In tomotherapy you use a fan beam (line dose delivery) which either treat the volume in a slice-by-slice mode similar to the earlier CT scanner or you use the same helical scanning that today is the standard technology in diagnostic CT scanning. The fan beam is intensity modulated by a kind of MLC technique. MLC methods (area dose delivery) uses beams which are either static or dynamic where the first type consists of a series of sub-beams delivered in sequence. The radiation is turned off in-between each sub-beam while the leaves move to the next position. Once the leaves are in position the dose for that segment is delivered. This delivery technique has been named Segmented MLC (SMLC). An earlier name has been step and shoot. The dynamic method can be described as a sweeping technique of each leaf-pair according to a predetermined pattern. This technique is named Dynamic MLC (DMLC). The pros and cons of the different techniques will be discussed during this session.

81 INVITED

Towards a realistic and effective Quality Assurance paradigm for IMRT

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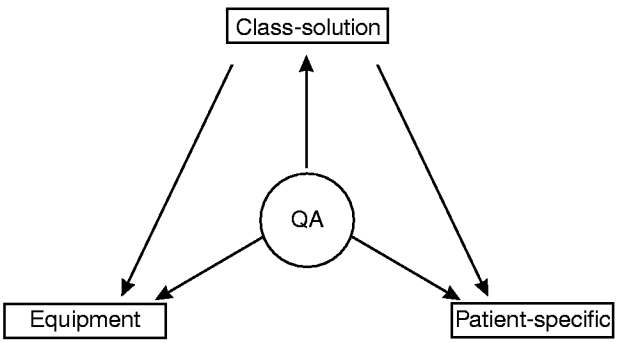
Quality Assurance (QA) of radiation therapy should ideally extend to the therapeutic outcome. Fortunately, the quality of IMRT is closely related to the absorbed dose distribution which can be elegantly expressed and tested quantitatively. The concept of a distribution inherently combines the positional and intrinsically dosimetric endpoints of IMRT.
Apart from IMRT-dedicated delivery systems, which are still scarce, the majority of IMRT treatments are delivered using traditional linear accelerators, equipped with multileaf collimators that were at the onset basically designed to replace shielding blocks. A great deal of QA activities should therefore be focused on machine performance characteristics that are rarely rigorously specified and usually receive little attention during maintenance and periodic quality control. This is the domain of **equipment QA**, which continues the commissioning phase of the radiation delivery equipment and the treatment planning system.
Class-solution QA comprises the experimental assessment of the total dose distribution delivered to an anthropomorphic phantom. Class-solution QA is the ultimate pre-treatment test for the planning and delivery chain of IMRT, including the human links. Dosimetric verification is achieved by comparing the delivered (measured in the phantom) dose distribution to the aimed (computed for the phantom) distribution. All critical parts of the dose distributions should be involved in the comparison, e.g., dose to PTV, dose to OARs and dose gradients. The clinical class solution itself, the delivery equipment, the planning approach followed within the class solution, and the experience gained by the IMRT team will determine the number of clinical cases required within a given class solution.
Patient specific QA should focus on the verification of patient positioning (during-treatment with image guided radiation therapy) and on the detection of possible gross errors (pre-treatment), e.g., of more than 5% in absolute dose (relative to the prescribed dose).



A pyramid-shaped conceptual approach will be presented that optimises and streamlines QA procedures within class solutions, rather than proliferating redundant QA checks. Then, as illustrated in the figure below, an IMRT QA program can be considered as a triad of three categories of QA. This paradigm stimulates familiarization with IMRT and keeps the level of alertness high.

Scientific Symposium
Apoptosis in drug and radiotherapy resistance

82 INVITED

Apoptosis: no life without death

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CD95, a member of the tumor necrosis factor (TNF) receptor superfamily induces apoptosis upon receptor oligomerization. The receptor and its ligand are important for apoptosis of peripheral T cells, for downregulation of an immune response and most likely, at least in part, also for peripheral T cell tolerance. In AIDS, apoptosis mediated by this system might contribute to the depletion of T helper lymphocytes. Likewise, in diseases in which liver cells are destroyed the CD95 system might play a major role. In a search to identify the intracellular signalling pathway of CD95 several molecules coupling to oligomerized CD95 were immunoprecipitated from apoptosis-sensitive human leukemic T cell and lymphoblastoid B cell lines. The following binding molecules were only associated with aggregated and not with monomeric CD95: phosphorylated FADD (MORT1) and caspase 8. Thus, caspase 8 was identified as the most CD95 receptor proximal protease which starts the cascade of protease reactions important for CD95-mediated apoptosis. Association of FADD and caspase 8 with CD95 was not observed with C-terminally truncated non-signalling CD95. FADD and FLICE did also not associate with a CD95 cytoplasmic tail carrying the lprcg amino acid replacement. FADD and caspase 8 form a death-inducing signalling complex (DISC) with the CD95 receptor and are, thus, the first CD95 associating proteins of a signalling cascade mediating apoptosis. The function of the DISC is discussed in detail, particularly with respect to its role in sensitivity and resistance to apoptosis.
The CD95 death system plays a role in destruction of liver tissue. In hepatitis cytotoxic T lymphocytes might use the CD95 system to kill infected hepatocytes. In M. Wilson copper overload leads to upregulation of the CD95 ligand that may finally contribute to acute liver failure. In HCC from patients treated with chemotherapeutic drugs the CD95 receptor and ligand are upregulated and may contribute to apoptosis of the tumor or, dependent on the drug sensitivity of the tumor, to the status of the tumor as an immunoprivileged site.

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83 INVITED

Chemoresistance and apoptosis: shifting from the apoptotic default pathway to the adaptive stress response

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Chemotherapy resistancle has often been related to disabled apoptosis with deficient caspase activation. We have recently found that, even in the absence of any adjuvant, tumor cells dying in response to anthracyclins can elicit an effective anti-tumor immune response that precludes the growth of inoculated tumors or leads to the regression of established neoplasia. Caspase inhibition by Z-VAD-fmk or transfection with the baculovirus inhibitor p35 did not inhibit doxorubicin-induced cell death (as measured as clonogenic survival), yet suppressed the immunogenicity of dying tumor cells in a variety of different rodent models of neoplasia. Depletion of DC in vivo curtailed the immune response against doxorubicin-treated apoptotic tumor cells. Caspase inhibition suppressed the capacity of doxorubicin-killed cells to be phagocytosed by dendritic cells (DC), yet had no effect on their capacity to elicit DC maturation. Freshly excised tumors became immunogenic upon doxorubicin treatment in vitro, and intratumoral inoculation of doxorubicin could trigger the regression of established tumors in immunocompetent mice. These results delineate a procedure for the generation of cancer vaccines and the stimulation of anti-neoplastic immune responses in vivo.
Moreover, they suggest that inhibition of caspase activation (which leads to a shift from apoptotic to non-apoptotic death modalities) can abrogate the immunogenic nature of cell death, thus favoring the escape of tumors from immune surveillance. In addition, I will discuss the role of HSP70 as an apoptosis inhibitor as well as an inhibitor of immunogenic cell death.