Is breast seroma after tumour resection associated with patient-reported breast appearance change following radiotherapy? Results from the IMPORT HIGH (CRUK/06/003) trial

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Abstract
Background: Seroma describes a collection of serous fluid within a cavity, occurring following surgery. Seroma is associated with normal tissue effects (NTE) following breast radiotherapy, as reported by clinicians and on photographs. This study investigates the association between seroma and the NTE breast appearance change collected using patient-reported outcome measures (PROMs) in IMPORT HIGH, as well as investigating the association between breast appearance change and patient/tumour/treatment factors.

Methods: Case–control methodology was used for seroma analysis within IMPORT HIGH. Cases were patients reporting moderate/marked breast appearance change and controls reported none/mild changes at year-3. One control was selected at random for each case. Seromas were graded as not visible/subtle or visible/highly visible on CT radiotherapy planning scans. Logistic regression tested associations, adjusting for patient/tumour/treatment factors.

Results: 1078/1149 patients consented to PROMs, of whom 836 (78%) reported whether they had 3-year breast appearance change; 231 cases and 231 controls were identified. 304/462 (66%) patients received chemotherapy. Seroma prevalence was 20% (41/202) in cases and 16% (32/205) in controls, and less frequent in patients receiving adjuvant chemotherapy [10% (24/246) compared with 29% (40/138) without]. Visible seroma was not significantly associated with breast appearance change [OR 1.38 (95%CI 0.83–2.29), p = 0.219]. Larger tumour size, haematoma, current smoking and body image concerns at baseline were independent risk factors.

Conclusions: Seroma was not associated with patient-reported breast appearance change, but haematoma and smoking were significant risk factors. Lack of association may be related to lower prevalence of seroma compared with previous reports, perhaps reflecting patients receiving adjuvant chemotherapy in whom seroma resolves prior to radiotherapy.

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Seroma formation describes the collection of serous fluid within a cavity and has been reported following breast surgery. Seroma prevalence of 37% and 57% was reported in the Cambridge IMRT [1] and FAST [2] trials respectively. Seroma has been associated with increased rates of post-operative infection and haematoma, and is an independent risk factor for normal tissue effects (NTE) following radiotherapy [1].

An association between seroma and NTE has been reported in the RAPID [3] and Cambridge IMRT trials [1]. The mechanisms by which seroma may lead to NTE following radiotherapy are unknown. As well as fibrosis and retraction of the seroma cavity being possible contributing factors [4], seroma leading to larger

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volumes receiving radiotherapy boost doses should also be con-
considered. In the EORTC ‘boost versus no boost’ trial there was an
increased risk of fibrosis in those patients receiving a boost [5] and
this risk was further increased in patients with a seroma. How-
ever, this was significant on univariate analysis only.

The majority of these trials used clinician assessments of NTE
and/or serial photographs. Patient-reported outcome measures
(PROMs) provide an opportunity to understand the patients’ own
perception of NTE and studies have found that patients report
more NTE compared with clinicians and those detected on pho-
tographs [6,7]. However, the association between the presence of
seroma and patient-reported NTE following breast radiotherapy
has not been investigated to date.

This analysis from IMPORT HIGH uniquely combines compre-
prehensive PROMs’ data with presence/absence of seroma whilst
accounting for other patient, tumour and treatment factors. The
primary aim of this study was to determine whether seroma is
associated with patient-reported breast appearance change follow-
ing breast radiotherapy. The secondary aim was to investigate
associations between other patient/tumour/treatment factors and
patient-reported breast appearance change.

Methods

Study population of IMPORT HIGH

The study population consisted of patients recruited to IMPORT
HIGH, a randomised, multi-centre phase III trial testing dose-
escàlèd simultaneous integrated boost (SIB) against sequential
boost each delivered by intensity-modulated radiotherapy for
early-stage breast cancer with higher than average risk of loca-
relapse. Women aged ≥ 18 after breast conservation surgery for
pT1-3 pN0-3a M0 invasive carcinoma were eligible for IMPORT
HIGH. Randomisation was 1:1:1 between 40 Gy/15 fractions (F) to
whole-breast (WB) + 16 Gy/8F sequential photon boost to tumour
bed (40 + 16 Gy) [control group], 36 Gy/15F to WB, 40 Gy to
partial-breast + 48 Gy (48 Gy) in 15F SIB to tumour bed [test group
1] or 36 Gy/15F to WB, 40 Gy to partial-breast + 53 Gy (53 Gy) in
15F SIB to tumour bed [test group 2] (Fig. 1) [8]. The trial was ini-
tiated with a primary endpoint of breast induration at 3-years.
However, this was subsequently amended to a primary endpoint
of local recurrence and patient accrual extended accordingly.

IMPORT HIGH was approved by East of England Cambridge
South Research Ethics Committee (08/H0305/13) and conducted
in accordance with the principles of Good Clinical Practice.

Study design – case–control methodology

For this exploratory analysis of seroma association, case–con-
trol methodology was used. As such, patients’ radiotherapy CT
planning scans for seroma were reviewed in a subset of patients,
rather than the whole cohort of patients in IMPORT HIGH (which
would have been highly resource intensive requiring review of
>2600 patients’ CT planning scans). The endpoint ‘change in breast
appearance’ reported by patients at year-3 was used to define cases
and controls. Patients scored breast appearance change using a 4-
point scale of ‘none’, ‘a little’, ‘quite a bit’ and ‘very much’. Cases
were defined as patients reporting ‘quite a bit’ or ‘very much’
(interpreted as moderate/marked breast appearance change) with
controls reporting ‘none’ or ‘a little’ (interpreted as none/mild
breast appearance change). The required number of controls (to
equal the number of cases) was selected at random from all avail-
able controls. Cases and controls were not matched on known pre-
dictors of NTE such as breast size and surgical deficit, as these data
were not available for all patients in our dataset, which would have
reduced the number of cases and controls for analysis. Also, we
wished to investigate associations between potential risk factors
for patient-reported change in breast appearance in addition to
seroma, and matching on these would have meant that we could
not test them in the analyses.

Assessment of seroma & breast density

Radiotherapy CT planning scans for cases and controls were
examined for the presence of seroma. Visualisation and Organisa-
tion of Data for Cancer Analysis (VODCA v5.4, Medical Software
Solutions GmbH, Hagendorn, Switzerland) software was used to
view radiotherapy planning CT scans. Seroma was identified on
axial CT images and graded as not visible/subtle or visible/highly
visible as per methodology used in the Cambridge IMRT study
[1]. Visible seroma was contoured on axial CT slices for each case
using a pre-defined protocol from the Cambridge IMRT study [1]
and total seroma volume recorded. Seroma contouring was under-
taken by one clinical research fellow (IB) who had received training
from the Chief Investigator of the Cambridge IMRT study and was
blinded to patients’ case–control status.

Breast density was assessed in the contralateral breast using a
ranking of 1–4 (1 = no or sparse distribution of fibroglandular tis-
uce, 2 = small dispersed clusters of fibroglandular tissue, 3 = large
cluster of fibroglandular tissue and 4 = mainly fibroglandular tis-
uce) [2].

Collection of dosimetric data

CT planning scan and dosimetry data were collected prospec-
tively by the Radiotherapy Trials Quality Assurance group (RTTQA)
for all IMPORT HIGH patients. Whole-breast planning target vol-
ume (PTV) dose–volume histograms (DVHs) were identified in
VODCA for all cases and controls. Doses were converted into equiv-
alent dose in 2 Gy (EQD2) per fraction using the Withers formula
(\(\alpha/\beta\) ratio 3) [9]. An \(\alpha/\beta\) ratio of 3 was used following published
data from the FAST and START trials, where \(\alpha/\beta\) ratios were esti-
mated at 2.3–2.6 and 3.5–4.7 respectively [10]. The whole-breast
PTV mean and maximum doses (in Gray) for each patient were cal-
tulated. The tumour bed clinical target volumes (CTV) (cm\(^3\)) were
recorded on planning assessment forms (completed at the treat-
ment centres) for all patients.

Collection of PROM data

Within IMPORT HIGH, NTE were assessed using PROMs, pho-
tographs and annual clinician assessments. All centres were
invited to participate in PROMs and photographic sub-studies
(until sufficient accrual was achieved). All patients at these centres
were invited to participate in the PROMs and photographic sub-
studies until the required sample size for each sub-study was
obtained.

PROMs were obtained at baseline, 6 months, 1 and 3 years
following radiotherapy. Baseline was pre-randomisation
(post-surgery, post-chemotherapy where relevant and pre-
radiotherapy). PROMs collected included: Hospital Anxiety and
Depression Scale (HADS) (scores of 8–10 indicating borderline anx-
xiety or depression, and scores of 11–21 indicating case levels of
anxiety or depression [11]); 10-item Body Image Scale where
higher scores indicate worse body image [12] and protocol-
specific questionnaire items including asking patients to score
‘change in breast appearance’ [13].

Patients consenting to the PROMs sub-study were invited to
participate in the photographic sub-study which involved assess-
ments at baseline and year-3. Breast size and surgical deficit were
scored on a 3-point scale (small, medium, large) from baseline pho-
tographs by a panel of observers blinded to patient identity and
treatment allocation [14]. Not all patients in the PROMs sub-study consented to photographs.

Information regarding smoking, co-morbidities (including diabetes mellitus, hypertension, cardiovascular disease, collagen vascular disease), antibiotics for tumour bed infection and haematoma were recorded at baseline. Details regarding timing of haematoma or whether the patient had any further surgical intervention for the haematoma were not recorded. Information regarding co-morbidities was collected (following a substantial amendment) 4-years after the trial opened to recruitment.

Statistical analysis

Logistic regression was used to test associations between visible seroma and patient, tumour and treatment-related factors with moderate/marked patient-reported breast appearance change at year-3, and results summarised using odds ratios (OR, with 95% confidence intervals, CI). Each factor was initially tested in univariate analysis, and those statistically significant \((p < 0.05)\) were included in a multivariable analysis.

Patient-related factors tested included age, breast size and density, smoking status, comorbidity, levels of anxiety and depression measured on HADS subscales, and Body Image Scale (BIS) score. Tumour and treatment factors tested were tumour size, grade and location, use of chemotherapy, radiotherapy treatment group, tumour bed clinical target volumes (CTV), mean and maximum dose to the whole-breast PTV, axillary lymph node status, axillary surgery, post-operative infection, haematoma, surgical deficit assessed on baseline photograph, presence of visible seroma and seroma volume. As individual dose levels were highly correlated with each other, a single dose level could not be selected. Therefore, summary metrics of mean and maximum dose were used. For analysis of seroma volume, volume was set to zero for patients without a seroma. The factors described above were clinician-reported with the exception of the PROMs (HADS subscales and BIS score).

All analyses were carried out using STATA version 14 based on a database snapshot taken on June 11 2018. The IMPORT HIGH trial is registered in the ISRCTN registry (ISRCTN47437448) and ClinicalTrials.gov (NCT00818051).

Role of the funder

Cancer Research UK (CRUK/06/003) provided peer-reviewed approval for the IMPORT HIGH trial but had no role in this study design, data collection, data analysis, data interpretation, or writing of the report.

Results

IMPORT HIGH trial

IMPORT HIGH recruited 2621 patients from 77 centres. A total of 1078 of the 1149 patients from the 51 centres participating in the sub-study consented to PROMs. Year-3 questionnaires were returned by 842/1078 (78%) patients. Of these 842 patients, 836 patients provided a response for breast appearance change at year-3 and 231/836 (28%) reported moderate or marked changes (defined as cases).

Seroma case–control analysis

In this study, 462 patients (231 cases and 231 controls) were identified (Table 1). Adjuvant chemotherapy was received by 147/231 (64%) cases and 132/231 (57%) controls, and neo-adjuvant chemotherapy by 9/231 (4%) cases and 16/231 (7%) controls. In patients who received adjuvant chemotherapy, the radiotherapy planning scan would have been done approximately 16–20 weeks post-surgery (based on standard UK practice). In patients receiving neo-adjuvant chemotherapy or no chemotherapy, the radiotherapy planning scan would be approximately 4 weeks post-surgery. Radiotherapy planning CT data were available for 407 patients (missing for 29 cases and 26 controls). Reasons for missing data included the inability to retrieve dose files from centres, corrupted dose files, or deviations from trial protocol.
Table 1
Summary of univariate analyses: associations between baseline characteristics and moderate/marked change in breast appearance at 3 years in the case–control population in IMPORT HIGH.

| Characteristics                        | Cases [Patients reporting moderate/marked change in breast appearance at 3 years] N = 231 (%) | Controls [Patients reporting none/mild change in breast appearance at 3 years] N = 231 (%) | Univariate analyses OR (95% CI) | P value |
|----------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|---------------------------------|---------|
| **Age years**                          | N = 231 49 (45–52)                                                                            | N = 231 49 (45–57)                                                                           | 0.98 (0.96–0.996)               | 0.019   |
| **Treatment group**                    |                                                                                               |                                                                                            |                                 |         |
| Control                                | 84/231 (36)                                                                                   | 77/231 (33)                                                                                 |                                 |         |
| Test group 1                           | 62/231 (27)                                                                                   | 74/231 (32)                                                                                 | 0.77 (0.49–1.21)               | 0.258   |
| Test group 2                           | 85/231 (37)                                                                                   | 80/231 (35)                                                                                 | 0.97 (0.63–1.50)               | 0.905   |
| **Tumour size (cm)**                   | N = 231                                                                                       | N = 231                                                                                     | 1.27 (1.07–1.50)               | 0.005   |
| Grade 1                                | 24/231 (10)                                                                                   | 17/231 (7)                                                                                  |                                 |         |
| Grade 2                                | 99/231 (43)                                                                                   | 93/231 (40)                                                                                 | 0.75 (0.38–1.49)               | 0.418   |
| Grade 3                                | 108/231 (47)                                                                                  | 121/231 (52)                                                                                | 0.63 (0.32–1.24)               | 0.182   |
| **Lymph nodes**                        |                                                                                               |                                                                                            |                                 |         |
| Positive                               | 77/231 (33)                                                                                   | 70/231 (30)                                                                                 |                                 |         |
| Negative                               | 154/231 (67)                                                                                  | 161/231 (70)                                                                                | 0.87 (0.59–1.29)               | 0.485   |
| **Tumour location**                    |                                                                                               |                                                                                            |                                 |         |
| Central                                | 38/230 (17)                                                                                   | 29/230 (13)                                                                                 |                                 |         |
| Upper outer quadrant                   | 106/230 (46)                                                                                  | 114/230 (50)                                                                                | 0.71 (0.41–1.23)               | 0.222   |
| Upper inner quadrant                   | 47/230 (20)                                                                                   | 48/230 (21)                                                                                 | 0.75 (0.40–1.40)               | 0.364   |
| Lower outer quadrant                   | 25/230 (11)                                                                                   | 24/230 (10)                                                                                 | 0.79 (0.38–1.67)               | 0.543   |
| Lower inner quadrant                   | 14/230 (6)                                                                                    | 15/230 (7)                                                                                  | 0.71 (0.30–1.71)               | 0.447   |
| CTV boost volume in cc                 | N = 161                                                                                       | N = 166                                                                                     | 1.02 (1.00–1.03)               | 0.008   |
| **Axillary surgery**                   |                                                                                               |                                                                                            |                                 |         |
| No                                     | 3/231 (1)                                                                                     | 3/231 (1)                                                                                   | 1.00 (0.20–5.0)                | >0.99   |
| Yes                                    | 228/231 (99)                                                                                  | 228/231 (99)                                                                                |                                 |         |
| **Post-op infection**                  |                                                                                               |                                                                                            |                                 |         |
| No                                     | 189/231 (82)                                                                                  | 207/231 (90)                                                                                |                                 |         |
| Yes                                    | 42/231 (18)                                                                                   | 22/231 (10)                                                                                 | 2.10 (1.20–3.63)               | 0.009   |
| **Post-op haematoma**                  |                                                                                               |                                                                                            |                                 |         |
| No                                     | 202/231 (87)                                                                                  | 219/229 (96)                                                                                |                                 |         |
| Yes                                    | 29/231 (13)                                                                                   | 10/229 (4)                                                                                  | 3.14 (1.49–6.61)               | 0.003   |
| **Smoking status**                     |                                                                                               |                                                                                            |                                 |         |
| Never smoker                           | 123/231 (53)                                                                                  | 141/229 (62)                                                                                |                                 |         |
| Current smoker                         | 41/231 (18)                                                                                   | 21/229 (9)                                                                                 | 2.24 (1.25–3.99)               | 0.006   |
| Previous smoker                        | 67/231 (29)                                                                                   | 67/229 (29)                                                                                 | 1.15 (0.76–1.74)               | 0.520   |
| **Cardiovascular disease**             |                                                                                               |                                                                                            |                                 |         |
| No                                     | 218/229 (95)                                                                                  | 210/226 (93)                                                                                |                                 |         |
| Yes                                    | 11/229 (5)                                                                                    | 16/226 (7)                                                                                  | 0.66 (0.30–1.46)               | 0.307   |
| **Adjuvant chemotherapy**              |                                                                                               |                                                                                            |                                 |         |
| No                                     | 75/231 (32)                                                                                   | 83/231 (36)                                                                                 |                                 |         |
| Yes                                    | 156/231 (68)                                                                                  | 148/231 (64)                                                                                | 1.17 (0.79–1.71)               | 0.433   |
| **Baseline HADs anxiety**              |                                                                                               |                                                                                            |                                 |         |
| Normal (0–7)                           | 133/214 (62)                                                                                  | 154/218 (71)                                                                                |                                 |         |
| Borderline (8–10)                      | 38/214 (18)                                                                                   | 46/218 (21)                                                                                 | 0.96 (0.59–1.56)               | 0.858   |
| Case (11+)                             | 43/214 (20)                                                                                   | 18/218 (8)                                                                                  | 2.77 (1.52–5.03)               | 0.001   |
| **Baseline HADs depression**           |                                                                                               |                                                                                            |                                 |         |
| Normal (0–7)                           | 167/215 (78)                                                                                  | 184/217 (85)                                                                                |                                 |         |
| Borderline (8–10)                      | 30/215 (14)                                                                                   | 26/217 (12)                                                                                 | 1.27 (0.72–2.24)               | 0.405   |
| Case (11+)                             | 18/215 (8)                                                                                    | 7/217 (3)                                                                                   | 2.83 (1.15–6.95)               | 0.023   |
| **Body Image Scale**                   |                                                                                               |                                                                                            |                                 |         |
| Median (IQR)                           | 9 (4–15)                                                                                      | 5 (1–11)                                                                                   |                                 |         |
| **Breast Size**                        |                                                                                               |                                                                                            |                                 |         |
| Small                                  | 57/140 (41)                                                                                   | 69/152 (45)                                                                                 |                                 |         |
| Medium                                 | 52/140 (37)                                                                                   | 66/152 (43)                                                                                 | 0.95 (0.58–1.58)               | 0.854   |
| Large                                  | 31/140 (22)                                                                                   | 17/152 (11)                                                                                 | 2.21 (1.11–4.39)               | 0.024   |

(continued on next page)
(where patients received local standard treatment, CT planning scans and dosimetric data were not collected for these patients). There were no differences in reasons for missing data between cases and controls. Seroma prevalence was 41/202 (20%) in the cases and 32/205 (16%) in the controls. In patients receiving adjuvant chemotherapy for whom seroma data were available, 10% (24/246 patients) had seroma compared with 29% (40/138) in patients receiving adjuvant chemotherapy (potentially resulting in seroma resolving prior to surgery). The lack of association between seroma and patient-reported breast appearance change on photographs at 5-years [OR = 1.8, (95%CI 1.0–3.4), p = 0.05] [1]. Juneea et al also showed an association between seroma and breast appearance change on photographs at 2-years [OR 3.44, (95%CI 1.28–9.21), p = 0.01] in the FAST-Pilot (patients received 30 Gy in 5F over 15 days) and UK FAST trials (randomising to 50 Gy in 25F versus 28.5 or 30 Gy in 5 once weekly fractions) [2].

The association between seroma and patient-reported breast appearance change may be related to the low overall prevalence of seroma within the case–control study in IMPORT HIGH: 20% in the cases and 16% in the controls. Clinically, this is lower than the 37% seroma prevalence reported in the Cambridge IMRT bridge IMRT study comparing 2-dimensional radiotherapy against forward-planned IMRT using 40 Gy in 15 fractions in both treatment groups, found a significant association between seroma and inferior cosmesis on photographs at 5-years [OR = 1.8, (95%CI 1.0–3.4), p = 0.05] [1].

Discussion

These results show, within IMPORT HIGH, there was no significant association between seroma and patient-reported breast appearance change at 3-years. However, haematoma, larger tumour size, current smoking and body image concerns at baseline were significant risk factors. In contrast to our findings, the Cambridge IMRT study comparing 2-dimensional radiotherapy against forward-planned IMRT using 40 Gy in 15 fractions in both treatment groups, found a significant association between seroma and inferior cosmesis on photographs at 5-years [OR = 1.8, (95%CI 1.0–3.4), p = 0.05] [1]. Juneea et al also showed an association between seroma and breast appearance change on photographs at 2-years [OR 3.44, (95%CI 1.28–9.21), p = 0.01] in the FAST-Pilot (patients received 30 Gy in 5F over 15 days) and UK FAST trials (randomising to 50 Gy in 25F versus 28.5 or 30 Gy in 5 once weekly fractions) [2].

The lack of association between seroma and patient-reported breast appearance change may be related to the low overall prevalence of seroma within the case–control study in IMPORT HIGH: 20% in the cases and 16% in the controls. Clinically, this is lower than the 37% seroma prevalence reported in the Cambridge IMRT study [1]. It is also lower than the 57% seroma prevalence reported in a case–control study using patients from the FAST-Pilot and UK FAST trials [2].

Reasons for the lower prevalence of seroma in IMPORT HIGH may be due to a larger proportion of patients receiving chemotherapy (potentially resulting in seroma resolving prior to

Table 1 (continued)

| Characteristics                  | Cases [Patients reporting moderate/marked change in breast appearance at 3 years] | Controls [Patients reporting none/mild change in breast appearance at 3 years] | Univariate analyses OR (95% CI) | P value |
|----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------|--------|
| Surgical deficit                 |                                                                               |                                                                                |                                |        |
| Small                            | 86/140 (61)                                                                   | 119/152 (78)                                                                  | 1                               |        |
| Medium                           | 39/140 (28)                                                                   | 28/152 (18)                                                                   | 1.93 (1.10–3.37)                | 0.021  |
| Large                            | 15/140 (11)                                                                   | 5/152 (3)                                                                     | 4.15 (1.45–11.86)               | 0.008  |
| Seroma volume (cc)               |                                                                               |                                                                                |                                |        |
| N = 198                          | 161/202 (80)                                                                  | 173/205 (84)                                                                  | 1                               |        |
| No                               | 41/202 (20)                                                                   | 32/205 (16)                                                                   | 1.38 (0.83–2.29)                | 0.219  |
| Yes                              | N = 203                                                                       |                                                                                 | #1.21 (1.02–1.44)               | 0.032  |
| Median (IQR)**                   | 20.3 (6.8–46.1)                                                               | 13.6 (7.4–19.0)                                                               |                                |        |
| Breast density                   |                                                                               |                                                                                |                                |        |
| Rank 1                           | 88/201 (44)                                                                   | 70/204 (34)                                                                   | 1                               |        |
| Rank 2                           | 51/201 (25)                                                                   | 57/204 (28)                                                                   | 0.71 (0.44–1.16)                | 0.175  |
| Rank 3                           | 50/201 (25)                                                                   | 51/204 (25)                                                                   | 0.78 (0.47–1.29)                | 0.330  |
| Rank 4                           | 12/201 (6)                                                                    | 26/204 (13)                                                                   | 0.37 (0.18–0.78)                | 0.009  |
| Mean dose in Gray                | 45.1 (43.2–49.2)                                                              | 44.0 (42.4–48.6)                                                              | 1.08 (1.02–1.14)                | 0.009  |
| Maximum dose in Gray             | N = 192                                                                       | N = 197                                                                       | 1.01 (0.97–1.05)                | 0.532  |
| N = 66–74                        | 66 (65–74)                                                                    | 66 (65–74)                                                                    |                                |        |

IQR = interquartile range. *Higher scores for body image scale indicate more problems (possible range 0–30). **Breast size and surgical deficit scored on baseline photographs (data not available for all patients as all patients in PROMs sub-study did not participate in the photographic sub-study). ***For seroma volume, patients without seroma included in analysis with zero volume. #Seroma volume assessed per 10 cc.
radiotherapy) and changes in surgical practice over time. The Cambridge IMRT and FAST trials recruited between 2003 and 2007, whereas IMPORT HIGH recruited from 2009 to 2015. In the Cambridge IMRT seroma study, 122/648 (19%) patients received chemotherapy [1] compared with 304/462 (66%) patients in our case–control study in IMPORT HIGH. In the patients receiving adjuvant chemotherapy in IMPORT HIGH (with a time lag of approximately 16–20 weeks from surgery to radiotherapy planning scan), 10% (24/246 patients) had seroma compared with 29% (40/138) in patients not receiving chemotherapy. One study demonstrated that seroma volume decreases with a longer time interval from surgery to radiotherapy [15].

Chemotherapy was also considered a potential confounder in IMPORT HIGH. However, in our study, adjusting for adjuvant chemotherapy use made little difference to the estimate of association between seroma and breast appearance change. Nevertheless, seromas persisting after chemotherapy may be more stable during radiotherapy such that dosimetric heterogeneities within the tumour bed region incurred by fluctuating seroma volume will be minimised. In addition, seromas persisting following chemotherapy may maintain volume within the tumour bed such that any distortion associated with their resolution may be less likely.

Surgical practices have changed since the FAST and Cambridge IMRT trials were conducted, from leaving the excision cavity open (which may be associated with seroma formation) towards primary closure of the defect by either direct suturing of cavity walls together, local glandular mobilisation or therapeutic mammaplasty. In patients who develop a seroma in an open cavity, fibrosis and retraction of tissue surrounding the excision cavity (following seroma reabsorption) could result in a noticeable defect [4]. In contrast, there is also evidence to suggest that the seroma cavity may not always contract and new tissue may be laid down in concentric rings [16]. With increasing use of oncoplastic surgery to redistribute breast tissue into locations of volume loss particularly in those requiring extensive resections, rates of seroma are likely to have reduced. One study reported significantly lower rates of seroma in patients undergoing oncoplastic surgery compared with standard breast conserving surgery: 1.7% versus 4.4%, p = 0.04 [17], albeit that seromas were diagnosed clinically in this study and thus rates were lower than described in the radiotherapy literature.

It is possible that our study was underpowered to detect a moderate effect of seroma; with around 200 cases and controls the study had 78% power to detect an odds ratio of 2, based on 16% seroma prevalence in our control population (alpha = 0.05). Although there was no significant association between seroma and breast appearance change, greater seroma volume was associated with breast appearance change on univariate analysis. For the analysis, seroma volume was set to zero for patients without seroma. Limited patient numbers with seroma may have contributed to the lack of significance on multivariable analysis, or it may be that the association between seroma and NTE is weaker than previously reported. The RAPID trial testing partial-breast radiotherapy using 3D conformal radiotherapy versus whole-breast radiotherapy reported an association between seroma volume and adverse cosmesis at 3-years [3].

The choice of endpoint used in our case–control study may also explain our results being different to those of other published studies. PROMs provide the patient-perspective of side-effects and it has been shown that patients report a higher prevalence of NTE compared with clinicians or photographs [6,7]. Therefore, PROMs may be a more sensitive endpoint. Furthermore, patients experiencing a large palpable seroma at baseline may be more perceptive of future NTE compared with clinicians or photographic scoring (where prior seroma may not be noted). Greater volume of seroma was associated with 3-year breast appearance change in IMPORT HIGH.

With respect to other tumour and treatment factors, haematoma was significantly associated with breast appearance change within IMPORT HIGH. Similarly, haematoma predicted moderate/severe fibrosis in the EORTC 2281-10882 ‘boost versus no boost’ trial [HR 1.80 (95%CI 1.32–2.47), p < 0.0001] [5]. Post-operative haematoma leading to worse cosmetic outcome may be related to glandular necrosis. Larger tumour size was also significantly associated with breast appearance change. Tumour size may be a proxy measure for surgical deficit. Larger surgical deficit at baseline predicted patient-reported breast appearance change in IMPORT LOW [18]. Also, larger excision volumes were associated with poorer cosmetic outcome in the EORTC ‘boost versus no boost’ trial [19]. With regard to patient factors, current smoking was strongly associated with patient-reported breast appearance change in IMPORT HIGH. Similarly in the RAPID trial, smoking was associated with adverse cosmesis [OR 2.42 (95%CI 1.56–3.75), p < 0.001] and a deterioration in cosmesis over 3-years [OR 1.58 (95%CI 1.01–2.46), p = 0.04] [3]. Smoking has been associated with impaired wound healing, post-operative complications and increased radiation toxicity [20,21].

Finally, body image concerns at baseline were also significantly associated with breast appearance change. Items in the BIS relate to patient perception of attractiveness and sexuality as a result of their disease or treatment. This association has not been previously investigated or reported in the literature.

**Implications of findings**

We were unable to show an association between seroma and patient-reported breast appearance change, however larger

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**Table 2**

Summary of multivariable analyses: associations between baseline characteristics and moderate/marked change in breast appearance at 3 years.

| Characteristics | Multivariable analyses Adjusted OR (95% CI) | P value |
|----------------|-------------------------------------------|---------|
| Age            | 0.98 (0.96–1.01)                           | 0.243   |
| Tumour size    | 1.43 (1.13–1.82)                           | 0.003   |
| Post-op infection | No = 1, Yes = 1.45 (0.68–3.07) | 0.335   |
| Post-op haematoma | No = 1, Yes = 5.96 (2.20–16.11) | <0.001  |
| Smoking status | Nevar smoker = 1, Current smoker = 2.25 (1.06–4.74), Previous smoker = 1.15 (0.67–1.97) | 0.034, 0.613 |
| Baseline HADS anxiety | Normal (0–7) = 1, Borderline (8–10) = 0.70 (0.37–1.32), Case (11+) = 2.17 (0.97–4.87) | 0.273, 0.060 |
| Baseline HADS depression | Normal (0–7) = 1, Borderline (8–10) = 0.90 (0.42–1.93), Case (11+) = 1.93 (0.35–6.99), Body Image Scale = 1.04 (1.00–1.09), Whole Breast PTV volume = 1.00 (0.99–1.00), Seroma volume = 1.01 (0.99–1.04) | 0.778, 0.317, 0.044, 0.226, 0.209 |
| Breast density | Rank 1 = 1, Rank 2 = 0.63 (0.34–1.16), Rank 3 = 0.86 (0.44–1.68), Rank 4 = 0.41 (0.16–1.08), Mean dose to whole breast in Gray = 1.05 (0.98–1.13) | 0.134, 0.062, 0.070, 0.190 |

Odds ratios adjusted for all variables shown in the table. Rank 1 = no or sparse distribution of fibroglandular tissue, 2 = small dispersed clusters of fibroglandular tissue, 3 = large cluster of fibroglandular tissue and 4 = mainly fibroglandular tissue.
tumour size, haematoma, current smoking and body image concerns at baseline were independent risk factors. This suggests that measures should be taken to reduce the risk of haematoma formation. For example, by achieving adequate haemostasis with return of patient blood pressure to normal prior to wound closure and avoidance of post-operative hypertension (eg due to pain). Also, smoking cessation should be encouraged, although we cannot determine the time interval required from smoking cessation to start of radiotherapy to reduce the risk of patient-reported breast appearance change.

In conclusion, seroma was not associated with patient-reported breast appearance change, but haematoma and smoking were significant risk factors. Lack of association may be related to lower prevalence of seroma compared with previous reports, perhaps reflecting patients receiving adjuvant chemotherapy in whom seroma resolves.

Conflicts of interest

IB, JH, CP, DE, SG, EH, CC, CK, AK have no conflicts of interest of interest to declare. JMB discloses Research Funding: AstraZeneca, Merck Sharp & Dohme, Medivation, Puma Biotechnology, Clovis Oncology, Pfizer, Janssen-Cilag, Novartis, Roche.

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