Author/s:
Chidley, P;Foroudi, F;Tacey, M;Khor, R;Yeh, J;Bevington, E;Hyett, A;Loh, SW;Chew, G;McCracken, J;Neoh, D;Yeo, B;Baker, C;Jassal, S;Law, M;Zantuck, N;Cokelek, M;Guerrieri, M;Brown, B;Stoney, D;Ng, M;Chao, M

Title:
Neoadjuvant radiotherapy for locally advanced and high-risk breast cancer

Date:
2021-06-01

Citation:
Chidley, P., Foroudi, F., Tacey, M., Khor, R., Yeh, J., Bevington, E., Hyett, A., Loh, S. W., Chew, G., McCracken, J., Neoh, D., Yeo, B., Baker, C., Jassal, S., Law, M., Zantuck, N., Cokelek, M., Guerrieri, M., Brown, B. ,... Chao, M. (2021). Neoadjuvant radiotherapy for locally advanced and high-risk breast cancer. Journal of Medical Imaging and Radiation Oncology, 65 (3), pp.345-353. https://doi.org/10.1111/1754-9485.13180.

Neoadjuvant Radiotherapy for Locally Advanced and High Risk Breast Cancer

Authors: Phoebe Chidley[a], Farshad Foroudi[a,b], Mark Tacey[a], Richard Khor[a], Janice Yeh[a], Elaine Bevington[a], Anthony Hyett[a], Su Wen Loh[a], Grace Chew[a], James McCracken[a], Derek Neoh[a], Belinda Yeo[a], Caroline Baker[c], Sunil Jassal[d], Michael Law[d], Natalie Zantuck[d], Margaret Cokelek[e], Mario Guerrieri[e], Belinda Brown[f], David Stoney[d], Michael Ng[e], Michael Chao[a,b,d,e]

Affiliations:

[a] Olivia Newton-John Cancer Wellness and Research Centre, Austin Health, 145 Studley Road, Heidelberg, Victoria, Australia.

[b] University of Melbourne, Melbourne, Victoria, Australia

[c] St Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, Victoria, Australia

[d] Eastern Health, 5 Arnold Street, Box Hill, Victoria, Australia

[e] Genesis Care Victoria, Ringwood Private Hospital, 36 Mount Dandenong Road, Ringwood East, Victoria, Australia

[f] Peninsula Health, 2 Hastings Road, Frankston 3199, Victoria, Australia

Corresponding Author Details:

Dr Phoebe Chidley.

Current address: Dept of Radiation Oncology, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne 3000, Victoria, Australia.

Phone: (03) 8559 5000. Mobile: 0401924570

Email: phoebe.chidley@petermac.org

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1754-9485.13180

DR. PHOEBE CHIDLEY (Orcid ID : 0000-0002-5691-7446)

A/PROF. FARSHAD FOROUDI (Orcid ID : 0000-0001-8387-0965)

Article type : Radiation Oncology Original Article

ABSTRACT:

Introduction: Neoadjuvant radiotherapy (NART) as part of a multi-modality approach for locally-advanced breast cancer (LABC) requires further investigation. Importantly, this approach may allow for a single-staged surgical procedure, with mastectomy and immediate autologous reconstruction. Multiple other potential benefits of NART include improved pathological downstaging of breast disease, reduced overall treatment time, elimination of time period with breast tissue deficit, and improved patient satisfaction.

Methods: This is a retrospective multi-institutional review of patients with LABC and high-risk breast disease undergoing NART. Eligible patients sequentially underwent neoadjuvant chemotherapy (NACT) with or without HER2-targeted therapy, NART, followed by mastectomy with immediate autologous breast reconstruction (BR) 4- 6 weeks post-completion of radiotherapy. Patient and tumour characteristics were analysed using descriptive statistics. Surgical complications were assessed using the Clavien-Dindo Classification[1].

Results: From 3/2013 to 9/2019, 153 patients were treated with NART. The median age was 47 years (IQR 42-52), with median body mass index of 27. Eighteen patients experienced Grade 3 acute surgical complications. This included 13 Grade 3B breast-site events and 9 Grade 3B donor-site events, where further surgical intervention was required for management of wound infection, wound dehiscence, flap or mastectomy skin necrosis, haematoma, and internal mammary venous anastomotic thrombosis. No autologous flap loss was observed.

Conclusion: NART facilitates a single-stage surgical procedure with mastectomy and immediate autologous BR, eliminating the delay to reconstructive surgery and thus shortening a woman's breast cancer journey. The findings of this review support the use of NART, with comparable rates of surgical complications to standard sequencing.

MeSH Keywords: Breast, Mastectomy, Neoadjuvant Therapy, Radiotherapy, Reconstructive Surgical Procedures

BODY

Introduction:

Breast cancer is the most common malignancy affecting women in the developed world and, in Australian women, it carries the second highest rate of cancer-related mortality[2]. For locally-advanced disease more aggressive management is indicated, with 5-year disease-free survival reported between 36-70%[3,4].

The treatment for locally-advanced breast cancer (LABC) has traditionally involved neoadjuvant chemotherapy (NACT), mastectomy and axillary dissection, post-mastectomy radiotherapy (PMRT), then autologous breast reconstruction (BR). Delayed BR are generally preferred to decrease risk of unfavourable surgical outcomes, especially with regards to longer term aesthetic results[5-7].

With this traditional sequence of events, there are multiple surgical procedures involved, and often a considerable lag-time before the final BR is completed. Additionally, the use of an interim tissue expander (TE) can cause considerable discomfort, with potential for severe complications. Lentz et al found a TE failure rate of up to 9.7% during the expansion period and a significantly higher number of severe complications with TE compared to immediate autologous reconstruction (55.6% vs 20.8%, *p=0.027*)[8].

NART allows for a single-staged surgical procedure, significantly shortening the overall breast cancer treatment time. Importantly for the patient, there is no time with breast tissue deficit as the BR is completed immediately. Patients experience significantly improved QOL compared to those with delayed BR[9].

From the oncological perspective, the risk of any delay in the commencement of PMRT from prolonged surgical recovery or complications is eliminated; radiotherapy dosimetric targets are more achievable without reconstructive materials in place; and there is improved likelihood of pathological downstaging and achieving a R0 resection[10]. From the healthcare service perspective, NART allows for more efficient utilisation of finite surgical resources.

Method:

The primary objective was to assess acute post-surgical complications to the breast- and donor-site following mastectomy and BR, as per the Clavien-Dindo Classification of Surgical Complications[1] (C-DC). The secondary objective was to assess rates of pathological

84 downstaging seen in the clinically-staged patient cohort. This study was approved by Austin
85 Health Ethics Committee (HREC reference number: LNR/19/Austin/11).
86
87 Patients with high risk or LABC (Stage II-III) who were deemed by their respective multi-
88 disciplinary team to require PMRT and were suitable for an autologous BR were offered NART.
89 The NART pathway included initial NACT, followed by NART after a three-week interval, and
90 finally definitive surgery with mastectomy (+/- axillary surgery) and immediate BR after a 4-6
91 week break.

92 Two different cohorts of patients were identified: clinically-staged and pathologically-staged.
93 Clinically-staged patients were assessed via clinical examination and imaging which included
94 mammogram, ultrasonography and magnetic-resonance imaging (MRI), with histological
95 confirmation obtained from the breast and axilla. Pathologically-staged patients all underwent
96 an initial wide local excision (WLE) and axillary surgery [sentinel nodal biopsy (SNB) or axillary
97 dissection (AD)] but were subsequently deemed to require a mastectomy for close or positive
98 margins, or for other considerations (gene mutation positive or patient preference).
99
100 Selection of NACT regimen was as per institutional guidelines, with use of HER2-directed
101 therapy according to HER2 status and adjuvant hormonal therapy according to hormone
102 receptor status. NART consisted of external beam radiotherapy of 50-50.4Gy (5 x 1.8-
103 2Gy/week) to the breast, supraclavicular fossa (SCF) and Level III axillary nodal volumes.
104 Further nodal coverage (internal mammary nodal (IMN) and Level I-II axilla) was undertaken at
105 the discretion of the treating radiation oncologist. Level I-II axilla was most typically included
106 when there were gross residual nodes seen post chemotherapy. Tissue equivalent bolus was
107 applied to skin surface on alternate days, except in the case of inflammatory breast cancer,
108 where daily bolus use was mandated.
109
110 Mastectomy was performed for all patients, with AD in all node-positive patients and SNB in
111 the remainder. Autologous BR was performed immediately, and techniques available included:
112 deep inferior epigastric perforator flap (DIEP), combination latissimus dorsi flap and
113 permanent implant (LD/PI), transverse rectus abdominis musculocutaneous flap (TRAM), and
114 others. Patients were evaluated at 2, 6, and 12 weeks post-operatively. Acute surgical
115 complications were defined as complications occurring within this 12-week period and scored
116 using the C-DC [1]. Events recorded included wound dehiscence, wound infection, flap necrosis

or loss, mastectomy skin necrosis, haematoma, and other acute complications, including thromboembolic events. The Miller-Payne Scoring system (M-P)[11] was utilised for assessing histological response to neoadjuvant treatment.

Descriptive statistics were prepared to compare clinically staged and pathologically staged patients and an assessment of factors associated with complications. Categorical variables are presented as counts and percentage frequencies and chi-squared or Fishers' Exact tests used to test for differences in groups. All continuous variables were skewed and thus presented as medians and inter-quartile ranges (IQR), with Mann-Whitney (ranksum) tests applied. Statistical analysis was conducted using Stata version 15.1 (StataCorp, College Station, Texas, USA) with p-values of less than 0.05 indicating statistical significance.

Results:

One hundred and fifty-three patients were treated between 3/2013 and 9/2019, with two patients treated for synchronous bilateral breast cancers, hence a total of 155 evaluable breasts. The median follow-up from date of surgery was 20.4 months (IQR 11.4-34.9). The median time interval from date of diagnosis to reconstruction surgery was 9.1 months (IQR 8.4-9.7), with a median time of 5.7 months (IQR 5.0-6.1) between date of diagnosis and completion of NACT.

The median age of the patient group was 47 years (IQR 42- 52). Five patients (3.3%) were current smokers at the time of treatment, with majority being non-smokers (83.7%). Of the 146 patients whose body mass index (BMI) was recorded, the median BMI was 27 (IQR 24-30). There were 23.5% of patients with a BMI 30-35, and 4.6% > 35. Comorbidities included hypertension (11.1%), hypercholesterolaemia (3.9%), and diabetes mellitus (2.0%).

The majority of patients (78.4%) were clinically-staged. The remaining 33 patients (21.6%) underwent pathological staging, whereby initial WLE and either AD (75.7% of pathologically-staged patients) or SNB (24.2%) were performed.

There was no statistically significant difference in median time interval from diagnosis to reconstructive surgery, with 277 days for clinically-staged and 283 days for pathologically-staged disease (p= 0.17).

There was no significant difference in staging group per clinical- versus pathological-staging detected (p=0.30). Details regarding tumour stage and histopathology is outlined in *Table i*. All patients underwent staging CT and whole-body bone scan, 3.9% PET/CT, and 18.7% MRI breast imaging.

Table i outlines further treatment information. Eighty percent of patients received 4 cycles AC and 12 cycles paclitaxel. There was a median time interval between completion of NACT to commencement of NART of 21 days (IQR 18-27). Approximately 17% of patients did not complete the full course of NACT.

For NART, the majority (96.1%) received 50 – 50.4Gy in 25-28 fractions. Nearly all patients received nodal irradiation to Level III axilla and supraclavicular fossa (98.1% and 99.4%); 20% received irradiation to internal mammary nodal (IMN) chain. NART median duration (first to last fraction) was 38 days (IQR 37-40), with median time interval to surgery of 46 days (IQR 40-51).

Skin-sparing mastectomy (SSM) in combination with AD was the most common oncological surgery performed (92 patients, 59.4%). AD was indicated for those patients who did not undergo initial AD. One patient underwent SNB without further AD. Five patients (3.2%) with inflammatory breast cancer underwent modified-radical mastectomy (MRM). DIEP reconstruction was undertaken in 85.2%. The median time from surgery to discharge from hospital was 6 days (IQR 5-7).

In clinically-staged patients, 55 (45.1%) achieved a M-P score of 5, with no viable tumour cells seen. This increased to 90% (18 patients) for the HER2-enriched phenotype. Only 3 patients (2.5%) had M-P score of 1, with no reduction in cellularity. See *Table ii.*

Using the C-DC, a total of 50 patients experienced Grade 1–3 post-operative complications, as shown in *Table iii*. There were 18 patients experiencing Grade 3 complications (*Table iv*). This included 13 Grade 3B breast-site events and 9 Grade 3B donor-site events, where further surgical intervention was required (*Table v)*. In the breast-site, this included management of wound infection (3 events, 1.9%), flap necrosis (3 events, 1.9%), mastectomy skin necrosis (5 events, 3.2%), haematoma (1 event, 0.6%), and internal mammary venous anastomotic thrombosis (1 event, 0.6%). In the donor-site, surgery was required for wound dehiscence (8 events, 5.2%), and haematoma (1 event, 0.7%). There was 1 other acute Grade 3B event for management of pericarditis. If a patient experienced more than one complication, ie breast-

and donor-site, it was counted as one patient. One patient experienced 3 Grade 3B events. No autologous flap loss occurred. There were no observed Grade 4 or 5 complications.

The presence of hypertension neared statistical significance for complication rate however other patient factors such as age, BMI, smoking and other comorbidities did not show increased risk of events. Higher NART dose was associated with higher rates surgical complications with 25% (1 in 4) of patients who received 60Gy in 30 fractions experiencing a Grade 3 breast complication ($p = 0.028$). There was an increased rate of Grade 3 breast site complications for those patients who underwent TRAM reconstruction (3 of 7 patients, 42.9%).

With a median follow-up of 20.4 months, there has been 2 patients in whom loco-regional recurrence has been identified, occurring synchronously with distant metastatic disease, within 6 months of surgery. Both patients' recurrences involved the mastectomy skin flaps, and both patients had triple negative breast cancer. In total, 16 patients have been identified to have subsequent distant metastatic disease: 5 (20.8%) of 24 triple negative cases, 5 (10.9%) of 46 HER2-enriched cases, and 6 (7.6%) of 85 Luminal A or B cases. Median time from hospital discharge to distant metastasis was 160 days (IQR: 80-160).

Discussion:

On review of available data, we have found comparable rates for post-surgical complications. Our review demonstrated a total of 18 patients (11.8% of 153 patients) requiring re-admission for management of post-surgical complications, with 22 C-DC Grade 3B events, whereby further surgical intervention was required. Breast site complications were more common (48 C-DC Grade 1-3 events in 33 patients) compared to donor site events (34 events in 25 patients). Higher NART dose (60Gy in 30 fractions) and TRAM flap reconstruction were associated with higher rates of breast complications; However sample size for both the 60Gy NART and TRAM flap groups is low, at 4 and 7 patients respectively. Less than 6% (9) patients required re-admission to hospital and further surgical intervention for donor site complications, with wound dehiscence the commonest event (11.1%). There was a trend seen for increased donor site complications with increased BMI however this did not reach statistical significance.

Monrigal et al reviewed outcomes of 210 patients, treated between 1990 and 2008 with NACT and NART. A comparable rate of early surgical revision was required (10.9%), noting that they

did allow implant reconstruction within their protocol. They had a larger cohort of TRAM flap reconstruction patients (n=56), and similarly found a significantly higher early complication rate with TRAM flap compared to latissimus dorsi reconstruction, with more necrosis, and higher surgical revision rates. They did find an increased risk of early complications in patients with a higher BMI (*p=0.*0009)[12]. Grinsell et al published their series of 29 patients with LABC (including those with bony metastatic disease) treated between 2010 and 2015 with NART, with a very low rate of surgical complications (one re-operation for haematoma)[13].

Singh et al published their systematic review of NART in 2019, reviewing 18 retrospective and prospective studies. Similar treatment schedules (6-8 weeks before surgery) and NART dose fractionation were utilised by the majority of studies, and patients underwent immediate breast reconstruction (either implant or autologous reconstructions). Post-operative complication rates varied from 3 to 26%[14]. O'Halloran et al compared outcomes for NART compared to PMRT, showing no difference in complication rates (*p=0.117*)[15].

Our cohort of relatively healthy patients with low rates of comorbidities represent a highly selected group whom the multi-disciplinary team deemed suitable candidates to undergo autologous reconstruction. The importance of collaboration within the multi-disciplinary team is paramount to ensure optimal patient selection.

NART with use of a single-staged surgical procedure eliminates time to reconstruction as well as avoiding any delay to radiotherapy due to post-surgical complications. Meta-analysis data from Whelan et al, published in 2000, demonstrates that the risk of any breast cancer recurrence, local breast recurrence and death were significantly reduced with loco-regional irradiation, and that delayed commencement of radiotherapy > 6 months from commencement of chemotherapy affected patient survival (*p=0.03*)[16].

Tansley et al summarise concerns found in the literature regarding increased rates of breast-site complications following PMRT. This includes post immediate BR (both autologous and implant-based) and with temporary TE (in anticipation of delayed BR)[17]. Variable rates of complications and morbidity are described and the optimal sequencing of events is yet to be fully defined. Autologous BR is widely shown to have lower morbidity compared to TE/PI-based BR (Barry et al meta-analysis, OR=0.21[18]). Immediate implant reconstruction is generally avoided due to increased incidence of post-radiotherapy capsular contracture, poorer cosmesis, pain and impaired wound healing[19].. Even with autologous TRAM/DIEP

reconstruction, Tansley et al summarise PMRT complications ranging from 13-44% for fat necrosis, 57-87% for flap shrinkage, 17-75% for progressive distortion of the reconstruction, and 78% for breast asymmetry[17].

Jagsi et al, though the Mastectomy Reconstruction Outcomes Consortium, reported their prospective cohort outcomes of 622 irradiated and 1625 unirradiated mastectomy patients. They also found that following PMRT, autologous reconstruction delivered lower risk of breast complications and improved patient-reported satisfaction compared to implant reconstruction. At 2 years, 38.9% of irradiated implant reconstruction patients had experienced at least one breast complication (33.2% major), compared to 25.6% of irradiated autologous reconstruction patients (17.6% major). Notably, however, within the autologous reconstruction group, they did not find differences in complication rates or breast-satisfaction scoring in irradiated versus unirradiated patients[20].

Delayed BR are advocated for by a number of groups to decrease risk of poorer surgical outcomes, particularly with regards to longer term aesthetic results[5-7], although others have found similar complication rates regardless of reconstruction timing[18], including Billig et al, with use of autologous abdominally-based breast reconstruction (complications with immediate 25.9% vs delayed 26.9%[9]). Shumway et al published a review article in May 2020 which outlines factors for consideration regarding timing and selection of reconstruction modality which may help guide clinical decision making[21].

The Clavien-Dindo Classification provided the investigators of this review with a standardised system for the recording of surgical complications, helping to ensure accurate documentation of events. This system has been validated and is used in many surgical fields but used minimally to date in NART trials.

Most literature to date shows overall pCR in 13 – 26% of patients post NACT[22,23], with highest rates of pCR in patients with HER2 positive and triple-negative disease (up to 45% respectively)[23]. The review by Singh et al showed a range of pCR in 17-55% of patients[14], which is consistent with our findings. In our clinically-staged patients pCR was achieved in 45.1% overall, with an increase to 90% for HER2-enriched and 55% for Triple Negative cases.

Previous trials have investigated the use of NART, with or without NACT, and have supported its use in terms of loco-regional control and survival, and post-surgical outcomes[12,24]. Monrigal et al found 14 cases of loco-regional relapse (LRR), with 5- and 10-year disease-free survival

(DFS) of 75.6% and 59%, and 5- and 10-year overall survival (OS) of 86.7% and 75.6%)[12]. The systematic review by Singh et al, with follow-up period range of 16.2-96 months showed 0%-10% incidence of LRR and 0%-26.3% of distant recurrence[14].

A SEER database review published by Poleszcuk et al 2017 reviewed outcomes for patients treated with either NART or adjuvant RT for early stage breast cancer, and found that there was a lower incidence of developing a second primary breast cancer following NART, and a lower rate of contralateral breast primary in patients treated with NART and mastectomy. There was no difference in OS rates between either group[25]. Their group discuss the proposal that NART may induce an anti-tumour immunity effect, helping to eradicate subclinical disease in the ipsi- and contralateral breast, as well as distant micrometastases, possibly leading to an immune memory that vaccinates against future tumours[3].

There are limited conclusions that can be drawn from these results to date regarding late complications and oncological outcomes, given the relatively short follow-up period of median 21 months. Limitations associated with the retrospective nature of this review are inherently present. . Use of patient-reported outcomes in future prospective studies should be strongly considered, as well as review of the health economics of this approach.

There is now evidence from the CREATE-X and KATHERINE trials demonstrating survival advantage with administration of further systemic therapy in those patients with residual tumour post NACT[26,27]. This needs to be taken into consideration particularly for those patients at higher risk of systemic relapse, ensuring that NART does not have a potential impact on these patients' access to further appropriate drug therapy.

Conclusion:

The use of the NART is supported by the results of this multi-institutional review, with comparable rates of acute complications, and encouraging rates of pathological tumour response. NART facilitates a single-staged surgical procedure with mastectomy and immediate autologous BR, eliminating the significant delay for reconstructive surgery, improving patient breast satisfaction, and more efficiently utilises limited health resources. Longer follow-up and

larger prospective trials are required to review late complication rates and oncological outcomes.

Acknowledgements:

No financial grants or other funding were received. We would like to acknowledge the contribution of colleagues within our treating institutions.

References:

1. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 pts and the results of a survey. Ann Surg 2004; 240:205-13, 244:931-7.
2. Australian Institute of Health and Welfare. Cancer in Australia 2019 Report. March 2019. DOI: 10.25816/5ebcc7a7fa7e9. https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019/data [Accessed 28th May, 2020].
3. Formenti S, Volm M, Skinner K, et al. Preoperative twice-weekly paclitaxel with concurrent radiation therapy followed by surgery and postoperative doxorubicin-based chemotherapy in locally advanced breast cancer: a Phase I/II trial. 2003. Journal of Clin Oncol. 21: 864-70.
4. American Joint Committee on Cancer. Cancer staging manual: breast chapter for 8th edition. Amin MB, Edge SB, Greene FL, et al (editors). https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx. [Accessed June 3rd, 2020].
5. Rogers N, Allen R. Radiation Effects on Breast Reconstruction with the Deep Inferior Epigastric Perforator Flap. Plastic and Reconstructive Surgery 2002. Vol 109; 6: 1919-1924
6. Tran N, Chang D, Gupta A, et al. Comparison of Immediate and Delayed Free TRAM Flap Breast Reconstruction in Patients Receiving Postmastectomy Radiation Therapy. Plastic and Reconstructive Surgery. 2001. Vol 108; 1: 78 -82
7. Albino F, Patel K, Smith J, Nahabedian M. Delayed versus Delayed-Immediate Autologous Breast Reconstruction: A Blinded Evaluation of Aesthetic Outcomes. Archives of Plastic Surgery. 2014. Vol 41; 3:264-270

8. Lentz R, Craig E, Higgins S, Salomon J, and Fusi S. Breast Reconstruction Outcome Study Following Radiation Therapy – Autologous DIEP (Deep Inferior Epigastric Perforator) Flap Versus Tissue Expander. European Journal of Surgical Oncology, 2012. Vol 38; 9: 875-875

9. Billig J, Jagsi R, Hamill J, et al. Should Immediate Autologous Breast Reconstruction Be Considered in Women Who Require Postmastectomy Radiation Therapy? A Prospective Analysis of Outcomes. June 2017. Plastic and Reconstructive Surgery. 139; 6: 1279-88

10. Gerlach B, Audretsch W, Gogolin F et al. Remission rates in breast cancer treated with preoperative chemotherapy and radiotherapy. Strahlenther. Onkol. 2003; 179: 306–11.

11. Ogston K, Miller I, Payne S, Hutcheon A, et al. A New Histological Grading System to Assess Response of Breast Cancers to Primary Chemotherapy: Prognostic Significance and Survival. Breast 2003;12: 320-7.

12. Monrigal E, Dauplat J, Gimbergues P, et al. Mastectomy with immediate breast reconstruction after neoadjuvant chemotherapy and radiation therapy. A new option for patients with operable invasive breast cancer. Results of a 20 years single institution study. Eur J Surg Oncol. 2011;37:864–870.

13. Grinsell D, Pitcher M, Wong S, Guerrieri M, Nielson H. Immediate autologous breast reconstruction after neoadjuvant chemoradiotherapy for breast cancer: initial results of the first 29 patients. ANZ Journal of Surgery. 2017;88:137-141.

14. Singh P, Hoffman K, Schaverien M, et al. Neoadjuvant Radiotherapy to Facilitate Immediate Breast Reconstruction: A Systematic Review and Current Clinical Trials. Ann Surg Oncol 2019; 26(10):3312-3320.

15. O'Halloran N, McVeigh T, Martin J, Keane M, Lowery A, Kerin M. Neoadjuvant chemoradiation and breast reconstruction: the potential for improved outcomes in the treatment of breast cancer. Irish J Med Sci 2019;188:75–83.

16. Whelan TJ, Julian J, Wright J, et al. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 2000;18:1220–9.

17. Tansley P, Ramsey K, Wong S, Guerrieri M, Pitcher M, Grinsell D. New treatment sequence protocol to reconstruct locally advanced breast cancer. ANZ J. Surg. 2013; 83: 630–5.

18. Barry M, Kell MR. Radiotherapy and breast reconstruction: a meta-analysis. Breast Cancer Res Treat 2011; 127: 15-22

19. Jagsi R, Jiang J, Momoh A, et al. Complications After Mastectomy and Immediate Breast Reconstruction for Breast Cancer. Ann Surg 2016; 263: 219-227

20. Jagsi R, Momoh A, Qi J, Hamill J, Billig J, et al. Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. J Natl Cancer Inst. 2018; 110(2): 157-165

21. Shumway D, Momoh A, Sabel M, Jagsi R. Integration of Breast Reconstruction and Postmastectomy Radiotherapy. J Clin Oncol. 2020; 38 (20): 2329-2338

22. Fisher E, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N. Pathobiology of preoperative chemotherapy. Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18. Cancer. 2002; 95(4);681-695. https://doi.org/10.1002/cncr.10741

23. Rouzier R, Perou C, Symmans W, Ibrahim N, Cristofanilli M, Anderson K, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Am Association for Cancer Research. 2005. 11(16):5678-85. PMID: 16115903

24. Paillocher N, Florczak A, Richard M, Classe J, et al. Evaluation of mastectomy with immediate autologous latissimus dorsi breast reconstruction following neoadjuvant chemotherapy and radiation therapy: A single institution study of 111 cases of invasive breast carcinoma. Eur J Surg Oncol. 2016; 42(7):949-955

25. Poleszczuk J, Luddy K, Chen L, et al. Neoadjuvant radiotherapy of early-stage breast cancer and long-term disease-free survival. Breast Cancer Research. 2017; 19:75. DOI 10.1186/s13058-017-0870-1

26. Masuda N, Lee S-J, Ohtani S, Im Y-H, Lee E-S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017; 376: 2147-2159. DOI: 10.1056/NEJMoa1612645

27. von Minckwitz G, Huang C-S, Mano M, Loibl S, Mamounas E, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019; 380: 617-628. DOI: 10.1056/NEJMoa1814017

Tables: *Please see separate file (landscape view)*

Tables:

Table i. Initial Tumour Staging and Treatment Received as per Clinically-Staged vs Pathologically-Staged Patients

	Combined Group	Clinically Staged	Pathologically Staged
TNM - T stage			
1	7 (4.5%)	4 (3.3%)	3 (9.1%)
2	71 (45.8%)	48 (39.3%)	23 (69.7%)
3	57 (36.8%)	51 (41.8%)	6 (18.2%)
4	19 (12.3%)	18 (14.8%)	1 (3.0%)
x	1 (0.6%)	1 (0.8%)	0 (0.0%)
TNM - N stage			
0	4 (2.6%)	4 (3.3%)	0 (0.0%)
1	98 (63.2%)	81 (66.4%)	17 (51.5%)
2	42 (27.1%)	31 (25.4%)	11 (33.3%)
3	11 (7.1%)	6 (4.9%)	5 (15.2%)
Staging Group			

2A	7 (4.5%)	5 (4.1%)	2 (6.1%)
2B	42 (27.1%)	32 (26.2%)	10 (30.3%)
3A	72 (46.5%)	58 (47.5%)	14 (42.4%)
3B	21 (13.5%)	19 (15.6%)	2 (6.1%)
3C	13 (8.4%)	8 (6.6%)	5 (15.2%)
Laterality			
Left	77 (49.7%)	61 (50.0%)	16 (48.5%)
Right	78 (50.3%)	61 (50.0%)	17 (51.5%)
Histopathological Subtype			
Invasive carcinoma NOS	138 (89.0%)	110 (90.2%)	28 (84.8%)
Invasive lobular carcinoma (ILC)	11 (7.1%)	8 (6.6%)	3 (9.1%)
Mixed Invasive NOS/ILC	4 (2.6%)	3 (2.5%)	1 (3.0%)
Micropapillary cancer	2 (1.3%)	1 (0.8%)	1 (3.0%)
Initial Tumour Grade (BRE)			
G1	3 (1.9%)	2 (1.6%)	1 (3.0%)
G2	32 (20.6%)	21 (17.2%)	11 (33.3%)
G3	120 (77.4%)	99 (81.1%)	21 (63.6%)

Initial Hormone Receptor/ HER2 Status			
ER Positive	105 (67.7%)	81 (66.4%)	24 (72.7%)
PR Positive	90 (58.1%)	68 (55.7%)	22 (66.7%)
HER2 Positive	46 (29.7%)	39 (32.0%)	7 (21.2%)
Phenotype			
HER2 Enriched	46 (29.6%)	39 (32%)	7 (21.3%)
Luminal A	26 (16.8%)	16 (13.1%)	10 (30.3%)
Luminal B	59 (38.1%)	47 (38.5%)	12 (36.4%)
Triple Negative Disease	24 (15.5%)	20 (16.4%)	4 (12.1%)
Chemotherapy regimen †			
AC x4 Taxol x12	125 (80.6%)	102 (83.6%)	23 (69.7%)
AX x4 Taxol x4	3 (1.9%)	2 (1.6%)	1 (3.0%)
FEC x3 Taxol x3	19 (12.3%)	12 (9.8%)	7 (21.2%)
FEC x4 Taxol x12	3 (1.9%)	2 (1.6%)	1 (3.0%)
TAC x6	1 (0.6%)	1 (0.8%)	0 (0.0%)
TCH x6	3 (1.9%)	3 (2.5%)	0 (0.0%)
TC x4	1 (0.6%)	0 (0.0%)	1 (3.0%)

NACT Ceased Early	27 (17.4%)	23 (18.9%)	4 (12.1%)
Her2-Directed Agents			
Trastuzumab	44 (28.4%)	37 (30.3%)	7 (21.2%)
Pertuzumab	16 (10.3%)	15 (12.3%)	1 (3.0%)
Nodal Irradiation			
Supraclavicular fossa	154 (99.4%)	121 (99.2%)	33 (100.0%)
Level 3	152 (98.1%)	119 (97.5%)	33 (100.0%)
Level 1-2	13 (8.4%)	10 (8.2%)	3 (9.1%)
Internal mammary nodal	31 (20.0%)	24 (19.7%)	7 (21.2%)
Radiotherapy Dose			
42.5Gy in 16#	1 (0.6%)	0 (0.0%)	1 (3.0%)
50Gy in 25#	31 (20.0%)	24 (19.7%)	7 (21.2%)
50.4Gy in 28#	118 (76.1%)	93 (76.2%)	25 (75.8%)
52.5Gy in 25#	1 (0.6%)	1 (0.8%)	0 (0.0%)
60Gy in 30#	4 (2.6%)	4 (3.3%)	0 (0.0%)
Surgery Group §			
SSM	150 (96.8%)	117 (95.9%)	33 (100.0%)

MRM	5 (3.2%)	5 (4.1%)	0 (0.0%)
Surgery Group			
Prophylactic Mastectomy	37 (23.9%)	26 (21.3%)	11 (33.3%)
Reconstruction Type §			
DIEP	132 (85.2%)	105 (86.1%)	27 (81.8%)
LD/PI (TE)	6 (3.9%)	5 (4.1%)	1 (3.0%)
TRAM	7 (4.5%)	4 (3.3%)	3 (9.1%)
Other	10 (6.5%)	8 (6.6%)	2 (6.1%)

Footnote: †*Chemotherapy: AC = doxorubicin, cyclophosphamide; AX = doxorubicin, capecitabine; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; TAC = docetaxel, Adriamycin, cyclophosphamide; TCH = docetaxel, carboplatin, trastuzumab; TC = docetaxel, cyclophosphamide.* § *Surgical/reconstructive procedures: SSM = skin-sparing mastectomy; MRM = modified radical mastectomy; DIEP = deep inferior epigastric perforator flap; LD/PI (TE) = latissimus dorsi flap and permanent implant (with tissue expander); TRAM = transverse rectus abdominis musculocutaneous flap.*

Table ii. Histopathological response post NACT/ NART for clinically-staged patients - Miller-Payne Score

Miller-Payne Score						
Phenotype	**1**	**2**	**3**	**4**	**5**	**Total**
HER2+	0 (0%)	0 (0%)	0 (0%)	2 (10%)	18 (90%)	20
HER2+ ER+	0 (0%)	0 (0%)	1 (5.6%)	4 (22.2%)	13 (72.2%)	18
HER2+ PR+	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1
Luminal A	0 (0%)	1 (6.3%)	3 (18.8%)	9 (56.2%)	3 (18.7%)	16
Luminal B	2 (4.3%)	3 (6.4%)	10 (21.3%)	23 (48.9%)	9 (19.1%)	47
Triple Negative	1 (5%)	0 (0%)	4 (20%)	4 (20%)	11 (55%)	20
	3 (2.5%)	4 (3.3%)	18 (14.7%)	42 (34.4%)	55(45.1%)	122

Table iii: Clavien-Dindo Classification Grade 1-3 acute surgical complications

Variable	**Any Breast Complication (n=155)**			**Any Donor Complication (n=153)**			**Total Complications (n=153)**		
	No	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
N	122	33		128	25		103	50	
Age at Diagnosis (years), median (IQR)	48 (42, 51) (n=122)	47 (42, 52) (n=33)	0.89	48 (42, 52) (n=128)	49 (42, 52) (n=25)	0.57	47 (42, 51) (n=103)	48 (42, 52) (n=50)	0.70

Age group			1.00			0.53			0.81
<=50	85 (69.7%)	23 (69.7%)		90 (70.3%)	16 (64.0%)		72 (69.9%)	34 (68.0%)	
>50	37 (30.3%)	10 (30.3%)		38 (29.7%)	9 (36.0%)		31 (30.1%)	16 (32.0%)	
Comorbidities									
Hypertension	10 (8.2%)	7 (21.2%)	0.054	15 (11.7%)	2 (8.0%)	0.74	9 (8.7%)	8 (16.0%)	0.18
Hyperlipidaemia	3 (2.5%)	3 (9.1%)	0.11	5 (3.9%)	1 (4.0%)	1.00	3 (2.9%)	3 (6.0%)	0.39
Diabetes Mellitus	1 (0.8%)	2 (6.1%)	0.11	2 (1.6%)	1 (4.0%)	0.42	1 (1.0%)	2 (4.0%)	0.25
Smoking Status			0.82			0.90			0.63
Non Smoker	101 (82.8%)	29 (87.9%)		106 (82.8%)	22 (88.0%)		84 (81.6%)	44 (88.0%)	
Ex-smoker	17 (13.9%)	3 (9.1%)		17 (13.3%)	3 (12.0%)		15 (14.6%)	5 (10.0%)	
Current Smoker	4 (3.3%)	1 (3.0%)		5 (3.9%)	0 (0.0%)		4 (3.9%)	1 (2.0%)	
BMI, median (IQR)	26 (24, 30) (n=116)	28 (25, 30) (n=32)	0.36	26 (24, 30) (n=121)	28 (25, 31) (n=25)	0.13	26 (24, 30) (n=97)	28 (25, 30) (n=49)	0.27
BMI categories			0.98			0.57			0.79
<30	82 (67.2%)	22 (66.7%)		86 (67.2%)	17 (68.0%)		69 (67.0%)	34 (68.0%)	
30-35	28 (23.0%)	9 (27.3%)		30 (23.4%)	6 (24.0%)		23 (22.3%)	13 (26.0%)	
>35	6 (4.9%)	1 (3.0%)		5 (3.9%)	2 (8.0%)		5 (4.9%)	2 (4.0%)	
Unknown	6 (4.9%)	1 (3.0%)		7 (5.5%)	0 (0.0%)		6 (5.8%)	1 (2.0%)	

Pre NACT Nodal Staging			0.66			0.045			0.51
FNA or Core Biopsy	81 (66.4%)	20 (60.6%)		85 (66.4%)	14 (56.0%)		68 (66.0%)	31 (62.0%)	
Axillary Dissection	20 (16.4%)	5 (15.2%)		23 (18.0%)	2 (8.0%)		18 (17.5%)	7 (14.0%)	
Sentinel Node Biopsy	21 (17.2%)	8 (24.2%)		20 (15.6%)	9 (36.0%)		17 (16.5%)	12 (24.0%)	
NART Nodal Irradiation									
Supraclavicular fossa and Level 3 axilla	121 (99.2%)	33 (100.0%)	0.60	127 (99.2%)	25 (100.0%)	0.66	102 (99.0%)	50 (100.0%)	0.48
Level 1-2 axilla	11 (9.0%)	2 (6.1%)	0.74	12 (9.4%)	1 (4.0%)	0.69	10 (9.7%)	3 (6.0%)	0.55
Internal Mammary Nodal	27 (22.1%)	4 (12.1%)	0.20	28 (21.9%)	3 (12.0%)	0.26	23 (22.3%)	8 (16.0%)	0.36
NART Dose			0.52			1.00			0.81
42.5Gy in 16#	1 (0.8%)	0 (0.0%)		1 (0.8%)	0 (0.0%)		1 (1.0%)	0 (0.0%)	
50Gy in 25#	23 (18.9%)	8 (24.2%)		26 (20.3%)	5 (20.0%)		19 (18.4%)	12 (24.0%)	
50.4Gy in 28#	95 (77.9%)	23 (69.7%)		96 (75.0%)	20 (80.0%)		80 (77.7%)	36 (72.0%)	
52.5Gy in 25#	1 (0.8%)	0 (0.0%)		1 (0.8%)	0 (0.0%)		1 (1.0%)	0 (0.0%)	
60Gy in 30#	2 (1.6%)	2 (6.1%)		4 (3.1%)	0 (0.0%)		2 (1.9%)	2 (4.0%)	
Surgery Type			0.48			0.17			0.19
SSM	117 (95.9%)	33 (100.0%)		125 (96.9%)	24 (96.0%)		99 (96.1%)	49 (98.0%)	
MRM	5 (4.1%)	0 (0.0%)		4 (3.1%)	1 (4.0%)		4 (3.9%)	1 (2.0%)	
Reconstruction Type ¶			0.45			0.65			0.84

DIEP	104 (85.2%)	28 (84.8%)	107 (83.6%)	23 (92.0%)	87 (84.5%)	43 (86.0%)
LD/PI (TE)	5 (4.1%)	1 (3.0%)	6 (4.7%)	0 (0.0%)	5 (4.9%)	1 (2.0%)
TRAM	4 (3.3%)	3 (9.1%)	7 (5.5%)	0 (0.0%)	4 (3.9%)	3 (6.0%)
Other	9 (7.4%)	1 (3.0%)	8 (6.3%)	2 (8.0%)	7 (6.8%)	3 (6.0%)

Footnote: ¶ Reconstruction Type: *DIEP = deep inferior epigastric perforator flap; LD/PI (TE) = latissimus dorsi flap and permanent implant (with tissue expander); TRAM = transverse rectus abdominis musculocutaneous flap.*

Table iv: Clavien-Dindo Classification Grade 3 acute surgical complications

Variable	Grade 3 Breast Complication (n=155)			Grade 3 Donor Complication (n=153)			Total Grade 3 Complications (n=153)		
	No	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
N	145	10		144	9		135	18	
Age at Diagnosis (years), median (IQR)	47 (42, 51) (n=145)	48 (45, 52) (n=10)	0.69	47 (42, 51) (n=144)	51 (45, 54) (n=9)	0.27	47 (42, 51) (n=135)	50 (45, 54) (n=18)	0.30
Age group			0.98			0.096			0.42
<=50	101 (69.7%)	7 (70.0%)		102 (70.8%)	4 (44.4%)		95 (70.4%)	11 (61.1%)	
>50	44 (30.3%)	3 (30.0%)		42 (29.2%)	5 (55.6%)		40 (29.6%)	7 (38.9%)	
Comorbidities									

Hypertension	14 (9.7%)	3 (30.0%)	0.081	16 (11.1%)	1 (11.1%)	1.00	14 (10.4%)	3 (16.7%)	0.43
Hyperlipidaemia	5 (3.4%)	1 (10.0%)	0.33	5 (3.5%)	1 (11.1%)	0.31	5 (3.7%)	1 (5.6%)	0.53
Diabetes Mellitus	2 (1.4%)	1 (10.0%)	0.18	2 (1.4%)	1 (11.1%)	0.17	2 (1.5%)	1 (5.6%)	0.31
Smoking Status			1.00			1.00			1.00
Non Smoker	121 (83.4%)	9 (90.0%)		120 (83.3%)	8 (88.9%)		112 (83.0%)	16 (88.9%)	
Ex-smoker	19 (13.1%)	1 (10.0%)		19 (13.2%)	1 (11.1%)		18 (13.3%)	2 (11.1%)	
Current Smoker	5 (3.4%)	0 (0.0%)		5 (3.5%)	0 (0.0%)		5 (3.7%)	0 (0.0%)	
BMI, median (IQR)	26 (24, 31) (n=138)	27 (26, 30) (n=10)	0.81	26 (24, 30) (n=137)	28 (27, 33) (n=9)	0.050	26 (24, 30) (n=128)	28 (26, 31) (n=18)	0.19
BMI categories			0.90			0.41			0.57
<30	97 (66.9%)	7 (70.0%)		98 (68.1%)	5 (55.6%)		92 (68.1%)	11 (61.1%)	
30-35	34 (23.4%)	3 (30.0%)		33 (22.9%)	3 (33.3%)		30 (22.2%)	6 (33.3%)	
>35	7 (4.8%)	0 (0.0%)		6 (4.2%)	1 (11.1%)		6 (4.4%)	1 (5.6%)	
Unknown	7 (4.8%)	0 (0.0%)		7 (4.9%)	0 (0.0%)		7 (5.2%)	0 (0.0%)	
Pre NACT Nodal Staging			0.86			0.13			0.54
FNA or Core Biopsy	94 (64.8%)	7 (70.0%)		95 (66.0%)	4 (44.4%)		88 (65.2%)	11 (61.1%)	
Axillary Dissection	24 (16.6%)	1 (10.0%)		24 (16.7%)	1 (11.1%)		23 (17.0%)	2 (11.1%)	
Sentinel Node Biopsy	27 (18.6%)	2 (20.0%)		25 (17.4%)	4 (44.4%)		24 (17.8%)	5 (27.8%)	

NART Nodal Irradiation									
Supraclavicular Fossa and Level 3 axilla	144 (99.3%)	10 (100.0%)	0.79	143 (99.3%)	9 (100.0%)	0.80	134 (99.3%)	18 (100.0%)	0.71
Level 1-2 axilla	12 (8.3%)	1 (10.0%)	0.59	13 (9.0%)	0 (0.0%)	1.00	12 (8.9%)	1 (5.6%)	1.00
Internal Mammary Nodal	29 (20.0%)	2 (20.0%)	1.00	31 (21.5%)	0 (0.0%)	0.12	28 (20.7%)	3 (16.7%)	0.69
NART Dose			0.028			1.00			0.13
42.5Gy in 16#	1 (0.7%)	0 (0.0%)		1 (0.7%)	0 (0.0%)		1 (0.7%)	0 (0.0%)	
50Gy in 25#	26 (17.9%)	5 (50.0%)		29 (20.1%)	2 (22.2%)		24 (17.8%)	7 (38.9%)	
50.4Gy in 28#	114 (78.6%)	4 (40.0%)		109 (75.7%)	7 (77.8%)		106 (78.5%)	10 (55.6%)	
52.5Gy in 25#	1 (0.7%)	0 (0.0%)		1 (0.7%)	0 (0.0%)		1 (0.7%)	0 (0.0%)	
60Gy in 30#	3 (2.1%)	1 (10.0%)		4 (2.8%)	0 (0.0%)		3 (2.2%)	1 (5.6%)	
Surgery Type			0.39			0.54			0.13
Skin-Sparing Mastectomy	140 (96.6%)	10 (100.0%)		139 (96.5%)	9 (100%)		130 (96.3%)	18 (100.0%)	
Modified-Radical Mastectomy	5 (3.4%)	0 (0.0%)		5 (3.5%)	0 (0.0%)		5 (3.7%)	0 (0.0%)	
Reconstruction Type ¶			0.017			1.00			0.10
DIEP	125 (86.2%)	7 (70.0%)		121 (84.0%)	9 (100.0%)		116 (85.9%)	14 (77.8%)	
LD/PI (TE)	6 (4.1%)	0 (0.0%)		6 (4.2%)	0 (0.0%)		6 (4.4%)	0 (0.0%)	
TRAM	4 (2.8%)	3 (30.0%)		7 (4.9%)	0 (0.0%)		4 (3.0%)	3 (16.7%)	
Other	10 (6.9%)	0 (0.0%)		10 (6.9%)	0 (0.0%)		9 (6.7%)	1 (5.6%)	

Footnote: ¶ Reconstruction Type: *DIEP = deep inferior epigastric perforator flap; LD/PI (TE) = latissimus dorsi flap and permanent implant (with tissue expander); TRAM = transverse rectus abdominis musculocutaneous flap.*

Table v: Clavien-Dindo Classification Grading per Complication Type – Number of Events

	Nil	Grade 1	Grade 2	Grade 3A	Grade 3B	Grade 4
Breast Site (n=155)						
Wound Dehiscence	151 (97.5%)	3 (1.9%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wound Infection	139 (89.7%)	0 (0.0%)	11 (7.1%)	2 (1.3%)	3 (1.9%)	0 (0.0%)
Flap Necrosis	148 (95.5%)	2 (1.3%)	2 (1.3%)	0 (0.0%)	3 (1.9%)	0 (0.0%)
Mastectomy Skin Necrosis	142 (91.7%)	7 (4.5%)	1 (0.6%)	0 (0.0%)	5 (3.2%)	0 (0.0%)
Haematoma	148 (95.5%)	5 (3.2%)	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Internal mammary venous anastomotic thrombosis	154 (99.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Donor Site (n=153)						
Wound Dehiscence	136 (88.9%)	7 (4.6%)	2 (1.3%)	0 (0.0%)	8 (5.2%)	0 (0.0%)
Wound Infection	138 (90.2%)	2 (1.3%)	12 (7.8%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Haematoma	151 (98.7%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)

Other Acute (n=153)						
Pericardial window for pericarditis	152 (99.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)