the chemotherapy arm 90% completed three courses of chemotherapy. 30% showed complete or partial remission; 50% showed stable disease; 20% showed progression. Median dose intensity was 98% (85%–106%) (In both arms radical margins were obtained in 90%. Preoperative chemotherapy did not increase surgical or radiotherapeutic morbidity.

137 eligible patients could be analyzed, at a median follow up of 4.5 years, for overall and disease-free survival.

No significant statistical difference was found for either overall survival or disease-free survival between the two arms. (p = 0.35 and 0.37 resp.)

**Conclusion:** The chemotherapy-regimen was feasible; the accrual was too slow. No long term benefit was shown with this regimen. Adjuvant chemotherapy in soft tissue sarcoma should only be studied in trials.

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## Achievements in the treatment of acute myelogenous leukemia (AML)

R. Zittoun. *for the EORTC Leukemia Cooperative Group; Service d'Hématologie, Hôtel-Dieu, 75181 Paris Cedex 04, France*

The induction and post-remission treatment in AML has been progressively intensified, this intensification being made tolerable by progresses in supportive care. Thus, the complete remission (CR) rate has increased from 60 to 70–80% in patients aged less than 60 yrs, most CR being achieved after a single induction course. The 5 yrs disease-free survival (DFS) is now between 30 and 50%, according to prognostic factors and post-CR treatment protocol. The overall survival (OS) is around 30%, all cooperative groups having the same level of achievement. The main treatment options, intensive chemotherapy, autologous stem cell transplantation and allogeneic BMT are currently assessed by EORTC and other groups.

In the elderly, the prognosis is far worse, due to host and tumor-related factors, with a 5 yrs OS not higher than 5–10%. Specific clinical trials are designed by the EORTC group, exploring the value of more intensive treatments in the elderly along with hematopoietic growth factors, and of maintenance treatment.

The main objectives in the future will be to overcome multiple drug resistance, to target cytotoxic drugs, to reduce morbidity of transplantation, and to control the leukemic cell regrowth through the use of various cytokines.

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## Genetic and cytogenetic alterations in ovarian cancer

T. Bauknecht. *Department of Obstetrics and Gynecology, University Hospital of Freiburg, Germany*

**Purpose:** Molecular genetic alterations on ovarian tumorigenesis have been identified recently. Approximately 90% of ovarian cancer are sporadic forms, 10% are estimated to be carriers of an ovarian/breast cancer susceptibility gene; these women are found primarily in families characterized by multiple cases of the early onset of ovarian cancer syndromes. Cancer susceptibility genes such as BRCA1 and BRCA2 have been recently identified and cloned.

**Methods:** Genetic and cytogenetic evaluation of ovarian cancer has utilized techniques including *in situ* hybridization, mutation and sequencing studies.

**Results:** Cytogenetic studies in sporadic ovarian cancer demonstrate in approximately 50% of cases chromosome abnormalities, 40% of those reveal clonal and 10% nonclonal changes. Disruption of chromosomes as numerical or structural changes involve most frequently chromosome X, 1, 2, 6, 7, 11, 12 and 19. However, detailed cytogenetic karyotype information is limited. Competitive *in-situ*-hybridization (comparative genome analysis [CGH]) demonstrates DNA gains of chromosomes 8q, 3 p, 20 q, 1 p, 19 p, 1 q, 12 p, 6 p, 2 q and losses on 18 q, 4, 13 q, 16 q as an indication for consistent chromosomal abnormalities and genetic instability. Germ line mutations of BRCA1 (80%) and BRCA2 (15%) are found in families that display heritable ovarian cancer syndroms. Over 111 unique BRCA1 mutations distributed throughout the gene have been described. DNA chip-based assay are now developed to scan large genes (as BRCA).

**Conclusion:** The general distribution of new technologies (DNA chip) for accurate and cost-efficient detection of genetic alterations is wanted. Further research is required for families with hereditary ovarian cancer syndrom to evaluate efficacy of counselling and prophylactic efforts. In sporadic ovarian cancer detection of gene mutations with phenotype modification (i.e. drug resistance) can be used to develop new therapeutic strategies.

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## Primary cytoreductive surgery in advanced ovarian carcinoma: Is it necessary in all patients?

I.B. Vergote[1], I De Wever[2]. [1]*Department of Gynecologic Oncology;* [2]*Department of Surgical Oncology, University Hospitals Leuven, Katholieke Universiteit Leuven, Belgium*

"Optimal" cytoreductive surgery has been defined in different ways. We suggest that optimal cytoreductive surgery should be defined as no or less than 1 g of total residual tumor load after primary surgery. In some subgroups of patients the survival does not improve with optimal surgery. For instance, patients with Stage IV disease or a total metastatic tumor load of more than 1000 g prior to cytoreductive surgery have a poor survival despite cytoreduction. Patients who can not be optimally debulked primarily should be very carefully selected. We compared retrospectively 96 patients with Stage III or IV disease treated according to the above mentioned principles with 112 patients from the former time period. In the latter group 89% of the patients were debulked to less 1.5 cm largest residual tumor mass. No significant survival differences were observed between the 2 groups. The improvement in survival after interval debulking surgery reported in a prospective randomized EORTC trial is encouraging (NEJM, 1995, 332: 629). Based on the total metastatic tumor load, the presence of Stage IV disease or of uncountable peritoneal metastases, etc., it may be possible to select patients for whom upfront chemotherapy followed by interval debulking surgery is an option. This concept needs to be tested in a prospective randomized study.

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## T cell retargeting for local and systemic control of disease

S. Canevan[1], D.R.M. Negri[1], M. Calabrese[2], V. Siliprandi[2], C. Botti[1], E. Seregni[1], M.I. Colnaghi[1], G. Bolis[1,2]. [1]*Istituto Nazionale Tumori, 20133 Milan;* [2]*University of Milan, Italy*

**Purpose:** Bispecific antibodies (bsmAbs) with specificity for a tumor target antigen on one arm and a lympho/monocyte activation molecule on the other represent new reagents able to target cytotoxic immune cells to tumors and offer a promising means of killing minimal residual disease (mrd) without adverse reactions. This type of approach is being used in numerous phase I/II trials.

*Methods:* Ovarian carcinoma patients with: a) intraperitoneal (ip) disease after conventional treatments, b) mrd after I line treatment and previous history of retroperitoneal lymph node involvement, c) evident tumor infiltration in lymph nodes, entered studies aimed to evaluate: a) the efficacy of ip treatment, b) the feasibility of systemic treatment and c) the localization of bsmAb-coated radiolabeled lymphocytes.

**Results:** Treatment with autologous activated lymphocytes retargeted with the bsmAb OC/TR resulted in an overall ip response rate of 27% with only mild and transient toxicity. The activity was mainly local and a persistent HAMA response precluded repeated treatments. The combination of iv and ip administration of OC/TR retargeted lymphocytes, which might possibly lead to an extraperitoneal cure, was feasible and clinical follow up of treated patients is ongoing. A method for radiolabeling lymphocytes was developed and localization studies are now in progress.

**Conclusions and Future Directions:** We expect further improvement of the retargeted-lymphocyte technology through the selection of reagents from human antibody phage libraries which will enable to repeat courses of treatment.

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## Ovarian cancer – Are we making progress?

T. Bjørge[1,2], A. Engeland[2], S. Hansen[2], C. Tropé[1]. [1]*Dept. of gynecologic oncology, The Norwegian Radium Hospital;* [2]*The Cancer Register of Norway, Montebello, 0310 Oslo, Norway*

Histology-specific long-term trends in the incidence of ovarian cancer and borderline tumours in Norway were examined, based on data from the population-based Cancer Registry of Norway. A total of 14,352 cases of ovarian cancer were diagnosed between 1954 and 1993, of which 94% of the histologically verified ovarian cancer was epithelial tumours. The age-adjusted incidence rate rose from 10 per 100 000 persons-year in 1954–58 to a peak of 14 per 100 000 person-year in 1984–88. In women older than 50 years, there was an increasing trend in incidence rates during the entire study period From the cohort perspective, the largest increase

was observed among women born between 1870 and 1899. a total of 2,343 borderline turnouts were diagnosed between 1970 and 1993. The age-adjusted incidence rate has increased since 1970, reading 4.8 per 1000 000 person-years in 1989–93. The prognosis of ovarian cancer is still poor, and the crude 5-year relative survival was 36% in the Nordic countries in the late 1980s. in the present study, histology-specific long-term trench in prognosis of patients with ovarian cancer and borderline turnouts in Norway were examined The age-adjusted 5-year relative survival rate of patients with ovarian cancer increased steadily from 1954 to 1993. The increase in survival was most pronounced in women below the age of 65 years. No improvement was seen for women older than 75 years. The 5-year relative survival of the serous turnouts improved continuously from 1970 to 1993. For the mucinous tumours, an increase in relative survival was seen until 1984–88, thereafter the rate declined. In multivariate survival analysis, the RR of dying decreased with period diagnosis. For all patients with ovarian cancer, a RR of 0.5 (95% CI = 0.4–0.5) was seen in 1989–93 compared with 1954–58. Restricting the analysis to patients with epithelial cancer (197093), a RR of 0.6 (95% CI = 0.6–0.7) was seen in 1989–93 compared with 1970–73. In an analysis restricted to patients with epithelial cane., the patients with mutinous, endometrioid and clear cell turnouts had the lowest odds for having distant metastases. The age-adjusted 5-year relative survival rate of patients with borderline tumours was almost constant between 1970 and 1993, at a level of about 95% For these patients, age turned out to be the strongest prognostic factor. RRs of 11 and 34 were found for the age groups 65–74 and 75–89 years, respectively, compared with women younger than 45 years.

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## Ovarian cancer: Progress in chemotherapy

J.P. Neijt. *Department of Internal Medicine, University of Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands*

In the last decade it has been shown that long-term survival is achievable for women with advanced ovarian cancer. With cisplatin-based combinations 10 year survival rates are about 20 percent and even 15 years after treatment patients survive free of disease. The present standard of care is paclitaxel 135 mg/m$^2$ in 24 hours with cisplatin. It can be expected that with paclitaxel in initial treatment programs the long-term survival rate will increase. A shorter time of administration and an increase of the dose of paclitaxel will enhance the incidence of neurotoxicity. For this reason carboplatin (a less toxic cisplatin analogue) appears to be an attractive agent to combine with paclitaxel. The combination causes less nausea and vomiting, less neurotoxicity and can be administered to outpatients. Current studies define the role of carboplatin, doxorubicin, gemcitabine and new drugs such as topotecan in combination with paclitaxel. There is a renewed interest for the intraperitoneal use of drugs but this route of administration remains investigational.

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## The management of recurrent epithelial ovarian cancer

P. Bösze. *Department of Gynecologic Oncology and Clinic of Cancer Genetics, Saint Stephen Hospital, Budapest, Hungary*

Recurrent epithelial ovarian carcinoma, i.e. relapse after a disease-free interval of at least 6 months following primary therapy, carries a poor prognosis, and the shorter the disease-free interval the worse the outcome. There has been considerable differences regarding the management, particularly, the role of surgery. In principle, recurrent disease has rarely, if ever, been considered as localized disease. Thus, it requires systemic therapy. Whether or not surgery has a place in combination with chemotherapy is still controversial. Clearly, if the recurrent tumor does not respond to chemotherapy surgery has little to offer, and is of palliative treatment. Should patients with recurrent ovarian carcinoma undergo cytoreductive surgery followed by chemotherapy as with primary disease? Alternatively, should they have induction chemotherapy, and only the responders be treated with interval surgery followed by further chemotherapy? These are some of the question that yet to be determined. Patients who initially responded to cisplatin based chemotherapy may well be treated again with such regimen. A response rate of 60% can be expected.

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## Genetic predisposition to multiple cancers

C. Bonaïti-Pellié[1], F. de Vathaire[1], A. Chompret[1,2], A. Abel[1,2], L. Brugières[2], A. Shamsaldim[3], O. Oberlin[2], J. Chavaudra[3], J. Lemerle[2], J. Feunteun[4]. [1]*Unit of Cancer Epidemiology (U351 INSERM);* [2]*Department of Paediatrics;* [3]*Department of Physics;* [4]*Laboratory of Genetic Oncology (URA 1967 CNRS), Institut Gustave Roussy, Villejuif, France*

Genes predisposing to cancer in childhood may be responsible of multiple tumours. P53 germline mutations account for a substantial part of second malignant neoplasms (SMN) after a first cancer in childhood. Among 33 patients treated in the Department of Paediatrics affected by a SMN and tested for p53, 8 (including 2 sibs) were found to be carriers of a germline mutation of this gene. Most of these cases displayed a family history suggestive of LFS. One case was due to a *de novo* mutation.

All the genes predisposing to cancer in childhood and possibly to SMN have not yet been identified and the observation of familial aggregation may be a good indicator of such genes. Some of them might interact with radiotherapy and chemotherapy which have been implicated in SMN occurrence. We instigated a case-control study (25 cases of SMN after a childhood cancer and 96 controls with no SMN) to evaluate the possible effect of unknown genetic factors, evaluated from familial aggregation, on the risk of SMN, and their potential interaction with the effects of treatment. We found an independent effect of both radiotherapy and family history on the risk of SMN, even after exclusion of cases with p53 mutations and Recklinghausen's disease. These results strongly suggest that other genes than the ones identified to date have to be looked for and that the follow-up of children treated for a cancer should take account of genetic predisposition.

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## The role of therapy in the incidence of second cancers

M.M. Hawkins[1], H.S. Burton[1], M.H.N. Potok[1], D.L. Winter[1], H.B. Marsden[2], M.A. Stovall[3]. [1]*University of Oxford;* [2]*University of Manchester, UK;* [3]*MD Anderson Cancer Center Houston, USA*

**Purpose:** Recent UK data suggest at least 60% of children with cancer are cured. Therefore 1 in a 1000 of the general population will soon be survivors of childhood cancer. What are the risks of carcinomas among these adult survivors? Are there particular elements of therapy for childhood cancer which increase the risk of carcinoma development?

**Methods:** A cohort of 13279 patients who survived at least three years after diagnosis of childhood cancer between 1940 and 1983 was established using the population-based National Registry of Childhood Tumours. A case-control study was also established: cases were patients developing carcinoma and up to 4 controls were matched to each case. Cumulative doses of radiation and chemotherapy were compared between cases and controls.

**Results:** 69 carcinomas were observed in the cohort, 25 skin and 44 of other sites. By 30 years from three-year survival 2.5% of patients had developed a carcinoma, 1% of skin and 1.5% of another site. There were 12, 9, 9 and 8 cancers diagnosed in digestive, breast, thyroid and genitourinary tissue, respectively. The risk of carcinoma increased with increased exposure to radiation. Patients whose tissue had received 20–30 Gy and at least 30 Gy experienced 18 and 12 times the risk associated with unirradiated tissue, both of these relative risks being associated with $p < 0.001$.

**Conclusions:** These data have implications for monitoring patients treated in the past, and for planning future treatment protocols to achieve an optimum balance between the risks and benefits of different elements of treatment in the long-term.

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## Growth from child to adult – Interference by radiotherapy

P.A. Voûte. *Institute of Emma Vinderzieleukuis, Dept. of Paediatric Oncology, Meibergdreef 9 1105 A3 Amsterdam, Netherlands*

The advances in treatment of childhood malignancies is reflected in improvement of survival. But the results are marred by delayed sequelae caused by the inability of radio- and antineoplastic therapy to discriminate between normal and target tissue. Irradiation to a growing child interferes with tissue growth. Radiation damage of the skin and the subcutaneous tissue and muscle can be serious. Radiotherapy to the thorax in a pre-pubertal female causes atrophy of the breast. Radiation to the small and large intestines