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LiFE report
Literature for ENYGO

LiFE | Literature for ENYGO

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Reviews covering publications from November 15, 2015 – February 15, 2016

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Preface

Dear colleagues,

this is the third consecutive edition of the LiFE report, containing reviews of publications in gynaecological oncology from November 15, 2015 - February 15, 2016. LiFE is an initiative of ENYGO supported by ESGO.

This edition covers more topics than previous reports; it contains 38 separate reports. The quality of the included reports has also improved significantly over time and we would like to acknowledge the continuous work and effort from each author. We would also like to give special thanks to all the authors who have agreed to cover additional topics. In addition, some new authors have joined the team – welcome!

The LiFE team is very grateful for the support of Beth Green in proofreading and also of our graphic designer Tomas Grünwald, who has designed a new logo and layout for this edition – we hope you like it.

To assist us in preparing future editions of the report, the LiFE team and Dr Jan Boostels, who is also working with the Belgian branch of the Dutch Cochrane Center (CEBAM), are preparing two webinars for LiFE authors. The first will focus on the development of an efficient literature search strategy and the second on the critical appraisal of medical literature. We will be in touch with details soon.

Also, from this issue forward, the LiFE report will be published under a Creative Commons 4.0 License (CC BY-NC-ND 4.0). This does not change the fact that the LiFE reports are free, ready to download and share.

We hope you will enjoy the third edition and find it interesting! Please let us know if you have any comments or other feedback.

And, if you are interested in becoming an author for LiFE, please get in touch and send us an email to enygo.life.project@esgomail.org.

Stay up to date!

Yours,
The LiFE team
Kristina Lindemann
Kamil Zalewski
Michael J. Halaska

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Surgical treatment of primary ovarian fallopian tube and peritoneal cancer

Editor Kristina Lindemann, Michael J. Halaska, Kamil Zalewski

Descriptive summary

Staging

This retrospective study from the Mayo Clinic Tumor Registry, on long-term survival in 116 node-positive OC, confirmed stage of disease and residual disease to be the most important prognostic factors. This is in line with results on short-term survival because events tend to happen early in follow-up and long-term survivors often are without evidence of disease [1].

Mueller et al. retrospectively reported on LN metastasis identified in clear cell carcinoma confined to the ovary [2]. Of 145 staged patients (>10 LN removed) only 7 (4.8 %) had LN metastasis; 6 of these cases (4.1 %) were isolated metastasis. The highest risk was observed in patients with positive washings and ovarian surface involvement. This confirms data from a much larger case series (Mahdi et al., 2013). These findings may help in the counselling of patients with apparent early-stage disease, but are not suitable to reconsider staging guidelines.

A retrospective analysis of the validated Tumour Bank Ovarian Cancer Network Database confirmed the prognostic differences in FIGO stage III OC as captured in the revised classification [3]. Patients with lymph node (LN) only involvement had superior survival compared to patients with peritoneal spread. Differences between groups by localisation of involved nodes were not statistically significant, probably due to small numbers.

HIPEC

Several reviews analysed the evidence of HIPEC in the management of OC; also, its current investigation in recurrent disease (https://clinicaltrials.gov/ct2/show/NCT01767675) is summarised [4,5,7,8]. A retrospective study reports long-term survival in 218 primary or recurrent ovarian cancer patients treated with cytoreductive surgery and HIPEC (paclitaxel) [6]. All stage IV patients had received 4-8 cycles of neoadjuvant chemotherapy. The median overall survival (OS) was 57 months. The overall morbidity was 34.9 %, Dindo-Clavien III or IV morbidity 13.8 %, the reoperation rate was 6.9 %, and a mortality rate of 1.4 % was reported. The debate becomes more interesting when adding the statement paper by the AGO [9] and the previously published review by Chiva et al. (A critical appraisal of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of advanced and recurrent ovarian cancer; Gynecol Oncol; 2015). Both papers argue that HIPEC remains experimental and should not be offered outside a clinical trial.

Interval debulking

The Cochrane review on the role of interval debulking surgery in advanced epithelial OC was recently updated and included three randomised trials [10]. The authors could still not conclude on the benefit of interval debulking compared to upfront surgery followed by chemotherapy. The studies may mainly present results from populations in which surgical effort was not sufficiently extensive or surgery was not performed by gynaeoncologists.

Some correspondence and comments on the CHORUS trial on the same question of primary chemotherapy versus primary surgery for OC [11-12] have been published.

Surgical treatment, general

A retrospective analysis of OC patients with FIGO stage IIIC-IV who had diaphragmatic surgery with either diaphragmatic peritoneal stripping (DPS) or full thickness resection (FTR), including pleurectomy, showed similar overall and specific morbidity after both procedures. Diaphragmatic involvement extends to the muscle in almost 30 % of the patients and to the pleura in 20 % [13]. Bogani et al. conducted a systematic review on the surgical techniques of diaphragm resection during cytoreduction [14]. The authors confirmed that both DPS and diaphragmatic FTR for OC are associated with low pulmonary complication and chest tube placement rates.

Ataseven et al. retrospectively analysed 326 patients with FIGO IV OC, of which 286 cases underwent surgical debulking. 41 % of the patients had Stage IV due to pleural effusions/involvement. Patients with FIGO stage IV disease did benefit from debulking surgery—even in the case of extensive upper abdominal surgery—if tumour reduction resulted in nil or < 10 mm residual tumour. The OS observed in patients with complete macroscopic tumour reduction was 50 months (95 % CI = 3–57 months). Of note, patients undergoing debulking surgery with postoperative residual disease >10 mm had a comparable prognosis to patients who did not undergo debulking surgery. According to the authors, upfront chemotherapy may be more beneficial in these patients [15].

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Surgical treatment of primary ovarian fallopian tube and peritoneal cancer

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	The impact of debulking surgery in patients with node-positive epithelial ovarian cancer: Analysis of prognostic factors related to overall survival and progression-free survival after an extended long-term follow-up period.	Pereira et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26979641
2	Staging Lymphadenectomy in Patients With Clear Cell Carcinoma of the Ovary.	Mueller et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26509849
3	Lymph Node Involvement Pattern and Survival Differences of FIGO IIIC and FIGO IIIA1 Ovarian Cancer Patients After Primary Complete Tumor Debulking Surgery: A 10-Year Retrospective Analysis of the Tumor Bank Ovarian Cancer Network.	Gasimli et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26832880
4	Cytoreductive surgery and intraperitoneal chemotherapy: an evidence-based review-past, present and future.	Dehal et al.	J Gastrointest Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26941992
5	Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer: A systematic review and meta-analysis.	Huo et al.	Eur J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26453145
6	Peritonectomy procedures and HIPEC in the treatment of peritoneal carcinomatosis from ovarian cancer: Long-term outcomes and perspectives from a high-volume center.	Muñoz-Casares et al.	Eur J Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26673283
7	Hyperthermic intraperitoneal chemotherapy for epithelial ovarian cancers: is there a role?	Boisen et al.	J Gastrointest Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26941980
8	Cytoreductive surgery and intraperitoneal chemotherapy: an evidence-based review-past, present and future.	Dehal et al.	J Gastrointest Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26941992
9	Statement of the AGO Kommission Ovar, AGO Study Group, NOGGO, AGO Austria and AGO Switzerland Regarding the Use of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer.	Harter et al.		http://www.ncbi.nlm.nih.gov/pubmed/26941446
10	Interval debulking surgery for advanced epithelial ovarian cancer.	Tangjitgamol et al.	Cochrane Database Syst Rev.	http://www.ncbi.nlm.nih.gov/pubmed/26747297
11	Primary chemotherapy versus primary surgery for ovarian cancer.	Gasparri et al.	Lancet.	http://www.ncbi.nlm.nih.gov/pubmed/26638961
12	Author's reply.	Kehoe et al.	Lancet.	http://www.ncbi.nlm.nih.gov/pubmed/26638963
13	Diaphragmatic peritonectomy vs. full thickness resection with pleurectomy during Visceral-Peritoneal Debulking (VPD) in 100 consecutive patients with stage IIIC-IV ovarian cancer: A surgical-histological analysis.	Soleymani Majd et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26691220
14	Surgical Techniques for Diaphragmatic Resection During Cytoreduction in Advanced or Recurrent Ovarian Carcinoma: A Systematic Review and Meta-analysis.	Bogani et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26588238
15	Prognostic impact of debulking surgery and residual tumor in patients with epithelial ovarian cancer FIGO stage IV.	Ataseven et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26691222

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Surgical treatment of recurrent ovarian cancer

Editor Patriciu Achimas-Cadariu

Descriptive summary

Within the search period no randomised phase III trials have been published and results of DESKTOP III (NCT01166737), GOG 213 (NCT00565851), and SOCceR (NTR3337) are still awaited to clarify some important issues within this field of gynaecologic oncology.

A single-centre study presented its data with regard to secondary cytoreductive surgery in patients with platinum-resistant ovarian cancer. The estimated 5-year overall survival rates were 57 % versus 23.5 %, in favour of patients who had undergone surgery. However, these results must be interpreted with caution, given the small sample size and retrospective nature [1].

For patients with isolated platinum-sensitive splenic relapse, optimal secondary cytoreduction with minimally invasive surgical technique by a well-trained surgeon is feasible, as reported by this prospective study (Gallota et al.). The authors reported limited intraoperative blood loss, a shorter hospital stay, and a shorter interval (median 16 days) from surgery to adjuvant chemotherapy [2].

Van de Laar et al. retrospectively studied outcome after secondary cytoreductive surgery in 38 Dutch hospitals [3]. 408 patients were included based on the criterion of two consecutive histopathological reports with at least 6 months in between. Patients were treated in hospitals that had at least 20 primary debulking surgeries annually. The study reports favourable outcomes after complete cytoreduction, but because of the retrospective design this study is prone to selection bias and results need to be interpreted with caution.

Prediction of optimal cytoreduction

The SeC-Score, a predictive score for platinum-sensitive recurrent ovarian cancer, was developed in a single-centre study to better predict optimal secondary cytoreduction. After radiologically documented relapse with a progression-free interval ≥12 months, a number of four variables (residual tumour at primary cytoreduction, preoperative CA-125 and HE4, ascites) were combined into a logistic regression model, with a sensitivity and specificity of 82 % and 83 %, respectively (PPV = 0.79, NPV = 0.81). However, explorative laparotomy determined if patients underwent secondary debulking or chemotherapy [4].

A high-volume U.S. centre recently evaluated the predictive value of the AGO score in patients undergoing secondary cytoreductive surgery (SCS) for recurrent ovarian cancer, in 192 patients. A positive score correlated well with complete cytoreduction (84 %), but the negative predictive value was low and suggested that refinement of the score is needed (disease-free interval and number of recurrence sites could increase the predictive value) [5].

HIPEC (hyperthermic intraperitoneal chemotherapy)

The use of HIPEC in treating peritoneal carcinomatosis is still controversial, and a single-centre comparative retrospective analysis of secondary cytoreductive surgery (SCS) versus SCS+HIPEC did not find any difference in survival between groups, although the second group had a significantly longer hospital stay and more NCI grade III-IV morbidity [6]. On the contrary, within a highly selected group of platinum-sensitive recurrent ovarian cancer patients treated with secondary cytoreductive surgery plus HIPEC, another study demonstrated favourable 5- and 7-year post relapse survival rates of 52.8 and 44.7 %, respectively, without long-term sequelae, indicating the need for further randomised data [7].

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No	Title	Authors	Journal	Link to abstract
1	Secondary Cytoreduction in Platinum-Resistant Recurrent Ovarian Cancer: A Single-Institution Experience.	Musella A et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=25801357
2	Laparoscopic Splenectomy for Secondary Cytoreduction in Ovarian Cancer Patients With Localized Spleen Recurrence: Feasibility and Technique.	Gallotta V et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=26776676
3	Surgery for Recurrent Epithelial Ovarian Cancer in the Netherlands: A Population-Based Cohort Study.	van de Laar R et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/?term=26588237
4	A Predictive Score for Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer (SeC-Score): A Single-Centre, Controlled Study for Preoperative Patient Selection.	Angioli R et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=25808099
5	Performance of AGO score for secondary cytoreduction in a high-volume U.S. center.	Janco JM et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=26836496
6	Hyperthermic Intraperitoneal Chemotherapy after Secondary Cytoreduction in Epithelial Ovarian Cancer: A Single-center Comparative Analysis.	Baiocchi G et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=26628430
7	Long-Term Survival for Platinum-Sensitive Recurrent Ovarian Cancer Patients Treated with Secondary Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC).	Petrillo M et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=26714958

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Medical treatment of primary ovarian cancer

Editor Kamil Zalewski, Kristina Lindemann, Michael J. Halaska

Descriptive summary

AGO-OVAR-12, a double-blind phase III trial randomised 1366 patients (2:1) with FIGO stage IIB-IV ovarian cancer (OC) to either to receive six cycles of carboplatin and paclitaxel with nintedanib or placebo after upfront debulking surgery [1]. Nintedanib inhibits the VEGF receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor. The addition of nintedanib significantly (p=0.024) increased progression-free survival (PFS) from 16.6 months (95 % CI 13.9–19.1) to 17.2 months (95 % CI 16.6–19.9). No significant differences were noted in subgroups according to residual tumour. Quality of life was not adversely affected during treatment with nintedanib, despite more frequent gastrointestinal side effects on nintedanib.

Chan et al. report on a phase III trial with 692 primary OC patients randomised to 6 cycles of 3 weekly paclitaxel (175 mg/m2) + carboplatin (6 AUC), or dose-dense weekly paclitaxel (80 mg/m2)/3 weekly carboplatin (AUC, 6). Patients elected for bevacizumab or not and were prospectively stratified for this factor [2]. Weekly paclitaxel was not associated with longer PFS, as compared with standard treatment (14.7 vs. 14.0 months, p=0.18) in the population as a whole. Among patients who did not receive bevacizumab, weekly paclitaxel was associated with superior PFS (14.2 vs. 10.3 months; hazard ratio, 0.62; 95 % CI, 0.40 to 0.95; P=0.03).

Tewari et al. analysed post-hoc whether time from surgery to initiation of chemotherapy impacts overall survival (OS) in GOG 218 [3]. For 81 patients with stage IV disease who underwent complete resection, the risk of death increased when the time from surgery to initiation of chemotherapy exceeded 25 days.

Bouchard-Fortier et al. retrospectively compared the toxicity and tolerability of intraperitoneal (IP) cisplatin to IP carboplatin in 141 women with optimally cytoreduced OC [4]. The IP cisplatin group experienced significantly more toxicities than those treated with IP carboplatin (grade 3 nausea and vomiting, grade 3 neuropathy and grade 2–3 neutropenia). No difference in PFS (p = 0.602) or OS (p = 0.107) was found between the groups. Three international randomised phase III trials (iPocc trial, GOG 252, OV-21/GCIG) which will hopefully provide level 1 evidence as to whether IP carboplatin is non-inferior to IP cisplatin.

The benefit of IP chemotherapy in OC has been confirmed by a Cochrane review. IP chemotherapy increases both PFS (5 studies, 1311 women; HR = 0.78; 95 % CI: 0.70 to 0.86) and OS (8 studies, 2026 women; HR = 0.81; 95 % confidence interval (CI): 0.72 to 0.90) [5]. The optimal indication remains unclear.

Another Cochrane review assessed the role of adjuvant chemotherapy (AC) in FIGO stage I-IIa OC [6]. Four studies were included and demonstrated that adjuvant platinum-based chemotherapy prolongs survival in women with early-stage OC (HR 0.67, 95 % CI 0.53 to 0.84; 1170 women). The survival benefits may be greatest in women with high-risk disease, but uncertainty remains for lower-risk early-stage disease. Decisions regarding adjuvant treatment in these patients should be mindful of this uncertainty, consider adverse events, and take individual factors into account.

Mahdi et al. retrospectively investigated whether patients with known BRCA status, (gBRCA_mut +, n=30 and gBRCA_mut -, n=106), who received platinum-based neoadjuvant chemotherapy (NAC) for FIGO II-IV ovarian, fallopian tube, and primary peritoneal cancers, had an improved outcome compared to patients with unknown BRCA status (BRCA_mut_unk, n=166) [7]. There was no difference in surgical outcome (rates of complete cytoreduction and bowel resection) between the groups. gBRCA_mut + patients had non-significantly longer PFS compared to gBRCA_mut_unk and gBRCA_mut – (19.1 vs. 15.1 vs. 15.7 months respectively). BRCA_mut + and BRCA_mut – patients had longer overall survival compared to BRCA_mut_unk patients (50.5 vs. 54.1 vs. 36.5 months respectively, p = 0.009). Selection bias may explain the favourable outcomes in BRCA_mut – patients, as patients who had good response to chemotherapy and favourable outcome may be more likely to undergo BRCA testing.

Grabowski et al. retrospectively analysed sensitivity to chemotherapy in 39 patients with primary low-grade serous ovarian cancer (LGSOC) in advanced disease stage after upfront surgery with macroscopic residual disease (RD) (>1 cm) in the AGO megadatabase [8]. An objective response to platinum-based chemotherapy was observed at 23.1 %, confirming the low response rate compared to high-grade serous ovarian cancer (HGSOC). Patients with complete cytoreduction had significantly better progression free survival and overall survival compared to those with RD after primary surgery.

Ruscito et al. discussed the current role of cediranib (a tyrosine kinase inhibitor targeting VEGF receptors) in the treatment of OC [9]. A systematic review on chemotherapy in ovarian germ cell tumours (OGCT) also summarised guidelines for the management of OGCT [10].

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Medical treatment of primary ovarian cancer

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1	Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial.	du Bois A et al.	Lancet Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26590673
2	Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer.	Chan JK et al.	N Engl J Med.	http://www.ncbi.nlm.nih.gov/pubmed/26933849
3	Early initiation of chemotherapy following complete resection of advanced ovarian cancer associated with improved survival: NRG Oncology/Gynecologic Oncology Group study.	Tewari KS et al.	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26487588
4	A comparison of the toxicity and tolerability of two intraperitoneal chemotherapy regimens for advanced-stage epithelial ovarian cancer.	Bouchard-Fortier G et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26546964
5	Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer.	Jaaback K et al.	Cochrane Database Syst Rev.	http://www.ncbi.nlm.nih.gov/pubmed/26755441
6	Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer.	Lawrie TA et al.	Cochrane Database Syst Rev.	http://www.ncbi.nlm.nih.gov/pubmed/26676202
7	Outcome of neoadjuvant chemotherapy in BRCA1/2 mutation positive women with advanced-stage Müllerian cancer.	Mahdi H et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26210778
8	Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO Study Group metadatabase.	Grabowski JP et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26807488
9	Cediranib in ovarian cancer: state of the art and future perspectives.	Ruscito I et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26753963
10	Chemotherapy in ovarian germ cell tumors: A systematic review.	Simone CG et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26873864

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Medical treatment of recurrent ovarian cancer

Editor Kamil Zalewski, Kristina Lindemann, Michael J. Halaska

Descriptive summary

In view of the common use of carboplatin plus pegylated liposomal doxorubicin (PLD) in patients with platinum-sensitive OC and the encouraging results of studies with farletuzumab (a monoclonal antibody against folate receptor alpha, FAB), a phase Ib study of FAR plus carboplatin and PLD was undertaken for the treatment of platinum-sensitive OC in first or second relapse [1]. The aim of the study was to assess the safety of this triple-agent combination in this disease context. Farletuzumab did not add substantial toxicity to the chemotherapy backbone.

Bell-McGuinn et al. failed to show iniparib (4-iodo-3-nitrobenzamide) monotherapy to be effective in patients with recurrent BRCA1- or BRCA2-associated OC [2]. None of the 12 patients responded.

Emons et al. reported a phase II study with platinum-refractory/resistant OC or advanced/recurrent endometrial cancer (EC) patients treated with mTOR inhibitor temsirolimus. Although toxicity was acceptable and durable disease stabilisation was observed in some patients, the low efficacy (progressive disease at 8 weeks in 10/21 and 8/20 patients with OC and EC, respectively) led to premature closure of the trial [3].

Pujade-Lauraine et al. published the results of a phase II trial evaluating volasertib (selective cell-cycle kinase inhibitor) or single-agent chemotherapy in patients with platinum-resistant or refractory OC [4]. Volasertib (selective cell-cycle kinase inhibitor) resulted in manageable adverse effects, which were mostly haematologic [4]. The median PFS for volasertib was 13.1 weeks and 20.6 weeks for the investigator's choice single-agent, nonplatinum, cytotoxic chemotherapy. In the volasertib arm, 11 % of patients achieved PFS greater than or equal to 1 year, in contrast to no patients in the chemotherapy arm.

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No	Title	Authors	Journal	Link to abstract
1	Phase 1b safety study of farletuzumab, carboplatin and pegylated liposomal doxorubicin in patients with platinum-sensitive epithelial ovarian cancer.	Kim KH et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26644263
2	A Phase 2, Single Arm Study of Iniparib in Patients With BRCA1 or BRCA2 Associated Advanced Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.	Bell-McGuinn KM et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26745694
3	Temsirolimus in women with platinum-refractory/resistant ovarian cancer or advanced/recurrent endometrial carcinoma. A phase II study. of the AGO-study group (AGO-GYN8).	Emons G et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26731724
4	Volasertib Versus Chemotherapy in Platinum-Resistant or -Refractory Ovarian Cancer: A Randomized Phase II Groupe des Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire Study.	Pujade-Lauraine E et al.	J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26755507

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Pathology/pathogenesis of malignant ovarian tumours

Editor Dogan Vatansever

Descriptive summary

Original Research

Hong et al. demonstrated that transfer of L1-CAM-specific CE7R+T cells may offer a novel immunotherapy strategy for advanced ovarian cancer. Recent clinical trials demonstrated that chimeric antigen receptor (CAR)-redirected T cells have a therapeutic role in haematological cancers, and there are emerging studies for a similar effect in solid cancers. They showed that L1-CAM, an adhesion molecule, is highly overexpressed in ovarian cancer cell lines and primary ovarian cancer tissue specimens. They genetically modified human memory-derived T cells to express an anti-L1-CAM CAR (CE7R) and found that CE7R+T cells are able to target primary ovarian cancer cells.

Du et al. reported the synergistic effect of c-Met and PARP inhibitors. *Please see the report from S. Giovannoni on "Hereditary ovarian cancer (BRCA1/2 mutation, genetic counselling, management)."*

Strickland et al. reported significantly higher predicted neo-antigens in BRCA1/2-mutated tumours compared to tumours without mutation. Hypermutated lesions such as melanomas and lung carcinomas harbour more tumour-specific neo-antigens that cause recruitment of increased number of tumour-infiltrating lymphocytes (TILs) counterbalanced by overexpression of immune checkpoints such as PD-1 or PD-L1. In this study, BRCA1/2-mutated high-grade serous ovarian cancers (HGSOCs) exhibited a higher mutational load and increased number of TILs and PD-1/PD-L1 expression. HR proficient HGSOCs with low number of TILs have a poor prognosis and BRCA1/2-mutated tumours with high number of TILs have a good prognosis. The results also suggest that BRCA1/2-mutated HGSOCs may be more sensitive to PD1/PD-L1 inhibitors compared to HR-proficient HGSOCs.

Reviews

Perets and Drapkin reported evidence of the tubal origin of ovarian cancer in this review article. They also summarised different experimental model systems (ex vivo, cell line, genetically engineered mouse models, and patient-derived tumour xenograft models).

Bregar et al. presented preclinical data that support the role of phosphatidyl-inositol-3-kinase (PI3K) pathway in ovarian, endometrial, and cervical cancers. Despite the differences among these cancer types, they share activation of the PI3K pathway as a common signature. They reported that up to 70 % of ovarian cancers show alterations in the PI3K pathway and summarised the preclinical and clinical data.

King et al. reviewed animal models on endometriosis. The evidence shows that endometriosis is a precursor of clear cell and endometrioid ovarian cancer. They describe various models that can be used to study the malignant transformation of endometriosis to epithelial ovarian cancer.

Morin et al. also reviewed the animal models of epithelial ovarian cancer (EOC). The mouse models generated were based on the belief that the ovarian surface epithelium was the cell origin of disease and may need to be re-evaluated as more recent evidence suggest that, rather, the fallopian tube epithelium may be the origin of EOC. They examined the mouse models of both and summarise the data that led to this paradigm shift.

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Pathology/pathogenesis of malignant ovarian tumours

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1	L1 Cell Adhesion Molecule-Specific Chimeric Antigen Receptor-Redirected Human T Cells Exhibit Specific and Efficient Antitumor Activity against Human Ovarian Cancer in Mice.	Hong H et al.	PLOS One.	http://dx.doi.org/10.1371/journal.pone.0146885
2	Blocking c-Met–mediated PARP1 phosphorylation enhances anti-tumor effects of PARP inhibitors.	Du Y et al.	Nat Med.	http://dx.doi.org/10.1038/nm.4032
3	Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer.	Strickland KC et al.	Oncotarget.	http://dx.doi.org/10.18632/oncotarget.7277
4	It's Totally Tubular….Riding The New Wave of Ovarian Cancer Research.	Perets R et al.	Cancer Res.	http://dx.doi.org/10.1158/0008-5472.CAN-15-1382
5	Emerging strategies for targeting PI3K in gynecologic cancer.	Bregar AJ et al.	Gynecol Oncol.	http://dx.doi.org/10.1016/j.ygyno.2015.09.083
6	Models of endometriosis and their utility in studying progression to ovarian clear cell carcinoma.	King CM et al.	J Pathol.	http://dx.doi.org/10.1002/path.4657
7	Genetically-defined ovarian cancer mouse models.	Morin PJ et al.	J Pathol.	http://dx.doi.org/10.1002/path.4663

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

- Editor Ignacio Zapardiel

- Descriptive summary

The key points of the articles retrieved are the following:

Prognostic factors:

In a metaanalysis [1], it has been found that the complete surgical staging of borderline ovarian tumours (BOT) could improve the relapse rate but does not affect overall survival, as reported previously by several authors. Ureyen et al. [2] suggested that surgical staging gives an idea of recurrence probability but not of the survival prognosis.

Lee et al. [3] published an anecdotal case report: a mucinous BOT was diagnosed in a 93-year-old woman who was treated by tumoural mass removal due to the patient's age. Two years prior to that admission she had already been diagnosed with a suspicious ovarian mass.

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Impact of surgical staging on prognosis in patients with borderline ovarian tumours: A meta-analysis.	Sheem SH et al.	Eur J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26735354
2	The Factors Predicting Recurrence in Patients With Serous Borderline Ovarian Tumor.	Ureyen I et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26512785
3	Mucinous Borderline Ovarian Tumor in Very Old Aged Postmenopausal Woman.	Lee SH et al.	J Menopausal Med.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4719091/

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

Emerging molecular targeted therapies or early preclinical trials in ovarian cancer

Editor Muhammad Rizki Yaznil

Descriptive summary

Targeted therapy is still challenged by heterogeneity of the disease.

Tan et al. [1] described a database (CSIOVDB) with microarrays of 3,431 ovarian cancers with molecular subtype, EMT status, clinico-pathological parameters and TCGA data. This database can enrich our ability to find new and significant molecular targets for therapies.

The Ovarian Cancer Association Consortium [2] has analysed 2.8 million SNPs with detailed chemotherapy and clinical follow-up data. Three SNPs in three long non-coding RNAs (lncRNAs) were associated with poor progression-free survival. One of these lies within a super-enhancer recently shown to be associated with poor prognosis in hepatocellular carcinoma.

miRNA is crucial for post-transcription regulation of gene expression. miRNAs are small (~22 bp) endogenous, non-protein-coding nucleotides that regulate gene expression.

Updates on this research topic:

- Restoration of miRNA activity may represent a way to inhibit cancer growth: Shields et al. [3] reported that miRNA mimic a toxicity screen in a large diverse spectrum of EOC cell lines. miR-181 and miR-155 are toxic in chemoresistant ovarian cancer cells through dual modulation of TGF and AKT signalling. miR-517a targets ARCN1.
- Boac et al. [4] identified 5 publically available micro-RNAs (miRNAs) associated with in vitro development of ovarian cancer chemoresistance. These target multiple pathways, the majority being associated with epithelial–mesenchymal transition (EMT).
- Van Jaarsveld et al. [5] found that miR-634 downregulation was associated with cisplatin resistance and overexpression of miR-634 resensitised resistant ovarian cancer cell lines and patient derived drug-resistant tumour cells to cisplatin. miR-634 interacted with the cell cycle regulator CCND1, and the Ras-MAPK pathway.
- Chen et al. [6] reports miR-509-3p downregulation in chemoresistant EOC. Restoring of miR-509-3p may downregulate the expression of XIAP (X-linked inhibitor of apoptosis) and inhibit EOC growth.

Resistance to chemotherapy is still a major problem in ovarian cancer, especially in recurrent disease.

Resensitisation of chemotherapy as a therapeutic approach is the topic of the following articles:

- Tang et al. [7] reported on a phase I study on CRM197, HB-EGF inhibitor (Heparin-binding epidermal growth factor-like growth factor) demonstrated that CRM197 could significantly reverse the resistance to paclitaxel in A2780/Taxol cells and xenografts which over-express HB-EGF and EGFR.
- Inhibition of CDK1 with alsterpaullone may help to overcome resistance to paclitaxel. Bae et al. [8] reported a reduction of tumour growth upon paclitaxel subsequent to alsterpaullone treatment in a EOC xenograft model.
- Dasatinib is an orally administered ATP-competitive kinase inhibitor of the SFKs Src-family kinases and has shown substantial activity in EOC in preclinical studies, but not in phase II studies. Pathak et al. [9] showed that of dasatinib and CX4945 (silmitasertib), the first and only clinically relevant CK2 inhibitor, showed significant synergy across a panel of EOC cell lines in reducing proliferation and increasing apoptosis.

The development of a new agent and molecular target for ovarian cancer:

- p53 is a tumour suppressor of paramount importance and p53 alterations are highly prevalent in ovarian cancer (>96 % HGSOC). Soragni et al [10]. designed a cell-penetrating peptide, ReACp53, rescuing p53 function. Rescued p53 behaves similarly to its wild-type counterpart in regulating target genes, reducing cell proliferation and increasing cell death. Intraperitoneal administration decreases tumour proliferation and shrinks xenografts in vivo.
- Catenin signalling is essential to developmental processes and is deregulated in cancer. The R-spondin (RSPO) protein family enhance -catenin signalling. Chartier et al. [11] generated specific monoclonal antibody RSPO antagonists and found that anti-RSPO treatment markedly inhibited tumour growth in human patient-derived tumour xenograft models, either as single agents or in combination with chemotherapy.

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Emerging molecular targeted therapies or early preclinical trials in ovarian cancer

- Descriptive summary (cont.)
  - Tetraspanins (TSPANs) are a family of small proteins that are parts of a specific signalling platform involved in many important cellular functions and malignant processes. Park et al. [12] found that TSPAN8 is overexpressed in about 52 % (14/27) of EOC tissues and was correlated with poor survival. It was a key regulator of EOC cell invasion and monotherapy with TSPAN8-blocking antibody showed significant reduction of the incidence of EOC metastasis without severe toxicity.
  - Stope et al. [13] reviewed the role of HSP (heat shock proteins) in ovarian cancer. HSPs were characterised as molecular chaperones and perform crucial roles in folding/unfolding, turnover, and transport of proteins as well as in the assembly of multiprotein complexes. HSP90 stabilises the mutant p53 protein in cancer cells. Pharmacologic inhibition of HSP90 destroys the complex between HSP90 and mutant p53 protein, thereby liberating mutant p53 and causing cytotoxicity in p53 mutant cancer cells in culture and in xenografts. Another European clinical trial studied the second-generation HSP90 inhibitor ganetespib (Synta Pharmaceutical, Lexington, MA, USA) in combination with weekly paclitaxel in mainly HGS platinum-resistant ovarian cancer patients.
  - The prognosis of advanced CCC is very poor, primarily because of its resistance to platinum-based chemotherapy. Matsuzaki et al. [14] highlighted several potential therapeutic targets in these patients based on molecular pathways.

Repurposing of drugs:

- Monensin (rumensin) is a polyether ionophore antibiotic secreted by the bacteria Streptomyces cinnamonensis. Monensin acted synergistically with EGFR inhibitors and oxaliplatin to inhibit cell proliferation and induce apoptosis of ovarian cancer cells. Xenograft studies showed that monensin effectively inhibits tumour growth by suppressing cell proliferation through targeting EGFR signalling (Deng et al.; 15).

A little insight on "double edge sword" immunology and immunotherapy in ovarian cancer:

- Carbotti et al. [16] described how IL-27 inhibits the growth and invasiveness of different cancers and therefore represents a potential anti-tumour agent. However, it also induces IDO or PD-L1 expression through STAT1 and STAT3 tyrosine phosphorylation. Immune-enhancing monoclonal antibodies (mAbs) that target immune checkpoints such as anti-PD-1 and anti-PD-L1 currently are being studied in EOC.

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- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	CSIOVDB: a microarray gene expression database of epithelial ovarian cancer subtype.	Tan TZ et al.	Oncotarget.	https://www.ncbi.nlm.nih.gov/pubmed/26549805
2	Genome-wide analysis identifies novel loci associated with ovarian cancer outcomes: findings from the Ovarian Cancer Association Consortium.	Johnatty SE et al.	Clin Cancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/26152742
3	A genome-scale screen reveals context-dependent ovarian cancer sensitivity to miRNA overexpression.	Shields BB et al.	Mol Sys Biol.	https://www.ncbi.nlm.nih.gov/pubmed/26655797
4	Micro-RNAs associated with the evolution of ovarian cancer cisplatin resistance.	Boac BM et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26731723
5	miR-634 restores drug sensitivity in resistant ovarian cancer cells by targeting the Ras-MAPK pathway.	van Jaarsveld MTM et al.	Mol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/26576679
6	MicroRNA-509-3p increases the sensitivity of epithelial ovarian cancer cells to cisplatin-induced apoptosis.	Chen W et al.	Pharmacogenomics.	https://www.ncbi.nlm.nih.gov/pubmed/26786897
7	Cross-reacting material 197 reverses the resistance to paclitaxel in paclitaxel-resistant human ovarian cancer	Tang X et al.	Tumour Biol..	https://www.ncbi.nlm.nih.gov/pubmed/26572150
8	Restoration of paclitaxel resistance by CDK1 intervention in drug resistant ovarian cancer.	Bae T et al.	Carcinogenesis.	https://www.ncbi.nlm.nih.gov/pubmed/26442525
9	A Synthetic Lethality Screen Using a Focused siRNA Library to Identify Sensitizers to Dasatinib Therapy for the Treatment of Epithelial Ovarian Cancer.	Pathak HB et al.	PLOS One.	https://www.ncbi.nlm.nih.gov/pubmed/26637171
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11	Therapeutic Targeting of Tumour-Derived R-Spondin Attenuates -Catenin Signaling and Tumorigenesis in Multiple Cancer Types.	Chartier C et al.	Cancer Research.	https://www.ncbi.nlm.nih.gov/pubmed/26719531
12	Therapeutic targeting of tetraspanin8 in epithelial ovarian cancer invasion and metastasis.	Park CS et al.	Oncogene.	https://www.ncbi.nlm.nih.gov/pubmed/26804173
13	Jump in the fire — heat shock proteins and their impact on ovarian cancer therapy.	Stope MB et al.	Crit Rev Oncol Hematol.	https://www.ncbi.nlm.nih.gov/pubmed/26318096
14	Potential target for ovarian clear cell carcinoma: a review of updates and future perspectives.	Matsuzaki S et al.	Cancer Cell Int.	https://www.ncbi.nlm.nih.gov/pubmed/26675567
15	Antibiotic monensin synergizes with EGFR inhibitors and oxaliplatin to suppress the proliferation of human ovarian cancer cells.	Deng Y et al.	Sci Rep.	https://www.ncbi.nlm.nih.gov/pubmed/26639992
16	IL-27 induces the expression of IDO and PD-L1 in human cancer cells.	Carbotti G et al.	Oncotarget.	https://www.ncbi.nlm.nih.gov/pubmed/26657115

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

Editor Sara Giovannoni

Descriptive summary

PARP inhibitors:

1. Domchek et al. published a subgroup analysis of Study 42 (phase II) including gBRCA1/2 mutated, heavily pre-treated ovarian cancer patients. In these 193 patients, the ORR on olaparib monotherapy was 34 %, and median DoR was 7.9 months. This study confirms the notable antitumour activity in this population and is comparable to the results for all ovarian cancer patients in Study 42.
2. Choi et al. identified a microRNA, miR-622 that regulates the expression of the ku-complex and suppresses NHEJ during S-phase. Consistent with this effect, over-expression of miR-622 rescues the HR-deficiency of BRCA1 mutant ovarian tumour lines and induces resistance to PARP inhibitors and platinum-based drugs.
3. Moudry et al. investigated the role of TOPB1 (Topoisomerase I -binding protein) and PARP inhibitor sensitivity. TOPBP1 seems to be crucial in HR repair and is involved in sensitizing human ovarian cancer cells to olaparib. These findings are important in order to predict the response to PARP inhibitors and to develop new molecular target agents.
4. Du et al. demonstrated that the receptor kinase c-Met may increase the efficacy of PARP by phosphorylation of PARP1 at Tyr907. PARP1 pY907 increases PARP1 enzymatic activity and reduces binding to a PARP inhibitor, thereby rendering cancer cells resistant to PARP inhibition. The combination of c-Met and PARP1 inhibitors synergised to suppress the growth of breast cancer cells in vitro and xenograft tumour models. So far there are no data on ovarian cancer, but PARP1Py907 may predict tumour resistance to PARP inhibitors and treatment with both c-Met and PARP inhibitors may be beneficial in patients with high c-Met expression who do not respond to PARP inhibition alone.
5. Two interesting reviews summarise the evidence of PARP inhibitors in ovarian cancer (Drew Y, BJC; Ledermann JA BJC).

Hereditary ovarian cancer/prevention/counselling:

1. Hartmann recently published an interesting review about the role of risk-reducing surgery in hereditary breast and ovarian cancer. A woman's age is highly relevant to her risk of breast or ovarian cancer. For ovarian cancer, BRCA1 carriers have an average cumulative risk by the age of 80 of 45 %, and BRCA2 carriers of 12 %. Current guidelines recommend RRSO for both mutation carriers between 35 and 40 years. However, BRCA 2 carriers tend to develop ovarian cancer later (1 % at the age of 50) and the authors think that the procedure can be delayed until approximately 45 years of age in in those patients. Salpingectomy alone is still an investigational approach. And even if most of the studies have shown a risk-reducing effect of RRSO on breast cancer risk later in life, most of the studies are prone to bias and the authors of this review recommend some caution in counselling these patients. Women should be informed about the expected effects (i.e., increased risk of osteoporosis, cardiovascular disease and possible cognitive decline) and management options for symptoms.
2. Lheureux published the results of two web-based surveys performed by the Gynecologic Cancer InterGroup (GCIG). The study highlights the need for collaborative efforts to devise international guidelines around BRCA1/2 testing in ovarian cancer to ensure consistent BRCA1/2 screening practices are adopted.
3. The new NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide recommendations for genetic testing, counselling and management for hereditary cancer syndromes.
4. Sermijn et al. studied the impact of an interventional counselling procedure in families with BRCA gene mutation. Informing relatives directly nearly doubles the number of relatives tested and is psychologically safe.

Treatment of infertility in BRCA carrier patients:

A matched case-control study of 941 pairs of BRCA1 or BRCA2 mutation carriers with and without a diagnosis of ovarian cancer published by Gronwald et al. suggested that infertility treatment does not significantly increase the risk of ovarian cancer in these women.

Survival/BRCA mutation status:

The ten-year survival data from 1,421 Canadian patients published by Kotsopulos and Rosen in January 2016, showed no association between survival and BRCA mutation status. The initial survival advantage among women with BRCA mutations may reflect a higher initial sensitivity of BRCA carriers to chemotherapy, but this response does not predict long-term survival. The authors suggest that differences in statistical modelling may explain the discrepancies between studies published to date. The strongest predictor of long-term survival is status of no residual disease at resection.

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

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy.	Domchek SM et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26723501
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3	TOPBP1 regulates RAD51 phosphorylation and chromatin loading and determines PARP inhibitor sensitivity.	Moudry P et al.	J Cell Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26811421
4	Blocking c-Met-mediated PARP1 phosphorylation enhances anti-tumour effects of PARP inhibitors.	Du Y et al.	Nat Med.	http://www.ncbi.nlm.nih.gov/pubmed/26779812
5	The development of PARP inhibitors in ovarian cancer: from bench to bedside.	Drew Y	Br J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26669452
6	PARP inhibitors in ovarian cancer: Clinical evidence for informed treatment decisions.	Ledermann JA	Br J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26669450
7	The Role of Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer.	Hartmann LC et al.	N Engl J Med.	http://www.ncbi.nlm.nih.gov/pubmed/26840135
8	Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2015.	Daly MB et al.	J Natl Compr Canc Netw.	http://www.ncbi.nlm.nih.gov/pubmed/26850485
9	Germline BRCA1/2 testing practices in ovarian cancer: Current state and opportunities for new directions.	Lheureux S et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26475959
10	The impact of an interventional counselling procedure in families with a BRCA1/2 gene mutation: efficacy and safety.	Sermijn E et al.	Fam Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26748927
11	Treatment of infertility does not increase the risk of ovarian cancer among women with a BRCA1 or BRCA2 mutation.	Gronwald J et al.	Fertil Steril.	http://www.ncbi.nlm.nih.gov/pubmed/26698676
12	Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status.	Kotsopoulos J et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26556769
13	BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next-generation sequencing.	Mafficini A et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26745875
14	Clinical features and outcomes of germline mutation BRCA1-linked versus sporadic ovarian cancer patients.	Synowiec A et al.	Hered Cancer Clin Pract.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4706695/
15	Clinical and Pathological Characteristics of Incidental Diagnostic Early Occult Malignancy After Risk-Reducing Salpingo-Oophorectomy in BRCA Mutation Carriers.	Lavie O et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26807561
16	Clinical Practice Guideline for the prevention and early detection of breast and ovarian cancer in women from HBOC (hereditary breast and ovarian cancer) families.	Singer CF et al.	Wien Klin Wochenschr.	http://www.ncbi.nlm.nih.gov/pubmed/26525377
17	Selecting Patients with Ovarian Cancer for Germline BRCA Mutation Testing: Findings from Guidelines and a Systematic Literature Review.	Eccles DM et al.	Adv Ther. 2016 Jan 25.	http://www.ncbi.nlm.nih.gov/pubmed/26809252

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Screening for ovarian and fallopian tube cancer

Editor Lucas Minig

Descriptive summary

The first survival outcomes from the largest ovarian cancer screening trial to date, the UKCTOCS protocol (UK Collaborative Trial of Ovarian Cancer Screening) have recently been published.

The aim of the study was to compare different methods of screening. A total of 200,000 postmenopausal women volunteers were randomised into 3 arms: 100,000 to no screening, 50,000 to annual transvaginal ultrasound (TVS), and 50,000 to multi-modal screening (MMS), with a follow-up of 15 years.

The MMS strategy includes annual measurement of CA 125, not considering outliers, but individual variability over the years. The research team developed the ROCA (Risk of Ovarian Cancer Algorithm) tool, which considers the age of the patient, family history risk, and CA 125 values over time. Based on that result, women were categorised as normal, intermediate or high risk. CA 125 determination was performed annually in women at normal risk (always recalculating risk). In the intermediate-risk patients, CA 125 was repeated every 3 months; in high-risk patients, a new CA 125, transvaginal ultrasound, and surgery (in case of persistent abnormal results) were performed within the following 6 weeks.

The study requires some considerations:

- The analysis with ROCA was centralised, and the values were not considered by the usual cut-off of 35, but changed over time.
- The transvaginal ultrasound was to be reported according to a strict protocol, which was modified during the study (e.g., simple ovarian cyst size om imaging was changed from 5 to 10 cm for the indication of surgery).

Previous reports of this study showed that the specificity of MMS was similar to TVS (99 %), a sensitivity of 88 % vs. 63 %, a positive predictive value of 24 vs. 4 %, and the number of operations performed by case detected was 4 vs. 25. By using MMS, they also showed a higher percentage of patients with early-stages (I/II), 39 vs. 33 % (this ratio was equal between low- and high-grade tumours).

The study failed to show whether these differences between the methods translated into decreased mortality: The MMS and TVS branches showed no statistically significant decrease in mortality of 15 % (95 % CI: -3, 30) and TVS 11 % (-7, 27) respectively, in comparison with the no-screening group.

For every 10 women who died in the follow-up arm, two could have been saved with MMS. There was a more pronounced reduction in mortality after long-term follow-up and after exclusion of prevalent cases. The reduction in mortality during the first seven years was 8 % and 2 % for MMS and TVS, respectively, but between in year 7-14, the estimated mortality for MMS reduction was 23 % (95 % CI: 1 to 46) and 21 % (95 % CI: - 2 to 42) for TVS. In conclusion, it would appear that finally a screening program in ovarian cancer could have an impact on survival. However, long-term follow-up is needed before any final conclusion in this regard.

There is evidence that müllerian duct cancers (i.e., ovarian or endometrial cancers). One study investigated 65 women (27 with benign lesions of genital organs, 30 with ovarian cancer, 5 with endometrial cancer and 3 with other cancers) to see if uterine lavage could detect malignant cells. Next generation sequencing was able to identify specific mutations in 24 (80 %) women with ovarian cancer, all 5 patients with endometrial cancer and 8 (29.6 %) women with benign diseases, including KRAS. The main mutations in ovarian cancer patients included TP53, KRAS and PIK3CA. One occult ovarian cancer was detected in an asymptomatic woman with BRCA-1 mutation submitted for risk-reduction salpingo-oophorectomy. Limitations include the small sample size, the inclusion of mainly advanced ovarian cancers and the detection of mutations also in the samples of patients with benign disease. Data regarding tolerability is also needed.

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial.	Jacobs IJ et al.	Lancet	http://www.ncbi.nlm.nih.gov/pubmed/26707054
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3	Lavage of the Uterine Cavity for Molecular Detection of Müllerian Duct Carcinomas: A Proof-of-Concept Study.	Maritschnegg E et al.	J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26552420

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

Editor Kastriot Dallaku

Descriptive summary

An overview of the most relevant studies on the treatment of endometrial hyperplasia covers two main aspects:

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

Metin et al. studied 61 patients and reported that transvaginal elastosonography (ES) can help to distinguish between endometrial carcinoma (EC) and endometrial hyperplasia (EH) with a sensitivity of 81.3 %, a specificity of 100 %, a positive predictive value of 100 % and a negative predictive value of 70 %. ES has also been shown in the study of Gultekin et al. to differentiate between pathological endometrial changes and normal endometrium in patients presenting with thickened endometrium. MR may also be suitable to differentiate between benign and malignant endometrial lesions (Shitano et al.).

A systematic review and meta-analysis of 12 studies on endometrial sampling in postmenopausal bleeding was carried out by van Hanegem et al. Although specificity was very high, authors reported a low sensitivity of endometrial sampling to detect both EC and atypical EH. They concluded that after a benign result of endometrial biopsy, further diagnostic work is warranted. In their retrospective study Louie et al. suggested that endometrial thickness of <15mm without vaginal bleeding in postmenopausal women might not warrant endometrial sampling.

Li et al. found Nup88 to be a potential biomarker for pre-malignant lesions and early-stage EC (expressed in 91 % and 76 % of samples respectively). Ørbo et al. studied the expression of PAX2 and PTEN prior and after treatment with three different regimes of progestins in EH. A levonorgestrel-impregnated intrauterine system (LNG-IUS) was significantly more efficient compared to oral progestin therapy in obtaining clearance of PAX2. Yang et al. studied PTEN expression in relation to EC risk factors.

Conservative and definitive treatment for patients with endometrial hyperplasia.

Treatment of endometrial hyperplasia, its risk of relapse and obesity as risk factor were reported by several publications. Nooh et al. reported that 6 months of treatment with depo-provera was more successful in achieving regression than norethisterone acetate (91.8 % vs. 67.1 %, respectively) in 146 patients with EH without atypia. Emarh found no significant difference between cyclic medroxyprogesterone acetate (MPA) and continuous MPA regimens in that group of patients, although the first one was better tolerated by patients. Baek et al. focused on the role of oral progestin therapy as an alternative treatment for women with complex atypical hyperplasia (CAH) or early-stage EC who desire fertility preservation. In their retrospective series 74.2 % (23 of 31 patients) achieved complete remission.

Dominick et al. evaluated the effectiveness of LNG-IUS in their systematic review of four trials with 543 women with breast cancer on adjuvant tamoxifen. The study confirmed the protective effect of LNG-IUS in these patients, reducing the incidence of endometrial polyps and hyperplasia.

Ørbo et al. evaluated the risk of EH relapse within 2 years of ceasing therapy with either the LNG-IUS or oral MPA. Relapse rate was similar in all groups and was independent of therapy regime. Mitsuhashi et al., in their phase II study with 36 patients, demonstrated that metformin (750-2250 mg/day) could prevent disease relapse after combined therapy with MPA, as a fertility-sparing treatment for atypical EH and EC.

Cholakian et al. demonstrated that oral progestin therapy compared with LNG-IUS for conservative treatment CAH or early-stage EC, was associated with increased weight gain. A systematic review by Wise et al. confirmed obesity to be a risk factor for CAH or EC in premenopausal women. Haggerty et al. reported that a 6-month lifestyle intervention via either telemedicine or text messaging resulted in weight loss among obese women with endometrial hyperplasia and cancer.

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

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No	Title	Authors	Journal	Link to abstract
1	Relapse risk of endometrial hyperplasia after treatment with the levonorgestrel-impregnated intrauterine system or oral pro-gestogens.	Ørbo A et al.	BJOG.	http://www.ncbi.nlm.nih.gov/pubmed/26630538
2	Differentiation between endometrial carcinoma and atypical endometrial hyperplasia with transvaginal sonographic elastography.	Metin MR et al.	Diagn Interv Imaging.	http://www.ncbi.nlm.nih.gov/pubmed/26711550
3	Can Nup88 expression be associated with atypical endometrial hyperplasia and endometrial cancer? A preliminary study.	Li Y et al.	Pathol Res Pract.	http://www.ncbi.nlm.nih.gov/pubmed/26839161
4	Cyclic versus continuous medroxyprogesterone acetate for treatment of endometrial hyperplasia without atypia: a 2-year observational study.	Emarh M.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26015309
5	Obesity and endometrial hyperplasia and cancer in premenopausal women: a systematic review.	Wise M et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26829507
6	The use of novel technology-based weight loss interventions for obese women with endometrial hyperplasia and cancer.	Haggerty AF et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26644265
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8	Depo-provera versus norethisterone acetate in management of endometrial hyperplasia without atypia.	Nooh AM et al.	Reprod Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26718306
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13	Threshold for endometrial sampling among postmenopausal patients without vaginal bleeding.	Louie M et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26658096
14	PTEN expression in benign human endometrial tissue and cancer in relation to endometrial cancer risk factors.	Yang HP et al.	Cancer Causes Control.	http://www.ncbi.nlm.nih.gov/pubmed/26376893
15	Effect of oral versus intrauterine progestins on weight in women undergoing fertility preserving therapy for complex atypical hyperplasia or endometrial cancer.	Cholakian D et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26706662
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17	MR appearance of normal uterine endometrium considering menstrual cycle: differentiation with benign and malignant endometrial lesions.	Shitano F et al.	Acta Radiol.	http://www.ncbi.nlm.nih.gov/pubmed/26787675

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

Editor Santiago Scasso

Descriptive summary

Within the period covered by the 3rd issue of LiFE report, the ESMO-ESTRO-ESGO consensus was one of the most important publications on endometrial cancer (EC).

The main recommendations of the "Prevention and screening" working group are as follows:

- Atypical hyperplasia (AH)/endometrial intraepithelial neoplasia (EIN) is the preferred terminology of the precursor lesion of EC.
- AH/EIN or grade 1 endometrioid endometrial cancer (EEC) must be confirmed/diagnosed by expert pathologist.
- Morphology (and not immunohistochemistry (IHC)) should be used to distinguish AH/EIN from EEC.
- Sometimes morphological criteria may be supported by IHC markers and molecular alterations to distinguish from benign mimic lesions.
- The differential diagnosis of AH/EIN includes endometrial hyperplasia without atypia, glandular and stromal breakdown, focal glandular crowding, and epithelial metaplasia. Loss of PTEN expression and loss of PAX-2 are the only IHC markers sufficiently studied and recommended to use on curettage material.
- IHC is not recommended to distinguish atypical polypoid adenomyoma (APA) from AH/EIN.
- The precursor of serous carcinoma, serous endometrial intraepithelial carcinoma (SEIC), is considered a non-invasive cancer rather than a precancer. Molecular alterations of serous carcinoma are already present in SEIC. A completely negative immunoreactive pattern for p53 is considered a surrogate for p53 mutation, and is present in almost all SEIC and invasive serous carcinomas. Therefore, p53 by IHC is recommended to distinguish SEIC from its mimics.
- In selected cases in which cervical involvement may confuse the origin of the uterine tumour, and considering that endocervical, ovarian, and endometrial adenocarcinomas may show histopathological overlap, it is recommended to use a panel of markers including at least ER, vimentin, CEA, and p16 by IHC. In addition, HPV analysis can be considered.
- Wilms tumour 1 gene by IHC is the recommended marker to determine the origin of serous cancer.

Other aspects to be highlighted in this literature review:

Lapinska-Szumczyk et al. analysed 400 formalin-fixed paraffin-embedded primary tumour samples, and reported a molecular subtype classification in EC, depending on the hormone receptor status (Oestrogen Receptor-ER, Progesterone Receptor-PR) and Human Epidermal growth factor Receptor 2 (HER2) analysed by IHC. Four molecular subtypes are recognised and show diversity in terms of prognosis, clinicopathological and molecular characteristics, with ER+/PR+/HER2- and ER-/PR-/HER2+ groups exhibiting exceptionally benign and aggressive behaviour, respectively. They have further characterised the subtypes with the known pathways endometrial carcinogenesis: PI3K-AKT pathway, TP53 system, and the mismatch repair (MMR) mechanism. It is to emphasise that the molecular subtype distinction, along with MMR and TP53 status, could become a useful diagnostic tool for guiding individualised therapy.

Dudley et al. focused on the pathogenesis and prognostic value of microsatellite instability (MSI) in EC in their review. MSI usually arises from either germline mutations in components of the mismatch repair (MMR) machinery (MSH2, MSH6, MLH1, PMS2) in patients with Lynch syndrome (LS) or from somatic hypermethylation of the MLH1 promoter. They reported significant responses of tumours with MSI to immunotherapy anti-PD-1 inhibitors in patients who failed conventional therapy. Authors concluded that MSI testing could have an expanded role as a tool in the armamentarium of precision medicine. 22 %-33 % is the estimated frequency of MSI in EC.

Shikama et al. suggest that analysing MMR status and searching for Lynch syndrome may identify a subset of patients with higher sensitivity to adjuvant therapies and favourable survival.

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

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up.	Colombo N et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4679344/
2	Immunohistochemical characterisation of molecular subtypes in endometrial cancer.	Lapinska-Szumczyk SM et al.	Int J Clin Exp Med.	http://www.ncbi.nlm.nih.gov/pubmed/26885170
3	Clinicopathologic implications of DNA mismatch repair status in endometrial carcinomas.	Shikama A et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26644264
4	Microsatellite instability as a biomarker for PD-1 blockade.	Dudley JC et al.	Clin Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26880610

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Screening for uterine cancer/hereditary uterine cancer

Editor María de los Reyes Oliver Pérez

Descriptive summary

Screening for uterine cancer [1-2]:

The consensus of the European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) has been recently published [1]. Regarding the screening of endometrial cancer (EC), the main recommendations are:

- There is no evidence for EC screening in the general population.
- Unopposed oestrogen treatment should not be started or should be discontinued in women with a uterus in situ.
- Routine surveillance in asymptomatic women with risk factors of EC (obesity, polycystic ovary syndrome, diabetes mellitus, infertility, nulliparity, or late menopause) is not recommended. However, asymptomatic women with risk factors for EC who have endometrial thickening and other positive findings on ultrasound should be managed on a case-by-case basis.
- Routine screening for EC in asymptomatic tamoxifen users is not recommended.
- For women with adult granulosa cell tumour, endometrial sampling is recommended. If this shows no evidence of (pre) malignancy, no further screening for EC is required.
- In patients with epithelial ovarian cancer undergoing fertility-sparing treatment, endometrial sampling is recommended.

Van Hanegem et al. [2] published a systematic review of the accuracy of endometrial sampling for the diagnosis of EC. The sensitivity of dilatation and curettage was 100 % (range 100-100 %). The sensitivity of the hysteroscopy was 90 % (range 50-100 %). The specificity was 98-100 % for both techniques.

Hereditary uterine cancer [3-6]:

The ESMO–ESGO–ESTRO consensus proposes in women with high risk for EC:

- Surveillance of the endometrium by gynaecological examination, transvaginal ultrasound, and aspiration biopsy starting from the age of 35 years (annually until hysterectomy) should be offered.
- Prophylactic surgery (hysterectomy and bilateral salpingo-oophorectomy) should be discussed at the age of 40 as an option for Lynch Syndrome (LS) mutation carriers.

Hall et al. [3] published a review of the genetic testing and management of hereditary cancer predisposition. In a group of women who have completed childbearing, prophylactic hysterectomy should be considered; screening should be reserved for the other cases. The authors also review the evidence on the use of oral contraceptive pills and high-dose aspirin to reduce the risk of EC in average-risk women.

There are two publications discussing new genetic testing for hereditary cancer predisposition and identification of (LS) in sporadic EC [4-5].

Although the prevalence of occult EC at the time of risk-reducing surgery in women with LS remains unknown, Frey et al. [6] emphasises the utility of endometrial sampling prior to risk-reducing hysterectomy to improve surgical planning in this population and to avoid a two-stage procedure for staging.

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	ESMO–ESGO–ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow up.	Colombo N et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26645990
2	Genetic testing for hereditary cancer predisposition: BRCA1/2, Lynch syndrome, and beyond.	Hall MJ et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26812021
3	The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis.	Van Hanegem N et al.	Eur J Obstet Gynecol Reprod Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26748390
4	Targeted next-generation sequencing of 22 mismatch repair genes identifies Lynch syndrome families.	Talseth-Palmer BA et al.	Cancer Med.	http://www.ncbi.nlm.nih.gov/pubmed/26811195
5	Clinicopathologic comparison of Lynch syndrome–associated and "Lynch-like" endometrial carcinomas identified on universal screening using mismatch repair protein Immunohistochemistry.	Mills AM et al.	Am J Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26523542
6	Utility of endometrial sampling prior to risk-reducing hysterectomy in a patient with Lynch syndrome.	Frey MK et al.	Ecancermedicalscience.	http://www.ncbi.nlm.nih.gov/pubmed/26823682

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Surgical treatment of primary uterine cancer

Editor Piotr Lepka

Descriptive summary

In the period covered by the third LiFE report, the -ESMO-ESTRO-ESGO recommendations and consensus on endometrial cancer (EC) treatment were published. Regarding the surgical treatment of EC, the main recommendations are:

- Peritoneal cytology is no longer considered mandatory for staging.
- If a lymphadenectomy is performed, systematic removal of pelvic and para-aortic nodes up to the level of the renal veins should be considered.
- Lymphadenectomy is a staging procedure and allows tailoring of adjuvant therapy (for patients with a low risk of lymph node involvement, it is not recommended; for intermediate risk, it can be considered for staging purposes; in the high-risk group, it is recommended).
- Lymphadenectomy to complete staging could be considered in previously incompletely operated high-risk patients.
- Radical hysterectomy is not recommended for the management of stage II EC; surgery should be tailored in order to obtain free margins. Lymphadenectomy is recommended for clinical or intra-operative stage II.
- Complete macroscopic cytoreduction and comprehensive staging is recommended in advanced endometrial cancer and multimodality therapy is required.
- In non-endometrioid endometrial cancer (apparent stage I) lymphadenectomy is recommended.
- Staging omentectomy is not mandatory in clear cell or undifferentiated endometrial carcinoma and carcinosarcoma but should be considered in serous carcinoma.

Other issues discussed in the available literature were:

- Preoperative evaluation. Su et al. retrospectively evaluated the accuracy of preoperative hysteroscopic biopsy compared to dilation and curettage (D&C) in patients with EC. The authors concluded that hysteroscopic biopsy could provide more precise information on histological grade of differentiation, compared to D&C. Knowledge of the correct grade would allow for a more accurate staging plan, based on the preoperative risk evaluation.
- EC in elderly women. Rauh-Hain et al. retrospectively analysed 2,468 patients with grade 3 adenocarcinomas, carcinosarcomas, clear-cell carcinomas and uterine serous carcinomas. They demonstrated that patients ≤ 55 years were more likely to undergo surgery (and lymph node dissection) than women >75 years. Older women were also less likely to be treated with chemo- and radiotherapy.
- Risk of nodal metastasis. Jorge et al. demonstrated in their retrospective analysis that lymphovascular space invasion (LVSI) is an independent predictor of lymph node metastases for women with <50 % myoinvasion. Regardless of the depth of invasion and tumour grade, LVSI was also an independent predictor of survival.
- Adenomyosis and EC. Gizzo et al. suggested that the intraoperative evaluation of the presence of adenomyosis in patients with EC (associated with lower grades in FIGO stage, myometrial invasion, lymphovascular space involvement, lymph node involvement, and tumour size) may aid surgeons in estimating oncological risk and tailoring surgical treatment.

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Surgical treatment of primary uterine cancer

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Accuracy of hysteroscopic biopsy, compared to dilation and curettage, as a predictor of final pathology inpatients with endometrial cancer.	Su H et al.	Taiwan J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26700998
2	Management for Elderly Women With Advanced-Stage, High-Grade Endometrial Cancer.	Rauh-Hain JA et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26551187
3	Prevalence of pelvic floor disorders in women with suspected gynecological malignancy: a survey-based study.	Bretschneider CE et al.	Int Urogynecol J.	http://www.ncbi.nlm.nih.gov/pubmed/26872646
4	Magnitude of risk for nodal metastasis associated with lymphvascular space invasion for endometrial cancer.	Jorge S et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26768835
5	Coexistence of adenomyosis and endometrioid endometrial cancer: Role in surgical guidance and prognosis estimation.	Gizzo S et al.	Oncol Lett.	http://www.ncbi.nlm.nih.gov/pubmed/26893721
6	ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer	Colombo N et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4679344/

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Medical (chemo and radiotherapy) treatment of primary uterine cancer

Editor David Lindquist

Descriptive summary

Two large registry-based studies [1,3] investigated the frequency of adjuvant treatment in uterine serous carcinoma (USC) and uterine carcinosarcoma. The authors included more than 10,000 women, and concluded that the use of chemotherapy has increased in both groups. A parallel increase in survival was noted and a relation with the increased use of adjuvant treatment is possible but cannot be established in such studies. The possible effect of adjuvant treatment in uterine carcinosarcoma was also investigated in a retrospective multi-institutional study including 300 patients [2]. This study also reported an increased use of adjuvant treatment over time and an increased survival in patients receiving treatment compared to the observation group. There are no recent randomised clinical trials evaluating the effect of adjuvant treatment for USC and uterine carcinosarcoma, but due to the aggressive nature of these diseases, adjuvant treatment is often offered and these studies provide at least some degree of evidence for this practice.

A Korean multi-centre study investigated the possible survival benefit of chemoradiotherapy in patients with endometrial carcinoma. 85 patients were included between 1990-2011 and only stage IIIC endometrial carcinomas were assessed. No additional effect was observed in survival outcomes compared with radiotherapy alone [4]. Half of the relapses in patients with stage IIIC1 were in the para-aortic lymph nodes, whereas the majority of relapses in patients with stage IIIC2 disease were distant metastasis. The authors of another retrospective study on 51 patients concluded that FIGO IB uterine cancer with high-risk histology showed benefit from adjuvant radiotherapy [5].

A series of 50 consecutive patients who were given SIB-VMAT adjuvant radiotherapy instead of vaginal brachytherapy combined with external beam radiotherapy showed that the side effects were not severe and that it could be an interesting alternative to standard treatment [6]. However, this needs to be assessed in a randomised controlled trial, but may present an alternative for patients who are not suitable for brachytherapy. Finally, one study including 208 patients reported different outcomes for black women compared with white women, and this is likely something which needs to be considered when designing future studies [7].

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Patterns of care, predictors and outcomes of chemotherapy for uterine carcinosarcoma: a National Cancer Database analysis.	Rauh-Hain JA et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=26307402
2	"A multi-institutional study of outcomes in stage I-III uterine carcinosarcoma."	Dickson EL et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=26348313
3	A multicenter analysis of adjuvant therapy after surgery for stage IIIC endometrial adenocarcinoma: A Korean Radiation Oncology Group study (KROG 13-17).	Yoon MS et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=26115977
4	Adjuvant radiation therapy is associated with improved pelvic control and overall survival in FIGO IB endometrial carcinoma with high grade histology.	Ly D et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=26095895
5	"Volumetric-modulated arc therapy with vaginal cuff simultaneous integrated boost as an alternative to brachytherapy in adjuvant irradiation for endometrial cancer: a prospective study."	Alongi F et al.	Anticancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/?term=25862871
6	Volumetric-modulated arc therapy with vaginal cuff simultaneous integrated boost as an alternative to brachytherapy in adjuvant irradiation for endometrial cancer: a prospective study.	Alongi F et al.	Anticancer Res.	https://www.ncbi.nlm.nih.gov/pubmed/?term=25862871
7	Effect of race and histology on patterns of failure in women with early stage endometrial cancer treated with high dose rate brachytherapy.	Ozen A et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/?term=26024766

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Medical treatment of recurrent endometrial cancer

Editor Ewa Surynt

Descriptive summary

During the period covered by the third edition of the LiFE report, medical treatment of recurrent uterine malignancies was discussed in two articles.

Han et al. retrospectively analysed 4 patients with advanced or recurrent uterine sarcoma, treated with bevacizumab (BEV) and chemotherapy. The chemotherapeutic drugs included dacarbazine (DTIC), cisplatin (DDP), etoposide (VP-16), adriamycin, paclitaxel, and carboplatin. The mean number of cycles was 8.3 (range 4–12 cycles). Of the 4 patients, 1 achieved complete response (CR), with a disease-free survival time of 96 months; 1 achieved partial response (PR), with progression-free survival (PFS) of 13 months and overall survival (OS) of 25 months; 1 achieved stable disease (SD), with PFS of 9 months and OS of 24 months; and 1 developed progressive disease, with PFS of 3 months and OS of 9 months. The response rate was 50 %, and the clinical benefit rate [CR + PR+ SD] was 75 %. Treatment-related adverse reactions occurred in all 4 patients, including bone marrow suppression and gastrointestinal reactions. One patient developed grade 4 thrombocytopenia, whereas the remaining 3 patients developed grade 2 leukopenia. Authors concluded that BEV combined with chemotherapy exhibits efficacy in the treatment of advanced or recurrent uterine sarcomas, with a tolerable toxicity profile, and may be considered as a safe and effective candidate treatment for this type of tumour, however, the extremely small sample size and the retrospective design challenge these conclusions.

On the background of contradictory and inconclusive recommendations on the treatment of recurrent and metastatic endometrial cancer, Battista et al. studied the pattern of care in more than 700 different German gynaecological departments between 2006 and 2013 at three different time points.

The major findings of this survey were: Progestins are the most commonly used endocrine agents in 2013 (79.8 %). Diverse chemotherapy regimen were used, but 65.3 of the participants responded that they used platinum. Local recurrence and distant metastasis of EC were often treated with surgery and radiotherapy and subgroup analyses only depicted differences in the preferred endocrine and cytostatic drugs, when stratified for hospital. Authors concluded that the lack of preferred cytostatic drug might be the result of inconsistent and limited literature not providing a real standard of care in recurrent and metastatic EC.

Please see the report by K. Zalewski "Medical treatment of recurrent ovarian cancer," on the activity and toxicity of mTOR inhibitor temsirolimus in patients with advanced/recurrent EC.

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Curative effect of bevacizumab combined with chemotherapy in advanced or recurrent uterine sarcoma.	Han Y et al.	Mol Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26893869
2	Management of recurrent or metastatic endometrial cancer in Germany: results of the nationwide AGO pattern of care studies from the years 2013, 2009 and 2006.	Battista MJ et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26099624

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Surgical treatment of recurrent endometrial cancer

Editor Arun Kalpdev

Descriptive summary

Due to a paucity of well-designed trials, there is still no final verdict for the management of recurrent endometrial cancer (REC). Recently, European experts on behalf of the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO), have developed recommendations and consensus on endometrial cancer diagnosis, treatment and follow-up [1]. The authors emphasise that recurrent disease should only be considered for surgery if cytoreduction with no macroscopic residual disease is achievable. The performance of lymphadenectomy in cytoreduction is not being favoured, due to lack of effect on overall survival (OS) and progression-free survival (PFS). The retrospective analysis of Papadia et al. supports these recommendations, showing better overall survival (OS) and progression-free survival (PFS) after optimal cytoreduction [2]. The estimated 5-year overall survival (OS) was 60 % and 30 % in optimally and suboptimally cytoreduced patients, respectively.

Hardarson et al. retrospectively evaluated the efficacy of radiotherapy and surgical treatment in a non-irradiated group of 33 patients with REC limited to the vaginal vault. Authors indicated that a surgical approach is an appropriate treatment for locally REC [3].

Turan et al. analysed the effects of salvage cytoreductive surgery among 34 patients with REC. An optimal result with no visible residual tumour was achieved in 68.2 % of the patients treated via the laparotomy route. None of the factors was associated with the achievement of optimal cytoreduction [4].

The following studies reported on different surgical techniques for the treatment of REC. Gallotta et al. presented a video of the laparoscopic management of REC, mainly focusing on small bowel resection with intracorporeal anastomosis and partial colpectomy [5]. Menderes et al. showed a surgical video in which an isolated hemidiaphragmatic tumour nodule was resected laparoscopically in a patient with isolated REC [6]. Kato et al. presented the cytoreduction of metastatic para-aortic lymph nodes with involvement of the inferior vena cava, requiring its partial resection and repair [7].

Relevant articles retrieved Nov 2015 - Feb 2016 (cont.)

No	Title	Authors	Journal	Link to abstract
1	ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up.	Colombo N et al.	Radiother Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26683800
2	Surgical Treatment of Recurrent Endometrial Cancer: Time for a Paradigm Shift.	Papadia A et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/25777095
3	Vaginal vault recurrences of endometrial cancer in non-irradiated patients - Radiotherapy or surgery.	Hardarson HA et al.	Gynecol Oncol Rep.	http://www.ncbi.nlm.nih.gov/pubmed/26076091
4	Salvage Cytoreductive Surgery for Recurrent Endometrial Cancer.	Turan et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26397154
5	Laparoscopic Management of a Small Bowel Recurrence of Endometrial Cancer.	Gallotta et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26408229
6	Laparoscopic Resection of the Diaphragmatic Tumor Nodule for Management of Recurrent Endometrial Cancer.	Menderes G et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26776674

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Uterine sarcoma (treatment and follow-up)

Editor Marcin Bobiński

Descriptive summary

The incidence of occult uterine sarcoma

Many retrospective studies, published in the period covered by the third LiFE report, discussed the incidence of unsuspected malignant disease at the time of myomectomy (MM) or total hysterectomy (TH) for benign indications.

- Kho et al. estimated that occult uterine sarcoma (US) occurs in 0.089 % (1 of 1,124 TH) [1].
- Picerno et al. estimated the incidence of malignancy to be 0.2 % (1 of 502), all cases were endometrial cancers; no cases of US [2].
- Raine-Bennett et al. found the incidence of US to be 1 of 278 or 3.60 (95 % confidence interval [CI] 2.97-4.23) and leiomyosarcoma (LMS) 1 of 429 or 2.33 (95 % CI 1.83-2.84) per 1,000 total hysterectomies [3].
- In the research by Paul et al. the incidence of US was found to be 0.29 % (1 in 335 patients) [4].
- Rodriguez et al. assessed the incidence of US to be 12.9 per 10,000 for patients younger than 49 [5].

Sarcoma patients' outcome after morcellation

- Gao et al. retrospectively analysed 59 patients who underwent fibroid morcellation (FM) without specimen retrieval bags or TH and had a postoperative diagnosis of US:
  - Only pathological grade level was a significant risk factor affecting recurrence free survival (RFS) and overall survival (OS)
  - The 5-year RFS and OS rates were both lower in the FM vs. the TH group, FM was not the statistically significant risk factor affecting RFS and OS [6].
- Harris et al. analysed 18,299 patients and compared various methods of TH and postoperative outcome before and after the Food and Drug Administration (FDA) warning. They reported:
  - Increased rate of abdominal and vaginal, decreased rate of laparoscopic TH (p=0.025, <0.01, <0.01; respectively)
  - Increased incidence of major postoperative complications and readmissions [7].
- Mandato et al. confirmed these findings in their survey conducted among Italian gynaecologists [8].

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Controversies around the FDA's report initiated an open letter addressed to this institution, in which it was suggested that the FDA guidance was based on misleading analysis and should be reconsidered [9]. The review by Bogani et al., concluding that intra-abdominal morcellation should be banned from clinical practice [10], adds to this debate.

Preoperative diagnostics of myometrial lesions

The problem of missing specific and sensitive enough methods to differentiate benign and malignant tumours is widely discussed by several authors:

- Cho et al. identified following preoperative risk factors that might be useful for discrimination of US and leiomyoma of the uterus: Neutrofil-to-lymphocyte ratio (>2.1), tumour size (>8cm), body mass index (BMI <=20) [11].
- Lin et al. presented data on the diagnostic accuracy of contrast-enhanced MRI and diffusion-weighted magnetic resonance imaging (DW MRI) in differentiation between uterine lesions. They reported (based on a relatively small group of patients) that CE MRI can provide accurate information regarding preoperative diagnosis (accuracy=0.94, sensitivity=0.88, specificity=0.96) and seems to be a superior method to DW MRI [12].

Treatment

The role of gemcitabine-based chemotherapy in sarcomas is discussed by Ducoulombier et al. in their systemic review, but they conclude that further research in this field is strongly recommended [13]. Ducie et al. highlighted the advances in adjuvant therapy in LMS over the last 5 years [14].

For treatment with bevacizumab therapy in patients with recurrent sarcoma, please see "Medical treatment of recurrent endometrial cancer" by E. Surynt.

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Uterine sarcoma (treatment and follow-up)

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Risk of Occult Uterine Sarcoma in Women Undergoing Hysterectomy for Benign Indications.	Kho et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26855091
2	Morcellation and the incidence of Occult uterine malignancy.	Picerno et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26332395
3	Occult Uterine Sarcoma and Leiomyosarcoma: Incidence of and Survival Associated With Morcellation.	Raine-Bennett et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26646120
4	Uterine Sarcomas in Patients Undergoing Surgery for Presumed Leiomyomas: 10 Years' Experience.	Paul et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26677821
5	Incidence of occult leiomyosarcoma in presumed morcellation cases: a database study.	Rodriguez et al.	Eur J Obstet Gynecol Reprod Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26699101
6	A Retrospective Analysis of the Impact of Myomectomy on Survival in Uterine Sarcoma.	Gao et al.	PLoS ONE.	http://www.ncbi.nlm.nih.gov/pubmed/26828206
7	Practice patterns and postoperative complications before and after US Food and Drug Administration safety communication on power morcellation.	Harris et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26314519
8	Impact of the Food and Drug Administration Safety Communication on the Use of Power Morcellator in Daily Clinical Practice: An Italian Survey.	Mandato et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26454195
9	An Open Letter to the Food and Drug Administration Regarding the Use of Morcellation Procedures in Women Having Surgery for Presumed Uterine Myomas.	Parker et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26773577
10	Morcellation of undiagnosed uterine sarcoma: A critical review.	Bogani et al	Crit Rev Oncol Hematol	http://www.ncbi.nlm.nih.gov/pubmed/26672915
11	Differential diagnosis between uterine sarcoma and leiomyoma using preoperative clinical characteristics.	Cho et al.	J Obstet Gynaecol Res.	http://www.ncbi.nlm.nih.gov/pubmed/26695124
12	Comparison of the diagnostic accuracy of contrast-enhanced MRI and diffusion weighted MRI in differentiation between uterine leiomyosarcoma/smooth muscle tumour of uncertain malignant potential and benign leiomyoma.	Lin et al.	Magn. Reson. Imaging	http://www.ncbi.nlm.nih.gov/pubmed/26383110
13	Gemcitabine-based chemotherapy in sarcomas: A systematic review of published trials.	Ducoulombier et al.	Crit Rev Oncol Hematol	http://www.ncbi.nlm.nih.gov/pubmed/26555460
14	The role of adjuvant therapy in uterine leiomyosarcoma.	Ducie et al.	Expert Rev Anticancer Ther.	http://www.ncbi.nlm.nih.gov/pubmed/26558647

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Emerging molecular targets in endometrial cancer

- Editor Ines Vasconcelos

- Descriptive summary

In this last quarter there was yet another disappointing trial on temsirolimus in endometrial cancer (EC). This phase II clinical trial evaluated temsirolimus—a mTOR inhibitor—and included 22 patients with advanced or recurrent EC. These women were no longer amenable to curative surgery and/or radiotherapy and had had no previous or only adjuvant chemotherapy. Patients received weekly IV infusions of 25 mg temsirolimus. After eight weeks of treatment, 8 of 20 evaluable patients had progressive disease, thus failing to meet the predefined trial efficacy criteria. *This study is also cited in "Medical treatment of recurrent ovarian cancer" by K. Zalewski.*

In the second article Papa et al. reviewed and highlighted the main angiogenetic molecular pathways and the anti-angiogenic agents in phase II clinical trials for EC treatment.

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Temsirolimus in women with platinum-refractory/resistant ovarian cancer or advanced/recurrent endometrial carcinoma. A phase II study of the AGO-study group (AGO-GYN8).	Emons G et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26731724
2	Targeting angiogenesis in endometrial cancer - new agents for tailored treatments.	Papa A et al.	Expert Opin Investig Drugs.	http://www.ncbi.nlm.nih.gov/pubmed/26560489

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

Cervical pre-invasive disease (diagnosis, management)

Editor Geanina Dragnea

Descriptive summary

Risk factors

Multiple HPV infections were not associated with increased risk for high-risk cervical lesions compared to the women infected with a single HPV genotype. This finding is suggestive of possible intergenotypic competition or a more effective immune response triggered by multiple infections. Further studies in larger, more diverse cohorts are needed [1].

Mitra et al. reported that a high diversity of vaginal microbiomes and low levels of Lactobacillus spp. (community state type-CST IV) to be associated with increasing CIN severity. Vaginal microbiota diversity may be involved in regulating viral persistence and disease progression [2].

Pathogenesis

A post-hoc analysis of the ATHENA study was performed to determine whether true HPV negative cervical lesions CIN2+ occur and whether they have clinical relevance. Of 55 CIN2+ women, 23 cases were negative by all HPV tests (11 CIN3/ACIS lesions). Further analysis with tissue PCR did not identify any true CIN3/ACIS not attributable to HPV (4 were positive for HPV types not considered oncogenic, 2 were positive for oncogenic genotypes and 1 was indeterminate) [3].

Vaccination

Prophylactic

The protective effect of HPV vaccination (quadrivalent vaccine) against CIN2+ was evaluated in a population-based study on 1,333,691 Swedish girls aged 13-29. Greater effectiveness was observed in younger age groups, with 75 % for those vaccinated before age 17, and 46 % and 22 % for those vaccinated at ages 17-19, and at ages 20-29, respectively [4].

Therapeutic

A randomised study on 1,711 women (18-25 years old) with hrHPV infection and 311 who underwent treatment for CIN and received HPV-16/18 vaccination (versus Hepatitis A vaccine) found that there was no evidence for a vaccine effect on the fate of detectable HPV infections; the vaccination does not protect against infections/lesions post-treatment [5].

Screening

A systematic review compared test accuracy of the HPV test, cytology, and unaided visual inspection with acetic acid (VIA) to detect CIN 2+. Despite large differences in sensitivity between tests, absolute differences in missed diagnoses were small. Differences in specificity may lead to overtreatment as demonstrated for assessment with VIA instead of the cervical smear (58 more per 1000 women) [6].

A retrospective study concluded that cytology+hrHPV co-testing remains the best strategy for detecting CIN2+ lesions, with a false-negative rate of only 1.2 %. The false-negative rates for hrHPV and Pap smears were 8.7 % and 9.1 %, respectively [7].

A Swedish population-based cohort study showed that atypical glandular cells (AGC) during cervical screening is associated with a high and persistent risk of cervical cancer for up to 15 years (cumulative incidence of 2.6 % at 15.5 years), particularly for cervical adenocarcinoma and women at age 30-39. Management of AGC seems to have been suboptimal in preventing cervical cancer. The current Swedish guidelines recommend immediate histology assessment and subsequent treatment for women with AGC (similar to HSIL management). This is likely to be insufficient, and a more aggressive assessment strategy, including both an additional histology test in one year and close long-term surveillance, could be considered to find the precursor lesions in time, with particular attention given to women aged 30-39 [8].

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Cervical pre-invasive disease (diagnosis, management)

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No	Title	Authors	Journal	Link to abstract
1	Multiple Human Papilloma Virus Infections and Their Impact on the Development of High-Risk Cervical Lesions.	Salazar KL et al.	Acta Cytol.	http://www.karger.com/Article/FullText/442512
2	Cervical intraepithelial neoplasia disease progression is associated with increased vaginal microbiome diversity.	Mitra A et al.	Sci Rep.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4648063/
3	Evaluating HPV negative CIN2+ in the ATHENA trial.	Petry KU et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26851121
4	Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study.	Herweijer E et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26856527
5	Impact of Human Papillomavirus (HPV) 16 and 18 Vaccination on Prevalent Infections and Rates of Cervical Lesions After Excisional Treatment.	Hildesheim A et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26892991
6	Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy.	Mustafa RA	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26851054
7	Clinical performance of the Food and Drug Administration-Approved high-risk HPV test for the detection of high-grade cervicovaginal lesions.	Zhou H et al.	Cancer Cytopathol.	http://www.ncbi.nlm.nih.gov/pubmed/26774025
8	Risk of invasive cervical cancer after atypical glandular cells in cervical screening: nationwide cohort study.	Wang J et al.	BMJ.	http://www.bmj.com/content/352/bmj.i276.long

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Pathology of cervical cancer

Editor Borja Otero

Descriptive summary

ICC development

HPV 16 and 18 are more frequent in women aged 30-39 compared to women ≥ 70 [1] and are the most prevalent genotypes in ICC specimens in different countries [2-6].

HPV infection needs some cofactors for ICC development such as an inflammatory microenvironment and hypoxia. The way these two mechanisms develop in ICC has been studied in two recent studies. Urokinase plasminogen activator receptor (uPAR) facilitates hypoxia-mediated invasion through HIF-1. uPAR expression has been detected in cervical cancer but not in normal cervix or cervical intraepithelial neoplasia (CIN) by immunohistopathological staining. Regarding the inflammatory microenvironment, fibroblasts support Th17 (T helper 17) cell infiltration and maintain chronic inflammation within high-grade cervical lesions further promoting cancer progression [7,8].

Finally, some individual characteristics such as CDKN1A and Interleukin-27 genetic polymorphisms might influence the development of ICC, giving some clues about the differences in interindividual progression of same HPV serotypes infections [9,10].

ICC diagnosis

When several cervical biopsies are performed during a colposcopy, CADM1/MAL methylation hyperexpression seems to be representative of the worst underlying lesion, particularly for CIN3 and cervical cancer. [12] This means that the degree of methylation in the CADM1/MAL genes can not only indicate how long an HPV infection has been present but also how severe the lesions produced by that infection are.

ICC prognosis

DNA methylation is an important epigenetic modification frequently altered in cancer and metabolites associated to this mechanism could be markers for ICC prognosis. Levels of 5-hydroxymethylcytosine have shown differential patterns between ICC and normal cervical tissues being an independent prognostic factor for both disease-free and overall survival [14].

TNF-related apoptosis-inducing ligand (TRAIL) induces apoptosis in cancer cells. Several TRAIL signalling members have been evaluated in ICC, showing that high c-FLIP expression is associated to poor prognosis; DR5 nuclear positive tumours have enhanced response to radiotherapy; and TRAIL as well as caspase-8 loss may be associated with malignant progression [15].

Eukaryotic initiation factor 5A2 (EIF5A2) plays an important role in tumour progression and its high expression is an independent prognostic factor for overall survival and disease-free survival [16].

ICC treatment outcome

Low Ku86 and XRCC4 expression, two markers of non-homologous end joining of DNA, a mechanism to repair DNA double-strand breaks induced by ionizing radiation, is a significant predictor of a pathological complete response to radiotherapy [17].

Tumour G-CSF expression is an indicator of an extremely poor prognosis in cervical cancer patients treated with chemotherapy. It seems that G-CSF-increases myeloid-derived suppressor cells (MDSC), which are involved in the development of chemoresistance. Moreover, the depletion of MDSC via splenectomy or the administration of anti-Gr-1 antibody sensitised G-CSF producing cervical cancer to cisplatin [18].

Novel therapeutic approaches

Prostate-specific membrane antigen-targeted therapy is a promising treatment of advanced carcinomas. One study has demonstrated that some ICC overexpress this protein, thus being candidates to receive this treatment [19].

BORIS sf6 is differentially expressed in cervical cancer stem-like cells and cancer-initiating cells, which are resistant to conventional radiotherapy and chemotherapy. These cells have been shown to be a target for specific cytotoxic T cells turning into candidates for immunotherapy [20].

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Pathology of cervical cancer

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Age-specific prevalence of HPV16/18 genotypes in cervical cancer: a systematic review and meta-analysis.	Hammer A et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26661889
2	Secular trends of HPV genotypes in invasive cervical cancer in Cali, Colombia 1950-1999.	Sanchez GI et al.	Cancer Epidemiol.	http://www.ncbi.nlm.nih.gov/pubmed/26771314
3	Prevalence of human papillomavirus genotypes among women with cervical cancer in Ghana.	Awua AK et al.	Infect Agent Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26816527
4	Prevalence of human papilloma virus (HPV) and its genotypes in cervical specimens of Egyptian women by linear array HPV genotyping test.	Youssef MA et al.	Infect Agent Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26889206
5	HPV prevalence and type-distribution in cervical cancer and premalignant lesions of the cervix: A population-based study from Northern Ireland.	Anderson LA et al.	J Med Virol.	http://www.ncbi.nlm.nih.gov/pubmed/26680281
6	Detection and Typing of Human Papilloma Viruses by Nested Multiplex Polymerase Chain Reaction Assay in Cervical Cancer.	Jalal Kiani S et al.	Jundishapur J Microbiol.	http://www.ncbi.nlm.nih.gov/pubmed/26865940
7	Hypoxia inducible factor-1 mediates upregulation of urokinase-type plasminogen activator receptor gene transcription during hypoxia in cervical cancer cells.	Nishi H et al.	Oncol Rep.	http://www.ncbi.nlm.nih.gov/pubmed/26718775
8	Stromal Fibroblasts Induce CCL20 through IL6/C/EBP to Support the Recruitment of Th17 Cells during Cervical Cancer Progression.	Walch-Rückheim B et al.	Cancer Res	http://www.ncbi.nlm.nih.gov/pubmed/26631268
9	Roles of CDKN1A gene polymorphisms (rs1801270 and rs1059234) in the development of cervical neoplasia.	Vargas-Torres SL et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26846214
10	Correlation of IL-27 genetic polymorphisms with the risk and survival of cervical cancer in a Chinese Han population.	Shi J, Yuan M et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26662568
11	Expressions of E2 and E7-HPV16 proteins in pre-malignant and malignant lesions of the uterine cervix.	Ramirez N et al.	Biotech Histochem.	http://www.ncbi.nlm.nih.gov/pubmed/26052817
12	CADM1 and MAL methylation status in cervical scrapes is representative of the most severe underlying lesion in women with multiple cervical biopsies.	van Baars R et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26219541
13	A study of the expression and localization of toll-like receptors 2 and 9 in different grades of cervical intraepithelial neoplasia and squamous cell carcinoma.	Ghosh A et al.	Exp Mol Pathol	http://www.ncbi.nlm.nih.gov/pubmed/26569074
14	5-Hydroxymethylcytosine expression is associated with poor survival in cervical squamous cell carcinoma.	Zhang LY et al.	Jpn J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26851753
15	Prognostic significance of TRAIL signalling molecules in cervical squamous cell carcinoma.	Yao Q et al.	J Clin Pathol	http://www.ncbi.nlm.nih.gov/pubmed/26254281
16	Overexpression of Eukaryotic Initiation Factor 5A2 is associated with cancer progression and poor prognosis in patients with early-stage cervical cancer.	Yang S et al.	Histopathology.	http://www.ncbi.nlm.nih.gov/pubmed/26799253
17	Influence of Ku86 and XRCC4 expression in uterine cervical cancer on the response to preoperative radiotherapy.	Takada Y et al.	Med Mol Morphol.	http://www.ncbi.nlm.nih.gov/pubmed/26867665
18	The significance of G-CSF expression and myeloid-derived suppressor cells in the chemoresistance of uterine cervical cancer.	Kawano M et al.	Sci Rep.	http://www.ncbi.nlm.nih.gov/pubmed/26666576
19	Prostate-specific Membrane Antigen (PSMA) Expression in the Neovasculature of Gynecologic Malignancies: Implications for PSMA-targeted Therapy.	Wernicke AG et al.	Appl Immunohistochem Mol Morphol.	http://www.ncbi.nlm.nih.gov/pubmed/26862945
20	Brother of the regulator of the imprinted site (BORIS) variant subfamily 6 is involved in cervical cancer stemness and can be a target of immunotherapy.	Asano T et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/26849232

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Surgical treatment of primary cervical cancer

Editor Mandic Aljosa and Matteo Morotti

Descriptive summary

Narducci et al. retrospectively analysed 29 patients with occult cervical cancer after inadvertent simple hysterectomy. Patients who underwent radical parametrectomy with pelvic lymph node dissection (n=13) dissection resulted in a better clinical outcome (OS and DFS) than radiotherapy (n=16) with acceptable minimal morbidity being observed. Although the cohort is quite small to draw conclusions from, minimally invasive surgery can be a good option in the management of these women.

Papadia et al. compared retrospectively SLN mapping in occult cervical cancer patients diagnosed after hysterectomy (group 1) with patients with uterus in situ (group 2). Overall and bilateral detection rates were higher when uterus was in situ with 66.6 % and 33.3 % (group 1) and 95.1 % and 87 % (group 2). No false-negative SLNs were identified in either group.

Benedetti Panici et al. retrospectively evaluated the feasibility and safety of type B (group 1) compared to type C (Group 2; 36 patients in each group) radical hysterectomy (RH) after clinical response to NACT. No differences in clinical outcome were reported between the two groups, however bladder dysfunction rate was significantly lower in Group 1 compared with Group 2 (13.9 vs. 69.4 %; $p < 0.0001$). Authors concluded that Type B RH after NACT in well-selected patients is a safe procedure that upholds the results of type C, reducing operative time and late postoperative morbidity, without detrimental effect on survival. However, further prospective trials are warranted to confirm these results.

Johansen et al. investigated the reproductive and oncologic outcome following robotic radical trachelectomy for early-stage cervical cancer (IA1-IB1). 56 women with a median age of 29 years (range 23–41) were followed for a median of 24 months (range 1–89). A local recurrence was seen in two of the 49 women (4 %), in whom the procedure was completed as planned. Seventeen of the 21 women (81 %) in the reproductive follow-up group conceived. 12 women (71 %) in gestational week ≥ 36. One (6 %) second trimester delivery occurred. According to these results the authors supported the feasibility of robotic fertility-sparing radical trachelectomy in women with early-stage cervical cancer.

Köhler et al. reported on the feasibility of surgical vs. clinical staging followed by chemoradiation in patients with stage IIB-IVA disease (Uterus-11). 255 patients with advanced cervical cancer (FIGO IIB-IVA) were randomised to surgical staging and RCTX (arm A) or clinical staging followed by RCTX (arm B). Brachytherapy was mandatory. The surgical approach was transperitoneal laparoscopy (93.4 %), with no operative mortality. A mean of 19 pelvic and 17 para-aortic nodes were removed. Operative staging led to upstaging in 40 of 121 (33 %). RCTX began between 7 and 21 days after surgery. Authors concluded that surgical staging in patients with locally advanced cervical cancer is safe and does not delay primary RCTX.

For quality assurance outcomes of this trial, see the report on "Medical treatment of primary or recurrent cervical cancer" by K. Lindemann.

Li et al. published on the postoperative recovery in patients with early cervical cancer. In this randomised trial, authors investigated the effect of a home-based, nurse-led health program on quality of life and family function (intervention group) compared to conventional nursing education (control). In the intervention group, significant improvements were found for the quality of life total scores, sexual function scores, cohesion scores, and adaptability scores compared to baseline. The change in scores for quality of life, sexual function, cohesion, and adaptability indicated significant improvement in the intervention group compared to controls. Authors concluded that a home-based, nurse-led, health promotion program improves the quality of life, sexual function, and social relations in these patients.

Jeong In Gab et al. reviewed 7 patients who underwent augmentation ileocystoplasty with ileal ureter replacement. The majority of the patients (4 of 7) were previously treated with radical hysterectomy plus radiotherapy. Ileal ureter replacement was performed on 11 renal units, and bilateral ileal ureter substitution was performed for 4 patients, with the largest ureteral defect being 15 cm. After the median hospital stay (23 days), 4 of 7 patients experienced major complications (grade C 3). During a mean follow-up duration of 38 months, none of the patients experienced deterioration of renal function after surgery, proving the feasibility of this technique for bridging long ureteral defects caused by ureteric stenosis from surgery, radiotherapy, or both, for pelvic tumours.

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Surgical treatment of primary cervical cancer

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No	Title	Authors	Journal	Link to abstract
1	Occult Invasive Cervical Cancer Found After Inadvertent Simple Hysterectomy: Is the Ideal Management: Systematic Parametrectomy With or Without Radiotherapy or Radiotherapy Only?	Narducci F et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/25297903
2	Accuracy of Sentinel Lymph Node Mapping After Previous Hysterectomy in Patients with Occult Cervical Cancer.	Papadia A et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26739305
3	Type B versus Type C Radical Hysterectomy After Neoadjuvant Chemotherapy in Locally Advanced Cervical Carcinoma: A Propensity-Matched Analysis.	Benedetti Panici P et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26597364
4	Reproductive and oncologic outcome following robot-assisted laparoscopic radical trachelectomy for early stage cervical cancer.	Johansen G et al.	Gynecologic Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26845228
5	Perioperative morbidity and rate of upstaging after laparoscopic staging for patients with locally advanced cervical cancer: results of a prospective randomized trial.	Köhler C et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/25986030
6	A home-based, nurse-led health program for postoperative patients with early-stage cervical cancer: A randomized controlled trial.	Li J et al.	Eur J Oncol Nurs.	http://www.ncbi.nlm.nih.gov/pubmed/26482004
7	Ileal Augmentation Cystoplasty Combined with Ileal Ureter Replacement After Radical Treatment for Cervical Cancer.	Jeong In Gab et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26714938

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

Editor Marcin Mardas

Descriptive summary

1. Xie et al. reported that volasertib (BI 6727), a highly selective and potent inhibitor of PLK1, can markedly induce cell growth inhibition, cell cycle arrest at G2/M phase and apoptosis with the decreased protein expressions of PLK1 substrates survivin and wee1 in human cervical cancer cells. Furthermore, volasertib also enhances the intracellular reactive oxidative species and significantly potentiates the activity of cisplatin to inhibit the growth of cervical cancer in vitro and in vivo.
2. Ji et al. reported unique nanoparticles with a size less than <200 nm (FPCC) prepared for the selective delivery of carboplatin to the cervical cancer cells. FPCC showed a superior cytotoxic effect - the IC50 (concentration of the drug required to kill 50 % of the cells) value of FPCC was 0.65 μg/ml comparing to 2.35 μg/ml for free carboplatin.
3. Lin et al. evaluated the antitumor effect of the fisetin, combined with sorafenib, against human cervical cancer cells in vitro and in vivo. Apoptosis induction was achieved by caspase-3 and caspase-8 activation. In vivo studies revealed that the combination of fisetin and sorafenib was superior to sorafenib treatment alone.
4. Milosevic et al. evaluated the role of sorafenib in patients with cervical cancer receiving radical radiotherapy and concurrent cisplatin. Sorafenib was administered daily for 7 days before the start of standard therapy in patients with early-stage, low-risk disease and also during radiochemotherapy in patients with high-risk disease. Sorafenib alone reduced tumour perfusion/permeability and an increase in hypoxia. This would make the tumour rather resistant to chemoradiation and lead to tumour growth rather than tumour control. The results led to early closure of the study.
5. Zhang et al. reported that propofol significantly decreased cell viability and increased cell apoptosis in Hela, Caski, and C-33A cells, while HOTAIR overexpression promoted cell viability and inhibited cell apoptosis. In vivo, propofol inhibited the tumour size but had no inhibition effect in HOTAIR overexpression group.
6. Pandurangan et al. investigated the cytotoxicity of copper oxide nanorods in human cervical carcinoma cells. They showed the cell rounding and nuclear fragmentation following the exposure of copper oxide nanorods. mRNA expression of p53 and caspase 3 was increased, confirming apoptosis at the transcriptional level.
7. Shao et al. reported that EM23, a natural sesquiterpene lactone, exhibited anti-cancer activity in human cervical cancer cell lines by inducing apoptosis as indicated by caspase 3 activation, XIAP downregulation, and mitochondrial dysfunction. Additionally, EM23 inhibited the Akt/mTOR pathway and induced autophagy, which was observed to be proapoptotic and mediated by ROS.
8. Zaman et al. reported a poly(lactic-co-glycolic acid)-based curcumin nanoparticle formulation (Nano-CUR). In comparison to free curcumin, Nano-CUR effectively inhibited cell growth, induced apoptosis, and arrested the cell cycle in cervical cancer cell lines. Nano-CUR treatment modulated entities such as miRNAs, transcription factors, and proteins associated with carcinogenesis. Moreover, Nano-CUR effectively reduced the tumour burden in a preclinical orthotopic mouse.
9. Lee et al. reported that snake venom toxin (SVT) inhibited the growth of cervical cancer cells by the induction of apoptotic cell death through the inhibition of NF- B. In vivo study also showed that SVT (0.5 and 1 mg/kg) inhibited tumour growth by inactivation of NF- B.

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

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No	Title	Authors	Journal	Link to abstract
1	Volasertib suppresses tumor growth and potentiates the activity of cisplatin in cervical cancer.	Xie FF et al.	Am J Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26885445
2	Enhanced Antiproliferative Effect of Carboplatin in Cervical Cancer Cells Utilizing Folate-Grafted Polymeric Nanoparticles.	Ji J et al.	Nanoscale Res Lett.	http://www.ncbi.nlm.nih.gov/pubmed/26608536
3	Synergistic effect of fisetin combined with sorafenib in human cervical cancer HeLa cells through activation of death receptor-5 mediated caspase-8/caspase-3 and the mitochondria-dependent apoptotic pathway.	Lin MT et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26662956
4	Sorafenib Increases TumorTumour Hypoxia in Cervical Cancer Patients Treated With Radiation Therapy: Results of a Phase 1 Clinical Study.	Milosevic MF et al.	Int J Radiat Oncol Biol Phys.	http://www.ncbi.nlm.nih.gov/pubmed/26547383
5	Propofol promotes cell apoptosis via inhibiting HOTAIR mediated mTOR pathway in cervical cancer.	Zhang D et al.	Biochem Biophys Res Commun.	http://www.ncbi.nlm.nih.gov/pubmed/26523512
6	Anti-Proliferative Effect of Copper Oxide Nanorods Against Human Cervical Carcinoma Cells.	Pandurangan M et al.	Biol Trace Elem Res.	http://www.ncbi.nlm.nih.gov/pubmed/26811107
7	EM23, a natural sesquiterpene lactone, targets thioredoxin reductase to activate JNK and cell death pathways in human cervical cancer cells.	Shao FY et al.	Oncotarget. 2016	http://www.ncbi.nlm.nih.gov/pubmed/26758418
8	Curcumin Nanoformulation for Cervical Cancer Treatment.	Zaman MS et al.	Sci Rep.	http://www.ncbi.nlm.nih.gov/pubmed/26837852
9	Inhibitory effect of snake venom toxin on NF- B activity prevents human cervical cancer cell growth via increase of death receptor 3 and 5 expression.	Lee HL et al.	Arch Toxicol.	http://www.ncbi.nlm.nih.gov/pubmed/25417048

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

Medical treatment of primary or recurrent cervical cancer

Editor Kristina Lindemann

Descriptive summary

Salihi et al. published a retrospective study on the feasibility of neoadjuvant chemotherapy followed by fertility sparing surgery for early cervical cancer. The objective was to study clinical outcomes after NACT followed by conization. The hypothesis being that radical trachelectomy still comes with increased risk of premature labour and considerable postoperative morbidity and may be avoidable in a selected subset of patients. Eleven patients were included, 10 with 1B1 and 1 with IB2 disease (refused radical treatment upfront). All patients underwent pelvic lymphadenectomy prior to NACT to ensure that only node-negative patients were included. 64 % of the patients had tumours <2cm. Patients were mainly treated with carboplatin/taxol in different dosing schedules. RECIST criteria showed complete response in 3 patients (64 %), partial response in three (27 %) and one patient (9 %) had progressive disease. 8 patients had complete pathological remission. Of the 9 patients treated with fertility-sparing (81 %), 6 got pregnant and 5 delivered a total of 7 babies (2 born prematurely). There was 1 recurrence after median 58 months. This study described the feasibility of this approach, but has its limitations in its retrospective design and small sample size. The funding of one large randomised trial on NACT+fertility sparing surgery is unfortunately still uncertain.

Tewari et al. published a prospective validation of a prognostic score in the GOG 240 study (4 arms, Taxol/Cis or Taxol/Topotecan +/- Bev). The "Moore criteria" combined five factors: Performance status >0, pelvic disease, African-American ancestry, disease-free interval <1 year, and prior platinum exposure. The risk score was tested in multiple subsets (by treatment arm), but only few significant differences could be found between the low-risk and high-risk group. Patients categorised as low-risk derived only non-significant benefits from the addition of Bev in terms of PFS. However, only 84 of the patients fell into this category. The authors suggest that in light of the toxicity associated with Bev, one could argue against the use of Bev in the low-risk group where potential benefit may be small. However, if risk (i.e., of fistula) differs remains uncertain, as toxicity was not specifically reported by risk group. Furthermore, it is not clear if the study was powered to detect any differences in subgroups, but the discussion of the results does unfortunately not cover its limitations. Questions remain regarding the applicability of the score to populations with a lower prevalence of African-Americans and if that factor is a surrogate for poorer access to health care services or represents true biological differences.

Marnitz et al. reported on a randomized trial on surgical vs. clinical staging followed by chemoradiation in patients with stage IIB-IVA disease (Uterus-11). Here, effects on toxicity and treatment quality are reported. 255 patients were randomised. It is unfortunately unclear how ITT, safety population, and per-protocol population were defined. Chemotherapy regimen differed significantly between the treatment arms. More patients in the surgical staging arm received extended field radiation, confirming that more patients are upstaged by surgery. There was generally more haematological but less non-haematological toxicity after IMRT. This is expected as IMRT is associated with a higher volume of bone marrow covered by lower doses. One interesting issue discussed in these articles, although not the primary outcome of the trial itself, is the quality indicators of radiotherapy. For the US, only 25 % of centres have been reported to meet certain quality benchmarks (the use of BT, >4 cycles of chemotherapy, and a RT duration of 56 days) (Smith et al. Int J Radiat Oncol Biol Phys 2015;92:260-267). In the presented study, median duration was 55 days, 98 % and 94 % had received BT and, at least in the clinical staging arm, >80 % of the patients had received >4 cycles of CT, confirming that the study met all quality indicators for chemoradiation. The oncological outcomes are not yet mature.

Xie et al. published a prospective study on the value of aldehyde hydrogenase 1 (ALDH 1) in predicting response to NACT. ALDH 1 has been reported to be a marker of stem cell proliferation. Patients with positive staining of the tumour tissue were less likely to respond to NACT and post-NACT ALDH 1 expression was associated with poorer survival outcomes. Unfortunately, it is not stated if the assessment of staining was performed blinded for clinical outcomes. Also, the RECIST criteria used for response do not correspond to the standard interpretation of RECIST. Differences in survival data were only assessed by a log-rank test, but median survival times with confidence intervals are not given. Also, postoperative treatment may have varied between the groups and is not adequately described.

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Medical treatment of primary or recurrent cervical cancer

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No	Title	Authors	Journal	Link to abstract
1	Neoadjuvant chemotherapy followed by large cone resection as fertility-sparing therapy in stage IB cervical cancer.	Salihi et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26050921
2	Prospective Validation of Pooled Prognostic Factors in Women with Advanced Cervical Cancer Treated with Chemotherapy with/without Bevacizumab: NRG Oncology/GOG Study.	Tewari et al.	Clin Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26672085
3	Role of Surgical Versus Clinical Staging in Chemoradiated FIGO Stage IIB-IVA Cervical Cancer Patients-Acute Toxicity and Treatment Quality of the Uterus-11 Multicenter Phase III Intergroup Trial of the German Radiation Oncology Group and the Gynecologic Cancer Group.	Marnitz et al.	Int J Radiat Oncol Biol Phys.	http://www.ncbi.nlm.nih.gov/pubmed/26853333
4	Aldehyde Dehydrogenase 1 Expression Predicts Chemoresistance and Poor Clinical Outcomes in Patients with Locally Advanced Cervical Cancer Treated with Neoadjuvant Chemotherapy Prior to Radical Hysterectomy.	Xie et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/25916979

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

- Editor Kamil Zalewski

- Descriptive summary

Lawrie et al. used Cochrane methodology to perform meta-analyses on medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia (uVIN). They reported that imiquimod or cidofovir may effectively treat about half of uVIN cases after a 16-week course of treatment. There is currently no evidence on how medical treatment compares with surgical treatment. Women who undergo surgical treatment for uVIN have about a 50 % chance of the condition recurring one year later. Multifocal uVIN lesions are at a higher risk of recurrence and progression. If occult cancer is suspected despite a biopsy diagnosis of uVIN, surgical excision remains the treatment of choice. If occult cancer is not a concern, treatment needs to be individualised. The authors concluded that combined modalities may hold the key to optimal treatment of this complex disease.

The ISSVD Terminology Committee presented their final version of vulvar squamous intraepithelial lesions. It contains the following: a) Low-grade SIL of the vulva or vulvar LSIL, encompassing flat condyloma or human papillomavirus effect. b) High-grade SIL or vulvar HSIL (which was termed "vulvar intraepithelial neoplasia usual type" in the 2004 ISSVD terminology). 3) Vulvar intraepithelial neoplasia, differentiated type.

Grimm et al. analysed sexual activity (SA) and sexual function (SF) of women with VIN and VSCC that had undergone vulvar surgery. The patients showed a remarkably high SA rate of 75 %. Although SF was notably impaired, both groups presented similar activity and function with a tendency towards better SF in the VIN group. Authors concluded that gynaecologists should inform about possible consequences of surgical treatment and discuss alternative topical treatment options especially for VIN.

Zhang et al. retrospectively reviewed records of 152 patients with vaginal intraepithelial neoplasia (VaIN) and demonstrated that 88.2 % of patients were HPV positive, 62.0 % of patients with VaIN1 regressed spontaneously. 36.8 % and 38.5 % of patients with VaIN2 and VaIN3 that underwent treatment experienced recurrence or progression, retrospectively.

Jentschke et al. retrospectively characterised the clinical presentation of 65 patients with VaIN and demonstrated that 55 % of lesions were found in the upper vaginal third and 42 % were multifocal. They also reported a high relapse rate and a high progression rate to invasive cancer especially if high-risk (HR) HPV positive was detected.

Koeneman et al., in their questionnaire-based study, assessed awareness and attitudes of gynaecologists regarding imiquimod for VaIN and cervical intraepithelial neoplasia treatment.

Youn et al. reported a case of refractory VaIN3 in the vaginal vault that was successfully treated with a total vaginectomy.

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

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Medical and surgical interventions for the treatment of usual-type vulval intraepithelial neoplasia.	Lawrie TA et al.	Cochrane Database Syst Rev.	http://www.ncbi.nlm.nih.gov/pubmed/26728940
2	The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions.	Bornstein J et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26942352
3	The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions.	Bornstein J et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/26704327
4	Sexual activity and function after surgical treatment in patients with (pre) invasive vulvar lesions.	Grimm D et al.	Support Care Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26094599
5	A retrospective study of 152 women with vaginal intraepithelial neoplasia.	Zhang J et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26797205
6	Clinical presentation, treatment and outcome of vaginal intraepithelial neoplasia.	Jentschke M et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26094599
7	Physicians' Awareness, Attitudes, and Experiences Regarding Imiquimod Treatment of Vaginal and Cervical Intraepithelial Neoplasia.	Koeneman MM et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/26579838
8	Total vaginectomy for refractory vaginal intraepithelial neoplasia III of the vaginal vault.	Youn JH et al.	Obstet Gynecol Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26866041

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

Vulvovaginal adenocarcinoma / melanoma / sarcoma

Editor Anna Dückelmann

Descriptive summary

Most cases of primary vaginal carcinoma are squamous cell carcinomas. Other histologic types such as adenocarcinoma are usually metastatic lesions, mainly originating from the uterus. Sadatomo et al. presented a rare case of isolated vaginal metastasis from rectal cancer, diagnosed by magnetic resonance imaging (MRI). Isolated vaginal metastases are an indication for surgical resection and adjuvant chemotherapy. In colorectal cancer, MRI is a useful tool to evaluate the vagina prior to therapy.

McCluggage gave a comprising overview about non-HPV-related adenocarcinomas of the lower female genital tract, the most common of which is so-called gastric type. Carleton et al. concentrated on the immunohistochemical profile of this kind of tumour. Adenocarcinomas exhibiting gastric differentiation are uncommon but represent the most common non-human papillomavirus (HPV)-related variant of cervical and vaginal adenocarcinoma. They exhibit considerable morphologic overlap with adenocarcinomas originating outside the female genital tract and could be distinguished, inter alia, by PAX8 staining.

Van Rosmalen et al. presented a case of a mucinous adenocarcinoma of the vulva with neuroendocrine differentiation based on immunohistochemical analysis, treated by partial vulvectomy.

Stefanović et al. reported on a 60-year-old woman presenting with a palpable tumour near the vaginal introitus and recurrent vaginal bleeding. Biopsy revealed a melanoma, which was treated with wide local excision and adequate safety margins. There is general acceptance that radical surgery does not improve the prognosis of primary malignant melanoma of the vagina (PMMV). Todo et al., however, argued for radical surgery in PMMV, formulating a scoring system of surgical radicality. This score quantitatively evaluates the radicality of the initial surgery by giving a certain number of points for the resected organs. According to the authors, the therapeutic significance of radical surgery for PMMV has not been evaluated appropriately in previous studies because of the lack of comparability among groups and differences in the definitions of surgical radicality. They called for a multicentre cooperative study to validate the clinical impact of their score on the prognosis of PMMV.

Sanchez et al. presented a retrospective study on epidemiology and disease-specific survival in primary genitourinary melanoma cases using a large population-based cohort. Synoptically, patients with primary genitourinary melanoma present with advanced stage and have a poor prognosis. Women have worse disease-specific survival compared to men. Disease-specific survival is negatively associated with advanced age at diagnosis, higher stage, and lymph node involvement.

Hu et al. described an exceptional case of myeloid sarcoma occurring on the vulvar mucosa as the presenting sign of acute myeloid leukaemia (AML) following bone marrow transplantation for myelodysplastic syndrome. The patient received systemic chemotherapy with cytarabine and idarubicin. Treatment led to a marked reduction in the size of the vulvar mass, but the patient died of septic shock and respiratory failure 3 months after diagnosis. Authors concluded that leukaemic infiltration should be suspected in any patient with a history of myeloid leukaemia or myelodysplastic syndrome who presents with a mass involving the skin or external mucosal surface.

Presenting an interesting case of a 32-year-old patient with epithelioid sarcoma of the vulva, Han et al. stressed the fact that disease-free-survival-time and mortality in the proximal-type epithelioid sarcoma are age-dependent according to literature. Younger patients might have a better prognosis than older patients. Early diagnosis with definite surgical treatment is absolutely essential for improvement of prognosis.

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Vulvovaginal adenocarcinoma / melanoma / sarcoma

- Relevant articles retrieved Mar-Nov 2015

No	Title	Authors	Journal	Link to abstract
1	An isolated vaginal metastasis from rectal cancer.	Sadatomo A et al.	Ann Med Surg.	http://www.ncbi.nlm.nih.gov/pubmed/26793313
2	A Detailed Immunohistochemical Analysis of a Large Series of Cervical and Vaginal Gastric-type Adenocarcinomas.	Carleton C et al.	Am J Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26685087
3	Recent developments in non–HPV-related adenocarcinomas of the lower female genital tract and their precursors.	McCluggage WG.	Adv Anat Pathol	http://www.ncbi.nlm.nih.gov/pubmed/26645463
4	Vulvar mucinous adenocarcinoma with neuroendocrine differentiation: A case report and review of the literature.	van Rosmalena MHJ et al.	Pathol Res Pract.	http://www.ncbi.nlm.nih.gov/pubmed/26861721
5	Primary melanoma of the vagina: a case report and review of literature.	Stefanović A et al.	Eur J Gynaecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26775368
6	Radicality of initial surgery for primary malignant melanoma of the vagina.	Todo Y et al.	Melanoma Res.	http://www.ncbi.nlm.nih.gov/pubmed/26825038
7	Primary genitourinary melanoma: Epidemiology and disease-specific survival in a large population-based cohort.	Sanchez A et al.	Urol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26739672
8	Myeloid sarcoma of the vulva as the initial presentation of acute myeloid leukaemia.	HU SCS et al.	Br J Dermatol.	http://www.ncbi.nlm.nih.gov/pubmed/26252545
9	Epithelioid sarcoma of the vulva and its clinical implication: A case report and review of the literature.	Han CH et al.	Gynecol Oncol Rep.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4750019/

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

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

Editor Kamil Zalewski

Descriptive summary

Day et al. retrospectively assessed 118 cases of normal vulvar skin and mucosa and found site-specific differences in stratum corneum morphology and parakeratosis at the mucocutaneous junction. These data should allow pathologists to be aware of site-related differences of the vulvar epithelium to avoid overdiagnosis of pathological conditions.

Rouzbahman et al. retrospectively reviewed clinical and morphological characteristics of the 44 cases of vulvovaginal melanomas. They identified BRAF, NRAS, and C-KIT mutations with slightly different frequencies compared to the published data in melanomas of general sites.

Jeffus et al. reviewed 143 consecutive resection specimens of vulvar squamous cell carcinoma (VSCC) and explored the prognostic significance of patterns of invasion and fibromyxoid stromal response. They demonstrated that tumours with an infiltrative pattern of invasion, a fibromyxoid stromal response, and perineural invasion represented an important subset of VSCCs that behave more aggressively. In particular, an infiltrative pattern of invasion and perineural invasion were highly associated with an increased risk for tumour recurrence, whereas a fibromyxoid stromal response was associated with increased risk for nodal metastases.

Members of the miR-17 family are among the best-studied microRNAs in cancer. De Melo Maia et al. designed a sponge construct containing miR-17 family member miRNA binding sites that was synthesised, cloned, and transfected into a vulvar cancer cell line. The miR-17-specific sponge effectively reduced the expression of five miR-17 family members (out of six), indicating that these sponges may have a therapeutic effect in VSCC.

Yang et al. documented that miR-590-5p is involved in the VSCC carcinogenesis and its upregulation in tumours was found to be associated with lymphatic metastases.

It has been reported that ras homologue gene family member A (RhoA) expression is an independent prognostic factor, however the role of RhoA in carcinoma of the vulva has not been reported. Wang J et al. demonstrated that the RhoA expression was significantly higher in stage III–IV VSCC tissue than in stage I–II and more poorly than that in well-differentiated VSCC. Cases with lymph node metastasis had higher positive RhoA expression than cases without lymph node metastasis. Authors suggested that the RhoA inhibitor lovastatin alters VSCC cell migration and proliferation and may be an effective drug for treating VSCC.

Lagerstedt et al. analysed 203 normal vulvar skin, lichen sclerosus (LS), vulvar intraepithelial neoplasia (VIN) and VSCC samples for oestrogen-related receptors (ERRs) by using immunohistochemistry. They demonstrated that the cytoplasmic expression of ERR was substantially decreased or lost in VSCC and LS and VIN lesions showed diminished ERR staining in relation to normal vulvar skin. They concluded that the role of ERR as a prognostic marker remains questionable.

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

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Normal vulvar histology: variation by site.	Day T et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/26704331
2	Malignant melanoma of vulva and vagina: a histomorphological review and mutation analysis-a single-center study.	Rouzbahman M et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/26225944
3	miRNA expression profile of vulvar squamous cell carcinoma and identification of the oncogenic role of miR-590-5p.	Yang X et al.	Oncol Rep.	http://www.ncbi.nlm.nih.gov/pubmed/26498065
4	A fibromyxoid stromal response is associated with an infiltrative tumor morphology, perineural invasion, and lymph node metastasis in squamous cell carcinoma of the vulva.	Jeffus SK et al.	Am J Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26274029
5	Design of a miRNA sponge for the miR-17 miRNA family as a therapeutic strategy against vulvar carcinoma.	de Melo Maia B et al.	Mol Cell Probes.	http://www.ncbi.nlm.nih.gov/pubmed/26297962
6	The role of RhoA in vulvar squamous cell carcinoma: a carcinogenesis, progression, and target therapy marker.	Wang J et al.	Tumour Biol.	https://www.ncbi.nlm.nih.gov/pubmed/26409448
7	Reduction in ERR is associated with lichen sclerosus and vulvar squamous cell carcinoma.	Lagerstedt M et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26499936

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Treatment of vaginal cancer

Editor Elis Ismail

Descriptive summary

PDQ (Physician Data Query) is a comprehensive, peer-reviewed, evidence-based, National Cancer Institute source of cancer information for health professionals. Recently, a summary on the treatment of vaginal cancer was released with updated statistics. The American Cancer Society estimates 5,950 new cases and 1,110 deaths from vulvar cancer in the United States in 2016 [1].

Greenwalt et al. retrospectively reviewed medical records of 71 patients with primary vaginal adenocarcinoma or squamous cell carcinoma treated with definitive radiotherapy [2]. The majority of patients (93 %) were treated with external beam radiation therapy (EBRT) plus brachytherapy. The distant metastasis-free survival rate was 87 % at 5 years and 85 % at 10 years. Recurrence generally occurred within 5 years of treatment but usually occurred within 2 years. The study also supports electively irradiating the inguinal nodes in patients with tumours in the distal one third of the vagina.

Chang et al., in their multi-institutional retrospective study, also focused on radiotherapy in 138 patients with primary vaginal cancer [3]. They presented results showing that the 5-year overall survival, cancer-specific survival (CSS), and progression-free survival (PFS) rates were 68 %, 80 %, and 68.7 %, respectively. A lower FIGO stage and prior hysterectomy were favourable prognostic factors of cancer-specific survival. The HPV status was not related to the survival outcome.

Robertson et al., based on the prospective data registry, reported a change in prognostic impression in 51 % and demonstrated a change in patient management (defined as a change to/from observation or additional imaging to/from biopsy or treatment) following FDG-PET/CT after 36 % of studies in patients with vulvar and vaginal carcinoma [4]. FDG-PET/CT identified nodal disease in 35 % of patients imaged. The authors concluded that FDG-PET/CT may play an important role in the staging of both vulvar and vaginal cancer.

Ozgul et al. presented a surgical video with en bloc radical removal of uterus and vagina in a patient with clinical early-stage vaginal cancer.

Akino et al. presented a case of vaginal cancer that occurred after usage of a vaginal pessary in a patient with an immunocompromised condition.

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Vaginal Cancer Treatment (PDQ®): Health Professional Version. 2016 Feb 9.	PDQ Adult Treatment Editorial Board	PDQ Cancer Information Summaries [Internet]	http://www.ncbi.nlm.nih.gov/books/NBK65801/
2	Outcomes of definitive radiation therapy for primary vaginal carcinoma.	Greenwalt JC et al.	Am J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/24136141
3	Definitive treatment of primary vaginal cancer with radiotherapy: multi-institutional retrospective study of the Korean Radiation Oncology Group (KROG 12-09).	Chang JH et al.	J Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26768782
4	The impact of FDG - PET/CT in the management of patients with vulvar and vaginal cancer.	Robertson NL et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26790773
5	Radical hysterecomy and abdominal vaginectomy for primary vaginal cancer.	Ozgul N et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/26825828
6	Vaginal cancer possibly caused by pessary and immunocompromised condition: multiple risk factors may influence vaginal cancer development.	Akino N et al.	J Obstet Gynaecol Res.	https://www.ncbi.nlm.nih.gov/pubmed/26914159

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Treatment of recurrent vulvar cancer

Editor María de los Reyes Oliver Pérez

Descriptive summary

Squamous cell carcinoma (SCC)

Surgical treatment: No randomised prospective studies are reported.

The recently published PDQ cancer information summary for health professionals [1] provides comprehensive, peer-reviewed, evidence-based information about the treatment of vulvar cancer. According to the authors, current management options for recurrent vulvar cancer are:

- Wide local excision with or without radiation in patients with local recurrence.
- Radical vulvectomy and pelvic exenteration in patients with local recurrence.
- Synchronous radiation and cytotoxic chemotherapy with or without surgery.

Van Doorn et al. [2] retrospectively assessed the feasibility of repeat sentinel lymph node (SLN) procedure in 27 patients with recurrent vulvar SCC who were not able or willing to undergo inguinofemoral lymphadenectomy as part of their treatment for recurrent disease. The main reasons not to perform a repeat SLN procedure in these patients is the assumption that the lymph flow might be altered because of previous surgery or radiotherapy. Investigators reported that in 77 % of patients and in 84 % of the groins the SLN procedure was performed as planned compared to reported success rates of more than 95 % in primary SLN procedures. In conclusion, the authors emphasise that a repeat SLN procedure in recurrent vulvar SCC is feasible to perform, but appears technically more challenging due to the changes of the lymphatic drainage to the groins and fibrosis at the vulvar and groin sites resulting in surgical complications.

Systemic treatment: No studies are reported.

Radiotherapy: Amsbaugh et al. [3] retrospectively reviewed 73 patients who received CT-planned interstitial brachytherapy (ISBT) for gynaecologic cancers (including 21 recurrences). Of them, 8 had vulvar cancer. The indication for ISBT was vaginal or vulvar involvement, pelvic sidewall involvement, anatomy not suitable for intercavitary BT, and dose-escalation and dose shaping. Median tumour size was 4 cm (range, 1.5-12.5 cm). With a median follow-up of 12 months, grade 3 vaginal, urinary, and rectal toxicity occurred in 17.8 %, 15.1 %, and 6.8 % of patients, respectively. No patients experienced grade 4 or 5 toxicity. Patients with the vagina and vulva as primary sites did not have a significantly different risk of death. Overall survival (OS) was not significantly different for patients receiving treatment for recurrent cancer compared with patients treated at the first presentation (p = 0.408). Authors concluded that ISBT is a safe treatment for gynaecologic malignancies.

Laliscia et al. [6] retrospectively assessed the clinical outcome of 31 patients with recurrent vulvar cancer treated with radiotherapy as definitive treatment. The site of relapse was local in 15 women (48.4 %), inguinal in 6 (19.3 %), local plus inguinal in 7 (22.6 %), and distant plus local and inguinal in 3 (9.7 %). Long-term control was achieved in only 20 % of the 15 local recurrences. Only 1 (16.7 %) out of the 6 patients with groin recurrence and only 1 (14.3 %) out of the 7 patients with local plus groin recurrence were recovered by salvage treatment, and all 3 patients with distant recurrence died of disease. Survival was significantly better for the patients with FIGO I-II stage compared to those with stage III disease at presentation (54 months vs. 23 months, p=0.005). There was a trend to better survival for patients with local recurrence compared with those with other sites of recurrence.

Treatment of metastatic disease: Alvarez et al. [4] presented the first description of an aggressive surgical approach for the treatment of a para-aortic nodal recurrence in vulvar cancer. Although the patient died of multiple lung metastases 5 months after surgery, authors suggest that an ultra-radical surgery could confer good survival outcomes.

No SSC vulvar cancers:

An analysis of 38 patients with invasive vulvar Paget disease was conducted by the authors of the VULCAN study [5], an international multicentre retrospective study of patients diagnosed with vulvar cancer. For local recurrence, the mean time to onset of recurrence was 64.2 ± 7.2 months versus 44.9 ± 1.7 months for distant recurrence, and the mean overall survival time was 58.5±0.5 months. Local recurrences were inversely associated with the caseload at the treating centre (P=0.01). Distant recurrences were associated with tumour size and FIGO stage (P<0.001). Adjuvant therapy (radiotherapy or chemotherapy) was associated with a reduced risk of distant metastases and increased overall survival (P<0.001).

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Treatment of recurrent vulvar cancer

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Vulvar Cancer Treatment (PDQ®) Health Professional Version PDQ Adult Treatment Editorial.	PDQ Adult Treatment Editorial Board	PDQ Cancer Information Summaries [Internet].	http://www.ncbi.nlm.nih.gov/pubmed/26889539
2	Repeat sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma is feasible.	van Doorn HC et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26797295
3	Radiotherapy as Definitive Treatment of Patients with Primary Vulvar Carcinoma Unfit for Surgery and with Recurrent Vulvar Carcinoma After Primary Radical Surgery: Results of a Retrospective Single-center Study.	Laliscia C et al.	Anticancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26722070
4	Computed tomography-planned interstitial brachytherapy for locally advanced gynecologic cancer: Outcomes and dosimetric predictors of urinary toxicity.	Amsbaugh MJ et at.	Brachytherapy.	http://www.ncbi.nlm.nih.gov/pubmed/26614237
5	An ultra-radical surgical approach for recurrent vulvar cancer involving en-bloc excision of the infra-renal aorta.	Alvarez RM et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26679350
6	Prognostic factors for recurrence and survival among patients with invasive vulvar Paget disease included in the VULCAN study.	Iacoponi S et al.	Brachytherapy.	http://www.ncbi.nlm.nih.gov/pubmed/26861886

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

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

Editor Elisa Piovano

Descriptive summary

During the period covered by the third edition of the LiFE report, a lot of published studies focused on intraoperative and postoperative complications, especially in endometrial cancer. In particular, Cunningham et al., Corrado et al. and Uccella et al. analysed the relationship between obesity, minimally invasive surgery, and complications. According to Cunningham et al. and Corrado et al, in robotic surgery, high BMI was not associated with a higher complications and conversion rates, with superimposable oncological outcomes. This was true even in severely obese patients (note that similar conclusions on BMI are reached in a parallel study by Mahdi et al. in patients affected by ovarian cancer submitted to robotic surgery, even in terms of postoperative mortality). Uccella et al., on the other hand, suggested a higher number of conversions from laparoscopy to laparotomy, total complications, wound complications, and venous thromboembolic events in obese women compared to non-obese women in a non-randomised study of 1,266 patients. They also report a lower number of lymphadenectomies performed in patients with BMI ≥40 in this last group of patients. Despite all this, in obese patients laparoscopy was a more favourable approach than laparotomy.

Guy et al. suggested, in their retrospective study on 16,980 women, that the risks of surgery (both laparotomic and robotic) increase with the age of the patient. A subanalysis on older patients found that robotic approach has statistically significantly lower rates of perioperative surgical complications (8.3 % vs. 20.5 %, P < .001) and shorter hospitalization than laparotomy. Nhokaew et al. studied 357 patients treated with laparotomic hysterectomy in terms of wound complications (including seroma, hematoma, separation, or infection). They report 7.8 % of wound complications are significantly associated with obesity, diabetes mellitus, and prior abdominal surgery.

Bogani et al. then analysed the incisional recurrences after endometrial cancer: This is a rare event (0.1 %) with a good prognosis if incisional recurrence is isolated and treated with integrated local and systemic treatment.

Another interesting topic, analysed by Minig et al. and Melamed et al., is the fast track care (removal of urinary catheter at the end of the surgery, early mobilization, and solid food intake) with same-day discharge in women undergoing laparoscopic hysterectomy. They reported there was no increased risk of complications and suggested larger prospective studies to definitively establish the safety of this approach. This could be a good point for a future multicentre study to be shared among ENYGO members.

Four interesting papers dealing with the role of critical care units, frailty, bowel obstruction and the use of PEG in gyne-onc patients were published. Davidovic-Grigoraki et al. reviewed the role of critical care units in the management of gynaecological oncology patients and in the prevention of postoperative complications, underlining that the management of patients in this setting should be part of gynaecologic oncology fellowship programmes. George et al. retrospectively analysed the correlation of frailty (defined as the loss of physical or mental reserve that impairs function, often in the absence of a defined comorbidity) and morbidity-mortality in patients undergoing major gynaecological surgery: They suggest that a modified frailty index correlates with more wound infections, severe complications, and mortality.

Furnes et al. investigated a series of women admitted to a surgical unit with bowel obstruction and a history of previous gynaecologic cancer: Bowel obstruction was frequently associated with recurrent malignancy and a short life expectancy. Ovarian cancer (OR: 6.29, 95 % CI 1.95-20.21), residual tumour during initial surgery (R2-stage) (OR: 18.7, 96 % CI: 4.35-80.46), and chemotherapy (OR: 7.19, 95 % CI: 2.28-22.67) were all associated with malignant bowel obstruction.

An Italian study by Zucchi et al. involved patients with small-bowel obstruction from advanced gynaecological and gastroenteric cancers who underwent PEG (decompressive percutaneous endoscopic gastrostomy) positioning for decompressive purposes (all of them were unfit for any other surgical procedures). The data from 158 patients suggest that PEG is feasible, effective, relieves nausea and vomiting and improves QoL, and therefore should be kept in mind in this difficult setting.

Among papers dealing with technical aspects of gyne-onc surgery, two papers should be pointed out: Buda et al. discussed the role of tachosil in preventing complications after inguinofemoral lymphadenectomy for gynaecological malignancies, with positive results in terms of drainage volume, lymphocyst requiring drainage, cellulitis, wound infection, and late lymphedema.

Hokenstad et al. presented a video demonstrating a technique for using a pedicled gracilis muscle flap to repair rectovaginal fistula.

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

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Body mass index, conversion rate and complications among patients undergoing robotic surgery for endometrial carcinoma.	Cunningham MJ et al.	J Robot Surg.	http://www.ncbi.nlm.nih.gov/pubmed/26530848
2	Robotic Hysterectomy in Severely Obese Patients With Endometrial Cancer: A Multicenter Study.	Corrado G et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26342450
3	The Impact of Obesity on the 30-day Morbidity and Mortality After Surgery for Ovarian Cancer.	Mahdi H et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26807563
4	Impact of obesity on surgical treatment for endometrial cancer: a multicenter study comparing laparoscopy vs. open surgery, with propensity-matched analysis.	Uccella S et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26282516
5	Comparative outcomes in older and younger women undergoing laparotomy or robotic surgical staging for endometrial cancer.	Guy MS et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26433173
6	Wound complications after laparotomy for endometrial cancer.	Nhokaew W et al.	Asian Pac J Cancer Prev.	http://www.ncbi.nlm.nih.gov/pubmed/26625795
7	Incisional recurrences after endometrial cancer surgery.	Bogani G et al.	Anticancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26504035
8	Clinical outcomes after fast-track care in women undergoing laparoscopic hysterectomy.	Minig L et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26386495
9	Same-day discharge after laparoscopic hysterectomy for endometrial cancer.	Melamed A et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/25956576
10	Do critical care units play a role in the management of gynaecological oncology patients? The contribution of gynaecologic oncologist in running critical care units.	Davidovic-Grigoraki M et al.	Eur J Cancer Care (Engl)	http://www.ncbi.nlm.nih.gov/pubmed/26805516
11	Measurement and validation of frailty as a predictor of outcomes in women undergoing major gynaecological surgery.	George EM et al.	BJOG	http://www.ncbi.nlm.nih.gov/pubmed/26301606
12	Challenges and outcome of surgery for bowel obstruction in women with gynaecologic cancer.	Furnes B et al	Int J Surg	http://www.ncbi.nlm.nih.gov/pubmed/26853847
13	Decompressive percutaneous endoscopic gastrostomy in advanced cancer patients with small-bowel obstruction is feasible and effective: a large prospective study.	Zucchi E et al.	Support Care Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26838026
14	The contribution of a collagen-fibrin patch (Tachosil) to prevent the postoperative lymphatic complications after groin lymphadenectomy: a double institution observational study.	Buda A et al.	Eur J Obstet Gynecol Reprod Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26765122
15	Rectovaginal fistula repair using a gracilis muscle flap.	Hokenstad ED et al.	Int Urogynecol J.	http://www.ncbi.nlm.nih.gov/pubmed/26811111

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Sentinel node mapping in gynaecological malignancies

Editor Anton Ilin

Descriptive summary

Endometrial cancer:

Sentinel lymph node mapping (SLNM) in patients with endometrial cancer is now actual and widely discussed, which was the result of great team work (ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer). Unfortunately, the role of SLNM in endometrial cancer is still not well established [1].

Laparoscopy has in some cases certain advantages over laparotomy – less tissue traumatisation, early activation of patient, decreased period of hospitalization and, as a consequence, decreased cost of treatment. Ghezzi F et al. published a case of SLND using a 5.8-mm 0° optical camera with a near-infrared high-intensity light source and 3-mm instruments. SLN was detected bilaterally. The operative time was 60 min, and the estimated blood loss was 50 ml [2]. Mini-laparoscopy is a less invasive approach, but the feasibility of using it instead of traditional laparoscopy requires further study.

Large series suggest that SLNM is feasible and even has benefits such as detection of micrometastases compared with conventional histology but the value of these findings is unclear.

Eriksson et al. reviewed the experience of two institutions with different nodal assessment approaches in patients with endometrial carcinoma and minimal myometrial invasion. In the first group (642 patients – 57 %) SLNM algorithm was used per institutional protocol. In other group (493 patients – 43 %) pelvic and para-aortic lymphadenectomy was performed for patients with grade 3 cancers and/or primary tumour diameter>2cm. Pelvic nodes (PLNs) were removed in 93 % and 58 % of patients, respectively; para-aortic nodes (PALNs) were removed in 14.5 % and 50 % of patients, respectively. Metastases to PLNs were detected in 5.1 % and 2.6 % of patients, respectively, and to PALNs in 0.8 % and 1.0 %, respectively [3]. 3-year DFS was similar in both groups (95 %). Based on the results, the authors conclude that SLND approach is feasible and could be recommended for endometrial cancer staging. An the same time it is necessary to standardize the methodology of the procedure and patient enrolment criteria to validate SLND in definite groups of patients as well as to determine the significance of ultramicrostaging.

Kataoka et al. published results of the prospective evaluation of 57 Japanese endometrial cancer patients undergoing sentinel node mapping using the scintigraphic method (hysteroscopic sub-endometrial injection of 99mTc). In 32 cases it was combined with the dye method. Sensitivity and negative predictive values were 100 %, 100 %, respectively [4]. A total of 56.3 % of positive lymph nodes were present in the pelvis while 43.8 % in PALNs, which is different from other reports. The combined method seems to be more effective compared to isolated procedures, but the significance of this advantage is debated because of the minor difference in results and technical complexity of the method. Buda et al. marked some critical drawbacks for hysteroscopic tracer injection: 1) The necessity for a more demanding technique with a longer learning curve compared to the cervical injection; requires the support of nuclear medicine when 99mTc is injected with the patient still awake during the procedure. 2) In the case of a focal endometrial lesion, it could be difficult to decide where to inject the dye. 3) Considering that the exclusive aortic migration can occur more frequently in the case of a fundal high grade tumour with a deep myometrial infiltration, it is really a commitment to standardize such a demanding technique for such a limited number of cases [5].

Cervical cancer:

Wuntakal et al. reviewed the experience of West Kent Gynaecological Oncology Centre in SLND for 132 patients with cervical cancer stage IA1-IIA. The most common SLN locations were the external iliac (38.6 %), obturator (25.3 %) and internal iliac (23.6 %) regions, that compared to results of previous studies. No SLN was found in the upper para-aortic region. Factors associated with unilateral detection of sentinel nodes were also assessed, finding older age as a solitary indipendent factor [6]. The authors supposed it could be a result of sclerosis in the lymphatic vessels or reduced perfusion in the pelvis that led to reduced accumulation of 99mTc and blue dye.

For SLNM with indocyanine green it seems to be a promising marker, not only because of a detection rate but also partly due to the safety and convenience of administration. Sara et al. published results of a retrospective study in which indocyanine green used for laparoscopic SLND for patients with cervical cancer. Overall detection rates were 83 % and 95.5 %, and bilateral detection rates were 61 and 95.5 % for 99mTc and patent blue dye group (36 patients) and indocyanine green group (22 patients), respectively.

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Sentinel node mapping in gynaecological malignancies

- Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer.	Colombo et al.	Int J Gynecol Cancer.	http://journals.lww.com/ijgc/Full-text/2016/01000/
2	Mini-laparoscopic Sentinel Node Detection in Endometrial Cancer: Further Reducing Invasiveness for Patients with Early-Stage Disease.	Ghezzi F et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26446007
3	Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion.	Eriksson AG et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26747778
4	The importance of para-aortic lymph nodes in sentinel lymph node mapping for endometrial cancer by using hysteroscopic radio-isotope tracer injection combined with subserosal dye injection: Prospective study.	Kataoka F et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26731727
5	Sentinel lymph node detection in endometrial cancer: hysteroscopic peritumoral versus cervical injection.	Buda A et al.	Int J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4695451/
6	Location of Sentinel Lymph Node in Cervical Carcinoma and Factors Associated With Unilateral Detection.	Wuntakal R et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26270124
7	A Comparison of Radiocolloid and Indocyanine Green Fluorescence Imaging, Sentinel Lymph Node Mapping in Patients with Cervical Cancer Undergoing Laparoscopic Surgery.	Imboden S et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4644188/

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Fertility-sparing treatment in gynaecological malignancies

Editor Dimitris Papatheodorou

Descriptive summary

In this literature search we retrieved articles on fertility-sparing treatment in gynaecological malignancies. They are classified according to the cancer site:

Endometrial cancer

A phase II study regarding the use of medroxyprogesterone acetate (MPA) plus metformin as a fertility -sparing treatment by Mitsuhashi et al. enroled 17 patients with atypical endometrial hyperplasia and 19 patients with endometrial cancer limited to the endometrium. The authors found that metformin inhibited disease relapse after MPA therapy and this particular drug combination should be studied further. *The study is also cited in "Treatment of endometrial hyperplasia (biology, conservative and definitive treatment, follow-up)" by K. Dallaku.*

A retrospective study by Gonthier et al. addressed the cancer incidence in patients with atypical endometrial hyperplasia (AEH) managed by primary hysterectomy or fertility-sparing treatment. In this multicentric study 111 patients with AEH were included and the authors conclude that the fertility -sparing management of AEH does not increase the risk of diagnosing EC from the hysterectomy specimen.

Cervical cancer

Johansen et al. conducted a retrospective study on reproductive and oncologic outcomes following robot-assisted laparoscopic radical trachelectomy of early-stage cervical cancer. 56 women were included in this study; 81 % in the reproductive follow-up group managed to conceive. A point of interest is the fact that the authors calculated only 21 patients of reproductive age although they performed radical trachelectomy in 49 patients in total. So overall the number of patients who managed to conceive is 34.6 % (17/49). The overall number of premature deliveries was low (6 %).

Ovarian cancer

Several systematic reviews were retrieved in this search, including "Fertility-sparing surgery in epithelial ovarian cancer" by Bentivegna et al. A meta-analysis by Shim et al. reported on a subgroup analysis on studies with recurrence data after staging and fertility-sparing surgery in patients with borderline ovarian tumours.

A comprehensive review by Zapardiel et al. regarding "Assisted reproductive techniques (AST) after fertility-sparing treatments in gynaecological cancers" was published. There is an apparent oncological safety of ART and pregnancy can be achieved, however, obstetrical outcomes may vary.

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Fertility-sparing treatment in gynaecological malignancies

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No	Title	Authors	Journal	Link to abstract
1	Reproductive and oncologic outcome following robot-assisted laparoscopic radical trachelectomy for early stage cervical cancer.	Johansen G et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26845228
2	Fertility-sparing surgery in epithelial ovarian cancer.	Bentivegna E et al.	Future Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26768952
3	Assisted reproductive techniques after fertility-sparing treatments in gynaecological cancers.	Zapardiel I et al.	Hum Reprod Update.	http://www.ncbi.nlm.nih.gov/pubmed/26759231
4	Impact of surgical staging on prognosis in patients with borderline ovarian tumours: A meta-analysis.	Shim SH et al.	Eur J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26735354
5	Fertility sparing treatment in women affected by cervical cancer larger than 2cm.	Estevez JP et al.	Bull Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26681641
6	Primary retroperitoneal mucinous cystadenocarcinoma (PRMCa): a systematic review of the literature and meta-analysis.	Myriokefalitaki E et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26681306
7	Cancer Incidence in Patients with Atypical Endometrial Hyperplasia Managed by Primary Hysterectomy or Fertility-sparing Treatment.	Gonthier C et al.	Anticancer Resea.	http://www.ncbi.nlm.nih.gov/pubmed/26637899
8	Robotic versus laparoscopic radical trachelectomy for early stage cervical cancer: A case report and review of literature.	Api M et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26631768
9	Phase II study of medroxyprogesterone acetate plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer.	Mitsuhashi A et al.	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26578736
10	Intraoperative Diagnosis Support Tool for Serous Ovarian Tumors Based on Microarray Data Using Multicategory Machine Learning.	Park JS et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26512784

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Follow-up after gynaecological malignancies

Editor Anne van Altena

Descriptive summary

General: Zola et al. analysed the follow up strategies for ovarian, endometrial, and cervical cancer. All of the topics discussed arose from the "ESGO State of Art Conference-Follow-up in gyneacological malignancies" in Turin. The main conclusion was that all surveillance procedures should be evidence-based with a clearly defined purpose: there is a need for prospective studies to compare the effectiveness of different follow-up regimens measuring overall survival, detection of recurrence, quality of life (QoL), and costs as outcomes. So far, this literature is lacking.

Faubian and colleagues wrote a, what they call, narrative review of the data and guidelines regarding care and surveillance of the gyneacologic cancer survivor based on a non-systematic literature search. They offer clinical recommendations for the management of gyneacologic cancer survivors based on this literature and their collective clinical experience. They conclude that a holistic approach to care extending beyond cancer treatment alone benefits gynea-cologic cancer survivors with guidance on hormonal, contraceptive, and fertility management and promotion of cardiovascular, bone, brain, and sexual health.

Another review, written by Elit et al provides recommendations re-garding follow-up care for women with gyneacologic malignancies. They too state that there is very little high-quality evidence available to guide follow-up care.

Endometrial cancer: A report from a consensus conference on endometrial cancer has been published. This report summarises the recommendations of a multidisciplinary panel of 40 leading experts in the management of endometrial cancer. Although the title suggests follow-up will be discussed as well, the recommendations do not apply to the follow-up of endometrial cancer patients who underwent primary and adjuvant therapy.

Angioli et al. evaluated the role of HE4, at primary diagnosis and as an indicator of endometrial cancer recurrence. It is a retrospective study on 252 patients. HE4 levels at primary diagnosis correlated with an increased risk of recurrent endometrial cancer (especially in endometrioid histology). HE4 cut-off of 201.3 pmol/L is able to correctly classify patients at high or low risk of EC recurrence, with a sensitivity of 80 % and a specificity of 91 %. So the marker could be used to identify patients who need a more intensive follow-up regimen but it is not used to identify recurrences.

Ye and colleagues asked all Canadian radiation oncologists about their experiences with follow-up. This survey dealt not only with oncologists treating gyneacological cancer patients but the complete field of oncology. Most would follow up gyneacological patients. Lack of resources and a belief that follow-up by family physicians is equally effective were the top reasons for not following. Treatment toxicity and possibility of further treatment were the most common reasons for routine follow-up. Transfer of follow-up care to family practitioners turned out to be desired and feasible.

Cost effectivnes of follow-up: One study group looked at the available literature on costs of follow-up. They evaluated 2 studies on gyneacologic cancers in general, 3 specific on ovarian cancer, 7 on endometrium, and 9 on cervix. The identified economic literature on economic evaluation of gyneacologic cancer follow-up procedures showed to be based on weak evidence of effectiveness and that they lack formal methodological approaches. They concluded that no properly designed randomised trials including cost-effectiveness analysis are available.

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Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Recommendations for Follow-up Care for Gynecologic Cancer Survivors.	Elit L et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26551194
2	ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up.	Colombo N et al.	Radiother Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26683800
3	ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up.	Colombo N et al.	. Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26645990
4	The role of HE4 in endometrial cancer recurrence: how to choose the optimal follow-up program.	Angioli R1 et al.	Tumour Biol.	http://www.ncbi.nlm.nih.gov/pubmed/26531723
5	Surveillance and Care of the Gynecologic Cancer Survivor.	Faubion SS et al.	J Womens Health (Larchmt).	http://www.ncbi.nlm.nih.gov/pubmed/26208166
6	Follow-up in Gynecological Malignancies: A State of Art.	Zola P et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26207784
7	Follow-up patterns of cancer survivors: a survey of Canadian radiation oncologists.	Ye AY et al.	J Cancer Surviv.	http://www.ncbi.nlm.nih.gov/pubmed/25231533
8	Economic Considerations on the Follow-Up Practice in Gynecologic Cancers: Few Lights and Many Shadows From a Literature Review.	Pagano E et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/25950132

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Cancer in pregnancy

Editor Michael J. Halaska

Descriptive summary

In total, six publications have been published within the selected period. They consist of several case reports on ocular melanoma, oesophageal carcinoma, and metastatic breast carcinoma. An Italian group published a series of 6 patients with tongue cancer, which presented a 50 % mortality rate. A Korean set of patients described single-centre data on 87 women diagnosed with cancer and pregnancy. The incidence of cancer were, in descending order, breast cancer, gastrointestinal cancer, haematologic malignancies, thyroid cancer, central nervous system tumours, and lastly cervical, ovarian, and lung cancer. In 20.7 %, the pregnancy was terminated, while others opted to retain the pregnancy. The mortality rate was 31 %, with the highest rates in patients with lung, gastrointestinal, haematologic, and breast cancer.

JCO published international guidelines for management of hematologic malignancies during pregnancy. The most common malignancy is Hodgkin disease, which usually has an excellent prognosis. Typically, it can be treated by ABVD during the second and third trimesters. There is insufficient data about BEACOPP during pregnancy. For non-Hodgkin disease, steroids could be used in the first trimester, while chemotherapy could be administered during the second and third trimesters. Increasing data suggests that rituximab could be chosen for the treatment of B-cell NHL after the first trimester. For chronic myeloid leukaemia, IFN is considered safe during pregnancy while TKI are not recommended. For acute leukaemias the treatment options are less available due to the teratogeneity of most agents used, therefore when diagnosed before the 20th week of pregnancy, a termination is usually proposed. Additionally, a disseminated intravascular coagulopathy should be prevented in specific haematologic malignancies during pregnancy.

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Tongue cancer during pregnancy: Surgery and more a multidisciplinary challenge.	Tagliabue M et al.	Crit Rev Oncol Hematol.	http://www.ncbi.nlm.nih.gov/pubmed/26476748
2	Clinical characteristics and outcome of cancer diagnosed during pregnancy.	Shim MH et al.	Obstet Gynecol Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26866029
3	Hematologic Malignancies in Pregnancy: Management Guidelines From an International Consensus Meeting.	Lishner M et al.	J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26628463

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Gestational trophoblastic disease

Editor Manuela Undurraga

Descriptive summary

Epidemiology and risk factors

Von Wessler et al. reviewed invasive moles in peri-menopausal women. They found that the GTD in women older than 50 years is rare, and that in these patients hysterectomy may be considered as a first-line treatment.

Couder et al. retrospectively analysed risk factors for relapse in patients with low-risk GTN treated with MTX alone. They found that the antecedent pregnancy resulting in a delivery, and number of methotrexate courses superior to 5, were independent predictive factors of recurrence.

Gockley et al. analysed the impact of age on the incidence of molar pregnancies. They found that the incidence of complete mole differed significantly among maternal age groups, with adolescents 7.0 times as likely and women of advance maternal age twice as likely to develop. The rate of PM did not vary significantly among age groups.

The Dutch team lead by Eysbouts analysed the trend in incidence of GTD over the last 20 years in their population. They found that incidence rates have stabilised since 2004, with an overall incidence rate of 1.67 per 1000 deliveries per year. They also found that partial and complete moles have reached similar incidences rates of 0.68 and 0.64 per 1,000 deliveries, respectively, from 2009 onwards, with a decline of unspecified hydatidiform mole diagnosis to 0.03 per 1,000 deliveries. They conclude that this is all probably due to improved diagnostic analyses and centralised pathological review.

Diagnosis

Lin et al. reviewed the use of Doppler ultrasound in the diagnosis of GTD. They found that Doppler is not useful to distinguish between partial and complete moles. For the prediction of development of GTN, they note that most studies have observed a lower resistance in the uterine artery (UA) is associated with the development of GTN but data in the literature remain controversial and further studies must be carried out. Doppler ultrasound seems to be a useful adjuvant tool in post-molar follow-up and GTN diagnosis because Doppler findings such as abnormal myometrial vascularization, lower uterine artery (UA) Doppler indices, increased vascularization of the myometrium, higher UA peak systolic velocity, and lower UA resistance index are correlated with invasive disease. Additional useful information for follow-up includes an inverse correlation between UA Doppler indices and hCG regression. Finally, they state that the utilization of Doppler ultrasound may help predict chemotherapy resistance; in particular, qualitative Doppler assessment might help in managing patients with a plateaued hCG.

Mangili et al. reviewed the possible role of PET in the diagnosis and follow up of GTD. They state that PET has a particularly useful role in evaluating disease recurrence and chemo resistance, as well as mapping possible sites of resectable disease. They conclude that further studies are required to draw definitive conclusions on the role of PET in diagnostic setting and the follow-up phase of GTD.

You et al. are in the process of validating a mathematical model of hCG kinetics that may help predict MTX resistance, using the GOG174 database. They state that the early predictive value of the modelled kinetic parameter hCGres regarding resistance seems promising, but that further prospective validation is warranted.

Follow-up and quality of life

One article investigated the psychological impact during illness and follow-up in patients with GTD. They found that patients with gestational trophoblastic neoplasia (GTN) have a more mature defence mechanism than patients with hydatidiform mole. Patients with less mature defence mechanism had a higher state of anxiety and a higher degree of infertility-related global stress.

Treatment

Faaborg et al. analysed their success rate with oral methotrexate (MTX). In a retrospective study that covered 30 years, they found that 49 % of patients (90 % of whom were classified as FIGO low-risk disease) had a complete response after-first line therapy with oral MTX, while 87 % had complete remission after oral MTX (first-line) and/or MTX plus dactinomycin (second-line). Patients who did not respond to oral MTX usually had higher hCG levels, larger tumour sizes, and higher FIGO scores.

In another retrospective study, Kizaki et al. compared the primary remission rates and predictors of drug resistance in patients with low-risk GTN treated with two different treatment regimens. They

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Gestational trophoblastic disease

Descriptive summary (cont.)

found that primary remission rates were significantly higher among patients treated with a 5-day drip infusion etoposide than with those treated with a 5-day intramuscular MTX regimen. Risk factors for drug resistance were higher FIGO scores and pre-treatment human chorionic gonadotropin (hCG) levels, as well as a <30 % decrease in hCG after the first cycles of MTX.

A third retrospective study by Peng compared tegafur plus actinomycin D (Act-D) vs. 5-FU plus Act-D in GTN. The complete response rates in the tegafur and 5-Fu groups were 74.24 % and 76.59 %, respectively, and the overall response rates were 90.63 % and 92.37 %, respectively. On the other hand, there was a significant difference in the side effects in nausea, vomiting, dental ulcers, skin lesions, and diarrhoea, favouring the tegafur group.

Finally, a Cochrane review was conducted on chemotherapy for resistant and recurrent GTN. They establish that RCTs in GTN are scarce. In case of MTX-resistant or recurrent low-risk GTN, 5-day dactinomycin is usually used (which exhibits more side effects than pulsed dactinomycin) , followed by MAC (methotrexate, dactinomycin, cyclophosphamide) or EMA/CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, vinblastine) if further salvage therapy is required. For high-risk GTN, EMA/CO is the most commonly used first-line therapy, with platinum-etoposide combinations, particularly EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin), being favoured as salvage therapy. Alternatives, including TP/TE (paclitaxel, cisplatin/ paclitaxel, etoposide), BEP (bleomycin, etoposide, cisplatin), FAEV (floxuridine, dactinomycin, etoposide, vincristine), and FA (5-fluoruracil, dactinomycin), may be as effective as EMA/EP and associated with fewer side effects. In all cases, international RCT are needed to better establish ideal treatment.

Of the articles that met the inclusion criteria, one case report is worthy of notice. Gonzalez Aguilera et al. described a patient with persistent low levels of serum hCG that did not respond to chemotherapy. After excluding disease persistence, the team decided to analyse the levels of hCG in urine and in a HBT tube, revealing no hCG in urine and the presence of phantom hCG due to heterophilic mouse antibodies interaction. After doing a review of the literature, they conclude that urinary hCG and/or a test for serum heterophilic antibodies should be done when appropriate.

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No	Title	Authors	Journal	Link to abstract
1	An invasive mole with bilateral kidney metastases: A case report.	Yao K et al.	Oncol Lett.	http://www.ncbi.nlm.nih.gov/pubmed/26788142
2	Medical termination of a partial hydatidiform mole and coexisting foetus during the second trimester: A case report.	Wang Y et al.	Oncol Lett.	http://www.ncbi.nlm.nih.gov/pubmed/26788180
3	Invasive mole in a perimenopausal woman: a case report and systematic review.	von Welser SF et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26050078
4	Gestational Trophoblastic Disease: psychological impact and the role of defence mechanisms during illness and follow-up.	Di Mattei VE et al.	Recenti Progre Med.	http://www.ncbi.nlm.nih.gov/pubmed/26780074
5	A 30-year experience in using oral methotrexate as initial treatment for gestational trophoblastic neoplasia regardless of risk group.	Faaborg L et al.	Acta Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26106854
6	Comparison of 5-day MTX and 5-day ETP treatment results and early predictors of drug resistance to 5-day MTX in patients with post-molar low-risk gestational trophoblastic neoplasia.	Kizaki S et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26456138
7	Tegafur Substitution for 5-Fu in Combination with Actinomycin D to Treat Gestational Trophoblastic Neoplasm.	Peng M et al.	Plos One.	http://www.ncbi.nlm.nih.gov/pubmed/26599757
8	Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia.	Alazzam M et al.	Cochrane Database Syst Rev.	http://www.ncbi.nlm.nih.gov/pubmed/26760424
9	Is Doppler ultrasound useful for evaluating gestational trophoblastic disease?	Lin LH et al.	Clinics.	http://www.ncbi.nlm.nih.gov/pubmed/26735221
10	[18F]fluorodeoxyglucose positron emission tomography/computed tomography and trophoblastic disease: the gynecologist perspective.	Mangili G et al.	Q J Nucl Med Mol Imaging.	http://www.ncbi.nlm.nih.gov/pubmed/26868372
11	Validation of the Predictive Value of Modeled Human Chorionic Gonadotrophin Residual Production in Low-Risk Gestational Trophoblastic Neoplasia Patients Treated in NRG Oncology/Gynecologic Oncology Group-174 Phase III Trial.	You B et al.	Int J of Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26569059
12	Predictive factors of relapse in low-risk gestational trophoblastic neoplasia patients successfully treated with methotrexate alone.	Couder F et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26829503
13	Persistent low levels of serum hCG due to heterophilic mouse antibodies: an unrecognized pitfall in the diagnosis of trophoblastic disease.	Gonzalez Aguilera B et al.	Gynecol Endocrinol.	http://www.ncbi.nlm.nih.gov/pubmed/26792068
14	The effect of adolescence and advanced maternal age on the incidence of complete and partial molar pregnancy.	Gockley AA et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26777992
15	Trends in incidence for gestational trophoblastic disease over the last 20 years in a population-based study.	Eysbouts YK et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26586414

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Immunotherapy in gynaecological cancers

Editor Zoltan Novak

Descriptive summary

In this update, three recent human gynaecologic cancer/precancer immunotherapy trials are reported. In a phase I/II trial, 14 high-risk disease-free ovarian and breast cancer patients were vaccinated with MUC1, ErbB2, and carcinoembryonic antigen peptides and montanide adjuvant after completion of standard therapies. 8 out of 14 patients showed specific CD8+ T cells to at least one antigen. Peptide vaccination proved to be safe and well-tolerated. Vaccination generated a long-lasting immune and some clinical response, having registered no deceased patients with a minimum follow-up of 8 years. [1]

In a randomised, double-blind, placebo-controlled phase IIb study, efficacy, safety, and immunogenicity of VGX-3100 synthetic plasmid vaccine targeting HPV-16 and HPV-18 E6 and E7 proteins were assessed in patients with CIN2/3. In the modified intention-to-treat analysis 55 (48·2 %) of 114 VGX-3100 recipients and 12 (30·0 %) of 40 placebo recipients had histopathological regression, which was statistically significant (p=0·034) [2]. Another multicentre open-label, randomised controlled trial was conducted in patients with HPV16+ high-grade VIN/VaIN.

The study investigated if imiquimod applied at the vaccine site could improve CD8+ T-cell reactivity, clinical efficacy, and safety of HPV16-synthetic long-peptide vaccination. Vaccine-induced clinical responses were observed in 18 of 34 (53 %) patients at 3 months, 8 of whom displayed a complete histological response. Viral clearance occurred in all but one of the patients with complete histological clearance, but imiquimod did not improve the outcomes of vaccination [3]. A paper reviewed the role of microsatellite instability (MSI) testing in predicting the clinical benefit of immune checkpoint blockade with anti-programmed death 1 inhibitors. If initial results are validated, MSI testing could have an expanded role as a tool in the armamentarium of precision medicine [4]. *Also see the report on "Pathology in endometrial cancer (prognostic factors, EIN, EIC)" by S. Scasso.*

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Triple peptide vaccination as consolidation treatment in women affected by ovarian and breast cancer: Clinical and immunological data of a phase I/II clinical trial.	Antonilli M et al.	Int J Oncol.	http://www.spandidos-publications.com/10.3892/ijo.2016.3386
2	Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial.	Trimble CL et al.	Lancet.	https://ncbi.nlm.nih.gov/pubmed/26386540
3	Vaccination against oncoproteins of HPV16 for non-invasive vulvar/vaginal lesions: lesion clearance is related to the strength of the T-cell response.	van Poelgeest MI et al.	Clin Cancer Res.	https://ncbi.nlm.nih.gov/pubmed/26813357
4	Microsatellite Instability as a Biomarker for PD-1 Blockade.	Dudley JC et al.	Clin Cancer Res.	https://ncbi.nlm.nih.gov/pubmed/26880610

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Treatment of elderly patients with gynaecological cancers

Editor Alex Mutombo

Descriptive summary

Age induces a progressive decline in functional reserve and impacts cancer treatments. Endometrial and ovarian cancer primarily affects elderly women. In addition, clinical trial data are limited for elderly patients because approximately one third of the elderly women who meet pathologic enrolment criteria for trials are excluded because of complex medical disease. Clark et al. performed a retrospective chart review of all endometrial cancer cases from a tertiary care institution from 2005 to 2010 and found that more adjuvant treatment was recommended in the elderly patients because of a higher incidence of advanced disease and aggressive histopathology. Approximately only half of those who were recommended treatment actually received it.

Fourcadier et al. found that elderly women with ovarian cancer were therapeutically disadvantaged compared to younger women. This was confirmed by Peled et al. when they compared postoperative recovery between elderly patients and younger patients after laparotomy for endometrial cancer staging. According to their study, the elderly ambulated later and recovered bowel function later than did the younger patients. That did not translate into prolonged hospital stays or excessive complications. They concluded that earlier intervention with physical therapy and stool softeners could possibly close this gap in recovery.

Moreover, Zhou et al. conducted a study to evaluate the effects of age and the clinical response to neoadjuvant chemotherapy (NACT) in patients with cervical cancer who received neoadjuvant chemotherapy followed by radical surgery. They found that responders to NACT aged 35 years or younger benefitted the most from NACT, while the young non-responders benefitted the least. Hence, age might represent an important factor to consider when offering neoadjuvant chemotherapy in patients with cervical cancer.

Some studies by Lin et al. in the United States and Or Knudsen in Denmark have focused on overall survival in women with gynaecologic cancer. The main conclusion was that both mortality rates and survival are age-dependent, with a significantly shorter survival in the elderly group.

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Telomere length is a prognostic biomarker in elderly advanced ovarian cancer patients: a multicenter GINECO study.	Falandry C et al.	Aging (Albany NY).	http://www.ncbi.nlm.nih.gov/pubmed/26638179
2	Under-treatment of elderly patients with ovarian cancer: a population based study.	Fourcadier E et al.	BMC Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26610814
3	Comparative outcomes in older and younger women undergoing laparotomy or robotic surgical staging for endometrial cancer.	Guy MS et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26433173
4	Association between Metformin Use and Mortality after Cervical Cancer in Older Women with Diabetes.	Han K et al.	Cancer Epidemiol Biomarkers Prev.	http://www.ncbi.nlm.nih.gov/pubmed/26721670
5	Endometrial cancer in elderly women: Which disease, which surgical management? A systematic review of the literature.	Bourgin C et al.	Eur J Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26647302
6	Adjuvant Treatment and Clinical Trials in Elderly Patients With Endometrial Cancer: A Time for Change?	Clark LH et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26745698
7	Ovarian Cancer Treatment and Survival Trends Among Women Older Than 65 Years of Age in the United States, 1995-2008.	Lin JJ et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26646132
8	Trends in gynecologic cancer among elderly women in Denmark, 1980-2012.	Or Knudsen A et al.	Acta Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26784001
9	Young Cervical Cancer Patients May Be More Responsive than Older Patients to Neoadjuvant Chemotherapy Followed by Radical Surgery.	Zhou J et al.	PLoS One.	http://www.ncbi.nlm.nih.gov/pubmed/26901776
10	Endometrial Cancer Surgery for Elderly Women--The Early Postoperative Period.	Peled Y et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26332393
11	Management for Elderly Women With Advanced-Stage, High-Grade Endometrial Cancer.	Rauh-Hain JA et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26551187

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Epidemiology of Gynaecological Cancers

Editor Dominic Blake

Descriptive summary

In this issue we focus on ovarian cancer. Trétarre et al. reported trends in incidence, mortality, and survival in women with ovarian cancer. Data was collected from cancer registries and included epithelial, sex-cord stromal, and germ cell tumours. The results were modelled in an age-period-cohort analysis to adjust for factors relating to age and the environment. Whilst the incidence of ovarian cancer increased, the mortality rate fell. The factors associated with the rise in incidence were a larger population size and an aging population. Survival in those with ovarian cancer remains poor despite advances in treatment.

Luke et al. presents a retrospective analysis of women undergoing assisted reproductive therapy. They concluded that in the short term the risk of developing ovarian cancer is not significantly increased, however, it calls for longer prospective studies.

Lee et al. examined a large pooled genetic dataset and confirmed that there appeared to be an association between endometriosis, clear cell, and serous cancers. However the functional significance of the genes analysed remains uncertain and calls for further analysis to confirm the association.

The Nordic twin study observed monozygotic and dizygotic twins for 32 years. It was a retrospective study using cancer registries and birth records. The data supports an association between ovarian cancer in dizygotic and monozygotic twins where one twin has developed ovarian cancer (9 % risk in dizygotic and 3 % in monozygotic). The period of time between twins developing cancer varied widely which supports the genetic and environmental impacts of developing cancer.

Shu et al. studied ovarian clear cell carcinomas (OCCC) in a retrospective cohort study that examined patients diagnosed and treated at a single institution and reported progression-free survival and overall survival. The study confirmed that most women present at a younger age and earlier stage as compared to serous cancers. The study undertook subgroup analysis to examine survival in patients with surgical 1C vs. 1C (surface disease/positive cytology) and found that survival was more closely related to early-stage disease in the surgical rupture group. Race did not appear to be a significant predictor of outcome in OCCC. Patients with advanced ovarian cancer were found to be more chemoresistant than those with earlier stage disease.

Victora et al. published a study on breast-feeding and its lifelong effects. The study included 41 meta-analyses of women undertaking breast-feeding and its effects on ovarian cancer risk. The results showed a risk reduction in breast-feeding women developing ovarian cancer and a suggested further risk reduction in those women undertaking more prolonged periods of breast-feeding.

The EPIC study collected data from 10 European countries. This produced a large dataset and examined whether reproductive factors effect survival in epithelial ovarian cancer. The study concluded that long-term use of menopausal hormone therapy (MHT) was associated with an improved survival, in contrast to previous studies. Other factors such as parity, breast-feeding status, total ovulation years, and prior hysterectomy were not associated with survival. The paper calls for further studies to confirm the positive findings in MHT users.

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Ovarian cancer in France: Trends in incidence, mortality and survival, 1980–2012 .	Trétarre et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26383829
2	Cancer in women after assisted reproductive technology.	Luke et al.	Fertil Steril.	http://www.ncbi.nlm.nih.gov/pubmed/26271227
3	Familial Risk and Heritability of Cancer Among Twins in Nordic Countries.	Mucci et al.	JAMA.	http://www.ncbi.nlm.nih.gov/pubmed/26746459
4	Ovarian clear cell carcinoma, outcomes by stage: The MSK experience.	Shu et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26404183
5	Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect.	Victora et al.	Lancet.	http://www.ncbi.nlm.nih.gov/pubmed/26869575
6	Reproductive factors and epithelial ovarian cancer survival in the EPIC cohort study.	Bešević et al.	Br J Cancer,	http://www.ncbi.nlm.nih.gov/pubmed/26554655
7	Evidence of a genetic link between endometriosis and ovarian cancer.	Lee et al.	Fertil Steril.	http://www.ncbi.nlm.nih.gov/pubmed/26477498

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Nutritional support/status in gynaecological cancer

Editor Jiri Presl

Descriptive summary

The first cited papers are recently published ERAS /Enhanced Recovery After Surgery/ Society guidelines applied in gynaecologic/ oncology surgery. The recommendations are divided into two parts. Part I deals with pre- and intraoperative care. It mentions items such as preoperative information education and counselling, preoperative optimization, bowel preparation, fasting and carbohydrate treatment, preanaesthetic medication, thromboembolism prophylaxis, antimicrobial prophylaxis and skin preparation, anaesthetic protocol, PONV, MIS, nasogastric intubation, preventing intraoperative hypothermia, and perioperative fluid management.

Part II deals with postoperative care and covers items such as prophylaxis against thromboembolism, fluid therapy, nutritional care, prevention of postoperative ileus, postoperative glucose control and analgesia, peritoneal and urinary drainage, and early mobilization.

The evidence base, recommendations, evidence level, and recommendation grade are provided for each individual ERAS item. The whole protocol combines unimodal evidence-based interventions aiming to enhance recovery after surgery and reduce length of stay.

De Groot et al. published a systematic review and meta-analysis of 31 records up to June 2014 on the current evidence of ERAS on postoperative outcome in women undergoing open gynaecologic surgery. Enhanced recovery pathways may reduce length of postoperative hospital stay in abdominal gynaecologic surgery.

Wijk et al., in their single centre prospective cohort study, compared outcomes among 121 consecutive patients undergoing abdominal hysterectomy and salpingo-oophorectomy for malignant or benign indications between 2012 and 2014. No difference was found, not in terms of LOS nor complications, reoperations, or readmissions. The ERAS protocol may be equally applicable to patients undergoing hysterectomy for malignant or for benign disease.

Purcell et al. reviewed the impact of body weight and particularly body composition on surgical complications, morbidity, chemotherapy dosing and toxicity (as predictors of prognosis), and survival in ovarian cancer patients. They conclude that body composition, as an indicator of nutritional status, is a better prognostic tool than body weight or BMI alone in ovarian cancer patients.

Relevant articles retrieved Nov 2015 - Feb 2016

No	Title	Authors	Journal	Link to abstract
1	Guidelines for pre- and intra-operative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations - Part I.	Nelson G et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26603969
2	Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations - Part II.	Nelson G et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26757238
3	Enhanced recovery pathways in abdominal gynecologic surgery: a systematic review and meta-analysis.	de Groot JJ et al.	Acta Obstet Gynecol Scand.	http://www.ncbi.nlm.nih.gov/pubmed/26613531
4	Enhanced Recovery after Surgery Protocol in Abdominal Hysterectomies for Malignant versus Benign Disease.	Wijk L et al.	Gynecol Obstet Invest.	http://www.ncbi.nlm.nih.gov/pubmed/26799328
5	Impact of Body Weight and Body Composition on Ovarian Cancer Prognosis.	Purcell SA et al.	Curr Oncol Rep.	http://www.ncbi.nlm.nih.gov/pubmed/26769113

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