Acta Oncologica, 2006; 45: 13–15

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EDITORIAL

Clinical relevance of pulmonary toxicity in adjuvant breast cancer irradiation

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Editorial

Presently, it is well established that postoperative radiation therapy (RT) both reduces the risk of local recurrence [1–5] and extends overall survival in patients with breast cancer (BC) [6–8]. Concerns have, however, been raised about the risk of acute and chronic RT-induced side effects as the number of treated individuals is large and their expected survival is long compared to most patients with other malignant diseases. Pneumonitis, cardiac toxicity, arm lymph edema [9,10], neuropathy, skin damage, and rib fractures are examples of the wide range of complications that has been associated with adjuvant BC-RT. The present article by Järvenpää and colleagues in this issue of Acta Oncologica, focuses on one aspect of the first mentioned RT-related complication, viz. lung density changes measured by conventional chest X-rays and computed tomography (CT) and their relation to clinical symptoms [11].

This comparatively large, prospective study by Järvenpää and coworkers admirably describes the many different signs of radiological lung and/or pleural changes that can be seen following BC-RT, and their time course, and points out that radiological signs of damage is not always accompanied by respiratory symptoms. An important point is that no patient developed a post-RT pleural exsudate. Radiological signs of the latter kind should, thus, alert the clinician that another cause must be explored if a patient develops pleural effusion in the post-RT setting, e.g. infection or recurrent cancer. Furthermore, we learn that a high-resolution CT of the chest can add valuable, additional information in cases where structural alterations are not found on the plain X-ray exam and that CT probably leads to a better characterization of the changes qualitatively and quantitatively. The addition of a CT exam can, thus, be considered in patients with respiratory distress following BC-RT where the chest X-ray does not reveal the cause for the symptoms, e.g. radiation pneumonitis (structural changes in agreement with the beam arrangement), infection, or disseminated malignant disease, and if pulmonary embolism should be excluded. It is also interesting to note that our Finnish colleagues in a series of about 200 patients did not diagnose one case of sporadic radiation pneumonitis, i.e. bilateral lymphocytic alveolitis resulting in an "out-of-field" response to localized pulmonary RT [12]. The latter entity was frequently discussed earlier but it is also in our experience extremely uncommon.

I would like to comment on the conclusion drawn that density changes on chest X-ray may disappear over time. In our experience, this may be a false interpretation as a severe reaction can lead to shrinkage and retraction of the affected tissue to the hilar region of the lung. The originally treated lung tissue will be replaced by hyperinflated non-irradiated tissue which can give a false impression of restitution.

The author could not detect a relation between radiological lung changes and symptoms, target volumes, i.e. local RT vs. loco-regional RT, dosimetric data, i.e. mean lung dose volume histogram (DVH) comparisons, or chemotherapy exposure. The rate of clinical pneumonitis was, however, in the present treatment series, low compared to

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(Received 7 November 2005; accepted 10 November 2005)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860500466632

previous reports, which limits the ability to test possible relationships. Chemotherapy was also administered only during one of the 25 treatment days and the regimen, the CMF-schedule, contained neither taxanes nor anthracyclins. Furthermore, the present study does not take into account the effect of volume/regional distribution of the radiological lung changes.

Our centre at Karolinska has studied the topic of post-RT lung side effects in BC extensively during the last 10 years. In contrast to the present report, we found a relationship between target volume/dosimetric data and clinical symptoms [13], reduction in pulmonary function [14] and radiological changes evaluated with either chest X-ray [15] or conventional CT [16,17]. We found it useful to include regional information on the distribution of the radiological changes, i.e. a quantitative dimension, which is an integral part of the original Arriagada classification system for post-RT chest X-ray changes [18].

Other groups have reported relations between tamoxifen intake and post-irradiatory changes on chest X-rays [19]. Furthermore, increased rates of symptomatic pneumonitis have been detected in other treatment series when chemotherapy has been combined with BC-RT [20,21].

We have reported that clinically significant radiation pneumonitis (CTC-score ≥ 2) [22] develops in $<1\%$ of patients which undergo local RT with a mean central lung distance [23] <2 cm or a mean ipsilateral V20 of $<7\%$ [13]. However, if loco-regional RT is administered with template techniques and without 3-D planning aimed at reducing dose to lung, short-term pulmonary toxicity of grade 2 is detected in roughly 10% of patients and predominantly in cases where the ipsilateral V20 is $\geq 30\%$ [13]. We are confirming this hypothesis by testing if dose volume constraints of the latter magnitude (ipsilateral V20 $<30\%$) will minimize clinically significant cases of pneumonitis and preliminary results support this strategy [24]. Interestingly, the mean lung DVH in the present study by Järvenpää and coworkers points to V20-values below this cut off level, which may explain the relatively low rate of symptomatic pneumonitis found. V20 is, however, not by itself the ideal predictor of post-RT pneumonitis as other factors as age and reduced pre-RT functional level also influence the development of symptoms [25]. Potential confounding effects of other factors for the development of post-RT pulmonary toxicity are still relatively poorly studied and we should collect outcome data continuously from large treatment series concerning the potential untoward effect of combining RT with chemo-, antihormonal-, and/or targeted therapies.

Finally, efforts should also be made to minimize the cardiac dose in patients with left-sided BC undergoing local or loco-regional RT. Earlier treatment series have reported an increase in non-cancer deaths in irradiated patients in comparison to unirradiated controls [26]. The development of post-RT heart perfusion defects has also been demonstrated in more recent treatment series where modern RT-techniques have been used which minimize dose to the myocardium [27]. Insufficient data are available on the long-term consequences of these perfusion defects and whether the addition of chemotherapy and/or targeted therapy, e.g. trastuzumab and bevacizumab, will lead to the enhancement of post-RT cardiac toxicity.

In conclusion, pulmonary and cardiac toxicity after loco-regional RT in patients with BC is still a field which needs further exploration with respect to improvements in RT-technique, aimed at minimizing dose to normal tissues [28], and better understanding of possible interactions with other therapies.

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