92 INVITED

Surgery in pelvic relapses of gynaecological cancer

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Surgery plays an important role in isolated pelvic relapse of cervical, endometrial and ovarian carcinomas, and in some (low grade) gynaecological sarcomas.
Cervical and endometrial pelvic relapses are usually first irradiated. Pelvic exenteration is often the only curative treatment modality in patients with isolated pelvic relapse following pelvic radiotherapy. New surgical techniques such as the colon pouch and continent urinary conduits have changed the quality of life of these patients substantially. In some instances partial bladder reconstruction with reconstruction with small bowel flaps makes it possible to offer the patient exenterative surgery without ileal conduit. In patients with irradiated pelvic relapse, exenteration combined with additional radiotherapy (e.g. brachytherapy or intraoperative radiotherapy) is sometimes an option.
Also in pelvic relapses of ovarian cancer are candidates for secondary surgery. Besides the presence of an isolated pelvic relapse other prognostic factors are important to consider surgery in ovarian cancer: young age, absence of extra-abdominal or liver metastases at primary diagnosis, complete response after first-line therapy, long treatment-free interval after primary treatment, absence of ascites or peritoneal carcinomatosis, and good general condition. Performing an (open) laparoscopy is often helpful in the selection of the patients for secondary surgery.
Pelvic relapse of (low grade) gynaecological sarcomas (e.g. endometrial stromal sarcoma) are often good candidates for surgery as they are often slowly growing and distant (hematogenous) spread at the time of relapse.

93 INVITED

Pelvic relapses in gynaecology: radiotherapy options

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The most common gynaecological malignancies relapsing in the pelvis are cervix and endometrium cancer. For deciding the appropriate treatment strategy the following information is essential: tumour location, size, and topography, previous treatment and exclusion of distant disease. The recurrence may be in the central pelvis (vagina, cervix, uterus) or at the pelvic side wall. It can be either superficial or deeply invading. In advanced and high risk disease there is significant risk for distant metastasis and therefore a poor overall prognosis. Previous treatment is either surgical with or without adjuvant radiotherapy or exclusive radiotherapy most often combining external beam radiotherapy (EBRT) and brachytherapy (BT).
Curative treatment of relapses using definitive radiotherapy or combined surgery and radiotherapy is indicated in not previously irradiated patients with favourable location and topography and limited size (<5 cm). Exceptions are patients treated postoperatively with vaginal vault brachytherapy alone and patients with small localised recurrences in the distal vagina who had received before EBRT and BT in the proximal vagina only. Central recurrences in the vagina (proximal, middle or distal third) can be treated with combined EBRT up to 45–50 Gy followed by BT. The brachytherapy technique depends on the EBRT response using either an endovaginal approach for superficially located tumours and tumours with good response or combined endovaginal and interstitial treatment for deeply invading and bad responding tumours. The aim is to apply additional 40 Gy using either High dose rate or Pulse dose rate brachytherapy.
Central recurrences in the cervix and/or uterus in primarily irradiated patients are localised within the high dose area of radiation and consequently not eligible for radiotherapy. A re-irradiation can be performed, usually in palliative intention, and may be recommended, if no surgical treatment is feasible.
For pelvic side wall recurrences the treatment of choice is extended surgery with or without postoperative radiotherapy, in favourable disease in curative intent. If no surgery can be performed palliative radiotherapy combining EBRT and BT or exclusive BT can be applied.

94 INVITED

Psychological issues and supportive care

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Supportive care is defined as care that aims to optimize the comfort, function, and social support of patients and their families at all stages of the illness. This definition incorporates the concept of health-related quality of life. Women with pelvic relapse in gynaecology are confronted with various psychosocial problems. The areas most affected are body image disturbances, disruption of family and social relationships, difficulty with intimacy and sexuality, increased general distress, and fear of recurrence and dying. Treating patients with pelvic relapse is challenging, since the goal of treatment has shifted from curative to palliative interventions. In patients with advanced cancer medical decision-making is closely related to maintaining or improving the quality of life of patients. Decisions are particularly problematic for patients with advanced gynaecological malignancies since treatment related risk have to be balanced with the benefits of treatment. The benefits often have to be weighed against the distressing side effects. A variety of factors may influence treatment decisions including the probability of survival or recovery, and perceived quality of life that reflects the patients' view and experiences with cancer treatment. The therapy selected should be consistent with the patient's values and preferences. In 'trade-off' situations patients may be willing to compromise on quantity to maximise quality of life. Physicians should therefore provide sufficient quality of life and survival data. Empirical results of quality of life research in gynaecological oncology will be presented in the context of medical decision-making. Assessment of patient preferences and expectations, quality of life outcomes, health status assessment and shared decision making in patients with pelvic relapse will also be discussed.

Scientific Symposium
Bone tumours in children and adolescents – future directions

95 INVITED

Prognostic importance of the molecular genetics

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Over the last two decades remarkable progress has been achieved in the therapy of paediatric cancers resulting in cure rates up to >90%. These improvements are primarily due to the development of successful treatment protocols for leukaemia, while effective therapy of solid tumours lags behind. This is particularly true for bone tumours and other sarcomas. Here, the presence of metastasis at diagnosis or early relapse is still almost invariably associated with dismal prognosis, while multi modal treatment of localized disease is successful in up to 70% of cases. Obviously, treatment failure is most frequently associated with systemic disease that may be assessed by the determination of minimal disseminated disease (MDD) at diagnosis. For this purpose, tumour specific genetic aberrations such as recurrent chromosomal translocations serve as optimal targets for high sensitivity detection with molecular methods. MDD may, however, escape detection and therapy by homing to remote skeletal locations. Alternatively, disseminated tumour cells may have acquired a dormant state that escapes detection due to altered tumour cell activity and phenotype. Molecular genetics comparing transcriptomes of tumour cells after experimental manipulation and among tumours of different prognosis aim at identifying gene expression patterns and eventually surrogate markers for different tumour cell phenotypes. Tumour cells may have either lost check point control for DNA damage and/or have increased survival mechanisms which, under therapeutic pressure, result in the rapid evolution to a therapy resistant phenotype. *Tp53* mutation and *INK4A* gene alterations are prominent aberrations associated with this type of therapy resistance and consequently with bad prognosis. With these and few other exceptions, markers that allow identify high risk patients already at diagnosis are scarce and, so far, not sufficiently reliable to predict outcome with certainty. In part, this is due to small sample sizes in retrospective analyses and the lack of large prospective validation studies. The multicentric EuroE.W.I.N.G.99 study is the first to prospectively evaluate two putative molecular prognostic markers identified in several small scale retrospective studies in Ewing's sarcoma, *EWS-FLI1* gene fusion structure and *EWS-FLI1* based MDD detection. However, treatment options for high risk patients are limited and no break through has been achieved in the therapy of these patients thus far. Therefore in the future, the search for reliable prognostic parameters might rather result in the identification of those patients that may possibly profit from reduced therapy than those for whom even intensified treatment is most likely going to fail.

96 Abstract not received

97 INVITED

Treatment of Ewing's tumors: current status and outlook for the future

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The Ewing sarcoma family of tumors comprises a group of well characterized neoplasms with aggressive behavior. Despite significant

progress with the use of multiagent chemotherapy and local control measures, 30–40% of patients with localized disease and 80% of patients with metastatic disease die due to disease progression. Recognition of prognostic factors has important implications for treatment stratification and the identification of new, effective therapeutic strategies is important to improve the prognosis of these patients.
In patients with localised disease, site of the primary disease (trunk or extremity) had a prognostic impact before that surgical approach was recommended in the management of the tumour. The impact of age at onset of disease has been debated. Several studies report a more favourable prognosis for younger patients. These different outcome could sometimes be related to the modality used for local therapy in younger and older patients. But when using similar treatment modality, the outcome were similar in younger and older patients.
In univariate analyse, the tumour size appears to be a significant factor both for local tumour control and survival. The modality used for local therapy has also a significant impact on the prognosis. The patients who undergo surgery fare significantly better than the patients who do not. Surgery impacts mainly on the local tumour control rate and does not impacts on the occurrence of metastases. In multivariate analyse, the histological response to induction chemotherapy is the main prognostic factor of survival in localised Ewing tumours treated with chemotherapy alone before surgery whereas, the size of the primary is the most predictive of outcome in patients who do not undergo surgery. These 2 factors (histological response to chemotherapy in patients who have surgery and size of the primary in patients treated by radiation therapy alone) could be used to define 2 risk groups with a very different outcome. The standard-risk group consists of patients who either demonstrate a good response to chemotherapy or do not undergo surgery and have a small tumor at diagnosis. The high-risk group consists of patients who either demonstrate a poor histological response or do not undergo surgery but have a large tumor at diagnosis. This results contributed to the definition of the risk groups in the on-going EURO-EWING trial.
With the use of molecular techniques in the staging of ESFT, it is evident that a significant proportion of patients with localized disease (20–30%) have micrometastatic disease in the bone marrow detected by PCR. The prognostic significance of this microstaging has been demonstrated within a French protocol using a mild chemotherapy. It is under evaluation within the EURO-EWING protocol based on a more intensive chemotherapy.
The most important prognostic factor remains the presence of metastatic disease at diagnosis. Advances in the treatment have only resulted in a very modest improvement in the outcome of those patients. The EURO EWING study is addressing in a randomised trial the role of high dose chemotherapy (Busulfan + melphalan) in comparison to conventional chemotherapy associated with lung irradiation in patients with lung-only metastases. The study is still in progress. For patients with multifocal bone disease, new therapeutic approaches should be considered.

98 INVITED

Osteosarcoma

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Osteosarcoma is the most frequent primary cancer of bone. When treated by surgery alone, it is almost invariably followed by metastatic dissemination and death. This dismal prognosis can be improved dramatically by combining surgery with multidrug chemotherapy. Today, approximately two thirds of patients with localized extremity primaries can achieve long-term survival with intensive multimodal therapy. Large tumor size, axial tumor site, and primary metastases are adverse prognostic factors, as is poor histological response to preoperative chemotherapy.
Large scale multinational intergroup trials are under way for both pediatric and adult patients. As previous attempts to identify effective salvage regimens for poor responders have been largely unsuccessful, these studies are again striving to improve outcomes for this group of patients. Also, biological therapies are being evaluated as adjuncts to chemotherapy. Even with very intensive chemotherapy, incomplete surgery is still associated with dismal outcomes. Innovative radiotherapeutic techniques are increasingly used to achieve local control in inoperable situations. Prospective, multi-institutional and international trials are essential in guaranteeing that as many patients as possible can benefit from modern, efficacious interdisciplinary therapeutic regimens and that further progress can be made.

Wednesday, 2 November 2005

SIOP Europe Special session

99 SIOP-Europe Award

The European Branch of the International Society of Paediatric Oncology (SIOP Europe) Award – Questions on treatment of children with cancer

P.A. Voute. *Emma Kinder Ziekenhuis, Academic Medical Centre, Amsterdam, The Netherlands*

The treatment of cancer in children, leukemias, lymphomas and solid tumours, has shown a considerable progress in the last 40 years. Treatment in the 1960s gave cure rates of 30%, nowadays in 2005 it is 70% for the total group of malignancies. But this 70% was already reached in the 1980s. In the last 20 or more years the treatment has been intensified for most of the malignancies, also for these patients groups that already reached a 60−70% cure. This intensification has considerable added to toxicity, but not clear to efficacy. A toxicity we are all aware of seeing the amounts of late effect studies that are performed. But do we use the data coming out of these late effect studies to see if treatments can be changed to prevent the late complications? Are we as doctors not focussed on reaching the 100% cure, without taking the responsibilities for the patients that can be cured with lesser treatments?
Is the quality of life after treatment, not just as important as life as such for the children cured of cancer?
We can ask ourselves these questions since the 1980s when 70% cure of cancer was reached for children.
Should we not have to focus our treatment efforts first on the 70% patient group, how to diminish treatment to prevent late effects?
Is it necessary to use certain drugs as for example ifosfamide when the less toxic drug cyclofosfamide is sufficient?
Should we not be much more critical in using anthracyclines in treatment protocols?
Evidence based studies on treatment results have to be done and are done now. Risk group strategies for the different diagnostic patient groups are obligatory to prevent normal risk group patients the heavy treatment protocols. But most of all it is to be expected that in the near future treatment protocols will be able to use the data coming from a line of investigation on genetic abnormalities. Research on targeted therapy, using the identification of gene abnormalities driving tumour development.

Keynote Lecture
Information age and surgical oncology

100 INVITED

Information age and surgical oncology

J. Marescaux. *IRCAD/EITS Institute, University of Strasbourg, Strasbourg, France*

Telecommunications, multimedia and computer technologies will introduce marked changes in the management of cancer. New modalities in the representation of patient's medical records using computer technology products and services allow unlimited cross-sharing of information. Education taught through multimedia methods, and through the Internet is available anywhere and any time just like surgical simulation, robotics and virtual reality. Thanks to computer and IT technologies, surgeons will be able to acquire, assess and validate new surgical procedures or concepts from any geographical location. Live demonstrations shared via videoconferencing facilitate mental development through the acquisition of the cognitive aspects of surgical procedures. Virtual reality is a major improvement in the processing of medical imaging. As a result, the interpretation and the simulation of therapeutic approaches to patients with cancer are facilitated through transparency, navigation and manipulation. The Internet eventually offers uninterrupted communication links between healthcare providers (teaching, training or multidisciplinary telementoring included). Computer and IT technologies will undoubtedly contribute to standardized cancer treatment modalities and determined guidelines for good clinical practice worldwide.