Radiotherapy

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ESTRO/VARIAN Award Lecture

No abstract

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Comparison of two conditioning regimens in allogeneic bone marrow transplantation (ABMT): Emphasis on the role of total body irradiation (TBI) for "high risk" patients

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Purpose: This retrospective analysis aimed at comparing the patients' outcome after two different preparative regimens (with or without TBI) for ABMT.

Methods and Materials: From January 1984 to December 1994, 171 patients with acute leukemia (AL, n = 97), chronic myelogenous leukemia (CML, n = 49), lymphoma (14) and aplastic anemia (11) were registered. Preparative regimen included cyclophosphamide with TBI (CTBI group, n = 117) or busulfan (CB group, n = 54). Median follow-up was 36 months (0.4–120). Two groups were constitued: a "standard risk" group (116) including patients with AL in first remission and CML in chronic phase, and a "high risk" group (55) presenting AL in relapse or refractory state, or with CML in accelerated or blastic phase.

Results: At 3 years, the outcome was similar for survival (58% vs 62%) and transplant-related mortality (74% vs 65%) between CTBI and CB groups. Relapses were less frequent in the CTBI group (10% vs 24%). "High risk" patients had a poorer survival and a higher relapse rate, especially in CB group (33% vs 64%). In multivariate analysis, decreased survival was associated with HLA incompatible transplants, interstitial pneumonitis, age, thrombopenia and "high risk" patients. Higher relapse rate was associated with CB group and no graft-vs-host disease.

Conclusion: CTBI provided an equivalent or better outcome than CB, particularly in "high risk" patients. CB could be an acceptable alternative for patients in whom TBI would not be feasible.

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Is acute mucositis dose limiting for altered fractionated radiotherapy?

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Purpose: To analyze the incidence and kinetics of acute mucosal reaction in radiotherapy for head and neck cancers depending on fractionation, dose intensity and overall treatment time.

Material and Methods: A review of 25 published data sets concerning conventional accelerated and hyperfractionated radiotherapy for head and neck cancer. Incidence, the onset and duration of healing of severe acute mucositis were analyzed in relation to accumulated dose per week, and Dose-Time Ratio (DTR) which is normalization factor expressing an average dose per day multiplied by an average fractions per day. Logistic regression analysis was used to estimate correlation between fractionation parameters and acute mucositis.

Results: It was found that incidence and the onset of acute mucositis strongly depends on accumulated dose per week (AD) and the risk of severe acute mucositis increases above 80% when the AD is larger than 14 Gy, and acute effect occurs sooner than on the end of second week of treatment. The risk of 100% of severe acute mucositis strongly correlates with accelerated fractionation. The risk significantly decreases to 40–20% when hyperfractionation is used.

Conclusions: For altered fractionation acute mucosal reactions became dose limiting. Acceptable risk of acute mucositis can be expected when accumulated dose per week is lower than 72 Gy and the DTR is below 2.5 Gy/day^2. High value of the AD (>14 Gy) and DTR above 10 Gy/day^2 lead to high risk of persistent confluent mucositis and consequential late necrosis.

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Is there a safe dose for spinal cord after hyperfractionated and conventional radiotherapy?

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Purpose: Animal experiments show that hyperfractionation spares spinal cord, but doses are not transferable from rodents to humans. We therefore tried to find out a "safe dose" for spinal cord using own clinical and literature data.

Patients and Methods: From standard radiotherapy techniques for ENT tumors (lateral opposing irregular portals, total dose 60–70 Gy (single dose 2 Gy) or 82.8 Gy (single dose 1.2 Gy twice daily) biologically effective dose (BED, a/β = 2.0 Gy) to the spinal cord was recalculated. In total, 1008 patients had been irradiated in that way. In 802 of them, planning target volume had to be extended to the posterior cervical lymph nodes, thus to the spinal cord. Aditionally, we tried to recalculate BED from 60 data sets taken from literature.

Results: In our patients, BED to spinal cord varied from 7.7 to 83.8 Gy_2. **We never saw signs of myelopathy.** Additionally, from 48 out of 60 papers BED could be calculated. Here myelopathy did not or very rarely occur after a BED of not more than 90 Gy_2.

Conclusion: Our data and those taken from literature indicate that a BED to spinal cord of 90 Gy seems safe. This relies to a conventional dose of 45 Gy (single dose 2 Gy) or a hyperfractionated dose of 56.5 Gy (single dose 1.2 Gy twice a day).

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N-oxide derivatives of chlorambucil as agents for overcoming hypoxic cell radiation resistance

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Purpose: To develop and test N-oxide (N-O) derivatives of chlorambucil (CL). The rationale being that the N-O group should deactivate CL thereby reducing systemic toxicity, but under hypoxic conditions, seen in most solid tumours, this N-O group will be reduced thus reactivating the drug.

Methods: Drugs were i.p. injected into CDF1 mice, with a 200 mm^3 C3H mammary carcinoma grown in the foot, before/after local tumour irradiation (15 Gy). The endpoint was tumour growth time (TGT; time to grow to 600 mm^3).

Results: CLN-O showed >2-fold less systemic toxicity than CL itself. At the highest dose tested (100 mg/kg) CLN-O increased the mean (± 1 SE) TGT for control mice from 4.8 (± 0.2) to 6.5 (± 0.4). It also increased the TGT for radiation from 16.4 (± 0.7) to 19.1 (± 1.1); this effect being independent of sequence and interval. Similar results were seen with an ethyl CLN-O derivative, although the benzyl form was more toxic. Comparable findings were seen in KHT tumours using an excision assay.

Conclusions: Some N-O forms of CL can decrease drug-induced systemic toxicity, while showing potent activity against hypoxic tumours.

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An obvious and underestimated predictive assay: Precise, cheap and easy prediction of radiotherapy outcome using tumor volume

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Purpose: A research strategy in radiotherapy is to develope assays that allow prediction of tumor response which in turn enable individualized prognosis and treatment decisions. For this purpose a wide variety of assays is currently being explored. In this contribution, the impact of tumor volume on radiotherapy outcome and its predictive potential is investigated.

Method: Re-evaluation of clinical data from the literature.

Results: Tumor volume significantly influences radiotherapy outcome. Tumor stage reflects tumor size only partially; it is mainly correlated to surgical operability. Tumors even of identical stage vary by factors of more

than 100 in volume. Neglect of heterogeneity in tumor volume reduces the power of a study considerably. Thus, clinically relevant effects can be overlooked if tumor size is not taken into account. As compared to presently applied predictive assays, tumor volume appears to be the most precise and most relevant predictor of radiotherapy outcome.

The precision requirements for the measurement of tumor volume are small. Statistical considerations show that a precision of ±50% is sufficient for reasonable results.

Conclusion: The data evaluated here clearly suggest that tumor volume is the most precise and most relevant predictor of radiotherapy outcome. Its determination is cheap and easy and with sufficient accuracy achievable in most radiotherapy departments. Individual tumor volume should always be reported in clinical studies and considered in data analyses.

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Randomized trial comparing preoperative irradiation versus the use of non-steroidal-antiinflammatory drugs for prevention of heterotopic ossification following prothetic total hip replacement

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Purpose: In vivo data support the effectiveness of *early* preoperative irradiation within 4 h before operation in suppressing the development of heterotopic ossification (HTO) after total hip replacement (THR). This procedure can entail logistical difficulties. A randomized trial was undertaken to assess the efficacy of *late* preoperative irradiation in the evening before the day of operation compared with the use of non-steroidal-antiinflammatory drugs (NSAID).

Methods: Between 1995 and 1996 103 patients with normal risk factors for HTO following elective hip replacement were randomized to receive preoperative irradiation (single 7 Gy fraction) or NSAID (diclofenac-colestyramin). X rays of treated hips were obtained immediately and 6 months after surgery. HTO was scored accending to the Brooker grading system. A group of 100 patients, who received no prophylactic therapy after THR between 1988 and 1992, were analysed as untreated historical control group.

Results: The incidence of HTO was 48% in the irradiation-group (Brooker Score I: 52%; II: 36%; III: 5%; IV: 0%), 9.3% in the NSAID-group (Brooker Score I: 7.5%; II: 1.8%; III: 0%; IV: 0%) and 65% in the untreated control group (Brooker Score I: 26%; II: 15%; III: 19%; IV: 5%). Regarding overall HTO there was a significant difference between the two treatment groups. Analysing the clinically significant HTO (Brooker score III or IV) no significant difference was noted between irradiated

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Factors determining late complications following postoperative radiotherapy in endometrial carcinoma

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Purpose: Our aim was to evaluate the influence of patient- and treatment-related factors on the risk of late effects of normal tissue (LENT) after postoperative radiotherapy (RT) in endometrial cancer (EC) patients (pts).

Methods: We performed the retrospective analysis of data of 247 EC pts treated with surgery followed by RT including Caesium or Radium brachytherapy (BRT) and external beam RT (XRT). Mean BRT dose rate at 0.5 cm was 0.75 ± 0.49 Gy/h (0.42–1.9 Gy/h) and mean BRT dose was 50.1 ± 11.7 Gy at 0.5 cm (14.5–71.0 Gy). Mean XRT dose within the target volume was 44.5 ± 3.4 Gy (20.0–60.0 Gy) given in fractions of 1.4 to 2.26 Gy (mean 1.82 ± 0.15 Gy). Median follow-up was 7.3 years. Normalised Total Dose (NTD) was calculated based on linear-quadratic equation including XRT and BRT doses. EORTC/RTOG scale with elements of SOMA/LENT table was used to score LENT.

Results: 144 pts experienced LENT, most frequently from rectum (49% pts) and urinary bladder (25% pts). Severe LENT (grade 3 or 4) were observed in 11% of pts. Multivariate Cox test showed that NTD ($p = 0.000$), XRT fraction dose ($p = 0.041$) and BRT dose rate ($p = 0.036$) were independent risk factors for LENT. Prolongation of RT time and box technique were correlated with lower LENT risk, but were not independent factors in multivariate test. No clinical factor (age, parity, prior abdominal surgery, FIGO stage, diabetes, hypertension) was independently associated with LENT.

Conclusion: The risk of LENT depends mainly on treatment-related factors. High rate of LENT in our pts was a basis of modification of RT schedule.

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Prognostic impact of reoxygenation in cervical cancers treated with definitive radiotherapy

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Objective: We have investigated the oxygenation status of cervical cancers in patients undergoing definitive radiotherapy.

Materials & Methods: 28 patients with squamous cell carcinoma of the cervix uteri FIGO II/III underwent polarographic measurement of tumor oxygenation with an Eppendorf pO_2-histograph prior to and during definitive radiotherapy (at 20 Gy and at the end of XRT). All received combined external irradiation and HDR-brachytherapy.

Results: We found a broad range of pO_2-values in the 28 patients. Significant hypoxic areas were detectable in one third of the patients. The mean and median pO_2-values did not correlate with tumor stage or tumor volume. 22 patients achieved a complete remission of the primary local tumor. In this subgroup of responders, the median pO_2 at 0 Gy and 20 Gy was higher than in patients with persistent or recurrent disease (at 0 Gy: 22 vs. 16 mmHg, $p < 0.01$; at 20 Gy: 37 vs. 13 mmHg, $p < 0.01$). A pretreatment pO_2 below 10 mm Hg, was found in 10/27 patients. In five of them, it persisted at 20 Gy and all failed (four locally, one distant). The other five tumors with a low initial pO_2 showed an increase in the median pO_2 at 20 Gy, and all five were locally controlled although one developed distant disease. In the 17 patients with a pretreatment pO_2 above 10 mm Hg, 16 were locally controlled.

Conclusions: An early increase in tumor tissue pO_2 is a favourable prognostic sign suggesting a role of "reoxygenation".

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Differentiation patterns of secondary skin fibroblasts from radiotherapy patients with different degrees of radiation-induced skin fibrosis

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Purpose: Radiation-induced terminal differentiation of fibroblasts is an important step in the development of fibrosis after radiotherapy. In a retrospective study of postmastectomy radiotherapy patients we have examined possible relations between the differentiation pattern and the risk of fibrosis in individual patients.

Methods: Quantitative differentiation patterns of fibroblast precursors (mitotic cell types MFI, MFII, MFIII) and functional fibrocytes (PMF) were determined by clonal culture of secondary fibroblasts established from biopsies from the unirradiated upper arm and correlated with the individual risk of fibrosis.

Results: In a pilot series of eight patients, a high risk of fibrosis was associated with an increased ratio of late relative to early mitotic fibroblasts indicating that progression towards later differentiation states may increase the risk of fibrosis.

Conclusion: The present results support the hypothesis that disturbance of the balanced composition of fibroblasts/fibrocytes is a factor in the development of radiation-induced fibrosis and suggests a potential predictive assay for radiation-induced fibrosis. A blind study of 31 patients is in progress.

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Malignant pleural mesothelioma (MM): Outcome following radiotherapy in 300 patients

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Background: The incidence of MM continues to increase, particularly in industrial regions. As MM is currently viewed with therapeutic pessimism,