

Impact of neoadjuvant chemotherapy on wound complications after breast surgery

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SUMMARY

Background: Benefits from the neoadjuvant approach are survival benefits and breast conservation surgery rather than mastectomy. The purpose of our study was to evaluate the incidence and risk factors that influence early local complications in patients that had breast surgery after neoadjuvant polychemotherapy.

Methods: This retrospective study was undertaken with 361 breast cancer patients (women) who were treated at the Oncology Institute of Vojvodina from January 2007 to December 2012. In the first group (N1=103) were the patients who underwent neoadjuvant polychemotherapy and in the second group (N2=258) were patients who did not take neoadjuvant polychemotherapy. Surgery procedures were breast conservative surgery, mastectomy, or nipple sparing mastectomy with immediate breast reconstruction, depending on tumor stage after polychemotherapy. Median follow-up of patients after operation was 49 months (ranging from 15 to 75 months).

Results: The average reduction of tumor volume after neoadjuvant polychemotherapy was 30%. Most common complications were prolonged seroma formation and minor skin necrosis. Obesity, older age, smoking, and diabetes mellitus were recognized as risk factors for early postoperative complications after neoadjuvant polychemotherapy ($p < 0.05$).

Conclusion: Obesity, older age, smoking, and diabetes mellitus were recognized as risk factors for early postoperative complications after neoadjuvant polychemotherapy.

Key words: Breast Neoplasms; Neoadjuvant Therapy; Drug Therapy; Postoperative Complications; Risk Factors

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INTRODUCTION

Neoadjuvant polychemotherapy (PCT) treatment of breast cancer is established as safe and often effective therapeutic approach of choice for locally advanced breast cancer, thus offering the possibility of reducing the extent of surgery (1-7).

There are several factors contributing to the decision which approach is better - the breast conserving surgery (BCS) or mastectomy - the first factor being the tumor/breast ratio. Women with large tumor and small breasts are candidates for mastectomy and *vice versa*. Benefits from the neoadjuvant approach may be complete response (survival benefits) and the possibility to undergo breast conservation, rather than mastectomy (1-7). Extensive ductal carcinoma *in situ* (DCIS), multiple and multicentric tumors may necessitate a mastectomy in order to ensure the complete tumor removal (8-16). After BCS, it is important to have a margin of normal breast tissue around the tumor. If cancer cells are found at or near the edges of the breast tissue removed, additional surgery may be necessary. If a large amount of tissue has been removed and the margins are still involved, mastectomy may be recommended. Tumors that are in the center of the breast or involve the nipple or the skin may be treated with a mastectomy or breast conserving surgery, depending upon the expected cosmetic results.

Some women may be candidates for BCS but may be at a high risk of developing another breast cancer. These include very young women, women with a known breast cancer gene mutation, or women with a very strong family history of breast cancer. These women may consider bilateral mastectomy to not only treat the known cancer, but also prevent a second cancer in the future (11).

Because breast is a peripheral soft tissue organ, many wound complications related to breast procedures are relatively minor and frequently are

managed on an outpatient basis. It is therefore difficult to establish accurate incidence rates for these events. Reported studies document that surgical morbidity from breast and/or axillary wound infections, seromas, and hematomas occur in up to 30% of cases (8-16). Less than half of these cases require a prolongation of hospital stay or a readmission for inpatient care. Obesity, older age, smoking of cigarettes and diabetes mellitus are considered as risk factors for breast wound sepsis.

The purpose of this study was to evaluate the incidence and risk factors that influence early local complications in patients who underwent breast surgery after neoadjuvant PCT.

PATIENTS AND METHODS

This retrospective study included 361 breast cancer patients (women) who were treated at the Oncology Institute of Vojvodina from January 2007 to December 2012. In the first group (N1=103) were the patients who underwent neoadjuvant PCT, and in the second group (N2=258) were patients who did not take neoadjuvant PCT.

Mean patient age was 47 years (range: 30 to 79 years). Most of them (145; 40.17%) were from 40 to 49 years of age.

Before surgery, all patients underwent clinical examination and imaging procedures: ultrasound (US), mammography, and magnetic resonance imaging (MRI) mammography. MRI mammography had to be done if the previous reviews were not reliable enough or when other methods could not exclude multicentricity of the tumor.

Histopathological (HP) confirmation of the diagnosis was established preoperatively with core biopsy. After HP confirmation of the diagnosis, all patients at N1 group were administrated neoadjuvant PCT (FAC in 85% and AC in 15% of patients).

All the patients preoperatively were administered with prophylactic dose of broad-spectrum antibiotics (1.5 g of cefuroxime), one hour before the operation and the same dose was repeated the following day.

Surgery procedure included breast conservative surgery, mastectomy or subcutaneous mastectomy with immediate breast reconstruction using silicone implants (Mentor Contour Profile®, Minneapolis, USA), depending of tumor stage after PCT.

After the operation, the patients were clinically controlled by the surgeon and medical oncologist every 3 months during the first year, and then every 6 months during the second and the third year. The appointments for further controls are made once a year. Radiological controls, mandatory US examinations of reconstructed breast and axilla, and other imaging are usual postoperative procedures. Median follow-up of patients after operation was 49 months (ranging from 15 to 75 months).

Statistical analysis

For statistical analysis of our data, we used the SPSS V.16. All the data were grouped and statistically analyzed (median, percentage, average value), and presented in tables and charts. Fischer's exact test and χ^2 tests were used to compare the data between the groups. Values of $p < 0.05$ were considered as statistically significant.

RESULTS

T3 stage tumors were found in 112 (31.02%) of patients and tumors from 2 cm to 5 cm in diameter (T2) were identified in 106 patients in both groups. Ductal carcinoma was found in 333 (92.24%) and lobular carcinoma in 28 (7.76%) patients. One hundred fifteen patients were in IIIA cancer stage, and 106 at IIB stage (Table 1 and Table 2).

Table 1. Tumor characteristics (T stage)

	N1 N (%)	N2 N (%)	Total N (%)
T2	26 (7.20)	80 (22.16)	106 (29.36)
T3	29 (8.03)	83 (22.99)	112 (31.02)
T4a	11 (3.05)	41 (11.36)	52 (14.40)
T4b	19 (5.26)	28 (7.76)	47 (13.02)
T4c	8 (2.22)	10 (2.77)	18 (4.99)
T4d	10 (2.77)	16 (4.43)	26 (7.20)
Total	103 (28.53)	258 (71.47)	361 (100.00)

Table 2. Clinical stage

	N1 N (%)	N2 N (%)	Total N (%)
IIb	26 (7.320)	80 (22.16)	106 (29.36)
IIIa	32 (8.86)	83 (22.99)	115 (31.86)
IIIb	35 (9.70)	69 (19.11)	104 (28.81)
IIIc	8 (2.22)	11 (3.05)	19 (5.26)
IV	2 (0.55)	15 (4.16)	17 (4.71)
Total	103 (28.53)	258 (71.47)	361 (100.00)

Average reduction of tumor volume after neoadjuvant PCT was 30%, (44.65 x 38.26 x 25.97 mm to 32.26 x 24.09 x 16.68 mm). Measurements were made by US before and after PCT. Complete response (T1 stage) was identified in 7 (6.78%) patients (5 patients with T2 stage and 2 patients with T3 stage). However, 12 patients (11.65%) had a progression of tumor stage (6 patients from T2 to T3, 5 from T4b, and 1 from T4c to T4d).

Operative treatment depends on tumor/breast volume. Because of that, in 98 (27.15%) patients we performed nipple-sparing mastectomy with immediate reconstruction with silicone implants, simple mastectomy was

Table 3. Breast surgery procedures

	N1		N2	
	Patient N (%)	Complications N (%)	Patient N (%)	Complications N (%)
Conservative surgery	39 (37.86)	8 (7.77)	159 (61.63)	18 (6.98)
Mastectomy	22 (21.36)	4 (3.88)	43 (16.67)	2 (0.78)
Nipple sparing mastectomy with immediate reconstruction	42 (40.78)	16 (15.53)	56 (21.71)	6 (2.33)
Total	103 (100.00)	28 (27.18)	258 (100.00)	26 (10.08)

Table 4. Postoperative complications

Complication	N1	N2
	Number N (%)	Number N (%)
Epidermolysis	2 (1.94)	3 (1.16)
Minor infection	3 (2.91)	2 (0.78)
Major infection	2 (1.94)	2 (0.78)
NAC necrosis	2 (1.94)	3 (1.16)
Skin and NAC necrosis	3 (2.91)	1 (0.39)
Major skin necrosis	4 (3.88)	1 (0.39)
Minor skin necrosis	5 (4.86)	1 (0.39)
Prolonged serosa formation	6 (5.83)	10 (3.88)
Hematoma	1 (0.97)	3 (1.16)
Prosthesis explantation due to postoperative complications	4 (3.88)	0 (0.00)
Total	28 (27.18)	26 (10.08)

Table 5. Risk factors for postoperative complications

FACTOR		N1		N2		p value
		COMPLICATIONS		COMPLICATIONS		
		YES	NO	YES	NO	
Obesity (BMI >27.5)	Yes	20	3	11	33	p<0.05
	No	8	72	15	199	
Older age < 65 years	Yes	11	5	13	30	p<0.05
	No	17	70	13	202	
Smoking	Yes	21	8	22	42	p<0.05
	No	7	67	4	190	
Diabetes mellitus (DM)	Yes	10	3	23	8	p<0.05
	No	18	72	3	224	

done in 65 (18.01%) patients, and breast conservative surgery in 198 (54.85%) patients (Table 3).

Most common complications were prolonged seroma formation and minor skin necrosis. In case of 4 patients (3.88%) from N1 group we removed silicone implant because of necrotic and inflammatory complications (Table 4).

Obesity, older age, smoking, and diabetes mellitus are recognized as risk factors in early postoperative complications after neoadjuvant PCT ($p<0.05$) (Table 5).

DISCUSSION

Female breast cancer incidence is strongly related to age, with the highest incidence being in older women. Most of our patients were between 40 to 69 years old (80.89%). Age-specific incidence rates highly increase from around age 35 to 39, then rise further to age 65 to 69, drop slightly for women aged 70 to 74 years, then increase steadily to reach an overall peak in the 85+ age group (1-18).

Stage of a cancer does not change over time, even if the cancer progresses. Most of our patients were in stage III of disease (65.93%). One hundred and six patients were in stage II and 17 patients were in stage IV. Because of disease stage, we performed 98 (27.15%) subcutaneous mastectomies with immediate reconstruction with silicone implants, 65 (18.01%) simple mastectomies and 198 (54.85%) breast conserving surgery (quadrantectomy, segmentectomy). That is in accordance with results from other authors (8-16). Some studies show that women with localized breast cancer have same chances to survive breast cancer, whether they are treated with breast conserving surgery or with mastectomy (17, 18).

Most common complications in our patients from both groups were prolonged seroma formation (4.43%) and minor skin necrosis (1.66%). There was statistical difference between number of complications in N1 and N2 group (27.18:10.08) ($p<0.05$). There was no consistent correlation between the risk of wound infection and mastectomy versus lumpectomy as definitive breast cancer surgery ($p>0.05$). Necrotic complications such as skin flap necrosis, partial nipple loss, and complete nipple loss are common complications after nipple sparing mastectomy. Erythema that resolved with oral antibiotic treatment was not included as a complication. Skin flap necrosis is defined as a full-thickness skin loss (14). In 4 patients (3.88%) from N1 group we removed silicone implant without replacement because of necrotic and

inflammatory complications, but it did not exclude the possibility of future (secondary) reconstruction. In comparing our result in necrotic complications after breast surgery (all operative procedures) with the results from other authors' we found similarity (14%:16%) (8-11, 14-16).

Patients who underwent operative treatment for breast cancer had a lower risk for wound infection if the diagnosis had been established by prior needle biopsy rather than by an open surgical biopsy (11, 12).

Use of preoperative antibiotic coverage to minimize infection rates has been evaluated in multiple retrospective trials, and in prospective, randomized, controlled trials. These studies have yielded disparate results; many have shown that a single dose of a preoperative antibiotic (usually a cephalosporin, administered approximately 30 minutes preoperatively) effectively reduces wound infection rates by 40% (12).

The rich lymphatic drainage of the breast from intramammary lymphatics to the axillary, supraclavicular, and internal mammary nodal basins establishes the tendency for seroma formation within any closed space that results from breast surgery. After a lumpectomy, this seroma is advantageous to the patient, because it usually preserves the normal breast contour even after a large-volume resection, eventually being replaced by scar formation as the cavity consolidates. Seroma formation under the skin flaps of axillary or mastectomy wounds impairs the healing process; therefore drains are usually left in place to evacuate postoperative fluid collections. After 1 to 3 weeks, the skin flaps heal and adhere to the chest wall, as evidenced by diminished drain output. Seroma collections that develop after drain removal can be managed by percutaneous aspiration. Seroma aspiration is necessary in 10% to 80% of axillary lymph node dissection and mastectomy cases, according to reported series and as reviewed in detail by Pogson and colleagues (15).

Widespread use of electrocautery has reduced the incidence of hematoma formation in breast surgery dramatically. The pressure of the implant reduces hematoma formation, but this complication still occurs in 2% to 10% of cases (10) (2% in both our groups). Large hematomas can be quite painful because of rapid expansion through the closed wound space and should be evacuated surgically, with aggressive wound irrigation and reclosure to optimize cosmetic output.

Unlike Decker (9), we showed that factors like obesity, older age, smoking, and diabetes mellitus are risk factors for early postoperative complications after neoadjuvant PCT.

CONCLUSION

1. The incidence of postoperative wound complications after neoadjuvant PCT and breast cancer surgery was 27% and only 10% after surgery without neoadjuvant PCT.
2. Obesity, older age, smoking, and diabetes mellitus were recognized as risk factors for early postoperative complications after neoadjuvant PCT.

Conflict of Interest

We declare no conflicts of interest.

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