training and workload is carefully considered to mitigate risks to patients.


OC-0395
Patient selection in head and neck adaptive radiotherapy
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Purpose or Objective: During the course of head and neck radiotherapy, anatomical changes may lead to underdosage or hotspots in target volumes, and overdosage in organs at risk (OARs). The largest dose differences between planned and actually given OAR dose have been reported for the parotid glands (PGs). Dose increase to the PGs could lead to an increase of radiation induced side effects, justifying adaptive radiotherapy (ART) to reduce the PG dose. Still, ART procedures are labour intensive and only a fraction of patients will benefit. The aim of this study was to develop and validate a method to predict dose deviations from the planned PG mean dose, to select patients for adaptive radiotherapy (ART) up-front.

Material and Methods: Planning and response (6 weeks after RT) CT-scans from 113 head and neck cancer patients (cohort A) were used to estimate deviations between planned and actually given PG mean dose (ΔDmean). Potential pre-treatment selection parameters presented in recent literature were included in the analysis. Uni- and multivariable linear regression analysis for the endpoint PG ΔDmean was performed to select pre-treatment parameters eligible for patient selection. ROC curve analysis was performed to determine cut off values for selecting patients with PG ΔDmean larger than 3 Gy with a sensitivity in the range of 70-100%. The proposed method of patient selection was validated in another patient cohort consisting of 43 head and neck cancer patients who received weekly rescan CTs (cohort B).

Results: In univariable analysis, pre-treatment parameters significantly associated with PG ΔDmean were: BMI, chemotherapy, T-stage, N-stage, volume of the GTV, tumour location, overlap of the PG with the high and low dose PTV, V20, V30, V40 and mean dose of the PG. In multivariable analysis, the initial PG mean dose remained the only significant parameter. ROC results were summarized in Table 1. Selection of patients for dose deviations larger than 3 Gy with a sensitivity of 90% could be obtained by a threshold of the initial PG mean dose of 22.2 Gy (Table 1). This would select 62% of patients for ART in cohort A and 76% in cohort B with a corresponding precision of 29 and 19%, saving 38 and 24% of patients from the labour-intensive ART procedure.

Conclusion: We succeeded to develop a method to select patients for ART up-front by using the initial mean dose to the parotid gland. The labour of ART could be reduced by 24-38% with 87-90% sensitivity, contributing to a more effective allocation of the department resources.

Table 1. Performance of the classification of patients for a parotid gland dose deviation > 3 Gy by using the initial mean dose of the parotid glands (PG Dmean)

<table>
<thead>
<tr>
<th>Cut off value PG Dmean (Gy)</th>
<th>0</th>
<th>3.6</th>
<th>22.2</th>
<th>24.7</th>
<th>27.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A Sensitivity (%)</td>
<td>100</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>0</td>
<td>33</td>
<td>45</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>% selected for ART</td>
<td>100</td>
<td>74</td>
<td>62</td>
<td>56</td>
<td>46</td>
</tr>
<tr>
<td>Precision (%)</td>
<td>20</td>
<td>27</td>
<td>29</td>
<td>29</td>
<td>30</td>
</tr>
</tbody>
</table>

Cohort B
Sensitivity (%) 100 100 87 60 40
Specificity (%) 0 0 19 38 46
% selected for ART 100 100 76 62 51
Precision (%) 18 18 19 17 14

Symposium with Proffered Papers: Time is not on our side: cardiovascular toxicity after radiotherapy

SP-0396
The risk of cardiovascular disease after breast cancer treatment: the clinician’s point of view
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Background: Breast cancer radiotherapy reduces the risk of cancer recurrence and death. However it usually involves some radiation exposure of the heart which may increase the risk of subsequent heart disease. Epidemiological data suggest that the major coronary event rate increases by 7.4% per Gy mean heart dose1. Estimates of the absolute risks of radiation-related heart disease are needed to help oncologists plan each individual woman’s treatment. The absolute risk for an individual woman depends on her estimated cardiac radiation dose and her background risk of ischaemic heart disease in the absence of radiotherapy. When the risk is known, it can then be compared with the absolute benefit of the radiotherapy.

Methods: Worldwide data on heart doses in breast cancer radiotherapy published during 2003-2013 were collated systematically. Analyses considered the variation in the typical mean heart dose according to various patient and treatment-related factors including laterality, target(s) irradiated and technique2. These heart doses were used to predict typical absolute cardiac risks from breast cancer radiotherapy using the dose-response relationship of a 7.4% per Gy increase in the rate of major coronary events. These risks were compared with estimates of the absolute benefits of breast cancer radiotherapy.

Results: In left breast cancer, mean heart dose averaged over 398 regimens in 149 studies from 28 countries was 5.4 Gy (range -0.1-26.6 Gy). In left-sided regimens that did not include the internal mammary chain, the average mean heart dose was 5.6 Gy (range -0.1-23.0) for inverse-planned intensity modulated radiation therapy, 3.4 Gy (range -0.1-12.4) for tangential irradiation, 2.2 Gy (range -0.1-3.8) for brachytherapy and 0.5 Gy (range 0.1-0.8) for proton beam therapy. On average, inclusion of the left IMC doubled the heart dose. In 93 regimens where the left IMC was irradiated, average mean heart dose was around 8 Gy for most photon or electron techniques, and it varied little according to which other targets were irradiated. In right-sided breast cancer, the average mean heart dose was 3.3 Gy based on 45
regimens in 23 studies. Applying these doses to estimated typical absolute cardiac risks showed the absolute risk of a radiation-induced major coronary event for many women today is less than 1%. So for them, the risk of radiotherapy is likely to be much smaller than the benefit. Nevertheless there is considerable variation in predicted absolute cardiac risks, depending on an individual woman’s background risk and on her heart radiation dose.

Conclusions: Exposure of the heart from breast cancer radiotherapy has reduced substantially over the past few decades but there is still considerable variation in published heart doses worldwide. In addition, there is variation in the risk of heart disease among patients being considered for radiotherapy. Thus there is likely to be substantial interpatient variability in the cardiac risks of radiotherapy. The population-based dose-response relationship can be used to provide reassurance for many women that their absolute risk of ischaemic heart disease from breast cancer radiotherapy is likely to be small compared with their likely absolute benefit. For other women, for example those with a high predicted heart radiation dose or for those with prior heart disease, the dose-response relationship can be used to identify the minority of women for whom the risk-benefit ratio is less favourable. In these women, consideration may be given to reducing cardiac radiation dose to reduce the radiation-related cardiac risk.

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Conflicts of Interest None

References

SP-0397 Predicting cardiac toxicity after breast irradiation: new quantitative data and new challenges
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The QUANTEC summary of data on dose-volume-response effect in heart after radiation therapy provided some answers and practical guidelines for the optimization of the dose distribution in breast cancer patients, and left a few problems open. The main dilemma centered on the fact that cardiac serious events are late, requiring long follow-up and rare, requiring large populations. Furthermore, in studies evaluating cardiac toxicities after irradiation the quality of the outcome clinical data was in general different from the quality of the dosimetical data. Similar considerations still apply to a few studies performed after QUANTEC.

A main step forward is represented by the increased size and design of the studies, e.g. as in the one by Darby et al (N Engl J Med 2013) which included about 2,000 women treated in Scandinavia. The paper provided among several results an estimation of the cumulative risk of death from ischemic heart disease for patients treated/not treated with radiation therapy and with different mean heart doses, obtained through reconstruction of the dose planning on a model patient.

Beyond size and type of study population another relevant factor investigated in several analysis is the relationship between fraction size and late cardiac effects. Mahrin (Int J Radiation Oncol Biol. Phys. 2007) performed an analysis on about 3,800 left sided respectively 3700 right sided breast cancer patients treated between 1984 and 2000, compared the different fractionation schedules and concluded that a statistical increase in overall and cardiac-specific mortality could not be found comparing left vs right breast cancer patients. Furthermore the hypofractionated adjuvant RT regimens did not significantly increase the risk of cardiac mortality. The 10 year follow-up of the START - UK Standardization of Breast Cancer Radiotherapy trials of radiotherapy hypofractionation (Havlind JS et al, Lancet Oncol 2013) confirmed the 5 years results that “appropriately dosed hypofractionated radiotherapy is safe and effective”. A norwegian study with a longer follow-up, but a smaller study population did irradiated in a different way concluded instead than the degree of hypofractionation and parasternal nodes contributed to an increased cardiac mortality in the patient cohort (Tjessem et al, Int J Radiation Oncology Biol. Phys. 2013).

Another perspective is given by the studies on cardiac dose-volume effects where dose distributions in subregions of the heart are investigated (e.g. Nilsson G et al, J Clin Oncol 2012; Johansen S, Breast cancer: basic and clinical research 2013). The results from these analysis might be very helpful in the design of treatment protocols.

Finally the technological development has to be taken into account (e.g. gating, DIBH etc), which in some cases might simply by-pass the issue of cardiac irradiation. This approach does not provide answers to the basic question, but provides a convenient solution.

SP-0398 Active surveillance for cardiovascular disease after Hodgkin lymphoma
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Hodgkin lymphoma is a relatively rare form of cancer, which mainly effects young adolescents and young adults. Over the past decades developments in treatment options for patients with Hodgkin lymphoma have led to improved outcome rates. As a result, there is an increasing number of Hodgkin lymphoma survivors. They are at risk of developing long-term toxicity due to treatment such as secondary malignancies or cardiovascular complications. There is an increased risk of developing valvular heart disease after mediastinal radiotherapy, although risk increases significantly after radiation treatment doses over 30 Gy (1). Recent studies also show a 4-6 fold increased standardized incidence ratio of heart failure and coronary heart disease (CHD), due to anthracycline containing chemotherapy regimens and radiotherapy (2). Severe CHD can even be present in the absence of typical symptoms such as chest pain (3). A linear dose-response relationship between mediastinal radiotherapy and CHD has been established with a 2.5-fold increased risk of CHD after receiving a mean heart dose of 20 Gy (4). This implies that even patients treated with current standard radiotherapy doses remain at serious risk of developing radiation induced CHD. At the same time, new strategies for non-invasive screening for CHD have developed, by means of CT coronary angiography, showing encouraging positive and negative predictive values for detecting significant CHD. In this lecture, an overview of recent efforts of screening for coronary artery disease in Hodgkin lymphoma patients is presented, and clinical implications are discussed.