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Editorial

Breast Cancer Following Treatment of Hodgkin's Disease—More Reasons for Less Radiotherapy?

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In Hodgkin's disease (HD), stage-adapted polychemotherapy in combination with radiation results in cure rates of up to 90% in early and intermediate stages and of approximately 50% in advanced stages. An increased risk of secondary cancers in patients surviving HD has been reported in several studies [1, 2]. In a 15-year follow-up survey of 1507 patients with HD disease at the Stanford University Medical Center, a 17.6% cumulative risk (6-fold relative risk) of secondary cancers was found [1]. Similarly, an analysis of the International Database on Hodgkin's disease (IDHD) encompassing 12 411 patients with HD indicated a 15-year cumulative incidence rate of 11.2% for the development of secondary cancer [2]. While the elevated risk of leukaemia was strongly correlated with previous chemotherapy in these studies, the increased risk for solid tumours could be attributed mainly to radiation therapy alone or in combination with chemotherapy. These secondary solid tumours included cancers of different anatomical sites, among them most frequently lung cancers and tended to increase continuously with time.

In these and several other studies, the overall risk for breast cancer was not or only slightly elevated. A strikingly different estimation of the risk of breast cancer as a secondary neoplasm after treatment of HD occurs if the analysis includes patient subgroups defined by the length of follow-up and by the age at diagnosis of HD. For instance, in the report of the IDHD mentioned above the relative risk (RR, ratio observed/expected cases) for breast cancer in the follow-up subgroups 1–4 years, 5–9 years and 10–14 years, respectively, after diagnosis of HD varied from 0.52 to 1.72. In contrast, the RR was 6.47 in the follow-up group 15–19 years. In 885 women treated for HD in Stanford between 1961 and 1990, the RR for breast cancer was 2.0 with follow-up under 15 years and 13.6 with follow-up equal to or exceeding 15 years [3]. In addition, the risk was strongly dependent on age at diagnosis with an RR of 136 for women treated before 15 years of age. Similarly, in Dutch patients surviving HD the RR for breast cancer was shown to depend on the follow-up period (10–14 years: RR 2.2; 15–19 years: RR 9.0; > 20 years: RR 20.4) and the age at diagnosis of HD (< 20 years: RR 28; 21–29 years RR 4.9) [4]. In patients over 30 years of age at diagnosis, the risk seems not to be elevated. The dramatically increased risk especially for young patients was recently confirmed in two studies. An RR of 75 was reported in a cohort of 1380 patients who were irradiated for HD when less than 16 years of age at diagnosis [5]. An RR of 17 was found in 1641 patients irradiated under the age of 20 years [6].

Thus, while the cumulative incidence for solid tumours following HD, in general, increases continuously after the end of therapy, the cumulative incidence for breast cancer starts to increase dramatically after a follow-up period of at least 10–15 years. This observation may explain results of earlier studies reporting no elevated risk of breast cancer after treatment of HD. Since breast cancer now has been identified as one of the major life-threatening risks for young women surviving HD, a precise clinical and pathological characterisation of these cases is necessary. This might offer more effective therapy of these cancers, optimise predisease screening and decrease the risk of secondary breast cancers by modification of the initial HD therapy.

In this issue of the journal, Cutuli and associates (pp. 2315–2320) [7] present pathological and clinical features of 63 women suffering from breast cancer after treatment of HD from 1941 to 1988 in France. In accordance with the studies mentioned above, the risk could be attributed mainly to young women and adolescents receiving radiotherapy alone or in combination with chemotherapy. Also in agreement with recent studies is the unusual high frequency of bilateral (synchronous and metachronous) tumours (20.5%). Pathology, prognostic factors and the clinical course of these secondary breast cancers do not show striking differences compared with primary breast carcinoma.

Although Cutuli and associates state that the secondary breast cancers could be observed in field, in border of field or out of field of the irradiation (as a rule mantle field irradiation), most previous studies reported occurrence nearly exclusively in field or in border of field. An estimation of the risk for breast cancer dependent on the radiation dose received at the site of the secondary neoplasm is impossible due to variations in irradiation techniques (e.g. the exact size of the radiation field or of lung protection blocks) on the one

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hand and variations in the breast size on the other. Most of the patients in the studies mentioned above were irradiated using megavolt linear accelerators, while only some were still irradiated using orthovoltage techniques. Also, some of the patients in the U.S.A. received irradiation of the lung. Nevertheless, the data in at least two of the studies provide some evidence that the intended total dose to the mantle field might influence the risk of breast cancer. In the Stanford series the 95% confidence intervals of the RR values show that a significantly increased risk has been proven only for radiation doses of 40 Gy and more, but not for lower doses [3]. In the paper of Bhatia and associates [5], the relative risk after doses of > 40 Gy was 32-fold, and 5.9-fold after 20–40 Gy.

The overwhelming majority of published data leads to the conclusion that the high risk of secondary breast cancer and of second solid tumours in general, following treatment of Hodgkin's disease, is mainly caused by radiotherapy. The consequences regarding prevention of the serious late effects seem to be obvious. Radiation fields in the therapy of Hodgkin's disease are to be restricted as much as possible. Irradiation of involved fields only instead of extended fields should be used in early stages of the disease, in the framework of combined modality treatment, applying chemotherapy of low toxicity, with limited cumulative doses of critical drugs, such as alkylating agents, anthracyclines, bleomycin and others. In the context of combined modality treatment, radiation doses should be reduced. Most of the paediatric therapy studies have successfully addressed such objectives, thus reducing late effects of radiotherapy [8–10]. Since the excellent treatment results have not been compromised using this strategy, it has to be emphasised that in paediatric Hodgkin's disease—except for patients with bulky mediastinal disease—'radiation adds nothing except toxicity to effective chemotherapy regimens' [11].

In adult HD, reduction in the irradiation dose in the extended field from 40 to 20 Gy after polychemotherapy does not impair the good treatment results in intermediate stage disease [12]. Whether extended field irradiation can be abandoned and substituted by involved field irradiation in the treatment of early and intermediate stage HD is being tested in current clinical trials of the European study groups for treatment of adult Hodgkin's disease, e.g. the European Organization for Research and Treatment of Cancer (EORTC) in association with the Group d'Etude des Lymphomes d'Adulte (GELA) and the German Hodgkin Lymphoma Study Group (GHSG). Since there is already enough evidence that, in the context of combined modality treatment, the introduction of new potent polychemotherapy regimens might render this therapeutic strategy possible without the risk of diminishing the excellent treatment results, these study groups plan to eliminate extended field irradiation in future studies.

Reduction of irradiation doses and field sizes most probably will diminish the occurrence of secondary breast cancer following treatment of HD. For those girls and young women with HD who already underwent or still will undergo irradiation of the mediastinum, and/or the axillary region, a careful screening programme for early detection of breast cancer has to be established in order to give them a second chance for cure from cancer.

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