



Prospective study: Radiation induced lymphedema in patients received hypofractionation schedules in adjuvant radiotherapy settings for non-metastatic breast cancer

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Abstract. Background: Hypofractionation was introduced in early breast cancer based on multiple clinical trials. The rationale behind hypofractionation is to deliver high dose per fraction over short duration without compromising the local control. The short fractionation was limited to early breast cancer with BCS. However, there are few data regarding the short course after mastectomy. In node positive disease, the role of hypofractionation schedules is limited due to afraid of late toxicity specially lymphedema. We conducted this study to assess the lymphedema in patient with high-risk early disease who received either moderate or ultra hypofractionation schedules.

Materials and methods: In this prospective study, one hundred patients received adjuvant radiotherapy using moderate or ultra hypofractionation schedules with either pT1-3 or pN0-2 were subjected for pretreatment lymphedema assessment using International Society of Lymphology staging of lymphoedema and then after radiotherapy every 3 months for 4 years. The primary end point was to assess the radiation induced lymphedema incidence and to assess factors affecting lymphedema before and after radiotherapy.

Results: Patients with modified radical mastectomy were associated with high incidence of lymphedema with significant difference compared to BCS. Eighty seven percent of patients with lymphedema had axillary dissection with significant difference compared to sentinel Lymph node biopsy. After radiotherapy, the ratio of positive node to total node dissected was associated with high incidence of lymphedema. In multivariate analysis. It was found that only axillary dissection was the most significant factor affecting lymphedema after 4 years with 4.9 odds ratio. Using either moderate hypofractionation or ultrahypofractionation had no effect on lymphedema incidence.

Conclusion: Axillary dissection is the most important risk factor for the development of lymphedema specially after radiotherapy. A higher dose per fraction did not increase the incidence of lymphedema even in patients with high-risk node positive early breast cancer.

Keywords: Lymphedema, Breast Cancer, Hypofractionation, Radiation

Introduction

The rationale behind hypofractionation is to deliver high dose per fraction over short duration without compromising the local control. It also had another advantage, to shorten the overall treatment time. ⁽¹⁾ In breast cancer, the alpha beta ratio (α/β) is around four which is slightly lower than other tumors such as head and neck. The lower the ratio the higher the dose per fraction is needed to compensate for the slower proliferating tumors. ⁽²⁾ Also, the overall treatment time could affect the local recurrence



of breast cancer which is increased with long duration of treatment.⁽³⁾ The role of hypofractionation schedules in node positive breast cancer are limited due to afraid of late toxicity specially lymphedema. Most of the lymphedema incidence was attributed to axillary dissection and heavy nodal infiltration.^(4, 5) However, the addition of nodal irradiation increases the incidence of lymphedema. In a systematic review, the incidence of arm lymphedema was 17% after nodal irradiation.⁽⁶⁾ Nodal irradiation was limited to less than 30 % of patients in Start A and B trials that lead to limit in the use of hypofractionation schedules in multiple lymph node involvement⁽³⁾. Furthermore, a new concept was introduced to finish the full course of treatment over one week as in the Fast Forward trial with local control was 2.4%, 2.1% and 1.7 % for 50 Gy, 27 Gy and 26 Gy respectively.⁽⁷⁾ With such extremes doses, we need a long data about late toxicities specially lymphedema. So, we conducted this study to detect the effects of such schedules on lymphedema incidence.

Methods

Patients

Female patients with non-metastatic breast cancer who received adjuvant hypofractionation radiotherapy either moderate 40 Gy/15 fractions or 26 Gy/5 fractions in alternative days were included. Patients with pathological T4 or N3 were excluded from the study.

In this prospective study, patients included were subjected to pre radiotherapy assessment using International Society of Lymphology staging of lymphoedema and were subjected to follow up every 3-6 months in the first four years.

Primary endpoints

1. Difference between incidences of Radiation induced limb lymphedema in moderate hypofractionation and ultra hypofractionation groups.
2. Factors affecting Radiation induced limb lymphedema.

Assessment of primary endpoints

Lymphedema was assessed clinically using International Society of Lymphology staging of lymphoedema and reordered at baseline and at every visit starting from 6 months after radiotherapy till four years after radiotherapy.

Statistics

Data were fed to the computer and analyzed using IBM SPSS software package version 26. Comparison between both treatment groups was done using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square



was conducted using Fisher's exact test or Monte Carlo correction. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

Comparison between mean was done using t test.

Logistic univariate regression was used to assess the effect of several factors on lymphedema. Multivariate logistic analysis was done to detect the most significant confounding factors. Model fit and assumptions were checked to ensure robustness, and statistical significance was set at $p < 0.05$. Analyses were performed.

Statistical analysis was conducted to evaluate the association between pre-radiotherapy arm lymphedema and post-radiotherapy arm lymphedema. Odds ratios (OR) with 95% confidence intervals (CI) were used as the primary measure of association.

Results

During the period from 2019 to 2021, one hundred non metastatic female patients were included from Alexandria clinical oncology department. Regarding Baseline characteristic, Median age was 56 years and most of the patients were postmenopausal. Forty-three patients underwent modified radical mastectomy (MRM). High incidence of Axillary dissection was encountered in 72% of patients. All patients received hypofractionation schedules either moderate or ultra hypofractionation (Table 1).

Table 1 - Patients Characteristics

		Median	Count	Column N %
Age		56 (50-80)		
Menstrual	Premenopausal		19	31.7%
	Postmenopausal		41	68.3%
Diabetes	No		69	69.0%
	Yes		31	31.0%
Hypertension	No		63	63.0%
	Yes		37	37.0%
Type of Surgery	BCS		57	57.0%
	MRM		43	43.0%
Axilla Surgery	SLN		28	28.0%
	AD		72	72.0%
Radiotherapy dose	Moderate		50	50%
	Ultra		50	50%



Baseline lymphedema was 20% distributed as 15% grade 1 and 5% grade 2. After 4 years follow up, the incidence of lymphedema increased and reached 33% as 21% grade 1 and 12% grade 2 (Table 2).

Table 2 - Difference between lymphedema grades from baseline and after four years

		Baseline Lymphedema		Four-year lymphedema		P value
		Count	Column N %	Count	Column N %	
Lymphedema Grade	G0	80	80.0%	67	67.0%	
	G1	15	15.0%	21	21.0%	<0.001
	G2	5	5.0%	12	12.0%	<0.001

Table 3 - Tumor Characteristics

		Median	Count	Column N %
Tumor Size		3.0 (0.2-7)		
Node positive		1.5 (0-10)		
Total Node		11 (0-35)		
Pathology Type	IDC		96	96.0%
	ILC		2	2.0%
	Other		2	2.0%
Grade	Grade 1		4	4.3%
	Grade 2		74	78.7%
	Grade 3		16	17.0%
LVI	No		30	30%
	Yes		60	60%
	Missing		10	10%
PNI	No		66	90.4%
	Yes		7	9.6%



Regarding tumor characteristics, median tumor size was 3 cm while the median positive lymph node was 1.5. Grade 2 was the most common tumor grade similarly Lymphovascular invasion (LVI) was seen in 60% of cases.

In univariate analysis, Baseline lymphedema was higher in patients who underwent axillary dissection although nonsignificant p value. No difference regarding positive lymph node status or Extra nodal extension (ENE). There were no effects on tumor size, number of node positive, number of node dissected and ratio of positive LN and dissected Node on baseline lymphedema (Table 3).

Table 4 - Factor affecting pre radiotherapy Lymphedema

		Baseline lymphedema state				P value
		No (80)		Yes (20)		
		N	%	N	%	
Surgery	BCS	48	84.2%	9	15.8%	0.229
	MRM	32	74.4%	11	25.6%	
Axilla Surgery	SLN	25	92.6%	2	7.4%	0.072
	AD	55	75.3%	18	24.7%	
Positive Node	No	35	79.5%	9	20.5%	0.92
	Yes	45	80.4%	11	19.6%	
ENE	No	34	79.1%	9	20.9%	0.450
	Yes	17	70.8%	7	29.2%	
Number of lymph node dissection	Less than 14	56	81.2%	13	18.8%	0.665
	14 or more	24	77.4%	7	22.6%	
Quantitative variables		Mean		Mean		
Tumor Size		2.9		3.1		0.448
Positive node		2.0		2.1		0.823
Total Node dissected		11		12		0.420
Positive node dissected ratio		19.78		14.85		0.538

After four years follow up, factors affecting lymphedema postoperative were assessed (in table 3). In univariate analysis, patients with MRM were associated with high incidence of lymphedema with nonsignificant difference compared to BCS. Forty-one percent of patients with axillary dissection had lymphedema with significant difference compared to SLN. After radiotherapy, the high ratio of positive node to total node dissected was associated with high incidence of lymphedema (Table 4).

In multivariate analysis. It was found that only axillary dissection was the most significant factor affecting lymphedema after 4 years with 4.9 odds to develop lymphedema with axillary dissection compared to sentinel lymph node.



Table 5: Factor affecting post radiotherapy Lymphedema.

		Four-year lymphedema				P value
		No		Yes		
		Count	Column N %	Count	Column N %	
Surgery	BCS	40	70.2%	17	29.8%	0.438
	MRM	27	62.8%	16	37.2%	
Axilla surgery	SLN	24	88.9%	3	11.1%	0.009
	AD	43	58.9%	30	41.1%	
LN involvement	No	31	70.5%	13	29.5%	0.515
	Yes	36	64.3%	20	35.7%	
Radiotherapy	Hypofractionation	36	72.0%	14	28.0%	0.289
	Ultra- hypofractionation	31	62.0%	19	38.0%	
Anthracycline	No	13	65.0%	7	35.0%	0.894
	Yes	54	67.5%	26	32.5%	
Number of lymph node dissected	Less than 14	52	75.4%	17	24.6%	0.009
	14 or more	15	48.4%	16	51.6%	
Quantitative variables		Mean		Mean		
Tumor Size		2.8		3.1		0.370
Positive node		2.0		1.9		0.818
Total Node dissected		10		14		0.002
Positive node dissected ratio		22.06		12.30		0.153
Mean dose Level 1 Axilla		28.60		26.28		0.126
Mean dose Level 2 Axilla		25.03		23.50		0.369
Mean dose Level 3 Axilla		20.726		19.888		0.754
Mean dose SCV		16.677		18.391		0.179

Table 6: Multivariate analysis of factors affecting post radiotherapy lymphedema

	OR	Ninety-five percent Confidence interval		P value
		Lower	Upper	
Type of surgery	0.911	0.349	2.374	0.848
Axilla Surgery	4.900	1.135	21.149	0.033
Number of lymph nodes dissected	2.177	0.823	5.757	0.117
Radiotherapy schedules	2.087	0.831	5.242	0.117
Constant	0.076			< 0.001



Discussion

The main concern of any hypofractionation regimens is the late toxicity specially lymphedema. In most of hypofractionation studies, regional nodal irradiation was limited to few numbers of cases that leads to unavailability of data regarding lymphedema in node positive cases treated with hypofractionation. The incidence of lymphedema post radiotherapy in our department was published in a study done by Mohamed et al. comparing old 2D and 3D conformal radiotherapy: 55% and 16.6%, respectively.⁽⁸⁾ The incidence is four times increased when comparing axillary dissection with SLN (20% vs 6%, respectively). Pathogenesis of lymphedema post irradiation is less likely to be related to direct damage. The main reason is external compression by extensive fibrosis.⁽⁹⁾ For proper grading, arm circumferences are measured at fixed points and compared to each limb. Several techniques could be used to assess lymphedema such as ultrasound, tonometry and perometry. Tonometry principle is to evaluate tissue resistance with pressure. However, this technique lacks standard measurements.⁽¹⁰⁾ Perometer is a device using a special sensor using infrared light to evaluate the volume of the limb.⁽¹¹⁾ It is more sensitive than other modalities and can even diagnose subclinical lymphedema. Other radiological modalities could be used to confirm the diagnosis and exclude other causes of lymphedema.⁽⁹⁾ For proper staging, several grading systems could be used. The most commonly used is international Society of Lymphology (ISL) and (CTCAE).^{(12) (13)}

In current study baseline lymphedema was 20% distributed as 15% grade 1 and 5% grade 2. After 4 years follow up, the incidence of lymphedema increased and reached 33% as 21% grade 1 and 12% grade 2. The latter incidence coincides with the preliminary published result of HypoG-01 4.78 year incidences of lymphedema as it was 33% in the hypofractionation arm compared to 32.8% in normofractionation arm⁽¹⁴⁾. However, in Start A trial and Start B trials the incidence of arm lymphedema were lower than current and HypoG-01 data as the incidence was around 12% in 50Gy arm and 41.6Gy arm. But we have to emphasize that in the latter studies node positive disease was 29% and 60% of them had no axillary dissection which explains the low incidence of lymphedema in comparison to 56% node positive and 72% axillary dissection in our study and 60% node positive and 83% axillary dissection in HypoG01. Similarly, SAPHIRE trial included 324 patients with locally advanced disease received either hypo or normo fractionated regional node irradiation using proton therapy, The Lymphedema was lower in the hypo arm 29% compared to 36% in conventional arm with significant difference.⁽¹⁵⁾ Astonishing 42% patients underwent mastectomy and 68% underwent axillary lymph node dissection. Furthermore, In the Fast-Forward study comparing moderate hypofractionation radiotherapy compared to ultra hypofractionation, they reported clinical assessment regarding normal tissue effects was worse in the 27 Gy arm compared to 40 Gy and 26 Gy, and the difference was statistically significant. Breast shrinkage was the most frequently noticed in the 27 Gy



arm (8.2%) while in the 40 Gy and 26 Gy arms the incidence was around 6%.⁽⁷⁾ However, no available data regarding lymphedema occurrence in such extreme fractionations. In current study, we found no difference in lymphedema incidence after using five fractions in alternative days over fifteen fractions as 28% in moderate arm and 38% in ultra-arm experienced lymphedema with non-significant difference.

It was found that axillary dissection had a higher incidence of lymphedema compared to sentinel lymph node surgery as incidence were 41% and 11%, respectively. That is why we had to limit the use of Axillary dissection. Although it is considered the standard treatment for axillary node positive, skin and/or chest wall involvement (T4a-c) or inflammatory breast cancer (T4d).^(16, 17) However, in SLNB with few positive nodes less than three, completion dissection is not mandatory if radiotherapy to the axillary lymph nodes would be added.^(18, 19) In the past, ALND was standard of care after neoadjuvant treatment. Recently, based on several trials such as the SENTINA trial, American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, and the Canadian Sentinel Node biopsy Following Neoadjuvant Chemotherapy (SN FNAC) trial, The false negative rate (FNR) of SLN post neoadjuvant were 12.6–14.2% and this emphasized the value of dual tracer technique throughout SLN to decrease FNR.^(20, 21) Moreover, the number of SLNs removed can decrease that value based on GANEA 2 study.⁽²²⁾

Other factors were attributed to lymphedema development such as number of lymph nodes dissected, Axillary dose and obesity. It should be mentioned that the higher the number of nodes dissected (14 nodes), the more is the BCAL, and the incidence increases dramatically if extracapsular extension is encountered.⁽²³⁾ Obesity was associated with a high incidence of lymphedema.⁽²⁴⁾ However, the number of dissected lymph nodes in our study was not associated with lymphedema before radiotherapy. After radiotherapy, the effect of dissected lymph node ratio became more apparent. As incidence of lymphedema was 51.6% in 14 or more dissected lymph node compared to 24.6% in less than 14 Lymph dissected.

Furthermore, the level I and II axillary irradiation was associated with high lymphedema risk.⁽²⁵⁾ As it was found that excluding level I and II even with extension of the fields beyond the humerus head reduced lymphedema from 37% to 7%. Not the region only but the volume also affected the lymphedema risk.⁽²⁶⁾ However, that concept was not verified in current study which coincides with the result of study conducted by Mohamed et. al. .⁽⁸⁾

In study conducted by Norman et. al.⁽²⁷⁾ Anthracycline chemotherapy was associated with high incidence of lymphedema with anthracycline HR 1.46. However, this was not validated in current study.

In multivariate analysis. It was found that only axillary dissection was the most significant factor affecting lymphedema after 4 years with 4.9 odds to develop lymphedema with axillary dissection compared to sentinel lymph node.



Limitation of the study:

1. Small number of patients included
2. Depending on the use of clinical score and lack of new modalities such as Perometer for accurate assessment of lymphedema

Conflict of Interest Disclosures: No conflict of interest

Informed consent: "Informed consent was obtained from all individual participants included in the study."

Ethical Declaration: This Protocol was approved by Ethical committee of Alexandria faculty of medicine under serial number 0201263.

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

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