OC-0596 Importance of dose to the atherosclerotic plaque in the LAD for cardiac toxicity in breast cancer
Van den Bogaard, V.; Spoor, D.; Van der Schaaf, A.; Van Dijk, L.; Langendijk, J.; Maduro, J.; Crijns, A.

Published in:
Radiotherapy and Oncology

DOI:
10.1016/s0167-8140(19)31016-3

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Purpose or Objective
To analyze the tolerance in the French randomized phase 3 trial (BONBIS) that investigated the role of the boost to the tumor bed after breast-conserving surgery for ductal carcinoma in situ (DCIS).

Material and Methods
From November 2008 to July 2014, 2004 DCIS patients were treated by tumorectomy followed by whole-breast irradiation (WBI) to a dose of 50 Gy in 25 fractions for 5 weeks. Patients were randomized after surgery and before WBI between an additional boost to the primary tumor bed (16 Gy in 8 fractions of 2 Gy, n=1002) and no further treatment (n=1002). Stratification factors were centre, age (below or above 40), hormonal therapy (yes or no), and histological grade (low or intermediate or high). Diagnosis mode (clinically or by mammography), surgical margins (1-2 mm vs 3 mm), acute toxicities were prospectively recorded from baseline to 3 months after radiotherapy completion.

Results
A total of 1928 DCIS patients were evaluable for acute tolerance. Median age was 57 years. Re-excision was needed in 20% of patients in each treatment arm, mainly due to involved margins or postoperative complications. Median time for radiotherapy initiation was 54 days from surgery [min=5; max=146]. Mean volumes of breast (CTV1) and of boost (CTV2) were 545 cc [min; max= 6; 2818] and 25 cc [min; max= 0; 754], respectively. A significant higher rate of radiotherapy disruption was observed in boost arm (3.9% vs 1.5%; p=0.015) due to acute toxicities occurrence with a mean time of disruption of 3 days. A significantly higher rate of grade ≥2 overall toxicities (including skin, edema, pain) was observed in the boost arm (54.6% vs 36.4%; p=0.001). Similarly, grade 3 erythema was significantly increased in the boost arm (5.4% vs 2.1%; p=0.001).

Conclusion
In the boost arm, a higher rate of grade ≥2 acute toxicities was observed compared to the control arm. However, grade 3 erythema was quite low even though its occurrence was significantly higher in the boost arm. A multivariate analysis of acute toxicities will be presented at the congress.

OC-0595 Does seroma predict patient-reported adverse effects following breast radiotherapy in IMPORT HIGH?
I.S. Bhattacharya¹, J.S. Haviland¹, C. Perotti², D. Eaton³, S. Gulliford⁴, E. Harris⁴, C.E. Coles⁵, C.C. Kirwan⁶, J.M. Bliss⁷, A. Kirby⁷
¹Institute of Cancer Research, Clinical Trials and Statistics Unit, London, United Kingdom; ²Royal Marsden NHS Foundation Trust, Radiotherapy and Imaging, London, United Kingdom; ³Mount Vernon Hospital, National Radiotherapy Trials QA Group, London, United Kingdom; ⁴Institute of Cancer Research, Radiotherapy and Imaging, London, United Kingdom; ⁵University of Manchester, Division of Cancer Sciences, Manchester, United Kingdom; ⁶Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Radiotherapy and Imaging, London, United Kingdom

Purpose or Objective
Seroma describes collection of serous fluid within a cavity and can occur following breast surgery. A seroma prevalence of 37.5% has been reported. Seroma is associated with adverse effects (AE) following breast radiotherapy. These AE have been predominantly assessed by clinicians and photographs, and not by patients. This study investigates if seroma is associated with patient-reported AE in IMPORT HIGH (CRUK/06/003).

Material and Methods
IMPORT HIGH (ISRCTN47437448) is a randomised, multicentre phase III trial testing dose-escalated simultaneous integrated boost against sequential boost each delivered by intensity modulated radiotherapy (RT) in women with breast cancer. AE assessment included patient-reported outcome measures (PROMs) in a planned sub-set of patients. A case-control methodology was used to investigate the association of seroma with patient-reported AE at 3 years. Cases were patients who reported moderate/marked breast appearance change and controls were those who reported none/mild changes. One control was selected at random for each case (unmatched). Seromas were identified on RT CT planning scans and graded as not visible/subtle or visible/highly visible. Logistic regression models were used to test associations between seroma and moderate/marked breast appearance change at 3 years, adjusting for patient and tumour/treatment factors. Tumour and treatment factors were reported by clinicians.

Results
2621 patients were recruited to IMPORT HIGH. 1078/1149 patients at centres participating in the PROMs sub-study consented to PROMs. 836 patients responded to whether they had breast appearance change at 3 years, of whom 231 (28%) patients reported moderate/marked changes (cases); 231 controls were identified. RT CT planning data were available for 202 cases and 205 controls. 156/231 (68%) cases and 148/231 (64%) controls received chemotherapy respectively. Seroma prevalence was 41/202 (20%) in cases and 32/205 (16%) in controls. A significant association was found between visible seroma and moderate/marked breast appearance change [odds ratio 1.38 (95% confidence interval 0.83-2.29), p=0.22] regardless of chemotherapy use. Larger seroma volume was significantly associated with worse breast appearance change on univariate analysis only [1.21 (1.02-1.44), p=0.03]. Treatment group was not significant on univariate analysis. On multivariable analysis, independent risk factors for worse breast appearance change were larger tumour size [1.43 (1.13-1.82), p=0.003], haematoma [5.96 (2.20-16.11), p=0.001], current smoking [2.25 (1.06-4.74), p=0.03] and body image concerns at baseline [1.04 (1.00-1.09), p=0.04].

Conclusion
Seroma prevalence in this study was lower than previously reported, perhaps reflecting the proportion of patients receiving chemotherapy in whom seroma resolves. Seroma was not associated with patient-reported breast appearance change but haematoma was a significant risk factor. Smoking cessation pre-radiotherapy should be encouraged to reduce AE.

OC-0596 Importance of dose to the atherosclerotic plaque in the LAD for cardiac toxicity in breast cancer
V. Van den Bogaard¹, D. Spoor¹, A. Van der Schaaf², L. Van Dijk¹, J. Langendijk¹, J. Maduro³, A. Crijns³
¹University Medical Center Groningen, Radiation Oncology, Groningen, The Netherlands

Purpose or Objective
The role of radiation dose in the development of cardiac toxicity in women with breast cancer has not been well established. The importance of dose to the atherosclerotic plaque in the LAD (left anterior descending coronary artery) for cardiac toxicity was investigated in the high-risk cohort of the HERA (Hypothesis Evaluation on Radiation-Induced Atherosclerosis) study. Cardiac toxicity was assessed by the Radiation Therapy Oncology Group (RTOG) Cardiac Subcommittee retrospectively.
Purpose or Objective
Recent studies have demonstrated a dose-effect relationship between radiation dose to the heart and the risk of an acute coronary event (ACE). However, knowledge on the exact underlying mechanisms behind this radiation-induced cardiac toxicity is lacking. Such information is crucial for the development of new strategies to optimize radiotherapy (RT) treatment planning.

We hypothesized that radiation dose to atherosclerotic plaques leads to subsequent inflammatory reactions and increased risk of ACEs. Thus, dose to the plaques may be a stronger predictor of an ACE after RT than the dose to the left anterior descending coronary artery (LAD). Therefore, the aim of this study was to investigate the association between radiation dose to the LAD and the LAD-plaques and the risk of an ACE in breast cancer (BC) patients treated with 3D conformal radiation therapy.

Material and Methods
The study cohort consisted of 952 BC patients treated with postoperative RT after breast conserving surgery. The LAD was delineated using an auto-segmentation tool. After calculation of the coronary artery calcium score, LAD-plaques with Hounsfield units manually delineated. The primary endpoint was the cumulative incidence of an ACE (defined according to Darby et al.) 9 years after treatment. For each individual patient, the mean heart dose (MHD), mean dose to the LAD and the mean dose to the LAD-plaques were collected from planning CT scans.

First, the relation between the dose to the LAD and the LAD-plaques and ACEs was analyzed with an univariable Cox-regression analysis. Then, an association analysis using a Cox-regression model was performed, only including patients who had a LAD-plaque. Furthermore, we used a multivariable Cox-regression analysis to calculate the excess risk of an ACE per patient including age, cardiac risk factors (0 or ≥1) and mean dose to the heart and LAD-plaques.

Results
The median follow-up time was 7.5 years (range: 0.1-10.1 years). In total, 31 patients developed an ACE during follow-up. 167 patients (17.5%) had a LAD-plaque. Univariable Cox-regression analysis showed that the impact of the dose to the LAD-plaque was much stronger than the impact of the MHD and the mean dose to the LAD (Figure 1). A significant but modest association between radiation dose to the LAD and ACEs was found (regression coefficient 0.053 (95% CI 1.014-1.096), P=0.008).

However, a much stronger and significant association was found between the mean dose to the LAD-plaques and ACEs (regression coefficient 0.323 (95% CI 1.129-1.689), P=0.002). In figure 2, the NTCP-curves are shown for a 50-year-old patient in the presence of a cardiac risk factor for ACE.

The results of this study suggest that mean dose to the atherosclerotic plaque in the LAD is more important for the development of an ACE in BC patients than the MHD, possibly due to radiation-induced inflammatory reactions in pre-existent plaques. This will be further investigated.

Conclusion