Published in final edited form as:

Plast Reconstr Surg. 2012 February ; 129(2): 305–314. doi:10.1097/PRS.0b013e31823ae86c.

Tamoxifen Increases the Risk of Microvascular Flap Complications in Patients Undergoing Microvascular Breast Reconstruction

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Abstract

Background—Tamoxifen citrate (tamoxifen) has been associated with increased rates of thromboembolic events, which have prompted concerns that tamoxifen may increase the risk of complications after microvascular breast reconstruction. Some centers have implemented protocols to temporarily stop tamoxifen before microvascular breast reconstruction. We sought to determine whether this practice is warranted.

Methods—We retrospectively compared rates of microvascular flap complications and pulmonary emboli between patients who were and were not receiving tamoxifen at the time of reconstruction in 670 patients who underwent delayed microsurgical breast reconstruction at our institution between January 2000 and April 2010.

Results—Two hundred five patients received tamoxifen within 28 days before reconstruction (these were considered to be receiving tamoxifen at reconstruction); 465 patients did not. Patients who received tamoxifen were significantly younger ($p < 0.0001$) and thinner ($p = 0.0025$) with less cardiovascular morbidity ($p = 0.04$) and shorter durations of surgery ($p = 0.05$). Despite fewer comorbidities, microvascular flap complications were significantly more common in patients who received tamoxifen (21.5% versus 15%; $p = 0.04$). Patients who received tamoxifen had 1.7 times the risk of complications ($p = 0.015$) and 1.8 times the risk of follow-up complications ($p = 0.03$) than patients in the no-tamoxifen group. In tamoxifen-group patients, cardiovascular comorbidities significantly increased the risk of flap complications ($p = 0.002$). Tamoxifen-group patients had a significantly increased rate of immediate total flap loss ($p = 0.041$) and a lower rate of flap salvage ($p = 0.023$). Tamoxifen did not appear to increase the risk of pulmonary embolus during or after delayed microvascular breast reconstruction.

Conclusions—Tamoxifen may increase the risk of microvascular flap complications. Surgeons should consider temporarily stopping the drug 14-days before microsurgical breast reconstruction.

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Disclosure

The authors have no financial interest to declare in relation to the content of this article.

INTRODUCTION

Breast cancer is the most common non-skin malignancy affecting women in the United States.¹ Breast tumors are often estrogen receptor positive and responsive to adjuvant chemotherapy with the selective estrogen receptor (ER) modulator (SERM) tamoxifen citrate (tamoxifen), which can produce dramatic reductions in recurrence and mortality.² The active metabolite of tamoxifen (N-desmethyl tamoxifen) functions by competitive antagonism with estrogen at ERs in the breast but has variable effects in other body tissues, including blood vessels. ERs are abundant in the endothelium of arteries and veins and are linked to arterial vasodilation and cyclooxygenase (COX) regulation.^{3,4} Although estrogen's effects on the vascular system are not fully understood, SERMs have been empirically noted to cause increased rates of thrombosis.⁴

There is strong evidence that tamoxifen therapy is associated with increased rates of thromboembolic events, including deep venous thrombosis and pulmonary embolism; reported risk ratios for these complications range from 1.3 to 7.0.^{5–10} Additionally, the first 2 years of therapy with tamoxifen appears to be the period during which the risk of thrombotic events is highest.¹⁰ Moreover, in rats undergoing microsurgery, tamoxifen has been associated with increased intimal and total vessel wall thickness.¹¹ This finding prompted concerns that tamoxifen therapy at the time of microsurgical breast reconstruction may increase the risk of ischemia, vessel thrombosis, partial necrosis, and total flap failure.

In response to these concerns, some surgical centers have implemented protocols to temporarily stop tamoxifen before microvascular breast reconstruction. We sought to determine whether this practice is warranted. To achieve this goal, we compared complication rates among breast cancer patients undergoing delayed breast reconstruction with a microsurgical autologous tissue flap between patients who were receiving adjuvant tamoxifen therapy at reconstruction and those who were not. Furthermore, we examined whether various factors—including patient age, body mass index, surgery duration, radiation therapy, and other factors—could provoke the occurrence of complications in patients who were receiving tamoxifen at reconstruction.

MATERIALS AND METHODS

Human Subjects Approval

The University of Texas MD Anderson Cancer Center Institutional Review Board approved this study and waived the requirement for informed consent.

Patient Selection

Using a combined database from the Departments of Plastic Surgery and Breast Medical Oncology, we reviewed the records of all patients at our institution who underwent delayed microvascular breast reconstruction between January 2000 and April 2010. A delayed microvascular breast reconstruction was defined as a reconstruction 1) performed as a surgical procedure separate from the mastectomy and 2) in which the blood supply to the autologous tissue flap was solely dependent on microvascular anastomoses. We chose to limit the study to patients who underwent delayed reconstruction as patients are usually given tamoxifen in an adjuvant setting. In the treatment of breast cancer and ductal carcinoma in situ, the Food and Drug Administration has recommended that tamoxifen be started after surgical intervention and standard chemotherapy and continued for 5 years after diagnosis.

Tamoxifen Usage Status

On the basis of the half-life of the active metabolite of tamoxifen (N-desmethyl tamoxifen), which is approximately 14 days, patients were considered to be receiving tamoxifen at the time of reconstruction if they had ingested tamoxifen during the 28 days before surgery (tamoxifen group). Conversely, patients who had not ingested tamoxifen during the 28 days before surgery (approximately 2 half-lives) and those who had never used tamoxifen were considered not to be receiving tamoxifen at the time of reconstruction (no-tamoxifen group).

Classification of Complications

Complications were considered immediate if they were found during surgery or after surgery but before the first postoperative clinic visit (usually 1 week after discharge or 2 weeks after surgery). Immediate complications were defined as arterial insufficiency, venous congestion, microvascular flap thrombosis, need for surgical re-exploration, partial flap necrosis, total flap loss, and pulmonary embolus. Follow-up complications were defined as those found at the first postoperative clinic visit or later and included fat necrosis of the flap, partial flap necrosis, total flap loss, and pulmonary embolus.

Statistical Analysis

Data were subjected to both univariate and multivariate analysis. First, differences between tamoxifen groups with respect to age, body mass index, baseline comorbidities, duration of surgery, and other surgical variables (flap type, use of systemic anticoagulants, and vein anastomosis technique) were examined using the chi-square test, Fisher's exact test, Student's *t* test, and the rank-sum test. We compared the prevalence of complications (any complication, immediate complications, and follow-up complications) between the tamoxifen and no-tamoxifen groups. Backward stepwise logistic regression analysis was used to identify factors that were associated with any complication in all patients and in the subset of patients receiving tamoxifen. Those analyses were repeated to identify factors associated with immediate and follow-up complications. Stata statistical software (SE9, StataCorp LP, College Station, TX) was used for statistical analyses. All *p* values were 2-tailed, and *p* = 0.05 was considered significant.

RESULTS

A total of 670 patients who underwent delayed microvascular breast reconstruction met the criteria for inclusion in this study. The following types of flaps used were used: transverse rectus abdominis myocutaneous (*n* = 419), deep inferior epigastric perforator (*n* = 198), superficial inferior epigastric artery (*n* = 32), superior gluteal artery perforator (*n* = 17), inferior gluteal perforator (*n* = 1), free latissimus dorsi myocutaneous (*n* = 2), and deep circumflex iliac artery (*n* = 1). Of the 670 patients in the study, 205 were receiving tamoxifen, and 465 were not.

Patients characteristics are summarized in Table 1. Compared to patients not receiving tamoxifen, patients receiving tamoxifen were significantly younger (*p* < 0.0001), had lower mean body mass index (*p* = 0.0025), had fewer cardiovascular comorbidities (*p* = 0.04) and less rheumatologic disease (*p* = 0.027), were more likely to receive preoperative radiation therapy (*p* = 0.052), had a shorter mean duration of surgery (525.2 minutes versus 550.1 minutes, *p* = 0.05), and had a shorter mean length of follow-up (21.6 months versus 26.3 months, *p* = 0.03).

Rates of microvascular flap complications are presented in Table 2. Overall, patients receiving tamoxifen were significantly more likely than patients not receiving tamoxifen to experience a complication (21.5% versus 15%, *p* = 0.04). However, there were no

significant differences between the groups in the occurrence of immediate or follow-up complications.

Backward stepwise logistic regression analysis showed that tamoxifen use within 28 days before microvascular breast reconstruction—independent of the influence of other factors—resulted in an increased risk of a complication ($p = 0.015$, odds ratio [OR] 1.7, 95% confidence interval [CI] 1.1–2.7) (Table 3). Patients receiving tamoxifen were also significantly more likely to experience a follow-up complication ($p = 0.03$, OR 1.8, 95% CI 1.1–3.1).

Table 4 summarizes the impact of comorbidities and surgical variables on the occurrence of complications in patients receiving tamoxifen. Factors associated with increased risk of complications were having 1 or more cardiovascular comorbidities (diabetes mellitus, peripheral vascular disease, coronary artery disease, or a previous myocardial infarction) ($p = 0.003$) and reconstruction with a gluteal flap, free latissimus dorsi myocutaneous flap, or deep circumflex iliac artery flap ($p = 0.02$). Surprisingly, the use of perioperative anticoagulants (heparin sulfate or aspirin) did not have a significant impact on the occurrence of microvascular flap complications in patients receiving tamoxifen.

Backward stepwise logistic regression analysis showed that among patients receiving tamoxifen, patients who had 1 or more cardiovascular comorbidities were significantly more likely to suffer a microvascular flap complication ($p = 0.002$, OR 3.1, 95% CI 1.5–6.5) (Table 5). Also, among patients receiving tamoxifen, patients who underwent reconstruction with a gluteal flap, free latissimus dorsi myocutaneous flap, or deep circumflex iliac artery flap were significantly more likely than patients who underwent reconstruction with another flap to have a complication in the immediate postoperative period ($p = 0.009$, OR 3.1, 95% CI 1.3–7.1).

Rates of immediate and follow-up complications by tamoxifen status are shown in Table 6. Tamoxifen-group patients had a significantly increased rate of immediate total flap loss ($p = 0.041$) and a lower rate of flap salvage ($p = 0.023$). However, tamoxifen did not appear to increase the risk of pulmonary embolus during or after delayed microvascular breast reconstruction. Ten (1.5%) microsurgical flaps were lost, 8 in patients receiving tamoxifen (flap loss rate 3.9%) and 2 in patients not receiving tamoxifen (flap loss rate 0.4%). There were 8 cases of immediate flap loss, 4 due to arterial thromboses and 4 due to venous thromboses. Six of the 8 cases of immediate flap loss were in patients receiving tamoxifen, and 2 were in patients not receiving tamoxifen. There were 2 cases of follow-up flap loss, 1 with arterial thrombosis on postoperative day 13 and 1 due to intrinsic venous congestion (insufficiency).

Two patients (pulmonary embolus rate 0.3%) experienced pulmonary emboli, 1 receiving tamoxifen (pulmonary embolus rate 0.5) and 1 not receiving tamoxifen (pulmonary embolus rate 0.2). One pulmonary embolus was detected during the immediate postoperative period and the other during longer follow-up.

DISCUSSION

The results of this study indicate that standard adjuvant tamoxifen therapy may increase the occurrence of microvascular flap complications in patients undergoing delayed microsurgical breast reconstruction. We found that patients receiving tamoxifen within 28 days before microsurgical breast reconstruction had an increased rate of microvascular flap complications, including total flap loss. This finding was confirmed by the results of multivariate analysis, which showed that the risk of microvascular flap complications was

1.7 times as high in patients receiving tamoxifen as in patients not receiving tamoxifen independent of other contributing factors. In addition, we found that among patients receiving tamoxifen, the risk of microvascular flap complications was 3.1 times as high in patients who had 1 or more pre-existing cardiovascular comorbidities as it was in patients without cardiovascular comorbidities. Tamoxifen did not appear to increase the risk of pulmonary embolus during or after delayed microvascular breast reconstruction.

Tamoxifen is a SERM that blocks the ability of estrogen to bind the nuclear ER. ERs are abundant in vascular endothelium and are linked to arterial and venous vasodilation through ERs' regulation of nitric oxide (NO) and the COX pathway. We hypothesize that the increased rate of microvascular flap complications in patients receiving tamoxifen in our study is a result of inhibition of NO-mediated vasodilation, increased proliferation of vascular endothelial smooth muscle due to loss of the inhibitory effect of estrogen, increased thromboxane-mediated and other-contractile-prostanoid-mediated vasoconstriction due to loss of the inhibitory effect of estrogen on production of these molecules, and increased platelet aggregation (Figures 1 and 2). This multimechanism hypothesis is also supported by the lack of a protective effect of heparin sulfate or aspirin against microvascular flap complications in the subset of our study patients who were receiving tamoxifen at the time of breast reconstruction. Further support for this multimechanism hypothesis may also come from our observation of a lower rate of flap salvage in patients with microvascular thromboses among patients receiving tamoxifen than among patients not receiving tamoxifen (27% versus 78%, Table 6). This finding may be a manifestation of the multiple mechanisms that tamoxifen uses to block the positive effects of estrogen on vascular endothelium.

One of the best-described rapid actions of estrogen is stimulation of endothelial nitric oxide synthetase (eNOS) in vascular endothelial cells (Figures 1 and 2). This stimulation of eNOS enhances endothelial-dependent vasodilator responses mediated by NO, a well-described effect of estrogen that has been demonstrated both in vitro and in vivo.¹²⁻¹⁴ Intracellular pathways also are activated by acute application of estrogen to isolated vascular smooth muscle cells. The physiological consequence in most cases is relaxation of vascular rings and inhibition of proliferation in cultured vascular smooth muscle cells.³

Vascular responsiveness to estrogen may differ by vascular bed and between arteries and veins. In arteries, in general, the most consistent effect of estrogen reported from a large number of studies conducted on isolated arteries, in experimental animals, and in humans is vasodilation or suppression of vascular tone.³ The most prominent effects of estrogen on vascular reactivity are mediated through direct effects on endothelial function.¹⁵ A plethora of studies in humans have clearly demonstrated that estrogen promotes vasodilation through an eNOS-dependent mechanism.¹⁵ Results of these studies include demonstration of an estrogen-stimulated increase in plasma concentrations of NO.³ In addition to enhancing endothelial production of NO, there is substantial evidence that estrogen increases or decreases production of other endothelial factors, including products of the COX pathway. Estrogen has been shown to result in a shift from COX-dependent vasoconstriction to vasodilation.¹⁶

Our finding that patients receiving tamoxifen at the time of delayed breast reconstruction were younger than patients not receiving tamoxifen is most likely explained by the fact that at our center adjuvant tamoxifen therapy is utilized in premenopausal women and adjuvant aromatase inhibitor-based therapy in postmenopausal patients. Although our study did not show that age affected the risk of complications in women receiving tamoxifen, perhaps because the mean age of the tamoxifen group was only 45.3 years compared with 49.9 years for the no-tamoxifen group, findings from several other studies suggest that younger

premenopausal women, the patients treated with SERMs, may be the group at highest risk for adverse effects of SERMs on microsurgical breast reconstruction. A study by Sherwood et al. found that the acute vascular responses of postmenopausal women to estrogen declined with age.¹⁷ In addition, premenopausal women have been shown to have more flow-mediated vasodilation in response to estrogen and therefore may encounter more severe vasoconstriction from the loss of the estrogenic effect.³ Other studies have found that in the absence of estrogen, endothelium-dependent release of NO is reduced, and the longer the individual is without estrogen exposure, the more the ability of estrogen to increase this response is abrogated.³ Although all patients treated with tamoxifen are premenopausal, it may be that the closer a patient is to menopause and its accompanying decreased estrogen exposure, the less sensitivity the patient has to the adverse vascular effects of tamoxifen and the potential for complications of microsurgical breast reconstruction. It may also be that the longer a patient has been receiving tamoxifen, the less pronounced the vasoconstrictive and platelet-aggregating effects may be due to loss of sensitivity of the eNOS and COX pathway.

We observed not only venous microvascular thrombosis but also arterial microvascular thrombosis and flap loss in patients receiving tamoxifen (Table 6). These findings may coincide with intimal hyperplasia, which has been observed within the arteries of rats treated with tamoxifen; this observation serves as a reminder that ERs are also located within the endothelium of arteries.¹¹ It is also known that the coronary and carotid vessels are at risk for atherosclerosis and thrombotic events from loss of estrogen exposure, and the internal mammary vessels—the most commonly utilized recipient vessels for microsurgical breast reconstruction—are in the direct vicinity of these vessels. However, it is unclear whether the use of tamoxifen would increase these risks for the internal mammary vessels and subsequently place microsurgical breast reconstruction at risk. In any case, the findings from the present study suggest that the impact of tamoxifen on microsurgical breast reconstruction is also related to the arterial anastomosis and not only the venous anastomosis.

Interestingly, we found a low incidence of pulmonary embolus in patients undergoing delayed microvascular breast reconstruction. Whether a patient was receiving tamoxifen or not did not appear to make a difference. The routine, early mobilization of patients from bed rest after breast reconstruction may have minimized the risk of pulmonary embolus. It is also possible that the effect of tamoxifen on the risk of pulmonary embolus in surgical patients is negligible.

However, we did find that among patients who were receiving tamoxifen, patients who underwent breast reconstruction with non-abdominal-based flaps, mainly gluteal flaps, were at higher risk of complications. Although we would expect a similar estrogen response in the pelvic and lower-extremity venous beds, ER response may vary by venous bed. For instance, a lower expression or signaling cascade response to estrogens in the lower extremities than in the pelvic vasculature could explain the negligible effect of tamoxifen on pulmonary embolus but significant problems with gluteal flaps in patients receiving tamoxifen. However, this hypothesis does not explain why nonsurgical patients receiving tamoxifen are known to be at increased risk for lower-extremity thromboembolic complications.³ The increased risk of microvascular flap complications associated with gluteal flap breast reconstruction among patients receiving tamoxifen may simply have been due to the increased complexity of gluteal flap-based microsurgical breast reconstruction.

We found that among patients receiving tamoxifen, those with cardiovascular comorbidities had a higher risk of microvascular flap complications. This finding is interesting because it suggests that patients with atherosclerotic disease may be predisposed to microvascular flap

complications caused by tamoxifen because the response of cells in the nonatherosclerotic artery may not be same as the response of cells in developing plaque. A study by Haas et al. suggests that in patients with atherosclerosis, estrogen may not cause relaxation of veins because of altered expression of ERs and signaling cascades different from those in women without atherosclerosis.¹⁸ Does tamoxifen in women with atherosclerosis further exacerbate the loss of vasodilation and antiplatelet aggregation, increasing the risk of microvascular thrombosis? Or does the endothelial damage associated with atherosclerotic disease act alone in down-regulating the expression and altering the configuration and function of the ERs thereby altering estrogen's ability to bind to ERs and direct the cascading effects?

The findings of our study indicate that concern is warranted with respect to the use of tamoxifen at the time of delayed microsurgical breast reconstruction. With any patient, safety must be assessed when a temporary break in tamoxifen therapy is being considered, and a proper risk-benefit analysis must be conducted. It is important for plastic surgeons to work in concert with both medical and surgical oncologists to coordinate appropriate treatment for each individual patient. At MD Anderson, our breast medical oncologists have allowed us to temporarily stop tamoxifen from 2 weeks prior to 2 weeks after microsurgical breast reconstruction, and this practice has not resulted in any known adverse oncologic consequences. We temporarily stop tamoxifen at least 2 weeks before delayed microvascular breast reconstruction because although the package insert for tamoxifen states that the drug has a half-life of 5 to 7 days, the active metabolite, N-desmethyl tamoxifen, has a half-life of 14 days.¹⁹

The limitations of this retrospective study are the small sample size and the multiple study variables. Flap complications are very rare and are critical patient care events. Surgical practices also vary greatly between surgeons and may even vary depending on patient diagnosis, body habitus, age, and other factors. Appropriate future studies are necessary to fully address these limitations. A long-term randomized prospective study evaluating the effects of tamoxifen on microvascular surgery would be appropriate, and similar retrospective studies at other surgical centers would be of interest.

Tamoxifen is commonly used as adjuvant therapy in patients with ER-positive breast cancer or ductal carcinoma in situ. However, the results of our study indicate that there is reason for concern that tamoxifen use at the time of delayed microsurgical breast reconstruction may increase the risk of flap failure or other microvascular flap complications. We suggest that plastic surgeons consider temporarily stopping tamoxifen for at least 14 days prior to surgery to avoid potential adverse effects of tamoxifen on the vascular endothelium of a micro surgically reconstructed breast.

Acknowledgments

Financial support: MD Anderson is supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant, CA016672.

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Fig. 1.

Effects of estrogen binding of the estrogen receptor on the vascular endothelium. Estrogen binding of the estrogen receptor in the nucleus of endothelial cells leads to stimulation of nitric oxide production and stimulation of the COX pathway. Stimulation of the cyclooxygenase pathway inhibits contractile prostanoids, like thromboxane, and inhibition of contractile prostanoids promotes vasodilation and inhibits platelet aggregation. ER, estrogen receptor; eNOS, endothelial nitric oxide synthetase; NO, nitric oxide; COX, cyclooxygenase; PG, prostaglandin.

Fig. 2.

Hypothesized effects of tamoxifen blockade of estrogen receptor. Tamoxifen blockade of the estrogen receptor or other vascular endothelial receptors may promote vasoconstriction, platelet aggregation, and inflammation due to smooth muscle proliferation through inhibition of endothelial nitric oxide synthetase; loss of inhibition of contractile prostanoids, like thromboxane; and loss of inhibition of smooth muscle proliferation within the endothelial wall. ER, estrogen receptor; eNOS, endothelial nitric oxide synthetase; PG, prostaglandin.

Table 1

Comorbidities and Surgical Management in Patients Receiving and Not Receiving Tamoxifen

Characteristic	No Tamoxifen (n = 465) n (%)	Tamoxifen (n = 205) n (%)	p
Age, years			<0.0001 [^]
Mean	49.9	45.3	
Median (range)	50 (24–72)	46(23–70)	
Body mass index, kg/m ²			0.0025
Mean	28.1	26.8	
Median (range)	28 (13–43)	26 (11–59)	
Cardiovascular comorbidities [§]			0.04 [*]
0	338 (72.7)	161 (78.5)	
1–2	124 (26.7)	40 (19.5)	
3	3 (0.6)	4 (2.0)	
Pulmonary disease			0.8 [*]
Yes	12 (2.6)	6 (2.9)	
No	453 (97.4)	199 (97.1)	
Preoperative radiation therapy			0.052
No	218 (46.9)	79 (38.5)	
Yes	247 (53.1)	126 (61.5)	
Rheumatologic disease			0.027 [*]
No	462 (99.3)	199 (97.1)	
Yes	3 (0.7)	6 (2.9)	
Smoking			1.0 [*]
Never or quit	436 (93.8)	192 (93.7)	
Current smoker	29 (6.2)	13 (6.3)	
Surgery duration, minutes			0.05 [^]
Mean	550.1	525.2	
Median (range)	540 (0–992)	508 (0–910)	
Supercharged flap			0.6 [*]
No	462 (99.4)	205 (100)	
Yes	3 (0.6)	0 (0)	
Free flap type			1.0 [*]
DIEP, TRAM, or SIEA	450 (96.8)	199 (97.1)	
Other [†]	15 (3.2)	6 (2.9)	
Systemic anticoagulants			0.3 [*]
None	419 (90.1)	183 (89.3)	
Aspirin	37 (8.0)	14 (6.8)	
Heparin sulfate	9 (1.9)	8 (3.9)	
Vein anastomosis technique			0.3 [*]
Interrupted	232 (49.9)	110 (53.7)	

Characteristic	No Tamoxifen (n = 465) n (%)	Tamoxifen (n = 205) n (%)	<i>p</i>
Coupler	155 (33.3)	55 (26.8)	
Running	76 (16.3)	40 (19.5)	
Both	2 (0.5)	0	

DIEP, deep inferior epigastric perforator; TRAM, transverse rectus abdominis myocutaneous; SIEA, superficial inferior epigastric artery.

[^] Rank-sum test.

^{*} Fisher's exact test.

[§] Includes diabetes mellitus (type 1 or 2), coronary artery disease, history of myocardial infarction, and peripheral vascular disease.

[†] Other flaps included superior gluteal artery perforator, inferior gluteal artery perforator, microvascular latissimus dorsi myocutaneous, and Rubens.

Table 2

Microvascular Flap Complications in Patients Receiving and Not Receiving Tamoxifen

Characteristic	No Tamoxifen n (%)	Tamoxifen n (%)	<i>p</i>
Any complication			0.04
No	395 (85.0)	161 (78.5)	
Yes	70 (15.0)	44 (21.5)	
Immediate complication			0.1
No	415 (92.8)	172 (89.1)	
Yes	32 (7.2)	21 (10.9)	
Follow-up complication			0.1
No	358 (89.1)	153 (84.5)	
Yes	44 (10.9)	28 (15.5)	

Table 3

Multivariate Comparison of Impact of Tamoxifen Status on Risk of Microvascular Flap Complications

Tamoxifen Status	Odds Ratio	Standard Error	<i>p</i>	95% Confidence Interval
Any complication				
No tamoxifen	Referent			
Tamoxifen	1.7	0.4	0.015	1.1–2.7
Follow-up complication				
No tamoxifen	Referent			
Tamoxifen	1.8	0.5	0.03	1.1–3.1
Immediate complication				
No tamoxifen	Referent			
Tamoxifen			NS	

Table 4

Impact of Comorbidities and Surgical Management on Microvascular Flap Complications in Patients Receiving Tamoxifen

Characteristics	No Complication with Tamoxifen (n = 161) n (%)	Any Complication with Tamoxifen (n = 44) n (%)	p
Age, years			0.2 [^]
Mean	44.9	46.7	
Median (range)	46 (23–70)	47(36–59)	
Body mass index, kg/m ²			0.4
Mean	26.6	27.4	
Median (range)	26 (12–59)	28 (11–44)	
Cardiovascular comorbidities [§]			0.003 [*]
0	134 (83.2)	27 (61.4)	
1	27 (16.8)	17 (38.6)	
Pulmonary disease			1.0 [*]
No	156 (96.9)	43 (97.7)	
Yes	5 (3.1)	1 (2.3)	
Preoperative radiation therapy			0.9 [*]
No	63 (39.1)	16 (36.4)	
Yes	98 (60.9)	28 (63.6)	
Rheumatologic disease			1.0 [*]
No	156 (96.9)	43 (97.7)	
Yes	5 (3.1)	1 (2.3)	
Smoking			1.0 [*]
Never or quit	151 (93.8)	41 (93.2)	
Current smoker	10 (6.2)	3 (6.8)	
Surgery duration, minutes			0.7
Mean	527.1	517.9	
Median (range)	510 (0–910)	499 (0–834)	
Flap type			0.02 [*]
TRAM, DIEP, or SIEA	159 (98.8)	40 (90.9)	
Other [†]	2 (1.2)	4 (9.1)	
Systemic anticoagulants			0.5 [*]
None	142 (88.2)	41 (93.2)	
Aspirin	13 (8.1)	1 (2.3)	
Heparin sulfate	6 (3.8)	2 (4.5)	
Vein anastomosis technique			0.5 [^]
Hand-sewn, interrupted	83 (51.5)	27 (61.4)	
Coupled	46 (28.6)	9 (20.4)	
Hand-sewn, running	32 (19.9)	8 (18.2)	

DIEP, deep inferior epigastric perforator; TRAM, transverse rectus abdominis myocutaneous; SIEA, superficial inferior epigastric artery.

[^] Rank-sum test.

^{*} Fisher's exact test.

[§] Includes diabetes mellitus (type 1 or 2), coronary artery disease, history of myocardial infarction, and peripheral vascular disease.

[†] Other flaps included superior gluteal artery perforator, inferior gluteal artery perforator, microvascular latissimus dorsi myocutaneous, and Rubens.

Table 5

Multivariate Comparison of Impact of Patient and Surgical Factors on Risk of Microvascular Flap Complications in Patients Receiving Tamoxifen

	Odds Ratio	Standard Error	<i>p</i>	95% Confidence Interval
Any complication				
Cardiovascular comorbidities [*]				
None	Referent			
1	3.1	1.2	0.002	1.5–6.5
Follow-up complication				
No associated factors				
Immediate complication				
Free flap type				
TRAM, DIEP, or SIEA	Referent			
Other [^]	3.1	1.3	0.009	1.3–7.1

DIEP, deep inferior epigastric perforator; TRAM, transverse rectus abdominis myocutaneous; SIEA, superficial inferior epigastric artery.

^{*} Diabetes mellitus (type 1 or 2), coronary artery disease, history of myocardial infarction, and peripheral vascular disease.

[^] Superior gluteal artery perforator, inferior gluteal artery perforator, microvascular latissimus dorsi myocutaneous, and Rubens.

Table 6Rates of Immediate and Follow-up Complications by Tamoxifen Status^{*}

	No Tamoxifen n (%)	Tamoxifen n (%)	<i>p</i>
Immediate complications			0.02
Arterial insufficiency [€]	2 (0.4)	0	
Flap thrombosis [¶]	7 (1.5)	3 (1.5)	
Partial flap necrosis	9 (1.9)	5 (2.4)	
Venous congestion [€]	4 (0.9)	7 (3.4)	
Total flap loss [‡]	2 (0.4)	6 (2.9)	
Pulmonary embolus	1 (0.2)	0	
Follow-up complications			0.08
Partial flap necrosis	42 (9.0)	23 (11.2)	
Fat necrosis	2 (0.4)	2 (1.0)	
Total flap loss [‡]	0	2 (1.0)	
Pulmonary embolus	0	1 (0.5)	

^{*} In patients with more than 1 complication, only 1 complication—the most detrimental complication—was counted. For example, if a patient had a flap loss due to a vessel thrombosis, only the flap loss was counted. Similarly, if a venous thrombosis occurred, venous congestion was not counted.

[€] Arterial insufficiency or venous congestion that did not result in vessel thrombosis or flap loss.

[¶] Flaps were not lost; rather, they were salvaged with revision of microsurgical anastomoses either at the time of initial surgery or postoperatively.

[‡] Of the 8 cases of immediate flap loss, 4 were due to arterial thromboses and 4 were due to venous thromboses

[‡] In 1 case, arterial thrombosis was noted on postoperative day 13. In the other case, there was venous congestion (insufficiency) postoperatively, and on a follow-up clinic visit, the flap was found to be not viable.