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SURGICAL OUTCOMES FOLLOWING BREAST RECONSTRUCTION IN PATIENTS WITH AND WITHOUT A HISTORY OF CHEST RADIOTHERAPY FOR HODGKIN LYMPHOMA: A MULTICENTER, MATCHED COHORT STUDY

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Highlights

- no increased risk of adverse surgical outcomes was demonstrated following postmastectomy breast reconstruction after previous chest radiotherapy for Hodgkin lymphoma
- subanalysis per breast reconstruction technique did not show worse surgical outcomes for Hodgkin lymphoma survivors
- patients with a history of chest radiotherapy for Hodgkin lymphoma may have an increased risk of admission to an Intensive Care Unit af
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Abstract (249/250)

Background:

Breast cancer is the most common treatment-related second malignancy among women with previous chest radiotherapy for Hodgkin lymphoma (HL). Little is known about the effects of this kind of radiotherapy on the outcomes of postmastectomy breast reconstruction (BR). This study compared adverse outcomes of BR after HL-related chest radiotherapy to matched controls.

Methods:

We conducted a retrospective, matched cohort study in two expert cancer centers in the Netherlands. BRs after therapeutic or prophylactic mastectomy in HL survivors who received chest radiotherapy were matched with BRs in nonirradiated patients without HL on age at mastectomy date, date of BR, and type of BR. The primary outcome was complication-related BR failure or conversion and secondary outcomes were complication-related re-operation, capsular contracture, major donor-site complications, and complication-related ICU admission. We analyzed all outcomes univariably using Fisher's exact tests and we assessed reconstruction failure, complication-related re-operation, and capsular contracture with multivariable Cox regression analysis adjusting for confounding and data clustering.

Results:

Seventy BRs in 41 patients who received chest radiotherapy for HL were matched to 121 BRs in 110 nonirradiated patients. Reconstruction failure did not differ between HL survivors (12.9%) and controls (12.4%). The comparison groups showed no differences in number of reoperations, major donor-site complications, or capsular contractures. BR in HL survivors more often let to ICU admission due to complications compared to controls (p=0.048).

Conclusions:

We observed no increased risk of adverse outcomes following BR after previous chest radiotherapy for HL. This is important information for counseling these patients and may improve shared decision-making.

Keywords

breast reconstruction; Hodgkin lymphoma; radiotherapy; outcomes; reconstructive failure; complications\

1. Introduction

Hodgkin lymphoma (HL) survivors currently have a good life expectancy due to effective treatment regimens, including chemotherapy and/or radiotherapy. From the 1960s to the late 1980s, primary treatment for HL frequently comprised extended field radiotherapy such as mantle field radiotherapy (MFRT). MFRT encompassed the supradiaphragmatic lymph node stations, in particular the cervical, supraclavicular, infraclavicular, axillary, hilar and mediastinal nodes (Figure 1). Although these radiation protocols proved successful treatments, they are also associated with increased risks of cardiovascular disease, impaired pulmonary or thyroid function and, second malignancies with substantial morbidity and mortality.(1-12)

Breast cancer (BC) is the most common treatment-related second malignancy among women who received chest radiotherapy for HL, accounting for almost 40% of second cancers.(4, 7, 8, 11, 13) Risks are higher if survivors were irradiated at young ages or received higher radiation doses, with more extensive irradiation fields including the breast.(3, 4, 13, 14) The increased risk of developing BC is observed from about 10 to at least 40 years after irradiation for HL.(8, 15, 16) The risk of BC is increased 37-fold compared to the general population and the cumulative risk of BC may amount to 48% forty years after treatment for HL.(13, 16-20)

BC treatment frequently includes mastectomy.(21) Postmastectomy breast reconstruction (BR) can improve quality of life and is an important and integrated optional part of BC treatment.(22) BR may be immediate or delayed, using implants, autologous tissue or a combination.(23) However, BR may be impeded by radiotherapy for BC due to its negative effects on the chest tissues, which are more profound in implant-based BR than in autologous BR. Therefore, the latter is often preferred after radiotherapy for BC.(24-26) However, the impact of radiotherapy for HL might differ from that for BC as the two differ in

two key respects. First, in BC radiotherapy the dose is higher, with an equivalent dose of 50-66 Gy in 2 Gy fractions, compared to 35-40 Gy in 1.75-2.0 Gy fractions in MFRT. Second, the target area for MFRT does not focus on the breast and the central part of the breast is typically positioned under lung shielding blocks. Studies on the effects of previous radiotherapy for HL on the outcomes of BR are scarce, have small sample sizes, lack appropriate control groups, and show conflicting results.(27-30) Therefore, the aim of the present study was to compare outcomes after BR in patients with previous chest radiotherapy for HL to matched controls without HL.

2. Material and methods

We performed a retrospective, matched cohort study nested within a cohort of 3905 HL survivors who were treated in the Netherlands between 1965 and 2000. The selection and methods of data collection for this cohort have been described previously.(1, 8, 15, 31, 32) From this cohort, all women were selected who had been diagnosed with BC after previous chest radiotherapy for HL and had undergone BR after therapeutic or prophylactic mastectomy at [ANONYMISED].

BRs of these patients were matched with BRs after therapeutic or prophylactic mastectomy in patients without a history of HL or chest radiotherapy (matched controls). Matching was performed on age at mastectomy (±five years), date of BR (±five years), and type of BR (direct-to-implant; tissue expander/implant; autologous with implant; autologous only) and timing of BR (immediate or delayed). We aimed to match each case to two controls. Breasts which had received radiotherapy for BC before BR were excluded. Patients were excluded if their electronic health records had missing data regarding supradiaphragmatic radiotherapy. Four types of BR were included, i.e. autologous BR, implant-based BR completed in one operation (direct-to-implant) or as a two-stage procedure using a tissue

expander and implant subsequently, and BR using a combination of an implant and autologous tissue.(33)

This study is in accordance with the Declaration of Helsinki, was approved by the Medical Ethical Research Committee of [ANONYMISED] and is registered at [ANONYMISED] (protocol accessible).(34) This work is in line with the STROCSS criteria.(35)

2.1 Data collection

Data on patient demographics, HL characteristics and treatment, BC characteristics and treatment, BR characteristics, and all reconstruction-related surgical procedures were collected directly from hard copy or electronic patient files.

2.2 Outcomes

Primary outcome was BR failure due to complications (referred to as 'reconstruction failure'), defined as complication-related removal of the reconstruction resulting in a flat chest or conversion to another BR type due to complications.

Secondary outcomes were reoperation due to complications, capsular contracture, major donor site complications, and complications leading to intensive care unit (ICU) admission (Clavien-Dindo grade IV).[36] Major complications were defined as those requiring reoperation or ICU admission.

2.3 Statistical Analysis

Baseline characteristics of BRs were compared using frequencies for categorical variables and medians with interquartile ranges for continuous variables. Fisher's exact tests were used to compare matching variables between cohorts and for univariable analysis of the

number of events per outcome measure. If radiotherapy was administered after reconstruction, BRs were censored from the starting date of radiotherapy to prevent obscuring the results with the known effect of radiotherapy for breast cancer. Subgroup analyses was performed for four types of BR.

Differences in reconstruction failure, reoperation due to complications, and capsular contracture between BRs in patients with and without a history chest radiotherapy for HL were assessed using Cox regression models, taking clustering of reconstructions within patients into account. For the first outcome, BRs were censored if a failure occurred due to another reason than a complication (e.g. due to patient dissatisfaction with outcome). For the second and third outcomes, BRs were censored if a failure occurred for any reason.

We considered the following variables as potential confounders: chemotherapy, smoking, ASA-class (American Society of Anesthesiologists Physical Status Classification System),(37) Body Mass Index, age at BR, and bilateral BR. Each potential confounder was added to the base model to assess its influence on the effect of history of HL the depended variable. A variable was retained in the model if the Hazard ratios (HR) for history of HL changed by more than 10%. The proportional hazards assumptions were assessed using residual-based methods. Kaplan-Meier curves were plotted to visualize the survival probabilities over time.

Two-sided p-values <0.05 were considered statistically significant. Analyses were conducted using R-software (version 3.6.1) and the 'survival' package (version 3.2-7).(38, 39)

3. Results

3.1 Baseline comparison of cohorts

Seventy BRs in 41 patients with previous chest radiotherapy for HL were matched to 121 control BRs in 110 patients without a history of HL and without chest radiotherapy.

Median age at mastectomy was 47 years (IQR=38-52) for HL survivors and 46 years (IQR=40-51) for controls. The majority of reconstructions was performed between 2005 and 2015. Immediate reconstruction was performed in 82%. Most reconstructions were implant-based with 44% direct-to-implant and 28% tissue expander/implant procedures. In 9% of reconstructions an implant (±tissue expander) was combined with autologous tissue (latissimus dorsi or thoracodorsal flap). In all alloplastic BRs, the implants were placed in a submuscular position and no acellular dermal matrices were used. Autologous reconstructions were performed in 19% and abdominal tissue was used in 89% of these cases. All BRs in HL survivors were performed following mastectomy for at least unilateral BC compared to 75% in matched controls. This largely explains the difference in the proportion of reconstructions exposed to chemotherapy for BC (41% in HL survivors vs. 25% in controls). HL survivors had more severe comorbidities with 20% being rated ASA III compared to 1% of controls. Smoking habits also differed with more current smokers and less former smokers in the comparison cohort (Table 1).

The median age at start of irradiation for HL was 21.6 years. The sites of all except two reconstructions in one HL survivor were exposed to Mantle field type radiotherapy. This patient received radiotherapy only to the left cervical and left hilar nodes. Additional therapy for HL included chemotherapy (46% of reconstructions) and splenectomy (20% of reconstructions) (Table 2).

3.2 Outcomes: univariable analysis

Thirteen percent of all reconstructions failed and this did not differ between cohorts (12.9% in HL survivors vs. 12.4% in controls). The percentage of reconstructions which did not need any complication-related revision surgery was similar for reconstructions in HL survivors compared to matched controls (66% vs. 64% respectively). However, if a

complication occurred that required surgery, HL survivors underwent more procedures compared to matched controls. This difference was statistically significant for tissue expander/implant BRs (p=0.001). In three HL survivors, complications after autologous reconstruction resulted in ICU admissions while this did not occur in the comparison cohort (p=0.048) (Table 3). One patient suffered from postoperative hypoxia due to atelectasis after DIEP flap reconstruction, one patient developed re-entry tachycardia for which she needed treatment with adenosine after latissimus dorsi flap reconstruction with a tissue expander, and one patient required prolonged ICU admission due to idiopathic low oxygen saturation after revision surgery for total flap failure of her SGAP flap reconstruction. All patients were ASA-II.

Sub-analysis per BR type showed no differences between HL survivors and matched controls in reconstruction failure, reoperation rates, capsular contracture or major donor site complications, except for reoperation rates after tissue expander/implant BR (Table 4). When combining all implant-related reconstructions, capsular contracture occurred less frequently in HL survivors than in the comparison cohort (5.4% vs. 17.2% respectively, p=0.045). There was no significant difference in major donor site complications when all reconstructions involving autologous tissue were combined (HL cohort 9.1% vs. comparison cohort 12.5%, p=1.00).

3.3 Outcomes: multivariable analysis

The HR for reconstruction failure comparing reconstructions in HL survivors to matched controls was 0.81 (95% confidence Interval (CI): 0.34-1.96) in multivariable analysis adjusting for postreconstruction chemotherapy (Table 5). Post-reconstruction chemotherapy was a risk factor for reconstruction failure (HR: 7.6; 95%CI: 3.4-16.9; p-value: <0.001).

Figure 2 shows the univariable Kaplan-Meier survival curves for reconstructions in HL survivors and matched controls.

The HR for complication-related reoperations comparing reconstructions in HL survivors to controls was 0.75 (95%CI: 0.40-1.43) in multivariable analysis adjusted for ASA-class (Table 5). Figure 3 shows univariable time-to-event plots (Kaplan-Meier) for complication-related reoperations in HL survivors and matched controls.

The HR for capsular contracture comparing reconstructions in HL survivors to controls was 0.33 (95%CI: 0.08-1.39) in multivariable analysis adjusted for active smoking (Table 5). Active smoking was a risk factor for this outcome (HR: 5.01; 95%CI: 1.66-15.11; p=0.004). Figure 4 shows univariable time-to-event plots (Kaplan-Meier) for capsular contracture for all implant-based reconstructions in HL survivors and matched controls.

3.4 Salvage BR

Thirteen salvage BRs were performed after the initial reconstruction failed due to complications; four in HL survivors and nine in the controls. These consisted of four tissue expander/implant BRs, three reconstructions combining an implant and autologous tissue, four microvascular autologous reconstructions, and two only using lipofilling. All salvage BRs were surgically successful.

4. Discussion

Offering BR to HL survivors with previous chest radiotherapy for HL remains controversial because of presumed increased risks of adverse outcomes. The present study represents the largest series of BR in HL survivors and is the first study to compare outcomes with matched controls. Our study showed no increased risks for developing complications

leading to BR failure or conversion, reoperation, major donor site complications, or capsular contracture in HL survivors.

BR in HL survivors resulted in more admissions to the ICU than in the comparison cohort. Although these HL survivors were categorized as ASA II, they needed (prolonged) ICU admission due to pulmonary and cardiac problems. This may be explained by the known increased risk of cardiovascular and pulmonary disease which might not have been recognized preoperatively resulting in a low ASA classification.(1, 5, 10) Notably, these ICU admissions were only seen after autologous flap reconstruction (both pedicled and free) which might be associated with a longer operation time in flap-based reconstruction compared to implant-based reconstruction. Our small sample size prevents a strong recommendation, but it seems advisable to preoperatively discuss the risk of postoperative complications in HL survivors associated with their history of radiotherapy for HL.

Sub-analysis per reconstruction type showed no differences between the matched cohorts except in reoperation rates after tissue expander/implant BR. Less tissue expander/implant BRs in HL survivors needed any revision surgery due to complications compared to controls. However, if any reoperation was required, generally more procedures were necessary to solve the complication. Another remarkable result was the lower capsular contracture rate in HL survivors compared to controls when analyzing all implant-related reconstructions.

Remarkably, chemotherapy after completing BR was an independent predictor of reconstruction failure compared to no or pre-reconstruction chemotherapy. It mostly concerned immediate implant-based BRs, which were exposed to adjuvant chemotherapy. Postreconstruction chemotherapy, compared to no or preoperative chemotherapy, may be associated with increased risk of complications and failure due to the negative effect of chemotherapy on wound healing.(40-42) If chemotherapy is planned before BR, it is possible

to postpone BR in case a patient experiences a significant chemotherapy-related health deterioration, thereby avoiding the development of complications while weaker. However, if chemotherapy is planned after BR, any delay in the start of chemotherapy usually is minimalized, risking commencement while postoperative complications may still exist. Previous literature has reported conflicting results on this topic.(43, 44)

Active smoking was an independent predictor for developing capsular contracture. This association was previously also reported by some studies, but could not be found by others.(45-47) Our finding might be explained by our longer follow-up compared to earlier literature. It may be an incidental finding, especially given our small cohort size. However, smoking is known to cause a systemic inflammatory response and is associated with decreased tissue oxygenation and increased risk of infection.(48) It is conceivable that smoking increases the risk of capsular contracture, because a popular hypothesis for the pathogenesis of capsular contracture involves chronic infection and inflammation.(49) In the present study, BRs in HL survivors were less often exposed to smoking than matched controls.

Radiotherapy for BC is associated with a higher risk of complications after BR.(24) Implant-based reconstruction has been shown to be associated with poorer outcomes than autologous reconstruction.(24-26) Our study suggest that BR can be safely done in patients with a history of chest radiotherapy for HL. This can be explained partly by the lower average dose of 39 Gy in HL survivors in our study compared to 50 Gy in BC patients, which is even higher if a boost is given. Also, during MFRT a proportion of the breast and overlying skin is protected with lung shielding blocks, protecting the future reconstruction site. Late effects of radiotherapy such as fibrosis may progress many years after treatment which could be a disadvantage for HL survivors as their interval between radiotherapy for HL and reconstruction is usually considerably longer than a typical interval between radiotherapy for

BC and reconstruction.(50) However, this longer interval also means that the severity of the late effects is clear by the time of reconstruction and can be taken into consideration when deciding on the reconstructive approach. Based on literature regarding the effect of radiotherapy for BC, one could argue autologous BR may be preferred over implant-based BR in HL survivors, however, our results showed no need for such a preference.

All salvage reconstructions after initially failed BR were surgically successful. This offers some perspective to those patients who initially experience a BR failure.

Only four studies on BR after chest radiotherapy for HL have been published previously, all of which lacked a comparison group of non-irradiated patients.(27-30) Bacilious et al. were the first to publish a series of seven patients who underwent eleven immediate tissue expander/implant BRs after MFRT for HL; they reported only one complication (9%) and no BR failure after a mean follow-up of 3 years.(28) Wong et al. evaluated the postoperative outcomes of 23 implant-based and four autologous reconstructions after mastectomy in 16 HL survivors who had received MFRT.(27) They reported a higher overall complication rate of 69% after an average follow-up of 3.7 years compared to Bacillious et al.(27, 28) Five implant-based reconstructions required implant removal and conversion to autologous reconstructions (22%), which is comparable to our 17%-rate after 7.6 years median follow-up in implant-based reconstruction without autologous tissue. The difference in overall complications may partly be explained because their series contained only 4% delayed reconstructions compared to 18% in our group. Freniere et al. evaluated 79 immediate implant-based and 18 immediate autologous reconstructions in 97 HL survivors who had received MFRT with a follow-up of 5.6 years.(29) They reported a complication rate of 33% and an unplanned operative revision rate of 30% overall, 21% for implant-based reconstruction and 72% for autologous reconstruction. We did not observe these large differences between BR types. They explained the relatively

high proportion of unplanned revisions in their autologous group by hypothesizing a potential lower threshold for revisions in the healthy, well vascularized tissue of an autologous BR compared to revising scars over implants in an irradiated mastectomy skin envelope. For the same reason, one of the two expert centers in our study preferred autologous over implant-based BR. Freniere et a. reported a complete reconstruction failure rate of 3.7% for implant-based and 0% for autologous reconstruction, averaging 3.0% overall. We reported 12.9% amongst HL survivors, but this included 2 conversions, leaving 10% (n=7) when restricted to failure only. Van Huizum et al. compared 42 immediate implant-based breast reconstructions after skin-sparing mastectomy in patients receiving radiotherapy for HL to 47 salvage breast reconstruction after breast conserving therapy and associated radiotherapy for BC.(30) They reported an increased risk for adverse outcomes after radiotherapy for BC, but not after radiotherapy for HL.

Our overall BR failure rates compare unfavorable to literature in general. For implant-based BR we observed a 15.3% failure rate compared to 3.3-5.4% in recent meta-analyses.(51-53) Another meta-analysis reported data separately for direct-to-implant (14.4%) and two-stage reconstruction (8.7%) techniques, compared to 15.5% and 15.1%, respectively, in the present study.(54) Massenburg, et al. reported 1.1% flap failure for a cohort latissimus dorsi flap reconstructions combined with an implant which is notebly lower than our 11.1% failure rate (including conversions and implant related failures) in the autologous plus implant cohort containing both latissimus dorsi and thoracodorsal artery perforator flaps.(55) Finally, we had 2.8% reconstruction failures in the autologous cohort which is comparable to rates reported in the literature of 1.0-4.4%.(53, 56-58) It is not fully clear why we found relatively high failure rates. Partly, it may be explained by a referral bias as patients were selected from two tertiary medical centers who generally operate more complex patients. More importantly, our definition of reconstruction failure also included conversions to another reconstruction

type. This broad definition also considered direct-to-implant reconstructions as failed if they required a tissue expander at any point, and reconstructions based on implants only were also scored as failed if a small thoracodorsal artery perforator flap was added secondarily. Finally, our small sample sizes may have attributed to inaccurate estimates.

Although the present study reports the first comparison of BRs in HL survivors who received chest radiotherapy with matched controls, it is limited by its retrospective study design and small sample size. We chose to focus on objective outcomes involving reoperation because reliable data on such outcomes can be collected retrospectively. Although selection bias due to loss-to-follow-up might have occurred as patients with more severe complications tend to be followed longer, our long-term follow-up of 7.6 years exceeds that of earlier publications. Furthermore, we adjusted for a number of potential confounding factors and data clustering. The limited number of outcome events reduced statistical power when making more detailed comparisons by reconstruction technique.

5. Conclusion

This first comparative study evaluating BR outcomes in HL survivors provides reliable and reassuring data suggesting that there is no increased risk of adverse surgical outcomes following BR after previous chest radiotherapy for HL, either using implants or autologous tissue. This is important information for counseling HL survivors with BC who need to undergo mastectomy and consider breast reconstruction and may also improve shared decision-making. In addition, our findings may be extrapolated to BR for breast cancer developed after thoracic radiotherapy exposures for other childhood or young adult cancers, such as sarcoma and thymoma where the breast receives an incidental dose.

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Table 1. Baseline characteristics of breast reconstructions performed in Hodgkin lymphoma survivors and matched controls.

Table 2. Disease characteristics of Hodgkin lymphoma survivors according to breast reconstruction.

Table 3. Adverse outcomes of breast reconstructions in Hodgkin lymphoma survivors compared to matched controls: all reconstruction types combined.

Table 4. Adverse outcomes of breast reconstructions in Hodgkin lymphoma survivors compared to matched controls: stratified per reconstruction type.

Table 5. Risks of various complications comparing breast reconstructions in Hodgkin lymphoma survivors with matched control, based on Cox regression models.

Figure 1. Schematic representation of target area for mantle field irradiation

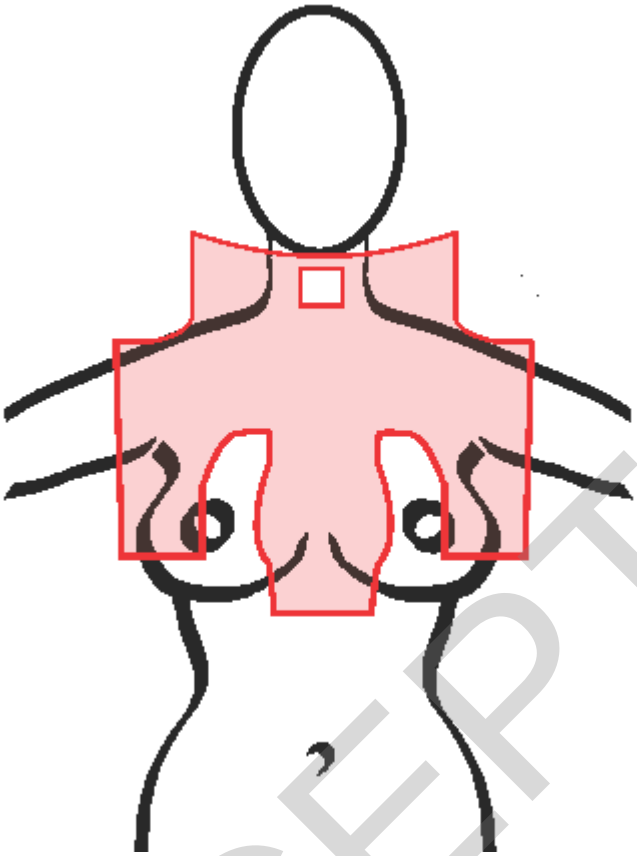

Figure 2. Univariable survival curve (Kaplan-Meier) for survival until failure or conversion of breast reconstruction due to a complication (unadjusted for clustering/confounding).

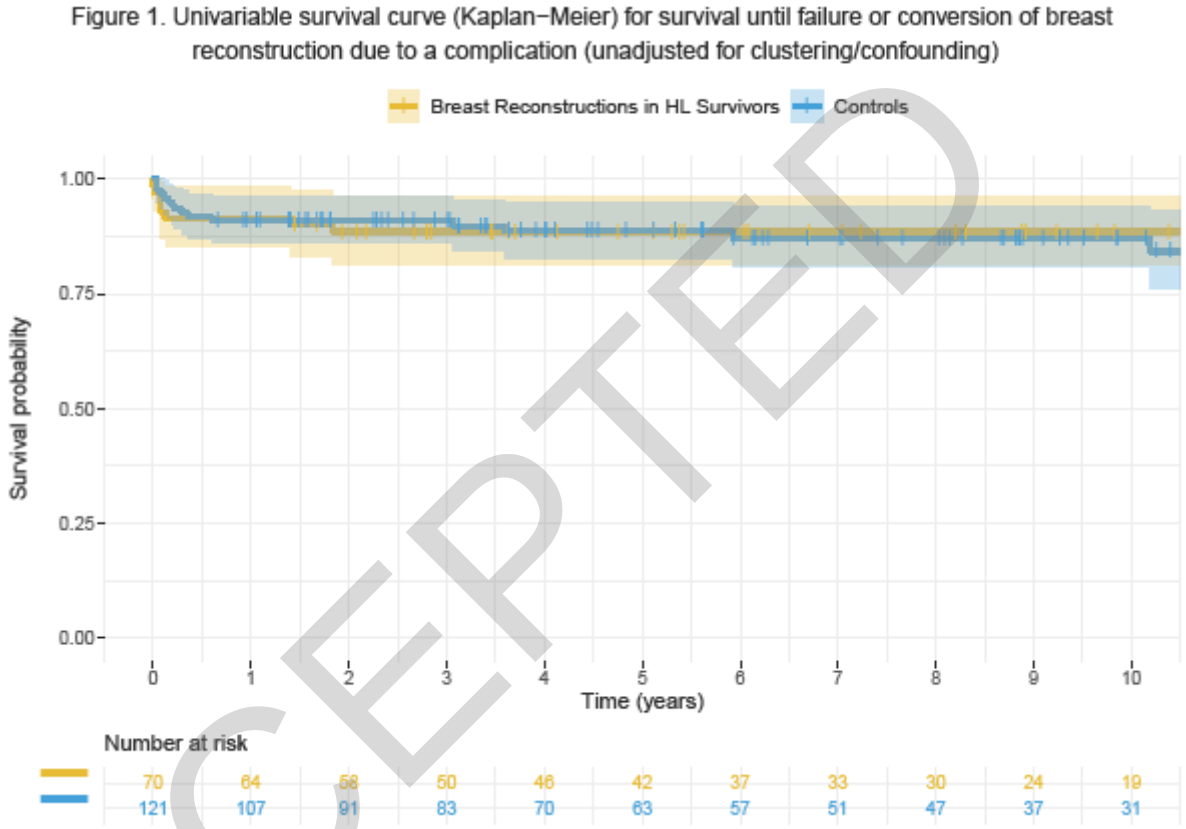

Figure 3. Univariable survival curve (Kaplan-Meier) for reoperation due to a complication after breast reconstruction (unadjusted for clustering/confounding).

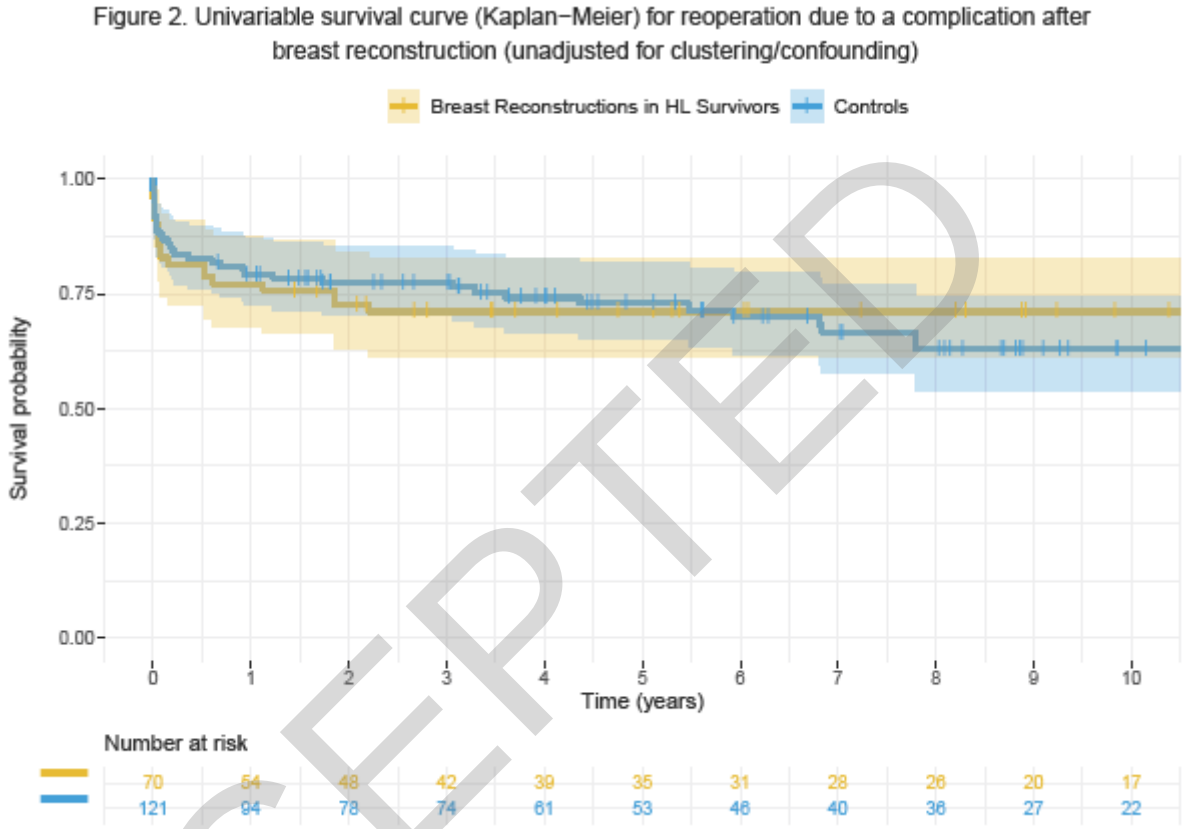

Figure 4. Univariable survival curve (Kaplan-Meier) for survival until capsular contracture for all breast reconstructions involving an implant (unadjusted for clustering/confounding).

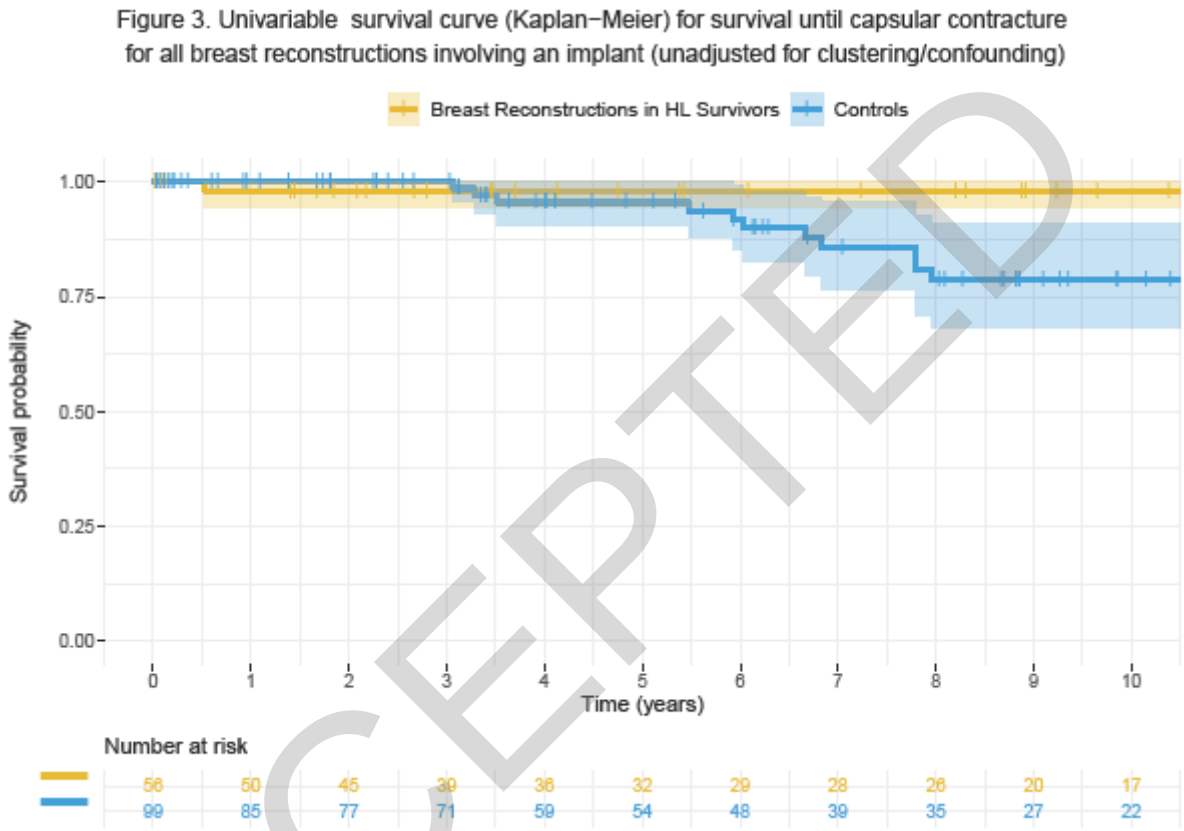

Table 1. Baseline characteristics of breast reconstructions performed in Hodgkin lymphoma survivors and matched controls.

		Overall	**Breast Reconstructions in HL Survivors**	**Controls**	**p-value**
Number of breasts		191	70	121	
Number of patients		151	41	110	
Age at mastectomy, n (%)[#]	<35 years	24 (12.6)	10 (14.3)	14 (11.6)	
	35-45 years	59 (30.9)	22 (31.4)	37 (30.6)	
	45-55 years	87 (45.5)	30 (42.9)	57 (47.1)	.918
	>55 years	21 (11.0)	8 (11.4)	13 (10.7)	
Year of breast reconstruction, n (%)[#]	<2000	19 (9.9)	8 (11.4)	11 (9.1)	
	2000-2005	32 (16.8)	11 (15.7)	21 (17.4)	
	2005-2010	73 (38.2)	26 (37.1)	47 (38.8)	.967
	2010-2015	46 (24.1)	18 (25.7)	28 (23.1)	
	>2015	21	7 (10.0)	14	

		(11.0)		(11.6)	
Timing of breast reconstuction, n (%)[#]	Immediate	157 (82.2)	56 (80.0)	101 (83.5)	
	Delayed	34 (17.8)	14 (20.0)	20 (16.5)	.561
Type of breast reconstuction, n (%)[#]	Direct-to-implant	84 (44.0)	29 (41.4)	55 (45.5)	
	Tissue expander/implant	53 (27.7)	19 (27.1)	34 (28.1)	
	Autologous[$] + implant	18 (9.4)	8 (11.4)	10 (8.3)	.854
	Autologous[&]	36 (18.8)	14 (20.0)	22 (18.2)	
Age at breast reconstruction, n (%)	<35 years	20 (10.5)	9 (12.9)	11 (9.1)	
	35-45 years	59 (30.9)	20 (28.6)	39 (32.2)	
	45-55 years	89 (46.6)	32 (45.7)	57 (47.1)	
	>55 years	23 (12.0)	9 (12.9)	14 (11.6)	
Breast cancer, n (%)	No	30 (15.7)	0 (0.0)	30 (24.8)	
	Unilateral	114 (59.7)	41 (58.6)	73 (60.3)	

	Bilateral	47 (24.6)	29 (41.4)	18 (14.9)
Indication for mastectomy, n (%)	Prophylactic	69 (36.1)	17 (24.3)	52 (43.0)
	Therapeutic	122 (63.9)	53 (75.7)	69 (57.0)
Mastectomy type, n (%)	Skin sparing mastectomy	148 (77.5)	54 (77.1)	94 (77.7)
	Nipple sparing mastectomy	9 (4.7)	3 (4.3)	6 (5.0)
	Modified radical mastectomy	19 (9.9)	9 (12.9)	10 (8.3)
	Unknown	15 (7.9)	4 (5.7)	11 (9.1)
Laterality reconstructive procedure, n (%)	Unilateral procedure	77 (40.3)	28 (40.0)	49 (40.5)
	Bilateral procedure	114 (59.7)	42 (60.0)	72 (59.5)
Type of autologous breast reconstuction, n (%)	Free flap	32 (59.3)	12 (54.5)	20 (62.5)
	Pedicled flap	22 (40.7)	10 (45.5)	12 (37.5)
Mastectomy specimen weight (gram), median [IQR]		435 [300, 603]	419 [291, 546]	449 [321, 630]
Chemotherapy for	Before BR	25	13 (18.6)	12

breast cancer, n (%)		(13.1)		(9.9)
	After BR	34 (17.8)	16 (22.9)	18 (14.9)
	No	132 (69.1)	41 (58.6)	91 (75.2)
Endocrine therapy for breast cancer, n (%)	Yes	31 (49.2)	11 (37.9)	20 (58.8)
ASA Classification, n (%)	ASA I	47 (24.6)	9 (12.9)	38 (31.4)
	ASA II	129 (67.5)	47 (67.1)	82 (67.8)
	ASA III	15 (7.9)	14 (20.0)	1 (0.8)
Body Mass Index (kg/m^2), n (%)	<25	118 (61.8)	43 (61.4)	75 (62.0)
	25-30	56 (29.3)	22 (31.4)	34 (28.1)
	>30	17 (8.9)	5 (7.1)	12 (9.9)
Smoker, n (%)	No	143 (74.9)	51 (72.9)	92 (76.0)
	Former	37 (19.4)	16 (22.9)	21 (17.4)
	Current	11 (5.8)	3 (4.3)	8 (6.6)

Follow-up (years), median [IQR]	7.55 [3.46, 10.98]	8.10 [4.28, 10.86]	7.04 [3.12, 10.98]

HL = Hodgkin Lymphoma; [#] variables used for matching; [$] 10 pedicled latissimus dorsi flaps, 8 thoracodorsal flaps; [&] 25 deep inferior epigastric perforator flaps, 1 muscle sparing transverse rectus abdominis muscle (TRAM) flap, 4 free TRAM flaps, 2 pedicled TRAM flaps, 1 superior gluteal artery perforator flap, 1 profunda artery perforator flap, 2 pedicled latissimus dorsi flaps; IQR = interquartile range.

Table 2. Disease characteristics of Hodgkin lymphoma survivors according to breast reconstruction.

	Breast Reconstructions in HL Survivors
Number of breasts	70
Number of patients	41
Age at start of irradiation for HL, median [IQR]	21.61 [18.63, 25.96]
HL RTx field, n (%)	
Subtotal nodal irradiation	2 (2.9)
Mantle field + para-aortic lymph nodes	19 (27.1)
Mantle field	44 (62.9)
Mantle field excluding axilary nodes	3 (4.3)
Left cervical and hilus nodes	2 (2.9)
Total RTx dosis, median [IQR]	39.48 [36.30, 40.02]
CTx for HL, n (%)	32 (45.7)
Splenectomy, n (%)	14 (20.0)
HL Recurrence, n (%)	7 (10.0)

HL = Hodgkin Lymphoma; RTx =

radiotherapy; CTx = chemotherapy; SD = standard deviation; IQR = interquartile range.

Table 3. Adverse outcomes of breast reconstructions in Hodgkin lymphoma survivors compared to matched controls: all reconstruction types combined.

	Breast Reconstructions in HL Survivors	**Controls**	**p-value**
n	70	21	
Failure or conversion of breast reconstruction due to a complication, n (%)	9 (12.9)	5 (12.4)	1.000
Reoperations due to a complication, n (%)	46 (65.7)	7 (63.6)	7 .350
+	14 (20.0)	3 (27.3)	3
	10 (14.3)	1 (9.1)	1
Intensive Care Unit Admission, n (%)	3 (4.3)	(0.0)	.048*

HL = Hodgkin Lymphoma; * indicates a significant test result

Table 4. Adverse outcomes of breast reconstructions in Hodgkin lymphoma survivors compared to matched controls: stratified per reconstruction type.

		Breast Reconstructions in HL Survivors	**Controls**	**p-value**
Direct-to-implant	n	29	5	
	Failure or conversion of breast reconstruction due to a complication, n (%)	5 (17.2)	(14.5)	.759
	Reoperations due to a complication, n (%)	20 (69.0)	6 (65.5)	.000
	+	6 (20.7)	2 (21.8)	
		3 (10.3)	(12.7)	
	Capsular contracture, n (%)	1 (3.4)	(14.5)	.154
expander/implant	n	19	4	
	Failure or conversion of breast reconstruction due to a complication, n (%)	3 (15.8)	(14.7)	.000

	Reoperations due to a complication, n (%)	12 (63.2)	8 (52.9)	.001 *
		2 (10.5)	6 (47.1)	
	+	5 (26.3)	0 (0.0)	
	Capsular contracture, n (%)	2 (10.5)	4 (26.5)	.290
Autologous with implant	n	8	0	
	Failure or conversion of breast reconstruction due to a complication, n (%)	0 (0.0)	1 (20.0)	.477
	Reoperations due to a complication, n (%)	7 (87.5)	3 (60.0)	.588
		1 (12.5)	1 (20.0)	
	+	0 (0.0)	1 (20.0)	
	Capsular contracture, n (%)	0 (0.0)	0 (0.0)	.000
	Major donor-site complications, n (%)	0 (0.0)	0 (0.0)	.000

Autologous only +	n	14	22	
	Failure or conversion of breast reconstruction due to a complication, n (%)	1 (7.1)	0 (0.0)	.389
	Reoperations due to a complication, n (%)	7 (50.0)	17 (77.3)	.200
		5 (35.7)	3 (13.6)	
		2 (14.3)	2 (9.1)	
	Major donor-site complications, n (%)	2 (14.3)	4 (18.2)	.000

HL = Hodgkin Lymphoma; * indicates a significant test result.

Table 5. Risks of various complications comparing breast reconstructions in Hodgkin lymphoma survivors with matched control, based on Cox regression models.

	Univariable			**Multivariable**		
	HR	95% CI	p-value	HR	95% CI	p-value
Failure or conversion due to a complication	1.03	0.41-2.61	0.95	0.81[a]	0.34-1.96	0.64
Reoperation due to a complication	0.93	0.53-1.61	0.79	0.75[b]	0.40-1.43	0.39
Capsular contracture	0.28	0.07-1.15	0.08	0.33[c]	0.08-1.39	0.13

HR = Hazard Ratio; CI = Confidence Interval; [a] corrected for postreconstruction chemotherapy; [b] corrected for ASA class; [c] corrected for active smoking; Both the univariable and multivariable model take clustering per patient into account.