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

M.J. Hooning[1], B.M.P. Aleman[2], M. Hauptmann[2], J.G.M. Klijn[3], R. Noyon[1], M. Stovall[4], F.E. van Leeuwen[1]. *[1]Netherlands Cancer Institute, Epidemiology, Amsterdam, The Netherlands; [2]Netherlands Cancer Institute, Radiation Oncology, Amsterdam, The Netherlands; [3]Erasmus MC Daniel den Hoed Cancer Center, Medical Oncology, Rotterdam, The Netherlands; [4]M.D. Anderson Cancer Center, Radiation Physics, Houston, USA*

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

F. Van Leeuwen[1], M.L. De Bruin[1], M.B. van 't Veer[2], E.M. Noordijk[3], J.M. Zijlstra[4], J.W.W. Coebergh[5], H. van den Berg[6], B.M.P. Aleman[7]. *[1]The Netherlands Cancer Institute, Department of Epidemiology, Amsterdam, The Netherlands; [2]Erasmus MC Daniel den Hoed Cancer Center, Department of Hematology, Rotterdam, The Netherlands; [3]Leiden University Medical Center, Department of Radiotherapy, Leiden, The Netherlands; [4]VU University Medical Center, Department of Hematology, Amsterdam, The Netherlands; [5]Comprehensive Cancer Centre South/Eindhoven Cancer Registry, Cancer Registry, Eindhoven, The Netherlands; [6]Emma Children Hospital Academic Medical Center, Department of Pediatric Oncology, Amsterdam, The Netherlands; [7]Netherlands Cancer Institute, Department of Radiotherapy, Amsterdam, The Netherlands*

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)?

J. Hammer[1], C. Track[2], D.H. Seewald[1], J. Feichtinger[1], H.D. Thames[3], W. Langsteger[4], A.L. Petzer[5], K. Spiegl[1], E. Bräutigam[1], S. Pöstlberger[6]. *[1]Barmherzige Schwestern Hospital, Radiation Oncology, Linz, Austria; [2]Barmherzige Schwestern Hospital, Radiation Oncology and Breast Health Center, Linz, Austria; [3]M.D. Anderson Cancer Center, Biostatistics and Applied Mathematics, Houston TX, USA; [4]Barmherzige Schwestern Hospital, Nuclear Medicine, Linz, Austria; [5]Barmherzige Schwestern Hospital, Internal Medicine/Hematology and Oncology, Linz, Austria; [6]Barmherzige Schwestern Hospital, Surgery and Breast Health Center, Linz, Austria*

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