

## **ESTRO Award**

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### **Creating the future of radiation oncology**

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Radiation therapy induces DNA damage that can be modulated in time and space. Temporal modulation is achieved by dose fractionation and throughout the history of radiotherapy this has been one of the most fruitful research areas for optimizing the therapeutic ratio between tumour control and normal tissues effects. Spatial modulation is achieved by geometrical shaping of the radiation field portals or by modulation of the intensity of radiation incident on the patient. Technological and conceptual advances, in particular the development of the multi-leaf collimator and the concept of inverse treatment planning, have led to the introduction of intensity modulated radiation therapy (IMRT) which has dramatically improved our ability to plan and deliver highly non-uniform dose distributions in the clinic. This again has forced us to re-think radiation oncology: refining the indication for radiotherapy, optimizing the prescription of dose distributions and considering how, based on clinical evidence, radiation can best be combined with other treatment modalities, surgery, cytotoxic chemotherapy and biologically targeted therapies. Parallel progress in basic cancer biology, genomics and proteomics, as well as biological imaging provides novel powerful tools for biological optimization of radiotherapy in a multi-modality setting. At the same time, the practice of radiation oncology is increasingly becoming evidence-based medicine and the new methods for planning and delivering radiotherapy will have to be tested in this framework. An improved dose distribution will only convince fellow radiation oncologists, what is required for rational progress is evidence from randomized controlled trials that outcome is improved as well and documentation that these improvements are cost-effective. Taken together, these exciting developments define the overall research direction – and the challenges – for translational and clinical research in radiation oncology in the coming decade.

## **SIOP Award**

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### **Therapy of acute leukaemia in children - the decisive first 25 years**

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History of acute leukaemia in children virtually is that of its treatment evolution. As to my knowledge, at the present, no comprehensive description is available. Almost all started in Boston/USA, inaugurated by and associated with the name of Sidney Farber with the recognition of drug-induced leukaemia remission (by aminopterin). Leukaemia remission inevitably was followed by recurrence of the disease, second remission was more difficult to achieve and "cure" was virtually beyond reality. Nevertheless, did some of the first generation physicians (not necessarily paediatricians) consider leukaemia to be controlled permanently? During the fifties, in the USA, France, UK and Australia (the core countries) no convincing efforts have been undertaken to address the treatment goal "cure". Drug combinations for induction and maintenance generated more remissions and longer median remission times (Bernard, Zuelzer), but no or only exceptional "cures" (Burchenal, Gasser). Toxic multi-drug therapy was not considered for use in children for being either unethical or intolerable. Leukaemia treatment should be similar to that of bacterial meningitis (Farber) or tuberculosis (Pinkel). In retrospect, even in these early days, sufficient powerful drugs have been available in order to imagine drug combinations with a curative outlook. Approaches in that direction started as late as in the early sixties, 15 years after SubbaRow synthesized aminopterin. In the meantime almost all antileukaemic drugs still today in use have been available (corticosteroids, methotrexate, 6-mercaptopurine and 6-thioguanine, cyclophosphamide, cytosine arabinoside, vincristine, daunorubicin). Drug combinations termed VAMP or POMP had no mayor impact on "cure", but opened the window for the therapeutic principle of "multi-drug chemotherapy" (Frei III, Freireich, Holland). During these years meningeal leukaemia was recognized worldwide, minimal meningeal leukaemia at diagnosis considered to be a major source for subsequent relapse and treated by skull irradiation (Pinkel) or more intensive intrathecal therapy (Sullivan). In the late sixties cure in leukaemia was for a minority of

children documented (Pinkel) and not longer unrealistic. Still combination chemotherapy, for the majority of patients, was not efficient enough to generate a more dramatic reduction of the leukaemic clone and/or to avoid the evolution of resistance, the two major causes of failure. In 1970 the Berlin pilot trial made use of all active drugs in combination (including L-asparaginase) to be administered front-line within a rather short time period (Riehm). In New York the L2-protocol followed a similar line (Wollner). Cure rates climbed up above 50%, the drug-related toxicity was controllable mainly by better supportive care measures. In order to eradicate residual disease, in the Berlin leukemia trial intensive reinduction therapy turned out to be the last step in the 25 years' success story for keeping 65% of children with acute lymphoblastic leukaemia continuously in first remission. During the last twenty-five years further progress was generated by the community of devoted and educated paediatric oncologists and researchers from many countries as a collective performance.

## **ESSO Award**

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### **What is new in breast cancer surgery: a tailored approach**

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It is now clear that breast cancer may be more or less aggressive and that several prognostic and predictive factors may play a major role in the choice of the most appropriate therapy and in the final results. Modern imaging, morphological and biological characterisation of the lesion (besides many other factors such as age, fitness and attitude of the patient towards the diagnosis of cancer), require a more flexible attitude from the surgeon.

The study of the primary tumour and of its pathological features together with a molecular portrait based on the gene expression patterns and modern technology in examining sentinel node (reverse transcriptase-polymerase chain reaction (RT-PCR)) will undoubtedly lead to a better understanding of breast cancers.

Moreover, the surgeon should never forget that correct treatment nowadays is the result of the correct blending of the surgical, radiotherapeutic and pharmacological techniques that are available. This obviously means that the surgeon is no longer alone when faced with the tumour. However, this demands great knowledge of the problems and the ability to face different situations and to evaluate each single situation in its entirety.

Surgical treatment may cure a high percentage of cases nowadays and this is due to early diagnosis. However, early diagnosis does not mean underestimating the risks and problems connected with breast cancer.

Conservative surgery is now the usual therapy for small *in situ* or invasive tumours, but many problems must be solved.

Practically, one can either be a maximalist, doing the utmost independently of the histology and biology of the tumour, carrying out as large an excision as possible, or a minimalist, guided by global evaluation of the situation and therefore highly personalised. Certainly the former is easier, more traditional and more easily repeatable in terms of respecting guidelines. The second is more eclectic, requires a deep knowledge of the problem and therefore patient management becomes more complex and difficult.

However, in the near future there will certainly be quality improvement in the diagnosis and treatment of breast cancer and keener attention to individual situations. In particular, everything should be codified, registered and subject to quality control. Every phase of the surgical procedure must be accurately recorded to favour quality control, to ensure completeness of excision, to avoid overtreatment of women with favourable lesions, to ensure that all necessary data are obtained for making decisions on adjuvant radiotherapy or adjuvant systemic therapy.

## **EACR Award**

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### **Rna polymerase III transcription and cancer – the opposing effects of RB, p53 and c-Myc**

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RNA polymerase (pol) III transcription is hyperactive in transformed cells. I shall describe our efforts to elucidate the mechanisms responsible. We