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ORIGINAL ARTICLE – BREAST ONCOLOGY

Decreasing Use of Axillary Dissection in Node-Positive Breast Cancer Patients Treated with Neoadjuvant Chemotherapy

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ABSTRACT

Background. Neoadjuvant chemotherapy (NAC) may downstage axillary disease in node-positive breast cancer. Several clinical trials have shown that sentinel lymph node (SLN) surgery after NAC is feasible for these patients. We sought to evaluate the use of SLN surgery and ALND in cN1 patients undergoing NAC.

Methods. We identified all patients with biopsy-proven cN1 breast cancer treated with NAC at our institution between January 2009 and December 2017. Approximated biologic subtype was determined by estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status. Cochran–Armitage trend and Chi square tests were used for statistical analysis.

Results. Of 430 cN1 patients treated with NAC, 93 (22%) underwent SLN surgery only, 100 (23%) underwent SLN and ALND, and 237 (55%) underwent ALND only. The use of SLN surgery (± ALND) increased from 28% in 2009 to 86% in 2017 ($p < 0.001$), while the performance of ALND decreased from 100% in 2009 to 38% in 2017 ($p < 0.001$). Among SLN+ patients who underwent ALND, disease was limited to the SLNs in 25/73 (34%) patients. The nodal pathologic complete response rate was 46% and varied by tumor subtype ($p < 0.001$). Among patients undergoing SLN surgery, ALND was avoided in 48% of patients overall and varied by biologic subtype: 55% ER−/HER2+, 61% ER+/HER2+, 62% ER−/HER2−, and 31% ER+/HER2− ($p = 0.001$). With short-term follow-up, no nodal recurrences have occurred in patients without ALND.

Conclusions. We observed a significant shift in axillary surgery for cN1 breast cancer patients treated with NAC, with increasing use of SLN surgery to assess nodal treatment response, and decreasing use of ALND.

Surgical management of the axilla in breast cancer continues to evolve. Incorporation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial into clinical practice has led to decreased use of axillary lymph node dissection (ALND) in women with clinical T1–2N0 disease treated with breast conservation with one to two positive sentinel lymph nodes (SLNs).[1]

Historically, neoadjuvant chemotherapy (NAC) has been used for inoperable or locally advanced breast cancer. However, in contemporary times, it is increasingly utilized to downsize operable disease in the breast and the axilla, especially in patients presenting with node-positive disease.[2–4] Since 20–70% of patients who present with node-positive disease have complete eradication of the disease in the axilla following chemotherapy,[5–8] much recent interest has been focused on decreasing the extent of axillary treatment for patients with an excellent response to NAC. Removal of negative axillary lymph nodes has not been shown to provide any clinical benefit, yet is associated with known morbidities of ALND, including limb dysfunction, paresthesia, and lymphedema.[9]

Until recently, ALND has been the standard of care in the surgical management of patients presenting with nodal disease prior to NAC, regardless of response. Three multi-institutional trials evaluated the use of SLN surgery to assess axillary response after NAC in this patient population and have potentially changed practice patterns.[10–12]

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The three trials reported SLN identification rates ranging from 87.6 to 97.2% and false negative rates (FNRs) of 8.4–14.2%. The studies varied by the definition of clinically node-positive disease (whether percutaneous biopsy was required), definition of pathologic node-positive disease (inclusion of N0[i+] disease), and minimum required number of SLNs resected. Techniques identified from the studies that decreased the FNR include resection of a minimum of two SLNs, using dual-agent tracers for SLN identification, use of immunohistochemistry (IHC) for pathological assessment of residual disease in the nodes, and ensuring removal of the biopsy-proven positive node.[13] These data have significant clinical implications, paving the way to increase the utilization of SLN surgery to assess axillary response after NAC, rather than committing all node-positive patients undergoing NAC to an ALND.

The goal of this study was to examine the effects of this paradigm change in surgical axillary staging of node-positive patients following NAC at the Mayo Clinic in Rochester, MN, USA.

METHODS

After Institutional Review Board approval, we identified all patients with biopsy-proven (cT0–T4), node-positive breast cancer (cN1) treated with NAC followed by surgery at our institution between 1 January 2009 and 12 December 2017. This included the timeframe when the ACOSOG Z1071 trial was open at our institution, as well as the Alliance A11202 trial, and these patients are included in this cohort. Patients with recurrent, metastatic, or inflammatory breast cancer were excluded, as were patients treated with neoadjuvant endocrine therapy. At our institution, all patients with newly diagnosed invasive breast cancer undergo axillary ultrasound, and, in cases with morphologically abnormal lymph nodes, percutaneous fine-needle aspiration (FNA) biopsy of the most suspicious lymph node is undertaken. Only patients with biopsy-proven, node-positive disease were included in this study. All surgical axillary staging is performed after completion of chemotherapy at our institution. Chemotherapy regimens varied as per standard at the time, as well as based on clinical trials open at our institution.

The selection of patients for SLN surgery versus ALND was based on the clinical discretion of the treating surgeon and discussion with the patient. The clinical and imaging response to chemotherapy, tumor biology, extent of disease at presentation and after chemotherapy, and patient age were all considered and a decision was made on a case-by-case basis.

Tumor-approximated biologic subtype was categorized based on estrogen receptor (ER) and human epidermal growth factor receptor (HER2) status. ER+ was defined as $\geq 1\%$ and HER2+ was defined as 3+ staining by IHC for the HER2 protein or evidence of HER2 gene amplification as per College of American Pathologists guidelines.

Trends across time were assessed using Cochran–Armitage trend tests. Trend tests were also used to compare ordinal variables such as stage between groups, while Wilcoxon rank-sum tests were used for numeric variables and likelihood ratio Chi square tests were used for nominal variables. Analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). All tests were two-sided with an α-level of 0.05.

RESULTS

A total of 430 patients with clinical N1 node-positive breast cancer treated with NAC were identified. Median age was 50.5 years (range 24–86). Overall, 93 patients (22%) underwent SLN surgery only, 100 patients (23%) underwent SLN and ALND, and 237 patients (55%) underwent ALND only (Table 1). The rate of nodal pathologic complete response (pCR) was 46% overall and varied by tumor subtype: 76% ER−/HER2+, 65% ER+/HER2+, 51% ER−/HER2−, and 25% ER+/HER2− ($p < 0.001$).

Patients Who Underwent Sentinel Lymph Node (SLN) Surgery (± Axillary Lymph Node Dissection [ALND])

Of the 193 patients who underwent SLN surgery (± ALND), clinical tumor category distribution prior to chemotherapy was 1 (0.5%) cT0, 33 (17%) cT1, 99 (51%) cT2, 55 (28.5%) cT3, and 5 (3%) cT4. SLN technique used both radioactive colloid and blue dye in 159/193 cases (82%). Among these 193 patients, ALND was avoided in 48% overall and this varied by biologic subtype: 55% ER−/HER2+, 61% ER+/HER2+, 62% ER−/HER2−, and 31% ER+/HER2− ($p = 0.001$). Among the 193 patients who underwent SLN surgery, final SLN pathology was negative in 100 (52%), positive in 84 (44%), and in 9 (5%) an SLN was not identified.

Patients with Negative SLNs on Final Pathology

One hundred of the 193 patients (52%) were found to have negative SLNs. In these patients, the mean number of SLNs resected was 3.7 (median 3, range 1–11). Eighteen patients (18%) underwent ALND, 12 as part of the Z1071 trial, 3 had false-positive SLNs intraoperatively, and in 3 cases the surgeon was uncomfortable with the SLN mapping and proceeded to ALND based on clinical judgment. Among these 18 patients, 16/18 (89%) were node-negative on ALND, and 2/18 (11%) with a negative SLN surgery

TABLE 1 Characteristics of 430 clinically node-positive (cN1) patients treated with neoadjuvant chemotherapy between January 2009 and December 2017

	Total [*N* = 430]
Age, years	
Mean (SD)	51.4 (11.5)
Median (range)	50.5 (24–86)
Sex	
Female	428 (99.5)
Male	2 (0.5)
Surgery year	
2009	32 (7.4)
2010	41 (9.5)
2011	50 (11.6)
2012	54 (12.6)
2013	54 (12.6)
2014	44 (10.2)
2015	59 (13.7)
2016	54 (12.6)
2017	42 (9.8)
Axillary operation	
ALND	237 (55.1)
SLN surgery and ALND	100 (23.3)
SLN surgery	93 (21.6)
SLN result and axillary operation	
ALND	237 (55.1)
SLN−/ALND	18 (4.2)
SLN−/no ALND	82 (19.1)
SLN+/ALND	73 (17.0)
SLN+/no ALND	11 (2.6)
SLN fail/ALND	9 (2.1)
Clinical T category	
T0	6 (1.4)
Tis	1 (0.2)
T1	55 (12.8)
T2	216 (50.2)
T3	136 (31.6)
T4	16 (3.7)
Pathologic T category	
T0	118 (27.4)
Tis	41 (9.5)
T1	122 (28.4)
T2	93 (21.6)
T3	52 (12.1)
T4	4 (0.9)
Pathologic N category	
N0	197 (45.8)
N1	131 (30.5)
N2	66 (15.3)
N3	36 (8.4)
ER/HER2 status	
ER−/HER2+	59 (13.7)
ER−/HER2−	90 (20.9)
ER+/HER2+	88 (20.5)
ER+/HER2−	193 (44.9)
Histology	
IDC	366 (85.1)
ILC	31 (7.2)
IMC	28 (6.5)
Other	5 (1.2)

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *ALND* axillary lymph node dissection, *SLN* sentinel lymph node, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *IMC* invasive mammary carcinoma

had positive nodes at ALND (false-negative SLN), with two positive non-sentinel axillary nodes.

Patients with Positive SLNs on Final Pathology

Eighty-four of the 193 (44%) patients who underwent SLN surgery were found to have one or more positive SLNs. In these patients, the mean number of SLNs resected was three (median 2, range 1–10). This was significantly lower than the mean number of SLNs resected in the patients with negative SLNs ($p = 0.001$). Of these 84 patients with positive SLNs, the mean number of positive SLNs was 1.8 (median 1.5, range 1–5). The mean size of SLNs was 7.3 mm (median 5 mm, range 0.3–40 mm) and 30 (36%) had SLN extranodal extension.

Seventy-three of the 84 patients with positive SLNs (87%) underwent ALND, among whom the median number of positive non-sentinel axillary nodes was one (range 0–19) and the median number of total positive axillary nodes was four (range 1–20). Among SLN+ patients who underwent ALND, disease was limited to the SLNs in 25 patients (34%), and in those with positive nodes on ALND, the median number of positive non-SLNs was three (range 1–19). Comparing patients whose disease was limited to the SLNs versus those with additional axillary disease, patients with a higher number of positive SLNs, SLN extranodal extension, higher pathologic T category, and HER2− tumor biology were more likely to have additional positive nodes at ALND (Table 2).

All 11 patients with positive SLNs who did not undergo ALND did receive axillary radiation. Four of these patients

TABLE 2 Associations with additional positive nodes on completion ALND among patients with positive SLNs who underwent ALND (n = 73)

	ALND− [N = 25]	ALND+ [N = 48]	p value
Age, years			0.50
Mean (SD)	52.1 (11.6)	49.8 (12.2)	
Median (range)	52 (32–74)	50.5 (25–71)	
Clinical T category			0.47
T1	4 (30.8)	9 (69.2)	
T2	15 (41.7)	21 (58.3)	
T3	6 (26.1)	17 (73.9)	
T4	0 (0)	1 (100)	
Pathologic T category			0.01
T0	3 (42.9)	4 (57.1)	
Tis	2 (66.7)	1 (33.3)	
T1	15 (45.5)	18 (54.5)	
T2	4 (21.1)	15 (78.9)	
T3	1 (10.0)	9 (90.0)	
T4	0 (0)	1 (100)	
Histology			0.11
IDC	25 (39.7)	38 (60.3)	
ILC	0 (0)	3 (100)	
IMC	0 (0)	6 (100)	
Other	0 (0)	1 (100)	
ER/HER2 status			0.01
ER−/HER2+	4 (80.0)	1 (20.0)	
ER−/HER2−	3 (27.3)	8 (72.7)	
ER+/HER2+	7 (63.6)	4 (36.4)	
ER+/HER2−	11 (23.9)	35 (76.1)	
Number of SLNs examined			0.96
Mean (SD)	2.8 (2.0)	3.0 (2.3)	
Median (range)	2 (1–9)	2 (1–10)	
Number of positive SLNs			0.002
Mean (SD)	1.4 (0.9)	2.0 (1.0)	
Median (range)	1 (1–4)	2 (1–5)	
Percentage of positive SLNs			0.06
Mean (SD)	64.9 (33.8)	80.2 (27.0)	
Median (range)	50 (11–100)	100 (20–100)	
Size of largest SLN metastasis, mm			0.002
Mean (SD)	4.9 (4.5)	8.9 (6.9)	
Median (range)	3 (0.3–17)	7 (0.3–40)	
SLN extranodal extension			0.04
Yes	6 (20.7)	23 (79.3)	
No	19 (43.2)	25 (56.8)	

Data are expressed as n (%) unless otherwise specified

Percentages reported are row percentages (i.e. the percentage of patients in a given category with ALND− and ALND+)

SD standard deviation, *ALND* axillary lymph node dissection, *SLNs* sentinel lymph nodes, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *IMC* invasive mammary carcinoma

had negative SLNs on intraoperative pathology but were positive on final SLN pathology; the median size of lymph node metastasis in the SLN was 2 mm (range 1–5). Of the remaining seven patients, four participated in the Alliance A11202 trial and were randomized to axillary radiation therapy and no ALND, and three patients declined ALND, opting for axillary radiation only.

Patients with Failure to Identify an SLN

SLN surgery failed to identify any SLNs in nine patients (5%), all of whom underwent ALND; four were found to be node-positive and five were found to be node-negative on ALND.

Patients Who Underwent ALND Only

Of the 237 patients who went directly to ALND without SLN surgery, 94 (40%) were pathologically node-negative and 143 (60%) were node-positive after NAC. Among the 143 who remained node-positive, 78 (55%) were ypN1, 42 (29%) were ypN2, and 23 (16%) were ypN3. Patients with higher pathologic T category were more likely to have positive ALND, with positive nodes in 13% of ypT0, 24% of ypTis, 61% of ypT1, 84% of ypT2, and 93% of ypT3/pT4 ($p < 0.001$). Approximated biologic subtype was also significantly associated with positive nodes on ALND; 77% of ER+/HER2−, 55% of ER−/HER2−, 41% of ER+/HER2+, and 29% of ER−/HER2+ ($p < 0.001$). The majority of these cases occurred in the earlier portion of this time period (prior to 2015). In recent years (2015–2017), pCR was more common in patients who had SLN surgery (44%) than those who had ALND only (24%, $p = 0.03$).

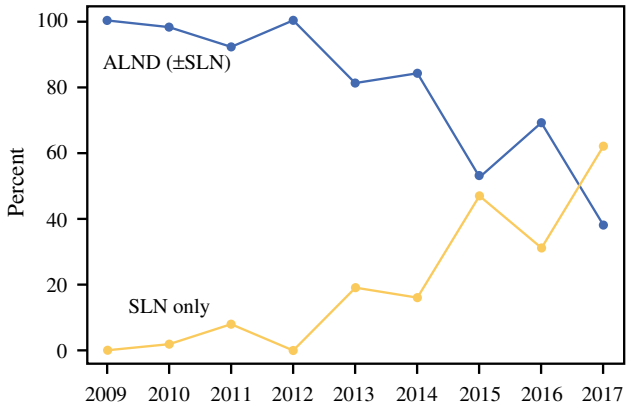

FIG. 1 Increasing use of SLN surgery only and decreasing use of ALND from 2009 to 2017 for cN1 patients treated with neoadjuvant chemotherapy. *ALND* axillary lymph node dissection, *SLN* sentinel lymph node

Change in Clinical Practice from 2009 to 2017

Overall, the proportion of patients undergoing ALND (± SLN) decreased from 100% in 2009 to 38% in 2017 ($p < 0.001$), and the use of axillary surgery limited to SLN only increased from 0 to 62% over this time period (Fig. 1). The use of SLN surgery (± ALND) increased from 28% in 2009 to 86% in 2017 ($p < 0.001$). Further stratified, the use of ALND only without SLN surgery dropped from 72% in 2009 to 14% in 2017, while SLN surgery followed by ALND for a positive SLN, and SLN surgery without ALND for negative SLN(s), both increased significantly (Fig. 2). Among SLN-negative patients, 10% avoided ALND in 2009–2010, compared with 96% in 2017 ($p < 0.001$).

As seen in Fig. 2, the major transition in practice had occurred by 2015. From 2015 to 2017, patients more likely to be selected for SLN surgery were those with cT0–cT2 disease compared with cT3–cT4 disease (85 vs. 67%, $p = 0.01$).

Recurrence

Forty-four recurrences occurred during short-term follow-up (median 9 months, range 0–8 years). The first recurrence was distant for 35/44, local in 6/44, and regional in 3/44. The three regional recurrences occurred in patients who underwent ALND, therefore no regional recurrence events were observed in patients when axillary surgery was limited to SLNs only (of whom 88% were SLN-negative).

DISCUSSION

Management of the axilla has been evolving and this contemporary study of axillary surgery in women diagnosed with node-positive breast cancer treated with NAC shows that in our practice, the use of SLN surgery in these

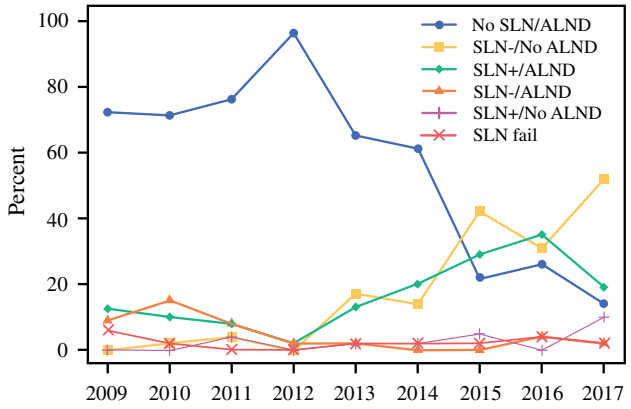

FIG. 2 Axillary surgery type distribution over time from 2009 to 2017 for cN1 patients treated with neoadjuvant chemotherapy. *ALND* axillary lymph node dissection, *SLN* sentinel lymph node

patients has increased and the rate of ALND has decreased. In our study, the overall rate of nodal pCR was 46%, with HER2+ and triple-negative disease having the highest rates and correspondingly higher rates of ALND omission than patients with hormone receptor-positive(HR+)/HER2− tumors. These results are similar to the findings in Z1071, where the overall nodal pCR was 41.1% and the highest rates were in patients with HER2+ and triple-negative disease (64.7 and 49.4%, respectively), while HR+/HER2− patients achieved a nodal pCR rate of only 21.1%.[7]

Similar temporal trends of omission of ALND are developing nationally since the publication of the ACOSOG Z1071 (in 2013), SENTINA (in 2013), and SN FNAC (in 2015) trials. In 2016, Mamtani et al.[14] reported on a series of 195 cN+ patients who had completed surgery, of whom 70% were eligible for SLN surgery, and ALND was avoided in 48% of these patients. In our study, the main practice shift of utilizing SLN surgery became evident in 2015 after the National Comprehensive Cancer Network (NCCN) guidelines acknowledged SLN surgery in this setting.[15]

The role of SLN surgery in patients who present with node-positive disease undergoing NAC is evolving, with data from prospective clinical trials and additional refinements in techniques to decrease the FNR. With improved systemic and targeted therapy in recent years, 20–70% of patients selected for NAC have a pCR in the affected axillary basin,[5–8] for whom removing non-malignant lymph nodes would not be expected to improve outcomes. As such, continued re-evaluation of the role of routine ALND is warranted. A 2016 meta-analysis of 3398 patients showed the use of SLN surgery in this setting has an FNR of 13% and an SLN identification rate of 91%.[16]

The importance of resecting the original lymph node with biopsy-proven metastatic disease at diagnosis was initially demonstrated in a subgroup analysis from the Z1071 trial.[13] Ensuring resection of this lymph node, along with the SLN(s), at the time of surgery has been coined targeted axillary dissection and is associated with a 2% FNR.[17] A Dutch group showed the MARI procedure (resection of the pathologic node alone without employing SLN surgery) was associated with a 7% FNR.[18] Taken together, these data support that achieving optimal post-NAC regional nodal staging with limited axillary surgery is possible in cN+ patients who have a good response to NAC.

Using the data from these trials, our group increasingly began to utilize SLN surgery, proceeding to ALND or clinical trial enrollment in cases where any of the SLNs were positive. From 2009 through 2011, the ACOSOG Z1071 trial was open at our institution and patients enrolled on this study underwent SLN and planned ALND regardless of SLN pathology. Once the results of the Z1071 and SENTINA prospective trials were presented in December 2012 and the manuscripts were published in 2013, our clinical practice evolved in parallel. At our institution, we usually use dual tracer and resection of at least two SLNs when performing SLN after NAC in patients with cN+ disease at presentation. We have not routinely performed IHC on SLNs. As seen in our study, the major practice change occurred in 2015 and has evolved further. At present, we clip the positive lymph node at the time of FNA prior to NAC, and localize the biopsy-proven positive node to ensure resection of the clipped node at the time of SLN surgery.

SLN surgery after NAC is not appropriate for all women with cN+ disease at presentation. Our surgeons performed SLN surgery in a selective fashion, considering multiple factors, including response to NAC by clinical examination and imaging in both the breast and the axilla, the extent of disease at presentation, and tumor biologic subtype. Current NCCN guidelines have incorporated SLN surgery after NAC as an accepted part of management, stating that "if ipsilateral axillary lymph node biopsy is positive, axilla may be restaged after preoperative systemic therapy with SLN surgery or ALND (category 2B)".[15]

Worldwide, there appears to be increasing and rapid acceptance of this approach. A survey of 148 surgical oncologists in The Netherlands between November 2014 and June 2015 revealed that 70% of participants stated that ALND could possibly be omitted in node-positive patients with a favorable response to NAC.[19] Although long-term follow-up of patients managed with SLN alone is sparse, the outcome of 147 patients presenting with node-positive disease undergoing NAC treated at the European Institute of Oncology in Milan, Italy, was recently reported. Seventy-seven patients had a positive SLN and proceeded to ALND, and 70 patients were SLN-negative and had no further axillary surgery.[20] At five years of follow-up, they reported only one axillary recurrence (0.7%), which occurred in an SLN-positive patient treated with ALND. To date, there have been no recurrences among SLN-negative patients treated with SLN surgery alone. Similarly, the short-term follow-up of patients in our cohort did not identify any axillary failures in the patients treated with SLN surgery without ALND.

Limitations of this series include the single-institution, retrospective nature of the study. In addition, management in each patient was carried out at the discretion of the surgeon involved and the patient. Therefore, as a result, the decision for which type of axillary staging surgery to perform was multifactorial. Lastly, although we have reported our practice patterns and recurrence data to date, disease-free survival and long-term outcome data are still needed. Although no isolated axillary failures in patients

with SLN surgery have occurred to date, longer term follow-up is needed to understand the patterns of nodal failure in cN1 patients having limited axillary surgery after NAC.

CONCLUSIONS

This study demonstrates the change in practice patterns at our institution in the axillary management of patients with node-positive disease prior to NAC. Application of results from trials such as Z1071 influenced this practice change. As a result, a significantly increased number of patients had SLN surgery alone and were spared an ALND. Further trials and long-term follow-up are needed to assess long-term outcomes in these patients.

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CONFLICT OF INTEREST Toan T. Nguyen, Tanya L. Hoskin, Courtney N. Day, Amy C. Degnim, James W. Jakub, Tina J. Hieken, and Judy C. Boughey have no conflicts of interest to declare.

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