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LiFE report
Literature for ENYGO

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Reviews covering publications from February 15, 2016 – September 15, 2016

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Preface

Dear colleagues,

This is the fourth consecutive edition of the LiFE report, containing reviews of publications in gynaecological oncology from February 15, 2016 - August 15, 2016. LiFE is an initiative of ENYGO supported by ESGO.

Some of the topics have found new authors, and we welcome Sileny Han (Belgium), Tania Nikolova (Macedonia), Javier Mejia Gomez (Canada), Vishal Bahall (Trinidad/Ireland), and Ilker Selcuk (Turkey) to the LiFE team. This edition covers 41 separate reports, written by authors from 24 countries. We are very proud of this international collaboration and would like to acknowledge the continuous work and effort from each author.

The LiFE team is very grateful for the support of Beth Green in proofreading and also of our graphic designer Tomas Grünwald, who is responsible for distinctive design, which supports our brand "LiFE".

This issue is again published as a supplement to the International Journal of Gynecological Cancer Vol 26, which adds to the scientific value and publicity of our work.

We hope you will enjoy LiFE 4 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
David Lindquist

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Miscellaneous

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Pathology / pathogenesis of malignant ovarian tumours

Editor Dogan Vatansever

Descriptive summary

Four original research articles and three review articles were considered relevant for this summary:

Original Research

- Cells communicate through the exchange of bioactive molecules via microvesicles. Exosomes are endosome-derived microvesicles and Yeung et al. demonstrated that omental stromal cell-derived exosomes isolated from cancer-associated adipocytes (CAAs) and fibroblasts (CAFs) carry significantly higher levels of microRNA-21 (miR21) that transfer to the cancer cells. miR21 suppresses ovarian cancer apoptosis and confers chemoresistance by binding to its direct novel target, APAF1. The study suggests that neighbouring stromal cells can alter the malignancy potential of cancer cells.
- Wu et al. demonstrated that miR-192 is a key regulator of angiogenesis, which plays a central role in tumour growth. They showed that using 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC) nanoliposomes miR-192 delivery leads to inhibition of tumour angiogenesis in multiple ovarian and renal tumour models. More importantly, this effect was more robust when compared to an anti-VEGF antibody.
- It was discovered nearly a century ago that, in highly proliferative cancer cells, glucose is mainly converted into lactate instead of entering into the mitochondria for generation of ATP through the Krebs cycle. The enzymes that regulate the flow of glycolysis are transcriptionally regulated mainly by three major transcription factors: hypoxia-inducible factor-1 (HIF-1), p53, and Myc. HIF-1 is the key player, and HIF-1 subunit is the regulatory part. Ai et al. studied cisplatin resistance and hypothesised that down-regulating HIF-1 is a promising strategy to overcome cisplatin resistance in ovarian cancer. They showed that cisplatin in combination with genetic knockdown of HIF-1 expression or pharmacological promotion of HIF-1 degradation can induce apoptosis in cisplatin-resistant ovarian cancer cells through directing their energy metabolism to the Krebs cycle, leading to overproduction of reactive oxygen species.
- Winterhoff et al. aimed to characterize the transcriptional profiles of high-grade clear cell (HGCCOC) or high-grade endometrioid ovarian cancer (HGEOC) in a similar manner to high-grade serous ovarian cancer (HGSOC). The latter is nicely reviewed by Kurman et al. The same four TCGA transcriptional subtypes that have been identified in HGSOC were also present in HGCCOC and HGEOC. Two additional clusters with distinct signatures were identified as one for HGCCOC and one for HGEOC. However, more importantly, they have been able to demonstrate that 70 % of the patients with this fifth transcriptional subtype in each group were of early stage (FIGO I-II) and had the best prognosis.

Reviews

- Nearly a decade ago, Kurman et al. proposed a dualistic model of epithelial ovarian carcinogenesis. In this new review, they provide an update and revision of their model. In their expanded model, type I carcinomas that arise from benign precursor lesions, i.e., endometriosis and papillary tubal hyperplasia, have been divided into three subtypes: i) endometriosis-related (endometrioid, clear cell, and seromucinous or mixed müllerian neoplasms), ii) tubal-related (low-grade serous tumours), and, iii) germ cell or transitional cell-related (mucinous and Brenner tumours). For type II carcinomas, which comprise HGSC, carcinosarcoma and undifferentiated carcinoma, morphologic data suggest division into the following subsets: the usual and SET (solid, pseudoendometrioid, transitional) variants. The molecular profiling revealing four clusters with distinct signatures (immunoreactive, differentiated, proliferative, and mesenchymal) is reviewed.
- Mills et al. discussed the rationales and relative merits of current Lynch syndrome-screening for endometrial and ovarian cancers. They conclude that the Amsterdam Criteria, which subsequently were refined by the Bethesda Consensus Group, miss an unacceptable number of Lynch syndrome patients. They reviewed possible screening strategies and diagnostic techniques.
- And last but not least, Malpica et al. reviewed the molecular pathology of ovarian serous borderline tumours (OSBT). They discussed the pathogenesis and the role of Kras and Braf mutations in the tumourigenesis of OSBT.

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Pathology / pathogenesis of malignant ovarian tumours

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1	Yeung et al.	Nature communications	https://www.ncbi.nlm.nih.gov/pubmed/27021436
2	A miR-192-EGR1-HOXB9 regulatory network controls the angiogenic switch in cancer	Wu et al.	Nature communications	https://www.ncbi.nlm.nih.gov/pubmed/27041221
3	Overcoming cisplatin resistance of ovarian cancer cells by targeting HIF-1-regulated cancer metabolism	Ai et al.	Cancer letters	https://www.ncbi.nlm.nih.gov/pubmed/26801746
4	Molecular classification of high grade endometrioid and clear cell ovarian cancer using TCGA gene expression signatures	Winterhoff et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27016234
5	Lynch Syndrome Screening in the Gynecologic Tract Current State of the Art	Mils et al.	Am J Surg Pathol	https://www.ncbi.nlm.nih.gov/pubmed/27012190
6	Lynch Syndrome Screening in the Gynecologic Tract Current State of the Art	Malpica et al.	Ann Oncol	https://www.ncbi.nlm.nih.gov/pubmed/26872009
7	The molecular pathology of ovarian serous borderline tumors	Malpica et al.	Annals of Oncology	https://www.ncbi.nlm.nih.gov/pubmed/27141064

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Screening for ovarian and fallopian tube cancer

Editor Lucas Minig

Descriptive summary

During this period, there were many comments regarding the UKCTOCS study, which was mentioned in the previous edition of LiFE.

In addition, two articles were considered relevant to ovarian cancer screening. They explored the validation of additional or novel biomarkers for the early detection of ovarian cancer.

A retrospective study aimed to investigate the use of biomarker combinations (CA 125, HE4, MMP-7, CA 72.4, CA 19.9, CA 15.3, CEA, sVCAM) in order to improve sensitivity over CA 125 alone, which has been considered for many years the main biomarker target for an early diagnosis of ovarian cancer (Simmons et al.). The authors compared the value of biomarkers in the pretreatment samples sera of 142 stage I ovarian cancer patients from the Gynaecologic Oncology Group study with five annual serum samples from 217 healthy postmenopausal women (aged 55-85 years) enrolled in the Normal Risk Ovarian Cancer Screening Study (NROSS) in the USA. They found that CA125, HE4, MMP-7, and CA72-4 had the highest sensitivity (83.2 %) at 98 % specificity. These values are better than those reported in the UKCTOCS study. Based on these results, researchers are now validating a new panel of biomarkers in a large blinded retrospective study using longitudinal cases and control specimens from the UKCTOCS trial.

In the same line of investigation, other researchers conducted a blinded evaluation of prospectively collected preclinical serum from participants in the UKCTOCS trial (Russell et al.). They identified 90 proteins that were differentially expressed between patients with ovarian cancer cases and controls. A second targeted mass-spectrometry analysis of 20 of these candidates identified Protein Z as a potential early detection biomarker for ovarian cancer. Protein Z was significantly down-regulated up to two years prediagnosis ($p = 0.0000004$) in eight out of 19 type I patients (more indolent tumours lacking mutations in TP53) whilst in five type II individuals (more aggressive cancers displaying TP53 mutations in >80 % of cases), it was significantly up-regulated up to four years before diagnosis ($p = 0.01$). Further validation, however, needs to be carried out before the clinical utility of Protein Z can be implemented. Such studies should include samples from patients with benign tumours and other unrelated diseases. Once this is completed, one can envision the clinical potential and utility of Protein Z. This protein could be useful as a biomarker for early detection as well as to differentiate between malign and benign adnexal masses.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Protein Z: A putative novel biomarker for early detection of ovarian cancer	Russell M et al.	International Journal of Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26815306
2	Validation of a biomarker panel and longitudinal biomarker performance for early detection of ovarian cancer	Simmons A et al.	International Journal of Gynecological Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27206285

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

Editor Ignacio Zapardiel

Descriptive summary

The majority of papers published during the search period focused on sonographic diagnosis and molecular patterns of borderline ovarian tumours together with some exceptional case reports. However, some interesting data on treatment and management have also been reported. The surgical treatment is still the preferred option in Borderline ovarian tumours (BOT). The vast majority of cases are diagnosed in early stages and 94.4 % are treated with surgery alone. Fertility-sparing surgery in young patients with BOTs is associated with a good pregnancy rate, up to 75 % obtained pregnancy after a follow-up of 48 months. However, the tumour stage and coexisting infertility factors are important considerations in selecting the optimal surgical approach. Specifically, in patients with bilateral tumours, elevated CA125, extra-ovarian tumourmanifestation or mucinous type, risks of conservative surgery should be carefully discussed and subsequent pregnancy should be attempted in the short term. Fertility preservation in BOT seems to be justified, although it has an increased relapse rate. Overall survival has been reported comparable to patients undergoing complete surgery, since the majority of patients will recur as BOT. Higher recurrence rates were reported to be related to tumour size assessed by ultrasound ultrasonographic. In advanced stages, the rate of recurrence seems to be significantly higher (OR: 3.87), but the overall survival did not show statistical differences when fertility-preserving surgery was carried out compared to the radical treatment. The relapse rate of borderline ovarian tumours is estimated to be around 3 % and increased rates have been observed in the presence of peritoneal implants, FIGO stage Ic, and after incomplete staging surgery. These aspects need to be taken into consideration at the time of initial treatment. Surgery remains the main treatment for relapsed disease. Regarding the management of mucinous BOT, an interesting paper reported that although 20 % of appendices can be macroscopically involved by tumour, no microscopic tumour was found in case of macroscopic absence of the disease in the appendix, even though it was systematically removed. This paper supports the concept of exclusively resection macroscopically involved surfaces, at least in mucinous BOT. A recent Cochrane review has evaluated the available data on the use of intraoperative frozen section for the diagnosis of ovarian cancer and BOT in ovarian masses. The metaanalysis showed a 2.9 % rate of false negative cases and a 0.4 % rate of false positive. The lack of accuracy was even higher when considering BOT cases only. This highlights the importance of the final diagnosis in large ovarian masses and the need to be conservative until the final diagnosis is reported.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Pregnancy after fertility-sparing surgery for borderline ovarian tumours.	Lian C et al.	Int J Gynaecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/27352738
2	The feasibility of fertility-sparing surgery in treating advanced-stage borderline ovarian tumours: A meta-analysis.	Huang Y et al.	Taiwan J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/27343308
3	Annual Report of the Committee on Gynecologic Oncology, Japan Society of Obstetrics and Gynecology: Patient Annual Report for 2013 and Treatment Annual Report for 2008.	Saito T et al.	J Obstet Gynaecol Res.	http://www.ncbi.nlm.nih.gov/pubmed/27338217
4	The Evaluation of Risk Factors Associated With Relapse and Recurrence of Borderline Ovarian Tumors With Long-Term Follow-up	Sobiczewski P et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27177283
5	Outcome of Appendicectomies at Surgery for Mucinous Ovarian Neoplasms: Report From A UK Center and Review of Literature.	Mukhopadhyay D et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27101589
6	Fertility-sparing surgery for young patients with borderline ovarian tumours (BOTs): single institution experience.	Chen RF et al.	J Ovarian Res.	http://www.ncbi.nlm.nih.gov/pubmed/26988551
7	Intraoperative frozen section analysis for the diagnosis of early stage ovarian cancer in suspicious pelvic masses.	Ratnavelu ND et al.	Cochrane Database Syst Rev.	http://www.ncbi.nlm.nih.gov/pubmed/26930463
8	Fertility Preservation Is Safe for Serous Borderline Ovarian Tumors.	Vancraeynest E et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27465897
9	Ultrasonographic diagnosis and longitudinal follow-up of recurrences after conservative surgery for Borderline Ovarian tumours.	Franchi D et al.	Am J Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/27443811

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Surgical treatment of primary ovarian cancer

Editor Sileny Han

Descriptive summary

Surgical technique

Three papers focused on specific surgical techniques. Sznurkowski describes a modified technique of en bloc pelvic resection, preceded by central ligation of vessels supplying the tumour bed. Tseng et al. examined the use of diverting loop ileostomy (DI) during cytoreduction. For a total of 331 patients who had colon resection during primary cytoreduction, 13 % underwent a DI. The overall anastomotic leak rate was 6 %, and did not differ between both groups. DI did not compromise postoperative outcomes or long-term survival. The publication by Sawyer et al. is a video showing extended left upper-quadrant resection, with en bloc omentectomy, transverse colectomy, splenectomy, distal pancreatectomy, and diaphragm peritonectomy, resulting in no residual disease.

Ataseven et al. retrospectively evaluated the impact of port-site metastasis (PSM) in patients with epithelial ovarian cancer (EOC) undergoing laparoscopy before subsequent primary cytoreduction. The median interval between laparoscopy and PDS was 25 days. In all, 46.7 % (100/214) developed PSM.

Complete cytoreduction

New ASCO guidelines published by Wright et al. (www.asco.org/NACT-ovarian-guideline and www.asco.org/guidelineswiki) emphasize that, for women with advanced epithelial ovarian cancer, cytoreduction to <1 cm of residual disease (ideally to no visible disease) should be aimed for. For details, see the report by Javier Cesar Mejia Gomez on "Medical treatment for primary ovarian cancer".

Dao et al. described the characteristics of 203 ten-year survivors with high-grade EOC, of whom 72.4 % had stage IIIc disease at presentation. The majority of women had undergone optimal surgical cytoreduction and had primary platinum-sensitive disease. Unexpected findings were: 14 % of patients had suboptimal cytoreduction; 11 % of patients had an initial platinum-free interval of <12 months until the first relapse; and 53 % of patients had at least one recurrence, yet still survived more than ten years after diagnosis.

Timing of surgery (primary debulking surgery (PDS) versus interval debulking surgery (IDS))

Makar et al. performed an analysis based on results of five phase III randomised controlled trials, three Cochrane reviews, and four meta-analyses on PDS and IDS in patients with advanced EOC. There is still no evidence that NACT-IDS is superior to PDS. Clinical status, tumour biology, and chemosensitivity should be taken into account to individualise surgical approach. Non-serous (type 1) tumours with favourable prognosis are less chemosensitive, and omitting optimal PDS will lead to a less favourable outcome. For patients with advanced serous ovarian cancer (type 2) associated with severe comorbidity or low performance status, NACT-IDS is the preferred option. NACT is also discussed in the report by Javier Cesar Mejia Gomez on "Medical treatment for primary ovarian cancer".

Fagotti et al. reported on the perioperative outcome in a phase III randomised trial comparing PDS versus NACT in advanced EOC with high tumour load (SCORPION trial). Despite the different extents of surgery, rates of complete cytoreduction were comparable between both groups (45.5 % versus 57.7 %; p=0.206). Perioperative moderate/severe morbidity, as well as quality of life scores, were shown to be more favourable in NACT/IDS arm compared to PDS in patients with a very high tumour load.

Centralisation of care

Dahm-Kähler et al. performed a retrospective regional population-based cohort study of primary ovarian or fallopian tube cancers diagnosed and registered in the Swedish Quality Registry for Gynaecological Cancer during 2008-2013. In this region, primary care of advanced stages was centralised in 2011. Complete cytoreduction was achieved in 37 % of patients before the centralisation, compared to 49 % after centralisation (p<0.03). The relative three-year survival rate increased from 40 % before centralisation to 61 % after centralisation (RR 0.59; 95 % CI 0.45-0.76).

Eggink et al. found that centralisation of care, which has taken place in the Netherlands in the past decade, led to a 10 % increase (from 42 % to 52 %) of complete cytoreduction rate (no visible disease) for women with FIGO stage IIB-IV EOC. Between 2004 and 2013, a 3 % annual reduction in risk of death was observed (HR 0.97, p<0.001).

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No	Title	Authors	Journal	Link to abstract
1	En bloc pelvic resection for advanced ovarian cancer preceded by central ligation of vessels supplying the tumour bed: a description of surgical technique and a feasibility study.	Sznurkowski JJ	World J Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27130224
2	Diverting ileostomy during primary debulking surgery for ovarian cancer: Associated factors and postoperative outcomes	Tseng JH et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27261325
3	Extended left upper quadrant resection during primary cytoreductive surgery for Stage IV ovarian cancer.	Sawyer BT et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27264212
4	Prognostic Impact of Port-Site Metastasis After Diagnostic Laparoscopy for Epithelial Ovarian Cancer	Ataseven B et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27406097
5	Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline.	Wright AA et al.	J Clin Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27502591
6	Characteristics of 10-year survivors of high-grade serous ovarian carcinoma	Dao F et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26968641
7	Advanced Ovarian Cancer: Primary or Interval Debulking? Five Categories of Patients in View of the Results of Randomised Trials and Tumor Biology: Primary Debulking Surgery and Interval Debulking Surgery for Advanced Ovarian Cancer.	Makar AP et al.	Oncologist	http://www.ncbi.nlm.nih.gov/pubmed/27009938
8	Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome.	Fagotti A et al.	Eur J Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26998845
9	Centralized primary care of advanced ovarian cancer improves complete cytoreduction and survival - A population-based cohort study.	Dahm-Kähler P et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27238084
10	Improved outcomes due to changes in organization of care for patients with ovarian cancer in the Netherlands.	Eggink FA et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27090157

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Surgical treatment of recurrent ovarian cancer

Editor Patriciu Achimas-Cadariu

Descriptive summary

A study using the SEER database assessed the survival rates of 1,635 women > 66 years with advanced stage ovarian cancer treated for their first recurrence from 1997 to 2007. The women were treated with complete primary debulking followed by six cycles of adjuvant chemotherapy at primary diagnosis. Seventy-two per cent received chemotherapy only, 16 % underwent a combination of surgery and chemotherapy, and the remaining 12 % opted for hospice care. There was a significant difference in median survival between the three groups; 4.1 years for the chemotherapy group, 5.4 years for the combination group, and 2.2 years for the hospice care group ($p<0.001$). The hazard ratio for women treated with surgery and chemotherapy in comparison with chemotherapy only was 1.67 (95 % CI 1.13-2.47). [1].

A narrative review article published by Gasparri et al. addressed the issue of hepatic resections in primary or recurrent ovarian cancer. The authors identified nine single-institution studies and concluded that in carefully selected patients where a complete cytoreduction is expected, hepatic resections are feasible and seem to improve the oncologic outcome with a relatively small number of resection-associated complications in relapsed ovarian cancer, although these results must be interpreted with caution given the small number of patients and the retrospective design. [2]

Another retrospective single-institution study investigated the role of secondary cytoreductive surgery and evaluated its impact in three different prognostic groups in 209 patients. Surgery was associated with a 66 % reduction in the risk of death and a 50 % reduction in the risk of relapse (HR, 0.34; 95 % CI, 0.15-0.76, $p = 0.008$ and HR, 0.50; 95 % CI, 0.30-0.84, $p = 0.008$), with a median OS of 109.5 months in the surgery group versus 16.3 months in the chemotherapy alone group ($p<0.001$). [3]

A retrospective chart review by Paik et al. investigated the feasibility of laparoscopic cytoreduction in 31 patients with localized recurrent epithelial ovarian cancer in comparison with the standard laparotomy approach in 48 patients. For carefully selected patients, the authors concluded that the new approach could represent a treatment option, without any detrimental effect regarding morbidity or survival and with improved operating time, estimated blood loss, and hospital stay. [3] The study is limited by the short follow-up time and its retrospective design, which makes it bias prone (i.e., differences in size of recurrence between the groups).

Minaguchi et al. investigated prognostic factors after secondary cytoreductive surgery in a retrospective single-institution study of 80 patients. The complete debulking rate was 60 % and four factors (TFI >12 months, absent distant metastasis, solitary disease, and performance status 0) were independently associated with a significantly better survival. Patients with 3-4 of the above factors had a complete resection rate of 79 % in comparison with 40 % in patients with two of the above factors. [4]

During the search period, a comprehensive review by Suh et al. analysed the available evidence for the surgical management of recurrent ovarian cancer, highlighting that surgery might be feasible and effective, especially for patients with good performance status, localised disease, and a long treatment-free interval. [5]

Another systematic literature review by Hotouras et al. analysed a pooled number of 1,168 patients regarding the role of HIPEC and cytoreductive surgery that seem to be associated with better oncological outcomes, but the majority of studies included were level IV evidence. [6]

The results of the three randomised trials on this topic (DESKTOP III, NCT01166737; GOG 213, NCT00565851; SOCceR, NTR3337) have not yet been published, and most of the available evidence is based on retrospective or small series studies.

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Surgical treatment of recurrent ovarian cancer

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No	Title	Authors	Journal	Link to abstract
1	Secondary Surgery Versus Chemotherapy for Recurrent Ovarian Cancer	Bickell NA et al.	Am J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/27391357
2	Hepatic resection during cytoreductive surgery for primary or recurrent epithelial ovarian cancer.	Gasparri ML et al.	J Cancer Res Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26660323
3	The Value of Secondary Cytoreductive Surgery in Recurrent Ovarian Cancer and Application of a Prognostic Score.	da Costa AA et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/26825830
4	Proposal for selection criteria of secondary cytoreductive surgery in recurrent epithelial ovarian, tubal, and peritoneal cancers.	Minaguchi T et al.	Int J Clin Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26475355
5	Surgical management of recurrent ovarian cancer.	Suh DH et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/27130407
6	Heated IntraPEritoneal Chemotherapy (HIPEC) for Patients With Recurrent Ovarian Cancer: A Systematic Literature Review.	Hotouras A et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/26844612

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Medical treatment of primary ovarian cancer

Editor Javier Cesar Mejia Gomez

Descriptive summary

Mueller et al. evaluated the use of neoadjuvant chemotherapy (NACT) and primary debulking surgery (PDS) at a single institution before and after the publication of results from a randomised trial showing non-inferiority between NACT and PDS in the management of advanced-stage ovarian carcinoma (EORTC/NCIC trial). The authors evaluated consecutive patients with advanced-stage ovarian cancer treated between 1/1/08-5/1/13. A total of 586 patients were evaluated; the median age was 62 years (range, 30-90). In all, 406 patients (69 %) had stage III disease while 570 (97 %) had disease of serous histology. Twenty-six per cent (154/586) were treated with NACT and 74 % (432/586) with PDS. Although patients who underwent PDS were more likely to experience grade 3/4 surgical complications than those who underwent NACT, those selected for PDS had a median OS of 71.7 months (CI, 59.8-not reached), compared with 42.9 months (CI 37.1-56.3) for those selected for NACT. Study limitations are thoroughly discussed, including its retrospective design, the high risk of selection bias selecting healthier patients to PDS, and the fact that details of medical treatment were not included. The main conclusion is that selection criteria for NACT needs to be refined to avoid PDS in patients who may not benefit.

Hall et al. reviewed the current literature on the use of neoadjuvant chemotherapy as a treatment strategy for patients with advanced epithelial ovarian cancer. Primary debulking surgery remains the standard of care in the United States for the treatment of advanced epithelial ovarian cancer. However, neoadjuvant chemotherapy with interval cytoreductive surgery is often employed in patients who are deemed too frail to undergo primary debulking surgery or in whom optimal cytoreduction would require procedures leading to considerable morbidity.

Mahner et al. reviewed the results of CHROUS and the EORTC trial. Both studies met their primary end point by demonstrating non-inferiority, neoadjuvant chemotherapy followed by interval debulking surgery. Nevertheless, the radicality of surgical therapy was below expectation, with median operating times of <3 h and complete gross resection in <20 % of the patients. Consecutively, survival rates of patients undergoing primary debulking surgery were low. The authors conclude that chemotherapy should not be used to reduce surgical radicality for ovarian cancer treatment. They also hope that the TRUST trial will achieve considerable complete gross resection rates in a considerable percentage of patients and will help to answer the question of PDS vs. NACT.

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Schlappe et al. published a retrospective cohort study analysing the reasons for not administering intraperitoneal chemotherapy after optimal cytoreduction, despite improved survival reported in randomised studies. The study included 330 patients, all of whom had optimal primary cytoreductive surgery for stage III ovarian, fallopian tube, or primary peritoneal carcinoma, and who also met eligibility criteria for GOG-172, and had received primary chemotherapy between 2006 and 2013. The majority (79 %) received at least one IV/IP cycle, and 62 % completed six cycles. The most common reason for giving IV-only therapy was postoperative status/complications. Potentially modifiable factors identified as leading to the use of IV-only chemotherapy were postoperative status and IP port complications, which if altered, could potentially lead to increased IP chemotherapy use.

Wright et al. presented the most recent Society of Gynecologic Oncology and the American Society of Clinical Oncology guidelines on the use of neoadjuvant chemotherapy and interval cytoreduction among women with stage IIIC or IV epithelial ovarian cancer. All women with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynaecologic oncologist prior to initiation of therapy. The primary clinical evaluation should include a CT of the abdomen and pelvis, and chest imaging (CT preferred). Women with a high perioperative risk profile or a low likelihood of achieving cytoreduction to <1 cm of residual disease (ideally to no visible disease) should receive neoadjuvant chemotherapy. Women who are fit for primary cytoreductive surgery, and with potentially resectable disease, may receive either neoadjuvant chemotherapy or primary cytoreductive surgery. However, primary cytoreductive surgery is preferred if there is a high likelihood of achieving cytoreduction to <1 cm (ideally to no visible disease) with acceptable morbidity.

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1	Neoadjuvant chemotherapy and primary debulking surgery utilization for advanced-stage ovarian cancer at a comprehensive cancer center.	Mueller JJ et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=26777991
2	Neoadjuvant chemotherapy for advanced epithelial ovarian cancer.	Hall TR Dizon DS.	Clin Adv Hematol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=27166608
3	Neoadjuvant chemotherapy in ovarian cancer revisited.	Mahner S et al.	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=27141067
4	Cited rationale for variance in the use of primary intraperitoneal chemotherapy following optimal cytoreduction for stage III ovarian carcinoma at a high intraperitoneal chemotherapy utilization center.	Schlappe BA et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=27189456
5	Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline.	Wright AA et al.	J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/?term=27502591

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

Medical treatment of recurrent ovarian cancer

Editor Ilker Selcuk

Descriptive summary

Response and the platinum-free interval to the first line chemotherapy after debulking surgery for ovarian cancer will often determine the next treatment regimen.

Selle et al. conducted a phase I study testing the maximum tolerated dose (MTD) of topotecan when administered with cyclophosphamide as high-dose chemotherapy in combination with hematopoietic stem cell transplantation. The maximum tolerated dose of topotecan was 9.0 mg/m2, and hematopoietic toxicities were favourable by that method. The regimen may still not be clinically feasible, due to the overall poor and short-termed responses and the considerably high mortality.

Landrum et al. conducted a phase I dose escalation study to evaluate MTD and dose-limiting toxicities (DLTs) of veliparib as intermittent or continuous dosing arms in combination with pegylated liposomal doxorubicin (PLD) and carboplatin (CD) in patients with recurrent, platinum-sensitive epithelial ovarian cancer. Some patients in each cohort were in addition treated with bevacizumab. Veliparib in combination with PLD and CD resulted in severe hematologic toxicities and the addition of bevacizumab increased the potential harmful effects. The MTD was 80 mg p.o.; the complete and partial tumour response rate was 68 % for patients with a measurable disease at the entry of study (17/25 patients).

As a non-VEGF dependent angiogenesis inhibitor, trebananib (AMG 386) targets angiopoietin-Tie-2 complex pathway with a distinct toxicity profile and its potential role in epithelial ovarian cancer is reviewed by Al Wadi et al.

Lederman et al. published outcomes related to the ICON6 trial that was initially announced at the ESMO Annual Meeting in 2013. Cediranib is an oral VEGFR 1-3 and c-Kit inhibitor and was evaluated in patients with relapsed platinum-sensitive ovarian cancer in a randomised, double-blind, placebo-controlled phase III trial. In this three-arm study, patients in arm A received platinum-based chemotherapy with a placebo, then placebo during maintenance; patients in arm B received once-daily oral cediranib, then placebo as maintenance; patients in arm C received once-daily oral cediranib and continued with cediranib during maintenance. However, the trial had to be redesigned because of the discontinuation of cediranib development in 2011. The median follow-up time was 19.5 months. The median progression free survival (PFS) for arms C, A, and B are 11, 8.7, and 9.9 months, respectively. The median overall survival (OS) for restricted 3 years was 26.3 and 21 months in arms C and A, respectively. During the maintenance period, diarrhoea, hypothyroidism, and voice changes were common toxicities. When taken in combination with chemotherapy, 32 % of the patients stopped the cediranib treatment, compared to 10 % in the placebo arm. During the maintenance period, these proportions were 10 % and 2 % for cediranib and placebo arms, respectively.

The Lancet has published an accompanying editorial by Norrie that provides an important opinion piece when critically appraising the data presented by Lederman et al. The scientific and ethical consideration when trials are changed midstream, in this case when the drug company involved (AstraZeneca) decided (on Sept 14, 2011) to cease commercial development of cediranib and thereby the drug supply, was thoroughly discussed. The lack of data for acceptability and quality of life with detailed side effects has been mentioned as well.

Gounaris et al. retrospectively evaluated patients who received intensive cisplatin and oral etoposide (Van der Burg protocol) at the Cambridge Gynae-Oncology Centre in and after 2001. The radiological response rate was 43 % and median PFS and OS were 5.8 and 14.1 months, respectively. Four (11 %) patients died, and toxicity was significant with grade 3/4 fatigue, nausea, and vomiting, affecting 46 %, 46 %, and 29 % of patients, respectively. The department has therefore abandoned this regimen in these patients who were treated with the aim of palliation.

Domchek et al. analysed the efficacy and safety of oral olaparib 400 mg in recurrent ovarian cancer patients with germline BRCA1/2 mutation who had received ≥3 prior chemotherapy lines. This is a subgroup analysis of the study. Objective response rates were 46 % and 30 % for platinum-sensitive and -resistant patients, and the duration of the response was 8.2 and 8 months, respectively. Grade ≥3 adverse effects occurred in over 50 %, but there were no new safety signals. Median PFS was 9.4 months (95 % CI 6.7-11.4) and 5.5 months (4.2-6.7) in the platinum-sensitive versus platinum-resistant subgroups, respectively.

All patients with relapsing ovarian cancer may ultimately develop platinum-resistant disease. Assessment of progressive disease by CA125 was compared to RECIST assessment in the Aurelia study. Lindemann et al. showed a lesser reliability for CA-125 follow-up in patients with a platinum-resistant disease, but the probability of clonal mutations regarding the previous different chemo-regimens and the CA-125 level did not have any prognostic value at the time of progression by this analysis. However, imaging may be a reasonable approach for evaluating disease progression in these patients; more importantly, we need reliable tools to assess any clinical benefit. The paper was accompanied by an editorial by Rustin et al.

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Medical treatment of recurrent ovarian cancer

Descriptive summary

Mirza et al. reported the results of the Ov16/NOVA study. In all, 553 patients with platinum-sensitive recurrent ovarian cancer were randomised to a 2:1 ratio to receive niraparib (300 mg) or placebo once daily. Two independent cohorts on the basis on the presence or absence of a germline BRCA mutation were enrolled. The non-gBRCA cohort also contained a subgroup of patients with tumours showing homologous recombination deficiency (HRD) (Myriad Genetics). Independent of BRCA mutation status, patients in the niraparib group had significantly longer progression-free survival than in the placebo group (P<0.001). In the gBRCA cohort, the median PFS was 21.0 months in the niraparib group and 5.5 months in the placebo group (HR 0.27; 95 % CI 0.17-0.41). Even more interesting were the results in both the HRD–positive subgroup and the non-gBRCA cohort, where niraparib also resulted in a major benefit for PFS (median PFS, 12.9 months vs. 3.8 months; HR 0.38; 95% CI 0.24-0.59, for HRD-pos tumours and median, 9.3 months vs. 3.9 months; HR 0.45; 95 % CI 0.34-0.61, non-gBRCA cohort). More myelotoxicity was noted on niraparib. The incidence of myelodysplastic syndrome was 1.4 % (5/367) in patients who received niraparib. There was one case each of the myelodysplastic syndrome and acute myeloid leukaemia among patients who received placebo.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	A Phase I Trial of High-Dose Chemotherapy Combining Topotecan plus Cyclophosphamide with Hematopoietic Stem Cell Transplantation for Ovarian Cancer: The ITOV 01bis Study.	Selle F et al.	Chemotherapy	http://www.ncbi.nlm.nih.gov/pubmed/26528705
2	A phase I trial of pegylated liposomal doxorubicin (PLD), carboplatin, bevacizumab and veliparib in recurrent, platinum-sensitive ovarian, primary peritoneal, and fallopian tube cancer: An NRG Oncology/Gynecologic Oncology Group study.	Landrum LM et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26616225
3	Efficacy of trebananib (AMG 386) in treating epithelial ovarian cancer.	Al Wadi et al.	Expert Opin Pharmacother.	http://www.ncbi.nlm.nih.gov/pubmed/26933765
4	Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial.	Ledermann et al.	Lancet	http://www.ncbi.nlm.nih.gov/pubmed/27025186
5	ICON-6: the danger of changing study design midstream	Norrie J	Lancet	http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00658-9/abstract
6	Intensive cisplatin/oral etoposide for epithelial ovarian cancer: the Cambridge Gynae-Oncology Centre experience: too toxic for relapse?	Gounaris et al.	Anticancer Drugs	http://www.ncbi.nlm.nih.gov/pubmed/26575000
7	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
8	Poor concordance between CA-125 and RECIST at the time of disease progression in patients with platinum-resistant ovarian cancer: analysis of the AURELIA trial.	Lindemann K et al.	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27407100
9	Is CA125 useful in monitoring patients with platinum-resistant ovarian cancer?	Rustin G et al.	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27358387
10	Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer	Mirza et al.	NEJM	https://www.ncbi.nlm.nih.gov/pubmed/ 27717299

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Treatment of ovarian sex cord stromal and germ cell tumours

Editor Anna Dueckelmann

Descriptive summary

Zhao et al. present retrospective data on 130 patients affected by malignant ovarian germ cell tumours, eight of them bilaterally. The selected treatment modalities should depend on the histological type of the tumour. Fertility-sparing surgery may be safe for patients affected by dysgerminoma; for primary ovarian choriocarcinoma the decision to preserve fertility may be associated with significant risks. However, the authors base this conclusion on two patients, one with dysgerminoma and one with choriocarcinoma.

The retrospective analysis of ovarian yolk sac tumours by De la Motte Rouge et al. demonstrates that the presence of ascites at diagnosis and an unfavourable early AFP decline in affected patients after surgery and chemotherapy are significant negative predictive factors for overall survival.

In an epidemiological study of Hinchcliff et al. based on the National Cancer Database it was demonstrated that, in the U.S., African Americans with ovarian germ cell tumours have significantly worse five-year survival when compared to white patients, despite similar rates and modalities of adjuvant treatment. The authors discuss the potential impact of social, environmental, and biological factors on the persistent racial disparities.

Steroid cell tumours not otherwise specified are rare and classified as sex cord stromal tumours. The case presented by Sood et al. emphasizes the importance of clinical suspicion for an occult testosterone-secreting ovarian tumour in a symptomatic woman without an obvious ovarian mass on radiologic studies. Prompt surgical management (bilateral salpingo-oophorectomy) can lead to complete resolution of virilising symptoms such as gradually progressive hirsutism, acne, deepening of voice, temporal baldness, amenorrhea, and an increase in libido, as well as normalization of excess testosterone levels within weeks.

In view of the rarity of Sertoli-Leydig cell tumours (SLCT), the majority of studies are case studies or case series. Fifteen per cent of SLCTs are designated retiform. They are found only in intermediate and poorly differentiated SLCTs and in younger patients and have a worse prognosis than SLCTs in general. Turkyilmaz et al. present a case of an 8-year-old girl who was treated initially by fertility-sparing unilateral salpingo-oophorectomy. A relapse ten months later was again treated by complete, but still fertility-preserving, removal. The patient received chemotherapy for another relapse three months later.

Another case of SLCT with retiform areas and heterologous elements is presented by Burnik Papler et al. A 70-year-old woman with a multilocular adnexal tumour and elevated CA 125 level received a complete cytoreduction without any adjutant treatment. The patient died of disease recurrence seven months later.

In SLCTs with retiform pattern, a primary surgical procedure should be considered as the first treatment choice. Follow-up care is necessary because of recurrence risk in the first year after surgery. Chemotherapy should be considered only in recurrence in advanced-stage and metastatic cases. However, there is no good evidence that postoperative adjuvant chemotherapy is effective in preventing recurrence of malignant SLCTs.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Management of bilateral malignant ovarian germ cell tumours: Experience of a single institute	Zhao T et al.	Molecular and clinical oncology	http://www.ncbi.nlm.nih.gov/pubmed/27446585
2	Prognostic significance of an early decline in serum alpha-fetoprotein during chemotherapy for ovarian yolk sac tumours	de la Motte Rouge T et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27401840
3	Racial disparities in survival in malignant germ cell tumours of the ovary	Hinchcliff E et al.	Gynecologic Oncology	http://www.ncbi.nlm.nih.gov/pubmed/26773470
4	Germ Cell Tumors in Adolescents and Young Adults	Calaminus G et al.	Prog Tumor Res	http://www.ncbi.nlm.nih.gov/pubmed/27595361
5	Sertoli - Leydig cell tumour with retiform areas and overgrowth of rhabdomyosarcomatous elements: case report and literature review	Burnik Papler T et al.	J Ovarian Res	http://www.ncbi.nlm.nih.gov/pubmed/27473538
6	Symptomatic ovarian steroid cell tumour not otherwise specified in a post-menopausal woman	Sood N et al.	Rare Tumors	http://www.ncbi.nlm.nih.gov/pubmed/27441075
7	Recurrent Sertoli–Leydig cell tumour of ovary in 8-year-old girl	Turkyilmaz Z et al.	Scottish Medical Journal	http://www.ncbi.nlm.nih.gov/pubmed/27334531
8	Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy for recurrent adult granulosa cell tumour: A case report	Dogan A et al.	Gynecologic Oncology Reports	http://www.ncbi.nlm.nih.gov/pubmed/27331130

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

Editor Muhammad Rizki Yaznil

Descriptive summary

Petrillo et al. have listed and classified the recently available evidence of targeted therapy and research in ovarian cancer according to the Hannahan and Weinberg "Hallmark of Cancer" and propose genomic instability, angiogenesis, and inflammatory state as main targets in high-grade ovarian cancer. This report summarizes in particular papers on research relevant to these hallmarks.

Genomic instability

PARP enzymes play an important role in base excision DNA repair. Inhibition of PARP results in single-strand DNA breaks and, ultimately, double-strand DNA breaks. In normal cells, these breaks are repaired by HR (homologous recombination) DNA repair pathway, but in BRCA1/2 mutated cells, these double-strand breaks cannot be repaired, which results in cell death. RAD52 is a member of the HR pathway that is important for maintenance of genome integrity. While single RAD52 mutations show no significant phenotype in mammals, their combinations with mutations in genes like BRCA1, BRCA2, PALB2, and RAD51C are lethal, so inhibition of RAD52 in combination with PARPi in BRCA-deficient cancer seems logical. Huang et al. report on compounds that specifically inhibit the biochemical activities of RAD52, suppress growth of BRCA1 and BRCA2 deficient cells and inhibit RAD52-dependent single-strand annealing (SSA) in human cells.

The most commonly recurrent genetic event in Ovarian Clear Cell Cancer (OCCC) is somatic mutation in the tumour suppressor gene ARID1A. Using a series of high-throughput cell-based drug screens in OCCC tumour cell models, Miller et al. have identified a synthetic lethal interaction between the kinase inhibitor dasatinib and a key driver (YES1) in ARID1A mutated OCCC.

Sustained proliferative signalling and evasion of growth suppressors

Takahashi et al. reported on the use of lurbinectedin, which is derived from trabectedin in ovarian clear cell carcinoma, and its combination with everolimus (mTOR inhibitor). Oda et al. reviewed the functions and alterations of TP53 signalling and RAS/PI3K signalling, with particular focus on endometrial and ovarian cancers and discuss the molecular-targeted drugs currently investigated in clinical trials. These drugs include dual phosphatidylinositol 3 kinase/mTOR inhibitors (NVP-BEZ235, DS-7423, SAR245409), an mTOR inhibitor (everolimus), a MEK inhibitor (pimasertib), an autophagy inhibitor (chloroquine), a cyclin-dependent kinases 4/6 inhibitor (PD0332991), and a poly (ADP-ribose) polymerase inhibitor (olaparib).

McLachlan et al. reviewed MAPK pathway in low-grade serous ovarian cancer.

Evasion of immune response and angiogenesis

Nuclear factor-kappa beta is a ubiquitous transcription factor that regulates the expression of various genes associated with immune responses, the cell cycle, and apoptosis. NF kappa beta is activated in ovarian cancers and is associated with cell proliferation, suppression of apoptosis, angiogenesis, metastasis, and chemoresistance. NF-kappa activation requires phosphorylation of inhibitor of kappa beta by the I-kappa beta kinase (IKK) complex. MD-0560 is a newly synthesized low-molecular-weight compound that selectively inhibits IKK beta in the IKK complex and showed promising therapeutic efficacy against ovarian cancer xenograft mice by inducing cell-cycle arrest and suppressing VEGF production from cancer cells (Sawada et al.).

Energy metabolism

Metformin leads to an imbalance in the AMP/ATP ratio and activates the master metabolic regulator AMPK (Adenosine Monophosphate-activated Kinase), resulting in inhibition of energy-consuming biosynthetic pathways like protein and nucleotide synthesis. Hijaz et al. found that combining PARP inhibitor (olaparib) with metformin enhances its antiproliferative activity in BRCA mutant ovarian cancer cells and also showed significant activity in BRCA wild-type cancer cells in vivo and in vitro.

Gadducci et al. reviewed the use of metformin in gynaecological cancer.

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

- Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Targeting the hallmarks of ovarian cancer: The big picture	Petrillo M et al.	Gynecologic Oncology	http://www.ncbi.nlm.nih.gov/pubmed/27058837
2	Targeting BRCA1- and BRCA2-deficient cells with RAD52 small molecule inhibitors	Huang F et al.	Nucleic Acid Research	http://www.ncbi.nlm.nih.gov/pubmed/26873923
3	Synthetic Lethal Targeting of ARID1A-Mutant Ovarian Clear Cell Tumors with Dasatinib	Miller RE et al.	Molecular Cancer Therapeutics	http://www.ncbi.nlm.nih.gov/pubmed/27364904
4	Preclinical Investigations of PM01183 (Lurbinectedin) as a Single Agent or in Combination with Other Anticancer Agents for Clear Cell Carcinoma of the Ovary	Takahashi R et al.	PloS One	http://www.ncbi.nlm.nih.gov/pubmed/26986199
5	Characterization of TP53 and PI3K signaling pathways as molecular targets in gynecologic malignancies	Oda K et al.	The Journal of Obstetrics and Gynaecology Research	http://www.ncbi.nlm.nih.gov/pubmed/27094348
6	Targeting the mitogen-activated protein kinase pathway in low-grade serous carcinoma of the ovary	McLachlan J et al.	Pharmacogenomics	http://www.ncbi.nlm.nih.gov/pubmed/27469379
7	The Novel IkappaB Kinase beta Inhibitor, IMD-0560, Has Potent Therapeutic Efficacy in Ovarian Cancer Xenograft Model Mice	Sawada I et al.	International Journal Gynecologic Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26905334
8	Preclinical evaluation of olaparib and metformin combination in BRCA1 wildtype ovarian cancer	Hijaz M et al.	Gynecologic Oncology	http://www.ncbi.nlm.nih.gov/pubmed/27282964
9	Metformin use and gynecological cancers: A novel treatment option emerging from drug repositioning	Gadducci A et al.	Critical Reviews in Oncology/Hematology	http://www.ncbi.nlm.nih.gov/pubmed/27378194
10	Rational selection of biomarker driven therapies for gynecologic cancers: The more we know, the more we know we don't know	Liu J et al.	Gynecologic Oncology	http://www.ncbi.nlm.nih.gov/pubmed/27016231
11	Genetic and epigenetic heterogeneity of epithelial ovarian cancer and the clinical implications for molecular targeted therapy.	Bai H et al.	Journal of Cellular and Molecular Medicine	http://www.ncbi.nlm.nih.gov/pubmed/26800494
12	Targeting the tumour microenvironment in ovarian cancer	Hansen JM et al.	European Journal of Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26849037
13	Therapeutic targets and new directions for antibodies developed for ovarian cancer	Bax HJ et al.	mAbs	http://www.ncbi.nlm.nih.gov/pubmed/27494775

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

Editor Sara Giovannoni

Descriptive summary

PARP inhibitors

Hijaz et al. report on a preclinical trial investigating the combination of olaparib and metformin in BRCA1 wild-type ovarian cancer. Ovarian cancer cell lines and xenografts models were treated with this combination with a significant reduction of cell proliferation and colony formation ($p<0.001$) compared to either of the drugs alone. The combination enhanced antiproliferative activity in BRCA mutant ovarian cell lines and showed significant activity in BRCA wild-type cancer cells in vitro and in vivo. This treatment approach seems promising for women with ovarian cancer independently of BRCA status. [1]

Moore and Monk published a very useful review on the management of symptoms during olaparib therapy for recurrent ovarian cancer. They focused on interventions to address adverse events in patients treated with olaparib and allow them to remain on therapy and improving the quality of life. [2]

Zhang et al. report the copy number of RAD50 (RAD50 deletion) to be a candidate marker for survival and response to PARP inhibitors in BRCA wild-type ovarian cancer. They analysed 220 BRCA wild-type ovarian cancer patients in TCGA. Those exhibiting the BRCAness signature had, as expected, improved OS and PFS (HR 0.33; p=0.004/ HR 0.51- p=0.077, respectively). RAD50 deletion was identified as a marker of BRCAness occurring in 18 % of BRCA wild-type ovarian cancer patients. It was associated with a better OS (HR 0.44) and PFS (HR 0.60). The role of RAD50 deletion in predicting ovarian cancer cell's response to olaparib and platinum should be explored in prospective trials. [3]

Trabectedin

Lorusso et al. published the final results of the MITO15 trial. The phase II single arm –study enrolled 100 patients with recurrent BRCA-mutated ovarian cancer and/or BRCAness phenotype (≥ 2 previous response to platinum) to receive single agent Trabectedin every three weeks. The ORR was 39.4 %. In the platinum-resistant and -sensitive patients the ORR was 31.2 % and 47.8 %, respectively. Median PFS was 18 weeks and OS 72 weeks. There was no difference in ORR, PFS, and OS according to BRCA 1-2 status or BRCAness phenotype, but also considerable myelo- and liver toxicity. The signature of "repeated platinum sensitivity" identified patients responsive to trabectedin, and the authors suggest it as a potential alternative in patients with contraindications to platinum. The results have prompted the design of MiTO23 exploring trabectedin in a randomised trial compared to chemotherapy of the physician's choice. [4]

Fertility BRCA-carriers patients

Giordano et al. evaluated 124 women without prior cancer and studied the association between BRCA status and AMH levels (anti-müllerian hormone) as a marker for ovarian reserve. A significant decline in AMH in patents with BRCA1 mutation ($p = 0.0011$) was noted. Furthermore, BRCA1 positive women > 35 years had ten times the odds of a low AMH compared with women < 35 years. The potential decrease in ovarian reserve should be considered when counselling these patients. (E.g., risk-reducing surgery.) [5]

Gronwald et al. conducted a matched case-control study of 941 women, the association of the use of fertility medication (i.e., selective oestrogen receptor modulator) or infertility treatment and the risk of ovarian cancer among BRCA1- or BRCA2-carrier women. Their findings suggest that treatment for infertility does not increase the risk of ovarian cancer in this population. [6] More papers are listed below for the interested reader.

The list of references contains a few more interesting publications on this topics.

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

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Preclinical evaluation of olaparib and metformin combination in BRCA1 wildtype ovarian cancer	Hijaz M et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27282964
2	Patient Counseling and Management of Symptoms During Olaparib Therapy for Recurrent Ovarian Cancer.	Moore KN et al.	Oncologist.	http://www.ncbi.nlm.nih.gov/pubmed/27256873
3	Copy number deletion of RAD50 as predictive marker of BRCAness and PARP inhibitor response in BRCA wild type ovarian cancer.	Zhang M et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27016230
4	Prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients: the MITO 15 trial.	Lorusso D et al.	Ann Oncol.	http://annonc.oxfordjournals.org/content/early/2015/12/16/annonc.mdv608
5	Association of BRCA1 Mutations with Impaired Ovarian Reserve: Connection Between Infertility and Breast/Ovarian Cancer Risk.	Giordano S et al.	J Adolesc Young Adult Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27513691
6	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
7	PARP inhibition and gynecologic malignancies: A review of current literature and on-going trials	Crafton SM et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27168003
8	Homologous recombination deficiency and ovarian cancer.	Ledermann JA et al.	Eur J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27065456
9	Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for post-progression poly(adenosine diphosphate ribose) polymerase inhibitor therapy.	Matulonis UA et al.	Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27062051
10	BRCA1/2 mutations associated with progression-free survival in ovarian cancer patients in the AGO-OVAR 16 study.	Harter P et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26740259
11	The effect of referral for genetic counseling on genetic testing and surgical prevention in women at high risk for ovarian cancer: Results from a randomised controlled trial.	Drescher CW et al.	Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27447168
12	MK-2206 sensitizes BRCA-deficient epithelial ovarian adenocarcinoma to cisplatin and olaparib	Whicker ME et al.	BMC Cancer.	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4964088/
13	Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer.	Drew Y et al.	Br J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27002934
14	Effects of lifestyle intervention in BRCA1/2 mutation carriers on nutrition, BMI, and physical fitness (LIBRE study): study protocol for a randomised controlled trial.	Kiechle M et al.	Trials.	http://www.ncbi.nlm.nih.gov/pubmed/27473440
15	Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer.	Hartmann LC et al.	N Engl J Med.	http://www.ncbi.nlm.nih.gov/pubmed/27305204
16	Recommendations for the implementation of BRCA testing in the care and treatment pathways of ovarian cancer patients.	Pinto C et al.	Future Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27241581
14	Effects of lifestyle intervention in BRCA1/2 mutation carriers on nutrition, BMI, and physical fitness (LIBRE study): study protocol for a randomised controlled trial.	Kiechle M et al.	Trials.	http://www.ncbi.nlm.nih.gov/pubmed/27473440
15	Risk-Reducing Surgery in Hereditary Breast and Ovarian Cancer.	Hartmann LC et al.	N Engl J Med.	http://www.ncbi.nlm.nih.gov/pubmed/27305204
16	Recommendations for the implementation of BRCA testing in the care and treatment pathways of ovarian cancer patients.	Pinto C et al.	Future Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27241581

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

Relevant articles retrieved Feb 2016 - Sep 2016 (cont.)

No	Title	Authors	Journal	Link to abstract
17	Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review.	Ludwig KK et al.	Am J Surg.	http://www.ncbi.nlm.nih.gov/pubmed/27649974
18	Olaparib for Maintenance Treatment of BRCA 1 or 2 Mutated, Relapsed, Platinum-Sensitive Ovarian, Fallopian Tube and Peritoneal Cancer in People Whose Relapsed Disease has Responded to Platinum-Based Chemotherapy: An Evidence Review Group Perspective of a NICE Single Technology Appraisal.	Tappenden P et al.	Pharmacoeconomics.	http://www.ncbi.nlm.nih.gov/pubmed/27506954
19	An Update on Poly(ADP-ribose)polymerase-1 (PARP-1) Inhibitors: Opportunities and Challenges in Cancer Therapy.	Wang YQ et al.	J Med Chem.	http://www.ncbi.nlm.nih.gov/pubmed/27416328
20	Changes of Socio-demographic data of clients seeking genetic counseling for hereditary breast and ovarian cancer due to the "Angelina Jolie Effect".	Staudigl C et al.	BMC Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27391110
21	PARP inhibitors in ovarian cancer.	Ledermann JA	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27141070
22	Progress in the treatment of ovarian cancer-lessons from homologous recombination deficiency-the first 10 years.	Kaye SB	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27141062
23	Evaluation of rucaparib and companion diagnostics in the PARP inhibitor landscape for recurrent ovarian cancer therapy.	Jenner ZB et al.	Future Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27087632
24	Fertility preservation in BRCA mutation carriers.	Revelli A et al.	Minerva Ginecol.	http://www.ncbi.nlm.nih.gov/pubmed/26997146
25	Veliparib for the treatment of ovarian cancer.	Bogliolo S et al.	Expert Opin Investig Drugs.	http://www.ncbi.nlm.nih.gov/pubmed/26807493
26	Olaparib for the treatment of BRCA-mutated advanced ovarian cancer.	Munroe M et al.	Am J Health Syst Pharm.	http://www.ncbi.nlm.nih.gov/pubmed/27385701
27	The status of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors in ovarian cancer, part 1: olaparib.	Miller RE et al.	Clin Adv Hematol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27487106
28	Olaparib for the treatment of epithelial ovarian cancer.	McLachlan J et al.	Expert Opin Pharmacother.	http://www.ncbi.nlm.nih.gov/pubmed/26967466
29	Olaparib monotherapy in patients with advanced relapsed ovarian cancer and a germline BRCA1/2 mutation: a multistudy analysis of response rates and safety.	Matulonis UA et al.	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26961146

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

Editor Santiago Scasso

Descriptive summary

Smogeli et al., in their retrospective study on 388 patients, failed to present L1 cell adhesion molecule (L1CAM) as a clinically relevant marker of poor prognosis in stage I endometrioid endometrial carcinoma. In a subgroup analysis of patients who had not received adjuvant chemotherapy, they found L1CAM expression significantly associated with disease-free survival. They reported that >10 % L1CAM staining defined as positive was associated with a more aggressive tumour type and more distant relapses. [1]

Köbel et al. reported the association of HR expression with overall survival from the Canadian High Risk Endometrial Cancer (CHREC) Consortium, with 541 patients included in a prospective multicentre study. Progesterone receptor expression was significantly associated with favourable overall survival in endometrioid grade 3, independent of age, stage, and lymph-vascular invasion (HR=0.457, 95 % CI 0.257–0.811, p = 0.0075) as well as in low-stage endometrial serous carcinomas (HR = 0.266, 95 % CI 0.094–0.750, p=0.0123). These data provide support for the assessment of the PR expression status in EC3 and ESC. Future work will be required to determine how PR expression may be incorporated into management of patients with EC3 and ESC. [2]

Rodriguez-Rodriguez et al. reported that the comprehensive genomic profiling (CGP) of tumour somatic molecular alterations reviewed by members of institutional molecular tumour board (MTB) might generate clinical recommendations. Evaluation of genomic and clinical data by the MTB led to the generation of targeted treatment options in all 64 patients (25 with EC), and the percentage of patients for whom one or more of these recommendations were implemented by the treating physician was 39 %. Sixty-four per cent of the patients receiving targeted therapy based on a CGP result experienced radiologic response or showed evidence of clinical benefit or stable disease. [3]

The April volume of Gynecologic Oncology was dedicated to the concept of "Precision Medicine" for the study of gynaecologic cancers. A few articles dedicated to EC defines to use tumour genomic, proteomic, and transcriptomic information to prevent, diagnose, or treat that disease. [4]

Morice et al. in their review not only reported current practice and recent trials of surgery, adjuvant treatment, and novel targeted therapies in endometrial cancer (EC) but also described its pathogenesis, histological, and molecular classification. [5]

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	L1CAM as a prognostic marker in stage I endometrial cancer: a validation study.	Smogeli E et al.	BMC Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27488577
2	Progesterone receptor expression is associated with longer overall survival within high-grade histotypes of endometrial carcinoma: A Canadian high risk endometrial cancer consortium (CHREC) study.	Köbel M et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27072807
3	Precision medicine	Coleman RL et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/27016221
4	Use of comprehensive genomic profiling to direct point-of-care management of patients with gynecologic cancers.	Rodriguez-Rodriguez L et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27016222
5	Endometrial cancer.	Morice P et al.	Lancet.	http://www.ncbi.nlm.nih.gov/pubmed/26354523

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Screening for uterine cancer/ hereditary uterine cancer

Editor María de los Reyes Oliver Pérez

Descriptive summary

Screening for uterine cancer

Commonly used techniques to access the endometrium include transvaginal ultrasound (TVUS), endometrial sampling, saline infusion sonography, and hysteroscopy.

TVUS and endometrial thickness (ET) in asymptomatic postmenopausal women.

Kim et al. determined in their retrospectives cohort study including 14,340 TVUS examinations, that endometrial stripe abnormality was significantly associated with EC (whereas thickened endometrium was not) in premenopausal and perimenopausal women. [1] This finding was also supported by Yasa et al. Sladkevicius et al. prospectively validated two mathematical models for calculating the likelihood of endometrial malignancy in patients with postmenopausal bleeding (PMPB), sonographic endometrial thickness (ET) ≥4.5 mm, and no fluid in the uterine cavity. The sensitivity and specificity ranged between 70 % - 79 % and 81 % - 93 %, respectively. [3]

Hysteroscopy

Ianieri et al. retrospectively evaluated all videos of diagnostic hysteroscopies performed before endometrial biopsies to note endometrial morphologic parameters suggestive of pathology. [4] The proposed scoring system showed a sensitivity and specificity of 63.3 % and 90.4 %, and 95.4 % and 98.2 % regarding atypical endometrial hyperplasia (AEH) and EC, respectively.

Endometrial sampling

The identification of biomarkers in uterine aspirate samples, which are collected during a minimally invasive procedure, would improve early diagnosis of EC. Martinez-García et al. present a sequential workflow to select EC biomarkers to enter a validation study. [5] The differential abundance of 26 biomarkers was observed and ten proteins showed a high sensitivity and specificity in the differentiation of 20 EC patients and eighteen non-EC controls. Heng et al. suggested that the determination of proprotein convertase activity in endocervical swabs may provide a simple, non-invasive and novel method to detect endometrial cancer in post-menopausal women. [6]

Hereditary uterine cancer (HUC)

In the period covered by the 4th edition of the LiFE report, seven literature reviews on screening of HUC have been found. Four of them are focused on Lynch syndrome (LS) [7-10] and the remaining three on all HUC [11-13]

The screening of EC for LS remains a subject of debate. Mills et al. discuss the rationales of current LS screening tests for endometrial and ovarian cancers and provides pathologists with an informed approach to LS testing in gynaecologic cancers (also see report on Pathology/pathogenesis of malignant ovarian tumours by D. Vatansever). [7-8] Hampel et al. emphasize the importance of detecting as many individuals with LS as possible. [9] This includes cascade testing among the at-risk relatives of those diagnosed with LS. Djordjevic et al. review the main tissue testing modalities for LS in the pathology laboratory, such as immunohistochemistry and PCR-based analyses and discusses their routine application. [10]

The National Comprehensive Cancer Network has published its clinical practice guidelines in genetic high-risk assessment for colorectal cancer (CR). [14] It reviews clinical criteria for LS and the management of these patients in screening in both CR and EC.

EC is associated with Lynch syndrome in 2 % to 6 % of cases. Douglas et al. retrospectively found seven of 328 (2.1 %) EC potentially associated with LS by using a targeted approach with combined age, morphology, and family history criteria. [15]

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Screening for uterine cancer/ hereditary uterine cancer

- Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Endometrial evaluation with transvaginal ultrasonography for the screening of endometrial hyperplasia or cancer in premenopausal and perimenopausal women	Min-Jeong K et al.	Obstet Gynecol Sci.	http://www.ncbi.nlm.nih.gov/pubmed/27200309-200
2	Evaluation of the diagnostic role of transvaginal ultrasound measurements of endometrial thickness to detect endometrial malignancy in asymptomatic postmenopausal women	Cenk Y et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/26946152
3	Prospective validation of two mathematical models to calculate the risk of endometrial malignancy in patients with postmenopausal bleeding and sonographic endometrial thickness _4.5 mm	Sladkevicius P et al.	Eur J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27043175
4	A New Hysteroscopic Risk Scoring System for Diagnosing Endometrial Hyperplasia and Adenocarcinoma	Ianieri MM et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26940400
5	Development of a sequential workflow based on LC-PRM for the verification of endometrial cancer protein biomarkers in uterine aspirate samples	Martinez-Garcia E et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/27447978
6	Measuring PC activity in endocervical swab may provide a simple and non-invasive method to detect endometrial cancer in post-menopausal women	Heng S et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/27374098
7	Lynch Syndrome Female Genital Tract Cancer Diagnosis and Screening	Mills AM et al.	Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/27241104
8	Lynch Syndrome Screening in the Gynecologic Tract. Current State of the Art	Mills AM et al.	Am J Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26872009-44.
9	Genetic counseling and cascade genetic testing in Lynch syndrome	Hampel H.	Fam Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26969309
10	Laboratory Assays in Evaluation of Lynch Syndrome in Patients with Endometrial Carcinoma	Djordjevic B et al.	Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/27241109
11	The genetic prediction of risk for gynecologic cancers	Randall LM et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27016223
12	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
13	Prophylactic Gynecologic Specimens from Hereditary Cancer Carriers	Shaw PA et al.	Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/27241111
14	Genetic/Familial High-Risk Assessment: Colorectal Version 1.2016	Provenzale D et al.	JNCCN.	http://www.ncbi.nlm.nih.gov/pubmed/27496117
15	Targeted Screening With Combined Age- and Morphology-Based Criteria Enriches Detection of Lynch Syndrome in Endometrial Cancer	Lin DI et al.	Int J Surg Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26842347
16	Analysis of Lynch Syndrome Mismatch Repair Genes in Women with Endometrial Cancer	Rubio I et al.	Oncology.	http://www.ncbi.nlm.nih.gov/pubmed/27398995

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

Editor Dr. Kastriot Dallaku and Dr. Elko Gliozheni

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 (EH)

Wise et al. reported that obesity is a risk factor for complex EH, and body mass index (BMI) should be an indicator for the decision to perform endometrial biopsy. [1] Also, Guraslan et al. concluded that women with abnormal bleeding and BMI ≥30, should undergo an endometrial biopsy. [2] Kubyshkin et al. suggested that inflammation may be considered as a factor in the promotion of progression from simple to complex EH. [3]

A new hysteroscopic scoring system for a differential diagnosis between EH and cancer was suggested by to by Ianieri et al.. It resulted in a good diagnostic performance, especially for less experienced surgeons. [4]

A metaanalysis by Bourdel et al. evaluated the accuracy of the method of endometrial sampling for the diagnosis of complex endometrial hyperplasia and found that hysteroscopic resection reduced the risk of underdiagnosed endometrial cancer. [5, 6]

A randomised controlled trial evaluated the effectiveness of hysteroscopy compared to expectant management in postmenopausal bleeding related to the detection and treatment of endometrial malignancies. Van Hanegem et al. concluded that, in women with postmenopausal bleeding, hysteroscopy does not decrease the recurrent bleeding but it may detect malignant lesions missed by blind endometrial sampling. [7]

Moschos et al. evaluated the sensitivity and specificity of saline infusion sonography (SIS) and SIS endometrial sampling (SISES) for benign and malignant lesions of the endometrium. The authors concluded that SISES might increase the specificity of diagnosis for malignant endometrial lesions. [8]

El Sharkawy et al. studied the efficacy of 3D ultrasonography and power Doppler for differential diagnosis between benign and malignant endometrial lesions in premenopausal abnormal bleeding. [9] The authors inferred that 3D ultrasonography and power Doppler (especially endometrial vascularization index) can help in differentiation between benign and malignant endometrium.

A systematic review of studies from 1990 to 2015 by de Rijk et al. estimated the risk of concurrent endometrial cancer in atypical endometrial polyps. After resection of an atypical endometrial polyp, the risk of endometrial cancer was estimated to be 5.6 %. [10] This is important in the context of patients' follow-up and further treatment.

Conservative and definitive treatment for patients with endometrial hyperplasia

The incidence of post-operative infections and the efficacy of antibiotic prophylaxis before hysteroscopy procedures were evaluated in the randomised controlled trial conducted by Muzii et al. The results of this study suggested that routine antibiotic prophylaxis was not beneficial. [11]

The risk of relapse of the endometrial hyperplasia and the risk of progression to endometrial cancer was reviewed by Gallos. [12]

Women identified to be in a high-risk group of relapse or progression to endometrial cancer were: Obese, under hormonal treatment, refusing to receive hormonal or surgical treatment, and women with atypical or complex EH. These women should undergo long-term endometrial hyperplasia surveillance. Kim et al., report their prospective multicentre study compromising 75 patients and showed that the Levonorgestrel intrauterine system is an effective and favourable method for treatment of EH. [13]

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

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Clinical Characteristics and Prognosis of Unexpected Uterine Sarcoma After Hysterectomy for Presumed Myoma With and Without Transvaginal Scalpel Morcellation.	Zhang et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26807642
2	Risk of Occult Uterine Sarcoma in Presumed Uterine Fibroids.	Cui et al.	Clin Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26645385
3	Uterine Sarcoma: Analysis of 13,089 Cases Based on Surveillance, Epidemiology, and End Results Database.	Hosh et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27177280
4	Impact of chemotherapy in uterine sarcoma (UtS): review of 13 clinical trials from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) involving advanced/metastatic UtS compared to other soft tissue sarcoma (STS) patients treated with first line chemotherapy.	Ray-Coquard et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27208537
5	Japan Society of Gynecologic Oncology guidelines 2013 for the treatment of uterine body neoplasms.	Ebina et al.	Int J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27116188
6	Cytoreductive Surgery and HIPEC as a Treatment Option for Laparoscopic Resection of Uterine Leiomyosarcoma with Morcellation: Early Results.	Sugarbaker et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26545375
7	Laparoscopic surgery on broken points for uterine sarcoma in the early stage decrease prognosis.	Liu et al.	Sci Rep.	http://www.ncbi.nlm.nih.gov/pubmed/27503773
8	N-of-1 Policymaking--Tragedy, Trade-offs, and the Demise of Morcellation	Rosenbaum et al.	N Engl J Med.	http://www.ncbi.nlm.nih.gov/pubmed/26962735
9	Uterine leiomyosarcoma and endometrial stromal sarcoma have unique miRNA signatures.	Ravid et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26768834
10	Progesterone Receptor Expression Is an Independent Prognosticator in FIGO Stage I Uterine Leiomyosarcoma.	Davidson et al.	Am J Clin Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/27149024
11	May Sonic Hedgehog proteins be markers for malignancy in uterine smooth muscle tumors?	Garcia et al.	Hum Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26997437
12	Uterine Sarcoma Treatment (PDQ®): Patient Version.	PDQ Adult Treatment Editorial Board.	PDQ Cancer Information Summaries. Bethesda: National Cancer Institute	http://www.ncbi.nlm.nih.gov/pubmed/27441353

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

Surgical treatment of primary uterine cancer

Editor Piotr Lepka

Descriptive summary

Uterine manipulator in endometrial cancer (EC)

In their retrospective study, Tinelli et al. compared results of total laparoscopic hysterectomy with systematic lymphadenectomy performed with or without uterine manipulator. During a mean follow-up of 38.5 months, they found that the rate of positive cytology and LVSI did not significantly differ between the groups. Also, it didn't influence the recurrence rate (RR).

Laparotomy vs. minimal invasive surgery

Marcos-Sanmartin et al. prospectively compared patients with EC (FIGO stage I) undergoing open and laparoscopic total hysterectomy. After 60 months of follow-up both, neither group differed in cumulative RR and overall survival (OS). Also Chu et al. found no significant difference in recurrence rate when comparing two techniques in another retrospective study. Guy et al. compared robotic surgery with laparotomy in nearly 17,000 women with EC. They showed the superiority of a robotic approach in a group of patients over 65 years old, in terms of perioperative complications, shorter length of stay, and higher discharge-to-home rates. Jason et al. retrospectively compared patients with FIGO stage I-III EC who underwent abdominal hysterectomy and minimal invasive method. Abdominal approach reveals a statistically higher overall complication rate and perioperative mortality. In the group treated with minimal invasive techniques, women were more likely to receive adjuvant pelvic radiation and brachytherapy. Those groups did not differ in OS and cancer-specific mortality.

Ablative procedures and EC

Singh et al. conducted a retrospective observational study examining the long-term incidence of EC in premenopausal women who had endometrial ablative procedures due to dysfunctional uterine bleeding. In the median follow-up of ten years, none of the included patients developed endometrial cancer. The authors suggested that incidence of endometrial cancer in patients who had endometrial ablation was much lower than in the general population. (0 % vs. 2-3 %).

Role of lymphadenectomy

Yoon et al. retrospectively evaluated 151 patients with FIGO stage IIIC EC that underwent total hysterectomy with pelvic lymph node dissection in all cases. Paraaortic lymph node dissection (PALND) was performed in 44.4 % of patients. Adjuvant radiotherapy (RT) or radiochemotherapy (CHRT) was given. The group with adjuvant RT and paraaotic lymph node dissection were affected statistically as follows: five-year disease-free survival (90.2 % vs. 58.9 %; p=0.16) and overall survival (100 % vs. 83.1 %; p=0.022). In the group with adjuvant CHRT, disease-free and overall survival did not differ statistically. PALND reduced the risk of paraaortic recurrence (0 % vs. 17.1 %) and distant metastasis (4.5 % vs. 19.5 %) in patients treated with adjuvant RT alone.

Less extensive PALND was associated with significantly increased paraaortic recurrence rates (≤10 vs. >10 dissected LNs; 17.1 % vs. 0 %) in patients with advanced tumour features treated with adjuvant CTRT.

Compartmental surgery

Kimming et al., based on clinical results and follow-up of their series of 68 consecutive patients (FIGO stage IAG1-IVBG3) treated by robotically assisted laparoscopy (different extent of surgical treatments), evaluated the feasibility and efficacy of embryologically based compartmental surgery for locoregional tumor control in intermediate and high-risk endometrial cancer. Eight patients (11.8 %) were treated with adjuvant radiation therapy instead of 56 % of the patients who should have been treated according ASTRO/ASCO Guidelines with respect to prevention of loco-regional recurrence. After 32 months (mean) of observation eight recurrences (2 loco-regional and 6 distant metastases) were observed (11.8 %). In the conclusions authors suggested to evaluate this concept in endometrial cancer in a multicentric approach.

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Surgical treatment of primary uterine cancer

- Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Laparoscopic treatment of early-stage endometrial cancer with and without uterine manipulator: Our experience and review of literature.	Tinelli R et al.	Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/27312035
2	Does the Type of Surgical Approach and the Use of Uterine Manipulators Influence the Disease-Free Survival and Recurrence Rates in Early-Stage Endometrial Cancer?	Marcos-Sanmartín J et al.	Int J Gynecol Cancer.	https://www.ncbi.nlm.nih.gov/pubmed/27518143
3	Comparison of the laparoscopic versus conventional open method for surgical staging of endometrial carcinoma.	Chu LH et al.	Taiwan J Obstet Gynecol.	https://www.ncbi.nlm.nih.gov/pubmed/27125400
4	Comparative outcomes in older and younger women undergoing laparotomy or robotic surgical staging for endometrial cancer.	Guy MS et al.	Am J Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/26433173
5	Is endometrial ablation protective against endometrial cancer? A retrospective observational study.	Singh M et al.	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/26498760
6	Impact of paraaortic lymphadenectomy for endometrial cancer with positive pelvic lymph nodes: A Korean Radiation Oncology Group study (KROG 13-17).	Yoon MS et al.	Eur J Surg Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27450638
7	Embryologically based radical hysterectomy as peritoneal mesometrial resection (PMMR) with pelvic and para-aortic lymphadenectomy for loco-regional tumour control in endometrial cancer: first evidence for efficacy.	Kimming R et al.	Arch Gynecol Obstet.	https://www.ncbi.nlm.nih.gov/pubmed/26596725

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Medical treatment of recurrent endometrial cancer

Editor Ewa Surynt

Descriptive summary

Ninomiya et al. analysed effectiveness of treatment with docetaxel-cisplatin (DP) therapy as second-line or third-line chemotherapy in 26 patients with recurrent endometrial cancer (REC). The response rate was 58 %, and the median progression-free survival (PFS) was 7.5 months. The group with a treatment-free interval of 6 months or more tended to have better PFS than that with less than 6 months (p=0.01).

According to the recently published guidelines of the Japan Society of Gynecologic Oncology (Ebina et al.), surgical resection should be considered in patients with pelvic REC without distant metastasis. A partial resection of the lung can be also considered in patients with a few small lung metastases. Chemotherapy (paclitaxel/carboplatin, doxorubicin/cisplatin or monotherapy) should be considered. Radiation should be considered as a palliative option for patients with REC. Progesterone therapy can be considered in recurrent cancer with positive progesterone receptors.

Elshaikh et al. published en expert consensus (American College of Radiology) on the most appropriate management options in patients with REC. Authors developed addressed five clinically common scenarios: 1) REC with no previous radiotherapy, 2) isolated vaginal cuff recurrence, 3) isolated pelvic recurrence, 4) paraaortic recurrence, 5) REC with previous radiotherapy.

Davidson et al. retrospectively analysed a group of patients with advanced or recurrent endometrioid endometrial adenocarcinoma, who received at least three cycles of chemotherapy. The majority (85 %) of patients received carboplatin and paclitaxel. They found that grade 2 tumours were more likely to respond to chemotherapy compared to grade 3 tumours and specifically more likely to respond to carboplatin/paclitaxel.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Retrospective Analysis on the Feasibility and Efficacy of Docetaxel-Cisplatin Therapy for Recurrent Endometrial Cancer.	Ninomiya T et al.	Anticancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/27069155
2	Japan Society of Gynecologic Oncology guidelines 2013 for the treatment of uterine body neoplasms.	Ebina Y et al.	Int J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27116188
3	ACR Appropriateness Criteria Management of Recurrent Endometrial Cancer.	Elshaikh MA et al.	Am J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27400117
4	Tumor grade and chemotherapy response in endometrioid endometrial cancer.	Davidson BA et al.	Gynecol Oncol Rep.	http://www.ncbi.nlm.nih.gov/pubmed/27354990

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Surgical treatment of recurrent endometrial cancer

Editor Arun Kalpdev

Descriptive summary

Multiple variables affect the outcome of patients with recurrent endometrial cancer (REC). For this reason, surgical treatment has been proposed for some refined indications. Recently, Zanfagnin et al. have reported their experience with surgical treatment in REC. [1] The authors specify that surgical treatment in cases of REC should be confined to vaginal or pelvic recurrences; retroperitoneal or localized intra-abdominal recurrence, when a maximal cytoreductive effort is likely to be achieved; and isolated distant recurrences when microscopically tumour-free margins can be achieved. Since factors like comorbidities, risks of intervention, and impact of treatment on quality of life are always associated, surgical treatment should be offered to selective patients only.

More strategies have been studied with the aim of giving patients with recurrent disease a better quality of life and long disease-free interval. Arians et al. have published a retrospective study describing the outcome of patients with local recurrent gynaecologic malignancies (12 patients with REC) after resection combined with intraoperative electron radiation therapy. [2] Patients with REC had a one-, two- and five-year overall survival (OS) of 83.3 % (1 yr.), 62.5 % (2 yr.), 50 % (5 yr.) respectively and local progression-free survival (PFS) was 76.2 % (1 yr.), 61 % (2yr.), and 40.6 % (5 yr.). This study indicates that the combination of surgery with additional therapy (i.e., intraoperative electron radiation therapy) can supplement the effective outcome.

Relevant articles retrieved Feb 2016 - Sep 2016 (cont.)

No	Title	Authors	Journal	Link to abstract
1	The role of surgery in recurrent endometrial cancer	Zanfagnin V et al.	Expert Rev Anticancer Ther.	http://www.ncbi.nlm.nih.gov/pubmed/27269480
2	Outcome of patients with local recurrent gynecologic malignancies after resection combined with intraoperative electron radiation therapy (IOERT)	Arians N et al.	Radiat Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26988089

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

Editor Ines Vasconcelos

Descriptive summary

The period covered by the 4th edition of LiFE was particularly fruitful in research that concerns early-phase trials evaluating novel therapies for endometrial cancer (EC).

In their single-arm, open-label trial, Makker et al. evaluated in 56 patients with recurrent or persistent EC (thirteen with well controlled diabetes) the activity of 40 mg of apitolisib daily (GDC-0980), a dual PI3K/mTOR inhibitor. The antitumor activity was limited by tolerability, especially in diabetic patients. Reasons for discontinuation were disease progression (24 patients; 43 %), adverse events (thirteen patients; 23 %), and withdrawal by subject (twelve patients; 21 %). The progression-free survival (PFS) rate at 6 months was 20 % (95 % CI, 7 %-33 %). The objective response rate was 6 %. The median PFS was 3.5 months (95 % CI, 2.7-3.7 months) and the median overall survival was 15.7 months (95 % CI, 9.2-17.0 months). Comprehensive molecular profiling of 46 evaluable archival tumour samples demonstrated that 57 % of patients had at least one alteration in PIK3CA, PTEN, or AKT1. All three patients with a confirmed response had at least one alteration in a PI3K pathway gene.

A pharmacodynamic phase II study (Santacana et al.) of the the PI3K/AKT/mTOR pathway aimed to characterise the biological effects on mTOR pathway of temsirolimus in eleven treatment-naive patients with primary EC, and to identify potential biomarkers associated with a short-term exposure to temsirolimus. p-S6K1 expression was reduced after treatment with temsirolimus in all patients. Variations of the expression of other mTOR-related proteins including p-4BEP1, PTEN, p-AKT, p53, p27, BAD, Bcl-2, Ki67, and cyclin D1 were also observed. Interestingly, the biological effects of the drug were more evident one week after the last dose of temsirolimus. Effects were less evident on tumors harboring mutations in NRAS. Toxicity was acceptable, mucositis being the most frequent adverse event.

Another phase II study (Del Campo et al.) aimed to assess clinical benefit response following treatment with PF-04691502 or gedatolisib, potent dual PI3K/mTOR inhibitors in patients with recurrent EC following platinum-containing chemotherapy. In stage 1 (the main study), eighteen patients were randomised to PF-04691502 and 40 to gedatolisib. PF-04691502 daily oral dosing was not well tolerated and had to be discontinued. Clinical benefit response rate was 53 % (10/19) in the gedatolisib/stathmin-low arm and 26 % (5/19) in the gedatolisib/stathmin-high arm. Clinical benefit response criteria for proceeding to stage 2 were met in the gedatolisib/stathmin-low arm. Stathmin-high expression did not correlate with greater treatment efficacy.

A phase II study by Myers et al. aimed to identify molecular biomarkers that could further guide clinical development of rapamycin analogs. They prospectively collected fixed primary tissue and whole blood from patients enrolled on GOG 248. Sequencing data obtained from tumors of 55 patients revealed mutation rates were consistent with already published reports: mutations in PTEN (45 %), PIK3CA (29 %), PIK3R1 (24 %), K-RAS (16 %), CTNNB1 (18 %) were common and mutations in AKT1 (4 %), TSC1 (2 %), TSC2 (2 %), NF1 (9 %) and FBXW7 (4 %) were less common. Increased PFS (HR 0.16; 95 % CI 0.01-0.78) and RR (response difference 0.83; 95 % CI 0.03-0.99) were noted for AKT1 mutation. An increase in PFS (HR 0.46; 95 % CI 0.20-0.97) but not RR (response difference 0.00, 95 % CI -0.34-0.34) was identified for CTNNB1 mutation. Both patients with TSC mutations had an objective response. There were no statistically significant associations between mutations in PIK3CA, PTEN, PIK3R1, or KRAS and PFS or RR.

Emons et al. published a phase II study designed to evaluate the activity and toxicity of mTOR inhibitor temsirolimus in 22 patients with platinum-refractory/resistant ovarian cancer (OC) or advanced/recurrent EC. Women with recurrent EC, no longer amenable to curative surgery and/or radiotherapy, were eligible when they had no previous or only adjuvant chemotherapy. Preceding endocrine therapy for metastatic/recurrent disease was allowed. After eight weeks of treatment, eight of twenty evaluable patients in the EC cohort had progressive disease. Thus efficacy did not meet the predefined levels during the first stage of recruitment, and the trial was stopped.

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

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	A multicenter, single-arm, open-label, phase 2 study of apitolisib (GDC-0980) for the treatment of recurrent or persistent endometrial carcinoma (MAGGIE study).	Makker V et al.	Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27603005
2	Biological Effects of Temsirolimus on the mTOR Pathway in Endometrial Carcinoma: A Pharmacodynamic Phase II Study.	Santacana M et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27258723
3	A randomised phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer.	Del Campo J et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27103175
4	Tumor mutational analysis of GOG248, a phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer (EC): An NRG Oncology/Gynecologic Oncology Group study.	Myers AP et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27016228
5	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

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

Uterine sarcoma

Editor Marcin Bobiński

Descriptive summary

The incidence of uterine sarcomas (US)

Zhang et al. analysed 3,021 hysterectomies; the incidence of occult US was 0.6 %. [1]

In their review, Cui et al. summarised recent studies regarding the risk of occult US in presumed uterine fibroids. [2]

Diagnostics

Hosh et al. presented the analysis of 13,089 patients with diagnosed uterine sarcomas and concluded that among clinical characteristics, advanced age, black race, and advanced disease stage are related to worse outcome. [3]

Treatment

Analysis of the impact of chemotherapy on the outcome of 269 patients with advanced US that entered EORTC-STBSG clinical trials between 1977 and 2010 was published by Ray-Coquard et al. The authors didn't find any impact of the type of chemotherapy regimen (containing doxorubicin vs. not) by histological subtype (leiomyosarcoma vs. other) on survival. Furthermore, the authors underline that these results support including patients with US in randomised trials exploring new options for patients with soft tissue sarcomas. [4]

A new, revised version of the Japanese Society of Gynaecologic Oncology guidelines 2013 for the treatment of uterine body neoplasms that includes treatment protocols for uterine sarcomas was released. [5]

Safety of morcellation

Sugarbaker et al. described the role of cytoreductive surgery and HIPEC in the treatment of leiomyosarcomas (LMS) disseminated by morcellation. (Early results based on the group of 6 patients). [6]

Liu et al. presented a review discussing the impact of laparoscopic surgery (and morcellation) on the outcomes of patients with LMS. Authors concluded that it may unfavourably affect prognosis. [7]

The problem of morcellation from an innovative, historical and social point of view is widely discussed by Rosenbaum, who concludes that rational debate and taking into account the patient's autonomy is needed in such topics. [8]

Molecular research

Ravid et al. performed the analysis of miRNA signatures of LMS (primary and metastatic) and endometrial stromal sarcomas (ESS), proving that these tumours present different signatures what suggest the differences in their transcriptional regulation. [9]

Davidson et al. presented the analysis of oestrogen (ER) and progesterone receptors (PR) in early LMS (294 FIGO stage I patients) and concluded that PR expression is related with longer patient overall survival (P = .042). [10]

Garcia et al., in their molecular analysis, proposed the sonic hedgehog proteins be used as markers in differentiation between various myometrial lesions. [11]

Vari

The editorial Board of the National Cancer Institute prepared the new patient version of Physician Data Query regarding the treatment of uterine sarcoma. This provides a wide range of knowledge about uterine sarcoma diagnostics and treatment designed for patients. [12]

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Uterine sarcoma

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Clinical Characteristics and Prognosis of Unexpected Uterine Sarcoma After Hysterectomy for Presumed Myoma With and Without Transvaginal Scalpel Morcellation.	Zhang et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26807642
2	Risk of Occult Uterine Sarcoma in Presumed Uterine Fibroids.	Cui et al.	Clin Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26645385
3	Uterine Sarcoma: Analysis of 13,089 Cases Based on Surveillance, Epidemiology, and End Results Database.	Hosh et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27177280
4	Impact of chemotherapy in uterine sarcoma (UtS): review of 13 clinical trials from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) involving advanced/metastatic UtS compared to other soft tissue sarcoma (STS) patients treated with first line chemotherapy.	Ray-Coquard et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27208537
5	Japan Society of Gynecologic Oncology guidelines 2013 for the treatment of uterine body neoplasms.	Ebina et al.	Int J Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27116188
6	Cytoreductive Surgery and HIPEC as a Treatment Option for Laparoscopic Resection of Uterine Leiomyosarcoma with Morcellation: Early Results.	Sugarbaker et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26545375
7	Laparoscopic surgery on broken points for uterine sarcoma in the early stage decrease prognosis.	Liu et al.	Sci Rep.	http://www.ncbi.nlm.nih.gov/pubmed/27503773
8	N-of-1 Policymaking--Tragedy, Trade-offs, and the Demise of Morcellation	Rosenbaum et al.	N Engl J Med.	http://www.ncbi.nlm.nih.gov/pubmed/26962735
9	Uterine leiomyosarcoma and endometrial stromal sarcoma have unique miRNA signatures.	Ravid et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26768834
10	Progesterone Receptor Expression Is an Independent Prognosticator in FIGO Stage I Uterine Leiomyosarcoma.	Davidson et al.	Am J Clin Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/27149024
11	May Sonic Hedgehog proteins be markers for malignancy in uterine smooth muscle tumors?	Garcia et al.	Hum Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26997437
12	Uterine Sarcoma Treatment (PDQ®): Patient Version.	PDQ Adult Treatment Editorial Board.	PDQ Cancer Information Summaries. Bethesda: National Cancer Institute	http://www.ncbi.nlm.nih.gov/pubmed/27441353

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

Cervical pre-invasive disease (diagnosis, management)

Editor Geanina Dragnea

Descriptive summary

Pathogenesis

- In women with multiple HPV types, serial type-specific viral-load measurements predict the natural history of the different HPV-types and elucidate HPV-genotype attribution. [1]
- High mRNA expression levels of TMEM45A, SERPINB5, and p16INK4a genes measured by microarray analysis on RNA extracted from cervical swabs at the baseline are associated with increased risk of CIN3+ in persistently HPV16-infected women, followed for up to nineteen years via a national pathology register. [2]

Screening

- Ten screening algorithms based on different combinations of cytology, HPV testing and HPV 16/18 genotyping were investigated. The best equilibrium between screening effectiveness and harm was found to be HPV testing with HPV 16/18 genotyping, referring HPV 16/18 positive women directly to colposcopy, and HR-HPV (non 16/18) positive women to reflex cytology (ASCUS threshold), as a triage method to colposcopy. This algorithm presented the optimal combination of sensitivity (82.9 %) and specificity relative to cytology alone (0.99) with 1.26 false positive rate relative to cytology alone. [3]

HPV vaccination

- In the VIVIAN study, a phase III, double-blind, randomised controlled trial, healthy women older than 25 years were randomly assigned to receive HPV 16/18 vaccine or aluminium hydroxide control. The results were that the HPV 16/18 vaccine continues to protect against persistent infections, cytological abnormalities, and lesions associated with HPV 16/18 and CIN1+ irrespective of HPV type, and infection with non-vaccine types HPV 31 and HPV 45 over seven years of follow-up. [4]

Non-cervical HPV-related cancers

- In a Danish population-based cohort study on nearly 2.8 million women, analyses in which time since CIN3 was first taken into account showed increased relative risks for anal [HR = 4.8; 95 % CI, 3.3-7.0], vulvar (HR = 3.2; 95 % CI, 2.0-5.3), and vaginal (HR = 5.5; 95 % CI, 2.4-12.3) cancers ≥25 years after CIN3 diagnosis. [5]

Treatment

- In a retrospective study on 179 women with CIN 2-3, a single topical 85 % trichloroacetic acid application resulted in high histologic CIN 2-3 regression rate (to CIN 1) of 87.7 % and remission rate of 80.3 %; 8 weeks after treatment, clearance rates of HPV 16 and 18 were 73.5 % and 75.0 %, respectively. [6]
- A systematic review and meta-analysis of 71 studies assessed the effect of treatment for CIN (excisional or ablative) on obstetric outcomes. Treatment significantly increased the risk of preterm birth, premature rupture of the membranes, chorioamnionitis, low birth weight, admission to neonatal intensive care, and perinatal mortality. Compared with no treatment, the risk of preterm birth was higher in women who had undergone more than one treatment and with increasing cone depth. [7]

Overtreatment

- A prospective observational study of 116 women who underwent large loop excision of the transformation zone because of biopsy-proven persistent (for 2 years) low-grade SIL, or because of a high-grade SIL and squamocolumnar junction completely visible concluded that small lesion size measured by colposcopy may predict absence of CIN, and colposcopy measurement of lesion size may avoid unnecessary treatment. Lesion size of ≤12 mm2 had a specificity of 90.9 % and a negative predictive value of 86.0 % to predict the absence of CIN in the surgical specimen. [8]

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Cervical pre-invasive disease (diagnosis, management)

- Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Linear viral load increase of a single HPV-type in women with multiple HPV infections predicts progression to cervical cancer.	Depuydt CE et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27339821
2	TMEM45A, SERPINB5 and p16INK4A transcript levels are predictive for development of high-grade cervical lesions.	Manawapat-Klopfer A et al.	Am J Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/27508094
3	Comparison of cytology, HPV DNA testing and HPV 16/18 genotyping alone or combined targeting to the more balanced methodology for cervical cancer screening.	Chatzistamatiou K et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27126005
4	Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study.	Wheeler CM et al.	Lancet Infect Dis.	http://www.ncbi.nlm.nih.gov/pubmed/27373900
5	Long-Term Risk for Noncervical Anogenital Cancer in Women with Previously Diagnosed High-Grade Cervical Intraepithelial Neoplasia: A Danish Nationwide Cohort Study.	Sand FL et al.	Cancer Epidemiol Biomarkers Prev.	http://www.ncbi.nlm.nih.gov/pubmed/27358257
6	Short-Term Efficacy of Trichloroacetic Acid in the Treatment of Cervical Intraepithelial Neoplasia.	Geisler S et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26942365
7	Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis.	Kyrgiou M et al.	BMJ.	http://www.ncbi.nlm.nih.gov/pubmed/27469988
8	Small lesion size measured by colposcopy may predict absence of cervical intraepithelial neoplasia in a large loop excision of the transformation zone specimen.	Munmany M et al.	BJOG.	http://www.ncbi.nlm.nih.gov/pubmed/27506510

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

Surgical treatment of primary and recurrent cervical cancer

Editor Mandic Aljosa and Matteo Morotti

Descriptive summary

In these last six months, two articles focused on the role of robotic surgery in the surgical treatment of cervical cancer. Mendivil et al. performed a retrospective study to compare the five-year survival outcomes of cervical cancer patients treated with open radical hysterectomy (ORH), robotic-assisted radical hysterectomy (RRH) or laparoscopic radical hysterectomy (LRH). Forty-nine patients were treated with LRH, 58 with RRH, and 39 patients underwent an ORH. The LRH patients had a significantly shorter operative duration than the RRH and ORH subjects: 1.78 h vs. 2.88h and ORH 2.39 h, respectively. Blood loss was higher in the ORH (475 cc) group compared to RRH = 207 cc and LRH = 312 cc, group ($P < 0.001$). No differences in clinical outcomes: progression-free survival (PFS) and overall survival (OS) were seen in the three groups.

Sert et al. compared in a multicentre retrospective study the perioperative and clinico-pathological outcomes of patients with early-stage cervical cancer who underwent RRH and ORH. In all, 491 cervical cancer patients were treated with RRH (n = 259) or ORH (n = 232) between 2005 and 2011. Again, PFS and OS were comparable in the two groups. Blood loss, intra-operative complications, and transfusion rates were lower in the RRH compared to the ORH one.

Escobar et al. evaluated the role of laser angiography with ICG in order to measure and analyse uterine perfusion during uterine artery sparing and non-sparing radical trachelectomy. A total of 20 patients met the inclusion criteria and were included in this study. Ten patients underwent uterine artery-sparing surgery, and ten patients underwent uterine artery non-sparing surgery. There was no statistical significance difference in the mean ICG fundal fluorescence intensity between the uterine artery-sparing group 162.5 (range, 137-188) and the uterine artery non-sparing group 160.5 (range, 135-186), p=0.22. In both groups, 100 % of the patients regained their menstrual function by postoperative week 8. The percentage of pregnancies was similar in both groups. Based on this study, the authors stated that it seems that there is no need to preserve the uterine artery during radical trachelectomy to maintain uterine viability.

Yang et al. compared retrospectively a cohort of 34 patients with LACC treated with chemoradiotherapy and subsequent extrafascial hysterectomy to a group (21 patients) who received only CCRT. PFS and OS were significantly higher in the surgery group compared to CCRT alone. Forty-seven per cent of the patients (16/34) had pathologic residue tumour on hysterectomy specimens. About 94 % patients (32/34) got complete remission after adjuvant surgery. No severe complications related to postradiation surgery were observed.

However, a bigger study comprising 54 patients who received hysterectomy after CCRT and image-guided adaptive brachytherapy (IGABT) and 157 patients in the definitive radiotherapy group (CCRT+ IGABT) showed no benefit from completion hysterectomy in terms of overall or disease-free survival rates. The cumulative incidence of severe late morbidity was significantly increased in the hysterectomy cohort: 22.5 % versus 6.5 % at 5 years (p=0.016)

Martinelli et al. evaluated in their retrospective cohort the rate of aortic lymph nodes (LN) metastases/recurrences among patients affected by LACC treated with NACT and radical surgery. In total, 261 patients were included in the study. Overall, 56 women (21.5 %) had LN metastases. Four out of 83 women (5 %) who underwent both pelvic and aortic LN dissection had aortic LN metastases, and all women had concomitant pelvic and aortic LN metastases. Overall 2 % of women (5/261) had aortic LN metastases/recurrence. This data suggest that aortic lymphadenectomy at the time of surgery is not routinely indicated in LACC after NACT, but should reserved in case of bulky LN in both pelvic and/or aortic area. The risk of isolated aortic LN relapse is negligible.

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Surgical treatment of primary and recurrent cervical cancer

- Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Survival rate comparisons amongst cervical cancer patients treated with an open, robotic-assisted or laparoscopic radical hysterectomy: A five year experience	Mendivil AA et al.	Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26409687
2	Robot-assisted versus open radical hysterectomy: A multi-institutional experience for early-stage cervical cancer	Sert BM et al.	Eur J Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26843445
3	Utility of indocyanine green (ICG) intra-operative angiography to determine uterine vascular perfusion at the time of radical trachelectomy.	Escobar PF et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27544455
4	Extrafascial hysterectomy after concurrent chemoradiotherapy in locally advanced cervical adenocarcinoma	Yang J et al.	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27102248
5	Post radiation hysterectomy in locally advanced cervical cancer: Outcomes and dosimetric impact.	Mazeron R et al.	Radiother Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27492204
6	s aortic lymphadenectomy indicated in locally advanced cervical cancer after neoadjuvant chemotherapy followed by radical surgery? A retrospective study on 261 women.	Martinelli F et al.	Eur J Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27378160
7	Survival rate comparisons amongst cervical cancer patients treated with an open, robotic-assisted or laparoscopic radical hysterectomy: A five year experience	Mendivil AA et al.	Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26409687
8	Robot-assisted versus open radical hysterectomy: A multi-institutional experience for early-stage cervical cancer	Sert BM et al.	Eur J Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26843445

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Medical treatment of primary or recurrent cervical cancer

Editor Kristina Lindemann

Descriptive summary

Li et al. report in their retrospective study of 133 cases of cervical cancer patients with stage IB1-IIA1 disease and deep stroma infiltration treated with either radiochemotherapy or chemotherapy (cisplatin/taxol). See report by Vishal Bahall for details.

Ruhlmann et al. (with comment by Schartzberg et al.) report on a placebo-controlled, double-blind, phase III trial

The addition of fosaprepitant to a standard combination of palonosetron and dexamethasone was tested for chemoradiation-induced nausea and vomiting prophylaxis in 234 patients with cervical cancer receiving fractionated radiotherapy for five weeks with cisplatin at 40 mg/m² weekly. A remarkable clinical improvement with sustained no emesis at 5 weeks in 65.7 % for the fosaprepitant group compared to 48.7 % for the placebo group (subhazard ratio 0.58, 95 % CI 0.39–0.87; p=0.008) was reported. The most common grade 3 adverse event during the five weeks of treatment was diarrhoea (9 % in the fosaprepitant group vs. 5 % in the placebo group). The trial raises the question if the prolonged administration of corticosteroids is feasible.

De Azevedo et al. have systematically reviewed the literature on studies of the use of neoadjuvant chemotherapy as an adjunct to chemoradiation. The lack of high-quality trials while Interlace is recruiting is highlighted. Data on NACT needs to be considered in light of contemporary protocols of chemoradiation with sufficient doses. It is also important that toxicity profiles may not delay chemoradiation in patients who do not respond or comprise completion of chemoradiation.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Chemotherapy versus radiotherapy for FIGO stages IB1 and IIA1 cervical carcinoma patients with postoperative isolated deep stromal invasion: A retrospective study BMC Cancer	Li et al.	BMC Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27387204
2	Efficacy and safety of fosaprepitant for the prevention of nausea and emesis during 5 weeks of chemoradiotherapy for cervical cancer (the GAND-emesis study): a multinational, randomised, placebo-controlled, double-blind, phase 3 trial.	Ruhlmann et al.	Lancet Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26952945
3	Comment to Ruhlmann et al.	Schwartzberg et al.	Lancet Oncolol	http://www.ncbi.nlm.nih.gov/pubmed/26952946
4	Neoadjuvant Chemotherapy Followed by Chemoradiation in Cervical Carcinoma: A Review	De Azevedo et al.	Int J Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26905327

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Radiotherapy in management of primary cervical cancer

Editor Vishal Bahall

Descriptive summary

Kumar et al. report on a prospective randomised study comparing late toxicities in women who received pulsed dose rate (PDR) vs. high dose rate (HDR) intra-cavitary radiotherapy for locally advanced cervical cancer (LACC). In all, 37 women were randomised into HDR (19 women- 7 Gy each in 3 fractions, repeated weekly) or PDR (18 women- 70 cGy hourly pulses for 39 hours, total 27 Gy) after external beam radiotherapy (EBRT). Authors reported fewer bladder, rectal, and vaginal toxicities in the PDR group but the differences were not statistically significant.

Sharma et al. present the results of a prospective randomised phase III trial comparing pure accelerated radiotherapy (ART) to concurrent chemo-radiation (CRT) for LACC (n=102). ART was given with 50 Gy in 25 fractions, 6 fractions weekly; CRT arm was administered as 50 Gy in 25 fractions with weekly cisplatin. Both arms received 85 Gy intra-cavitary brachytherapy (ICBT) to point A). After a median follow-up of 36 months there was no difference in OS and DFS but fewer toxicities in the ART arm.

Tergas et al. reviewed the factors associated with prolonged radiation and its impact on survival for LACC. They reviewed 7,209 women who received primary chemoradiation (47.1 % and 52.8 % completed treatment in <8 and >8 weeks, respectively) and found no overall survival difference for radiation duration <8 vs. >8 weeks. Inferior overall survival is only observed with a radiation duration of >10-12 weeks.

Refaat et al. reported the long-term adverse events and outcomes of 129 women who underwent definitive radiotherapy with external-beam radiation concomitant with cisplatin-based chemotherapy and boosted by low dose rate (LDR) brachytherapy (BT) for cervical cancer (1B1-1VA). The median follow-up was 37 months and the authors concluded that this form of treatment was an effective, feasible, and tolerable treatment modality for cervical cancer. There was a superior overall survival but inferior local control with worse toxicity profile when LDR BT was compared with MRI-guided brachytherapy.

Kirchheiner et al. analysed functioning and symptom scores of 744 women after definitive chemoradiation for LACC. General QOL and functioning were impaired prior to treatment and resolved after treatment. However, some immediate (diarrhoea, menopausal symptoms, peripheral neuropathy, and sexual functioning) and late (lymphedema and dyspnoea) treatment-related symptoms persisted.

Bae et al. retrospectively reviewed 397 women to identify predictive factors for radiation field failure in women who had definitive chemoradiation treatment for LACC. After a median follow-up of 7.2 years, loco-regional (LR) failure occurred in 51 (12.9 %) women. The estimated three-year rate of LR control was 89 %, whereas the overall survival rate was 82 %. Authors concluded that tumour size (>5 cm), age (<40 years), non-squamous histology, positive lymph node on magnetic resonance imaging, and advanced stage are predictors of LR failure after definitive platinum-based chemoradiation in patients with LACC.

Kobayashi et al. retrospectively reviewed 137 women with cervical cancer (1B-1VA) who were treated with definitive radiotherapy (RT) to identify recurrent sites. After a median follow-up of 57 months, complete response was achieved in 121 patients (88 %). Cancer recurred in 36 (30 %) of these women. Recurrences occurred within the RT field in 9 women, all of whom had local disease and no lymph node involvement. Outside RT recurrences occurred in 20 women, with lung as the most frequent site. Incidence of pelvic lymph node (PLN) recurrence or persistence in the entire cohort, including 48 PLN- positive women, was 5.1 % (7).

Chargari et al. reviewed 109 women who had pulsed-dose-rate image-guided adaptive brachytherapy after concurrent pelvic chemoradiation to identify patterns of relapse according to high-risk clinical target volume (HR-CTV) and to the D90 HR-CTV. Women with extra pelvic disease were excluded. The median follow-up was 39 months. The authors found that there was a poorer local failure-free survival when HR-CTV volume was greater than 40 cm3 and a high propensity for distant relapse with D90 HR-CTV planning and an HR-CTV volume >40 cm3.

L. Li et al. retrospectively reviewed 133 women who received adjuvant chemotherapy (CT) vs. radiotherapy (RT) for deep stromal invasion (DSI) post radical hysterectomy and pelvic lymphadenectomy. Survival outcomes, recurrent patterns and toxicities were recorded for CT group (65 women) and RT group (68 women) with stages IB1 to IIA1. After a median follow-up of 33.7 months, there was a significantly improved DFS in RT group with no difference in OS. Authors concluded that RT alone could reduce the risk of recurrence in this cohort of women compared to chemotherapy alone, with acceptable morbidity.

Zhang et al. retrospectively reviewed 171 women to investigate the therapeutic efficiency of preoperative intracavitary radiotherapy combined with radical surgery vs. radical surgery alone on postoperative complications and long-term survival in patients with stage IB2 and IIA2 cervical cancer. They concluded that preoperative radiotherapy combined with radical surgery improved loco-regional control rate, with no increase postoperative complications.

Mongula et al. reviewed 42 women to evaluate the usefulness of MRI in identifying local residual disease during and after radiotherapy for LACC. Two blinded radiologists scored the likelihood of residual tumour using subjective and objective (predefined criteria) visual evaluation. They concluded that use of objective MRI criteria increased the diagnostic performance and decreased observer dependency for residual tumour after radiotherapy.

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Radiotherapy in management of primary cervical cancer

Descriptive summary (cont.)

Siavashpour et al. retrospectively reviewed 32 women treated with chemoradiation to analyse the optimum organ filling point for organs at risk (OAR) dose in cervical cancer HDR brachytherapy. The authors concluded that selecting a bladder volume of ≤70cm3 is better with regards to the dose to the bladder, rectum, and sigmoid.

Kong et al. prospectively evaluated three rectal retraction techniques (RR- rectal retractor blade, VP- vaginal gauze packing, and FB – tandem foley balloon) on 11 women undergoing chemoradiation for cervical cancer. The authors concluded that RR provides best sparing to rectum and sigmoid compared to VP and FB. No difference was identified between VP and FB.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Low-Dose-Rate Brachytherapy Boosting Concurrent Chemoradiation as a Definitive Treatment Modality for Cervical Cancer: Long-term Clinical Results of Outcomes and Associated Toxicity	Refaat et al.	American Journal of Clinical Oncology	http://www.ncbi.nlm.nih.gov/pubmed/24487420
2	Radiation Duration in Women with Cervical Cancer Treated with Primary Chemoradiation: A Population-Based Analysis	Tergas AI et al.	Cancer Investigation	http://www.ncbi.nlm.nih.gov/pubmed/26986809
3	Health-Related Quality of Life in Locally Advanced Cervical Cancer Patients After Definitive Chemoradiation Therapy Including Image Guided Adaptive Brachytherapy: An Analysis From the EMBRACE Study	Kirchheiner K et al.	International Journal of Radiation Oncology, Biology, Physics	http://www.ncbi.nlm.nih.gov/pubmed/26876955
4	Predictors of radiation field failure after definitive chemoradiation in patients with locally advanced cervical cancer	Bae HS et al.	International Journal of Gynecological Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26937749
5	Correlations between radiation dose in bone marrow and hematological toxicity in patients with cervical cancer: A comparison of 3DCRT, IMRT, and RapidARC.	Chang Y et al.	International Journal of Gynecological Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26844613
6	Image-guided adaptive brachytherapy in cervical cancer: Patterns of relapse by brachytherapy planning parameters	Chargari C et al.	Brachytherapy	http://www.ncbi.nlm.nih.gov/pubmed/27180129
7	Rectal and bladder dose reduction with the addition of intravaginal balloons to vaginal packing in intracavitary brachytherapy for cervical cancer.	Eng TY et al.	Brachytherapy	http://www.ncbi.nlm.nih.gov/pubmed/27032995
8	Details of recurrence sites after definitive radiation therapy for cervical cancer.	Kobayashi R et al.	Journal of Gynecologic Oncology	http://www.ncbi.nlm.nih.gov/pubmed/26463432
9	Prospective comparison of rectal dose reduction during intracavitary brachytherapy for cervical cancer using three rectal retraction techniques	Kong I et al.	Brachytherapy	http://www.ncbi.nlm.nih.gov/pubmed/27090224
10	Predictive criteria for MRI-based evaluation of response both during and after radiotherapy for cervical cancer.	Mongula J et al.	Journal of Contemporary Brachytherapy	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4965503/
11	Analysis of the effect of adjuvant radiotherapy on outcomes and complications after radical hysterectomy in FIGO stage IB1 cervical cancer patients with intermediate risk factors (GOTIC Study)	Nakamura K et al.	World Journal of Surgical Oncology	http://www.ncbi.nlm.nih.gov/pubmed/27356862
12	Can pure accelerated radiotherapy given as six fractions weekly be an option in locally advanced carcinoma cervix: Results of a prospective randomised phase III trial.	Sharma M et al.	Journal of Cancer Research and Therapeutics	http://www.ncbi.nlm.nih.gov/pubmed/27072219
13	Pulsed-dose-rate vs. high-dose-rate intracavitary radiotherapy for locally advanced carcinoma of cervix: A prospective randomised study	Kumar P et al.	Brachytherapy	http://www.ncbi.nlm.nih.gov/pubmed/26996595
14	Chemotherapy versus radiotherapy for FIGO stages IB1 and IIA1 cervical carcinoma patients with postoperative isolated deep stromal invasion: A retrospective study BMC Cancer	Li L et al.	BMC Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27387204
15	Optimum organ volume ranges for organs at risk dose in cervical cancer intracavitary brachytherapy	Siavashpour Z et al.	Journal of Contemporary Brachytherapy	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4873556/
16	Effect of preoperative radiotherapy on stage IB2 and IIA2 cervical cancer: A retrospective cohort study	Zhang T et al.	International Journal of Surgery	http://www.ncbi.nlm.nih.gov/pubmed/27084347

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

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

Editor Marcin Mardas

Descriptive summary

Pan et al. showed that treatment with Glaucocalyxin B inhibits the proliferation of HeLa and SiHa cervical cancer cell lines in a dose-dependent manner, which increases the apoptotic cell population and induces autophagy.

Zhao et al. showed that dioscin notably induces apoptosis in HeLa and SiHa cells through adjusting ROS-mediated DNA damage and the mitochondrial signalling pathway (dioscin caused the release of cytochrome C from mitochondria into the cytosol and up-regulated the protein levels of Bak, Bax, Bid, p53, caspase-3, caspase-9, and down-regulated the protein levels of Bcl-2 and Bcl-xl).

Murahashi et al. presented results of a phase I clinical trial of a five-peptide cancer vaccine combined with cyclophosphamide in advanced solid tumours showing safety and promising immune responses that correlated with vaccine-induced T-cell responses. However, from eighteen included patients only one was diagnosed with cervical cancer.

Hasanpourghadi et al. demonstrated the distinctive microtubule destabilizing effects of Methyl2-(5-fluoro-2-hydroxyphenyl)-1H-benzo[d]imidazole-5-carboxylate (MBIC), a benzimidazole derivative against cervical cancer cells in vitro. MBIC additionally exhibited synergistic effects with low doses of selected anticancer drugs (colchicine, nocodazole, paclitaxel and doxorubicin).

Matsumoto et al. focused on the ubiquitin proteasome inhibitor MG132 (carbobenzoxy-Leu-Leu-leucinal) incorporated into micellar nanomedicines showing strong tumour inhibitory in vivo (mice) effect against HPV-positive tumours from HeLa and CaSki cells, and even in HPV-negative tumours from C33A cells. Repeated injection showed no significant toxicity.

Zhao et al. investigated the effects of valproic acid (VPA), a histone deacetylase inhibitor, on the angiogenesis of cervical cancer and reported that inhibition of PI3K/Akt and ERK1/2 signals are involved in VPA-induced HIF-1 and VEGF suppression of cervical cancer cells.

Von Hoff et al. presented results of a phase I study of PSMA-Targeted Docetaxel-Containing Nanoparticle BIND-014 (novel, tumour prostate-specific membrane antigen (PSMA)-targeted nanoparticle, containing docetaxel) in patients with advanced solid tumours. Out of the 52 patients, only one was diagnosed with cervical cancer; however, this patient had a complete response.

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Liu et al. tested whether targeting the HPV E7 antigen to dendritic cells (DC) in vivo would elicit therapeutic antitumor cytotoxic T lymphocyte response. Authors generated the DEC205-specific single-chain variable fragment (scFv) and E7 long peptide fusion protein [scFv(DEC205)-E7] demonstrating highly efficient DCI-targeting in vivo and elicited a much stronger protective cytotoxic T lymphocyte response than non-DC-targeting control vaccine in naive mice.

Zhang et al. prepared folate (FA)-modified, cisplatin-loaded lipid carriers (folate containing polyethylene glycol (PEG)-distearoylphosphatidylethanolamine (DSPE) (FA-PEG-DSPE) loaded with cisplatin) for cervical cancer treatment. Authors investigated anti-tumour efficacies of the carriers on HeLa cells and in vivo on a mice-bearing cervical cancer model showing they were efficient in selective delivery to cancer cells over-expressing FA receptors. The authors suggested that novel constructed agent could function as outstanding nanocarriers for the delivery of drugs for the targeted treatment of cervical cancers.

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

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Glaucocalyxin B induces apoptosis and autophagy in human cervical cancer cells.	Pan Y et al.	Mol Med Rep.	http://www.ncbi.nlm.nih.gov/pubmed/27356884
2	Dioscin Induces Apoptosis in Human Cervical Carcinoma HeLa and SiHa Cells through ROS-Mediated DNA Damage and the Mitochondrial Signaling Pathway.	Zhao X et al.	Molecules	http://www.ncbi.nlm.nih.gov/pubmed/27271587
3	Phase I clinical trial of a five-peptide cancer vaccine combined with cyclophosphamide in advanced solid tumours.	Murahashi M et al.	Clin Immunol.	http://www.ncbi.nlm.nih.gov/pubmed/27072896
4	Targeting of tubulin polymerization and induction of mitotic blockage by Methyl 2-(5-fluoro-2-hydroxyphenyl)-1H-benzo[d]imidazole-5-carboxylate (MBIC) in human cervical cancer HeLa cell.	Hasanpourghadi M et al.	J Exp Clin Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/27030360
5	Enhanced efficacy against cervical carcinomas through polymeric micelles physically incorporating the proteasome inhibitor MG132.	Matsumoto Y et al.	Cancer Sci.	http://www.ncbi.nlm.nih.gov/pubmed/26987571
6	Valproic acid inhibits the angiogenic potential of cervical cancer cells via HIF-1 /VEGF signals.	Zhao Y et al.	Clin Transl Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26942921
7	Phase I Study of PSMA-Targeted Docetaxel-Containing Nanoparticle BIND-014 in Patients with Advanced Solid Tumors.	Von Hoff DD et al.	Clin Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26847057
8	A novel dendritic cell targeting HPV16 E7 synthetic vaccine in combination with PD-L1 blockade elicits therapeutic antitumor immunity in mice.	Liu Z et al.	Oncoimmunology.	http://www.ncbi.nlm.nih.gov/pubmed/27471615
9	Folate-modified, cisplatin-loaded lipid carriers for cervical cancer chemotherapy.	Zhang G et al.	Drug Deliv.	http://www.ncbi.nlm.nih.gov/pubmed/26165422

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

Lavorato-Rocha et al. identified two novel prognostic markers in vulvar cancer: one with a favourable prognosis (GNB3) and the other with unfavourable prognosis (PLXDC2).

Holthoff et al. suggested that the development of epithelial-mesenchymal transition may be a mechanism by which infiltrative vulvar tumours with a fibromyxoid stromal response behave more aggressively and convey worse outcomes than tumours that do not exhibit these pathologic features.

de Melo Maia et al. reported that low p63 protein expression levels are correlated with deeper tumour invasion ($p = 0.0491$) and lower patient overall survival ($p = 0.0494$). The authors points out miR-223-5p overexpression as a putative pathological mechanism of tumour invasion and a promising therapeutic target. The importance of both miR-223-5p and p63 as prognostic factors in vulvar cancer is highlighted.

Sznurkowski et al., based on their immunohistochemical study, presented that P16(ink4a)-overexpression was correlated with prolonged overall survival (OS) ($p = 0.009$), and predicted a better response to radiotherapy ($p < 0.001$). The multivariate analysis has demonstrated that it was also an independent prognostic factor for OS in patients with vulvar squamous cell carcinoma.

Trietsch et al. reported that vulvar squamous cell carcinomas presented high L1-cell adhesion molecule (L1CAM)-expression at the infiltrating margin. Patients with L1CAM-expression had a significantly worse prognosis compared to L1CAM-negative tumours.

Cao et al., in their meta-analysis based on seventeen studies with 2,309 patients, suggested that the overexpression of p16INK4a might be associated with better survival indicating a better prognosis of vulvar cancer.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	An Integrative Approach Uncovers Biomarkers that Associate with Clinically Relevant Disease Outcomes in Vulvar Carcinoma.	Lavorato-Rocha AM et al.	Mol Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/27170308
2	Pathologic features of aggressive vulvar carcinoma are associated with epithelial-mesenchymal transition.	Holthoff ER et al.	Hum Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/27327194
3	MiR-223-5p works as an oncomiR in vulvar carcinoma by TP63 suppression.	de Melo Maia B et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/27359057
4	The overexpression of p16 is not a surrogate marker for high-risk human papilloma virus genotypes and predicts clinical outcomes for vulvar cancer.	Sznurkowski JJ et al.	BMC Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27411473
5	Prognostic value and clinicopathologic characteristics of L1 cell adhesion molecule (L1CAM) in a large series of vulvar squamous cell carcinomas.	Trietsch MD et al.	Oncotarget.	http://www.ncbi.nlm.nih.gov/pubmed/27028855
6	Prognostic Value of Overexpressed p16INK4a in Vulvar Cancer: A Meta-Analysis.	Cao H et al.	PLoS One.	http://www.ncbi.nlm.nih.gov/pubmed/27031618

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

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

Editor Kamil Zalewski

Descriptive summary

VIN

Regauer et al. report on the rare occurrence of HPV-induced vulvar precancers in patients with vulvar lichen planus (LP). This was a less frequent event (1.2 %) than development of d-VIN or HPV-negative SCC in LP (3 %).

Podoll et al. evaluated CK17 in 29 dVIN cases in comparison with lichen sclerosus (8 patients), lichen simplex chronicus (7 patients), and usual VIN (9 patients). It appeared to not be a specific marker for dVIN.

Micheletti et al., report on a retrospective study of 976 women with vulvar lichen sclerosus (VLS) where 34 patients developed a vulvar intraepithelial neoplasia (n=8) or keratinizing superficially invasive squamous cell carcinoma (n=6) or keratinizing invasive squamous cell carcinoma (n=20). The neoplasia incidence risk was 3.5 %. The median progression-free survival was significantly shorter in older women (≥70 years) when compared with younger women (p = .003).

Bradbury et al. reviewed the clinical presentation, management, and survival outcomes of VIN in 107 HIV-positive women. When compared with HIV-negative women they had shorter RFS and PFS and presented with multifocal and multicentric disease more frequently (63.6 vs. 22.2 % and 84.8 vs. 43.3 %, respectively, P<0.0001).

Bigby et al. reviewed the histopathological biopsies (n= 47) of 21 women who had had biopsies performed at least six months before presentation with SCCV. They found that in fourteen biopsies SCCV had not been previously recognized and the subsequent cancer developed in the same region as the previous biopsy showing dVIN in six of the eight women. They concluded that both clinical and histologic underrecognition contribute to the apparent rarity of dVIN as a solitary diagnosis.

Hoang et al. reviewed the classification, epidemiology, clinical features, histomorphology, ancillary markers, and molecular genetics of both types of VIN, and discussed the morphological challenges faced by pathologists in interpreting these lesions.

Bleeker et al. retrieved from the Dutch Pathology Registry data of 3,038 women diagnosed with lichen sclerosus. They showed a nearly 100 % increase in incidence of lichen sclerosus between 1991 and 2011 and identified concurrent VIN and age ≥70 years at time of lichen sclerosus diagnosis as an important risk factors for vulvar cancer development.

VaIN

Sopracordevole et al. published a retrospective study evaluating colposcopic patterns observed in women with a histopathological diagnosis of VaIN 1-3.

Tainio et al. produced a prospective study on 30 patients (77 % hrHPV positive) with histologically confirmed VAIN 2 or 3 randomised into three arms: vaginally administered imiquimod, laser vaporisation, and expectant management. HPV clearance was significantly higher in the imiquimod arm (63 %) than in the laser arm (11 %) and expectant management arm (17 %). None of the lesions progressed during the follow-up (16 weeks). Histological regression (≤VAIN 1) was observed in majority of patients.

Hodeib et al. retrospectively identified 42 patients with biopsy-proven VAIN II-III No specific primary treatment was significantly more effective in preventing recurrence that appeared at a median of 17.4 months (7-78 months) from the time of initial diagnosis. Five (12 %) patients developed invasive cancer of the lower genital tract. The authors failed to identify clear risk factors or histopathologic criteria that predicted recurrence or progression.

VIN/VaIN

van Poelgeest et al. reported on a multicentre open-label, randomised controlled trial on patients with HPV16(+) high-grade VIN/VaIN in which it was randomised to therapeutic vaccination (ISA101) with (n = 21) or without (n = 22) application of 5 % imiquimod at the vaccine site. Authors observed that imiquimod did not improve the outcomes of vaccination and vaccine-induced T-cell responses were significantly stronger in patients with complete responses.

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

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Human papillomavirus-induced squamous intraepithelial lesions in vulvar lichen planus.	Regauer S et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/27490079
2	Assessment of CK17 as a marker for the diagnosis of differentiated vulvar intraepithelial neoplasia.	Podoll MB et al.	Int J Gynecol Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/27513074
3	Vulvar Lichen Sclerosus and Neoplastic Transformation: A Retrospective Study of 976 Cases.	Micheletti L et al.	J Low Genit Tract Dis.	http://www.ncbi.nlm.nih.gov/pubmed/26882123
4	Vulvar intraepithelial neoplasia: clinical presentation, management and outcomes in women infected with HIV.	Bradbury M et al.	AIDS.	http://www.ncbi.nlm.nih.gov/pubmed/26959352
5	The natural history of vulvar intraepithelial neoplasia, differentiated type: evidence for progression and diagnostic challenges.	Bigby SM et al.	Int J Gynecol Pathol.	http://www.ncbi.nlm.nih.gov/pubmed/26974999
6	Squamous precursor lesions of the vulva: current classification and diagnostic challenges.	Hoang LN et al.	Pathology.	http://www.ncbi.nlm.nih.gov/pubmed/27113549
7	Lichen Sclerosus: Incidence and Risk of Vulvar Squamous Cell Carcinoma.	Bleeker MC et al.	Cancer Epidemiol Biomarkers Prev.	http://www.ncbi.nlm.nih.gov/pubmed/27257093
8	Colposcopic patterns of vaginal intraepithelial neoplasia: a study from the Italian Society of Colposcopy and Cervico-Vaginal Pathology.	Sopracordevole F et al.	Eur J Cancer Prev.	http://www.ncbi.nlm.nih.gov/pubmed/27428398
9	Randomised trial on treatment of vaginal intraepithelial neoplasia-Imiquimod, laser vaporisation and expectant management.	Tainio K et al.	Int J Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27428506
10	Recurrence and risk of progression to lower genital tract malignancy in women with high grade VAIN.	Hodeib M et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27032375
11	Vaccination against oncoproteins of HPV16 for noninvasive vulvar/vaginal lesions: lesion clearance is related to the strength of the T-Cell response.	van Poelgeest MI et al.	Clin Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/26813357

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Vulvovaginal adenocarcinoma / melanoma / sarcoma

Editor Anna Dückelmann

Descriptive summary

Melanomas represent 6 % of all vulvar cancers. The prognosis of patients with a vulvar melanoma is considerably worse compared to women with cutaneous melanomas, probably due to dissimilarities in aetiology and biological behaviour. According to an analysis of the Dutch Cancer Registry (Pleunis et al.), five-year relative survival for melanomas increased from 37 % in 1989–1999 to 45 % in 2000–2012. The authors discuss an effect of the centralization of care advocated in the Dutch guideline since 2000.

Another epidemiological study (by Vyas et al.) showed that genitourinary melanomas occur about ten times more frequently in women compared with men, and the most commonly affected site is the vulva. The incidence over the past 25 years remained stable for both women and men. Unlike in cutaneous melanomas, there was a survival disadvantage for women.

Satellitosis and CD117 immunohistochemical expression are a valuable predictor of prognosis and survival, especially in thick (> 4 mm) melanoma (Salcedo-Hernández et al.).

Mueller et al. describe a case of vaginal mesonephric adenocarcinoma treated successfully by local excision of the lesion and adjuvant radio-chemotherapy. Mesonephric adenocarcinomas may arise in females out of remnants of the Wolffian ducts. These rare tumours seem to be sensitive to adjuvant chemoradiation. Compared to the malignant mixed Müllerian tumour, it seems that mesonephric adenocarcinomas located in the female genital tract have a better prognosis.

Sui et al., presenting a rare case of vulvar mucinous adenocarcinoma, recommend local excision, with or without chemotherapy, as an effective treatment for early-stage vulvar mucinous adenocarcinoma.

Alnafisah et al. present a case of locally recurrent vulvar leiomyosarcoma of the Bartholin gland with distant metastasis to the lung, after surgical and systemic treatment as well as adjuvant radiation. The authors suggest to secure a histological diagnosis by taking a biopsy, if a mass of the Bartholin gland is firm or solid on palpation, and if it is ulcerated or found in a slightly different location than the usual Bartholin gland cyst. Early diagnosis and treatment are important because these smooth muscle neoplasms have a high risk of recurrence, and patients may require adjuvant radiotherapy in addition to adequate surgical excision.

A myeloid sarcoma is a tumour mass with effaced tissue architecture consisting of myeloid blasts occurring at any extra medullary site. There are six cases of vulvar myeloid sarcoma described in the literature so far (review of Sahu et al.). Myeloid sarcoma can be isolated, precede AML, coincide with AML, represent blast transformation of myeloproliferative neoplasms or represent a relapse in a previously treated AML. Isolated myeloid sarcoma should be tackled aggressively with anti-leukemic therapy followed by consolidation with allogeneic HSCT.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Satellitosis and CD117 immunohistochemical expression correlates with poor outcome in thick vulvar melanoma	Salcedo-Hernández RA et al.	G Ital Dermatol Venereol.	http://www.ncbi.nlm.nih.gov/pubmed/27377140
2	Epidemiology of genitourinary melanoma in the United States: 1992 through 2012	Vyas R et al.	J Am Acad Dermatol.	http://www.ncbi.nlm.nih.gov/pubmed/27317515
3	Rare vulvar malignancies; incidence, treatment and survival in the Netherlands	Pleunis N et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27126004
4	Mesonephric adenocarcinoma of the vagina	Mueller I et al.	Strahlenther Onkol.	http://www.ncbi.nlm.nih.gov/pubmed/27349710
5	Primary mucinous adenocarcinoma of the vulva: A case report and review of the literature	Sui Y et al.	Mol Clin Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27073659
6	Lung metastasis in a case of recurrent poorly differentiated leiomyosarcoma of the bartholin gland: A case report and review of the literature	Alnafisah F et al.	Cureus.	http://www.ncbi.nlm.nih.gov/pubmed/27158579
7	Myeloid Sarcoma Of Vulva: A Short Update	Sahu KK et al.	Indian J Hematol Blood Transfus	http://www.ncbi.nlm.nih.gov/pubmed/27408359

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Treatment of vaginal cancer

Editor Elis Ismail

Descriptive summary

Due to the absence of prospective randomised data, the current treatment recommendations for primary vaginal cancer (VC) are based primarily on retrospective single institutional series or extrapolation from the management of other gynaecologic cancers. Prospective, randomised data does not exist to guide treatment in patients with primary VC.

Orton et al., using the SEER database, evaluated the impact of brachytherapy (BT) on survival in 2,517 VC patients. [1] They found that median overall survival for patients receiving external beam radiation therapy (EBRT) alone was 3.6 years (95 % CI, 3.0-4.2 years) versus 6.1 years (95 % CI 5.2-7.2 years) for patients receiving brachytherapy (alone or in combination of EBRT) (p=<0.001). Brachytherapy reduced the risk of death among patients in all FIGO stages. Brachytherapy benefited both patients with squamous cell carcinoma (HR 0.80; 95 % CI 0.70-0.92) and adenocarcinoma (HR 0.69; 95 % CI 0.49-0.95). Tumours larger than 5cm had the greatest benefit from brachytherapy (HR 0.68; 95 % CI 0.50-0.91). The authors concluded that the use of BT, as a boost or as primary definitive treatment, should be considered for all suitable patients. Neither FIGO stage IVA disease nor large tumour size should be considered contraindications to BT.

Jain et al. performed a retrospective analysis of eleven VC patients (FIGO stage I and II) evaluating the efficacy of radical vaginectomy with or without radical hysterectomy. [2] Adjuvant treatment was given to patients with positive margins or lymph nodes. The authors reported the twelve-month disease-free survival of 88.9 % and twelve-month overall survival of 100 %.

Lopez et al., in their literature review, included 34 patients with the primary carcinoma of the recto-vaginal septum. [3] Although surgery with adjuvant chemoradiation therapy seems to be the most common treatment option, due to mutilation and permanent terminal colostomy related to this method of treatment, authors suggest that primary platinum-based chemoradiation therapy should be considered.

Chandrasekaran et al. reported a clinical case of a woman with vaginal cancer (VC) and breast metastasis. [4] Successfully treated with the robot-assisted extrafascial total hysterectomy, local vaginal mass excision, partial mastectomy of the left breast, and postoperative chemotherapy followed by breast and pelvic radiotherapy. The patient remained in remission for three years of follow-up. Yan et al. reported another case report of the patient with advanced small-cell carcinoma of the vagina with lung metastasis. [5] After radiotherapy combined with six cycles of chemotherapy (paclitaxel plus cisplatin) and achieved complete response, there was no sign of disease after 21 months of follow-up.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Brachytherapy improves survival in primary vaginal cancer.	Orton A et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27036631
2	Role of Radical Surgery in Early Stages of Vaginal Cancer-Our Experience.	Jain V et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27327154
3	Carcinoma of the recto-vaginal septum. Comprehensive literature review.	Lopez N et al.	J Obstet Gynaecol.	http://www.ncbi.nlm.nih.gov/pubmed/26467428
4	Breast metastasis from vaginal cancer.	Chandrasekaran N et al.	BMJ Case Rep.	http://www.ncbi.nlm.nih.gov/pubmed/27444140
5	Primary small cell carcinoma of the vagina with pulmonary metastasis: a case report.	Yan WX et al.	Eur J Gynaecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27048125

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Treatment of recurrent vulvar cancer

Editor María de los Reyes Oliver Pérez

Descriptive summary

Squamous cell carcinoma of the vulva (VSCC)

The rate of VSCC recurrence ranges from 20 % to 50 %. There has been little in the literature regarding treatment for recurrent VSCC. Reports often are based on a limited number of cases observed over long periods of time with non-uniform criteria. In the period covered by the 4th edition of the LiFE report, three eligible retrospectives studies and one literature review have been found.

Groin recurrences after negative sentinel lymph node biopsy (SLN) have been reported in 2–3 % of the patients. Van Doorn et al. in their multicentre retrospective cohort study reported for the first time the results of the SLN procedure in 27 patients with recurrent VSCC. [1] In 78 % of patients and in 84 % of the groins the repeat SLN procedure was successful (less than 95 % reported in primary SLN procedures), but it was more challenging compared to primary procedures. There were no groin recurrences documented after a median follow-up period of 27.4 months (range 2–96).

Frey et al. have assessed the influence of multimodal treatment on survival after groin recurrence in VSCC patients. [2] In their multicentre retrospective cohort study, 23 patients with isolated groin recurrence and seven patients with combined groin and pelvic recurrence were included. The median time of follow-up was 22 months (range 9-123). The overall survival rate was estimated to be 50 % after seven years. Patients with multimodal groin relapse treatment such as surgery and radiotherapy or chemoradiation, performed better than those with single-mode treatment (HR, 0.25; P = 0.037). The time from diagnosis to groin recurrence had no influence on survival. The authors concluded that groin recurrence should no longer be considered as a palliative situation.

Nevertheless, recurrent VSCC occurs predominantly in elderly patients with severe comorbidities that often restrict the surgical treatment options. Interstitial brachytherapy is one of the possible treatment modalities in selected patients. Kellas-Sleczka et al. reported a retrospective analysis of eight women with recurrent VSCC after previous radical surgery that were treated using high-dose-rate interstitial brachytherapy. [3] The median follow-up was 28 months. Fifty per cent of the women experienced relapse. The one-year and three-year overall survival was 100 % and 80 %, respectively. Median time to failure was 31 months (range 13-76). Two patients (14.3 %) had severe late toxicity (G3).

Pellegrino et al. [4] published the results of a preliminary study to evaluate the safety, local efficacy, acceptability, and quality of life of electrochemotherapy with bleomycin in reducing the size of tumours in patients with vulvar carcinoma with locoregional cutaneous recurrence unsuitable for standard treatments. The cases recruited consisted in nine recurrences of cutaneous vulvar cancer, and one case of primitive Paget tumour of the vulva. Objective responses with local control of the tumour were obtained in 80 %. After a mean follow-up of twelve (3–22) months, six patients (60 %) were alive.

Finally, targeted therapies might serve as an alternative therapeutic approach beyond chemotherapy in metastatic and/or inoperable VSCC. A literature review on molecular targets of prognostic significance and targeted agents of therapeutic relevance to VSCC have been published by Clancy et al. The authors described extracellular regulators of cellular activity as well as inhibitors of angiogenesis that are clinically evaluated in VSCC. [5]

No SCC vulvar cancers

A prospective pilot study assessing the clinical and histologic effects of topical imiquimod therapy on recurrent extramammary Paget's disease of the vulva has been published by Cowan et al. [6]. Eight patients with recurrent extramammary Paget's disease were treated with 5 % imiquimod cream three times per week for twelve weeks. Complete clinical and histologic response was achieved in six (75 %) patients. Of the two remaining patients, one had a complete clinical response but no significant histologic response; the other patient was removed from the study protocol due to the intolerable local irritation.

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Treatment of recurrent vulvar cancer

- Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	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
2	Should groin recurrence still be considered as a palliative situation in vulvar cancer patients? A brief report.	Janine N. et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26894938
3	Interstitial high-dose-rate brachytherapy in locally advanced and recurrent vulvar cancer.	Kellas-Sleczka S et al.	J Contemp Brachytherapy.	http://www.ncbi.nlm.nih.gov/pubmed/26985195
4	Outcomes of Bleomycin-based electrochemotherapy in patients with repeated loco-regional recurrences of vulvar cancer.	Pellegrino A et al.	Acta Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26882959
5	The forgotten woman's cancer: vulvar squamous cell carcinoma (VSCC) and a targeted approach to therapy.	Clancy A et al.	Ann Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27329249
6	A pilot study of topical imiquimod therapy for the treatment of recurrent extramammary Paget's disease.	Renee A et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27112632

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Minimal invasive surgery in gynaecological cancer (laparoscopy, robotics)

Editor Borja Otero

Descriptive summary

Minimally invasive surgery (MIS) has become a topic of increasing interest for the treatment of gynaecological malignancies, laparoscopy becoming the standard route for radical hysterectomy in many centres as described in a tertiary Spanish centre. [1]

Even though the risk of venous thromboembolism is low after major laparoscopic surgery, it is still associated with increased 30-day mortality, as shown in a recent analysis of the ACS-NSQIP database. VTE was found in between 5 %-8 % of patients. [2] There was a trend toward a higher risk of VTE among patients with disseminated cancer, compared with those with early cancers (3.6 % vs. 0.6 %, p = .05). No difference was found in the risk of VTE based on operative time or cancer site.

Two recent papers have compared the use of 3D laparoscopy versus 2D laparoscopy and open surgery for the treatment of cervical and endometrial cancer, respectively, concluding that its use is safe and it provides benefits such as shorter operating time for novice surgeons using 3D. [3, 4]

Regarding robotic-assisted laparoscopy, a new robotic device (Telelap ALF-X) has been evaluated in a retrospective cohort study of 43 patients for the treatment of early-stage endometrial cancer, showing that its use could be comparable to standard laparoscopy, although further studies should be conducted to assess the role of this device in endometrial cancer staging. [5]

Cervical cancer

A case-control study compared a robotic versus laparoscopic approach for total mesometrial resection for the treatment of early-stage cervical cancer. In the short term, there does not seem to be any clinically relevant difference between groups regarding operative time or intraoperative and postoperative complications. [6]

Two reviews of literature and a meta-analysis comparing robotic and laparoscopic approaches for both radical trachelectomy and radical hysterectomy conclude that both routes might be comparable and longer follow-up periods should be reported to define long-term oncological outcomes. [7-9]

Endometrial cancer

A randomised controlled trial in 101 patients comparing robotic versus traditional laparoscopic surgery demonstrates that, in a well-trained team, robotic surgery was shorter and had fewer conversions to laparotomy than laparoscopy, with no differences in the number of lymph nodes removed, bleeding, or the length of postoperative hospital stay. [10] The robotic approach seems to have similar 30-day costs than open staging, based upon its lower postoperative complications, shorter median length of stay, and lower readmission rate. [11]

The increased risk of positive cytology during laparoscopic surgery for uterine cancer using a uterine manipulator is a major issue of concern, and two papers have reassured the fact that this risk is not increased based on retrospective single institution data. [12,13]

Finally, transumbilical laparoendoscopic single-site surgery has been compared to traditional laparoscopic surgery for endometrial cancer in a retrospective study of 36 patients, showing similar short-term surgical outcomes with increased cosmetic satisfaction. [14]

Ovarian cancer

This tumour remains the most controversial gynaecologic malignancy in which an MIS approach could be used.

Laparoscopy has been previously described as a valid tool to predict the ability to resect tumour to no gross residual disease when performed prior to primary debulking surgery. A paper published by Bresson et al. has compared classic laparoscopy versus single-port laparoscopy for this purpose, showing that single-port laparoscopy is an accurate and safe technique to assess the peritoneal cancer index, thus helping guide therapeutic decisions in advanced epithelial ovarian cancer. [15]

Laparoscopy has also been compared to laparotomy as a valid option for the treatment of early-stage ovarian cancer, showing that four-year progression free survival and overall survival achieved with this technique have no statistical significant differences with the ones achieved by laparotomy. [16] Robotic-assisted laparoscopy has also been evaluated in these patients with the same results. [17]

MIS has also been evaluated as an option for the treatment of interval debulking surgery in patients with clinical complete response after neoadjuvant chemotherapy. The MISSION trial has demonstrated its safeness in terms of preoperative outcomes and short-term survival rate, although these results should be confirmed with a longer follow-up period. [18]

Finally, laparoscopy may help to also predict the risk of developing major complications after primary debulking surgery (PDS) as demonstrated by Vizzielli et al. Data from 555 patients undergoing staging laparoscopy prior to primary debulking surgery were prospectively collected and retrospectively analysed,to develop a score (including presence of ascites, Ca-125 levels, amount of laparoscopic tumour load etc) to predict risk of major complication during the primary debulking surgery. [19]

The STELLA trial has compared transperitoneal versus extraperitoneal laparoscopic aortic lymphadenectomy for surgical staging of endometrial and ovarian cancer, concluding that both approaches are comparable in providing similar preoperative outcomes and lymph node recruitment. [20]

The prevalence of port site metastases in these patients could be as high as 46.7 % of 250 cases, as demonstrated by Ataseven et al. Although these port-site metastases had no impact on survival, they were associated with more postoperative complications. [21] Also see report on "Surgical treatment of primary ovarian cancer" by Sileny Han.

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Minimal invasive surgery in gynaecological cancer (laparoscopy, robotics)

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Evolution of radical hysterectomy for cervical cancer along the last two decades: single institution experience.	Arispe C et al.	Chin J Cancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/27199519
2	Risk of venous thromboembolism following laparoscopic surgery for gynaecologic malignancy.	Mahdi H et al.	J Minim Invasive Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/27353413
3	Incorporating 3D laparoscopy for the management of locally advanced cervical cancer: a comparison with open surgery.	Raspagliesi F et al.	Tumori	http://www.ncbi.nlm.nih.gov/pubmed/27373783
4	How Technology Can Impact Surgeon Performance: A Randomised Trial Comparing 3-Dimensional versus 2-Dimensional Laparoscopy in Gynecology Oncology.	Fanfani F et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/27046747
5	Telelap ALF-X vs. Standard Laparoscopy for the Treatment of Early-Stage Endometrial Cancer: A Single-Institution Retrospective Cohort Study.	Gueli Alletti S et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26602025
6	Robotic Total Mesometrial Resection versus Laparoscopic Total Mesometrial Resection in Early Cervical Cancer: A Case-Control Study.	Vizzielli G et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/27109189
7	Robotic Versus Laparoscopic Radical Trachelectomy for Early-Stage Cervical Cancer: Case Report and Review of Literature.	Api M et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26631768
8	Robot-assisted hysterectomy for endometrial and cervical cancers: a systematic review.	Nevis IF et al.	J Robot Surg.	http://www.ncbi.nlm.nih.gov/pubmed/27424111
9	Robotic vs. laparoscopic radical hysterectomy for cervical cancer: a meta-analysis.	Zhou J et al.	Int J Med Robot.	http://www.ncbi.nlm.nih.gov/pubmed/25823530
10	Robotic-assisted vs. traditional laparoscopic surgery for endometrial cancer: a randomised controlled trial.	Mäenpää MM et al.	Am J Obstet Gynecol. 2016	http://www.ncbi.nlm.nih.gov/pubmed/27288987
11	Incorporating robotic-assisted surgery for endometrial cancer staging: Analysis of morbidity and costs.	Bogani G1 et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/26896826
12	Laparoscopic treatment of early-stage endometrial cancer with and without uterine manipulator: Our experience and review of literature.	Tinelli R et al.	Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27312035
13	Conversion of intraperitoneal cytology during laparoscopic surgery of uterine cancer.	von Heesen A et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/27177538
14	Treatment of Early Stage Endometrial Cancer by Transumbilical Laparoendoscopic Single-Site Surgery Versus Traditional Laparoscopic Surgery: A Comparison Study.	Cai HH et al.	Medicine (Baltimore).	http://www.ncbi.nlm.nih.gov/pubmed/27057851
15	Single-port or Classic Laparoscopy Compared With Laparotomy to Assess the Peritoneal Cancer Index in Primary Advanced Epithelial Ovarian Cancer.	Bresson L et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/27068278
16	Laparoscopic Versus Laparotomic Surgical Staging for Early-Stage Ovarian Cancer: A Case-Control Study.	Gallotta V et al.	J Minim Invasive Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/26995493
17	Feasibility and surgical outcomes of conventional and robot-assisted laparoscopy for early-stage ovarian cancer: a retrospective, multicenter analysis.	Bellia A et al.	Arch Gynecol Obstet	http://www.ncbi.nlm.nih.gov/pubmed/27040423
18	Minimally invasive interval debulking surgery in ovarian neoplasm (MISSION trial-NCT02324595): a feasibility study.	Gueli Alletti S et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26529370
19	A laparoscopic risk-adjusted model to predict major complications after primary debulking surgery in ovarian cancer: A single-institution assessment.	Vizzielli G et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27103179
20	Prospective Randomised Trial Comparing Transperitoneal Versus Extraperitoneal Laparoscopic Aortic Lymphadenectomy for Surgical Staging of Endometrial and Ovarian Cancer: The STELLA Trial.	Díaz-Feijoo B et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27098143
21	Prognostic Impact of Port-Site Metastasis After Diagnostic Laparoscopy for Epithelial Ovarian Cancer.	Ataseven B et al.	Ann Surg Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27406097

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Sentinel node mapping in gynaecological malignancies

Editor Anton Ilin

Descriptive summary

Vulvar cancer

For vulvar cancer it seems controversial whether to perform lymph node dissection (LND) for patients with unilateral positive sentinel node or not. Woelber et al. presented the first data that answers this question. In this retrospective analysis, 33 patients with a unilateral metastatic sentinel lymph node (SLN) were analysed. Twenty-eight had a negative sentinel node in the contralateral groin but nevertheless underwent bilateral inguinofemoral lymphadenectomy. No contralateral nonsentinel node metastases were found. The other five patients underwent ipsilateral inguinofemoral lymphadenectomy. No groin recurrences in the contralateral groin were observed in these patients. [1] In their study, Woelber et al. did not distinguish between lateralized and midline lesions.

Where in lateralized lesions it is considered safe to accept unilateral sentinel node detection, in midline lesions bilateral sentinel node identification is advised. [2] For recurrent vulvar cancer after SLN detection procedure, the most common management is inguino femoral lymphadenectomy with local excision. Doorn et al. in their study showed a feasibility of repeat SLN procedure on 27 patients. In 78 % of patients and in 84 % of the groins, the repeat SLN procedure was successful. [3]

Endometrial cancer

There is no common opinion about injection technique and rout of tracer administration for endometrial cancer (EC). It is known that there are two major routes of lymphatic drainage from the uterus. The main one follows the uterine vessels through the parametrium (the one identified through cervical injection) and another way follows the ovarian vessels to nodal basins into the para-aortic area (this one may be identified using corporal or deep cervical injection techniques).

Bogani et al., based on a literature review and own data, concluded that the hysteroscopic way may significantly increase positive paraaortic nodes identification. [4]

SLN mapping with 99mTc, blue dye, and indocyanine green (ICG has been reported by Papadia et al., who published results of a retrospective analysis of 75 EC patients undergoing ICG SLN mapping ± pelvic and/or para-aortic lymphadenectomy. Overall and bilateral detection rates were 96 % (72/75) and 88 % (66/75), respectively. The false negative rate was 8.3 %. Estimated blood loss and operative time were significantly lower in patients undergoing SLN mapping only. Authors concluded that ICG SLN mapping has excellent overall and bilateral detection rates and a low false-negative rate. [5]

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In cervical and endometrial cancer, ICG SLN mapping seems to be equivalent to the combination of blue dye and 99mTc in terms of overall and bilateral detection rates. Ruscito et al. published results of meta-analysis where they assessed indocyanine green with other conventional methods. In all, 538 patients were included. Compared with blue dye, ICG SLN mapping had higher overall (odds ratio [OR] 0.27; 95 % confidence interval [CI] 0.15–0.50; p 0.0001) and bilateral detection rates (OR 0.27; 95 % CI 0.19–0.40; p 0.00001). No differences were found between ICG and 99mTc, although these results are based on data from a single series. [6]

Cervical cancer

Fagotti et al. allocated a group of patients with cervical cancer stage IA1-IB1/IIA1 that had a low risk of lymph node metastases. A total of 368 patients were identified. Tumour diameter ≥20 mm was the only independent predictor of positive LN status (P = 0.003). None of the 106 patients with negative MRI nodal assessment, with squamous and adenosquamous histotype, and a tumour diameter less than 2 cm had positive LNs. [7] Application of this surgical algorithm could safely reduce LND performed in patients with very low-risk early-stage cervical cancer.

Results obtained using indocyanine green fluorescence (ICG) for SLN mapping are often compared with results with the radiotracer Tc-99m and blue dye (BD). In most cases, the detection rate was similar for both. Buda et al. presented results of a retrospective study of 144 patients with cervical cancer stage 1A2 to 1B1. The detection rate of SLN mapping was 96 % and 100 % for Tc-99m with BD and ICG, respectively [8]. Bilateral mapping was achieved in 98.5 % for ICG and 76.3 % for Tc-99m with BD. This difference was statistically significant ($p < 0.0001$). Taking into account accuracy, safety, and reproducibility of using ICG it seems to be a reasonable alternative to standard radiocolloid and BD.

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Sentinel node mapping in gynaecological malignancies

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	The risk of contralateral non sentinel metastasis in patients with primary vulvar cancer and unilaterally positive sentinel node.	Woelber L et al.	Ann Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26856721
2	The Risk of Contralateral Nonsentinel Metastasis in Patients with Primary Vulvar Cancer and Unilaterally Positive Sentinel Node	Oonk MHM et al.	Ann Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/27027311
3	Repeat sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma is feasible	van Doorn HC et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/26797295
4	Sentinel lymph node detection in endometrial cancer: make injection site the difference?	Bogani G et al.	Gynecol Oncol.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4717228/
5	Laparoscopic Indocyanine Green Sentinel Lymph Node Mapping in Endometrial Cancer	Papadia A et al	Ann Surg Oncol.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4889624/
6	Sentinel Node Mapping in Cervical and Endometrial Cancer: Indocyanine Green Versus Other Conventional Dyes—A Meta-Analysis	Ruscito I et al.	Ann Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/27160526
7	Beyond sentinel node algorithm. Toward a more tailored surgery for cervical cancer patients	Fagotti A et al.	Cancer Med.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4971900/
8	From Conventional Radiotracer Tc-99(m) with Blue Dye to Indocyanine Green Fluorescence: A Comparison of Methods Towards Optimization of Sentinel Lymph Node Mapping in Early Stage Cervical Cancer for a Laparoscopic Approach.	Buda A et al.	Ann Surg Oncol.	https://www.ncbi.nlm.nih.gov/pubmed/27126631

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

Editor Elisa Piovano

Descriptive summary

During the period covered, fourteen papers were considered important for the LIFE report.

Lymphocele / lymphedema / chylous ascites

Minig et al. describe their initial favourable experience in eighteen women treated with TachoSil® (fibrin sealant patch) to prevent symptomatic lymphocele after debulking surgery with lymphadenectomy for advanced stage ovarian cancer.

Boccardo et al. describe the LYMPHA technique (performing multiple lymphatic-venous anastomoses after inguinofemoral lymph node completion) in vulva cancer and melanoma, to prevent lymphedema. They report a favourable experience in eleven patients.

Baek et al. describe an interesting technique to perform a lymphatic embolization in the treatment of pelvic lymphoceles. Their experience with five patients is described, with promising results especially in those lymphoceles with a single inflow vessel.

Ki et al. show a direct correlation between the number of lymph nodes resected in 413 ovarian cancer surgeries and the incidence of lower extremity lymphedema.

Thiel et al. show the same direct correlation between the number of nodes dissected in gynae-onc surgery and the incidence of chylous ascites, with an incidence of 3 % in their patients submitted to pelvic and paraaortic lymphadenectomy. Moreover, they report a stronger correlation between chylous ascites and laparoscopic lymphadenectomy when compared to open surgery.

Surgical site infection (SSI)

Tuomi et al. present a very interesting study analysing the incidence and risk factors for SSI in a cohort of 1,164 women with endometrial carcinoma. SSI was diagnosed in 8.1 % of patients. Obesity (body mass index ≥ 30 kg/m(2)), diabetes, and long operative time (>80th centile) were independently associated with a higher risk of incisional infection, whereas minimally invasive surgery was associated with a smaller risk.

Johnson et al. describe their experience implementing a bundle (set of evidence-based practices performed collectively) to reduce 30-day SSI in gynae-onc patients. The relative risk reduction in SSI was 82.4 % (p=.01).

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Lynam et al. suggest a potential role of prophylactic negative pressure wound therapy (NPWT) in obese patients at the time of laparotomy for gynae-onc surgery.

Venous thromboembolic disease (VTE)

Barber et al. retrospectively compare the 30-das postoperative VTE rate in minimally invasive surgery (MIS) and in open surgery in 9,948 patients and showed a significantly lower rate of VTE after MIS (0.7 vs. 2.2 %, p<.001). However, data regarding the compliance with of perioperative venous thromboembolism prophylaxis were not available; therefore these results are quite difficult to generalise.

Wright et al. examine the utilisation and effectiveness of extended-duration low molecular weight heparin in prophylaxis in high-risk cancer patients. Analysing 63,280 patients, they discovered that, even if the extended prophylaxis is recommended in national guidelines, its use is low among cancer patients undergoing surgery. In contrast to previous randomised controlled trials, they found no association between the use of extended-duration prophylaxis and the reduction in the risk of VTE, but noted a small increased risk of adverse events.

Freeman et al. focused instead on mechanical VTE prophylaxis vs. combined mechanical+pharmacological prophylaxis in 1,413 patients with EC treated by MIS. The incidence of VTE was very low: 0.23 % (mechanical+ pharmacological) and 0.55 % (mechanical) (p=.38), suggesting that mechanical prophylaxis is sufficient for these women undergoing MIS.

Predicting complications

Rivard et al. tested the ability of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) surgical risk calculator to predict complications in gynaecological oncology patients undergoing laparotomy. Specific serious complications, such as postoperative death and cardiac complications, were adequately predicted. However, the overall performance of the calculator was worse for gynaecological oncology patients than reported in general surgery patients. A tailored prediction model may be needed for this patient population.

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

Descriptive summary (cont.)

Reporting complications

Meghelli et al. systematically reviewed 179 consecutive studies in the reporting on adverse events (AEs) in surgery in oesophagogastric or gynaecological cancer. Postoperative AEs were described in 90 % of the studies, but the definition of AEs and the grading scale (NCI-CTC AE, Dindo-Clavien scale, etc.) were given only in 27.3 % and 16.8 % of the studies, respectively. Reporting of AEs did not improve over time nor was it better in high-impact-factor journals.

In conclusion, a review by Becker et al. summarises complications in gynaecological minimal-access oncosurgery, detailing the major causes of and the strategies for prevention, early detection, and intra- and postoperative management.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Use of TachoSil to Prevent Symptomatic Lymphocele after an Aggressive Tumor Debulking with Lymphadenectomy for Advanced Stage Ovarian Cancer. A Pilot Study.	Minig L et al.	Gynecol Obstet Invest.	http://www.ncbi.nlm.nih.gov/pubmed/27046053
2	LYMPHA Technique to Prevent Secondary Lower Limb Lymphedema.	Boccardo F et al.	Ann Surg Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27221358
3	Lymphatic Embolization for the Treatment of Pelvic Lymphoceles: Preliminary Experience in Five Patients.	Baek Y et al.	J Vasc Interv Radiol.	http://www.ncbi.nlm.nih.gov/pubmed/27241389
4	Incidence and Risk Factors of Lower Extremity Lymphedema After Gynecologic Surgery in Ovarian Cancer.	Ki EY et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27400319
5	Chylous ascites after lymphadenectomy for gynecological malignancies.	Thiel FC et al.	J Surg Oncol.	www.ncbi.nlm.nih.gov/pubmed/27378217
6	Incidence of and risk factors for surgical site infections in women undergoing hysterectomy for endometrial carcinoma.	Tuomi T et al.	Acta Obstet Gynecol Scand.	http://www.ncbi.nlm.nih.gov/pubmed/26661044
7	Using Bundled Interventions to Reduce Surgical Site Infection After Major Gynecologic Cancer Surgery.	Johnson MP et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/27159744
8	Primary Placement of Incisional Negative Pressure Wound Therapy at Time of Laparotomy for Gynecologic Malignancies.	Lynam S et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27488215
9	Venous Thromboembolism in Minimally Invasive Compared With Open Hysterectomy for Endometrial Cancer.	Barber EL et al.	Obstet Gynecol.	http://www.ncbi.nlm.nih.gov/pubmed/27275805
10	Prescription of extended-duration thromboprophylaxis after high-risk, abdominopelvic cancer surgery.	Wright JD et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27032377
11	Venous thromboembolism following minimally invasive surgery among women with endometrial cancer.	Freeman AH et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/27264213
12	Evaluation of the performance of the ACS NSQIP surgical risk calculator in gynaecologic oncology patients undergoing laparotomy.	Rivard C et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26899020
13	Reporting adverse events in cancer surgery randomised trials: A systematic review of published trials in oesophago-gastric and gynecological cancer patients.	Meghelli L et al.	Crit Rev Oncol Hematol.	http://www.ncbi.nlm.nih.gov/pubmed/27323658
14	Complications in gynaecological minimal-access oncosurgery	Becker et al.	Best Pract Clin Obstetr Gynaecol	http://www.ncbi.nlm.nih.gov/pubmed/27066936

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Technical aspects / tricks of surgery in management of gynaecological malignancies

Editor Elisa Piovano

Descriptive summary

Technical aspects

During the period covered by the fourth edition of the LiFE report, six interesting papers dealing with technical aspects of gynae-onc surgery were published.

Two papers dealt with surgical material that can mimic an ovarian cancer or an ovarian cancer relapse. The first, by Cormio et al., is a case report focused on Surgicel® (absorbable sterile mesh composed of oxidized cellulose that is used to control intraoperative capillary or venous bleeding) mimicking an ovarian cancer. The second paper by Kwon et al. focuses on Surgi-Wrap® (anti-adhesion material) mimicking ovarian cancer relapses. They present a retrospective series of 92 patients: 9/92 had local recurrence based on the imaging findings, with normal tumour marker levels. Six of them underwent laparoscopic exploration with biopsies, which showed a foreign body reaction in five women. The authors of these papers suggest always removing the Surgicel® after use and to avoid the use of Surgi-Wrap® in ovarian cancer surgery.

Advanced ovarian cancer surgery

Another four papers focus on surgery in advanced ovarian cancer (AOC) and in particular on upper abdomen and thoracic surgery.

Di Guilmi et al. analysed 187 patients with suspected ovarian cancer submitted to video-assisted thoracoscopic surgery (VATS): Among patients with pleural effusions, VATS revealed pleural disease in 57 % of patients, and 73 % of patients with positive pleural cytology had the evidence of pleural disease at the time of VATS. In addition, 23.5 % of patients with negative pleural cytology had evidence of pleural disease at the time of VATS. In all, 41 % of patients had a change of disease stage after VATS.

A Japanese paper by Kato et al. described their early experience with a ventral liver mobilization technique to remove diaphragmatic tumours with liver involvement in AOC.

Panuccio et al. dealt with the role and the complications of extensive cytoreduction with PlasmaJet® (a neutral plasma surgery system designed for cutting, coagulation and the removal of soft tissue by vaporization) in nineteen AOC patients with peritoneal carcinomatosis. They obtained a complete resection of all macroscopic disease in all patients, with thirteen adverse events (AEs) <= G2, one G3 AE, and no postoperative mortality.

Prader et al. evaluated the outcome of systematic resection of suspicious cardiophrenic lymph nodes detected on preoperative CT-scan in patients with AOC in a prospective series of 196 consecutive patients undergoing primary debulking surgery. Suspicious cardiophrenic lymph nodes were defined as ≥10mm on the short axis diagnosed in pre-operative CT-scan and were removed if intra-abdominal debulking resulted in complete resection or residual tumour <10mm. Removal of suspicious cardiophrenic lymph nodes was performed via a trans-diaphragmatic approach. In all, 15 % of patients had both suspicious cardiophrenic lymph nodes and complete resection or residual tumour <10mm, and in 90 % of them, metastasis was histologically confirmed. The authors conclude by defining this surgical procedure feasible without major complications if performed by experienced gynae-oncologists, but the prognostic value of this procedure should be evaluated in larger controlled studies.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Surgicel granuloma mimicking ovarian cancer: A case report.	Cormio L et al.	Oncol Lett.	http://www.ncbi.nlm.nih.gov/pubmed/27446398
2	Foreign body reaction from anti-adhesion material during follow-up of gynaecological malignancies: Mimicking local recurrence.	Kwon YS et al.	Aust N Z J Obstet Gynaecol.	http://www.ncbi.nlm.nih.gov/pubmed/27297456
3	Role of Video-Assisted Thoracoscopy in Advanced Ovarian Cancer: A Literature Review.	Di Guilmi J et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/26937753
4	Cytoreduction of diaphragmatic metastasis from ovarian cancer with involvement of the liver using a ventral liver mobilization technique.	Kato K et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26801940
5	Use of PlasmaJet for Peritoneal Carcinomatosis in Ovarian Cancer.	Panuccio E et al.	Int J Gynecol Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27488213
6	Surgical management of cardiophrenic lymph nodes in patients with advanced ovarian cancer.	Prader S et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26972337

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Fertility-sparing treatment in gynaecological malignancies

Editor Dimitris Papatheodorou

Descriptive summary

In this literature search we retrieved several 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. enrolled seventeen patients with atypical endometrial hyperplasia and nineteen 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 multicentre 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. In all, 56 women were included in this study; 81 % in the reproductive follow-up group managed to conceive. Interestingly, 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.

Relevant articles retrieved Feb 2016 - Sep 2016

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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Imaging in gynaecologic malignancies

Editor Tanja Nikolova and Natasha Nikolova

Descriptive summary

Published studies covering the problem of imaging in gynaecological malignancies were critically appraised and analysed, and results and conclusions are briefly presented in separate sections according to the cancer localization.

Malignancies of the endometrium

Angioli et al. compared the accuracy of transvaginal sonography (TVS), MRI and human epididymis protein 4 (HE4) in preoperative endometrial cancer staging in 79 patients. Concerning myometrial invasion, MRI and TVS results were comparable. Concerning cervical infiltration, the association between TVS and HE4 is characterized by a better preoperative diagnostic validity in comparison to MRI and TVS taken alone (TVS + HE4 96.3 % vs. 91 % for MRI and 85 % for the TVS). [1]

Rodríguez-Trujillo et al. analysed the usefulness of TVS and MRI as predictors of myometrial invasion in endometrial cancer in 98 patients and found sensitivity, specificity, and accuracy of 77 %, 83 %, and 81 %, respectively, for the ultrasound and 69 %, 86 %, and 81 %, respectively, for MRI. [2]

Lee et al. analysed 389 patients with stage I and II endometrial cancer and report the low utility of chest x-ray, MRI, PET/CT, and TVS in posttreatment surveillance. [3]

Caobelli et al., in a multicentric study including 168 patients, have found that (18)F-FDG PET/CT has an important prognostic value in assessing the risk of endometrial cancer progression and mortality rate. [4]

Arnaiz et al. assessed the efficacy of MRI in 91 patients in predicting the surgical stage of endometrial carcinoma as a diagnostic tool in a routine clinical setting and found that MRI and surgical stage correlated significantly. [5]

Uterine leiomyosarcoma

In the study of Skorstad et al. are presented data from 212 patients diagnosed with uterine leiomyosarcoma. Magnetic resonance imaging (MRI) suggested malignancy in 81 % of examinations, while CT in 59.8 %. [6] Gaetke-Udager et al. did not identify any morphologic parameter to be a significant predictor of leiomyosarcoma. [7]

Cervical cancer

Mongula et al. have analysed the predictive criteria for MRI in evaluation of response both during and after radiotherapy for cervical cancer. For a less experienced observer, the MRI criteria set significantly improved the prediction of residual tumours compared to a "subjective" visual evaluation of T2 weighted MRI images. [8]

Marconi et al. in 66 cases have investigated the association of DW-MRI parameters with baseline clinical features and clinical outcomes, local regional control, disease-free survival and disease-specific survival in cervical cancer patients treated with definitive chemoradiation. Women with disease stage III-IV (FIGO) had significantly higher mean apparent diffusion coefficient (ADCmax) values compared with those with stage I-II (1.806 vs. 1.485, p=0.01). Patients with imaging-defined positive nodes also had significantly higher mean ADCmax values compared with lymph node negative patients (1.995 vs. 1.551, p=0.03). [9]

Bhosale et al. determined the ability of MRI in detecting tumour-free margins from the internal os in 79 patients. They report sensitivity, specificity, PPV, and NPV of: 73 %, 98.3 %, 95 %, and 88.1 %, respectively, which makes MRI suitable for treatment planning in patients desiring trachelectomy to preserve fertility. [10]

Yang et al. evaluated the value of PET/CT in correcting the clinical stages and predicting pathological parameters preoperatively in 113 cervical cancer cases. They found that the accuracy of tumour staging by PET/CT was 94.7 %, thus appearing as more objective compared to the traditional staging system. [11]

Hoogendam et al. explored the accuracy of 99mTc SPECT/MRI fusion for the selective assessment of nonenlarged sentinel lymph nodes (SLNs) for diagnosing metastases in early-stage cervical cancer patients. They found that in cases without enlarged lymph nodes, selective evaluation of only SLNs for size and absence of sharp demarcation can be used to noninvasively assess the presence of metastases. [12]

Ho et al., in a prospective study with bulky cervical cancer (≥ 4 cm), analysed the role of intratumoral metabolic heterogeneity on PET (standardised uptake values, metabolic tumour volume, and total lesion glycolysis) during concurrent chemoradiotherapy in predicting survival outcomes in 44 patients. The five-year overall survival rate for the high-risk was significantly worse than that for the low-risk group (42 % vs. 81 %, respectively, P = 0.001). This gives the opportunity to adjust individualised regimens early in the treatment course. [13]

Chung et al. have investigated the prognostic value of intratumoural [^{1} F] fluorodeoxyglucose uptake heterogeneity derived from PET/CT in 85 patients with cervical cancer and have found that its preoperative quantity was significantly associated with cervical cancer recurrence. [14]

Ovarian cancer

Fischerova et al., in the largest imaging study on ovarian cancer staging, analysed the accuracy of ultrasound in assessing pelvic and intra-abdominal disease in 394 patients with ovarian cancer. The over-

Continued on the next page ➲

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Imaging in gynaecologic malignancies

Descriptive summary (cont.)

all accuracy in evaluating multiple abdominal peritoneal compartments and retroperitoneal lymph nodes reached 85.3 % and 84.5 %, respectively. A lower accuracy than 85 % was found in the assessment of diaphragm, infracolic omentum, mesentery, and retroperitoneal lymph nodes, but accuracy was at 90 % and higher for the evaluation of supracolic omentum, abdominal wall, and visceral peritoneum. [15]

Vulvar and vaginal carcinoma

Robertson et al. evaluated the changes in prognosis and management following PET/CT in 50 patients with vulvar and vaginal carcinoma and found that FDG-PET/CT may play an important role in the management of vulvar and vaginal carcinoma. [16]

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Preoperative local staging of endometrial cancer: the challenge of imaging techniques and serum biomarkers.	Angioli R et al.	Arch Gynecol Obstet.	http://www.ncbi.nlm.nih.gov/pubmed/27535757
2	Preoperative Assessment of Myometrial Invasion in Endometrial Cancer by 3D Ultrasound and Diffusion-Weighted Magnetic Resonance Imaging: A Comparative Study.	Rodríguez-Trujillo A et al.	Int J Gynecol Cancer Off J Int Gynecol Cancer Soc.	http://www.ncbi.nlm.nih.gov/pubmed/27177278
3	Detecting Asymptomatic Recurrence in Early-Stage Endometrial Cancer: The Value of Vaginal Cytology, Imaging Studies, and CA-125.	Lee J-Y et al.	Int J Gynecol Cancer Off J Int Gynecol Cancer Soc.	http://www.ncbi.nlm.nih.gov/pubmed/27465903
4	Predictive value of (18)F-FDG PET/CT in restaging patients affected by ovarian carcinoma: a multicentre study.	Caobelli F et al.	Eur J Nucl Med Mol Imaging.	http://www.ncbi.nlm.nih.gov/pubmed/26381775
5	Magnetic Resonance Imaging for the Pre-Surgical Assessment of Endometrial Cancer: Results in a Routine Clinical Setting, Outside Dedicated Trials; a Cross-sectional Study.	Arnaiz J et al.	Anticancer Res.	http://www.ncbi.nlm.nih.gov/pubmed/27069176
6	Preoperative evaluation in women with uterine leiomyosarcoma. A nation-wide cohort study.	Skorstad M et al.	Acta Obstet Gynecol Scand.	http://www.ncbi.nlm.nih.gov/pubmed/27564388
7	Diagnostic Accuracy of Ultrasound, Contrast-enhanced CT, and Conventional MRI for Differentiating Leiomyoma From Leiomyosarcoma.	Gaetke-Udager K et al.	Acad Radiol.	http://www.ncbi.nlm.nih.gov/pubmed/27396800
8	Predictive criteria for MRI-based evaluation of response both during and after radiotherapy for cervical cancer.	Mongula J et al.	J Contemp Brachytherapy.	http://www.ncbi.nlm.nih.gov/pubmed/27504126
9	Pre-treatment MRI minimum apparent diffusion coefficient value is a potential prognostic imaging biomarker in cervical cancer patients treated with definitive chemoradiation.	Marconi DG et al.	BMC Cancer.	http://www.ncbi.nlm.nih.gov/pubmed/27469349
10	Is MRI helpful in assessing the distance of the tumour from the internal os in patients with cervical cancer below FIGO Stage IB2?	Bhosale PR et al.	Clin Radiol.	http://www.ncbi.nlm.nih.gov/pubmed/27012496
11	(18)F-FDG PET/CT can correct the clinical stages and predict pathological parameters before operation in cervical cancer.	Yang Z et al.	Eur J Radiol.	http://www.ncbi.nlm.nih.gov/pubmed/27130046
12	99mTc-Nanocolloid SPECT/MRI Fusion for the Selective Assessment of Nonenlarged Sentinel Lymph Nodes in Patients with Early-Stage Cervical Cancer.	Hoogendam JP et al.	J Nucl Med Off Publ Soc Nucl Med.	http://www.ncbi.nlm.nih.gov/pubmed/26678614
13	A preliminary investigation into textural features of intratumoral metabolic heterogeneity in (18)F-FDG PET for overall survival prognosis in patients with bulky cervical cancer treated with definitive concurrent chemoradiotherapy.	Ho K-C et al.	Am J Nucl Med Mol Imaging.	http://www.ncbi.nlm.nih.gov/pubmed/27508103
14	Prognostic value of preoperative intratumoral FDG uptake heterogeneity in early stage uterine cervical cancer.	Chung HH et al.	J Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26768781
15	Ultrasound in preoperative assessment of pelvis and abdominal spread in patients with ovarian cancer: a prospective study	Fischerova et al.	Ultrasouns Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/27091633
16	The impact of FDG-PET/CT in the management of patients with vulvar and vaginal cancer.	Robertson NL et al.	Gynecol Oncol.	http://www.ncbi.nlm.nih.gov/pubmed/26790773

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

Editor Manuela Undurraga

Descriptive summary

The articles published during the period were mainly case reports, retrospective studies, and reviews. There was one prospective trial, one randomised controlled trial, and one meta-analysis, as well as one patient information summary by the National Cancer Institute.

Different reviews were conducted on specific types of gestational trophoblastic neoplasia (GTN). The Jiao team analysed intraplacental choriocarcinoma reporting its excellent maternal and neonatal prognosis. They propose management guidance. Zhao studied identify prognostic factors and treatment strategies for placental site trophoblastic tumour (PSTT). Only stage IV was a significant negative predictive factor for survival, and suggest that preservation of fertility may be considered in certain patients. Moreover, in most stage I patients, surgery alone will be curative. Choriocarcinoma was studied by Li, who found that the most important risk factors for prognosis were FIGO score >12 and resistance to chemotherapy. It is important to note that most of their chemotherapy regimen contained 5-FU, which differs from European guidelines, and seems to be more effective in the Chinese population, as corroborated by Yang.

Pathology

Hao analysed the clinical significance of the expression of Wnt11 and BCLA2A1 in complete moles, and found that their expression was highest in moles that later developed to GTN. Braga analysed the apoptotic index in moles and subsequent development of GTN and found that caspase-3 apoptotic index was a strong risk factor. Colgan found that after using molecular genotyping and selective use of p57 staining, the observed incidence of hydatidiform mole (HM) was higher than in previous studies due to the improvement of partial mole diagnosis. Complete moles were half as common as patial moles and they suggest to use this ratio for benchmarking laboratory diagnosis. Aranake suggests that short tandem repeat analysis may be useful to establish the molar origin in unusual presentations of trophoblastic tumours and their mimics.

In the differential diagnosis of choriocarcinoma and PSTT, Stichelbout found that SALL4 may be an important marker, as it is expressed in 100 % of choriocarcinomas but not in other trophoblastic tumours.

Diagnosis

Gockley reported no significant difference in presenting symptoms, gestational age at diagnosis, and pre-evacuation serum human chorionic gonadotropin (hCG) level by race/ethnicity. However, Hispanics are significantly less likely than whites to develop GTN.

The role of positron emission tomography (PET) for diagnosis and follow-up of GTD was analysed in a review by Mangili, who found that it may play a role in cases of disease recurrence, chemo-resistance, or surgical planification in choriocarcinoma and PSTT. Its use is still controversial and requires further studies.

Soylu found no difference in platelet parameters in patients with molar pregnancies.

Treatment

There were different publications studying the treatment of low-risk GTN (LRGTN). A Cochrane Database review was done to determine the efficacy and safety of first-line chemotherapy in the treatment of low-risk GTN (LRGTN). They found that actinomycine D (Act-D) is probably more likely to achieve a primary cure in women with LRGTN, and less likely to result in treatment failure than methotrexate (MTX), but may be associated with a greater risk of severe adverse events. This is in contradiction with a prospective randomised trial by Yarandi that compared iv MTX with iv Act-D and did not find any difference in response or resistance rates. Wang compared intracervical MTC + Act-D with 5-FU + Act-D and found the same response rates but higher costs and toxicity with the 5-FU+ Act-D regimen. Lertkhachonsuk found no difference when analysing cost effectiveness of both treatments in the Thai population. Buyn looked at the use of EMA in patients with resistant, high risk. or metastatic disease not amenable to treatment with EMA-CO, finding a high response rate without an increase in adverse effects (when compared to cyclophosphamide/vincristine). Nevado analysed the use of Etoposide and Act-D in salvage therapy for LRGTN and found a high remission rate after two or three cycles with tolerable side effects. Kani et al. evaluated the role of pulmonary resection in GTD. They found that, in patients with pulmonary metastasis and chemo-resistant GTD, the cure rate was at 73 %

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

Descriptive summary (cont.)

after surgery, with no mortality or morbidity. Bolze et al. analysed the mortality rate of patients with GTN with FIGO scores of >= 13, finding an increased risk of death overall, and particularly early death. They suggest that these patients may probably benefit from the use of induction low-dose etoposide and cisplatin and propose that they be treated in highly specialized GTD centres.

Follow-up

Two articles analysed the follow-up of patients with low persistent hCG. Qian found that almost all patients with low levels of hCG returned to normal in a twelve-month period, even those that were considered resistant to chemotherapy and in whom therapy was suspended, as long as they had no detectable lesions in imaging.

Taylor analysed the outcome of women with raised but falling hCG six months after evacuation of molar pregnancies and found that most of these women can be followed safely and can usually avoid chemotherapy, as long as the hCG levels continue to fall.

Pregnancy

A study evaluating fertility analysed the AMH values in three patients and found that low serum AMH is not a reliable predictor of reduced short-term fertility postchemotherapy for GTN. Gaducci found that obstetric outcomes of patients who were treated with chemotherapy for GTN are similar to those of the general population.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Conservative Chemotherapy in Gestational Trophoblastic Disease: Experience With Etoposide, Methotrexate, and Dactinomycin Chemotherapy	Buyn SW et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27057813
2	Pulmonary Resection in the Management of High-Risk Gestational Trophoblastic Neoplasia.	Kanir MJ et. al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26905332
3	Five-Day Intravascular Methotrexate Versus Biweekly Actinomycin-D in the Treatment of Low-Risk Gestational Trophoblastic Neoplasia: A Clinical Randomised Trial.	Yarandi F et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27101581
4	Comparison of MACT and 5Fu+ACT-D chemotherapy regimens in the treatment of low-risk gestational trophoblastic neoplasia.	Wang Y et al.	J Chemother	http://www.ncbi.nlm.nih.gov/pubmed/27105436
5	First-line chemotherapy in low-risk gestational trophoblastic neoplasia.	Lawrie TA et al.	Cochrane Database	http://www.ncbi.nlm.nih.gov/pubmed/27281496
6	Etoposide-Actinomycin as Salvage Regimen for the Treatment of Nonmetastatic and Low-Risk Metastatic Gestational Trophoblastic Neoplasia: Experience at the Philippine General Hospital.	Nevado-Gammad MS et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27206220
7	Effect of race/ethnicity on clinical presentation and risk of gestational trophoblastic neoplasia in patients with complete and partial molar pregnancy at a tertiary care referral center.	Gockley AA et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/27130239
8	[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
9	Immunohistochemical Expression and Clinical Significance of Wnt11 and BCL2A1 in Complete Moles	Hao Z et al.	Anal Quant Cytophatolo Histopathol	http://www.ncbi.nlm.nih.gov/pubmed/27386628
10	A Reappraisal of the Incidence of Placental Hydatidiform Mole Using Selective Molecular Genotyping	Colgan TJ et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27258730
11	The effect of molar pregnancies on platelet parameters	Soylu Karapinar O et al.	J Obstet Gynaecol	http://www.ncbi.nlm.nih.gov/pubmed/27183899
12	Apoptotic index for prediction of postmolar gestational trophoblastic neoplasia	Braga A et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/27094961

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

Relevant articles retrieved Feb 2016 - Sep 2016 (cont.)

No	Title	Authors	Journal	Link to abstract
13	SALL4 expression in gestational trophoblastic tumors: a useful tool to distinguish choriocarcinoma from placental site trophoblastic tumor and epithelioid trophoblastic tumor.	Stichelbout M et al.	Hum Pathol	http://www.ncbi.nlm.nih.gov/pubmed/27068524
14	Intraplacental choriocarcinoma: Systematic review and management guidance.	Jiao L et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27020699
15	Use of short tandem repeat analysis in unusual presentations of trophoblastic tumors and their mimics.	Aranake-Chrisinger J et al.	Hum Pathol	http://www.ncbi.nlm.nih.gov/pubmed/26980014
16	Long-term outcome of patients with persistent low-level elevation of human chorionic gonadotrophin	Qian XQ et al.	J Obstet Gynaecol Res	http://www.ncbi.nlm.nih.gov/pubmed/26916449
17	Late spontaneous resolution of persistent molar pregnancy	Taylor F et al.	BJOG	http://www.ncbi.nlm.nih.gov/pubmed/26774079
18	Changing Trends in the Clinical Presentation and Management of Complete Hydatidiform Mole Among Brazilian Women	Braga A et al.	Int J Gynecol Cancer	http://www.ncbi.nlm.nih.gov/pubmed/26905335
19	Placental site trophoblastic tumor: A review of 108 cases and their implications for prognosis and treatment.	Zhao J et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27168005
20	Mortality rate of gestational trophoblastic neoplasia with a FIGO score of ≥13	Bolze PA et al.	Am J Obstet Gynecol	http://www.ncbi.nlm.nih.gov/pubmed/26433171
21	Clinical characteristics and prognosis of 272 postterm choriocarcinoma patients at Peking Union Medical College Hospital: a retrospective cohort study.	Li J et al.	BMC Cancer	http://www.ncbi.nlm.nih.gov/pubmed/27251425
22	Comparison of Cost-Effectiveness Between Actinomycin D Versus Methotrexate-Folinic Acid in the Treatment of Low-Risk Gestational Trophoblastic Neoplasia.	Lertkhachonsuk AA et al.	J Reprod Med	http://www.ncbi.nlm.nih.gov/pubmed/27424364
23	Anti-Müllerian Hormone in Patients Treated with Chemotherapy for Gestational Trophoblastic Neoplasia Does Not Predict Short-Term Fertility	Ghorani E et al.	J Reprod Med	http://www.ncbi.nlm.nih.gov/pubmed/27424359
24	Prognosis of Patients with Gestational Trophoblastic Neoplasia and Obstetric Outcomes of Those Conceiving After Chemotherapy.	Gadducci A et al.	Anticancer Res	http://www.ncbi.nlm.nih.gov/pubmed/27354611
25	Primary treatment of stage IV gestational trophoblastic neoplasia with floxuridine, dactinomycin, etoposide and vincristine (FAEV): A report based on our 10-year clinical experiences	Yang J et al.	Gynecol Oncol	http://www.ncbi.nlm.nih.gov/pubmed/27426306
26	Gestational Trophoblastic Disease Treatment (PDQ®): Patient Version.	PDQ Adult Treatment Editorial Board.	NCI	http://www.ncbi.nlm.nih.gov/pubmed/27489928

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Cancer in pregnancy

Editor Michael J. Halaska

Descriptive summary

Fifteen papers have been retrieved within the period. Eight of them were reviews summarising current literature on cervical, colorectal, and ovarian cancer and melanoma.

A paper evaluating pregnancy-associated colorectal carcinoma (CRC) found a significant delay of detection of CRC in pregnancy. A case report presenting a patient with breast cancer showed a favourable outcome with treatment with trastuzumab during the first trimester. This is an interesting finding as administration during the 2nd and 3rd trimesters leads to anhydramnios and often infaust prognosis of the fetus, whereas some incidental reports showed that trastuzumab during the 1st trimester did not cause such negative effects. In an interesting epidemiologic study on 126 patients diagnosed during pregnancy with cervical cancer, the hazard ratio for death due to cervical cancer was 1.77 (95 % confidence interval, 1.21-2.60), which is different from previous studies that found a similar prognosis of cervical cancer when diagnosed during and outside of pregnancy. On the other hand, FIGO stage and treatment details were not included in the analysis. Another report on cervical cancer collected 126 from published case reports concentrating on treatment choice, which is mainly directed by gestational age at diagnosis and the wish to preserve the pregnancy.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Management of colorectal neoplasia during pregnancy and in the postpartum period.	Aytac E	World J Gastrointest Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27559434
2	Trastuzumab use during pregnancy: long-term survival after locally advanced breast cancer and long-term infant follow-up.	Andrade JM	Anticancer Drugs	https://www.ncbi.nlm.nih.gov/pubmed/26825868
3	Mortality Among Women With Cervical Cancer During or Shortly After a Pregnancy in Denmark 1968 to 2006.	Eibye S	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27101585
4	Individual management of cervical cancer in pregnancy.	Hecking T	Arch Gynecol Obstet	https://www.ncbi.nlm.nih.gov/pubmed/26728388

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Immunotherapy in gynaecological cancers

Editor Zoltan Novak

Descriptive summary

In this update, we are reporting two papers describing the role of the immune system in ovarian cancer chemoresistance. They were chosen based on a subjective evaluation of their possible clinical impact. The first paper uncovers the mode of action of effector T cells: They abrogate stromal-mediated chemoresistance by altering fibroblast glutathione and cystine metabolism. This work underlines the importance of the interplay between chemotherapy and immunotherapy. [1] MicroRNAs (miRNAs) are a class of small noncoding RNA molecules that post-transcriptionally modulate gene expression. In this paper, researchers show that programmed death-1 ligand 1 (PD-L1) overexpression is associated with chemoresistance. Blocking the PD-L1 and the CD80 expression using MicroRNAs (miRNAs) enhanced the sensitivity of cancer cells to drug treatment and was accompanied by T-cell activation. These data suggest a biological and functional interaction between PD-L1 and chemoresistance through the microRNA regulatory cascade. [2] There were also clinical trials published using vaccines in precancerous lesions.

Alvarez et al. report the safety, efficacy, and immunogenicity of a plasmid vaccine, pNGVL4a-CRT-E7(detox), administered in patients with HPV16-associated CIN2/3. The vaccine was well tolerated; histologic regression occurred in 8 of 27 (30 %) patients and the most robust immune response occurred when administered intralesionally. [3] A phase I clinical trial investigated the safety of a therapeutic vaccine called PepCan, which consists of peptides covering the HPV type 16 E6 protein and Candida skin test reagent in patients with histologically confirmed CIN2/3. No dose-limiting toxicities were observed, and the histological regression rate was 45 % overall (14 of 31). Immune profiling revealed increased effector and decreased regulatory T cell levels following vaccination. Of subjects in whom HPV 16 was detected at entry, it became undetectable in three subjects after vaccination, and the viral loads significantly decreased in nine subjects in whom HPV 16 infection was detected at entry and exit. [4] The authors report the results of a multicentre open-label, randomised controlled trial in patients with HPV16+ high-grade VIN/VaIN following therapeutic vaccination with HPV16 E6 and E7 synthetic long peptides (SLP). The authors studied if imiquimod applied at the vaccine site could improve CD8+ T-cell reactivity, clinical efficacy, and safety of the SLP vaccine. The results confirm that clinical efficacy of the vaccination is related to the strength of vaccine-induced HPV16-specific T-cell immunity and is an effective therapy for HPV16-induced high-grade VIN/VaIN with 53 % of the patients showing a clinical response. However, imiquimod did not improve the outcomes of vaccination. [5] In this update, we report three interesting review papers about the development of a therapeutic HPV vaccine, the current role of immune checkpoint inhibitors in the treatment of gynaecologic cancer patients, and the opportunities of immunotherapy in ovarian cancer patients [6-8].

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Effector T Cells Abrogate Stroma-Mediated Chemoresistance in Ovarian Cancer	Wang W et al.	Cell	http://www.sciencedirect.com/science/article/pii/S0092867416304007
2	miR-424(322) reverses chemoresistance via T-cell immune response activation by blocking the PD-L1 immune checkpoint	Xu S et al.	Nat Commun	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4858750/
3	A pilot study of pNGVL4a-CRT/E7(detox) for the treatment of patients with HPV16+ cervical intraepithelial neoplasia 2/3 (CIN2/3).	Alvarez RD et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/26616223
4	Human papillomavirus type 16 viral load is decreased following a therapeutic vaccination.	Coleman HN et al.	Cancer Immunol Immunother.	https://www.ncbi.nlm.nih.gov/pubmed/26980480
5	Vaccination against Oncoproteins of HPV16 for Noninvasive Vulvar/Vaginal Lesions: Lesion Clearance Is Related to the Strength of the T-Cell Response.	van Poelgeest MI et al.	Clin Cancer Res	http://clincancerres.aacrjournals.org/content/22/10/2342.long
6	Current state in the development of candidate therapeutic HPV vaccines.	Yang A et al.	Expert Rev Vaccines	http://www.tandfonline.com/doi/full/10.1586/14760584.2016.1157477
7	Immune checkpoint inhibitors in gynecologic cancers with lessons learned from non-gynecologic cancers.	Menderes G et al.	Expert Opin Biol Ther	https://www.ncbi.nlm.nih.gov/pubmed/27070175
8	Opportunities in immunotherapy of ovarian cancer	Coukos G et al.	Ann Oncol	http://annonc.oxfordjournals.org/content/27/suppl_1/i11.long

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Treatment of elderly patients with gynaecological cancers

Editor Alex Mutombo

Descriptive summary

Clinical trial data are limited for elderly patients because approximately one-third of the women aged 70 years and older who meet pathologic enrolment criteria for trials are excluded because of complex medical disease, according to a study by Clark et al.

Elderly patients have more advanced disease at diagnosis, and age is an important factor in the allocation of treatment for patients with gynaecological cancer. Poor outcome seemed to be mainly the result of more advanced stage and treatment allocation rather than age itself (Nogueira-Rodrigues et al.). Thus, adjuvant treatment is recommended more often in elderly patients because of a higher incidence of advanced disease and aggressive histopathology.

Duska et al. suggest the introduction of the components of comprehensive geriatric assessment and their practical implication for older women with cancer in general and older women with endometrial cancer specifically. The same approach of personalized care was examined by Gibson et al. for elderly patients with ovarian cancer.

Performance status alone has been shown to be an inadequate tool to predict toxicity of older patients from chemotherapy. Use of formal geriatric assessment tools is a promising direction for stratifying older patients in trials. Elderly-specific trials, adjustments to the eligibility criteria, modified treatment regimens, and interventions to decrease morbidities in the vulnerable older population should be encouraged.

Backes et al. found that elderly patients can safely undergo robotic endometrial cancer staging with improved outcomes compared to laparotomy. The benefits of robotic staging include a higher incidence of completion of lymphadenectomy, decreased hospital stay (without an increase in readmissions or reoperations), decreased administration of transfusions, and decreased wound and fascial complications. Although the risks of surgery increase with age, in patients age >/=65 years, a robotic approach for endometrial cancer appears to be safe.

A cumulative dose of metformin use after cervical cancer diagnosis among older women with diabetes may be associated with a significant decrease in cervical-cancer-specific mortality and overall mortality in a dose-dependent fashion (HR 0.79; 95 % confidence interval (CI), 0.63-0.98; and HR 0.95; 95 % CI, 0.90-0.996) per each additional 365 g of metformin use. This finding by Han et al. has important implications if validated prospectively, as metformin is inexpensive and can be easily combined with standard treatment for cervical cancer.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Perioperative Outcomes for Laparotomy Compared to Robotic Surgical Staging of Endometrial Cancer in the Elderly: A Retrospective Cohort	Backes FJ al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27575633
2	Adjuvant Treatment and Clinical Trials in Elderly Patients With Endometrial Cancer: A Time for Change?	Clark LH et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/26745698
3	Treatment of Older Women With Endometrial Cancer: Improving Outcomes With Personalized Care	Duska L et al.	Am Soc Clin Oncol Educ Book	https://www.ncbi.nlm.nih.gov/pubmed/27249697
4	The Application and Outcome of Standard of Care Treatment in Elderly Women with Ovarian Cancer: A Literature Review over the Last 10 Years	Gibson SJ et al.	Front Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27047797
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	https://www.ncbi.nlm.nih.gov/pubmed/26433173
6	Association between Metformin Use and Mortality after Cervical Cancer in Older Women with Diabetes	Han K et al.	Cancer Epidemiol Biomarkers Prev	https://www.ncbi.nlm.nih.gov/pubmed/26721670
7	The problems of cervical conization for postmenopausal patients	Hasegawa et al.	Eur J Gynaecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27352558
8	Carcinoma of the cervix in elderly patients treated with radiotherapy: patterns of care and treatment outcomes	Lin MY et al.	J Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27550405
9	Is age a prognostic biomarker for survival among women with locally advanced cervical cancer treated with chemoradiation? An NRG Oncology/Gynecologic Oncology Group ancillary data analysis	Moore KN et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27542967
10	Patterns of Care and Outcome of Elderly Women Diagnosed With Cervical Cancer in the Developing World	Nogueira-Rodrigues A et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/27465885
11	Use of Hematopoietic Growth Factors and Risk of Thromboembolic and Pulmonary Toxicities in Elderly Patients with Advanced Ovarian Cancer	Poonawalla B et al.	Womens Health Issues	https://www.ncbi.nlm.nih.gov/pubmed/27365286
12	Ovarian cancer in the older woman	Tew WP	J Geriatr Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27499341

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Epidemiology of gynaecological cancers

Editor Dominic Blake

Descriptive summary

In this edition, we focus on studies relating to the epidemiology of ovarian, vulval, and vaginal cancers. Nasioudis et al. studied squamous ovarian carcinoma (SOC), as little information exists to aid maximal patient care. They undertook a retrospective study examining clinicopathological features, demographics, and prognosis. Patient details were collected from the SEER database between 1988-2012.

Of the 341 patients identified, there was a wide range of stages at presentation with survival reducing with increasing stage. Survival appeared to be better in those women who underwent lymphadenectomy. Postoperative radiotherapy did not appear to improve survival. Stage I patients have a good survival rate in this study. However this paper calls for further prospective studies to examine this rare group of patients to aid with better treatment strategies. With lacking information about adolescents and young adults (AYAs) aged 15 to 39 with cancer, Keegan et al. studied thirteen regions in the USA from the SEER database to compare cancer survival trends.

The study found that, whilst there had been an overall improvement in the survival of ovarian cancer in adults, the size of the improvement was less in AYAs and the authors called for further studies to examine this.

Kalapotharakos et al. undertook a population-based survey of borderline ovarian tumours in Sweden from 1960-2007. The study showed an increase in the incidence of borderline tumours over time but provided reassurance that long-term survival remains good. There was no difference in survival between mucinous and serous borderline tumours.

Urban et al. presented the outcomes of patients with stage III/IV ovarian cancer from the SEER database between 1995-2007. In all, 44 % of patients died within one year. Of those, 26 % died within 90 days. These patients tended to be older with increased morbidity, stage IV disease, and lack of visit with a gynaecological oncologist and surgery. Chemotherapy improved the 90-day survival. The study calls for further research into this group of patients to aid allocation of resources or methods of improving survival.

There were no epidemiological studies in vulval and vaginal cancers in the review period.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Ovarian cancer outcomes: Predictors of early death.	Urban et al.	Gynecol Oncol	www.ncbi.nlm.nih.gov/pubmed/26743531
3	Long-term survival in women with borderline ovarian tumors: a population-based survey of borderline ovarian tumors in Sweden 1960-2007.	Kalapotharakos et al.	Acta obstetricia et gynecologica Scandinavica	www.ncbi.nlm.nih.gov/pubmed/26714557
4	Comparison of cancer survival trends in the United States of adolescents	Keegan et al.	Cancer	www.ncbi.nlm.nih.gov/pubmed/26848927
5	Epidemiology and outcomes of squamous ovarian carcinoma	Nasioudis et al.	Gynecol Oncol	www.ncbi.nlm.nih.gov/pubmed/26867989

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Nutritional support / status in gynaecological cancer

Editor Jiri Presl

Descriptive summary

Malnutrition is a crucial problem in a great proportion of patients suffering from gynaecological cancer and is a considerable predictor for mortality. Yim et al. in their study point to the population of advanced ovarian cancer patients, where the moderate and severe malnourished group has poorer year-year overall survival (45.3 %) compared to the normal and mild groups (64.0 %).

The paper by Rutten et al. describes the role of changes in skeletal muscle mass in patients undergoing surgical and adjuvant treatment for advanced ovarian cancer. The loss of skeletal muscle mass was associated with significantly lower median overall survival. The attenuation of skeletal muscle mass-sarcopenia can be used as an increased chemotherapy toxicity marker in epithelial ovarian cancer patients after primary debulking surgery (Kumar et al.).

Postoperative nausea and vomiting (PONV) is another serious negative aspect for our patients to deal with. To identify those patients threatened the most by PONV, de Souza et al. prospectively collected data and assessed the risk factors from 82 adult gynaecological cancer patients who underwent surgical treatment in general anaesthesia. The highest incidence of PONV was found in non-smokers and in patients with high intravenous hydration.

A multicentre randomised clinical trial of Gavazii et al. compares the effectiveness of home enteral nutrition to nutritional counselling after discharge in post-surgical patients treated for gastrointestinal cancer. Compared to patients in the nutritional counselling group, patients on home enteral nutrition maintained their mean body weight and had a higher chance of completing the chemotherapy as planned. Improved overall survival was also associated with body weight gain in the analysis of Mardas et al. A systematic search of web databases, despite the weaknesses of the vast majority of collected articles, confirmed the loss of body weight during primary chemotherapy to be associated with poor overall survival in patients with epithelial ovarian cancer.

A comparison of enteral nutrition versus total parenteral nutrition in patients after abdominal surgery for gastrointestinal cancer, a meta-analysis made by Zhao et al., supported the major role of enteral nutrition. The shorter hospital stay, the shorter time to flatus and significantly higher albumin levels underlined the importance of enteral nutrition.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Malnutrition Identified by the Nutritional Risk Index and Poor Prognosis in Advanced Epithelial Ovarian Carcinoma	Yim GW et al.	Nutrition and cancer	http://www.ncbi.nlm.nih.gov/pubmed/27044606
2	Loss of skeletal muscle during neoadjuvant chemotherapy is related to decreased survival in ovarian cancer patients	Rutten IJ et al.	J Cachexia Sarcopenia Muscle	https://www.ncbi.nlm.nih.gov/pubmed/27030813
3	Predisposing factors for postoperative nausea and vomiting in gynecologic tumor patients	de Souza D et al.	Support Care Cancer	http://link.springer.com/article/10.1007%2Fs00520-016-3311-2
4	Impact of home enteral nutrition in malnourished patients with upper gastrointestinal cancer: A multicentre randomised clinical trial	Gavazzi C et al.	European journal of cancer	http://www.ejcancer.com/article/S0959-8049(16)32199-2/abstract
5	Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer	Kumar A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27235857
6	Influence of body weight changes on survival in patients undergoing chemotherapy for epithelial ovarian cancer	Mardas M et al.	European review for medical and pharmacological sciences	http://www.europeanreview.org/article/10821
7	Enteral nutrition versus parenteral nutrition after major abdominal surgery in patients with gastrointestinal cancer: a systematic review and meta-analysis	Zhao XF et al.	Journal of investigative medicine	http://jim.bmj.com/content/64/5/1061

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Quality of life and sexual function in gynaecological cancers / palliative care

Editor Cosyns Stef

Descriptive summary

As reported earlier on this topic, depression and anxiety are frequent in ovarian cancer patients. An excellent meta-analysis from Watts et al. emphasizes the high prevalence among 3,623 patients. Depression prevalence is as high as 25 % pre-treatment, 23 % on-treatment, and 13 % post-treatment. For anxiety, prevalence rates of 13 %, 26 %, and 27 %, respectively, were reported. Underdiagnosis and undertreatment are probably high in these patients.

Meta-analysis on the effects of lifestyle interventions on QoL in survivors of endometrial and ovarian cancer shows a potential effect to increase QoL by reducing fatigue and improve physical functioning in endometrial cancer survivors (3RCTs) even though without significant improvement in global QoL. In ovarian cancer survivors, non-randomised trials suggest QoL improvement. (Smits et al.)

The long-term impact (seven-year follow-up) of EBRT or VBT among Portec-2 trial patients (endometrial cancer) was evaluated with health-related EORTC QLQ-C30 QoL questionnaires and showed persisting higher rates of bowel symptoms with EBRT, without significant differences in global health or any of the functioning scales. Fecal leakage (10.6 %), diarrhoea (8.4 %), limitations due to bowel symptoms (10.5 %), and bowel urgency (23.3 %) were significantly higher in the EBRT group. Urgency was frequently reported in both groups: 39 % (EBRT) and 25 % (VBT). No difference was seen in sexual activity.

In their comprehensive review and clinical guide, Huffman et al. studied the maintaining of sexual health throughout gynaecologic cancer survivorship. They conclude that patients do expect their healthcare providers to address sexual health concerns, but the majority have never discussed this with their physician. An open discussion on this topic could have a significant impact on the QoL of gynaecologic cancer survivors. This review addresses simple strategies for the different gynae-cancers separately in a clinically very useful way.

Noteworthy is a Brazilian pilot study by Grion et al. investigating the sexual function and QoL in women with cervical cancer undergoing radiotherapy prior to their diagnosis and treatment. The mean age of the 80 women included was 48 years (57 % pre-menopausal, 55 % clinical stage IIIb). Remarkably, only 30 % had been sexually active in the three months prior to their interviews. The major adverse effects were bleeding, lack of pleasure, and dyspareunia.

An interesting study was published by Kim et al. demonstrating a significant association between HRQOL scores in disease-free cervical cancer survivors and survival. Age, time since diagnosis, and physical activity were independent prognostic factors. Health-related quality-of-life measures through functional scales (physical, role, social, and emotional functioning), global health status, symptom scales (pain and appetite loss), and cervical cancer module items (body image, sexual inactivity, and sexual worry) were significantly associated with survival ($P < 0.05$).

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Depression and anxiety in ovarian cancer: a systematic review and meta-analysis of prevalence rates.	Watts S et al.	BMJ Open	https://www.ncbi.nlm.nih.gov/pubmed/26621509
2	The effect of lifestyle interventions on the quality of life of gynaecological cancer survivors: A systematic review and meta-analysis.	Smits A et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/26441008
3	Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomised PORTEC-2 Trial.	de Boer SM et al.	Int J Radiat Oncol Biol Phys	https://www.ncbi.nlm.nih.gov/pubmed/26530748
4	Maintaining sexual health throughout gynecologic cancer survivorship: A comprehensive review and clinical guide.	Huffman LB et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/26556768
5	Sexual function and quality of life in women with cervical cancer before radiotherapy: a pilot study.	Grion RC et al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/26319157
6	Health-Related Quality of Life and Sociodemographic Characteristics as Prognostic Indicators of Long-term Survival in Disease-Free Cervical Cancer Survivors.	Kim MK et al.	Int J Gynecol Cancer	https://www.ncbi.nlm.nih.gov/pubmed/26905329

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Follow-up after gynaecological malignancies

Editor Anne van Altena

Descriptive summary

Wright et al. looked into the practice of diagnostic tests in the follow-up of stage I-II endometrioid endometrial cancer patients. They performed a retrospective population-based study of over 17,000 patients. Between 1992 and 2011, the use of chest radiography decreased, and the use of cytology decreased in the last few years. The mean per-patient number of the more costly imaging techniques that they studied (chest CT, abdominopelvic CT, and positron emission tomographies) increased over this study period.

The second study, by Beaver et al., also looked into the follow-up of endometrial cancer patients. A multicentre randomised trial was performed in stage I endometrial cancer patients. The 259 women were allocated to receive traditional hospital-based follow-up or nurse-led telephone follow-up. They studied psychological morbidity and patient satisfaction with the information provided as primary outcome and satisfaction with service, quality of life, and time to recurrence detection as secondary outcome. No difference in patient satisfaction was seen, and no physical or psychological difference between the two groups was shown either.

A mini commentary was published in the BJOG about telephone follow-up in addition to Beaver's article. Leeson states that there is no proof that survival improvement by regular hospital visits. To improve the quality of life of cancer survivors, telephone follow-up may be as effective as hospital visits. There is a lack of studies on this topic, and this author agreed with Beavers et al to focus on patient-centred care.

One study looked at squamous cell carcinoma antigen (SCC-Ag) during surveillance of cervical cancer patients (Salvatici et al.). The aim was to assess the effect of SCC-Ag measurement on the early diagnosis of cervical cancer recurrence. A retrospective analysis of SCC-Ag levels of 197 stage I or II cervical squamous cancer patients was performed. An association was seen between a positive test and a recurrence and serum SCC-AG level was an independent prognostic factor for overall and progression-free survival. However, the level of SCC-Ag was not associated with survival time. SCC-AG may lead to earlier detection of a recurrence but this advantage did not show to improve survival probably due to the lack of curative treatment options.

The most recent published study was published in the JAMA by Esselen et al. it reported on the use of CA125 and computed tomographic (CT) scans in ovarian cancer survivors in the USA. The use of both diagnostic tests was examined before and after 2009 (when the study by Rustin et al. on CA125 in follow-up was published) and the economic effect of testing was estimated. A prospective cohort of 1,241 women in clinical remission was followed up. The use of CT scans and CA125 measurements were similar before and after 2009. Also, the time to retreatment after doubling of the CA125 level did not differ. Costs were calculated. They conclude that even though there is no proven benefit of these tests, they are still routinely performed.

Relevant articles retrieved Feb 2016 - Sep 2016

No	Title	Authors	Journal	Link to abstract
1	Use of CA-125 Tests and Computed Tomographic Scans for Surveillance in Ovarian Cancer	Esselen KM1 et. al.	JAMA Oncology	https://www.ncbi.nlm.nih.gov/pubmed/27442965
2	Telephone follow up of gynaecological malignancies: time to rethink our postoperative care?	Leeson SC	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/27132159
3	Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: Role in the early diagnosis of recurrence.	Salvatici M1 et. al.	Gynecol Oncol	https://www.ncbi.nlm.nih.gov/pubmed/27117922
4	Comparing hospital and telephone follow-up for patients treated for stage-I endometrial cancer (ENDCAT trial): a randomised, multicentre, non-inferiority trial.	Beaver K1 et. al.	BJOG	https://www.ncbi.nlm.nih.gov/pubmed/27062690
5	Trends in Periodic Surveillance Testing for Early-Stage Uterine Cancer Survivors.	Wright JD1 et. al.	Obstet Gynecol	https://www.ncbi.nlm.nih.gov/pubmed/26855104

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