

Impact of Neoadjuvant Chemotherapy on Surgical Outcomes and Bleeding Complications in Breast Cancer Patients: A Multicenter Retrospective Cohort Study

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Abstract

Background: Neoadjuvant chemotherapy (NACT) in breast cancer treatment effectively reduces tumour size and facilitates breast-conserving surgery but presents challenges such as potential postoperative complications and increased surgical difficulty due to tissue fibrosis. Although NACT does not significantly increase the risk of postoperative bleeding, factors like the timing of surgery and patient-specific characteristics must be carefully managed to optimize outcomes.

Methods: This retrospective multicentre cohort study analysed data from six centres across two countries, examining perioperative and postoperative outcomes in adult female patients who underwent breast cancer surgery from 2017 to 2021, with a focus on haemoglobin level changes, blood transfusion needs, and complications, utilising both descriptive and inferential statistical methods.

Results: The study analysed 2,620 patients with all kinds of breast cancer operations, finding that those who received NACT had a higher average resection mass ($p=0.002$) and

operation duration ($p<0.0001$), but a smaller average drop in haemoglobin levels compared to those who did not receive NACT. Despite a higher rate of blood transfusions (4.1% vs 2.1%) due to lower preoperative haemoglobin levels in the NACT group, there was no significant difference in overall complication rates between the two groups.

Conclusion: The study concludes that NACT in breast cancer patients results in lower preoperative haemoglobin levels and higher transfusion needs; but despite longer surgeries and higher resection masses, overall complication rates are comparable to those not receiving NACT, emphasising the importance of meticulous surgical planning and multidisciplinary collaboration to manage these complexities.

Keywords: *Neoadjuvant chemotherapy (NACT), breast cancer surgery, postoperative complications, wound healing and bleeding, blood-loss*

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1. Introduction

The treatment of breast cancer often requires a multimodal treatment approach, including neoadjuvant chemotherapy (NACT) followed by surgery. In the past, NACT had been associated with an effective reduction of tumour size with downstaging especially of the axilla by reducing metastasis to axillary lymph nodes, thereby facilitating surgical resection and increasing the feasibility of breast-conserving surgery. Thus, NACT may allow surgical resection of previously inoperable tumours or allow less extensive surgery in many cases. The benefits of NACT are especially crucial for patients with locally advanced breast cancer [1].

Furthermore, studies have shown that patients undergoing NACT have higher rates of breast-conserving surgery (BCS), which is significant for improving cosmetic outcomes and for reducing the psychological impact of breast cancer surgery [2, 3]. Other studies have confirmed that NACT resulted in conversion from mastectomy to BCS or to implant based reconstruction (IBR) following mastectomy in 16-17% of patients [4, 5]. While downsizing and downstaging are the most obvious benefits of NACT, NACT also gives the medical professional treating the patient the opportunity to analyse the tumour response to chemotherapy, thus facilitating decision-making process for further adjuvant chemotherapy on an individual level [5-8].

Despite these benefits, NACT is associated with several challenges that may impact surgical planning and outcomes. Its impact on postoperative complications, particularly on bleeding and operation time, for example, remains less commonly investigated. Furthermore, although tumour shrinkage is beneficial, it can be uneven, posing difficulties in accurately determining tumour margins. This discrepancy may lead to incomplete tumour resection or unnecessary removal of healthy tissue, potentially affecting cosmetic outcomes and functionality [9]. Additionally, NACT can increase breast tissue fibrosis, complicating dissections and potentially prolonging the surgery, thereby increasing the risk of complications [1]. Further problems may arise from

complications of the management of axillary lymph nodes. It can change the nodal status from positive to negative, affecting decisions about the extent of axillary surgery required. This situation requires precise evaluation to balance the benefits of node removal against the risks of lymphedema [10]. Finally, the systemic effects of NACT, such as reduced immunity and overall patient resilience, can affect postoperative recovery. These effects might increase the risk of infections and poor wound healing, posing additional challenges in the postoperative management of patients [9].

Besides that, the depression of hematopoietic and lymphopoietic cell-lines with the occurrence of neutropenia and thrombocytopenia, a common side-effect of chemotherapy, is considered one key factor for the increase of postoperative complications including postoperative bleeding after NACT [11]. However, a systematic review and meta-analysis conducted by Lorentzen *et al.* (2021) which examined the impact of NACT on surgical complications in breast cancer patients further investigated this topic. The analysis pooled data from numerous studies to assess the broader implications of NACT on postoperative outcomes. The findings indicated that NACT doesn't significantly elevate the risk of overall postoperative complications, including bleeding, thus can be administered without substantially increasing the risks of postoperative complications bleeding [12]. However, studies confirming these findings are scarce and further investigations are needed to better assess risks associated with NACT.

The timing of surgery after the completion of NACT, known as the time to surgery (TTS), is also a crucial factor. A study by Sutton *et al.* (2020) highlighted that a shorter TTS was linked with a higher incidence of wound complications, which included bleeding. The authors suggested that extending the interval between the end of chemotherapy and the surgical procedure could potentially lower the risk of such complications, indicating the need for strategic surgical planning to optimize patient outcomes [13].

Furthermore, the type of chemotherapy regimen and its specific agents are also pivotal factors. Some agents

might be associated with greater disruption to coagulation processes or platelet counts, thereby influencing bleeding risks differently, especially regimens containing agents known to cause marrow suppression.

In addition to chemotherapy type and TTS, individual patient characteristics significantly influence postoperative bleeding risks. Factors such as age, overall health status, and pre-existing conditions like diabetes or hypertension can affect how a patient responds to surgery following NACT. These patient-specific variables must also be considered. Consequently, it remains unclear to which degree the postoperative complications in general and the postoperative bleeding in particular are increased due to NACT and to which degree this may be attributed to other above-mentioned factors.

2. Materials and Methods

This study was conducted as a retrospective multicentre cohort study with six centres from two countries included in the data analysis from 2017 to 2021. These six centres were LMU Munich, Medical University of Innsbruck, Medical University of Vienna, Hanusch hospital, Clinic Ottakring, and Clinic Hietzing. The study was approved by the ethics committees of the Medical University of Vienna and the City of Vienna. Inclusion criteria were defined as all female patients aged 18 to 99 years who underwent unilateral breast cancer operation within this timeframe. Criteria were set to exclude male patients, individuals under 18 years of age, or those undergoing bilateral surgeries. The study was approved from several ethic committees attached to our centres. First permission was from the ethic committee of the medical university of Vienna with the number 1353/2022.

Data were systematically collected from clinical records, anonymised, and analysed in accordance with ethical guidelines to ensure patient confidentiality. The dataset included comprehensive demographic details, clinical characteristics, and perioperative and postoperative outcomes. Primary variables assessed were age, body mass index (BMI), menopausal status,

smoking habits, and comorbidities. The primary outcome focused on the haemoglobin level differences before and after surgery. Furthermore, the necessity of blood transfusions, postoperative complications, duration of surgery, as well as mass of resection were assessed.

Statistical analyses were performed using IBM SPSS Statistics Version 29.0.0.0 as well as Microsoft Excel 365, where patients were stratified based on whether they received neoadjuvant therapy. Both descriptive and inferential statistical methods were used to explore the data. Descriptive statistics helped characterize the demographic and clinical profiles of the study cohorts, while inferential statistics, including independent sample t-tests and Chi-square tests, addressed primary and secondary research questions.

3. Results

The present study included 2,620 patients who underwent breast cancer surgery. Of these, 714 (27.2%) received NACT, while 1,906 (72.8%) did not. The average age at surgery was 54.9 years (SD = 12.6) in the NACT group, compared to 61.8 years (SD = 13.1) in the non-NACT group. The BMI showed no significant difference between the groups, with an average value of 26.2 (SD = 5.3) for the NACT group and 26.3 (SD = 5.5) for the non-NACT group. The analysis of basic patient data also included tobacco consumption, comorbidities, and menopausal status. In the NACT group, 124 patients (17.4%) were smokers and 406 patients (56.9%) were non-smokers, in 184 patients there were no data to this question. In the non-NACT group, 331 patients (17.4%) reported being smokers, while 1,040 patients (54.6%) did not smoke, and 535 patients did not respond. Additionally, 211 patients (29.6%) in the NACT group reported having comorbidities, whereas 484 patients (67.8%) reported none; 19 patients did not respond.

In the non-NACT group, 785 patients (41.2%) had comorbidities, while 1,050 patients (55.1%) had none; 71 patients did not respond. Regarding menopausal status, in the NACT group, 357 patients (50%) were post-menopausal, and 239 patients (33.5%) were pre-menopausal, with 118 patients not providing this

information. In the non-NACT group, 1,302 patients (68.3%) were post-menopausal, 327 patients (17.2%) were pre-menopausal, and 277 patients did not provide

this information. An overview of the patient characteristics can be found in (Table 1).

TABLE 1. Baseline characteristics of the neoadjuvant chemotherapy (NACT) group and the non-NACT group.

	NACT group	Non-NACT group
Total	714	1906
Age (Average) [Years]	54.9 (+/- 12.6)	61.8 (+/- 13.1)
BMI [kg/m ²]	26.2 (+/- 5.3)	26.3 (+/- 5.5)
Smokers	124 (17.4%)	331 (17.4%)
Comorbidities	211 (29.6%)	785 (41.2%)
Menopause	357 (50%)	1302 (68.3%)

In addition to patient-specific characteristics, surgery-specific characteristics were also assessed. Mastectomy was necessary for 144 patients in the NACT group and 282 patients in the non-NACT group. BCS was achieved for 402 patients in the NACT group and 1,297 patients in the control group. Reconstructive surgery was performed on 166 patients in the NACT group (81 immediate breast reconstruction [IBR], 85 autologous tissue reconstruction [ATR]) and 323 patients in the control group (227 IBR, 96 ATR). Regarding IBR, a nipple-sparing mastectomy (NSM) was utilised for 35 patients in the NACT group and 96 patients in the control group. Skin-sparing mastectomy (SSM) was performed on 11 patients in the NACT group and 39 in the control group. Mastectomy with an expander was implemented for 30 patients in the NACT group and 85 in the control group. Five patients in the NACT group and seven in the control group received secondary reconstructions with an expander.

Among those reconstructed with autologous tissue, a transverse rectus abdominis myocutaneous (TRAM) flap was used for 25 patients in the NACT group and 20 in the non-NACT group; a deep inferior epigastric perforator (DIEP) flap was used for 39 patients in the NACT group and 54 in the non-NACT group; a transverse myocutaneous gracilis (TMG) was used for four patients in the NACT group and two in the control group; and a latissimus dorsi flap was performed for 14 patients in the NACT group, with one patient also receiving an implant, and 11 patients in the control group, with one additional implant recipient. Three patients in the NACT group and nine in the non-NACT group received other types of reconstructive surgeries, including vertical rectus abdominis myocutaneous (VRAM), superficial inferior epigastric artery (SIEA), anterolateral thigh (ALT), transverse upper gracilis (TUG), and profunda artery perforator (PAP) flaps. An overview of the surgical interventions can be found in (Table 2).

TABLE 2. Baseline distribution of surgical techniques in the NACT-group and the non-NACT group.

Surgery	NACT-group	Non-NACT group
BCS	402 (56.5%)	1297 (68.2%)
Mastectomy	144 (20.2%)	282 (14.8%)
IBR	81 (11.4%)	227 (11.9%)
- NSM	35	96
- SSM	11	39
- Ablation + Expander	30	85
- Only Expander (secondary reconstruction)	5	7
ATR	85 (11.9%)	96 (5.1%)
- TRAM	25	20

- DIEP	39	54
- TMG	4	2
- Latissimus Dorsi Flap	13	10
- Latissimus + implant	1	1
- Others (VRAM, SIEA, ALT, TUG, PAP)	3	9

BCS: Breast-Conserving Surgery; IBR: Implant-Based Reconstructive Surgery; NSM: Nipple-Sparing Mastectomy; SSM: skin-sparing mastectomy; ATR: autologous tissue reconstruction; TRAM: Transverse Rectus Abdominis Myocutaneous Flap; DIEP: Deep Inferior Epigastric Perforator Flap; TMG: Transverse Myocutaneous Gracilis Flap; VRAM: Vertical Rectus Abdominis Myocutaneous Flap; SIEA: Superficial Inferior Epigastric Artery Flap; ALT: Anterolateral Thigh Flap; TUG: Transverse Upper Gracilis Flap; PAP: Profunda Artery Perforator Flap.

The main analysis evaluated several parameters, including differences in haemoglobin (Hb) levels, the necessity for blood transfusions, operation duration, overall complication rates, and the mass of resection. The average decrease in Hb levels from preoperative to postoperative was 1.87 g/dl (SD = 1.42) in the NACT group and 2.26 g/dl (SD = 1.64) in the non-NACT group. The drop in Hb levels was significantly greater in the non-NACT group (p = 0.003).

Additionally, the preoperative Hb levels were significantly lower in the NACT group (11.86 g/dl) compared to the non-NACT group (13.5 g/dl), with a p-value less than 0.001. This was associated with a higher need for blood transfusions in the NACT group (26 out of 628 patients, 4.1%) compared to the non-NACT group (32 out of 1557 patients, 2.1%; p = 0.006) (Figure 1).

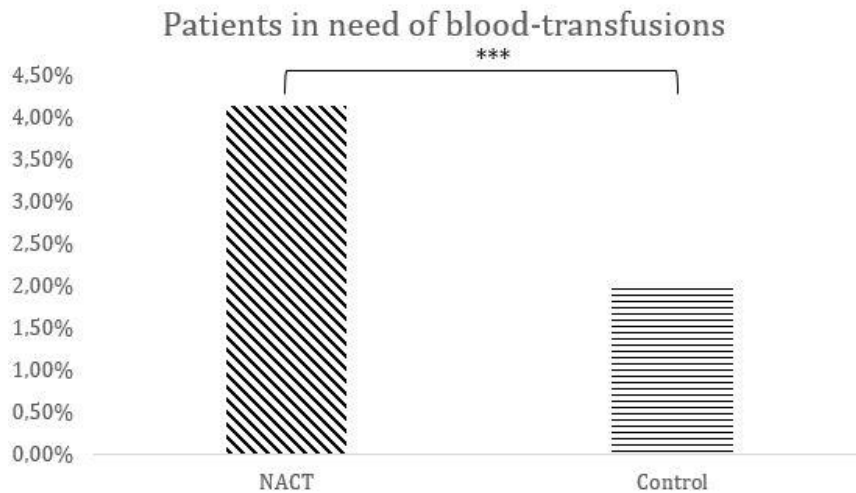


FIGURE 1. Comparison of patients, who received a blood-transfusion at least once peri- or postoperatively. The need of blood-transfusions in patients after NACT was significantly higher in context with surgery, compared to those, who didn't receive NACT (p=0.006).

Although the overall Hb difference post-operation was significantly lower in the NACT group, there was no significant difference in Hb drop within each reconstructive surgical group (IBR or ATR). However, the type of reconstruction affected the Hb drop; it was significantly higher after ATR than IBR in both the non-NACT group (3.46 g/dl vs. 2.55 g/dl; p = 0.002) and the NACT group (2.82 g/dl vs. 1.93 g/dl; p <

0.001). Also the need of blood transfusions (21.5% vs. 5.4% in the NACT group, p=0.016: 20.4% vs. 5.8% in the non-NACT group, p=0.009) and the complication rate (53% vs. 19.7% in the NACT group, p<0.001; 50% vs. 21.4% in the non-NACT group, p<0.001) was higher in the ATR compared to IBR. It was also hypothesised that the Hb difference in the NACT group might correlate with the delay of operation post-

chemotherapy. However, no correlation was found between the Hb difference and the delay post-chemotherapy, with a Pearson r of 0.02657 and a p-value of 0.74.

Despite a higher rate of bleeding complications in the non-NACT group, there was no significant difference in the overall incidence of complications, with 15.7% (112 out of 712) in the NACT group and 14.1% (265 out of 1884) in the non-NACT group (p = 0.283).

Regarding the duration of the operations, the average time was 107 minutes (SD = 98.4) for patients in the NACT group, compared to only 84.2 minutes (SD = 68.1) for those in the non-NACT group (Figure 2), with this difference being statistically significant (p < 0.001). Additionally, patients in the NACT group had a significantly higher (p=0.002) average resection mass (542.5 g) compared to those in the non-NACT group (418.9 g). An overview of all results can be found in (Table 3).

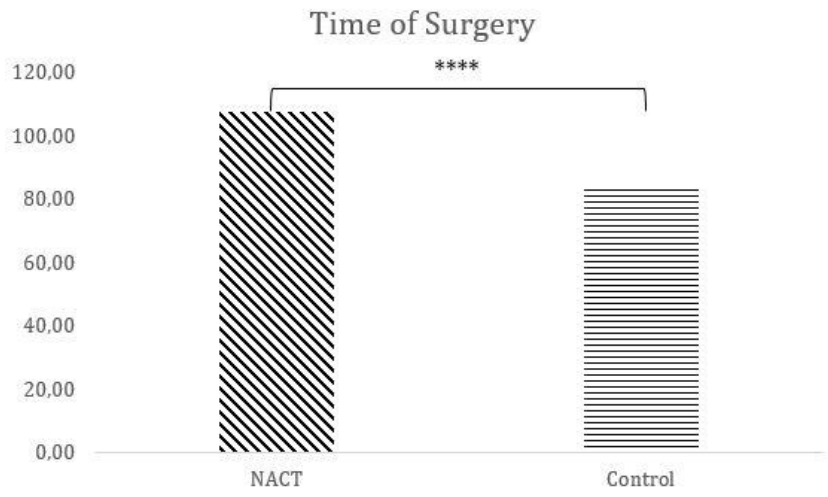


FIGURE 2. Comparison of surgery time between the NACT-group and the control-group. The NACT-group had significant longer surgery time compared to the control-group (p<0.0001).

TABLE 3. Comparison of Hb differences, blood transfusions, complications, operation durations, and mass of resections in both, the NACT-group and the non-NACT group.

	NACT-group	Non-NACT group	p-Value
Preoperative Hb	11.86 g/dl (SD = 1.36)	13.5 g/dl (SD = 1.23)	<0.001
Hb difference	1.87 g/dl (SD = 1.42)	2.26 g/dl (SD = 1.64)	0.003
Hb difference IBR	1.93 g/dl (SD = 1.13)	2.55 g/dl (SD = 1.49)	0.012
Hb difference ATR	2.82 g/dl (SD = 1.43)	3.46 g/dl (SD = 1.88)	0.023
- p-value Hb difference IBR vs. ATR	<0.001	0.002	
Blood transfusions	4.1% (26 of 628)	2.1% (32 of 1557)	0.006
- with IBR	5.4% (3 of 56)	5.8% (7 of 120)	
- with ATR	21.5% (14 of 65)	20.4% (10 of 49)	
- without reconstruction	1.8% (9 of 507)	1.1% (15 of 1386)	
Complications overall	15.7% (112 of 712)	14.1 % (265 of 1884)	0.283
- with IBR	19,7% (15 of 76)	21.4% (36 of 168)	
- with ATR	53% (35 of 66)	50% (24 of 48)	
- without reconstruction	10.9% (62 of 570)	12.2% (203 of 1666)	
Operation length	107 minutes (SD = 98.4)	84.2 minutes (SD = 68.1)	<0.001
Mass of resection	542.5 g (SD = 941.1)	418.9 g (SD = 754)	0.002

4. Discussion

The present study evaluated 2,620 patients who underwent surgery due to breast-cancer, with 714 receiving NACT and 1,906 not receiving it. Key findings included a significantly lower average age at surgery in the NACT group (54.9 years) compared to the non-NACT group (61.8 years). Preoperative Hb-levels were significantly lower in the NACT group (11.86 g/dl) versus the non-NACT group (13.5 g/dl), leading to a higher need for blood transfusions in the NACT group. The average decrease in Hb levels was greater in the non-NACT group, while the duration of surgeries was longer, and the average resection mass was higher in the NACT group. Despite these differences, the overall incidence of complications was similar between the groups. These findings underscore the complex impacts of NACT on patient and surgical outcomes.

Our study's finding of lower preoperative Hb levels in the NACT group aligns with previous research. Beresford *et al.* (2006) indicated that while pre-treatment Hb levels did not significantly influence the response to NACT, lower levels were associated with poorer overall outcomes [14]. Additionally, Ji *et al.* (2022) identified that lower baseline haemoglobin levels and significant drops after the first chemotherapy cycle were risk factors for severe anaemia and increased transfusion needs, supporting our findings [15]. The lower preoperative haemoglobin levels observed in the NACT group can be attributed to several physiological and treatment-related factors. Chemotherapy is known to cause myelosuppression. This is a well-documented side effect of many chemotherapeutic agents used in breast cancer treatment, such as anthracyclines and taxanes. Furthermore, chemotherapy can induce gastrointestinal toxicity, leading to malabsorption of nutrients essential for erythropoiesis. The chronic inflammatory state induced by cancer, exacerbated by chemotherapy, can also lead to anaemia of chronic disease, characterised by impaired iron utilisation and reduced erythropoietin response [14]. These combined effects contribute to the lower preoperative haemoglobin levels observed in patients receiving NACT.

The need for blood transfusions was higher in the NACT group, consistent with findings from Atkinson *et al.* (2011) who reported increased transfusion requirements in patients receiving NACT for bladder cancer [16]. Similarly, O'Shea *et al.* (2018) observed that ovarian cancer patients receiving NACT had higher rates of anaemia and transfusions compared to those undergoing primary surgery [17]. ATR is associated with a more significant haemoglobin drop compared to IBR. This is likely due to the extensive nature of ATR procedures, which often involve major muscle and tissue dissection, such as in TRAM or DIEP-flaps. These procedures can result in higher intraoperative blood loss and more substantial postoperative haemoglobin reductions due to the larger surgical fields and more complex vascular anastomoses required [18]. These findings have several important clinical implications. Patients receiving NACT should be closely monitored for anaemia and may benefit from preoperative optimisation strategies to improve haemoglobin levels and reduce transfusion needs [19]. Surgeons should employ techniques to minimise blood loss, such as meticulous haemostasis and intraoperative blood salvage, especially in ATR procedures [20].

In the treatment of breast cancer, it is crucial to evaluate the complications associated with different regimens, including NACT and non-NACT treatments. Despite concerns about higher rates of bleeding complications in the non-NACT group, overall complication rates appear to be similar between the two groups, as shown in our data. Lorentzen *et al.* (2021) demonstrated that NACT did not significantly increase the overall complication rate for breast cancer surgeries compared to a control group, despite a considerable difference in blood loss favouring the NACT group [12]. Similarly, a study by Srouf *et al.* (2020) reported no significant difference in 30-day postoperative morbidity among patients undergoing partial or total mastectomy after NACT compared to those who did not receive NACT. Although bilateral mastectomies had higher morbidity rates, the overall complication rates across different surgeries were similar [21]. Yang *et al.* (2021) analysed complications in immediate breast reconstruction following NACT and found no

significant differences in complication rates between patients who received NACT and those who did not. This suggests that the type of chemotherapy regimen does not significantly impact the overall complication rates [22]. Further supporting this, Chatterjee *et al.* (2015) compared early postoperative complications between BCS and simple mastectomy (SM). The study revealed that the SM group had higher rates of bleeding, wound complications, infections, and overall complications compared to the BCS group. This highlights that, while specific complications like bleeding may vary, overall complication rates can still be similar [23]. Thus, despite higher rates of bleeding complications in the non-NACT group, overall complication rates between NACT and non-NACT groups in breast cancer surgeries are comparable.

The longer operation times and higher resection masses observed in the NACT group could be attributed to the extensive tumour reduction achieved through chemotherapy, necessitating more complex surgical procedures. Additionally, NACT often blurs tumour boundaries, making it challenging for surgeons to delineate the precise margins of the tumour. This can lead to longer operation times and the resection of more healthy tissue, contributing to a higher resection mass. This finding is supported by Woeste *et al.* (2020), who noted that NACT increases the rates of breast-conserving surgery but can complicate surgical outcomes due to less clear tumour margins [24]. Furthermore, Sapunar and Smith (2000) discussed that, while it can downstage tumours, NACT may also result in complex surgical scenarios requiring careful planning [18]. Thus, surgeons should utilise advanced imaging techniques and meticulous preoperative planning to better define tumour boundaries and plan the extent of resection. MR imaging, for instance, has been shown to provide more reliable assessment of tumour size and vascularity changes during and after chemotherapy [25]. Intraoperative guidance tools, such as real-time imaging or margin assessment technologies, can help delineate tumour margins more precisely, reducing the resection of healthy tissue [26].

Additionally, a multidisciplinary team approach involving oncologists, radiologists, and surgeons is essential for optimal treatment planning and

execution, ensuring that the complexities of NACT-induced changes are effectively managed [12]. Patients should also be informed about the potential for longer surgeries and more extensive tissue removal, which can help in setting realistic expectations and preparing for postoperative recovery. These strategies can help mitigate the challenges associated with the surgical complexity induced by NACT, ultimately improving surgical outcomes and patient satisfaction.

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Conflicts of Interest

None.

Compliance with Ethical Standard

In the present study, there are no conflicts of interest to disclose. All procedures performed involving human participants adhered to the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study. This declaration aims to assure the research community and the public of our commitment to ethical conduct and integrity in our research. We understand the importance of these ethical considerations and believe that our adherence to these principles will contribute to the credibility and reliability of our findings.

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