Original Article

Does neoadjuvant chemotherapy for breast cancer increase complications during immediate breast reconstruction?

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Background: Neoadjuvant chemotherapy (NAC) has been administered since the 1990s and is now one of the major treatments for breast cancer. It can achieve extremely positive results in some patients. Whether NAC affects immediate breast reconstruction (IBR) using an expander, however, remains unclear.

Methods: A retrospective study was performed at Tokyo Medical and Dental University (TMDU) hospital. Seventy-five cases of immediate breast reconstruction using an expander were performed in 69 patients between January 2001 and January 2007. The patients were evaluated for tumor size, histological type, sites of invasion, staging, lymph node metastasis, NAC regimen, response to NAC, type of immediate breast reconstruction (IBR), complications, and prognosis.

Results: In patients treated with an expander, there was no significant difference in the complication rate between those who underwent NAC and those who did not.

Conclusions: NAC did not increase the complication rate after IBR using an expander. However, for reconstruction using autologous tissue, more data are needed.

Key Words: Neoadjuvant Chemotherapy, Immediate Breast Reconstruction.

Introduction

In Japan, neoadjuvant chemotherapy (NAC) has been administered to patients with breast cancer since the 1990s and is now becoming the standard treatment. NAC enables downstaging of the tumor and conservation of the breast during subsequent surgery. Although it was at first administered only to patients with locally advanced disease, as efficacy and availability have improved, NAC has been extended to patients with earlier stage disease without affecting the treatment outcome. This reflects a global trend that recognizes the value of NAC in line with growing acknowledgement of the utility of chemotherapeutic agents.

Breast reconstruction also plays an important role in ongoing treatment for breast cancer. Historically, there was anxiety that immediate breast reconstruction (IBR) might adversely affect prognosis, hence breast reconstruction was not performed until the patient had completed oncological treatment and risk of recurrence was therefore low. However IBR has since been demonstrated to have many advantages over secondary breast reconstruction in terms of psychological, esthetic, and economic benefits. As more and more patients choose IBR over secondary breast reconstruction, it seems likely that IBR will be performed with increasing frequency.

Therefore, both NAC and IBR are valuable in treating breast cancer patients and improving their quality of life. At present, the literature contains few studies of the effect of NAC on IBR. We retrospectively investigated whether NAC increases complications after IBR.
Table 1 patient characteristics

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<th>non NAC</th>
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<td>63</td>
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<td>43.3(30-57)</td>
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<tr>
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Patients and Methods

Between January 2001 and January 2007, we performed IBR using an expander following breast resection in 69 patients (75 breasts) at Tokyo Medical and Dental University (TMDU) Hospital.

We divided the patients into two groups: one that underwent NAC (NAC group; 9 patients, 12 breasts) and one that did not (non-NAC group; 60 patients, 63 breasts). Average patient age was 45.3 years (range=26-63) and 43.3 years (30-57) respectively. In the NAC group and non-NAC groups, stage II comprised the majority. Invasive ductal carcinoma was the most frequent histological type. Three cases were classified as Phyllodes type, which is not staged according to the same system as other breast tumors. The stage and histological type were determined by the Japanese Breast Cancer Society’s General Rules for Clinical and Pathological Recording of Breast Cancer. (Table 1)

NAC was defined here as chemotherapy that preceded surgical treatment and used chemotherapeutic regimens including EC (epirubicin, cyclophosphamide), FEC (fluorouracil, epirubicin and cyclophosphamide), paclitaxel, and docetaxel, but excluding endocrine therapy. Patients were eligible for NAC if the following conditions were met: i ) tumor larger than 2 cm; ii ) stage 2 or 3 disease; iii ) age under 60; and iv ) performance status 0~1. At our hospital, we recommend NAC to all suitable candidates. If patients consent to NAC, we start the regimen immediately and perform thorough follow-up with magnetic resonance imaging every two months. Nevertheless, many patients are reluctant to undergo NAC and prefer to have surgery as soon as possible.

For patients undergoing NAC, we do not usually administer postoperative chemotherapy, contrary to standard practice abroad, which places almost equal
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emphasizes on postoperative chemotherapy and NAC. 28 to 71 days after the completion of NAC, breast resection and breast reconstruction were performed. For patients wanting breast reconstruction, we present 3 methods: expander, transverse rectus abdominis musculocutaneous (TRAM) flap, and latissimus dorsi (LD) flap. We explain the advantages and disadvantages of each method and select according to the patients’ wishes. When an expander is used, we place it under pectoralis major and gradually inflate it at outpatient clinic visits. After 4-6 months, the expander is replaced with a breast implant.

We performed 52 nipple-sparing mastectomies and 23 skin-sparing mastectomies among the present patients (Table 1).

After discharge, we continued to follow the patients, initially once a week, gradually prolonging the interval between examinations. We investigated all signs of complications.

Data were analyzed using computer software (Microsoft Office Excel 2007). Fisher’s exact test was used to assess the significance of differences between the NAC group and the non-NAC group, and in the NAC group. Student’s t test was used to assess the significance of differences between those who experienced complications and those who did not in terms of duration of NAC and interval from NAC to reconstruction. For all analyses P values <0.05 were considered significant.

Results

We respectively examined the complication rate in the NAC and non-NAC groups. In the non-NAC group, nipple-areola necrosis occurred in 8/44 (18.2%), skin flap necrosis in 7 (11.1%), infection in 2 (3.2%), hematoma in 3 (4.8%), seroma in 2 (3.2%), and the overall complication rate was 19 of 63 breasts (30.2%). In the NAC group, nipple-areola necrosis occurred in 1/8 (12.5%), skin flap necrosis in 2 (16.7%), infection in 1 (8.3%), hematoma in 1 (8.3%), seroma in 0 (0%), and the overall complication rate was 3 of 12 breasts (25%). (Figure 1) All patients who developed nipple-areola necrosis underwent nipple-sparing mastectomy.

There were no significant differences between the two groups in terms of each complication and overall complications.

During follow-up, we confirmed no local recurrences and 2 distant metastases in the non NAC group (average 32 months after surgery), and no local recurrences and 1 distant metastasis in the NAC group (11 months after surgery).

Among patients who underwent NAC, those with complications were compared to those without. Average duration of NAC was significantly shorter in those with complications than in those without (150 days, range=148-155 days vs. 167 days, range=150-177 days; P=0.024). (Figure 2)
Average interval from completion of NAC to reconstruction was significantly longer in those with complications than in those without (64.3 days, range=51-71 days vs. 36.4 days, range=28-48 days; P<0.005). (Figure 3)

NAC was found to be histologically effective to a greater or lesser extent in 9 of 12 breasts (data on the other 3 were not available). Treatment effect was assessed as Grade I (less than 2/3 of tumor cells were confirmed to be responsive) in 5 breasts and Grade II (more than 2/3 were) in 4 according Japanese Breast Cancer Society.

Discussion

In the past, chemotherapy was administered to inoperable patients in the terminal stages of cancer, often on a palliative basis. However, particularly in breast cancer, chemotherapy has been demonstrated very effective in shrinking the tumor and downstaging the disease.

Based on this clinical experience, many chemotherapeutic agents and regimens have been developed, and large scale clinical series have been
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examined to confirm the effects. Since the 1990s, chemotherapy has been administered before surgery in patients who have a high risk of recurrence and metastasis. This treatment, known as NAC, has two effects: one is to make tumors more amenable to breast-conserving surgical techniques, and the other is to eradicate micrometastases that cannot be visualized with existing imaging techniques. The efficacy of NAC is now well established. According to the Breast Conservative Treatment Guidelines produced by the Japan Breast Cancer Society, breast-conserving surgery can be performed when there is no spreading calcification and tumors are smaller than 3 cm in diameter. In some cases, NAC is sufficiently effective to allow the conservative treatment that many patients hope for.

NAC has limitations, however, including cancer progression in cases of low clinical response, and side effects such as bone marrow inhibition, vomiting, and alopecia. Moreover, patients on NAC must attend hospital for regular follow-up, and cost benefit ratio is not always favorable.

For the patients scheduled for breast resection or those in whom breast deformity is expected after NAC, breast reconstruction is the best way to relieve psychological distress and improve quality of life. IBR is particularly attractive to patients because it provides significant psychological, practical, and psychological and practical benefits. In our hospital, patients hoping for reconstruction usually prefer immediate reconstruction to secondary reconstruction.

There was previously some anxiety about whether IBR would delay discovery of local recurrence, reducing the long-term survival rate. Furthermore, there was concern that it might delay the resumption of postoperative therapies. Thus, IBR was not initially favored from an oncological perspective and reconstruction was usually performed in a second procedure after the completion of adjuvant therapies. During the past decade, however, many surgical teams have demonstrated the safety of IBR.

In such situations, concern naturally arises about the safety of IBR after NAC. One major area for concern is the possibility of an increase in complications. Disruption of wound-healing and induction of postoperative infection are major factors related to complications. Several variables influence wound healing in the context of chemotherapy. Wound healing is completed by a series of events involving many factors such as cytokines, collagen fibers, and other substances needed for neovascularization. Chemotherapeutic agents have an immunosuppressive effect and are known to interfere with the healing of surgical wounds. However, the majority of patients do not show any significant delay in wound healing. This is in part attributable to variation in chemotherapeutic agents, dosage, and duration, and the complex interaction of these factors influences the patient’s condition after chemotherapy. It is therefore difficult to draw conclusions regarding the effect of NAC on wound healing.

White blood cell (WBC) count is another major factor related to complications. Leukopenia can delay the timing of surgery and induce infection. Some authors recommend that the WBC count should be 3000 or greater at the time of surgery. In this study, the only patient not to meet this requirement was one woman who had a WBC of only 1700 19 days before surgery. Nonetheless, this patient developed no complications despite having bilateral cancers. This finding supports a lower WBC limit of 3000 as an appropriate value in a study of this scale.

NAC duration and the interval between NAC completion and surgery may also affect the complication rate. We examined data from 12 breasts of 9 patients receiving NAC and found that those developing complications had a shorter duration of NAC and longer interval between NAC completion and surgery against our expectation. This indicates that these two factors are not decisive when judging relation to complications.

Limited literature is available on the combination of NAC and immediate reconstruction. In 1995, Godfrey et al. examined 11 patients receiving NAC and found no significant difference in complications compared to 10 patients who underwent immediate reconstruction with autologous tissue. In 1999, Deutsch et al. reported that immediate reconstruction with a TRAM flap could be performed safely in patients on a neoadjuvant protocol. Reconstruction with autologous tissue after NAC has been mentioned in some articles, and the safety of this approach is gradually being established. In the present study, however, only 3 patients (3 breasts) undergoing NAC had IBR using autologous tissue, which makes analysis of complications related to this combination difficult.

One limitation of this study is the heterogeneity
of the chemotherapy. Not all patients received the same chemotherapeutic agents; therefore, there may be differences in subsequent events because of the different mechanisms.

In summary, this study demonstrates that in patients treated with an expander there was no significant difference in the complication rate between the NAC group and the non NAC group. However, because of the small size and retrospective nature of this study, further investigation is needed to confirm the conclusion.

References