 4.5 years. Frumovitz et al. evaluated the secondary endpoint quality of life among 496 patients who completed four validated questionnaires. Postoperative quality of life was similar between the two treatment groups and underlines the recommendation for open radical hysterectomy for patients with early-stage cervical cancer due to the lower recurrence rates and longer disease-free survival. [3]

To assess the training in palliative care in gynaecologic oncology, La Russa et al. performed a web-based questionnaire among the members of the European Network of Young Gynae-Oncologists (ENYGO). The 142 responses showed a substantial gap in teaching and education in palliative care as well as a lack of supervision and feedback when it comes to consultation or treatment decisions. [4]

Blagden et al. analysed the secondary end point quality of life in the ICON8 study, which was an open-label, randomised controlled phase 3 trial comparing weekly vs. 3 weekly platinum-based chemotherapy in women with newly diagnosed ovarian cancer. The results are discussed in the chapter on Medical treatment of primary ovarian cancer by Selcuk. [5]

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

No	Title	Authors	Journal	Link to abstract
1	Development of a screening tool to improve the referral of patients with breast and gynecological cancer to outpatient palliative care	Paiva CE et al.	Gynecol Oncol	https://pubmed.ncbi.nlm.nih.gov/32362569/
2	Elderly gynaecological cancer patients at risk for poor end of life care: a population-based study from the Swedish Register of Palliative Care	Lindemann K et al.	Acta Oncol	https://pubmed.ncbi.nlm.nih.gov/32238040/
3	Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): a secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial	Frumovitz M et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/32502445/
4	Assessment of palliative care training in gynaecological oncology: a survey among European Network of Young Gynae-Oncologists (ENYGO) members	La Russa M et al.	BMJ Support Palliat Care	https://pubmed.ncbi.nlm.nih.gov/32958506/
5	Weekly platinum-based chemotherapy versus 3-weekly platinum-based chemotherapy for newly diagnosed ovarian cancer (ICON8): quality-of-life results of a phase 3, randomised, controlled trial	Blagden SP et al.	Lancet Oncol	https://pubmed.ncbi.nlm.nih.gov/32615110/

Treatment of elderly patients with gynaecological cancers

Alex Mutombo

Aviki et al. evaluated whether provider volume or other factors are associated with chemotherapy guideline compliance in a cohort of elderly Medicare patients with advanced epithelial ovarian cancer. They found a 70.3% overall rate of compliance with a significant association between provider volume and compliance (64.5% for low-volume, 72.2% for medium-volume, 71.7% for high-volume, $p = 0.02$). There was a significant difference in median overall survival across provider volume tertiles. In addition to the limitation inherent in any large database study, this study was limited by the absence of information regarding resection status, potential patient migration to a new provider, and the difficulty of characterisation of truly high- or low-volume providers. [1]

Kato et al. used an ovarian cancer database to clarify treatment patterns in elderly patients with recurrent ovarian cancer. In the resistant group, the percentage of patients aged over 70 years who received chemotherapy was significantly lower than the percentage among patients aged below 64 years. This study was limited by its retrospective nature and by the fact that the possibility of factors other than age affecting the results could not be excluded. [2]

Joueidi et al. evaluated the management of young, elderly, and very elderly patients with ovarian cancer and its impact on survival in a retrospective multicentre study of 979 women. Women in the 65–74 age group were more likely to have serous ovarian cancer ($p = 0.048$); women > 75 years had fewer standard procedures. More residual disease was found in two older groups (30%, respectively) than a younger group (20%) ($p < 0.05$). Women > 75 years had fewer neoadjuvant/adjuvant cycles than two other younger groups of women. Limitations included the retrospective nature of the study, the lack of a validated cut-off for the elderly and very elderly, as well as the absence of reasons for cessation of chemotherapy. [3]

In a retrospective cohort of 1,651 cervical cancer patients aged > 65 years, Shao et al. found that elderly patients had a poor prognosis, with a median survival of 14 months or less, and had no standard of care for second-line chemotherapy, with a substantial economic burden from $7,000 to $9,000 per patient per month. However, this study only included the subset of patients > 65 years and did not address costs and treatment patterns across the disease continuum. [4]

In a survey by Yamamoto et al. on gynaecologic oncologists to investigate the status of treatment policies for elderly Japanese patients (age > 65 years), 48% were aware of comprehensive geriatric assessment (CGA), but only 6% had conducted it. Age, comorbidities, performance status, and pre-treatment evaluations were determinant for the treatment strategy. Invasive treatments tended to have age limits, highlighting the importance of developing a new tool for predicting treatment outcomes for elderly patients with gynaecologic cancer. [5]

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

No	Title	Authors	Journal	Link to abstract
1	Impact of provider volume on front-line chemotherapy guideline compliance and overall survival in elderly patients with advanced ovarian cancer	Aviki EM et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/32814642
2	Treatment strategies for recurrent ovarian cancer in older adult patients in Japan: A study based on real-world data	Kato MK et al.	J Cancer Res Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/32144536
3	Management and survival of elderly and very elderly patients with ovarian cancer: An age-stratified study of 1123 women from the FRANCOGYN group	Joueidi V et al.	J Clin Med	https://www.ncbi.nlm.nih.gov/pubmed/32414065
4	Chemotherapy treatments, costs of care, and survival for elderly patients diagnosed with cervical cancer: an observational study	Shao C et al.	Curr Med Res Opin	https://www.ncbi.nlm.nih.gov/pubmed/32314603
5	How do doctors choose treatment for older gynecological cancer patients? A Japanese Gynecologic Oncology Group survey of gynecologic oncologists	Yamamoto M et al.	Int J Clin Oncol	https://www.ncbi.nlm.nih.gov/pubmed/31728682

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We are also most grateful to Helena Opolecka (Executive Manager, ESGO) for her administrative support, Tomáš Grünwald for design and layout, and Beth Green for proofreading.