and analysed using Allred scoring in epithelium and mast cell counts per high powered field in epithelial and stromal compartments.
Results: Paired samples were available from 4 patients who had received radiotherapy 1.5−23 years prior to mastectomy. Of the transcripts differentially expressed in the epithelial compartment, KIT was reduced in the irradiated samples, and its ligand KITLG (stem cell factor, KIT ligand) was increased although statistical significance was not achieved. Preliminary validation with immunohistochemical staining in 4 sample pairs confirmed a striking reduction in the expression of c-Kit in the lobular epithelial cells of the previously irradiated breast compared to the unirradiated breast ($p = 0.01$). Preliminary data suggest an increase in c-Kit positive mast cell numbers in both the epithelial and stromal compartments, confirming also that the epithelial cells are responsible for the reduction in expression levels of c-Kit.
Conclusions: c-Kit expression is reduced in normal epithelium of irradiated human breast and c-Kit positive mast cell numbers may be increased in both stromal and epithelial compartments. This is of particular interest because of known involvement of mast cells in many fibrotic conditions, and previously only animal data has been reported for radiation fibrosis. We plan further immunohistochemical analysis for both c-Kit and its ligand stem cell factor in an extended sample set.

903 ORAL

Long-term risk of contralateral breast cancer in relation to treatment

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Purpose: To assess long-term risk of contralateral breast cancer (CBC) in a predominantly young breast cancer (BC) population, focusing on the effect of different radiation regimens, chemotherapy and family history of BC.
Methods: We studied incidence of CBC in 7221 1-year survivors of breast cancer who were treated between 1970 and 1986. Treatment-specific risk of CBC was evaluated in Cox proportional hazards regression models.
Results: RT-associated risk of CBC increased with decreasing age at first treatment (for age >35: hazard ratio (HR) = 3.4, 95% CI, 0.8 to14.8; for age >45: HR = 1.14, 95% CI, 0.83 to 1.55; Ptrend < 0.05). Among women irradiated before age 45 those who had postlumpectomy RT experienced 1.5-fold (95% CI, 1.1 to 2.1) increased risk of CBC compared with those who had postmastectomy RT. The joint effects of postlumpectomy RT (HR = 1.35) and positive family history for BC (HR = 1.21) on risk of CBC were greater than expected when individual risks were summed (HR = 3.26, 95% CI, 1.91 to 5.58). Young irradiated patients with positive family history developed predominantly medially located CBCs (82% vs 42% in patients without family history; P = 0.01). Treatment with adjuvant chemotherapy (cyclophosphamide, methotrexate and fluorouracil) exerted a protective effect on the risk of developing a CBC in the first 5 years of follow-up.
Conclusions: Young BC patients treated with postlumpectomy RT experience increased risk of CBC, specifically in case of a positive family history of BC. This finding questions the rationale for breast-conserving therapy in mutation carriers and warrants further research.

904 ORAL

Breast cancer risk in 5-year survivors of Hodgkin's lymphoma, the influence of treatment and premature menopause

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Background: Female Hodgkin's lymphoma (HL) survivors are at increased risk of breast cancer (BC) up to 25 years after treatment, especially those irradiated to the breast area at young ages. We assessed the cumulative risk after 25 years and the influence of gonadotoxic therapy on the risk of BC in patients irradiated to the breast area.
Methods: We performed a cohort study in 1155 women, treated for HL in the period 1965–1995 before age 51 (32% (RT), 8% CT, 60% RT+CT). We compared the incidence of BC with the general population and calculated standardized incidence ratios (SIRs) and absolute excess risks (AERs). We assessed absolute risk at 30 years using Kaplan-Meier risk estimation and competing risk techniques. Cox regression analyses was performed to study therapy-effects in relation to gonadotoxicity.
Results: During follow-up (median 18.2 years), 100 women, of whom 99 were irradiated to the breast area, developed BC (SIR 5.4 [95%CI 4.4−6.6], AER 54 per 10,000 patients per year). The risk remained high after prolonged follow-up (>30 years after treatment SIR 8.7 [4.2−16.0]). Although women treated before age 21 experienced the highest risk (SIR 16.9 [11.1−24.9], the risk among women aged 31−40 at treatment was still elevated (SIR 2.9 [1.8−4.5]). The cumulative risk (Kaplan-Meier) for BC 30 years after first treatment was 22%, whereas the cumulative incidence accounting for death as a competing risk was 17% at that time. Among women irradiated to the breast area, treatment with procarbazine ($\leqslant 8.4$ g/m^2: HR 0.6 [0.3−1.1], >8.4 g/m^2: HR 0.4 [0.1−1.0]), as well as RT to the ovaries (HR 0.3 [0.0−1.1]) lowered the risk for BC. In addition, women who retained normal ovarian function $\geqslant$16 years after treatment were at an increased risk for BC compared to those with <8 years of intact ovarian function (HR 5.4 [2.1−13.8]). Smoking and use of oral contraceptives did not influence the risk of BC, whereas obese women had a higher risk for BC (HR 1.8 [1.0−2.9]).
Conclusion: The risk of BC remains elevated up to >30 years after treatment, which suggests need for lifetime surveillance. The Kaplan-Meier method substantially overestimated the absolute risk of BC after HL compared with the method accounting for death as a competing risk. Gonadotoxic therapy lowers the risk of BC in patients irradiated to the breast area.

905 ORAL

Risk analysis in breast cancer patients younger than 45 years: which risk parameters gain in importance after breast conserving surgery (BCS), systemic therapy (ST) and radiation therapy (RT)?

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Background: We evaluate residual risk after breast conserving surgery (BCS), chemo- and/or hormone-therapy (ST) and radiotherapy (RT) in women younger than 45 years.
Materials and Methods: From 1984 to 1997, 220/1635 patients with breast cancer who underwent BCS and ST, and RT in our institution presented younger than 45 years (pre-menopausal). Recursive partitioning analysis was carried out for the endpoints local recurrence (LR) and disease free survival rate (DFR). Covariates included were age, T-stage, N-stage, ratio of involved lymph nodes and excised nodes (n-ratio), location of the index tumor, ER/PR status, and menopausal status. The relative hazard ratio (RHR, HR relative to median patient) was estimated in sub-groups of at least 20 patients.

Table A.

Risk group	n	n-ratio	PR	RHR
Low	98	<0.16	pos	0.32
Intermediate	90	<0.16	neg	1.16
High	32	<0.16	any	2.88

Table B

Risk group	n	n-ratio	loc	T-stage	RHR
Low	106	<0.09	lat	any	0.48
Low-interm	66	<0.09	med/centr	any	1.16
High-interm	25	$\geqslant$0.09	any	T1	1.51
High	23	$\geqslant$0.09	any	T2	3.42

Results: After a mean f/u of 105 months the rate of LR at 10 years was 12.0%, and the DFR was 70.8% in this young patient set. Age was not a significant cut point for either endpoint. For LR the n-ratio was the first cut point (table A) at 16%, followed by PR status. For DFR there was a dramatically low cut point in n-ratio of 9%, followed by tumor location and T-stage (table B).
Conclusion: We hypothesize that after BCS, ST and RT, subgroups of young patients are at higher risk, determined mostly by the n-ratio, not number of positive nodes. Higher risk is also indicated for medially and centrally located tumors, in PR negative patients and in women presenting with T2 N pos tumors. These subgroups may need a more aggressive therapy. The present results differ from most published reports, where lymph node status is not found critical to the likelihood of local recurrence.

906 ORAL

An interobserver study comparing CT and MRI for GTV delineation in radiotherapy for cervical cancer

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Background: This study evaluated the interobserver and intermodality variation using CT and MR imaging for delineation of gross tumour volume (GTV) in cervical tumours.
Methods: 4 observers (2 radiation oncologists and 2 radiologists) with specialisation in gynaecological oncology outlined the GTV independently on contrast-enhanced CT and MRI scans of 18 patients with cervical cancer. The scans were co-registered and areas of spatial difference between observers and modalities were determined. The volume common to all observers on each scan (V_{com}) and the total encompassed volume (V_{tot}) were measured to assess interobserver variation.
Results: *Intermodality comparison*: The mean tumour volume with CT was 133.9 cm^3 (range 28.2–422.5, SD 119.4) and 73 cm^3 (range 9.4–236 cm^3, SD 74.7) using MRI. The average CT/MRI ratio was 2.5 (SD 1.4), and in all cases the CT volume was larger than with MRI. There was greater interscan variation with smaller tumours, with CT/MRI ratio 3.1 for tumours <50 cm^3 on MRI compared to a ratio of 1.6 for volumes >50 cm^3. The largest discrepancy between modalities was in the superior-inferior directions, with large variation in contours involving the uterine body and vagina. For smaller tumours the entire cervix was often outlined on the CT images due to observer uncertainty.
Interobserver variation: The V_{tot}/V_{com} ratio was 3.3 (SD 1.6) for CT and 3.7 (SD 2.4) for MRI. For all 36 scans, the V_{com} was always smaller than smallest individual observer volume. The interobserver variation was greatest for smaller tumours, with ratio 4.8 for tumours <50 cm^3, and 1.9 for volume >50 cm^3 on MRI, and 4.1 for tumours <100 cm^3 and 2.5 tumours >100 cm^3 on CT. The average ratio between the individual volume and mean tumour volume (and SD), was 0.9 (0.3), 1.0 (0.3), 1.1 (0.2), 1.0 (0.2) for CT, and 0.7 (0.2), 1.2 (0.3), 1.2 (0.3), 0.9 (0.1) for MRI for observers 1, 2, 3 and 4 respectively.
Conclusion: The GTV was on average 250% larger on CT compared to MRI. The MRI scans were particularly useful for defining uterine and vaginal extent of disease. There is large interobserver variation, which has similar magnitude with both CT and MRI, and is greatest with small tumours. This variation should be taken into account when defining GTV, which is increasingly required for planning an integrated boost with IMRT and for 3D brachytherapy.

907 ORAL

Dose escalation with simultaneous integrated boost intensity-modulated radiotherapy for cervical cancer – impact of interfractional organ motion

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Aims: To assess whether the dosimetric advantage of IMRT compared to conformal radiotherapy (CRT) in reducing normal tissue doses is maintained throughout a course of radiotherapy, and that target volume definition is sufficient to account for interfractional movement. In addition, the feasibility of dose escalation with simultaneous integrated boost (SIB-IMRT) to be used in conjunction with intrauterine brachytherapy was evaluated.
Methods: 10 patients with cervical cancer had an RT planning CT scan, and 2 additional scans in the 2nd and 4th weeks of treatment. GTV, CTV and normal structures were outlined on all 30 scans. SIB-IMRT plans were produced to deliver 54, 58 and 60 Gy to PTV1 (GTV+5 mm) and 50.4$_{eq}$ Gy to PTV2 (CTV+15 mm). These were compared to delivering standard dose 50.4 Gy to PTV2 with CRT and IMRT. Treatment fields were applied to subsequent scans, and the impact of organ motion on dose to GTV, CTV and normal tissues were assessed.
Results: On the initial scans, normal tissue receiving >50.4 Gy with CRT, IMRT and SIB-IMRT (60 Gy) respectively were: bladder: 35%, 21%, 30%; rectum: 29%, 24%, 31%; large bowel: 43 cm^3, 12 cm^3, 14 cm^3; small bowel: 138 cm^3, 27 cm^3, 51 cm^3. The mean GTV volume reduced from 68 cm^3 to 59 cm^3, 53 cm^3, and the CTV from 656 cm^3 to 610 cm^3, 576 cm^3 in weeks 2 and 4 respectively. Coverage by 95% isodose of GTV, CTV was: CRT 100%, 99.6% and IMRT 99.9%, 99.5% in week 2; CRT 100%, 99.4% and IMRT 100%, 99.3% in week 4. SIB-IMRT$_{60}$ mean tumour dose was 59.9 Gy, and 93.9% GTV received >57 Gy. Normal tissue doses on repeat scans with CRT, IMRT and IMRT-SIB were: bladder: 33%, 24%, 31%; rectum: 22%, 18%, 26%; large bowel: 77 cm^3, 30 cm^3, 41 cm^3; small bowel: 144 cm^3, 52 cm^3, 64 cm^3 in week 2, and bladder: 36%, 32%, 36%; rectum: 37%, 28%, 35%; large bowel: 79 cm^3, 42 cm^3, 52 cm^3; small bowel: 189 cm^3, 88 cm^3, 99 cm^3 in week 4.
Conclusions: IMRT reduces dose to normal structures by up to 40% on the initial scan. SIB-IMRT can increase the external beam dose to tumour by 20% whilst maintaining normal tissue doses less than with CRT. With interfractional movement, there is increased normal tissue doses with all techniques, but IMRT and SIB-IMRT still irradiate less normal tissue than CRT. The selected CTV-PTV margin is sufficient to ensure adequate dose to GTV and CTV throughout treatment.

Poster presentations (Wed, 26 Sep, 14:00−17:00)
Radiotherapy/radiobiology

908 POSTER

The up-regulation of Integrin Linked Kinase in oral epithelium (mouse) by fractionated irradiation is accelerated by Keratinocyte Growth Factor (Palifermin)

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Background: Early radiation effects in oral mucosa are a severe and often dose-limiting side effect of radiotherapy for advanced head-and-neck tumours. The regeneration response to daily fractionated irradiation, summarized as "repopulation", occurs with a delay of about 1 week after the first fraction, and subsequently results in an increase in mucosal radiation tolerance with increasing overall treatment time. The present study in mouse tongue mucosa was initiated to determine changes in the expression of Integrin Linked Kinase (ILK) during fractionated irradiation, and their modulation by administration of Keratinocyte Growth Factor. ILK links integrins with growth factor receptors and thus modulates intracellular signal transduction. Variations in ILK expression hence may contribute to the regulation of the repopulation processes.
Materials and Methods: Daily fractionated irradiation with 5 X 3 Gylweek was given to the snouts of mice over a total of 2 weeks. In an additional experimental arm, Keratinocyte Growth Factor (Palifermin) was administered as a single injection of 15 mg/kg at the day before the first fraction. Groups of 3 mice per day were sacrificed from day 0 to 16, and the tongues were processed for immunohistochemistry. ILK expression was analysed semi-quantitatively using an arbitrary score for the staining signal.
Results: Compared to un-irradiated controls, an increase in the expression of ILK was found at the end of the first treatment week, i.e. in coincidence with the onset of repopulation. Administration of Palifermin on day −1 resulted in an almost immediate stimulation of ILK expression already on day 0, which remained elevated during the entire first week of irradiation, before a return to control values was observed at the beginning of week 2.
Conclusions: Fractionated irradiation results in a delayed increase in the expression of ILK in oral epithelium, indicating a regulatory role of this protein in the mucosal regeneration response. The earlier stimulation of ILK expression by KGF suggests that this growth factor modulates the intracellular signal transduction via this pathway, eventually resulting in increased mucosal tolerance to fractionated irradiation.
This study was supported by AMGEN Inc., Thousand Oaks, CA, USA.

909 POSTER

Updated results of high dose proton beam therapy (PBT) for stage I non-small cell lung cancer (NSCLC)

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Background: Proton beam has a distinctive depth-dose curve that enables us to deliver higher doses to the tumor without increasing doses to the