ESGO
European Society of Gynaecological Oncology

Report from ESGO 16

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Nearly 2000 delegates from 78 countries packed the halls at ESGO's biennial international congress in Belgrade for a programme that ably demonstrated the significant progress that has been made in tailoring treatment more closely to the needs of individual women, with a strong emphasis on tissue and nerve-sparing surgery and fertility preserving treatments.

Many presentations stressed the importance of focusing expertise at specialist centres, particularly for the treatment of rarer gynecological cancers. In addition, delegates were brought up to date with recent developments in ESGO's training programmes for the new generation of gynecological oncologists in Europe.

In a year which saw rapid uptake of the new human papillomavirus (HPV) vaccines in public health programmes around the world, ESGO was especially fortunate that Harald zur Hausen – who won the 2008 Nobel Prize in Physiology or Medicine for his discovery of HPV as the cause of cervical cancer – accepted an invitation to give the keynote lecture on *The Search for Infectious Agents in Human Cancer.*

Prevention and early detection of gynaecological cancers

In countries where screening has significantly reduced the incidence of cervical cancer, it is possible to forget that this remains the second largest cause of female cancer mortality worldwide, with more than half a million new cases each year. Serbia has the highest incidence and mortality for cervical cancer in Europe, and plans for the introduction of a national screening

programme were agreed by the Serbian government in 2008. However, results of a large survey of female students carried out by Dr Olivera Tĕsić, from the Oncology Institute of Vojvodina, Serbia, showed that 77% of sexually active students had never had a smear, and only 27% were aware of the role of HPV in cervical cancer. About half of the students in the study were medical students and, with such lack of knowledge among a relatively well-educated group, a major educational campaign will clearly be needed to ensure the success of the new screening programme.

Even in countries where screening programmes are well established, it appears there is continuing room for improvement. In the Netherlands, Dr Roosmarie de Bie and co-researchers at the University Nijmegen Medical Centre, Nijmegen, presented data showing that limiting screening to women aged 30-60 years misses significant numbers of cases. Dr de Bie recommended interventions to increase the participation rate and the sensitivity of the screening test.

Already underway in Nijmegen is a pilot project of the use of HPV DNA tests on samples that have been taken by the women themselves – something which is likely to be seen increasingly in industrialised countries, as governments try to reach more women who are currently missing out on conventional smear tests, taken by general practitioners.

Update on HPV vaccine efficacy and safety

New human papillomavirus (HPV) vaccine studies presented at ESGO 16 confirmed sustained protection from immunisation against precancerous cervical lesions in healthy young women, as well as beneficial effects for women treated for precancerous conditions prior to HPV vaccination. Latest safety data also confirm the low levels of adverse events associated with the vaccines.

In a study of more than 1000 healthy women aged 15-25 years vaccinated with the anti-HPV 16/18 vaccine, Cervarix, sustained immunogenicity and 100% efficacy against HPV 16 and 18 related cervical intraepithelial neoplasia 2 (CIN2+) lesions was reported at 7.3 years follow up – the longest to date with the vaccine. Medically significant adverse events occurred in 8.1% of vaccinated women and 6.2% of placebo-treated women, and serious adverse events occurred in 1.8% and 2.4% respectively.

An analysis of more than 500 recipients of definitive therapy for previous cervical lesions, who subsequently took part in a placebo controlled study of the anti-HPV 6,11,16,18 vaccine, Gardasil, showed efficacy of 74% against CIN associated with HPV16/18 and 79% against vulvar (VIN1-3), vaginal (VaIN1-3) or genital warts associated with HPV6/11 infection.

Treatment of cervical cancer

In an ideal world, gynecological surgeons would master all the surgical options for cervical cancer, including laparoscopic hysterectomy, with or without robotic assistance for obese patients, vaginal hysterectomy for prolapsed patients, and vaginal trachelectomy for women wanting to preserve their fertility. But it can be difficult to gain the necessary expertise outside centres treating large numbers of women and, as techniques continue to evolve, there are new questions to be answered, such as whether sparing techniques can reduce complications, without jeopardising survival.

Dr Francesco Raspagliesi, from the National Cancer Institute in Milan, Italy, described the outcomes of class III nerve-sparing radical hysterectomy in 170 evaluable cases out of an original 200 consecutive patients with stage IB1 to IIB cervical cancer. In 151 patients, surgery was preceded by neoadjuvant chemotherapy and median follow-up was 31 months. At 89% and 81% respectively, the two and five year disease free survival rates were comparable with those seen with other forms of radical hysterectomy. But the 3.5% complication rate (1.7% early, 1.7% late) was significantly lower than that seen with conventional techniques.

In a second study, Dr David Cibula and colleagues at the General Faculty Hospital of Charles University, Prague, Czech Republic, compared morbidity six months after nerve-sparing radical hysterectomy with that seen with type C and type D radical hysterectomy techniques in 87 women with cervical cancer. Those who had nerve-sparing surgery had significantly less urinary incontinence, defecation irregularity, nocturia and straining to void than those who had type C or D procedures ($p<0.05$ all parameters).

No differences were seen in complication rates between type C and D radical hysterectomy. Dr Cibula concluded that it was nerve-sparing techniques which made the difference to the

complications that women experienced after surgery, rather than the size of the parametrial resection, and recommended that nerve-sparing techniques should now be considered for all cervical cancer surgery. However, randomised trials on this issue are still not available.

Treatment of uterine/endometrial cancer

Surgeons treating uterine cancer are also trying to balance the advantages of fewer postoperative complications against the need to optimise survival. Dr Claudia Bijen, from the University of Groningen, the Netherlands, presented data from a randomised trial in which 185 women with early endometrial cancer underwent laparoscopic hysterectomy and 94 who had open surgery. While there was no significant difference in major complications between patients in the two groups (14.6% vs 14.9% respectively), those undergoing laparoscopic surgery had significantly better quality of life scores (SF36) six weeks after surgery, less pain and were able to return to work more quickly than those who had open procedures. At three and six months, some of the earlier advantages of laparoscopic surgery had diminished so that, by six months, benefits were seen only in SF36 and return to work – neither of which were statistically significant.

Dr Bijen stressed that the study design ensured that laparoscopic surgery was carried out by skilled surgeons – something which would be important if the laparoscopic technique becomes more widespread in clinical practice.

The Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC) series of studies is providing important information about the merits of radiotherapy in women with early stage endometrial cancer. Fifteen year follow-up data on PORTEC 1, presented by Dr Carien Creutzberg, from Leiden University Medical Center, Leiden, have confirmed that reduced recurrence following external beam radiation (EBRT) did not translate into survival benefit (49% vs 58%, $p=0.14$), or failure-free survival (47% vs 52%, $p=0.93$). However, women who had EBRT had lower quality of life scores for physical functioning and clinically relevant higher rates of urinary and bowel symptoms (both $p< 0.001$).

PORTEC-2 showed a non significant increase in distant metastases with vaginal brachytherapy compared to EBRT at 45 months follow up, but no differences in disease free or overall survival, in high-intermediate risk endometrial cancer. However, a central pathology review, reported by the Leiden group at ESGO 16, showed 8% of patients in the

study had high-risk features, with accompanying inferior outcomes. Distant metastases occurred in 22.4% of these patients vs 4.9% for true high-intermediate risk patients, $p < 0.001$, and there was lower overall survival (65.2% vs 92.8%, $p < 0.001$).

The researchers concluded that vaginal brachytherapy was the treatment of choice for patients with true high-intermediate risk endometrial cancer, owing to its greater tolerability and better quality of life effects compared with EBRT.

Treatment of ovarian cancer

The majority of women with ovarian cancer are likely to have chemotherapy at some point in their treatment after initial surgery, and a number of studies discussed at ESGO considered the optimal approach.

Final results of the GCIG Phase III (AGO-OVAR-9, GINECO-TCG, NSGO-OC-0102) have failed to show any advantage of adding gemcitabine to paclitaxel and carboplatin in first line chemotherapy, and progression-free survival was better with standard therapy (median 19.3 vs 17.8 months; $p = 0.0066$).

Dose dense cisplatin treatment (weekly cisplatin 50 mg/m^2 for 9 weeks) appears to confer no progression-free or overall survival advantage over standard treatment (cisplatin 75 mg/m^2 every 3 weeks for 6 cycles) for women with newly-diagnosed epithelial advanced ovarian cancer, according to long term follow up data presented by investigators at San Gerardo Hospital, University of Milan-Bicocca, Monza, Italy.

For women with relapsed platinum-sensitive ovarian cancer, the combination of carboplatin and pegylated liposomal doxorubicin prolongs progression-free survival and is associated with a lower risk of severe, long-lasting nerve damage than standard carboplatin/paclitaxel treatment, according to analysis of results from the international multicentre CALYPSO trial reported by Dr Mark Heywood, from the BCCA Vancouver Cancer Centre, Vancouver, Cancer.

Data from 986 patients treated in 16 countries in Europe, North America, the Middle East, Australia and New Zealand showed progression-free survival of 11.3 months and 9.4 months respectively ($p=0.005$) for the carboplatin/pegylated doxorubicin vs carboplatin/paclitaxel combinations in women with relapsed platinum sensitive disease.

Severe neutropenia occurred in 35% and 46% respectively of patients in the two groups, severe neuropathy in 5% and 28% and alopecia in 7% and 84%. Hand-foot syndrome – a well documented inflammatory condition associated with pegylated doxorubicin – was more common in the carboplatin/pegylated doxorubicin group (13% vs 2%) and severe thrombocytopenia was also more common (16% vs 6%).

Treatment of vulvar cancer

In the Netherlands, there are 250 new cases of vulvar cancer per year, compared to 14,000 of breast cancer. As in other countries, therefore, it is important that care of women with this challenging disease is concentrated at centres with specialist expertise, not least in the sentinel node (SN) biopsy procedures that are being incorporated into diagnosis as a result of recent research findings. Results of the Groningen International Study on Sentinel nodes in Vulvar cancer VI (GROINNS VI) showed that sentinel node (SN) detection using radioactive tracer and blue dye in women with early stage, unifocal vulvar cancer (<4cm) was associated with reduced short and long term morbidity compared to inguinofemoral lymphadenectomy, without adversely affecting groin recurrence and survival.

Support for this approach has come from GOG 173 in women with squamous carcinomas (2-6cm) and clinically non suspicious lymph nodes, with new data presented at ESGO 16 by Dr Robert Coleman, from the University of Texas, M. D. Anderson, Houston, US. The study showed a 90% sensitivity and 96% negative predictive value for SN detection, and Dr Coleman recommended that SN localisation should be incorporated into future trials and considered standard clinical practice in this setting.

Indeed GROINNS VII, started in 2006, is now investigating the benefits of radiotherapy (50Gy) in women with T1/T2 tumours <4cm and positive SN, without full lymphadenectomy. However, as Dr Gillian Thomas. from Toronto Sunnybrook Cancer Center, Toronto, Canada, demonstrated in her presentation at the congress, there is continuing discussion about whether 50Gy will prove to be the optimal dose of radiotherapy for such women, and whether prognosis could be improved by including chemotherapy as well.

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Fertility preservation

According to a recent ESGO survey, accredited European gynaecological cancer centres are typically treating eight patients per year with fertility-sparing surgery, underlining the need for centralised expertise. At a Fertility Task Force Workshop held at ESGO 16, speakers reviewed latest evidence on appropriate use of fertility-sparing techniques in cervical, early endometrial and (borderline) ovarian cancer. For cervical cancer, the dilemma is whether pregnancy rates after abdominal radical trachelectomy can be improved to the level of those achieved with the more technically demanding vaginal approach with its shorter hospitalisation times and other quality of life benefits. For early endometrial cancer, the issue is whether patients can be selected for hormonal therapy instead of surgery without jeopardising their chances of survival, as about one quarter of women do not respond to hormonal treatment and one third of those who respond initially will relapse. A number of factors including a well-differentiated tumour, no myometrial invasion, no suspicion of pelvic or paraortic nodal involvement, no ovarian tumour and no other contraindications have been identified as potentially predicting a good outcome from conservative management.

Recurrence is also increased in women with borderline ovarian tumours treated with conservative surgery, rather than more aggressively. But survival does not appear to be reduced, and pregnancy rates of 30-40% are reported. Recent data also support the use of conservative surgery in women with stage IA grade 1 or 2 epithelial ovarian cancer, but not for those with stage 1A grade 3 disease.

By contributing to the new web-based ESGO registry of cancer patients undergoing fertility - sparing surgery, being set up in 2010, it is hoped that ESGO members can add to the growing understanding of which patients can be safely treated in this way, and how effective these approaches can be in achieving the desired outcome of successful pregnancies.

The search for infectious agents in gynaecological and other cancers

If everyone who could benefit from vaccination against HPV and hepatitis B were immunised, the global cancer burden for women would be reduced by 12-14% and that for men by 4-5%, predicted Professor Prof Harald zur Hausen, during his keynote lecture.

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Estimating that 21% of the global cancer incidence is caused by infectious agents (64% by viruses, 35% by bacteria and 0.8% by parasites), Professor Zur Hausen proposed that the search for infectious causes of cancer should focus on cancers that are commonly associated with immunosuppression and those whose incidence or risk factors are linked to infection. However, he suggested that breast cancer was the most likely gynecological-related cancer to have an infectious cause, possibly through the human endogenous retrovirus K (HERV-K) gene – products of which have recently been shown to trigger immune responses in breast cancer patients, but not in healthy women. Turning to the evidence linking red meat eating to human cancer, Professor Zur Hausen raised the possibility that latent animal infections transmitted to humans in food could ultimately be shown to have a role in causing cancer. He also suggested that the reason why white meat from poultry has never been linked to cancer may be related to the cooking process, ie: red meat is often eaten rare, while white meat is always eaten fully cooked. He concluded that while people with intact immune systems may be able to combat viruses such as polyomaviruses and papillomaviruses transmitted in meat, those with suppressed immune systems may find it more difficult, resulting in a higher risk of cancer.

Future directions

By the time that ESGO17 opens in 2011, fresh insights will have been gained from results of many of the ongoing studies that were discussed in Belgrade. Significant progress can be expected in translational research activities resulting in more effective collaboration between laboratory and clinic, and advances are also likely in epigenetics and other techniques for further tailoring treatment to individual patient characteristics. Thanks to the continuing expansion of ESGO's accreditation and training programmes, we can expect further development of gynaecological oncology as a specialty across Europe – something which must surely benefit the many thousands of women who need this expertise.

The programme for ESGO 17 will undoubtedly reflect all these exciting changes and planning is already well underway. We look forward to seeing you in Milan from 11-14 September 2011.

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