The effect of chemotherapy on the complication rates of implant and free flap breast reconstruction: A Systematic Review

Ishith Seth (ishithseth1@gmail.com)  
Bendigo Health  
https://orcid.org/0000-0001-5444-8925

Gabriella Bulloch  
The University of Melbourne Melbourne Medical School

Damien Gibson  
St George’s Hospital

Nimish Seth  
Alfred Health

David J Hunter-Smith  
Peninsula Health

Warren M Rozen  
Peninsula Health

Research Article

Keywords: Neoadjuvant systemic therapy, Adjuvant systemic therapy, Chemotherapy, complications, Free flap breast reconstruction, Implant breast reconstruction

Posted Date: December 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1144851/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Purpose

This study investigated the impact of chemotherapy on complication rates of implant and free flap breast reconstruction. The effect of timing and dosage of chemotherapy in minimizing the breast reconstruction surgery (BRS) complications were also investigated.

Methods

PRISMA guidelines were used to search relevant studies published from January 2009 to September 2021. Quality of selected studies were assessed using GRADE assessment and risk of bias was performed using Cochrane Collaboration’s tool and ROBINS-I. Rates of major and minor complications of neoadjuvant systemic therapy (NST) and adjuvant systemic therapy (AST) were compared by t-test using GraphPad Prism v.9.3.0 and P value <0.05 was considered statistically significant.

Results

A total of 19 studies comprising 49,217 patients were included. The GRADE assessment showed low risk of bias and good quality across studies. Three-hundred and twenty patients had implant reconstruction, 3,172 had flap reconstruction and 46,062 had both flap and implant reconstruction surgery. There was no significant difference in complication rates of patients between flap reconstruction surgery and implants. (P=0.4) In all studies, total complication rates for post-chemotherapy BRS patients was 46.03% compared to 32.49% without chemotherapy (P=0.09). Overall major complications rate was 14.5% (P=0.61) with NST and 21.1% (P=0.69) with AST. Minor complications rate was 28.8% (P=0.97) with NST and 39.5% (P=0.59) with AST. Complication rate of NST was lower than AST, but not statistically significant (P=0.64). No significant correlation was found between timing/duration of chemotherapy and rates of BRS complications (P=0.76).

Conclusion

No significant difference in BRS complications with and without chemotherapy was established. Despite these results suggesting little difference between NST and AST or chemotherapy in BRS complications, prospective control studies are currently limited, and more are necessary to better inform surgeons and their patients.

Introduction

Breast cancer is the most common cancer in women and the second most common site of cancer across both genders [1, 28]. In 2020, 2.3 million new cases of breast cancer were diagnosed, and 68,500 deaths
were recorded worldwide [32, 48]. One in eight women are affected by invasive breast cancer during their lifetime, and a majority need a mixture of surgery, radiation therapy, pharmacological interventions, and chemotherapy [16, 47]. Chemotherapy is a known contributor to the complication rate and burdens post-operative recovery due to its immunosuppressive effects, however the difference between pre-and post-operative chemotherapy administration on complication rates is a contentious topic.

Neoadjuvant systemic therapy (NST) involves the administration of chemotherapy prior to surgical treatment and aims to reduce tumor size in cases where this was a contraindication to surgery [18, 36]. In contrast, adjuvant systemic therapy (AST) is used after surgery to reduce the likelihood of residual cancer cell survival. Both methods reduce recurrence and mortality related to breast cancer by stopping or delaying the progression of occult micro-metastases [7, 8].

Following mastectomy, an increasing number of women are opting for breast reconstruction surgery (BRS) [34, 38]. Two major techniques for BRS exist: alloplastic implant-based breast reconstruction and autologous tissue reconstruction with the latter originating from pedicle regional flaps and free flaps [38]. Free flap BRS can present with early complications including donor and recipient site ischemia, venous congestion, necrosis, infection, hematoma, delayed wound healing, seroma, and other systemic complications [10, 37]. Long-term complications may include tissue flap necrosis, fat necrosis, donor site hernia, and abdominal muscle weakness [11]. Factors for post-operative BRS complications include chemotherapy, radiotherapy, smoking status, obesity, and chronic health conditions which interfere with normal wound healing [11].

While complete recovery and a better prognosis have been recorded in high dose chemotherapy, NST is not advisable for patients who could otherwise be treated with standard management procedures [18]. Duration and timing of chemotherapy is a critical factor for successful treatment, with a shorter duration of chemotherapy on higher doses known to be equivalent or better than longer therapies with lower doses [18]. Because of NST’s immunosuppressive effects, BRS is scheduled several weeks after NST to allow for immune system recovery and minimize complications [14, 23, 25]. For this reason, women who receive NST are not usually offered immediate BRS [21].

As it stands, the difference between NST and AST on complication rates is contentious. This will be the first systematic review to highlight the impact of chemotherapy (NST and AST) on complication rates following free flap and implant BRS, and will aid to clarify currently disputed literature. It will also complicate other factors to chemotherapy (NST and AST) success such as timing and dosage which may give insights to minimizing complications. This review will inform oncologists and surgeons about complications risk in different BRS types and guide optimal management.

Methods

Search strategy
This review adhered to the Preferred Reporting in Systematic Review & Meta-Analysis (PRISMA) guidelines and was listed retrospectively on the PROSPERO International Prospective Register of Systematic Review (CRD 420212292943). PubMed, Google Scholar, Science Direct, Cochrane CENTRAL, and trial registries (http://clinicaltrials.gov/) were searched for relevant studies published from January 2009 to September 2021. The search terms include: “neoadjuvant” “chemotherapy” OR “systemic therapy” AND “complications” AND “breast reconstruction”. The titles and abstracts of the studies were then manually screened by two authors to narrow down those relevant to this review. Finally, full texts of the studies were assessed for eligibility.

**Study selection and outcomes**

Inclusion criteria:

1. Studies with a target population including women with breast cancer who got systemic therapy before or after breast reconstruction surgery.
2. Studies that investigated the timing of systemic therapy on complications.
3. Studies that investigated the dosage of systemic therapy on complications.
4. Any study design was accepted if any one of the above criteria was met.

Exclusion criteria:

1. Studies before the year 2009.
2. Studies with less than 40 participants/patients.
3. Studies not published or translated to the English language.
4. Reviews, pre-prints, case reports, conference proceedings, conference abstracts, and letters or editorial opinions.
5. Studies on breast reconstruction surgery complications without specific reference to chemotherapy/systemic therapy.

**Data collection and extraction**

Titles and abstracts of studies identified during the search were imported into Endnote X9 (https://endote.com) for preliminary screening. Full texts of potentially relevant papers were further screened using the eligibility criteria. These were done by two independent reviewers (IS and GB), and any disparity in either selecting eligible studies or assessing findings between the two reviewers was resolved through consultation with a third reviewer (NS). The following data were collected from all the eligible studies: Year of publication, number of participants/patients, type of chemotherapy given (NST or AST), and the patients’ outcomes along with the complications.

**Data synthesis**

Data extracted from the studies were analyzed and combined in a narrative synthesis. Information from the studies were organized under subheadings. Tables and charts were used to visualize the results. The
rates of major and minor complications of NST and AST were compared by $t$-test using GraphPad Prism v.9.3.0 (GraphPad Software, San Diego, CA, USA), and $P$ value $<0.05$ was considered statistically significant.

Definitions

The major complications were defined as any of the following: partial or total flap loss, venous congestion, infection, implant/expander loss (I/E), skip flap necrosis, and wound dehiscence. Minor complications were defined as any of the following: donor wound site problems, hematoma, seroma, and fat necrosis. Donor wound site complications included any of the following: dehiscence, delayed healing, epidermolysis, donor site breakdown, and infection. Flap loss was defined as loss of circulation in the autologous flap, implant loss was defined as removal of prosthesis without immediate replacement, hematoma was defined as a collection of blood within a breast that required surgical management, seroma was defined as fluid collection that warranted aspiration, and infection was defined as localized or systemic evidence of infection that led to administration of antibiotics.

NST was defined as systemic chemotherapy administered prior to BRS, and AST was defined as systemic chemotherapy administered after BRS.

Results

A total of 83 non-duplicated publications were collected in the initial search, and 27 publications were assessed for eligibility. 21 publications fitted the inclusion criteria; however, 2 studies were later removed due to the irrelevant outcomes. The search process is illustrated in Figure 1. The interventions were variable (e.g., DIEP flap breast reconstructions, breast reconstruction using tissue expanders, TRAM flap, SGAP flap, TMG flap and SIEA flap etc.) but the focus of all selected reviews included the effects of NST breast reconstruction.

Study characteristics

Nineteen studies were analyzed in this systemic review. Four were prospective studies [29, 35, 44, 49] with one of them being randomized control trial (RCT) [35], six studies were retrospective RCT style [3, 5, 9, 12, 21, 31], and eight of them were retrospective cohort studies (Table 1) [13, 22, 24, 26, 30, 41-43, 46].

The mean age range of candidates was 46-59 years. A total of 49,217 patients were included in these 19 selected studies. All the patients were females (100%) with no male mastectomy case included in the studies. The duration of these studies ranged from three to 11 years with a mean duration of six years. Eight of the studies were conducted in the United States of America [9, 13, 21, 29, 41, 42, 44, 46]. One study was translated into English from Hebrew [22]. Fifteen studies had patients with flap reconstruction surgery [3, 22, 26, 29, 30, 31, 35, 43, 44, 49], six studies had patients with both flap and implant reconstruction surgery [9, 12, 13, 21, 42, 46] and two studies had patients with implant reconstruction
surgery [5, 24]. From the available studies, a total of 671 patients were on implants following BRS and 48,416 with flap reconstruction.

Four studies were the timing of NST administration [9, 13, 42, 46], twelve studies assessed the complication rates of BRS due to NST [3, 5, 12, 13, 22, 24, 26, 30, 31, 35, 43], and three studies investigated complications and timing of NST [21, 46, 49]. Four studies [9, 21, 46, 49] included patients of AST and NST (Table 1).

**Intervention characteristics**

Invasive ductal carcinoma was the most common breast cancer diagnosis in seven of the studies [3, 9, 21, 35, 41, 46, 49]. The type of breast cancer diagnosis was not reported in the remaining 12 studies [5, 12, 13, 21, 22, 24, 26, 29-31, 43, 44]. The most used NST chemotherapy regimen was the ACT regimen (doxorubicin hydrochloride (Adriamycin) and cyclophosphamide, followed by treatment with paclitaxel (Taxol)) and fluorouracil, epirubicin, and cyclophosphamide [3, 5, 9, 12, 21, 24, 26, 30, 31, 35, 41-44, 46, 49].

**Quality assessment**

Quality assessment was performed by Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines that reported all included studies were of good and moderate quality (n=19, 91.6%). Points were given based on the four indicators: random sequence: yes 1 no 0, allocation concealment: yes 1 no 0, complete outcome data: yes 1 no 0, selective reporting: yes 0 no 1 (Table 2). Any study that scored 2-3 was considered good quality and a score of 4 was regarded as an excellent quality study.

The risk of bias of the six included RCT was calculated by Cochrane Collaboration's tool [20], majority of studies had low risk (Table 3). The risk of bias of all other non-randomized studies calculated by ROBINS-I [40] was also low (Table 4). Overall, the risk of bias of the included studies was low and the quality of this systematic review was good.

**Impact of NST on complication rates in free flap and implant BRS**

Fifteen studies (2721 patients out of total 49,217 patients received NST) assessed the effect of NST on the complication rate of BRS performed (Table 5) [3, 5, 12, 13, 21, 22, 24, 26, 29-31, 35, 43, 44, 46, 49]. The major complications identified were partial or total flap loss, venous congestion, infection, hematoma, seroma, fat necrosis, and wound dehiscence. Thirteen studies concluded there was no significant difference in the complication rates of patients who received NST and those who did not [3, 5, 12, 13, 21, 22, 24, 26, 31, 35, 43, 44, 46, 49]. In the pooled analysis, when comparing BRS complications with and without NST, the overall NST patient complication rates were higher (10.61%), but not statistically significant (NST = 44.07%, Control = 33.46%, P=0.21). Based on the complications associated with the type of BRS done, 11.5% (275 out of 671 patients on implants or tissue) had complications after the procedure while 26.9% (1051 out of 48,416 with Flap reconstruction surgery) had complications. Thus it
was concluded that there was no significant difference in the complication rates of patients who had flap reconstruction surgery and those on implants or tissue expanders. (Flap = 26.9%, Implants = 11.5%, \( P=0.4 \))

In the pooled analysis, major complication rates for NST were 14.5% (\( P=0.61 \)) and 21.1% (\( P=0.69 \)) with AST, while minor complication rates were 28.8% (\( P=0.97 \)) with NST and 39.4% (\( P=0.59 \)) with AST. When comparing NST and AST, overall rate of BRS major complications with NST were lower than the overall major complications of AST but did not reach significance (\( P=0.64 \)). Similarly, the overall rate of minor complications of NST were also lower than the overall minor complications of AST without statistical difference (\( P=0.70 \)) (Table 1). Mehrara et al., concluded NST significantly increased the rate of complications [29]. Most recorded complications were of minor nature and few major complications were observed (7.7%) [29]. Decker et al., deemed wound dehiscence was significantly (\( P=0.009 \)) higher in patients who underwent BRS without NST [13]. Two other studies deemed the seromas, hematoma, and surgical site infections (SSIs) were not significantly lower in patients who received NST [22, 35].

**NST optimum timing**

Seven studies comprising of 1,810 patients (906 received NST) assessed the effect of timing on the postoperative complications of BRS [9, 21, 41, 42, 44, 46, 49]. While the time durations were variable, and no studies concluded a significant change in the complications with or without the use of NST. Postmastectomy patients with a time interval of cytotoxic chemotherapy to surgery <28 days had significantly (\( P=0.02 \)) increased wound related complications compared to the patients >28 days [41]. Cohen et al., investigated complications rates over 3 different time points and concluded NST timing had no effect on complications [9]. Complications were fewer when surgery was performed >60 days after NST, but no statistical significance was found between those who performed surgery at <30 days and 30-60 days [9]. Compared with delayed BRS following NST, immediate BRS had statistically significant higher complication rates (37.1%, \( P=0.02 \)) [21].

**AST complications and timing**

The impact of AST on postmastectomy complications was investigated in four studies [9, 21, 46, 49] and the optimum timing of administration was investigated in one [9]. When comparing AST BRS complications to no AST overall rates were higher without statistical significance (\( P=0.42 \)) in AST patients. Major and minor complications were higher without statistical significance in AST patients (\( P=0.69, P=0.59 \), respectively). Peled et al. found among NST and AST patients, the AST cohort developed significantly more (44%) postmastectomy complications compared with the NST cohort (23%, \( P=0.05 \)) [46]. These results differ from Hu et al. who found no statistical difference but more complications for NST (28.3%) than for AST (26.2%, \( P=0.72 \)) [21]. Cohen et al. concluded that postmastectomy complications can be reduced by decreasing the time span between chemotherapy and reconstruction surgery although findings were not statistically significant [9]. The impact of AST on complication rates has been summarized in Table 6.
Discussion

To date, this is the first systematic review to assess the impact of chemotherapy on complication rates following free flap and implant BRS. Complications were not significantly higher in NST or AST groups when compared with control groups, and is congruent with another recent meta-analysis [27]. In all studies, the total complication rate for post-chemotherapy BRS patients was 46.03% compared to 32.49% in patients without chemotherapy (P = 0.09). BRS major and minor complication rates were not significantly higher in AST than NST (21.1% and 14.5%, respectively for major; 39.4% versus 28.8%, respectively for minor). In our studies, there was no significant difference in the complication rates of patients who had flap reconstruction surgery and those on implants or tissue expanders, (26.9% and 11.5% respectively, P = 0.4) These findings suggest there is little significance to the type of chemotherapy, the duration/timing of chemotherapy, and whether chemotherapy effects BRS complication rates. This is a positive indication for both chemotherapy options for women with breast cancer, which may negate anxiety about the effects of NST and AST on BRS recovery.

Of the 19 included studies, 13 of them (comprising 97.1% of pooled cohort size) reported no statistically significant difference in the complication rates between patients who did and did not receive NST [3, 5, 12, 13, 21, 22, 24, 26, 31, 35, 43, 44, 46, 49]. Of these, the reported minor complications included seromas, hematoma, and SSIs, whilst major complications were partial or total flap loss, hematoma, venous congestion, seroma, infection, fat necrosis, and wound dehiscence. Overall, no significant effect was observed when comparing complication rates between patients who did or did not receive NST before BRS (Table 5 and 6).

These findings are congruent with previous systematic reviews which found the rates of surgical complications after immediate BRS were not associated with NST prior to surgery (P = 0.34) [3, 9, 21]. Song et al., considered BRS to be a safer procedure after administration of NST because pooled data showed it was not associated with increased implant/expander-based reconstruction loss OR = 1.59; 95% CI = 0.91 - 2.79) [39]. Despite these results showing promise, they are outdated and are of retrospective design which may hinder their generalizability to the current day [30, 43]. Further large, longitudinal prospective studies are required before conclusive statements are made regarding NST’s association with complication rates.

Seven of nineteen included studies (comprising of 3.9% of pooled cohort size) investigated the effect of timing on postoperative complications in patients who received NST prior to BRS [9, 21, 41, 42, 44, 46, 49]. The rate of complications varied in these cohorts but there was no significant correlation between rate of complications and timing of chemotherapy were reported (P = 0.76). Cohen et al. divided their patients into 3 stratified groups according to timing of surgery, but no statistically significant difference was observed in complication rate groups that underwent NST 0 to 30, 30 to 60 or >60 days prior to BRS (33.8%, 31.4%, and 36.4% respectively, P = 0.7) [9]. Varghese et al. and Song et al. stated NST did not show statistically significant survival benefit in comparison with AST, and so BRS should be recommended with AST rather than NST when this method is safe for the patient [39, 45].
Heeg et al. studied the impact of immediate breast reconstruction (IBR) postmastectomy on the timing of AST administration and concluded that IBR reduced the likelihood of receiving AST within 6 weeks but not between 9 or 12 weeks (OR 0.76, 95% CI=0.66-0.87) [19]. They concluded IBR is not a contraindication for patients needing AST postmastectomy.

Understanding the underlying pathophysiology of chemotherapy will help to contextualize the current findings. Chemotherapy targets proliferating cells by inducing apoptosis and necrosis, leading to death of cancerous tissue [2, 4]. Chemotherapy reduces wound strength and healing by alkylating DNA nucleotides and disrupting cell division and protein synthesis [33]. At the site of administration, cellular metabolism, angiogenesis, and cell division are inhibited, ultimately inhibiting critical pathways of wound repair [15]. Chemotherapeutic agents also alter immune functioning and cause transient aplastic anaemia which impedes normal inflammation in response to trauma, increases the risk of wound infections, alters haemostasis, and reduces oxygen delivery [17]. These effects explain the vulnerability that NST and AST patients have to wound infection, poor wound healing, and wound dehiscence, and why chemotherapy must be timed so that immune functioning recovery can occur and reduce adverse outcomes [17].

The vascular complications of chemotherapy are the result of poor specificity to cancer cells, which ultimately result in local endothelial dysfunction. Chemotherapy decreases the availability of nitric oxide which enhances platelet activity and decreases vasodilation, leading to hypercoagulable states [6]. Reduced vascular endothelial growth factors also inhibit angiogenesis needed for wound healing [6]. Hence, complications like flap loss, haemorrhage, thrombosis, and necrosis whereby the vasculature is lost may be attributed to chemotherapy.

The quality of this systematic review was determined by GRADE guidelines and found to be of good and moderate quality (n=19, 91.6%). Indirectness, which is a GRADE criteria parameter, was not utilised as this study design was such that the included studies showed a direct effect of NST on postmastectomy cancer patients and was assessed and compared with both placebo and alternate active (AST) group. In comparison to previous systematic reviews, the current study has a better GRADE score, includes a greater number of studies, and uses prospective studies [45]. Despite these strengths, there is still a deficit of prospective case/control studies in the current literature which compromises reliability of results. Furthermore, because this study is a systematic review there was no meta-analysis which would check for homogeneity of data and show degrees of error across studies. This would allow for more definitive statements to be made on chemotherapy options and complication rates.

**Conclusion**

Our findings suggest that there was no significant difference between BRS complications with and without chemotherapy. Similarly, there was no significant difference between BRS complication rates with the type of breast reconstruction surgery done, AST or NST and duration/timing of chemotherapy. Despite these results suggesting little difference between NST and AST or chemotherapy generally, there remains a strong need for prospective control studies to confirm these associations.
Declarations

Acknowledgment: None

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector. The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Authors contribution: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ishith Seth, Gabriella Bulloch, Nimish Seth, and Damien Gibson. The first draft of the manuscript was written by Ishith Seth, Gabriella Bulloch, and Damien Gibson and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability statement: Data is not publicly available, however can be available upon reasonable request to the corresponding author.

References

1. Worldwide cancer data |World Cancer Research Fund International
2. Bagnyukova TV, Serebriiskii IG, Zhou Y, Hopper-Borge EA, Golemis EA, Astsaturov I (2010) Chemotherapy and signaling: How can targeted therapies supercharge cytotoxic agents? Cancer Biol Ther 10:839–853. doi: 10.4161/cbt.10.9.13738
3. Beugels J, Meijvogel JLW, Tuinder SMH, Tjan-Heijnen VCG, Heuts EM, Piatkowski A, van der Hulst RRWJ (2019) The influence of neoadjuvant chemotherapy on complications of immediate DIEP flap breast reconstructions. Breast Cancer Res Treat 176:367–375. doi: 10.1007/s10549-019-05241-9
4. Bracci L, Schiavoni G, Sistigu A, Belardelli F (2014) Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death & Differentiation 21:15–25. doi: 10.1038/cdd.2013.67
5. Cabañuz M, Arribas MD, Romea I, Rivera M, Domínguez R, Guemes A (2019) Reconstrucción inmediata mediante implante directo tras quimioterapia neoadyuvante. ¿Es una práctica segura? Cirugía Española 97.. doi: 10.1016/j.ciresp.2019.07.003
6. Cameron AC, Touyz RM, Lang NN (2016) Vascular Complications of Cancer Chemotherapy. Can J Cardiol 32:852–862. doi: 10.1016/j.cjca.2015.12.023
7. Carlson RW, Hudis CA, Pritchard KI (2006) Adjuvant endocrine therapy in hormone receptor-positive postmenopausal breast cancer: evolution of NCCN, ASCO, and St Gallen recommendations. J Natl Compr Canc Netw 4:971–979. doi: 10.6004/jnccn.2006.0082
8. Chia S, Swain SM, Byrd DR, Mankoff DA (2008) Locally advanced and inflammatory breast cancer. J Clin Oncol 26:786–790. doi: 10.1200/jco.2008.15.0243
9. Cohen O, Lam G, Choi M, Karp N, Ceradini D (2017) Does the Timing of Chemotherapy Affect Post-Mastectomy Breast Reconstruction Complications? Clin Breast Cancer 17:307–315. doi: 10.1016/j.clbc.2017.02.003

10. Cordeiro PG, McCarthy CM (2006) A single surgeon's 12-year experience with tissue expander/implant breast reconstruction: part I. A prospective analysis of early complications. Plast Reconstr Surg 118:825–831. doi: 10.1097/01.prs.0000232362.82402.e8

11. Cordeiro PG, McCarthy CM (2006) A single surgeon's 12-year experience with tissue expander/implant breast reconstruction: part II. An analysis of long-term complications, aesthetic outcomes, and patient satisfaction. Plast Reconstr Surg 118:832–839. doi: 10.1097/01.prs.0000232397.14818.0e

12. D’Alessandro GS, Povedano A, dos Santos LKIL, Munhoz AM, Gemperli R, de Sampaio Góes JC (2017) Effect of neoadjuvant chemotherapy on women undergoing breast cancer surgery and immediate breast reconstruction with latissimus dorsi flap and silicone implants. Eur J Plast Surg 40:299–308. doi: 10.1007/s00238-016-1263-x

14. Decker MR, Greenblatt DY, Havlena J, Wilke LG, Greenberg LG, Neuman HB, Decker MR, & Greenblatt DY (2012) Impact of neoadjuvant chemotherapy on wound complications after breast surgery. J Surg Oncol 115:2012–2018. doi: 10.1007/s13199-012-9921-9

15. Franz MG, Steed DL, Robson MC (2007) Optimizing healing of the acute wound by minimizing complications. Curr Probl Surg 44:691–763. doi: 10.1067/j.cpsurg.2007.07.001

16. Gucalp A, Traina TA, Eisner JR, Parker JS, Selitsky SR, Park BH, Elias AD, Baskin-Bey ES, Cardoso F (2019) Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat 173:37–48. doi: 10.1007/s10549-018-4921-9

17. Guo S, Dipietro LA (2010) Factors affecting wound healing. J Dent Res 89:219–229. doi: 10.1177/0022034509359125

18. Hayat MA (2010) Methods of cancer diagnosis, therapy and prognosis. Volume 8:8

19. Heeg E, Harmeling JX, Becherer BE, Marang-van de Mheen PJ, Vrancken Peeters MTFD, Mureau MAM (2019) Nationwide population-based study of the impact of immediate breast reconstruction after mastectomy on the timing of adjuvant chemotherapy. Br J Surg 106:1640–1648. doi: 10.1002/bjs.11300

20. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JAC (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928. doi: 10.1136/bmj.d5928
21. Hu YY, Weeks CM, In H, Dodgion CM, Golshan M, Chun YS, Hassett MJ, Corso KA, Gu X, Lipsitz SR, Greenberg CC (2011) Impact of neoadjuvant chemotherapy on breast reconstruction. Cancer 117:2833–2841. doi: 10.1002/cncr.25872

22. Kracoff-Sella S, Allweis T, Egozi D (2020) [Does neoadjuvant chemotherapy affect the immediate postoperative complication rate after breast reconstruction?]. Harefuah 159:575–579

23. Kuerer HM, Hunt KK, Newman LA, Ross MI, Armes FC, Singletary SE (2000) Neoadjuvant chemotherapy in women with invasive breast carcinoma: conceptual basis and fundamental surgical issues. J Am Coll Surg 190:350–363. doi: 10.1016/s1072-7515(99)00272-0

24. Lardi AM, Ho-Asjoe M, Mohanna PN, Farhadi J (2014) Immediate breast reconstruction with acellular dermal matrix: factors affecting outcome. J Plast Reconstr Aesthet Surg 67:1098–1105. doi: 10.1016/j.bjps.2014.05.020

25. Lawrence WT, Talbot TL, Norton JA (1986) Preoperative or postoperative doxorubicin hydrochloride (adriamycin): which is better for wound healing? Surgery 100:9–13

26. Lee TJ, Oh TS, Kim EK, Suh H, Ahn SH, Son BH, Lee JW, Cho J, Eom JS (2016) Risk factors of mastectomy skin flap necrosis in immediate breast reconstruction using low abdominal flaps. J Plast Surg Hand Surg 50:302–306. doi: 10.3109/2000656x.2016.1170026

27. Lorentzen T, Heidemann LN, Möller S, Bille C (2021) Impact of neoadjuvant chemotherapy on surgical complications in breast cancer: A systematic review and meta-analysis. European Journal of Surgical Oncology

28. McGuire S (2016) World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv Nutr 7:418-419. doi: 10.3945/an.116.012211

29. Mehrara BJ, Santoro TD, Arcilla E, Watson JP, Shaw WW, Da Lio AL (2006) Complications after microvascular breast reconstruction: experience with 1195 flaps. Plast Reconstr Surg 118:1100–1109. doi: 10.1097/01.prs.0000236898.87398.d6

30. Moon KC, Baek SO, Yoon ES, Lee BI, Park SH (2020) Predictors affecting complications and aesthetic outcomes in autologous breast reconstruction with free muscle-sparing transverse rectus abdominis myocutaneous flaps. Microsurgery 40:38–43. doi: 10.1002/micr.30442

31. Narui K, Ishikawa T, Satake T, Adachi S, Yamada A, Shimada K, Shimizu D, Kida K, Sugae S, Ichikawa Y, Tanabe M, Sasaki T, Endo I (2015) Outcomes of immediate perforator flap reconstruction after skin-sparing mastectomy following neoadjuvant chemotherapy. Eur J Surg Oncol 41:94–99. doi: 10.1016/j.ejso.2014.09.001

32. Parada H Jr, Sun X, Tse CK, Olshan AF, Troester MA (2019) Lifestyle Patterns and Survival Following Breast Cancer in the Carolina Breast Cancer Study. Epidemiology 30:83–92. doi: 10.1097/ede.0000000000000933

33. Regan P (2007) The impact of cancer and its treatment on wound healing. Wounds UK3

34. Rojas K, Stuckey A (2016) Breast Cancer Epidemiology and Risk Factors. Clin Obstet Gynecol 59:651–672. doi: 10.1097/grf.0000000000000239
35. Schaverien MV, Munnoch DA (2013) Effect of neoadjuvant chemotherapy on outcomes of immediate free autologous breast reconstruction. Eur J Surg Oncol 39:430–436. doi: 10.1016/j.ejso.2013.02.015

36. Sharma GN, Dave R, Sanadya J, Sharma P, Sharma KK (2010) Various types and management of breast cancer: an overview. J Adv Pharm Technol Res 1:109–126

37. Sharma HR, Rozen WM, Mathur B, Ramakrishnan V (2019) 100 Steps of a DIEP Flap-A Prospective Comparative Cohort Series Demonstrating the Successful Implementation of Process Mapping in Microsurgery. Plast Reconstr Surg Glob Open 7:e2016. doi: 10.1097/gox.0000000000002016

38. Somogyi RB, Ziolkowski N, Osman F, Ginty A, Brown M (2018) Breast reconstruction: Updated overview for primary care physicians. Can Fam Physician 64:424–432

39. Song J, Zhang X, Liu Q, Peng J, Liang X, Shen Y, Liu H, Li H (2014) Impact of neoadjuvant chemotherapy on immediate breast reconstruction: a meta-analysis. PLoS ONE 9:e98225–e98225. doi: 10.1371/journal.pone.0098225

40. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan A-W, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Juni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355:i4919. doi: 10.1136/bmj.i4919

41. Sutton TL, Johnson N, Schlitt A, Gardiner SK, Garreau JR (2020) Surgical timing following neoadjuvant chemotherapy for breast cancer affects postoperative complication rates. Am J Surg 219:741–745. doi: 10.1016/j.amjsurg.2020.02.061

42. Teotia SS, Venutolo C, Haddock NT (2019) Outcomes in Patients Receiving Neoadjuvant Chemotherapy Undergoing Immediate Breast Reconstruction: Effect of Timing, Postoperative Complications, and Delay to Radiation Therapy. Plast Reconstr Surg 144:732e–742e. doi: 10.1097/prs.0000000000006112

43. Terao Y, Taniguchi K, Fujii M, Moriyama S (2017) Postmastectomy radiation therapy and breast reconstruction with autologous tissue. Breast Cancer 24:505–510. doi: 10.1007/s12282-017-0760-5

44. Thiruchelvam P, Hadjiminas D, Cleator S, Wood S, Leff D, Jallali N, James S, MacNeill F (2017) Abstract P3-14-07: Neoadjuvant radiotherapy in mastectomy and immediate autologous free flap reconstruction. Findings from the primary radiotherapy and DIEP flap (PRADA) pilot study. Cancer Res 77:P3. 14-07-P3-14-07 .. doi: 10.1158/1538-7445.Sabcs16-p3-14-07

45. Varghese J, Gohari SS, Rizki H, Faheem M, Langridge M, Kümmel S, Johnson L, Schmid P (2021) A systematic review and meta-analysis on the effect of neoadjuvant chemotherapy on complications following immediate breast reconstruction. Breast 55:55–62. doi: 10.1016/j.breast.2020.11.023
46. Warren Peled A, Itakura K, Foster RD, Hamolsky D, Tanaka J, Ewing C, Alvarado M, Esserman LJ, Hwang ES (2010) Impact of Chemotherapy on Postoperative Complications After Mastectomy and Immediate Breast Reconstruction. Arch Surg 145:880–885. doi: 10.1001/archsurg.2010.163

47. White AJ, Bradshaw PT, Hamra GB (2018) Air pollution and Breast Cancer: A Review. Curr Epidemiol Rep 5:92–100. doi: 10.1007/s40471-018-0143-2

48. World Health Organization (2021) Breast Cancer

49. Zweifel-schlatter MMD, Darhouse NM MM, Roblin PMD, Ross DMD, Zweifel MMDP, Farhadi JMD (2010) Immediate Microvascular Breast Reconstruction After Neoadjuvant Chemotherapy: Complication Rates and Effect on Start of Adjuvant Treatment. Ann Surg Oncol 17:2945–2950. doi: http://dx.doi.org/10.1245/s10434-010-1195-9

**Tables**

Tables 1-6 are available in the Supplementary Files section.

**Figures**
Figure 1

PRISMA flow diagram of selected studies

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx