



## Cohort Study

# Avoiding breast cancer surgery in a select cohort of complete responders to neoadjuvant chemotherapy: The long-term outcomes

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## ABSTRACT

**Background:** Lately, there has been a resurgence of interest in de-escalation of breast surgery in complete responders to neoadjuvant chemotherapy (NAC). Advanced cytotoxic & targeted therapies have improved tumour response.

This study evaluates long-term outcomes of post-NAC breast cancer patients, in relation to their surgical management dictated by the NAC response.

**Materials and methods:** Post-NAC breast cancer patients from January 2000 to December 2010 were divided into “No surgery”, “WLE” and “Mastectomy” groups. ANOVA and Kaplan-Meier statistical analyses were used to compare overall survival (OS) and disease-free-survival (DFS) in these groups.

**Results:** This retrospective study included 121 patients with a long median follow-up of 11.5 years. At 10 years the OS was 66.10% and DFS was 59.82%. Complete NAC-responders did not undergo breast surgery but received radiotherapy. Patients were divided into No surgery (n = 28), WLE (n = 44), Mastectomy (n = 49) groups. Comparisons of OS and DFS between groups showed statistically significant differences (p = 0.0003, p = 0.0007 respectively). The no surgery group showed low local recurrence (7.14%).

**Conclusion:** The observed slightly better long-term outcomes with low local recurrences in complete NAC-responders who did not undergo breast surgery but received radiotherapy could be linked to cautious response assessment and meticulous patient selection with early, biologically favourable breast cancer.

Importance of PCR assessment cannot be underestimated if breast surgery were to be de-escalated or even omitted in complete NAC-responders.

Considering the study limitations, avoiding surgery in all complete NAC-responders may still not be the preferred option. Future appropriate clinical trials with well-defined protocols may pave the way forward.

## 1. Introduction

In the 1970's, use of neoadjuvant chemotherapy (NAC) was largely restricted to treating locally advanced, inoperable and inflammatory breast cancers. An increased understanding of tumour biology, use of gene assays along with advances in fundamental molecular research have shown to improve the medical management of breast cancer.

Breast conservation after downsizing the tumour using NAC reduces surgical morbidity and improves cosmesis without compromising oncological safety. Triple negative breast cancers (TNBC) and HER2-positive tumours now mandate the use of NAC even in small cancers where wide local excision (WLE) is still possible. The long-term outcomes of breast cancer patients post NAC have also shown considerable

improvement [1,2]. As opposed to adjuvant chemotherapy, the response to NAC can be clinically observed and radiologically monitored. NAC allows time for complex surgical planning and organisation especially in gene mutation carriers.

An appropriate assessment of the tumour response is crucial in planning individualised, less radical breast and axillary surgery post NAC. Axillary lymph nodes (LNs) are most accurately assessed by ultrasound scan (USS). Magnetic resonance imaging (MRI) has become an increasingly important modality as it is highly specific (90.70%) and sensitive (63.10%) in predicting the post-NAC tumour response in breast cancer patients [3]. A study by Sheikhabaie *et al.* demonstrated that MRI assessment is most accurate in HER2-positive cancers and TNBC [4]. Tumour response is a surrogate marker for overall survival in breast

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cancer. Advances in systemic NAC and targeted therapies improved pathological complete response (PCR) rates and hence improved recurrence-free and breast cancer specific long-term survival [5–7].

Heterogeneity in surgical management of breast and axilla post NAC continues to exist across breast units in the UK. Currently surgery following NAC is either WLE or mastectomy for the breast and appropriate axillary surgery depending on the response. Since the 1970's attempts have been made to omit breast surgery in patients showing a complete clinico-radiological response to NAC, but studies found a higher rate of loco-regional recurrence [8–10].

In our Breast Unit in the year 2000, a team of clinicians set up guidelines and advocated “no breast surgery” in patients with radiological complete response (RCR) to NAC. After MDT discussion, the surgical options were discussed with patients and breast surgery was planned in accordance with patients' preference. This was practiced until December 2010.

Lately, there has been a resurgence of interest in de-escalation of breast surgery following NAC and MD Anderson Cancer Centre is running such a trial for omission of surgery [11]. On that background, this retrospective study was carried out with the objective of evaluating the long-term outcomes of breast cancer patients who received NAC, in relation to their surgical management dictated by the response to NAC.

## 2. Methods

This study includes patients who received NAC during January 2000 to December 2010 in our breast unit. Breast cancer management practised at that time was as follows. Triple assessment was performed for all patients. MRI was only used after 2008 in 7 cases mainly for mammographically occult cancers, multifocal tumours and for accurate size assessment which was difficult on conventional imaging. USS of axilla showing morphologically suspicious LN or LN with enlarged cortex was subjected to fine needle aspiration (fine needle aspiration (FNA)). Core biopsy of axillary LNs was not routinely performed in the initial part of the study.

Patients with positive axilla, underwent staging investigations such as chest X-ray and USS-Liver. Pre-NAC marker clip insertion in the tumour was practised regularly after 2004 except in patients needing mastectomy.

All the surgical treatment options including “no surgery” were discussed with the patients who demonstrated RCR after NAC. Those who did not undergo surgery received radiotherapy (RT) to the breast. They were followed up with annual mammograms for 10 years and clinically until 2020. Some patients preferred surgery even after RCR. Partial- or non-responders to NAC underwent WLE or mastectomy depending upon residual tumour size and skin involvement.

Patients with positive axillary LNs at presentation underwent axillary LN clearance (ANC) irrespective of the response to NAC. Patients with a negative axilla at presentation underwent blue dye-guided axillary LN sampling (ANS) in the early part of the study and later sentinel lymph node biopsy (SLNB) with the dual technique using blue dye and radioactive tracer was introduced. In addition to breast and chest wall, RT included supra-clavicular fossa in patients who had more than 4 positive LNs and had not responded to NAC. Endocrine and anti-HER2 treatment was given appropriately. HER2 status was assessed on core biopsy after 2005 and considered in MDT meetings as part of the protocol to determine the use of NAC.

This practice of “no surgery” in complete responders to NAC was changed after 2010 as more evidence of high recurrence rates emerged in studies conducted by other units. Thereafter, all the patients receiving NAC underwent surgery.

This retrospective study had appropriate approval from the trust's audit department. It included breast cancer patients receiving NAC from January 2000 to December 2010. Those diagnosed with distant metastasis on staging investigations during NAC were subsequently excluded from the study. Data on patients' demographics, details of clinical,

radiological and pathological assessments, oncological and surgical treatments was collected. Analysis of data focussed primarily on the type of surgical intervention. Patients were divided into 3 groups: 1) No surgery, 2) WLE 3) Mastectomy. In addition, pathological complete responders from each of these three main groups were also compared in the subgroup analysis.

The radiological response in percentage was calculated using RECIST criteria for evaluation of target lesions [12,13] and assessed to evaluate pre- and post-NAC tumour sizes. Patients with 100% response were classified as complete responders. Partial responders showed  $\geq 30\%$ –99% response to NAC. Non-responder group included patients with 0–29% response to NAC, stable disease and progressive disease.

Dates of loco-regional or distant recurrences were documented for assessing recurrence-free survival referred to as disease-free survival (DFS) in this article. Similarly dates of deaths were documented for calculating breast cancer-related survival referred to as overall survival (OS). Non-breast cancer-related deaths were excluded (9/121 cases) from the survival calculations.

Confidentiality was maintained in compliance with the Data Protection Act 1998. For statistical inference, the means of OS and DFS were compared using one-way analysis of variance (ANOVA). Kaplan-Meier survival analysis was performed using SPSS software. The P-value was obtained using ANOVA and the Log Rank (Mantel-cox) analysis. The study has been reported in line with the STROCSS criteria [14].

## 3. Results

The number of patients included in the study was 121. Patients' mean age was 49 years (range 27–72 years).

The NAC regimes used included CMF (Cyclophosphamide, Methotrexate, Fluorouracil) and FEC (5 Fluorouracil, Epirubicin, Cyclophosphamide) [15]. However, between 2004 and 2009 the regimes used were predominantly AC/T (Adriamycin, Cyclophosphamide, followed by Taxol) and EC/T (Epirubicin, Cyclophosphamide, followed by Taxol).

The median follow-up was 11.5 years. Nine patients died following non-breast related conditions and have not been included in the survival calculations. The OS at 5 years was 72.32% (81/112) whilst at 10 years it was 66.10% (74/112). DFS at 5 years was 64.30% (72/112) and at 10 years it was 59.82% (67/112).

The dataset was divided into No surgery, WLE, and Mastectomy groups as per the surgical management.

Table 1 summarizes the number of patients and the tumour biology for each group.

### 3.1. Analysis of groups

The treatment received, recurrences and mortality in “No surgery”, “WLE” and “Mastectomy” groups are shown in Table 2.

Radiotherapy was given to SCF for 11 patients from WLE group and 15 patients from the mastectomy group. Pre-menopausal women received tamoxifen. Post-menopausal women were given anastrozole in the earlier part of the study, while subsequently letrozole was the drug of choice [16].

In the no surgery group, 1 patient died due to ovarian cancer. Four patients from each of WLE and mastectomy groups died of non-breast cancer related causes. These have been excluded from the survival analysis.

### 3.2. Comparison of OS and DFS within groups

A 10-year OS in the no surgery group was 92.60% (25/27), WLE was 65% (26/40) and in the mastectomy group, it was 48.89% (22/45).

Similarly, at 10 years, DFS in the no surgery, WLE and mastectomy groups was 88.89% (24/27), 57.50% (23/40) and 44.44% (20/45) respectively.

Table 3 and Fig. 1 show the mean OS and DFS in months for each

**Table 1**  
Data groups and tumour biology.

		No Surgery		WLE		Mastectomy	
No. of patients		28 (23.14%)		44 (36.36%)		49 (40.5%)	
Tumour Type	IDC/IDC + DCIS	23		38		28	
	ILC/ILC + DCIS	1		1		13	
	DCIS	0		2		4	
	Mixed	4		3		2	
	Other	0		0		2	
Tumour Grade	G1	1		4		4	
	G2	8		11		23	
	G3	19 (includes one axillary adeno Ca)		26		20	
	DCIS (High)	0		2		1	
	DCIS (Low-intermediate)	0		1		1	
Tumour Size (yPT)		Pre-NAC	Post-NAC	Pre-NAC	Post- Surgery	Pre-NAC	Post- Surgery
	T0	0	28	0	8	0	6
	T1	3	0	1	27	4	18
	T2	22	0	41	9	26	16
	T3	3	0	2	0	19	8
	Diffuse thickening	–	–	–	–	0	1
ER status	Positive	13		19		28	
	Negative	15		24		20	
	Not available	0		1		1	
HER2 status	Positive	9		8		10	
	Negative	11		31		30	
	Not available	8		5		9	

**Table 2**  
Treatments, recurrences and mortality in the No Surgery, WLE and Mastectomy groups.

	No Surgery	WLE	Mastectomy
Number of patients	28	44	49
Axillary surgery	ANC ANS/ SLNB	10 18	29 15
Breast Radiotherapy	28	44	45
Endocrine treatment	13	19	28
Anti-HER2 treatment	9	8	10
Local Recurrences	7.14% (2/28)	22.73% (10/44)	8.16% (4/49)
Distant Recurrences	10.71% (3/28)	27.27% (12/44)	44.9% (22/49)
Breast Cancer related mortality	7.41% (2/27)	37.50% (15/40)	55.56% (25/45)
Non-Breast cancer deaths	1	4	4

**Table 3**  
OS and DFS (months) in No Surgery, WLE and Mastectomy groups.

	No Surgery	WLE	Mastectomy
Mean OS (Months)	167	114.4	108
Mean DFS (Months)	156	104	95

group.

The OS in these three groups was compared using ANOVA and the Log Rank (Mantel-cox) analysis. Both showed a statistically significant difference in these groups with  $p = 0.0003$  and  $p = 0.001$ , respectively. Comparison of OS is plotted using Kaplan-Meier curve as shown in Fig. 2.

Similarly, the comparison of DFS in these three groups also showed significant difference on statistical analysis using ANOVA ( $p = 0.0007$ ) and the Log Rank (Mantel-cox) analysis ( $p = 0.002$ ). The Kaplan-Meier curve in Fig. 3 shows the comparison of DFS in these three groups.

### 3.3. Comparison of radiological and pathological responses to NAC within groups

As shown in Table 4, all the 28 patients in no surgery group had RCR and were considered to have a PCR even though in only 5 of them it was

proven by performing multiple core biopsies during August 2005 to July 2006.

Although RCR was noted in 3 patients from WLE group and 6 from Mastectomy group, these patients underwent surgeries as per their choice. Two patients from the mastectomy group were recommended mastectomy due to residual diffuse skin thickening.

### 3.4. Subgroup analysis of pathological complete responders

The subgroups of pathological complete responders in no surgery ( $n = 28$ ), WLE ( $n = 8$ ) and mastectomy ( $n = 7$ ) groups were compared. The mean OS and DFS in these subgroups are shown in Table 5.

Comparison of OS and DFS in pathological complete responders in these subgroups did not show any statistical difference.

## 4. Discussion

De-escalation of breast surgery with no surgical intervention is currently not in practice as previous attempts have shown higher local recurrence rates (LRR) [9,10,17]. Studies undertaken so far, lacked in standardised protocols, adequate imaging and adequacy of proving PCR after NAC. However, de-escalation of axillary surgery has been tried widely following ACOSOG Z0011 [18]. Contrary to breast cancers, chemoradiation therapy can be considered as a definitive treatment in prostate, anal, gastro-oesophageal, and laryngeal cancers [9].

In our study, the tumour sizes were assessed using mammogram and USS at initial presentation. However, some inconsistencies were noted while assessing the tumour response after the 5th or 6th cycle of NAC. In many cases the size was measured only by USS which is subjective and operator-dependent.

MRI was not performed routinely. After 2008, it was performed only in 7 cases. The ability of MRI to accurately assess the chemotherapy response and the residual disease burden has been recognised in various studies and is now well proven. MRI is more accurate in HER2-positive cancers and TNBCs compared to ER-positive/HER2-negative cancers. Combining MRI with USS or with 18F-FDG-PET is more useful in predicting RCR post NAC than MRI alone [4,19,20].

While considering the de-escalation of breast surgery in complete responders, mammography/USS/MRI alone does not prove to be sufficiently reliable to identify patients with PCR where surgery could be an overtreatment. The imaging cannot replace the histopathological diagnosis of a surgical specimen [21]. Various interventional techniques,

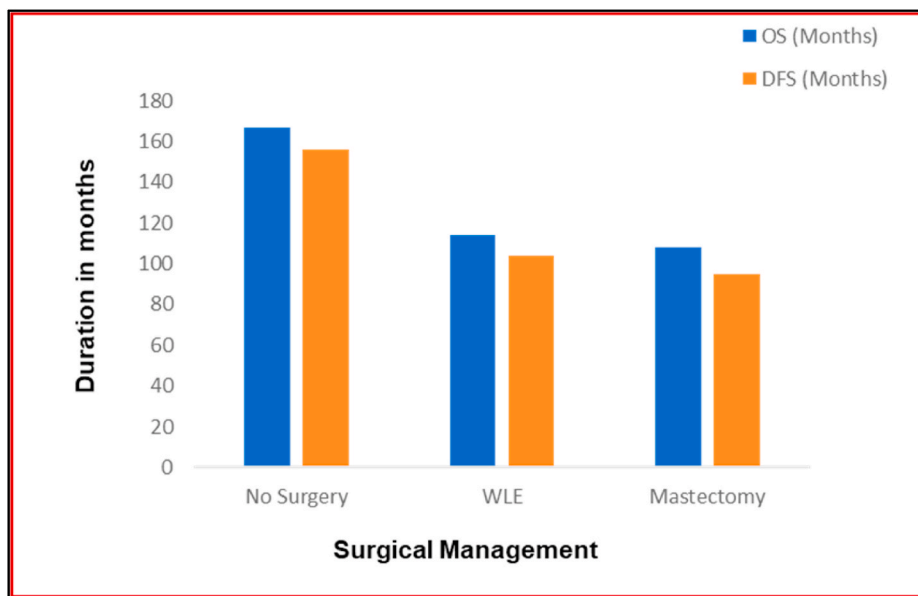


Fig. 1. Graph representing OS & DFS in No Surgery, WLE & Mastectomy groups.

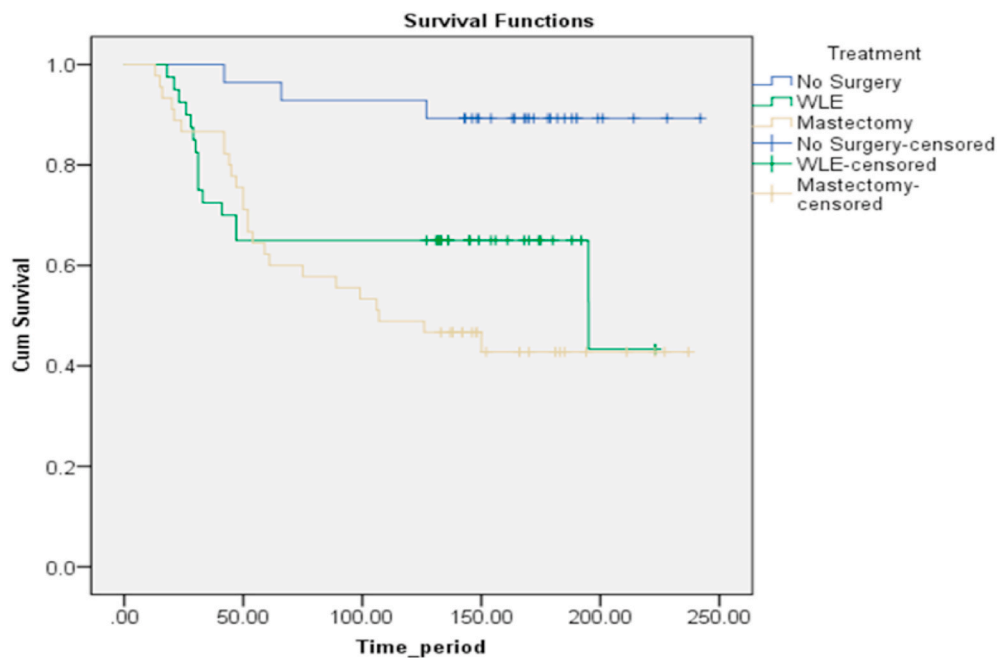


Fig. 2. Kaplan-Meier curve comparing OS in No Surgery, WLE and Mastectomy groups.

such as USS- or stereo-guided core biopsies, FNA or vacuum assisted biopsy (VAB) can be performed to prove PCR, where omission of surgery could be considered [20,22–24]. A study by Victoria Teoh *et al.* showed that image-guided VAB after NAC had 86.96% overall accuracy and 9.10% false negative rate in predicting PCR in HER2-positive cancers and TNBC [25,26]. A feasibility study for avoiding breast surgery in TNBC and HER2-positive breast cancers with complete response to NAC undertaken by M D Anderson Centre showed that the combined image guided FNA/VAB had an accuracy of 98% and a false negative rate of 5% [11]. Many other contemporary trials like MICRA [27], NOSTRA [28], RESPONDER [29] and NRG-BR005 [30], CRBr [24] continue to explore the concept of de-escalating breast surgery.

In our study 23.14% (28/121) patients had RCR and did not undergo any breast surgery. Of these, 75% (21/28) patients received

combination of EC/T chemotherapy. We observed an exceptionally low LRR of 7.14% (2/28 patients) compared to 31% observed by Daveau *et al.* [31]. Distant recurrence in this group was seen in 10.71% (3/28) patients and they have all subsequently died. One of them had lobular cancer with diffuse infiltration of breast at presentation. Post-NAC mammogram and USS showed complete response. This highlights the limitations of USS and mammograms to accurately assess the tumour response to NAC in diffuse lobular cancers. It also stresses the need for more advanced radiological techniques such as MRI, to assess the response to chemotherapy [3,4,19,20]. Another patient with bony metastasis remained stable after treatment, but she later died of ovarian cancer. This raises questions around the guidelines for genetic testing, and the even more difficult question as to whether genetic testing should be done retrospectively.

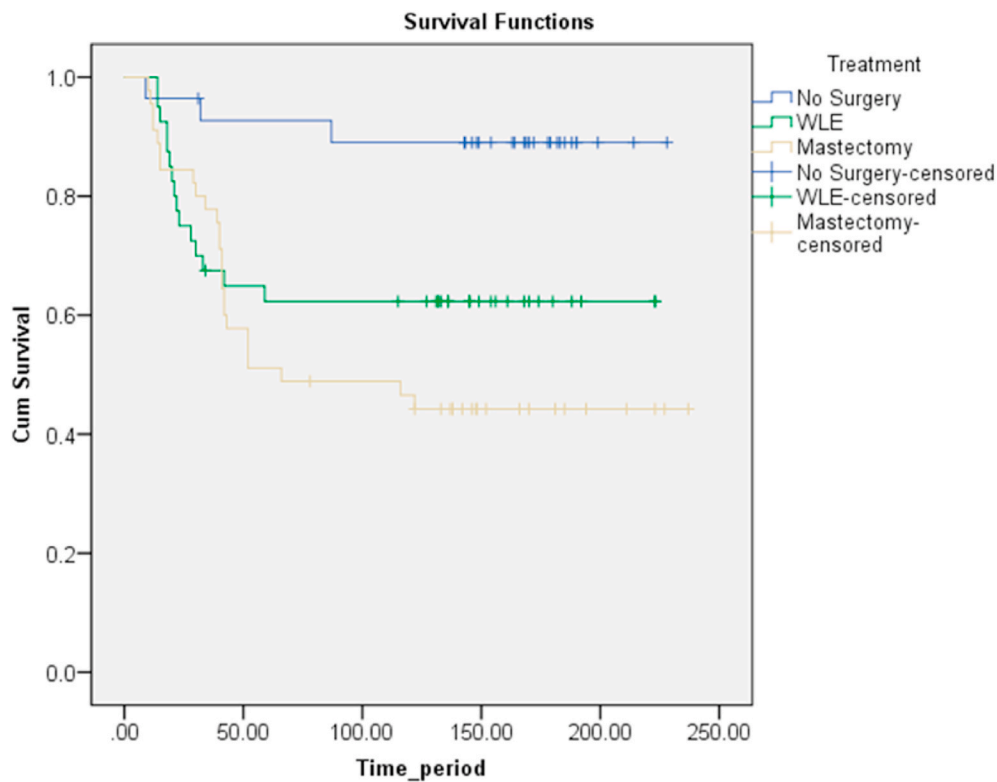


Fig. 3. Kaplan-Meier curve comparing DFS in the No Surgery, WLE and Mastectomy groups.

Table 4  
Radiological and pathological responses in No surgery, WLE & Mastectomy groups.

Surgical management	Radiological Response to NAC			Pathological Response to NAC		
	Complete Response	Partial Response	No Response	Complete Response	Partial Response	No Response
No Surgery	28	0	0	28 (5 proven by core biopsy and 23 considered as PCR)	0	0
WLE	3	38	3	8	33	3
Mastectomy	6	32	11	7	29	13

Table 5  
OS and DFS in pathological complete responders in each subgroup.

	Pathological complete responders		
	No Surgery	WLE	Mastectomy
Mean OS (months)	165.8	109.25	68.86
Mean DFS (months)	154	105	60

Although RCR was seen in 3 patients in the WLE group, patients preferred surgery. WLE was possible in these patients as they had marker clips inserted in the lesion before NAC. Two of these were TNBCs. They developed distant liver and bony recurrences and died at 40 months. TNBCs with axillary metastasis have shown to have poor prognosis [32].

The mortality rate in the mastectomy group was the highest (55.56%) among the three groups. This could be attributed to the fact that this group had large aggressive or multifocal tumours, fungating and inflammatory breast cancers requiring mastectomy. RT to chest wall & SCF had reduced loco-regional recurrences but do not appear to significantly improve the survival. LN positivity at ANC was also considerably higher in this group and predicted poor prognosis [33].

Comparisons of OS and DFS in these three groups (No surgery, WLE and Mastectomy) showed statistically significant differences [ANOVA-OS (p = 0.0003), DFS (p = 0.0007)]. The no surgery group showed the most favourable outcome with a 10-year OS of 92.60% and a 10-year DFS of 89.89% (Figs. 2 and 3). Irrespective of the type of surgery,

grade 3 tumours with no response to NAC had a poor prognosis. In a similar study to ours, Enver Özkurt *et al.* retrospectively assessed 350 patients receiving NAC who did not undergo surgery and demonstrated that the OS was better in the clinical complete response (CCR) group than in the no-CCR group (p = 0.004) [34].

When RCR and PCR were compared in these three groups (Table 3), it was found that a greater number of patients had PCR than those showing RCR in WLE and mastectomy groups. This could be attributed to cautious assessments of response to NAC using strict criteria and appropriate meticulous selection of patients.

Comparison of subgroups of pathological complete responders amongst the three main groups (No surgery, WLE and Mastectomy) indicated no statistical differences in OS and DFS (Table 5). This demonstrated that patients who underwent breast surgery did not necessarily have a better outcome, which raises the debate about avoidance of unnecessary radical surgical procedure in these exceptional pathological complete responders. This also highlights the need for accurate assessment to confirm PCR post NAC if complete omission of surgical intervention is to be considered.

In our study, although the LRR and OS in the no surgery group were better, there could be many variables which may have contributed to this outcome.

Their tumour biology might have been an important factor with less aggressive disease in the conservative group. Hence any conclusive evidence has to be very carefully extrapolated.

Authors recognise that there is likely to be a bias in patient selection due to lack of standardised methodology based on patients' cancer type and radiological assessment of tumours. Some aggressive tumours showed partial or no response to NAC and needed mastectomy. Other limitations included lack of MRI assessments and histopathological proof of PCR in patients who achieved RCR. During August 2005 to July 2006, five of these patients underwent multiple core biopsies from the tumour bed to prove the PCR similar to the study by Clouth, B *et al.* [35]. This was not practised throughout the study. Prior to 2004, not inserting a marker clip in the tumour, made it difficult to prove PCR by core biopsies. Another limitation of the study was a smaller dataset which makes comparisons and conclusions difficult. However, this study has a longer follow-up for a median period of 11.5 years.

Future trials on select groups of patients, mainly HER2-positive and TNBC, use of advanced, and more effective chemotherapy along with targeted biological treatments, accurate assessment of tumour size & response and proving PCR by performing percutaneous core or vacuum biopsies, would be of great value if no surgery is contemplated. The surgical management can be adapted to the NAC response and tailored more appropriately to the individual breast cancer [36]. A trial called "ASTARTE" has been setup by Tasoulis *et al.* to look at effects of avoiding surgery in breast cancer patients who are exceptional responders to NAC [37]. Patients with no surgery may need regular follow-up, more intensive imaging and biopsies and lifelong hormonal blockade if the tumours are ER-positive. The side effects of endocrine treatment, patients' anxiety and safety will have to be at the centre of the decision-making processes, when options are being discussed.

## 5. Conclusion

De-escalation of surgical treatment in complete responders to NAC is an ongoing debate. This study demonstrates a slightly better long-term outcome and low LRR in complete NAC-responders, who did not undergo any breast surgery but received radiotherapy. This could be linked to the cautious approach in NAC response assessment and meticulous selection of patients with early, biologically favourable breast cancer.

If breast surgery were to be de-escalated or even omitted in complete responders to NAC, the importance of accurate assessment of PCR by repeat biopsy of tumour bed cannot be overemphasised.

Considering the limitations of this study which have already been discussed, recommendation on avoiding surgery in all complete responders cannot be a foregone conclusion.

However, the observations do call for a debate on the de-escalation or even omission of surgical intervention in this subset of exceptional pathological responders. Future appropriate clinical trials with well-defined protocols may pave the way forward.

## Ethical approval

Ethical approval was not required. This retrospective study was registered with the Audit department of the institute. Audit Number: C14-07A.

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## Author contribution

**Anuradha Apte:** Conception of study, data collection and analysis, manuscript writing, corresponding author.

**Simon Marsh:** Editing the manuscript.

**Sankaran Chandrasekharan:** Review of the study design, Editing the manuscript.

**Arunmoy Chakravorty:** Writing and Editing the manuscript and

abstract.

## Consent

Not Applicable.

## Registration of research studies

1. Name of the registry: Research Registry.
2. Unique Identifying number or registration ID: researchregistry6561.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): <https://www.researchregistry.com/browse-the-registry#home/>

## Guarantor

Miss Anuradha APTE.

## Provenance and peer review

Not commissioned, externally peer reviewed.

## Declaration of competing interest

The authors have no competing interests to declare regarding this study.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102380>.

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