Radiotherapy

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Radiotherapy I

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Randomised trial of standard 2D radiotherapy (RT) versus 3D intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy

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Aim: To test standard 2D versus 3D intensity modulated radiotherapy (IMRT) in terms of late changes in breast appearance, discomfort and hardness.
Methods: Between 1997 and 2000, 306 women with larger than average breast size requiring whole breast radiotherapy after breast conservation surgery for early stage cancer were randomised to 2D radiotherapy delivered using standard wedge compensators or to 3D IMRT (test arm). The latter was delivered using physical compensators or a multiple static field technique delivered using a multileaf collimator. The 2D standard wedged plan was calculated on a single transverse contour of the patient through the centre of the breast, accounting for lung. The IMRT compensation was determined from transit dosimetry using electronic portal imaging. Patients were treated with 6 or 10 MV photons. The primary endpoint was change in breast appearance scored from serial photographs taken under standard conditions before radiotherapy and at 1, 2 and 5 years by 3 blinded observers applying a 3-point graded scale (no change, some change, a lot of change). Secondary endpoints included patient self-assessments of breast discomfort, breast hardness, EORTC QLQ C-30/BR-23 and physician assessments of breast induration. Analysis was by intention to treat.
Results: Factors influencing change in breast appearance, including breast size, surgical deficit, axillary surgery, systemic therapies and lymphatic radiotherapy, were well balanced between treatment arms. By 5 years, 44 (14%) patients had died and 9 (3%) had further surgery or reconstruction surgery making assessment impossible. Of the remaining 253 patients, 242 (96%) had clinical assessments, including 237 with photographs. At 5 years, any change (some change or a lot of change) in breast appearance was scored in 73/122 (60%) allocated standard 2D treatment and in 55/115 (48%) patients allocated IMRT ($p = 0.06$). In patients whose maximum dose was >105% or ⩽105% of the prescribed dose, the rates of any change in breast appearance were 71/118 (60%) and 49/107 (46%), respectively ($p = 0.03$). No difference between treatment arms was observed by patients in terms of breast discomfort, hardness or quality of life.
Conclusion: The final analysis strongly suggests that reduction in unwanted radiation dose inhomogeneity in the breast reduces late adverse effects to statistically and clinically significant extents. A beneficial effect on quality of life remains to be demonstrated.

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Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis

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Background: Radiation-induced fibrosis (RIF), a late damage to normal tissue after radiotherapy (RT), is traditionally considered irreversible. Significant RIF regression has been achieved after treatment combining pentoxifylline (PTX) and tocopherol (vit. E). We focus here on the maximum response, how long it takes to achieve, and changes after treatment discontinuation.
Methods: Among more than 300 treated patients with chronic RT damage, 62 homogenous patients had 74 measurable and symptomatic superficial RIF. RIF analyzed with complete data were assessed in patients treated by RT for breast cancer a mean 7 years previously, in a long (24–48 months) PTX-vit. E (L.PE) group of 37 patients (47 RIF sites) and in a short (6–12 months) PTX-vit. E (S.PE) group of 7 patients (8 RIF sites). Between April 1995 and April 2000, the women were treated with a daily oral combination of PTX (800 mg) and Vit. E (1000 IU). The main endpoint measure was the relative regression of RIF surface area, every 6 months over 5 years, during and after the end of treatment.
Results: Combined PTX-vit. E was continuously effective over several years and resulted in RIF surface area regression (S.PE/ L.PE): −46/−68% at 6 months, −58/−69% at 12 months, −63/−68% at 18 months, −68% at 24 and 36 months. The best representative model of the time-course of regression was found to be of the exponential form $f(t) = a.\exp(-bt) - a$ with t (time from treatment onset), a (maximal surface area regression), and b (kinetics of response). The estimated maximal treatment effect was a mean 68% RIF surface area regression. The time to this effect was a mean 24 months, and was shorter (16 months) in more recent RIF (<6 years since RT) than in longer standing RIF (28 months) ($p = 0.0003$). Symptom severity was halved in both groups: mean SOMA score of −54% at 6 months in S.PE and −47% at 18 months in L.PE. After treatment discontinuation, mean RIF surface area at one year had increased by +40% in S.PE (rebound) and +8.5% in L.PE.
Conclusions: Under combined PTX-vit. E treatment, RIF surface area regression was exponential with a two-thirds maximum response after a mean 2 years. There was a risk of a rebound effect if treatment was too short. Long treatment (⩾3 years) is recommended in severe cases.

References

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Normal tissue protection and modulation of tumor radiation sensitivity by the combination of Pravastatin with radiotherapy

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Background: Tumor elimination while minimizing the damage to the surrounding normal tissues is a major goal to improve the therapeutic index of radiation therapy. Recently, R Weichselbaum [1] proposed that "new biological strategies [should] sensitize tumors to radiation and protect normal tissues".
Our laboratory investigates the physiopathological mechanisms of late radiation injury to normal tissue in order to define new therapeutic targets. We recently showed the activation of the Rho pathway in initiation and maintenance of radiation-induced intestinal fibrosis. Furthermore using a pharmacological inhibitor of the Rho pathway, Pravastatin, we have been able to limit radiation-induced fibrogenic differentiation both *in vitro* and *in vivo*, suggesting that Rho inhibition may become a novel anti-fibrotic therapy. Before transfering to the clinical applications, assessment of the effect of [Pravastatin+irradiation] combination on tumor control was required. Therefore, in the present study the effect of Pravastatin+irradiation on tumor radiation response was assessed *in vitro* and *in vivo*.
Material and methods: Modulation of radiation sensitivity was assessed *in vitro* using clonogenic cell survival assay. Cervix carcinoma (HeLa), Colon carcinoma (HT-29) and glioblastoma (SF763) cell lines were subcultured in DMEM complemented with 10% charcoal-stripped FCS and incubated with Pravastatin alone (100–500 &,mu;M), irradiated at 2–6 Gy or treated with combination. Tumor growth delay is currently studied *in vivo*, using HeLa and HT-29 xenograft in nude mice and treated with Pravastatin (30 mg/kg/J), irradiation (2×7.5 Gy) or combination.
Results: Consistent with previous published observations [2], the present *in vitro* experiments showed that Pravastatin exposure alone was able to decrease clonogenic survival at 500 μM (500 μM correspond to Pravastatin ED^{50} *in vitro*). Interestingly, combination of Pravastatin and irradiation more potently decreased clonogenic survival in a dose dependent manner. Additional experiments are currently performed to determine whether the effect is additive or synergistic and the underling molecular mechanisms. Furthermore, the *in vivo* experiments are under analysis.
Conclusion: The present results suggests that the anti fibrogenic agent Pravastatin can sensitize tumor cells to ionising radiation. The molecular mechanism involved are yet undefined, but one attractive hypothesis concerns the inhibition of RhoB, a small GTPase involved in radiation resistance of SF763 and HeLa cells [3]. In addition, combination of Pravastatin with irradiation may allow to achieve a dual objective: simultaneous normal tissue protection and tumor sensitisation.
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References

[1] Weichselbaum, Nat Med, 2005.