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Title page

(i) Title

Radiation-associated breast cancers in a late-effects cohort: long term surveillance is essential

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Abstract

Aims

Survivors of childhood, adolescent and young adulthood (CAYA) malignancies have an increased risk of subsequent primary malignancies, particularly after exposure to therapeutic radiation. This study aims to evaluate mode of surveillance and surveillance compliance, incidence and mode of detection of breast cancer, breast cancer phenotype and outcomes after radiation-associated breast cancer (RBC) in a late-effects cohort.

Methods

Women exposed to therapeutic radiation attending the Late Effects service from 1st January 2000 to 20th February 2013. All invasive and in-situ cancers, benign tumours and deaths were evaluated. The incidence of breast cancer was compared to the Australian general population. Compliance with breast surveillance recommendations, clinico-pathological features and management of breast cancers were examined.

Results

The prevalence of RBC was 17.1%. Twenty-eight cases of RBC occurred in 24 women, out of 140 women exposed to chest radiation. Patients whose first attendance was  $\geq 15$  years after radiation exposure experienced the highest incidence of RBC at 23%. The incidence of breast cancer was 11.2 times the general population ( $p < 0.001$ ). Compliance with surveillance mammography was observed in 18.4%. Breast cancers diagnosed after the first attendance to the service were more likely screen-detected ( $p = 0.002$ ). Most were hormone receptor positive (84.0%), invasive ductal carcinomas (82.1%) managed with mastectomy (89.3%).

Conclusions

Patients attending a dedicated late effects service have a high burden of subsequent malignancies generally occurring after long latency. Judicious management with adherence to long-term surveillance guidelines is advocated.

## Introduction

Therapeutic chest irradiation is an established risk factor for breast cancer. It has been extensively reported in survivors of childhood, adolescent and young adulthood (CAYA) malignancies, especially Hodgkin lymphoma (HL), where historically, treatment for early stage HL typically involved treating a mantle field with radiation doses  $\geq 40$  Gray (Gy). Transition to combined-modality therapy with chemotherapy and advances in radiation therapy has allowed substantial reductions in radiation field and dose. At present, involved field radiotherapy based on diseased nodal regions<sup>1</sup> is being replaced by targeted therapy to detectable involved node or involved site at lower doses (20-30Gy)<sup>2</sup>. However, the long latency of radiation-associated cancers means there are many current survivors successfully treated with radiation at risk of a radiation-associated breast cancer (RBC).

The Late Effects (LE) service at our institution was established in 2000 and is the first adult service of its kind in Australia. The service is available to cancer survivors aged over 18 and at least 5 years post completion of therapy for their index cancer. It provides ongoing multidisciplinary care for survivors of cancer, in particular CAYA malignancies in order to improve or maintain their biopsychosocial wellbeing from the effects of cancer or its treatment. A previous study reported that referrals to the service come from children's hospitals (49.4%), adult hospitals (38.3%), general practitioners (6.3%), self-referrals (4.1%) and other sources (1.9%)<sup>3</sup>.

The LE service has an online screening and surveillance guideline for general practitioners<sup>4</sup>, adapted from the Children's Oncology Group (COG) guidelines (Version 3.0 – October 2008)<sup>5</sup>. At the time of this study, patients exposed to chest radiation  $\geq 20$ Gy were recommended to have yearly breast examination and annual mammography and/or breast ultrasound beginning from age 25 or 8 years after radiotherapy, whichever occurs last. The COG and International Childhood Harmonization Guidelines (IGHG)<sup>6</sup> recommend annual

mammography and breast MRI<sup>7</sup>.

Given the unique cohort, we aimed to assess the incidence of RBC in the LE cohort and compliance with screening, mode of presentation and subsequent clinical outcomes after RBC.

## Material and Methods

All women exposed to therapeutic chest radiation attending the LE service from the 1<sup>st</sup> January 2000 up to 20<sup>th</sup> February 2013 were extracted from the LE database. Patients were excluded from the study if they reported a cancer predisposing genetic mutation, or were less than five years from completion of curative treatment for the primary cancer to death or last follow-up by the LE service.

Clinical information was retrieved from the electronic records. Demographics and treatment-specific information were collected including primary malignancy type and year of diagnosis, date of first and last attendance at the LE service, radiotherapy field (classified according to body region), dose and treatment dates, date and cause of death.

All invasive and in-situ breast cancers and benign tumour events were recorded; events were collected from both internal and external patient correspondence and confirmed with pathology and medical imaging reports where available. DCIS of the breast that occurred after radiation to the chest was classified as a RBC.

### *Incidence analysis*

Time-to-event analyses were performed and patients were stratified by the time interval from the completion of radiation treatment and the time of first attendance to the LE service (0-5, 5-

10, 10-15, 15+ years). Kaplan-Meier product limit curves for time from first LE attendance until date of diagnosis of RBC was produced for each stratum and presented on the same set of axes.

A comparison was performed between the incidence of RBC diagnosed whilst under the guidance of the LE service and the number that would be expected in a sample from the Australian general population of the same size, gender and age distribution. The number of patient-years and RBC observed in the sample for each 5-year age bracket was compared to the age-specific incidence per 100,000 patients in the Australian general population, as reported by the Australian Institute of Health and Welfare (AIHW)<sup>8</sup> based on incidence data from the 2013 version of the Australian Cancer Database (ACD).

#### *Surveillance compliance analysis*

Compliance with breast surveillance was assessed by dividing the number of screen events by the duration at risk in years. Compliance with breast surveillance was defined as a ratio of  $\geq 0.8$  (ie. 1 screen event per 1.25 year).

#### *Additional radiation-associated breast cancer analyses*

Median age at diagnosis of breast malignancy and latency from the completion of chest radiation were captured. The mode of presentation of breast malignancies, compliance to screening, performance of mammography and MRI, surgery and reconstructions performed, stage and subtype were captured and underlying familial risk were noted. Local and systemic recurrence were recorded and all deaths in the cohort of women exposed to chest irradiation were also considered.

#### Results

There were 144 women with a history of chest irradiation that attended the LE service. Four patients were excluded from analysis of breast cancer risk because 3 patients received chest

radiation as adjuvant treatment for breast cancer and 1 patient had breast cancer prior to chest irradiation for NHL. The distribution of primary malignancy diagnoses in the 140 women, the median age at radiation and median radiation dose to the chest are presented in Table 1. The majority of the women exposed to chest irradiation were treated for primary HL (47.9%) or a central nervous system tumour (21.4%). All the women with HL received radiation to a supra-diaphragmatic field with a median chest dose of 36.0Gy, 19.4% were also treated to an infra-diaphragmatic field.

#### Breast screening compliance

Ninety-eight of the 140 women exposed to chest radiation were assessed for compliance with breast surveillance imaging. Forty-two patients were excluded; 23 had not commenced surveillance, either because they were <25yo or <8 years post completion of chest irradiation at their last attendance; 13 had a diagnosis of breast cancer prior to the first attendance and 6 attended on a single occasion. Overall compliance with screening mammography alone was 18.4% and screening with any breast surveillance modality (mammography or ultrasound or MRI) was 28.6%. Chest radiation dose was <20Gy, ≥20Gy and unknown in 16, 113 and 11 women respectively. Amongst women exposed to ≥20Gy chest radiation, there was no difference in compliance between those exposed when younger than 30 or ≥30 years old (p=NS). There was also no significant difference in the compliance ratio between those women exposed to ≥20Gy chest radiation and those receiving lower doses (p=NS). Overall, surveillance breast MRI was sporadically used in 9.3% (n=13) of women exposed to chest irradiation. Breast ultrasound and MRI identified 9 out of 12 (75%) asymptomatic lesions that were biopsied with a benign result (ultrasound 5, MRI 4).

### Radiation-associated breast malignancy prevalence and incidence

The prevalence of RBC was 17.1%. There were 28 cancers in 24 women, of 140 exposed to chest radiation. Four women had bilateral cancers (3 metachronous, 1 synchronous) (16.7%).

Figure 1 shows the Kaplan-Meier curve for RBC, stratified by the interval from completion of radiation until the first LE service attendance. This analysis considered 121 women, including 10 who developed a RBC during surveillance by the LE service. Nineteen women were excluded because 8 attended the clinic once and 14 developed a RBC outside the period of LE service attendance; 3 women had both reasons for exclusion. Most (44.6%) women first attended the LE service >15 years from completion of chest radiation and had the highest incidence of RBC; 13% and 23% had a RBC at 5 and 10 years of subsequent follow-up respectively (Table 2). There were no breast cancers in women first seen 0-5 years after completion of chest irradiation. Although there was a trend that the incidence of breast cancer increased with increasing interval between completion of chest radiation and first LE attendance, the confidence intervals overlapped between the strata, likely due to the few numbers of cases.

Based on Australian population data, a total of 0.89 breast malignancies should be expected to occur in the LE sample. The malignancy rate in the LE cohort was 11.2 times the expected number of cases ( $p < 0.001$ ).

### Clinicopathological features of radiation-associated breast malignancies

Twenty-four women developed 28 RBC. The median ages at chest radiation exposure and index breast cancer were 20.6 (range 4.4-50.1) and 49.3 (range 26.9-75.9) years old respectively. Median latency to index breast cancer was 24.9 years (range 9.0-46.0 years). Four women were exposed to chest radiation after age 30 and their breast cancer may reflect a weaker association

with radiation. At the time of index cancer diagnosis, 8 women were pre-menopausal, 15 were post-menopausal and menopausal status was unknown in 1 patient. Based on the FRA-BOC online tool for assessment of familial breast cancer risk<sup>9</sup>, of the women diagnosed with a breast malignancy, 91.7% were “at average risk” , 8.3% were at “moderately increased risk” and no women were “potentially high risk”.

Of the 28 breast cancers, 17 (60.7%) were screen-detected and 11 (39.3%) presented symptomatically. Twelve cancers were right-sided, 8 were left-sided and 4 were bilateral. The metachronous cancers were diagnosed at 1.2, 9.2 and 10.3 years after the index case. Most malignancies were located in the upper outer quadrant (48.1%). Twenty-six of the 28 cancers (92.9%) were visible on mammography. Two cancers were mammographically occult; one was an impalpable cancer detected on breast MRI and the other was a palpable lobular cancer detected on breast MRI and ultrasound.

The clinico-pathologic features of the 28 cancers are outlined in Table 3. The majority of the cancers (82.1%, n=23) were invasive ductal carcinomas, 1 was a mixed invasive ductal/lobular carcinoma (3.6%), 1 was an invasive lobular carcinoma (3.6%) and 3 (10.7%) were ductal carcinoma in-situ. Most breast cancers were early stage. Although there was a trend that screen-detected malignancies were earlier stage, the association between the stage and mode of presentation did not reach significance (p=0.11). Of the 25 invasive breast cancers (excluding 3 DCIS cases), histological grade was 1, 2 and 3 in 20% (n=5), 44% (n=11) and 36% (n=9) respectively. Most cancers were hormone receptor positive (87.5%) and HER-2 non-amplified or HER-2 IHC 0/1+ (94.7%) (Table 3). The Ki-67 result was available in only 5 cases and results varied widely from <5% to 75%.

Twenty-five of the 28 breast cancers (89.3%) were managed with a mastectomy; 3 (10.7%) were managed with breast-conserving surgery. Four women (16.7%) had a contralateral prophylactic mastectomy. Breast reconstruction was performed following 19 of the 29 mastectomies (25 therapeutic and 4 prophylactic) (65.5%); the method of reconstruction was autologous and implant-based in 75% and 25% respectively.

Radiation therapy was infrequently administered with only one patient receiving adjuvant radiation. Radiation was not administered to the 3 patients managed with breast conserving surgery; they remained disease free at last follow-up at 3, 6 and 11 years. Chemotherapy and endocrine therapy were prescribed for 48.1% and 74.1% of cancers respectively. All hormone receptor positive invasive breast cancers received endocrine therapy except for one patient who refused.

The median follow-up was 7.9 years (range 0.4-20.4 years) from index breast cancer diagnosis. Three patients developed metachronous contralateral cancers. Two patients developed a local recurrence at 3.2 and 3.6 years after their index breast cancer. Five patients developed metastatic disease (20.8%) of whom 3 died at 4.9, 7.8 and 8.6 years after the initial breast cancer diagnosis. There were 5 non-breast malignancy deaths in the cohort of 140 women exposed to chest irradiation; due to a cardiac cause (n=2), accident (n=1), radiation-associated brain tumour (n=1) and unknown cause (n=1).

None of the women exposed to chest irradiation were prescribed endocrine prevention therapy or underwent bilateral prophylactic mastectomies.

## Discussion

This study has used the term “radiation-associated” instead of “radiation-induced” that is widely used in the late effects literature as this implies causation. There is no genetic or histological

signature for radiation causation as yet and this study has defined cancers as radiation associated based on breast cancer occurrence within the field of chest radiation alone. It is likely that RBC is multifactorial and, in some cases, the association with radiation may be weaker, such as women with primary NHL who received chest radiation at an older age median age 29.23 (range 23.92-50.09).

Our study supports intensive surveillance due to the increased risk of breast cancer and long latency of RBC. The risk of breast cancer was increased 11.2 times compared to the general population. Two of the cases were DCIS, which is considered an event in locoregional breast cancer studies, but technically may be considered as overdiagnosis. However, the incidence of DCIS is low compared to invasive breast cancer (14.4 versus 122.5 per 100000 women).

RBC is the most common solid cancer in female survivors of childhood Hodgkin's Lymphoma (HL)<sup>10-13</sup>. The only meta-analysis of HL survivors included 34 studies, involving 957 cases of SCB in 25,305 female HL survivors with a median follow-up of 14.5 years from diagnosis of HL. The pooled overall relative risk (RR) of RBC compared to the general population was 8.23 (95% CI, 5.43-12.47)<sup>14</sup>. The risk of breast cancer by age 50 is comparable to Breast Cancer susceptibility gene 1 (BRCA1) mutation carriers; namely 35% and 31% in HL survivors and BRCA1 carriers respectively<sup>15</sup>.

Long-term surveillance is essential as RBC due to the long latency, occurring at a median 24.9 years after chest radiation (range 9.0-46.0years), with the highest incidence in patients seen >15 years after chest radiation. Although there was a trend that screen-detected cancers were identified at an earlier stage, screen detected cancers constituted 3 of the 5 cases that metastasised.

International guidelines recommend annual mammography and MRI for women treated with  $\geq 20\text{Gy}$  chest irradiation before age 30, beginning 8 years after radiation or age 25, whichever occurs later<sup>6,16,17</sup>. This is consistent with evidence that breast MRI will detect more cancers in survivors exposed to chest radiation<sup>18-21</sup>. Mathematical modeling predicts that early screening from age 25, in particular with breast MRI will reduce breast cancer mortality<sup>22</sup>. Ng et al.'s prospective study identified 18 malignancies in 148 HL survivors screened with annual breast MRI and digital mammography over a 3-year period. Significantly, there were no interval cancers and the detection rate remained at about 5% each year<sup>21</sup>.

MRI breast was sporadically used by the LE service as it is not funded by Medicare. MRI breast identified two additional mammographically occult cancers. Breast density was not assessed in this study, but is reported to be at least moderately dense in 52-79% of women irradiated for HL<sup>23,24</sup>. More recently, women with prior chest irradiation were found to have a significantly greater background parenchymal enhancement on breast MRI; this may account for its lower sensitivity compared to other high-risk populations (67-92% versus 93-100%)<sup>25</sup>. Together, these findings support the use of both mammography and breast MRI in women at risk of RCB.

Recommendations for screening must be assessed with consideration of screening compliance, which has only been scarcely reported in the literature and not to the same level of detail as this study<sup>26-28</sup>. Our definition provides a gauge of commitment to regular screening over the duration of LE service attendance. Compliance was only achieved in a minority of women. This study has not explored the reasons for non-compliance as this was not possible from the information available. Nonetheless, issues that featured prominently in this cohort that may impact screening compliance include childbearing, breastfeeding, family and work commitments and other medical issues.

Similar to reports of breast cancer in CAYA populations, breast malignancies in the LE cohort were more often bilateral (16.7%)<sup>29-40</sup> with a contralateral rate of 1.36–3.2% per year<sup>31,37,41</sup> and 18% at 5 years<sup>35</sup>, most commonly invasive ductal carcinomas (82.1%), located in the upper outer quadrant (48.1%)<sup>29-33,35,37,41-44</sup> and within or at the margin of the radiation field (75-85%)<sup>32,37,45</sup>. They are usually managed with mastectomy (89.3%)<sup>29-31,33,35,38,41,46-48</sup> and rarely treated with radiation therapy (3.6%). The median age at diagnosis of breast malignancy was older than in meta-analysis by Ibrahim (49.3 versus 35.0 years old) and the majority were HR positive (84.0%), in contrast to series that report a higher proportion of HR negative cancers (27-49%)<sup>39,47</sup>.

Stratified by time since HL, Dores et al. reported a greater increase in the risk of ER negative high-grade cancers, suggesting radiation contributes to the development of cancers with a poorer prognosis<sup>43</sup>. However, other matched cohort studies have not found a significant difference in ER status, grade or rate of lymphovascular invasion compared to primary breast cancers (PBC)<sup>33,35,41</sup>. When reported, human epidermal growth factor receptor-2 (HER-2) was amplified in up to 13.7% of SCB with no significant difference compared to PBC<sup>26,29,35,38,39,46</sup>.

No significant difference in breast cancer event-free survival and breast cancer-specific mortality has been demonstrated between SCB in women following HL and PBC<sup>35</sup>. However, there is a significantly worse overall survival in women with prior HL that is mainly attributable to competing conditions such as cardiac disease and non-breast cancers<sup>35,47</sup>.

There is a paucity of studies about breast cancer prevention in the LE population. A feasibility study to assess the role of tamoxifen in HL survivors treated with chest irradiation found that 86% of eligible participants declined and 31% of those who commenced tamoxifen failed to complete a one year course; nearly half due to side-effects<sup>49</sup>.

This study is limited in the retrospective nature of integrating a prospective database which is dependent on quality and completeness of data from the patient's medical records. In particular, it was not possible to assess a dose-risk relationship as information about the precise breast dose was not available, compounded by breast development especially in patients treated before puberty.

#### Conclusion

Radiation-associated breast cancers occurred in patients after a long latency and were the leading cause of death in this cohort, reinforcing the importance of ongoing long-term follow-up of this unique population of patients. An individualised, comprehensive multisystem risk management and surveillance strategy is required for these survivors of late effects - an iatrogenic disease of success.

#### Conflict of interest:

None of the authors have any conflict of interest.

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#### Ethics:

This research was conducted with full institutional ethics.

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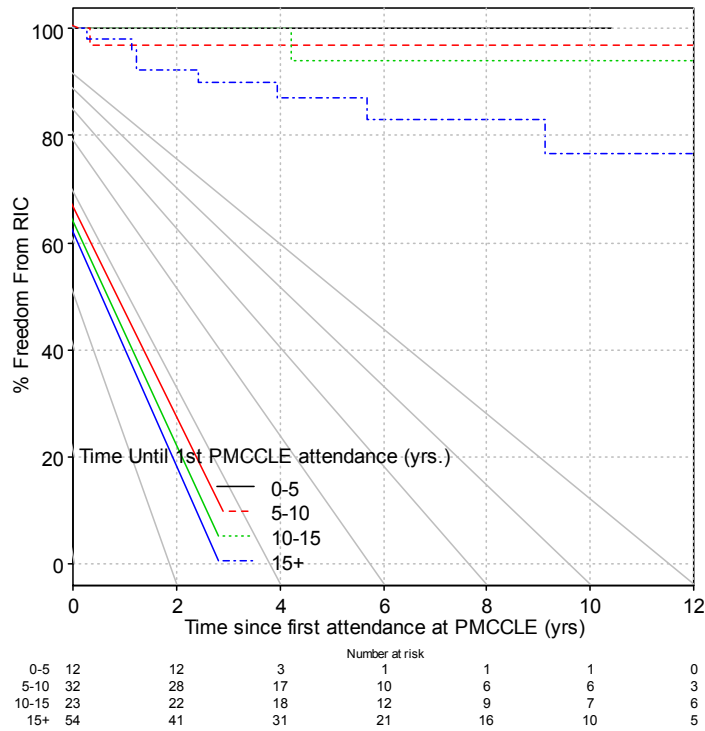


Figure 1: Kaplan-Meier curve for radiation-associated breast cancer

Abbreviation PMCCLE=Peter MacCallum Cancer Centre Late Effect Service

Table 1: LE cohort of women exposed to chest radiation (n=140)

Primary cancer	n (%)	Median age at chest radiation (years, range)	Median chest dose (Gy, range)
Hodgkin lymphoma	67 (47.9)	25.00 (10.05-50.88)	36.0 (10-40)
CNS tumour*	30 (21.4)	9.33 (0.80-32.88)	35.0 (20-46)
NHL	11 (7.9)	29.23 (23.92-50.09)	36.0 (12-50)
Leukemia	10 (7.1)	26.62 (3.54-55.33)	12.6 (12-24)

Sarcoma	10 (7.1)	9.94 (5.54-18.19)	45.2 (15-68)
Wilm's tumour	8 (5.7)	5.20 (3.52-6.89)	21.75 (scatter-30)
Other / Benign	4 (2.9)	12.92 (0.16-50.29)	12.0 (6-40)
<b>TOTAL</b>	140	20.26 (0.16-55.33)	35.0 (scatter-68Gy)

Abbreviations

Gy

Gray

CNS Central nervous system

(1),

\*CNS tumours include medulloblastoma (20), ependymoma (6), astrocytoma pituitary germinoma (1), pituitary choriocarcinoma (1), neuroblastoma (1),

NHL Non-Hodgkin lymphoma

Table 2: Freedom from radiation-associated breast malignancy at 5 &amp; 10 years follow-up

<b>Time from completion of chest irradiation until 1<sup>st</sup> LE service attendance (years)</b>	<b>Subsequent follow-up (years)</b>	<b>Freedom from radiation-associated breast malignancy (%) [95% CI]</b>
<b>0-5</b>	5	100% [100%, 100%]
<b>0-5</b>	10	100% [100%, 100%]
<b>5-10</b>	5	97% [91%, 100%]
<b>5-10</b>	10	97% [91%, 100%]
<b>10-15</b>	5	94% [84%, 100%]
<b>10-15</b>	10	94% [84%, 100%]
<b>15+</b>	5	87% [78%, 97%]
<b>15+</b>	10	77% [62%, 95%]

Table 3: Clinicopathological feature of 28 breast malignancies in 24 patients

Pat-ient	Prim ary diag nosi s	Age at che st XR T (ye ars)	Radiati on field/d ose (Gy)	Age at bre ast can cer (ye ars)	Symp tom/ scree n	Path ology	T size (m m)	N o. + ve L N	Gr ade	E R	P R	HE R2/ cer b2	Sur gery	X R T	Che mo	ET	Re cur	Dea th
1	HL	19. 3	Chest, axilla and other sites  (dose NA)	58. 2	Scree n	DCIS	Tis						M, SNB	N	N	N	N	N
2	HL	17. 1	Mantle (36Gy)	50. 8	Scree n	IDC	8	0	2	7	5	-ve	M, SNB , Rec	N	N	Y	N	N

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														on					
3	HL	18.6	Mantle, paraaortic, pelvic (36Gy)	39.3	Symptom	IDC	20	0	1	8	3	-ve	M, SNB, Rec on	N	N	Y	Y	N	
				39.3	Screen	DCIS	Tis								M, Rec on	N	N	N	
4	HL	18.0	Mantle (36Gy)	26.9	Screen	DCIS	Tis						M, Rec on	N	N	N	N	N	
5	HL	23.3	Mantle (36Gy)	52.2	Screen	IDC	9	0	2	8	7	-ve	M, SNB, Rec on	N	N	Y	N	N	
6	HL	20.9	Mantle, pelvic (36Gy)	33.1	Screen	IDC	22, 8	0	2	7	8	-ve	M, SNB, Rec on	N	N	Y	Y	N	
7	HL	20.3	Mantle, invert	45.2	Screen	IDC	8	0	1	7	8	-ve	M, SNB, Rec on	N	N	Y	N	N	

			d Y (dose NA)										Rec on					
				46. 4	Scree n	IDC	5	0	2	8	8	-ve	M, SNB , Rec on	N	N	Y		
8	HL	35. 4	Mantle (dose NA)	66. 2	Scree n	IDC	9	0	1	7	7	NA	WL E, SNB	N	N	Y	N	Y *
9	HL	23. 2	Mantle, paraaor tic (36Gy)	55. 6	Scree n	IDC	10	0	1	8	7	-ve	WL E, SNB	N	N	Y	N	N
10	HL	21. 1	Mantle (40Gy)	38. 2	Symp tom	IDC	20	1	3	0	0	-ve	M, SNB , AN D, Rec on	N	Y	N	Y	Y
11	HL	17. 6	Mantle (36Gy)	34. 8	Symp tom	IDC	17	0	3	0	0	-ve	M, SNB , Rec	N	Y	N	N	N

Pat-ient	Prim ary diag nosis	Age at che st XR T (ye ars)	Radiati on field/d ose (Gy)	Age at bre ast can cer (ye ars)	Symp tom/ scree n	Path ology	T size (m m)	N o. + ve L N	Gr ade	E R	P R	HE R2/ cer b2	Sur gery	X R T	Che mo	ET	Re cur	Dea th
				44. 0	Scree n**	IDC	13	2 ( m i)	3	8	8	-ve	M, SNB , Rec on					
12	HL	18. 9	Mantle (36Gy)	34. 5	Scree n	IDC	16	2	3	8	8	-ve	M, SNB , AN D, Rec on	N	Y	N (ref use)	N	N
13	HL	19. 9	Mantle (36Gy)	44. 8	Symp tom	IDC	20	0	2	6	0	-ve	M, AN D, Rec on	N	Y	Y	N	N

14	HL	17.5	Mantle, Waldeyer (32Gy)	51.2	Symptom	IDC	17	0	2	7	7	NA	M, AN D, Rec on	N	Y	Y	N	N
15	HL	25.7	Mantle (36Gy)	45.1	Screen	IDC	15	0	3	8	4	-ve	M, SNB, Rec on	N	Y	Y	N	N
16	HL	17.8	Mantle (32Gy)	49.5	Screen	IDC	14, 8	2	3	7	7	-ve	M, SNB, AN D	N	Y	Y	Y	Y
17	HL	37.1	Mantle (36Gy)	50.9	Screen	IDC	22	4	1	+	+	NA	M, SNB, AN D	N	Y	Y	Y	Y
18	HL	27.8	Mantle (10Gy)	50.7	Symptom	IDC/ LC	40, 7	2	2	4	6	NA	M, SNB, AN D, Rec	N	Y	Y	N	N

													on					
19	HL	29.9	Mantle (36Gy)	75.9	Symptom**	ILC	17	0	2	8	7	-ve	M, SNB	N	N	Y	N	N
20	NHL	30.8	Total nodal (40Gy)	65.2	Screen	IDC	12	0	2	8	6	-ve	M, SNB	N	N	Y	N	N
21	NHL	50.1	Involved field right neck,	59.8	Screen	IDC	22	0	2	8	6	-ve	M, SNB	N	N	Y	N	N
22	NHL	28.3	Mediastinum, axilla (40 +10Gy boost axilla)	46.9	Symptom	IDC	42	1	3	0	5	-ve	WLE, SNB, AND	N	Y	Y	N	N
23	Wil m's tumor	4.4	Right hemithorax (dose NA)	38.4	Symptom	IDC	30	0	3	NA	NA	NA	M, AND	N	Y	N	N	N
				48.7	Symptom	IDC	>45 mm IBC	+ve	3	0	0	+ve	M, SNB, AND	Y	Y (neo)	N		

24	CVL	5.7	Right chest wall (6Gy)	49.2	Symptom	IDC	9	1	2	7	7	NA	M, AND	N	Y	Y	N	N
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Abbreviations NA=Not available; Gy=Gray; No.=Number; LN=Lymph node; ER=Oestrogen receptor (Allred score); PR=Progesterone receptor (Allred score); XRT=Radiation; Chemo=Chemotherapy; ET=Endocrine therapy; NA=Not available; HL=Hodgkin lymphoma; NHL=Non-Hodgkin lymphoma; CVL=Congenital vascular lymphangioma;

DCIS=Ductal carcinoma in situ; IDC=Invasive ductal carcinoma; ILC=Invasive lobular carcinoma; IBC=Inflammatory breast cancer; M=Mastectomy;

WLE=Wide local excision; SNB=Sentinel lymph node biopsy; AND=Axillary lymph node dissection; Recon=Breast reconstruction; mi=Micrometastasis; neo=Neoadjuvant; +ve=Positive; -ve=Negative

\*cardiac cause of death \*\*Mammographically occult