Preoperative Chemotherapy for Operable Breast Cancer Improves Surgical Outcomes in the Community Hospital Setting

IAN K. KOMENAKA,^{a,b} MICHAEL L. HIBBARD,^a CHIU-HSIEH HSU,^{b,c} BOO GHEE LOW,^d
JASON A. SALGANICK,^e MARCIA E. BOUTON,^a CHANDRA JHA^f

^aMaricopa Medical Center, Department of Surgery, Phoenix, Arizona, USA; ^bArizona Cancer Center, University of Arizona, Tucson, Arizona, USA; ^cMel and Enid Zuckerman Arizona College of Public Health, University of Arizona, Tucson, Arizona, USA; ^dSouthwest Hematology Oncology, Phoenix, Arizona, USA; ^eUS Oncology, Arizona Oncology Associates, Phoenix, Arizona, USA; ^fMaricopa Medical Center, Department of Medicine, Phoenix, Arizona, USA

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ABSTRACT

Background. Preoperative chemotherapy (PC) for operable breast cancer has demonstrated significant benefits in clinical trials. Many patients are treated in the community setting and some may question the applicability of PC outside the university setting. The potential benefits of PC in terms of surgical outcomes in a community practice were examined.

Methods. A retrospective review was performed of stage II and stage IIIA breast cancer patients from January 1, 2002 to July 31, 2009. Surgical outcomes of margin status, volume of lumpectomy, rate of lumpectomy, and re-excision lumpectomy were evaluated.

Results. There were 212 patients included. Seventy-nine percent of patients who underwent PC had a clinical

response and 25% had a pathologic complete response. For clinical stage T2 and stage T3 tumors, the PC group underwent lumpectomy more often than patients in the adjuvant chemotherapy (AC) group (78% versus 50%; $p = .016$ and 60% versus 29%; $p = .015$, respectively). The rate of close or positive margins in the PC group was half the rate in the AC group (23% versus 46%; $p = .04$) and this resulted in fewer re-excisions ($p = .01$). The volume of tissue removed was also smaller in the PC group (143.6 cm³ versus 273.9 cm³; $p = .003$).

Conclusions. PC for operable breast cancer can significantly improve surgical outcomes in community-based practice. *The Oncologist* 2011;16:752–759

INTRODUCTION

Patients treated with preoperative chemotherapy (PC) for operable breast cancer had similar survival benefits to those

treated with adjuvant chemotherapy (AC) in the prospective, randomized clinical trials National Surgical Adjuvant Breast and Bowel Project (NSABP) B18 and NSABP B27

Correspondence: Ian K. Komenaka, M.D., Hogan Building, 2nd Floor, 2601 E Roosevelt Street, Phoenix, Arizona 85008, USA. Telephone: 602-344-5368; Fax: 602-344-1299; e-mail: Komenaka@hotmail.com Received August 10, 2010; accepted for publication February 22, 2011; first published online in *The Oncologist Express* on May 9, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 doi: 10.1634/theoncologist.2010-0268

[1–4]. Although there were no differences in survival outcomes, there were significant benefits recognized in patients who received PC. First, PC allows an *in vivo* test of chemosensitivity of the cancer. Tumor response as measured by the postchemotherapy pathologic tumor burden in the breast and lymph nodes correlates with overall survival [3–5]. In addition, in patients who do not respond to the chemotherapeutic regimen, optimization of therapy can be achieved by terminating the current regimen and changing to a different regimen or different type of treatment [5, 6]. In patients undergoing AC, this type of adjustment is not possible because there is no reliable clinical marker for monitoring tumor response in the adjuvant setting once the primary tumor and lymph nodes have been removed.

Although there is no difference in survival compared with mastectomy, breast-conserving operations are the preferred operative management for patients with early-stage breast cancer [7, 8]. In the NSABP B18 and NSABP B27 studies, PC resulted in a higher rate of breast-conserving operations performed and higher rate of pathologically negative lymph nodes than in patients who underwent AC [1, 2]. The higher rate of breast-conserving operations was obtained without a significantly higher risk for local recurrence [1–3, 5]. In patients with cancers ≥ 3 cm in size, Bonadonna et al. [3] demonstrated a 6.8% risk for local recurrence as a first event at 65 months of follow-up in patients who underwent a breast-conserving operation after PC. Outside the clinical trial setting and away from the tertiary cancer center, however, surgical intervention remains the most common initial treatment for operable breast cancer.

Evaluation of breast cancer operations cannot be limited only to assessment of the rate of breast conservation. Attainment of negative margins is one of the most important factors in performing the breast-conserving operation and is critical to minimizing the risk for local recurrence [9]. The goal of attaining a negative margin must be balanced with cosmetic outcome. Although removal of a larger volume of tissue may facilitate attainment of negative margins, this results in a poorer cosmetic outcome [10, 11]. For most women, breast cancer treatment significantly impacts multiple facets of their lives and their quality of life [8, 12]. Therefore, achievement of negative margins by removing the smallest volume of tissue should be the goal for breast-conserving operations.

Perhaps one reason for the lack of use of PC is the question of its applicability away from the high-volume tertiary referral cancer center. Many patients are treated in the community setting and some physicians may question the benefits of PC and its applicability in the “nonresearch” patient care practice. Some practitioners may believe that because

overall survival is the same whether chemotherapy is given preoperatively or in the adjuvant setting, the only clinical indication for PC is to give a patient with a large cancer the possibility of conserving her breast. In modern breast cancer treatment, with better technology allowing physicians to determine more accurately which patients benefit from chemotherapy, PC can be applied to a more appropriate and carefully selected patient population [13–22].

We sought to examine the applicability of PC for operable breast cancer in the community setting and the potential benefits to surgical outcomes.

METHODS

Maricopa Medical Center is a 679-bed facility that is the county, safety-net hospital in Phoenix, Arizona, and serves a patient base that is 34.5% non-English speaking, and the majority of the patients treated are underinsured. Underinsured patients were considered to be all patients without commercial insurance. In the state of Arizona, these patients are covered by Medicare and the Arizona Health Care Cost Containment System (AHCCCS, Medicaid). Patients ineligible for AHCCCS were classified as uninsured self-pay or charity care patients. Institutional review board approval was obtained prior to the start of the study.

A retrospective review was performed of all breast cancer patients treated for their primary breast cancer in January 1, 2002 to July 31, 2009. Only patients who presented with American Joint Committee on Cancer (AJCC) clinical stage IIA, IIB, or IIIA breast cancer were included in the study. All patients having their primary operation prior to January 1, 2002 were excluded. Patients presenting with AJCC clinical stage 0, I, IIB (T4), or IV cancers were excluded. Other criteria excluded all male patients and all patients with a second primary or recurrence who had their primary breast cancer prior to January 1, 2002. After exclusions, a total of 212 patients comprised the study population. Sociodemographic information, clinical characteristics, and surgical outcomes for all patients were collected. Patients were offered PC if they satisfied the following criteria. First, they had to have been determined to require chemotherapy as part of their treatment based on their clinical presentation and diagnostic biopsy results. Second, they had to be interested in preserving their breast but the size of the cancer at presentation required a mastectomy. Finally, in some patients who were already candidates for breast conservation, PC was offered to allow a smaller, more cosmetically acceptable lumpectomy; if the patient had clinically suspicious lymph nodes (with the hope of avoiding an axillary dissection); or if the patient was interested in personal clinical response to the chemotherapy. For all patients, the chemotherapeutic regimen was

the choice of the treating oncologist. In the PC group, the regimens included doxorubicin and cyclophosphamide (six of 57 patients, 11%), doxorubicin and cyclophosphamide followed by paclitaxel (29 of 57 patients, 51%), doxorubicin and cyclophosphamide followed by docetaxel (eight of 57 patients, 14%), docetaxel, doxorubicin, and cyclophosphamide (five of 57 patients, 9%), trastuzumab-containing regimens (seven of 57 patients, 12%) and other regimens (two of 57 patients, 4%).

Surgical Outcomes

Patients were classified into two groups based on whether they underwent PC (PC group) or AC (AC group). Then, based on presenting clinical tumor size, the initial operation performed was reported (mastectomy or breast-conserving operation). The preoperative history and physical examination note, operative note, and mammogram report were reviewed. If a patient had a documented contraindication to breast conservation (i.e., multicentric disease, extensive microcalcifications, etc.) and therefore underwent a mastectomy, she was excluded from the analysis. Margin status was evaluated in all patients who underwent a breast-conserving operation. Those with microscopic evidence of a transected (tumor touching ink) margin were considered to have a positive margin. Those with microscopic evidence of a tumor within 1 mm of an inked margin were considered to have a close margin. The number of patients who underwent a re-excision lumpectomy was recorded. The volume of breast tissue removed was determined by the product of the anterior–posterior, medial–lateral, and inferior–superior diameters listed on the pathology report.

Pathologic nodal status was the nodal status determined at operation. The sentinel node procedure at our institution has been described previously [23]. In brief, the sentinel node procedure was performed using the combination technique of blue dye and radioactive isotope. The radiocolloid injection was performed in the nuclear medicine suite approximately 1–7 hours prior to the operation in an intradermal periareolar fashion. Three milliliters to 5 ml of blue dye (isosulfan or methylene) was injected in the operating room after anesthesia was administered. The blue dye was injected intraparenchymally in a subareolar fashion. All nodes that were identified as blue stained or radioactively the hottest, and any node with a radioactive count within 10% of the hottest node were considered sentinel nodes. In addition, any node that was palpably abnormal was considered a sentinel node. A level I and level II axillary dissection was performed if any of the sentinel lymph nodes were involved with cancer. If a micrometastasis (<2 mm) was identified in any of the sentinel nodes, a completion axillary

dissection was performed at the discretion of the attending surgeon after discussion with the patient.

Statistical Considerations

The study population was classified into two groups based on whether the patient received PC or was expected to have AC by the treating physician. Differences in sociodemographic characteristics, clinical measures, and outcomes of breast cancer care were evaluated in the study population. For categorical variables, the Fisher's exact test for independence was used to determine differences between the two populations. For each continuous variable, for example, age, body mass index, etc., the mean and standard deviation were reported. Unpaired (two-sample) *t*-tests were used to compare means of the two populations. All statistical tests were two-sided and a *p*-value $\leq .05$ was considered statistically significant.

RESULTS

There were 212 patients included in the study period. Sociodemographic information is shown in Table 1. Patients in the PC group were significantly younger and more likely to be premenopausal than patients in the AC group. Patients in the PC group were more likely to be employed than those in the AC group. There was no difference, however, in insurance status between the two groups. Most patients in both groups were Hispanic and insured by AHCCCS (Medicaid) or uninsured. Very few patients in either group had undergone a screening mammogram within 2 years of diagnosis (Table 1).

The clinical presentation of patients in the PC group was more advanced than that of patients in the AC group. Patients in the PC group presented with a larger mean tumor size (4.6 cm versus 3.3 cm) and later clinical stage (Table 2). The histopathologic factors were similar with respect to predominant histology, histologic grade, estrogen receptor status, progesterone receptor status, and rate of triple-negative disease. There was a high rate of poorly differentiated tumors in both groups. Patients in the PC group were more likely to have human epidermal growth factor receptor 2/neu overexpressed by immunohistochemistry or amplified by fluorescence in situ hybridization than patients in the AC group.

PC resulted in a clinical response in 79% (45 of 57) of patients. Of these, 54% (31 of 57) had a clinical complete response and 25% (14 of 57) had a clinical partial response. The remaining 21% (12 of 57) had either stable disease or disease progression and were classified as nonresponders. Overall 25% (14 of 57) of patients had a pathologic complete response.

For clinical stage T2 (2–5 cm) breast cancers, patients in

Table 1. Sociodemographic information and use of screening mammography for stage IIA, IIB, and IIIA patients

Characteristic	Adjuvant chemotherapy (n = 155)	Preoperative chemotherapy (n = 57)	p-value ^a
Mean age (SD)	53.6 (14.46)	44.1 (9.96)	.0001
<50 yrs	70 (45%)	38 (67%)	.008
≥50 yrs	85 (55%)	19 (33%)	
Menopausal status			.003
Pre-/perimenopausal	67 (43%)	38 (67%)	
Postmenopausal	88 (57%)	19 (33%)	
Mean BMI (SD), kg/m ²	29.3 (7.72)	28.5 (6.22)	.48
Race/ethnicity			.41
White	54 (35%)	16 (28%)	
African American	10 (6%)	4 (7%)	
Hispanic	83 (54%)	35 (61%)	
Other	8 (5%)	2 (4%)	
Employment status			.0001
Employed	27 (17%)	26 (46%)	
Unemployed	94 (61%)	27 (47%)	
Retired/disabled	34 (22%)	4 (7%)	
Insurance			.44
Commercial	2 (1%)	3 (5%)	
Medicare	32 (21%)	6 (11%)	
Medicaid	58 (37%)	23 (40%)	
None	63 (41%)	25 (44%)	
Screening mammogram in the 2 yrs prior to diagnosis (age, 40+ yrs)	14/128 (11%)	2/35 (6%)	.52
Current smoker	41 (26%)	11 (19%)	.37

^aDerived from a Fisher's exact test for categorical variables and a two-sample *t*-test for continuous variables. Abbreviations: BMI, body mass index; SD, standard deviation.

the PC group initially underwent a breast-conserving operation significantly more often than those in the AC group—78% (21 of 27 patients) versus 50% (56 of 111 patients), respectively ($p = .016$) (Table 3). For clinical stage T3 (>5 cm) breast cancers, patients in the PC group initially underwent a breast-conserving operation more often than those in the AC group—60% (18 of 30 patients) versus 29% (12 of 41 patients), respectively ($p = .01$). Some patients in both the AC group and the PC group chose to have a mastectomy despite being considered a candidate for breast conservation. When these patients were excluded from the analysis, the results changed little—for stage T2 disease: PC group, 91% (21 of 23 patients) versus AC group, 58% (56 of 97 patients) ($p = .003$); for stage T3 disease: PC group, 69% (18 of 26 patients) versus AC group, 32% (12 of 38 patients) ($p = .005$). For those patients who did undergo a breast-conserving operation, the rate of close (<1 mm) or positive margins in the PC group was half the rate in the AC group—23% (nine of 38 patients) versus 46% (31 of 68 pa-

tients) ($p = .04$). This resulted in significantly fewer re-excision lumpectomies in the PC group (18%, seven of 38 patients) than in the AC group (41%, 28 of 68 patients) ($p = .01$). The volume of tissue removed was also significantly smaller in the PC group (143.6 cm³) than in the AC group (273.9 cm³) ($p = .003$). For those who underwent a second operation for close or positive margins, more patients underwent a mastectomy in the AC group (six patients) than in the PC group (one patient). The final surgical procedure for those presenting with clinical stage T2 breast cancers was more often a breast-conserving operation in the PC group (74%, 20 of 27 patients) than in the AC group (45%, 51 of 114 patients) ($p = .006$). Similarly, in patients who presented with clinical stage T3 breast cancers, the final operation was a breast-conserving procedure more often in the PC group (60%, 18 of 30 patients) than in the AC group (27%, 11 of 43 patients) ($p = .007$). The rate of pathologically positive nodes was lower in patients in the PC group; however, this difference was not statistically significant.

Table 2. Clinical and tumor characteristics of stage IIA, IIB, and IIIA patients

Characteristic	Adjuvant chemotherapy (n = 155)	Preoperative chemotherapy (n = 57)	p-value ^a
Mean clinical tumor size (SD), cm	3.3 (1.68)	4.6 (1.62)	.0001
Tumor stage			
T2	114 (74%)	27 (47%)	.0005
T3	41 (26%)	30 (53%)	
Clinical stage at presentation			.0001
IIA	113 (73%)	20 (35%)	
IIB	36 (23%)	29 (51%)	
IIIA	6 (4%)	8 (14%)	
Predominant histology			.80
Ductal	140 (90%)	51 (89%)	
Lobular	8 (5%)	5 (9%)	
Other	7 (5%)	1 (2%)	
Histologic grade ^b			.86
Well differentiated	14 (10%)	3 (6%)	
Moderately differentiated	34 (23%)	13 (25%)	
Poorly differentiated	98 (67%)	36 (69%)	
Estrogen receptor ^c			.34
Positive	101 (66%)	33 (58%)	
Negative	53 (34%)	24 (42%)	
Progesterone receptor ^c			.54
Positive	86 (56%)	29 (51%)	
Negative	68 (44%)	28 (49%)	
HER-2/neu status (IHC 3+ or FISH+) ^d			.05
Yes	23 (15%)	16 (39%)	
No	127 (85%)	41 (61%)	
Triple negative ^e	38/150 (25%)	16/57 (28%)	.72

^aDerived from a Fisher's exact test for categorical variables and a two-sample *t*-test for continuous variables.

^bNine patients in the adjuvant chemotherapy group and five patients in the preoperative chemotherapy group did not have histologic grade assigned either because it was an infiltrating lobular carcinoma or it was not done.

^cOne patient in the adjuvant chemotherapy group did not have estrogen receptor or progesterone receptor testing performed.

^dFive patients did not have HER-2/neu testing performed.

^eHormone receptor and HER-2/neu not expressed/not amplified.

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; SD, standard deviation.

There was no significant difference in the ipsilateral breast tumor recurrence rate between the AC group (one of 62 patients, 2%) and the PC group (three of 38 patients, 8%) ($p = .15$); however, the mean follow-up was relatively short, at 37 months.

DISCUSSION

PC led to significantly better breast cancer surgical outcomes in this community-based practice of underinsured county hospital patients. Patients who underwent PC had a higher rate of breast-conserving operations, a lower rate of close or positive margins, smaller lumpectomies, fewer re-excisions, and a lower rate of histologically positive nodes despite presentation at a more advanced clinical stage.

Several prospective, randomized clinical trials have shown that patients treated with PC have a similar overall survival duration as patients treated with AC [1–3]. Evaluation of breast cancer care, with its long history of patient advocacy, however, cannot be evaluated simply by outcomes as limited as overall survival. For most women, breast cancer treatment significantly impacts multiple facets of their lives and their quality of life [8, 12]. Despite a larger clinical tumor size at presentation, patients who underwent PC were significantly more likely to undergo a breast-conserving operation for both stage T2 and stage T3 cancers (Table 3). This finding of a higher rate of breast preservation was similar to the significant benefit demonstrated in the NSABP B18 study for stage T2 (71% for PC

Table 3. Surgical outcomes of stage IIA, IIB, and IIIA patients			
Outcome	Adjuvant chemotherapy (n = 155)	Preoperative chemotherapy (n = 57)	p-value^a
Initial operation for stage T2			.016
Breast conservation	56 (50%)	21 (78%)	
Mastectomy	55 (50%)	6 (22%)	
Initial operation for stage T2 ^b			.003
Breast conservation	56 (58%)	21 (91%)	
Mastectomy	41 (42%)	2 (9%)	
Initial operation for stage T3			.015
Breast conservation	12 (29%)	18 (60%)	
Mastectomy	29 (71%)	12 (40%)	
Initial operation for stage T3 ^b			.005
Breast conservation	12 (32%)	18 (69%)	
Mastectomy	26 (68%)	8 (31%)	
Lumpectomy margins			.04
Positive/close (<1 mm)	31/68 (46%)	9/38 (23%)	
Re-excision lumpectomy	28/68 (41%)	7/38 (18%)	.01
Breast conservation			.003
Volume of specimen, cm ³	273.9	143.6	
Final operation for stage T2			.006
Breast conservation	51 (45%)	20 (74%)	
Mastectomy	63 (55%)	7 (26%)	
Final operation for stage T3			.007
Breast conservation	11 (27%)	18 (60%)	
Mastectomy	30 (73%)	12 (40%)	
Clinical stage II IDC			.46
Pathologic node positive	44/110 (40%)	6/20 (30%)	
Clinical stage IIB/III IDC			.35
Pathologic node positive	25/39 (64%)	19/37(51%)	

^aDerived from a Fisher's exact test for categorical variables and a two-sample *t*-test for continuous variables.
^bExcluding patients who elected mastectomy over breast conservation.
Abbreviation: IDC, infiltrating ductal carcinoma.

versus 63% for AC) and stage T3 (22% for PC versus 8% for AC) cancers [24]. Although the 22% rate of breast conservation appears low, more recent and subsequent data have found higher rates of breast conservation for patients with stage T3 tumors after PC. The prospective study reported by Bonadonna et al. [3] showed rates of breast conservation of 89% for stage T2 tumors and 62% for stage T3 tumors. Boughy et al. [6] found that, in patients with stage T2 and stage T3 tumors, those who underwent PC in prospective randomized trials at MD Anderson Cancer Center experienced a nonsignificantly higher lumpectomy rate (44% versus 33%) than patients who underwent AC. Christy et al. [25] found a statistically significant higher breast-conserving operation rate (64% versus 45%; *p* = .05) in patients with stage T2 cancers.

Evaluation of the breast-conserving operation cannot be limited only to its rate of performance because there are other factors that determine the success of the surgical procedure. Margin status is perhaps the most important immediate outcome of breast-conserving operations because inadequate margins are one of the strongest predictors of local failure [9]. The achievement of negative margins is also of importance because a higher number of operations to obtain negative margins results in a greater volume of tissue excised and a poorer cosmetic result [9, 10, 26, 27]. In some series, the re-excision rate to obtain negative margins can be as high as 69% [28]. In the current study, patients in the AC group had a rate of close (<1 mm) or positive margins double that of those who underwent PC (46% versus 23%; *p* = .04) (Table 3). This resulted in a statistically significant

higher rate of re-excision lumpectomy in the AC group than in the PC group (41% versus 18%; $p = .01$). In patients who underwent a second operation because of involved margins, more patients underwent a mastectomy in the AC group than in the PC group (Table 3). Similarly, data from the University of Michigan showed that the re-excision rate in patients who underwent PC was almost half that of those who did not undergo PC (59% versus 31%; $p < 0.001$) [29]. Data from Yale University [25] for stage T2 cancers also showed a statistically significant lower rate of positive margins (32% versus 10%; $p < .01$) and need for re-excision lumpectomy (37% versus 6%; $p = .01$). In the current study, the significantly better margin status and lumpectomy rate cannot be explained by a larger lumpectomy specimen volume in the PC group because the volume of the lumpectomy specimens in the PC group was nearly half that of the AC group (143 cm³ versus 273 cm³; $p = .003$). Therefore, not only did the PC group have a lower rate of close and positive margins, those patients also had significantly less tissue removed in breast-conserving operations. The lower lumpectomy volume in those undergoing PC was also demonstrated in a combined analysis of prospective, randomized data from the MD Anderson Cancer Center. A similar statistically significant lower resected volume was found (113 cm³ versus 213 cm³; $p = .004$), with no difference in local recurrence at 33 months of follow-up [6]. These findings of a smaller lumpectomy volume in the PC groups alleviate concerns about diffuse residual tumor burden dispersed throughout the original tumor volume.

The benefits in the PC group were also seen in the lymph node status. Proportionally, 25% fewer patients who presented with clinical stage IIA disease and 20% fewer stage IIB/IIIA patients were node positive in the PC group. Data from the NSABP B18 study demonstrated that PC resulted in a 30%–40% lower rate of lymph node positivity. When the results of the NSABP B18 trial were reported in 1997, the difference in lymph node status affected the postchemotherapy stage of the patients [1]. In 2010, however, additional benefits could be realized. PC was initially considered a contraindication to the sentinel node procedure. Subsequent data from the NSABP B27 study reported by Mamounas et al. [30] as well as data from a meta-analysis [31] demonstrated that the sentinel node procedure is as accurate after PC as it is without prior chemotherapy. These data have resulted in national guidelines stating the acceptability of the sentinel node procedure after PC [32]. Therefore, because a significant proportion of patients can have their lymph nodes downstaged, PC could save many patients the morbidity of an axillary lymph node dissection. Although reported morbidity rates related to axillary lymph

node dissection vary greatly, data from the largest published prospective, randomized clinical trial to date comparing axillary lymph node dissection with sentinel node biopsy, reported by Veronesi et al. [33], demonstrated that 91% and 85% of patients experienced pain and numbness, respectively, for 6 months after an axillary dissection. That was compared with only 16% and 2% in the sentinel node group. This difference in morbidity should not be underestimated because 6 months is a long time to suffer through an iatrogenic problem.

This study has several limitations. Retrospective studies are subject to inherent limitations and biases. Data from prospective studies involving minority patients, however, are very difficult to obtain even in a disease as common as breast cancer. Most patients who participate in clinical trials are non-Hispanic whites and insured, making prospective study of the racial/ethnic minority and underinsured populations extremely difficult. This study was relatively small and performed at one institution with one patient population. The small size of the study, however, demonstrates that the benefits of PC can apply even to a low-volume community-based practice. The applicability to other patient populations, however, does need to be considered. Finally, follow-up was limited in this study and continued evaluation of patients will be necessary to determine whether these better surgical outcomes will translate into better long-term outcomes.

Breast cancer is a heterogeneous disease and patient populations are equally diverse. In certain populations, although overall survival is similar in patients undergoing AC and PC, patients undergoing PC may experience benefits in terms of surgical outcomes over the same treatment given in the adjuvant setting. The surgical benefits of PC demonstrated in prospective, randomized studies and at large tertiary cancer centers can be realized even in a lower volume community-based practice.

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AUTHOR CONTRIBUTIONS

Conception/Design: Ian K. Komenaka, Michael Hibbard, Chandra Jha, Boo Ghee Low

Provision of study material or patients: Ian K. Komenaka, Chandra Jha, Boo Ghee Low, Jason Salganick, Marcia Bouton

Collection and/or assembly of data: Ian K. Komenaka, Chiu-Hsieh Hsu, Marcia Bouton

Data analysis and interpretation: Chiu-Hsieh Hsu

Manuscript writing: Ian K. Komenaka, Michael Hibbard, Chiu-Hsieh Hsu, Boo Ghee Low, Jason Salganick, Marcia Bouton

Final approval of manuscript: Ian K. Komenaka, Michael Hibbard, Chandra Jha, Chiu-Hsieh Hsu, Boo Ghee Low, Jason Salganick, Marcia Bouton

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