European Journal of Surgical Oncology 51 (2025) 110511

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

# Impact of neoadjuvant immunotherapy on postoperative complications in oncoplastic breast cancer surgery

Capucine Barjot [a,g,*], Thomas Gaillard [a,g], Romain-David Seban [b,g], Lauren Darrigues [a,g], Delphine Loirat [c,g], Luc Cabel [c,g], Jean-Guillaume Feron [a,g], Virginie Fourchotte [a,g], Benoit Couturaud [a,g], Claire Bonneau [d,e,g], Kim Cao [f,g], Fabien Reyal [a,g], Enora Laas [a,g]

[a] Department of Breast, Gynecology and Reconstructive Surgery, Institut Curie, 75005, Paris, France
[b] Department of Nuclear Medicine and endocrine Oncology, Institut Curie, Saint-Cloud, France
[c] Department of Medical Oncology, Institut Curie, 75005, Paris, France
[d] Department of Breast, Gynecology and Reconstructive Surgery, Institut Curie, 92210, Saint-Cloud, France
[e] University of Versailles Saint-Quentin en Yvelines, U1331 STAMPM Team, Saint Cloud, France
[f] Department of Radiotherapy, Institut Curie, 75005, Paris, France
[g] Institut of Women Cancer, Institut Curie, Paris, France

ARTICLE INFO

*Keywords:*
Neoadjuvant pembrolizumab
Postoperative complications
Triple-negative breast cancer
Implant
Oncoplastic surgery

STRUCTURED ABSTRACT

*Background:* Neoadjuvant pembrolizumab combined with chemotherapy is now standard treatment for stage II and III triple-negative breast cancer (TNBC). However, its impact on postoperative complications remains underexplored especially in oncoplastic or reconstructive procedures.

*Methods:* A retrospective before-and-after study was conducted at a single institution from January 2019 to May 2023. Patients with early-stage TNBC treated with chemotherapy alone (CT group) or chemotherapy plus pembrolizumab (CT + P group) were included. Postoperative complications (including delayed wound healing, abscesses, hematomas, infections, implant exposure, and skin necrosis) were compared using univariate and multivariate logistic regression.

*Results:* Among 254 patients (CT: n = 136; CT + P: n = 118), the overall complication rate was 15.7 %. No significant difference was observed between groups (p = 0.061). Delayed wound healing was more frequent in the CT + P group (10 % vs. 3.8 %, p = 0.031). After adjustment, immunotherapy was not independently associated with higher risk (OR 1.27, p = 0.5). Oncoplastic surgeries were associated with higher complication rates in univariate analysis but not in multivariate analysis (OR 1.74, p = 0.2). Complications were more frequent when surgery occurred <14 or >30 days post-treatment (p = 0.029), especially among CT + P patients (interaction p = 0.01).

*Conclusion:* Neoadjuvant pembrolizumab does not significantly increase postoperative complications. Surgical timing appears to be a modifiable factor influencing outcomes.

## 1. Introduction

Neoadjuvant chemotherapy is now standard of care in stage II-III Triple Negative Breast Cancer (TNBC) as it allows tailoring the post neoadjuvant treatment, according to the tumor's response [1].

In recent years, immunotherapy has emerged as a major component of cancer management, given the critical role of immune evasion in tumor progression. Monoclonal antibodies targeting PD-1, such as pembrolizumab, have been developed to block PD-L1 expressed on tumor or immune cells, leading to T cells death [2]. In TNBC, pembrolizumab has been shown to improve survival outcomes and has been routinely used in the neoadjuvant setting since 2022 since it is indicated for tumors ≥ T2 and/or node-positive disease [3].

Despite its benefits, pembrolizumab is associated with known adverse effects, including nausea, alopecia, and rash [3,4]. In the KEYNOTE-522 trial, a higher incidence of severe cutaneous reactions was reported in the pembrolizumab group (4.4 % vs. 1 %). Regarding the surgical impact of immunotherapy, data from other cancers where

* Corresponding author. nstitut Curie, Paris, France.
*E-mail addresses:* capucine.barjot@gmail.com, enora.laas@curie.fr (C. Barjot).

https://doi.org/10.1016/j.ejso.2025.110511
Received 17 June 2025; Received in revised form 26 September 2025; Accepted 15 October 2025
Available online 16 October 2025

immunotherapy has been used longer have yielded conflicting results. No increase in postoperative morbidity was observed in lung, gastric, or esophageal cancers [5–8], whereas higher complication rates were reported in head and neck cancers involving flap reconstruction [9].

Breast cancer surgery encompasses a wide range of procedures, from simple lumpectomy or mastectomy to more complex reconstructions using free flaps or implants. Common complications include delayed wound healing, surgical site infections (reported rates: 2–19 %) [10,11], hematomas, and lymphoceles, with mortality rates typically below 1 %. Previous studies have not shown a significant increase in complication rates following conventional chemotherapy [12–15].

With immunotherapy now incorporated into the neoadjuvant setting, concerns have been raised about its potential effects on postoperative outcomes, particularly regarding wound healing and infection risk, which may lead to increased complication rates. However, data on its surgical impact in breast cancer remain limited. An analysis of the KEYNOTE-522 study found similar overall wound complication rates between groups but noted a higher rate of wound infections (16 vs. 0.8 %) and seromas (24 vs. 16 %) in the pembrolizumab group [16]. To date, the only 2 studies specifically assessing the impact of neoadjuvant chemoimmunotherapy on surgical outcomes and time to radiation in TNBC [17,18], did not report any clinically significant differences in overall postoperative complications between treatment groups, comparing with neoadjuvant chemotherapy alone. Although immune-related adverse events (IrAEs) were associated with delays in adjuvant radiotherapy [17], they did not affect postoperative complication rates or time to surgery including in case of breast reconstruction with expander implant and flap [18].

The objective of this study was to compare postoperative complications in patients with early-stage TNBC who received pembrolizumab combined with neoadjuvant chemotherapy versus those treated with chemotherapy alone.

## 2. Materials and methods

### 1. Study Population

We conducted a retrospective, observational, before-and-after study between January 1, 2019, and May 30, 2023. Patients with invasive, unilateral, or bilateral triple-negative breast cancer (defined as ER $<10$ %, PR $<10$ %, and HER2 1+ or 2+ or FISH-negative, according to French and ASCO guidelines) who were treated at the Curie Institute during the study period were included.

Patients had an indication for neoadjuvant treatment according to national and international guidelines, based on tumor size $\geq 2$ cm and/or nodal involvement. Between 2019 and 2021, patients received standard neoadjuvant chemotherapy consisting of four cycles of doxorubicin or epirubicin with cyclophosphamide, followed by paclitaxel or docetaxel (CT group). Since 2022, following the results of the KEYNOTE-522 study, patients received four cycles of pembrolizumab (200 mg every three weeks) combined with paclitaxel and carboplatin, followed by four cycles of pembrolizumab with doxorubicin or epirubicin and cyclophosphamide (CT + P group).

Surgery was scheduled at least three weeks after the final chemotherapy session. The choice of breast surgical technique was based on tumor response, breast volume, tumor location, and patient preference. When feasible, conservative surgery (with or without oncoplastic techniques) was performed. Otherwise, patients underwent radical mastectomy with or without immediate reconstructive surgery (using either implants or flaps).

Axillary surgery consisted of sentinel lymph node biopsy in cases of initially cN0 disease, or cN1 converting to cN0 after neoadjuvant treatment. Axillary dissection was performed in all other cases.

Antibioprophylaxis protocol remains the same during the period of the study. All patients undergoing prosthetic breast reconstruction followed a standardized institutional preoperative decolonization protocol, including nasal mupirocin, antiseptic body wash, and oral chlorhexidine starting the day before surgery. Intraoperative antibiotic prophylaxis with 2 g of cefazolin was systematically administered at the beginning of surgery.

Systematic postoperative follow-up occurred three weeks after surgery to review pathology results and assess wound healing.

Postoperative radiotherapy was administered according to national guidelines in cases of breast-conserving surgery, T3 or T4 tumors, node-positive disease, or other high-risk features following total mastectomy.

Clinical data were extracted from electronic medical records and included baseline characteristics (age, menopausal status, body mass index [BMI], comorbidities), history of autoimmune disease or immunosuppressant use, laterality (unilateral or bilateral disease), type of surgery (unilateral or bilateral), time interval between neoadjuvant treatment and surgery, and details of oncoplastic or reconstructive procedures.

The study was conducted in compliance with institutional and ethical guidelines for research involving human participants. Informed consent was deemed unnecessary in accordance with applicable regulations.

### 2. Outcome Measures

Postoperative complications included hematoma, skin necrosis, implant exposure, abscess, and delayed wound healing, and were recorded for both the breast and axillary sites. Complications were classified according to the Clavien-Dindo classification. Lymphocele rates were recorded but were not considered complications unless associated with infection or other adverse outcomes.

Postoperative infectious complications were defined as any antibiotic treatment initiated after surgery in response to clinical signs (e.g., erythema, swelling, wound discharge, fever) or microbiological confirmation (e.g., positive culture from seroma or hematoma aspiration). According to institutional guidelines, postoperative prophylactic antibiotics are not routinely prescribed, and empirical antibiotic use without clinical suspicion or positive culture is discouraged. Antibiotic prescriptions given solely as part of standard perioperative care were not classified as complications. Any administration of antibiotics for wound-related concerns—excluding unrelated infections such as urinary tract infections—was considered an infectious complication, regardless of culture results.

Delayed wound healing and skin necrosis were diagnosed by physical examination and were classified as complications regardless of the treatment required. Hematomas and seromas were identified either on physical examination or by ultrasound imaging.

Complications and related data were identified during the immediate postoperative period, either at scheduled postoperative visits or through spontaneous reports by patients to the medical team. All events were documented in the electronic medical records. The time of onset for each complication was recorded and categorized as immediate (within 24 h post-surgery), intermediate (within 7 days), or late (occurring more than 7 days post-surgery).

### 3. Statistical Analysis

Continuous variables were described using medians and interquartile ranges (IQR), while categorical variables were expressed as counts and percentages. Clinical characteristics were compared using univariate analysis: the Chi-squared or Fisher's exact test was applied for categorical variables, Log rank test for censored variable and the Wilcoxon-Mann-Whitney test was used for continuous variables.

Risk factors for postoperative complications were first analyzed using univariate logistic regression. Variables with a p-value $<0.10$ in univariate analysis were then included in a multivariate logistic regression model to adjust for potential confounders. Results were reported as odds ratios (ORs) with 95 % confidence intervals (CIs).

The statistical unit of analysis was the breast, rather than the patient, to account for variations in surgical technique and outcomes. All statistical tests were two-sided, with a significance threshold set at 5 %. Analyses were conducted using R software, version 4.0.1.

## 3. Results

### 1. Clinical characteristics

During the study period, 254 patients received neoadjuvant treatment: 136 in the CT group (chemotherapy group) and 118 in the CT + P group (chemotherapy + pembrolizumab group). The two groups were comparable in terms of demographic and clinical characteristics. The median age was 47 years in the CT + P group and 49 years in the CT group (p = 0.14) (Table 1). No significant differences were observed in the prevalence of comorbidities (36 % vs. 37 %, p = 0.6). Although the median BMI was similar between groups, the CT + P group had a slightly higher proportion of obese patients (25 % vs. 14 %, p = 0.04). No significant difference in tumor size was observed between the two treatment groups (p = 0.3); nonetheless, axillary involvement was significantly lower in patients receiving CT alone compared with those treated with CT + P (N0: 71 % in CT group vs 23 % in CT + P group, p < 0.001).

The median interval between the end of neoadjuvant treatment and surgery was comparable (29 days in the CT + P group vs. 28 days in the CT group, p = 0.5). Adjuvant radiotherapy was administered to 97 % of patients in both groups (p = 0.9).

### 2. Surgical characteristics

Regarding surgical techniques, a higher rate of bilateral surgeries with symmetry procedures was observed in the CT + P group (25 % vs. 15 % in the CT group, p = 0.032) (Table 1). Oncoplastic procedures were more frequently performed in the CT + P group, accounting for 41 % of surgeries, whereas lumpectomies were more common in the CT group (43 % vs. 26 % in the CT + P group, p = 0.008). The rates of total mastectomy (TM) and immediate breast reconstruction (IBR) were similar between groups. All IBRs were performed using implants, with retropectoral placement more common in the CT group and prepectoral placement more common in the CT + P group. No significant difference was found in implant volume between the two groups. Regarding the type of axillary surgery, and in line with the extent of nodal involvement observed in the two groups, there was a significantly higher rate of sentinel lymph node biopsy in the CT group and a higher rate of Axillary lymph node dissection in the CT + P group (p < 0.001) (Supplemental Table S3).

### 3. *Complications*

The overall complication rate of total surgeries was 15.5 % (and 15.7 % of patients able S1), with no significant difference between the groups (CT group: n = 19; CT + P group: n = 28; p = 0.1) (Fig. 1). The mean time to complication onset was 20 days (IQR: 11–37), with more delayed complications in the CT + P group (26 days in the CT + P group vs. 17 days in the CT group, p = 0.02) (Table 2).

The rates of rehospitalization and surgical revision were 2 % and 3 % respectively. According to the Clavien-Dindo classification adapted for breast cancer [19], most complications were classified as Grade 1, indicating that they did not require medical intervention beyond standard postoperative care.

The most frequent complication was delayed wound healing occurring in 6.9 % (n = 21) of surgeries, followed by abscesses (3.6 %, n = 11) and hematomas (3.6 %, n = 11). The rate of skin necrosis was similar between the two groups. There was one case of implant exposure in the CT + P group and one case of prosthesis infection in the CT group (Fig. 1). A significantly higher rate of delayed wound healing was

**Table 1**
Patient and surgeries characteristics by treatment group.

| Variable | Total N = 254 | CT + P, N = 118 | CT, N = 136 | p-value |
|---|---|---|---|---|
| **Age** | 48 (40, 57) | 47 (40, 55) | 49 (41, 58) | 0.14 |
| **BMI (kg/m$^2$)** | 24.2 (21.5, 27.8) | 24.3 (21.5, 28.3) | 24.2 (21.6, 27.6) | 0.8 |
| **BMI (kg/m$^2$)** | | | | **0.044** |
| 21–25 | 104 (41 %) | 45 (38 %) | 59 (44 %) | |
| ≤20 | 37 (15 %) | 20 (17 %) | 17 (13 %) | |
| 26–30 | 73 (29 %) | 28 (24 %) | 45 (33 %) | |
| >30 | 39 (15 %) | 25 (21 %) | 14 (10 %) | |
| **Comorbidities** | 73 (29 %) | 36 (31 %) | 37 (28 %) | 0.6 |
| Diabetes | 8 (3.1 %) | 4 (3.4 %) | 4 (2.9 %) | >0.9 |
| Hypertension | 27 (11 %) | 13 (11 %) | 14 (10 %) | 0.9 |
| Smoking | 32 (13 %) | 16 (14 %) | 16 (12 %) | 0.7 |
| Autoimmune disease | 12 (4.7 %) | 7 (5.9 %) | 5 (3.7 %) | 0.4 |
| Immunosuppressant intake | 2 (0.8 %) | 2 (1.7 %) | 0 (0 %) | 0.2 |
| Others | 25 (9.8 %) | 11 (9.3 %) | 14 (10 %) | 0.8 |
| **Unilateral or bilateral cancer** | | | | 0.6 |
| Unilateral | 241 (98 %) | 108 (99 %) | 133 (98 %) | |
| Bilateral | 4 (1.6 %) | 1 (0.9 %) | 3 (2.2 %) | |
| **Unilateral or bilateral surgery** | | | | **0.032** |
| Unilateral | 204 (80 %) | 88 (75 %) | 116 (85 %) | |
| Bilateral | 50 (20 %) | 30 (25 %) | 20 (15 %) | |
| **Time from end of treatment to surgery (days)** | 28 (22, 35) | 29 (24, 34) | 28 (21, 36) | 0.5 |
| **Radiotherapy** | 244 (97 %) | 112 (97 %) | 132 (97 %) | >0.9 |
| **Cancer Surgery or Contralateral surgery for symmetrization** | | | | **0.049** |
| Cancer | 259 (85 %) | 120 (81 %) | 139 (89 %) | |
| Symmetrization | 45 (15 %) | 28 (19 %) | 17 (11 %) | |
| **Type of Surgery** | | | | **0.008** |
| Lumpectomy | 105 (35 %) | 38 (26 %) | 67 (43 %) | |
| Total mastectomy | 60 (20 %) | 31 (21 %) | 29 (19 %) | |
| Oncoplastic surgery | 102 (34 %) | 61 (41 %) | 41 (26 %) | |
| IBR | 37 (12 %) | 18 (12 %) | 19 (12 %) | |
| **Type of Oncoplastic surgery** | | | | **0.015** |
| External Plastic Surgery | 14 (14 %) | 7 (11 %) | 7 (17 %) | |
| Superior Pedicle | 35 (34 %) | 27 (44 %) | 8 (20 %) | |
| Inferior Pedicle | 11 (11 %) | 9 (15 %) | 2 (4.9 %) | |
| Roundblock | 27 (26 %) | 11 (18 %) | 16 (39 %) | |
| Others | 15 (15 %) | 7 (11 %) | 9 (21 %) | |
| IBR | 37 (12 %) | 18 (12 %) | 19 (12 %) | 0.8 |
| **Type of IBR** | | | | **0.031** |
| Retropectoral Implant | 23 (62 %) | 8 (44 %) | 15 (79 %) | |
| Prepectoral Implant | 14 (38 %) | 10 (56 %) | 4 (21 %) | |
| **T Stage** | | | | 0.3 |
| T1 | 24 (9.4 %) | 11 (9.3 %) | 13 (9.6 %) | |
| T2 | 169 (67 %) | 72 (61 %) | 97 (71 %) | |
| T3 | 39 (15 %) | 23 (19 %) | 16 (12 %) | |
| T4 | 22 (8.7 %) | 12 (10 %) | 10 (7.4 %) | |
| **N Status** | | | | **<0.001** |
| N0 | 124 (49 %) | 27 (23 %) | 97 (71 %) | |
| N1 | 104 (41 %) | 72 (61 %) | 32 (24 %) | |
| N2 | 13 (5.1 %) | 10 (8.5 %) | 3 (2.2 %) | |
| N3 | 13 (5.1 %) | 9 (7.6 %) | 4 (2.9 %) | |

BMI: Body Mass Index, IBR: Immediate Breast Reconstruction CT: chemotherapy alone; CT + P: chemotherapy + Pembrolizumab, T stage: tumour size, N status: Nodal status.
n(%), median (IQR).

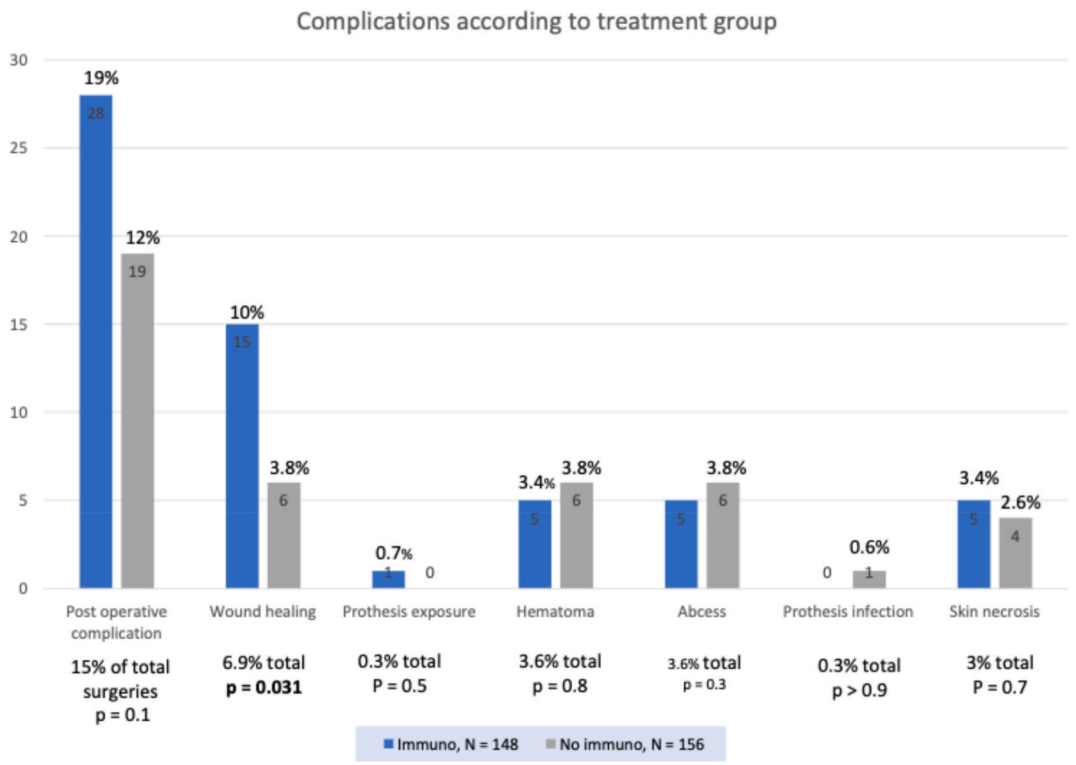


**Fig. 1. Complications with and without pembrolizumab** (immuno: chemotherapy + Pembrolizumab; No immuno: Chemotherapy alone).

**Table 2**
Postoperative outcomes by treatment group.

| Variable | All Surgeries, N = 304 | CT + P group, N = 148 | CT group, N = 156 | p-value |
|---|---|---|---|---|
| Time to complication (days) | 20 (11–37) | 26 (11–46) | 17 (11–22) | **0.02** |
| **Rehospitalization** | 6 (2.0 %) | 3 (2.0 %) | 3 (2.0 %) | >0.9 |
| **Surgical Revision** | 9 (3.0 %) | 6 (4.1 %) | 3 (2.0 %) | 0.3 |
| **Antibiotic Therapy** | 13 (4.3 %) | 8 (5.4 %) | 5 (3.3 %) | 0.4 |
| **Time to Surgical Revision** | | | | >0.9 |
| 1 day | 2 (22 %) | 1 (17 %) | 1 (33 %) | |
| 10–30 days | 4 (44 %) | 3 (50 %) | 1 (33 %) | |
| >30 days | 3 (33 %) | 2 (33 %) | 1 (33 %) | |
| **Clavien-Dindo Classification** | | | | >0.9 |
| I | 24 (56 %) | 15 (56 %) | 9 (56 %) | |
| II | 10 (23 %) | 6 (22 %) | 4 (25 %) | |
| IIIB | 9 (21 %) | 6 (22 %) | 3 (19 %) | |

CT: chemotherapy alone; CT + P: chemotherapy + Pembrolizumab.
n(%), median (IQR).

observed in the CT + P group (n = 15, 10 %) compared to the CT group (n = 6, 3.8 %) (p = 0.031).

When stratified by type of surgery, oncoplastic procedures were associated with the highest complication rate, accounting for 45 % of all reported complications (n = 21; p = 0.016) (Supplemental Table S2). Regarding the axillary surgery type, there was no significant difference between the two types of procedure (Supplemental Table S2).

In univariate analysis, the use of CT + P was not significantly associated with an increased risk of postoperative complications (OR 1.68, p = 0.10). Significant risk factors for complications included increasing age (OR 0,96, p = 0.001), BMI (OR 3.14 for patients with BMI >30 compared to those with BMI 21–25, p = 0.021), bilateral surgery (OR 2.49, p = 0.005), and type of breast surgery: compared to simple lumpectomy, the odds ratios for complications were 1.41 for radical mastectomy, 2.77 for oncoplastic surgery, and 3.95 for immediate breast reconstruction surgery (IBR), with an overall p-value of 0.017 (Fig. 2A).

After adjusting for age, BMI, menopausal status, bilateral surgery, type of surgery, and the interval between completion of chemotherapy and surgery, immunotherapy was not associated with a significant increase in postoperative complications (adjusted OR 1.27, p = 0.50). No significant interaction was found between immunotherapy and type of surgery (p = 0.15), indicating that the risk of complications did not vary by surgical technique in the context of immunotherapy (Fig. 2B).

Interestingly, time to surgery was significantly associated with the complication rate. Patients operated either early (7–14 days) or late (>30 days) had higher complication rates compared to those who underwent surgery between 21- and 28-days post-chemotherapy (p = 0.029).

An interaction was observed between time to surgery and immunotherapy use, with a higher risk of complications in patients treated with immunotherapy who underwent surgery after more than 30 days (p = 0.01). No significant interaction was found between immunotherapy and type of surgery (p = 0.15), indicating that the risk of complications did not vary by surgical technique in the context of immunotherapy (Fig. 3).

## 4. Discussion

In this cohort of patients treated with or without neoadjuvant immunotherapy for early TNBC, pembrolizumab was not associated with an increased risk of postoperative complications. This finding was consistent across all types of breast surgery. However, timing of surgery appeared to influence outcomes, with a higher complication rate observed when surgery was performed either too early (<14 days) or late (>30 days) after neoadjuvant treatment.

The overall complication rate in our study (15.7 %) aligns with previously reported rates for breast surgery [20,21] which vary by surgical technique—ranging from 15 to 30 % for oncoplastic procedures [22,23] to 24 %–32.9 % for implant or flap-based reconstruction [24,25]. In our cohort, oncoplastic surgery was associated with more complications in univariate analysis, though this did not persist after

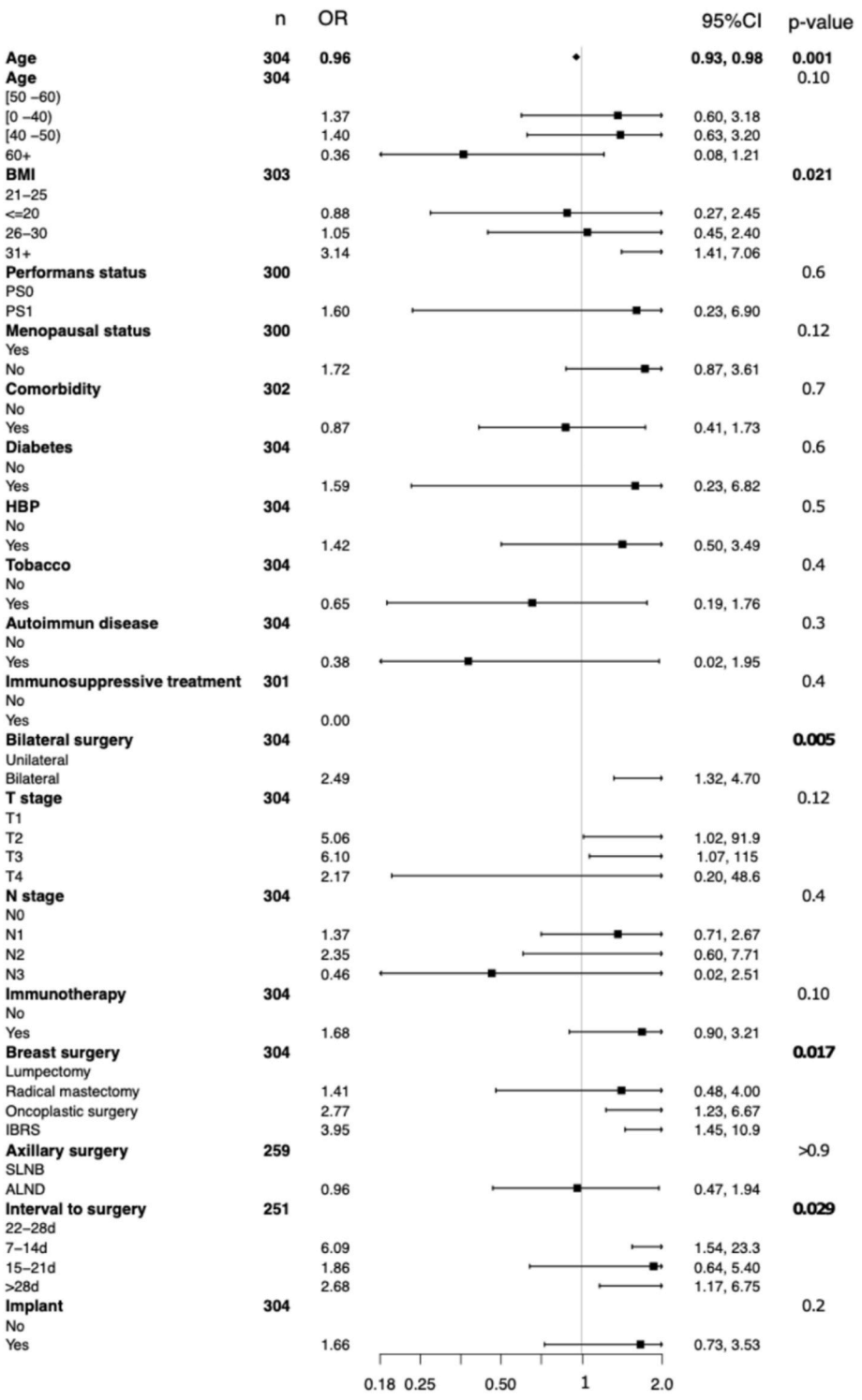


**Fig. 2A.** Potential predictive factors for complication, univariate analysis
BMI: Body Mass Index, HBP: high blood pressure, No immuno: CT group, Immuno: CT + P group, IBRS: Immediate breast reconstructions, SLNB: Sentinel lymph Node Biopsy, ALND: Axillary Lymph Node Dissection; d: days; OR: Odds ratio; CI confidence interval.

multivariate adjustment. Importantly, no interaction was found between immunotherapy and the type of surgery, including reconstructive procedures.

Understanding the surgical safety profile of immunotherapy is crucial, particularly as pembrolizumab becomes standard in early TNBC. While immune checkpoint inhibitors are associated with systemic immune-related adverse events, including dermatitis and endocrine dysfunction, we did not observe a significant increase in wound infections or healing delays in patients receiving pembrolizumab.

Interestingly, other cancers have reported similar findings: studies in lung, gastric, and esophageal cancers showed no increased post-operative complications after neoadjuvant immunotherapy [5–7,26], although increased fibrosis was noted in lung resections. In contrast, a study in head and neck cancer found higher complication rates following flap surgeries in patients treated with pembrolizumab [8], raising questions about its safety in flap-based breast reconstruction.

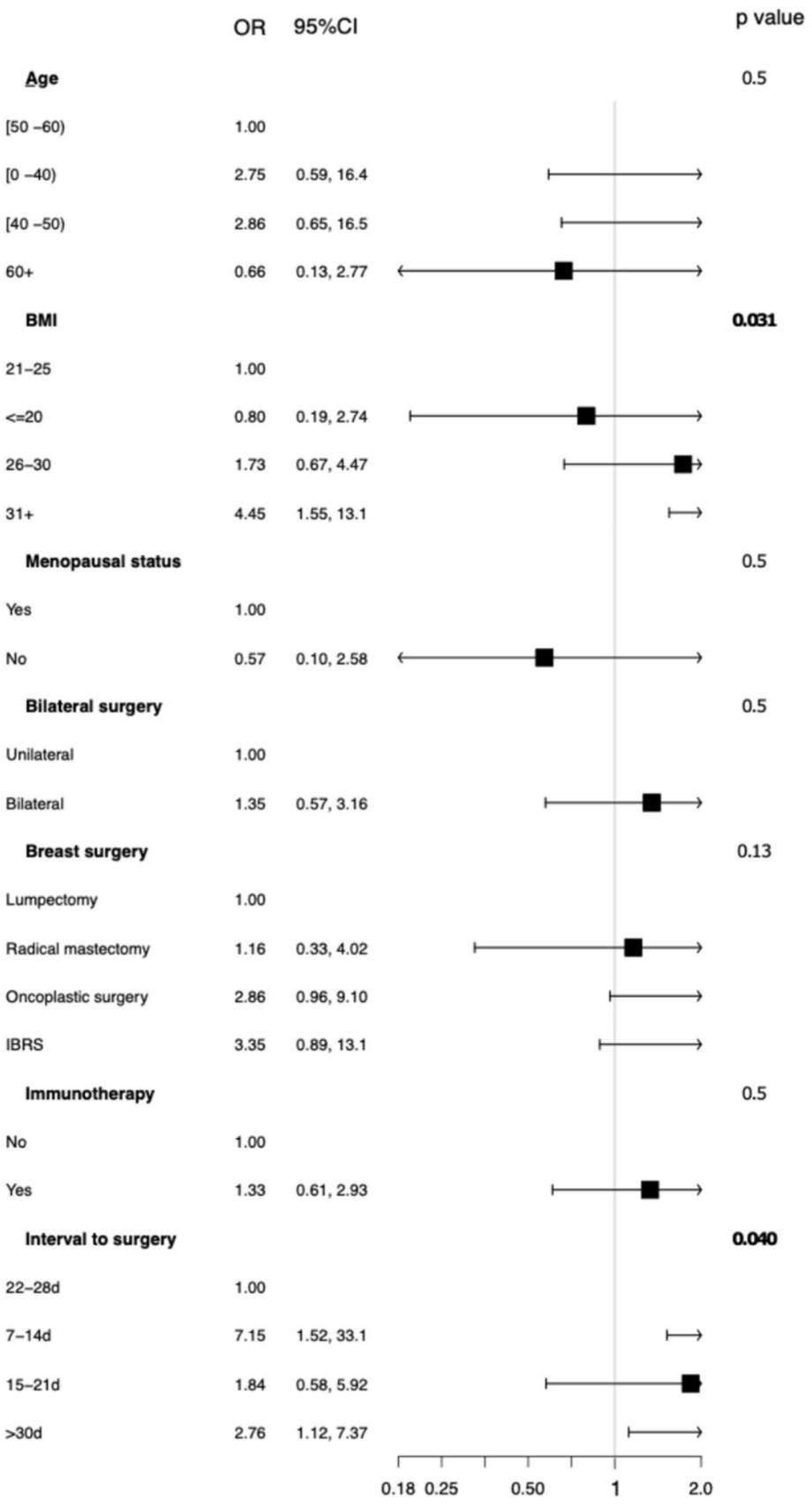


**Fig. 2B.** Potential predictive factors for complication, multivariate analysis
BMI: Body Mass Index, No immuno: CT group, Immuno: CT + P group, IBRS: Immediate breast reconstructions: OR: Odds ratio; CI confidence interval.

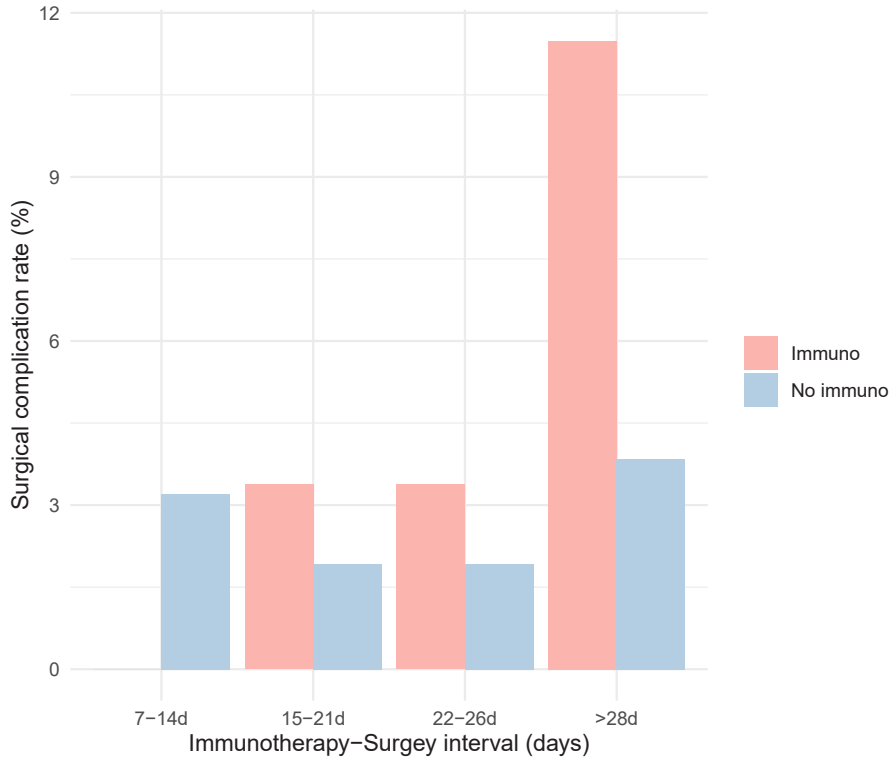


**Fig. 3. Surgical complication rate according to the treatment – Surgery interval between the 2 treatment groups** d = days; Immuno = CT + P group; No immuno = CT alone group.

In breast cancer, three studies have so far investigated surgical complications following immunotherapy. However, these studies either lacked a control group or did not account for oncoplastic or reconstructive procedures. In the study of Holt and al [18], including 54 patients, there were no association between immunotherapy and complication rate (total n = 19, 35.2 % p > 0.99). In this study, 24.1 % of patients underwent autologous reconstruction after neoadjuvant chemotherapy alone (n = 3) or with immunotherapy (n = 4), and while there was one patient with flap necrosis in the neoadjuvant alone group, autologous reconstruction was successful for all patients undergoing immunotherapy. Myers et al. [17] found no increased risk but without detailed analysis of surgical techniques. The study by Woodfin reported a 24.1 % complication rate—mainly infections—but did not include a control group [27].

The timing of surgery appears to be a modifiable factor. Our study suggests increased complications when surgery was performed too early or beyond 30 days after neoadjuvant treatment. An interaction between timing and immunotherapy was also observed, with higher risk in patients undergoing surgery >30 days after treatment. Immune activation and inflammation may peak shortly after treatment, potentially interfering with early tissue healing processes, while delays beyond 30 days could prolong the inflammatory state and similarly impact recovery. In some cases, delayed surgery may reflect a patient's deteriorated general condition, which can complicate the procedure and indirectly increase the risk of postoperative complications. Our findings underscore the importance of optimizing surgical timing in patients receiving chemotherapy and immunotherapy to mitigate these potential risks. However, no "ideal" timing for surgery after neoadjuvant immunotherapy has been clearly established to minimize the risk of complications. Literature on this topic is limited, though one study showed increased complications when surgery occurred before 28 days [28].

This study is one of the first to evaluate the impact of neoadjuvant immunotherapy on postoperative complication rates in breast cancer, while also comparing surgical techniques. Strengths include a large sample size and a broad range of procedures. Limitations include the retrospective design, potential underreporting of complications, and the single center setting as well as the fact that the neoadjuvant chemotherapy isn't the same between the 2 groups with the addition of carboplatin in the CT + P group. Nonetheless, carboplatin hasn't been associated with higher rate of surgical complication in other setting [29–32]. In addition, no patient underwent flap reconstruction, limiting conclusions for this subgroup. Another limitation of this study is the lack of detailed information regarding adjuvant radiotherapy. Specifics such as radiation fields (e.g., whole breast, chest wall, or regional nodal irradiation), fractionation schedules (conventional vs hypofractionated), and use of boost were not consistently documented in the retrospective dataset. These elements could potentially influence postoperative complication rates, particularly wound healing and seroma formation, and should be considered in future prospective studies.

## 5. Conclusion

Neoadjuvant immunotherapy with pembrolizumab does not appear to increase postoperative complication rates in breast cancer surgery, including oncoplastic and implant-based reconstruction. Although our study was not powered to define an optimal timing for surgery, complication rates appeared lower when surgery was performed between 21 and 28 days after the end of neoadjuvant treatment. These findings suggest that surgical timing may influence postoperative outcomes and warrant further investigation in prospective trials which are needed to confirm these findings and guide perioperative management in this evolving treatment landscape.

## Registration and protocol

The protocol can be requested from the corresponding author. The review was not registered.

## Ethics approval and consent to participate

The study was conducted in accordance with institutional ethical guidelines. Patient consent was not required due to the retrospective nature of the study.

## Credit author statement

CB: Conceptualization, Data curation, Writing – original draft. EL: Conceptualization, Writing – original draft. TG: Data curation. LD: Data curation. DL: Data curation. LC: Interpretation, Writing – review & editing. JGF: Interpretation, Writing – review & editing. VF: Interpretation, Writing – review & editing. BC: Interpretation, Writing – review & editing. All authors: Writing – review & editing, Approval of the final version.

## Funding

No specific funding was received for this study.

## Declaration of competing interes

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The authors thank the entire breast surgery and oncology teams at Institut Curie.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.110511.

## Data availability

Data available upon reasonable request.

## References

[1] Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017 Jun;376(22):2147–59.
[2] Wimberly H, Brown JR, Schalper K, Haack H, Silver MR, Nixon C, et al. PD-L1 expression correlates with tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy in breast cancer. Cancer Immunol Res 2015 Apr 1;3(4):326–32.
[3] Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med 2022 Feb 10;386(6):556–67.
[4] Ribas A, Hamid O, Daud A, Hodi FS, Wolchok JD, Kefford R, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. JAMA 2016 Apr 19;315(15):1600.
[5] Tong BC, Gu L, Wang X, Wigle DA, Phillips JD, Harpole DH, et al. Perioperative outcomes of pulmonary resection after neoadjuvant pembrolizumab in patients with non–small cell lung cancer. J Thorac Cardiovasc Surg 2022 Feb;163(2):427–36.
[6] Bott MJ, Cools-Lartigue J, Tan KS, Dycoco J, Bains MS, Downey RJ, et al. Safety and feasibility of lung resection after immunotherapy for metastatic or unresectable tumors. Ann Thorac Surg 2018 Jul;106(1):178–83.
[7] Su J, Guo W, Chen Z, Wang L, Liu H, Zhao L, et al. Safety and short-term outcomes of laparoscopic surgery for advanced gastric cancer after neoadjuvant immunotherapy: a retrospective cohort study. Front Immunol 2022 Dec 8;13:1078196.
[8] Cheng J, Guo M, Yang Y, Liu Y, Hu W, Shang Q, et al. Perioperative outcomes of minimally invasive esophagectomy after neoadjuvant immunotherapy for patients with locally advanced esophageal squamous cell carcinoma. Front Immunol 2022 Mar 11;13:848881.
[9] Mays AC, Yarlagadda B, Achim V, Jackson R, Pipkorn P, Huang AT, et al. Examining the relationship of immunotherapy and wound complications following flap reconstruction in patients with head and neck cancer. Head Neck 2021 May;43(5):1509–20.
[10] Rotstein C, Ferguson R, Cummings KM, Piedmonte MR, Lucey J, Banish A. Determinants of clean surgical wound infections for breast procedures at an oncology center. Infect Control Hosp Epidemiol 1992 Apr;13(4):207–14.
[11] Vitug AF, Newman LA. Complications in breast surgery. Surg Clin 2007 Apr;87(2):431–51.
[12] Decker MR, Greenblatt DY, Havlena J, Wilke LG, Greenberg CC, Neuman HB. Impact of neoadjuvant chemotherapy on wound complications after breast surgery. Surgery 2012 Sep;152(3):382–8.
[13] Hu YY, Weeks CM, In H, Dodgion CM, Golshan M, Chun YS, et al. Impact of neoadjuvant chemotherapy on breast reconstruction. Cancer 2011 Jul 1;117(13):2833–41.
[14] Broadwater JR, Edwards MJ, Kuglen C, Hortobagyi GN, Ames FC, Balch CM. Mastectomy following preoperative chemotherapy strict operative criteria control operative morbidity. Ann Surg 1991 Feb;213(2):126–9.
[15] Lorentzen T, Heidemann LN, Möller S, Bille C. Impact of neoadjuvant chemotherapy on surgical complications in breast cancer: a systematic review and meta-analysis. Eur J Surg Oncol 2022 Jan;48(1):44–52.
[16] Kümmel S, Schmid P, Harbeck N, Takahashi M, Untch M, Boileau JF, et al. P125 neoadjuvant pembrolizumab + chemotherapy vs placebo + chemotherapy followed by adjuvant pembrolizumab vs placebo for early TNBC: surgical outcomes from the phase 3 KEYNOTE-522 study. Breast 2023 Apr;68:S63–4.
[17] Myers SP, Sevilimedu V, Jones VM, Abuhadra N, Montagna G, Plitas G, et al. Impact of neoadjuvant chemoimmunotherapy on surgical outcomes and time to radiation in triple-negative breast cancer. Ann Surg Oncol 2024 Aug;31(8):5180–8.
[18] Holt AC, Smith CA, Berkowitz MJ, Baker JL, McAndrew NP, Kapoor NS. Surgical outcomes following neoadjuvant chemotherapy with and without immunotherapy in patients with triple-negative breast cancer. Discov Oncol 2024 Sep 20;15(1):467.
[19] Panhofer P, Ferenc V, Schütz M, Gleiss A, Dubsky P, Jakesz R, et al. Standardization of morbidity assessment in breast cancer surgery using the clavien dindo classification. Int J Surg 2014 Apr;12(4):334–9.
[20] Koppiker CB, Kelkar DA, Kulkarni M, Kadu S, Pai M, Dhar U, et al. Impact of oncoplasty in increasing breast conservation rates post neo-adjuvant chemotherapy. Front Oncol 2023 Sep 7;13:1176609.
[21] Campbell EJ, Romics L. Oncological safety and cosmetic outcomes in oncoplastic breast conservation surgery, a review of the best level of evidence literature. BCTT 2017 Aug;9:521–30.
[22] Losken A, Dugal CS, Styblo TM, Carlson GW. A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique. Ann Plast Surg 2014 Feb;72(2):145–9.
[23] Kabir SA, Stallard S, Weiler-Mithoff E, Mansell J, Mallon E, Doughty JC, et al. Six-year follow-up of patients treated with oncoplastic reduction mammoplasty: a cohort study. Int J Surg 2016 Feb;26:38–42.
[24] Allué Cabañuz M, Arribas Del Amo MD, Gil Romea I, Val-Carreres Rivera MP, Sousa Domínguez R, Güemes Sánchez AT. Reconstrucción inmediata mediante implante directo tras quimioterapia neoadyuvante. ¿Es una práctica segura? Cirugía Española 2019 Dec;97(10):575–81.
[25] Bennett KG, Qi J, Kim HM, Hamill JB, Pusic AL, Wilkins EG. Comparison of 2-Year complication rates among common techniques for postmastectomy breast reconstruction. JAMA Surg 2018 Oct 1;153(10):901.
[26] Spicer JD, Garassino MC, Wakelee H, Liberman M, Kato T, Tsuboi M, et al. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2024 Sep;404(10459):1240–52.
[27] Woodfin AA, Yam C, Teshome M, Kuerer HM, Hunt KK, Meric-Bernstam F, et al. Axillary nodal metastases conversion and perioperative complications with neoadjuvant pembrolizumab therapy in triple-negative breast cancer. Ann Surg Oncol 2024 Feb;31(2):974–80.
[28] Sutton TL, Johnson N, Schlitt A, Gardiner SK, Garreau JR. Surgical timing following neoadjuvant chemotherapy for breast cancer affects postoperative complication rates. Am J Surg 2020 May;219(5):741–5.
[29] Romero Román A, Campo-Cañaveral De La Cruz JL, Macía I, Escobar Campuzano I, Figueroa Almánzar S, Delgado Roel M, et al. Outcomes of surgical resection after neoadjuvant chemoimmunotherapy in locally advanced stage IIIA non-small-cell lung cancer. Eur J Cardio Thorac Surg 2021 Jul 14;60(1):81–8.
[30] Machida H, Tokunaga H, Matsuo K, Matsumura N, Kobayashi Y, Tabata T, et al. Survival outcome and perioperative complication related to neoadjuvant chemotherapy with carboplatin and paclitaxel for advanced ovarian cancer: a systematic review and meta-analysis. Eur J Surg Oncol 2020 May;46(5):868–75.
[31] Van Hagen P, Hulshof MCCM, Van Lanschot JJB, Steyerberg EW, Henegouwen MIVB, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012 May 31;366(22):2074–84.
[32] Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, et al. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome. Eur J Cancer 2016 May;59:22–33.