ESTRO Award

3

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

4

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 scull 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

5

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, radiotherapeutical 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 upmost 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

6

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

have uncovered a network of unanticipated links to key oncogenes and tumour suppressors. In so doing, we revealed novel functions for RB, p53 and c-Myc that may help explain their profound biological effects, as pol III activity is a major determinant of a cell's capacity for growth.

Pol III manufactures essential products such as tRNA and 5S rRNA. Although it requires a unique set of transcription factors, we discovered that it is also repressed in healthy cells by the retinoblastoma protein RB (1). This offered an immediate explanation for the deregulation of pol III transcription in malignancies, as loss of RB function may be a necessary step for tumour progression. Subtle mutations in RB that arose in SCLCs and retinoblastomas ablate its ability to repress pol III. Multiple DNA tumour viruses can deregulate pol III by neutralising RB, e.g. in cervical carcinomas. In addition, pol III is derepressed when RB is aberrantly phosphorylated, e.g. in breast cancers that amplify cyclin D1. Loss of RB function may contribute substantially to elevated pol III output in most malignancies (2).

p53 binds and represses the same pol III-specific transcription factor as RB (3). The fact that it is targeted by two key unrelated tumour suppressors provides a clear indication of the importance of restraining pol III output. P53-mediated control of pol III can be subverted by HPV E6 or Mdm2 and by substitutions which arise in p53 in cancers. Furthermore, Li-Fraumeni syndrome patients sometimes have aberrant pol III activity.

As well as the negative control exerted by RB and p53, the pol III system is also directly activated by several oncogenic factors. For example, c-Myc is recruited to tRNA and 5S rRNA genes in living cells (4). Pol III transcription is stimulated strongly by c-Myc and may help mediate the potent growth-promoting effects of this oncoprotein. Deregulation of c-Myc will further increase pol III output in many malignancies, e.g. Burkitt's lymphomas.

Some tumour types consistently overexpress pol III-specific transcription factors, e.g. breast and ovarian carcinomas (5). This provides another route to raise pol III output as cancers develop.

In summary, the tumour suppressors RB and p53 restrain pol III transcription in healthy cells and their inactivation during tumour development will derepress pol III. It is further activated in some cancers by c-Myc or by elevated expression of pol III-specific factors. There is strong selection to raise pol III output as tumours develop. This can have dramatic effects on cell growth and proliferation.

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