Loco-regional therapy for isolated locoregional lymph node recurrence of breast cancer: focusing on surgical treatment with combined therapy

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Abstract: Advances have been made in systemic as well as locoregional treatment of primary breast cancer. Evidence, based established therapeutic strategies, for isolated locoregional lymph node recurrence is not yet sufficient. In this series, we focused especially on isolated axillary lymph node recurrence (AR) and supraclavicular lymph node recurrence (SR) in patients receiving systemic and/or radiation therapy combined with surgery. Disease free survival (DFS) in patients with AR ranged from 20 to 36 months. From 69% to 77% of all patients underwent surgical excision. The 5-year overall survival (OS) ranged from 39% to 46%. Positive lymph node metastases of primary cancer, size of the primary tumor, and R0 resection were associated with good outcomes. Longer DFS is associated with good outcomes. Limited SR data showed DFS to range from 25–27%. Median progression free survival (PFS) was 18 months, 5-year OS rates were 24–42%, and 5-year OS were 29–34 months. Combination therapy was an independent factor associated with better PFS as compared to local therapy only. Salvage treatment and grade of the primary tumor significantly were associated with OS on multivariate analysis. Available data, retrospective and not randomized, showed therapy combining systemic treatments and/or radiotherapy with surgery might contribute to good local control, better PFS, and longer OS.

Keywords: Breast cancer; locoregional lymph node metastases; axillary recurrence; supraclavicular recurrence

Introduction

Locoregional treatment as well as systemic therapy for primary breast cancer have both changed. NSABP B-04 (1) showed that axillary lymph node dissection (ALND) did not significantly improve 10-year overall survival (OS). Furthermore, OS did not differ significantly between patients who did not receive ALND and those undergoing ALND after receiving a diagnosis of axillary lymph node recurrence (AR). NSABP B-32 (2), ACOSOG Z0010 (3) and other studies have provided evidence supporting the use of sentinel lymph node (SN) biopsy in patients with clinically node negative breast cancer. Omitting ALND in node negative breast cancer resulted in significantly better quality of life due to avoidance of lymphedema. Furthermore, the Z0011 trial showed that ALND could be omitted even in selected patients with positive SN status. The 10-year postoperative locoregional recurrence rate of primary breast cancer is reportedly approximately 10% (4).

The frequency of ipsilateral AR or ipsilateral supraclavicular lymph node recurrence (SR) was reported to be 3% or less. However, omitting ALND of SN positive patients might increase the rate of AR (5,6). On the other hand, SR worsens distant disease free survival (DFS) and increases the risk of death (7-9).

We do not presently have sufficient evidence based established therapeutic strategies for isolated locoregional lymph node recurrence. For AR, if possible, surgical excision should be carried out followed by radiotherapy, if the patients have not previously undergone radiotherapy. As for SR, combining systemic therapy and radiotherapy, rather than performing surgery, might be recommended (10). These strategies tend to be individually tailored, and consistent decision-making policies are needed. In this review series, we focused especially on isolated AR and SR in patients receiving systemic therapies combined with surgery.

Treatment of AR

AR rates were 0.8–1.3% (11,12) in patients who underwent surgical intervention for primary breast cancer. We reviewed 4 studies (12-15) taking surgical treatment into consideration. The first author's name, year of publication, study period, and primary breast cancer information (pathological stage of primary disease, surgical therapy and adjuvant radiotherapy) are listed *Table 1*. The numbers of patients were 44 to 220. Lee *et al.* reported isolated locoregional recurrence. The patient ages ranged from 48 to 61 years. The pathological primary disease stage was mentioned in two studies (12,15), and stages I and II accounted for at least 75% of tumors. The types of surgery performed for primary breast cancer are also listed. From 66% to 100% of patients underwent ALND. Radiotherapy was administered to 15% to 73% of patients.

Types of treatment and clinical outcomes of patients with AR are listed in *Table 2*. DFS was 20 to 36 months. Surgery and either radiotherapy or systemic treatments were selected. From 69% to 77% of patients underwent surgery. The 5-year OS rates ranged from 39% to 46%. Lee *et al.* reported isolated locoregional recurrence, and their results are thus not included in this series. de Boer *et al.* reported the distant DFS rate to be 35%. Negative and positive prognostic factors are also listed. de Boer *et al.* concluded that "positive lymph node metastases of primary cancer", "tumor size of primary cancer" and "eradication of AR (R0)" were associated with good outcomes. R0

status was confirmed in 47% of patients. The R0 group had significantly better outcomes than those with residual tumor (median OS was 4.8 *vs.* 1.9 years, P=0.01). Lee *et al.* and Konkin *et al.* noted long DFS to be associated with good outcomes. Konkin *et al.* mentioned that regimens combining surgery with other therapies contributed to good outcomes. Newman *et al.* reported initial therapies for AR: 45.5% of patients underwent surgery; 45.5% received chemotherapy; 4.5% radiotherapy; and 4.5% hormone therapy. Subtypes of AR tumors were provided in the report by Lee *et al.* (hormone receptor positive/HER2 negative 34%, HER2 positive/hormone receptor positive or negative 35%, triple negative 14%, unknown 17%).

We do not have data from a prospective randomized control study of surgical therapy for AR. While there are selection biases for AR surgery, these data show that surgery when combined with radiotherapy and/or systemic therapy has clinical benefits.

Treatment of SR

As to primary treatment of advanced breast cancer, aggressive resection of supraclavicular lymph node metastases did not improve patient outcomes (16). In terms of SR, there are no randomized control studies examining whether outcomes of patients with SR and AR improve with versus without surgical treatment. Isolated SR is a more extensive disease than isolated AR. Isolated SR was observed in 0.8–2.6% of patients who underwent curative surgery for primary breast cancer. However, patients with isolated SR have better outcomes than those with SR and distant metastases (5,17-19). van der Sangen *et al.* (5) reported outcomes of isolated SR, without distant metastases, in 42 patients diagnosed with breast cancer during the period from 1984 to 1994. Median time to diagnosis of SR was 2.5 years. In total, radiotherapy was administered to 25 patients. Radiotherapy only was administered to 4 patients, while 5 received both radiotherapy and surgery, and 16 patients underwent radiotherapy with surgery and/ or hormone therapy. Seventeen patients in total were not given radiotherapy. Eleven patients received hormone therapy only, 4 chemotherapy only, and one surgery only, while one patient was untreated. Thirty-five (38%) patients achieved complete remission, but recurrences were observed in 12 (34% of those with complete remission). The 5-year actuarial OS rate was 38% (95% CI, 23–53%). The 5-year DFS rate was 22% (95% CI, 8–35%). The distant DFS was better for patients given radiotherapy than

Table 1 Stage details and adjuvant therapy for primary tumor

Author, year (reference)	Study period	n	Age (years)	Stage			Surgery	Radiotherapy
				I	II	III		
de Boer, 2001, (12)	1984–1994	59	61 [39–99]	NS	NS	NS	Mastectomy + ALND 41%; BCS + ALND 56%	54%
Newman, 2000, (13)	1982–1992	44	48 [25–74]*	18%	55%	25%	Mastectomy 5%; Mastectomy + ALND 66%; BCS 4%; BCS + ALND 25%	NS
Lee, 2016, (14)	2000–2010	104	<40 28%; 40–50 44%; >50 28%*	43%	39%	17%	Mastectomy 41%; BCS 59%**	73%
Konkin, 2006, (15)	1989–2003	220	59.5 (mean)*	NS	NS	NS	ALND 81%; no ALND 19%***	15%

*, primary diagnosis; **, axillary surgery not described; ***, breast surgery not described. NS, not stated; BCS, breast conserving surgery; ALND, axillary lymph node dissection; DFS, disease free survival.

Table 2 Therapy types, clinical outcomes, and prognostic factors of axillary lymph node recurrence (AR)

Author, year (reference)	DFS (months)	Combined therapy	Types of systemic therapy	5y-OS (median)	Negative or positive prognostic factors
de Boer, 2001, (12)	31 [4–128]	Surgery and/or RT and/or systemic 69%; RT and/or systemic 30%	NS	39%	Good: negative for lymph node metastases of primary cancer, small primary tumor, R0 resection of AR
Newman, 2000, (13)	20 [3–117]	Surgery in combination 75%; surgery only 2%; RT only 2%; systemic only 21%	NS	NS	NS
Lee, 2016, (14)	36 [4–132]	NS	CT 30%; HT 35%; RT 35%	77%**	Negative: age <35, high grade of primary tumor, early recurrence (<24 months), triple negative subtype of primary tumor
Konkin, 2006, (15)	26 [2–143]	Surgery 73%*	CT 24%; HT 68%; RT 65%	46%	positive factors for OS: long DFS (>2.5 years), no RT with primary surgery, no symptoms, combination of surgery with RT and/or systemic therapy

*, combination therapy not described; **, all data pertaining to isolated locoregional recurrence. NS, not stated; DFS, disease free survival; RT, radiotherapy; CT, chemotherapy; HT, hormone therapy; R0, microscopic complete resection.

for those not receiving radiotherapy (P=0.06). However, only a few retrospective studies with small sample sizes have examined this issue (19,20). Reddy *et al.* (17) reviewed long-term outcomes of patients with SR after initial treatment with doxorubicin-based chemotherapy and mastectomy. Although the patients with locoregional recurrence including SR and lymphatic invasion or vascular invasion of primary tumors have poorer distant DFS (hazard ratio, 1.96, P=0.004), OS of patients with isolated SR did not different significantly from that of those with more extensive locoregional disease.

There are a few reports describing the utility of surgical treatment for isolated SR (18,21). However, there have been no randomized controlled trials comparing surgical to non-surgical treatment for SR. Chen *et al.* identified 63 patients with SR without distant metastases in a single institute. Median follow-up was 58.3 months. Thirty-five (56%) of the 63 patients died within the observation period. Median DFS was 25 months. The only significant risk factor was age at diagnosis of SR (>40). The 5-year OS rate was significantly better for patients in the operation group (42.4% *vs.* 16.3%). The patients with isolated SR had 5-year OS nearly equivalent to that of patients who had isolated local recurrence (33.6% *vs.* 34.9%), but better than

that of patients with distant metastases (33.6% *vs.* 9.1%). Of course, there might be a selection bias, not only in terms of systemic therapy or radiotherapy, but also surgery for SR which is effective for neck control and improving the survival rate. Pederson *et al.* investigated early breast cancer patients with isolated ipsilateral SR. They extracted 305 patients diagnosed with SR, but free of distant metastases, from the database of the Danish Breast Cancer Cooperative Group. As to the primary tumor, 74% of patients had axillary lymph node metastases. Forty-six percent of patients were hormone receptor positive. DFS was 27 months (range, 2–114 months). The tumor sizes of SR cases were ≤10 mm in 30%, 11–20 mm in 34%, and >20 mm in 19%. Nearly half of the patients had developed SR by 2 years after the primary surgery. The types of therapy for SR were surgery and radiotherapy in 10% (excisional surgery: 19%, curative radiotherapy: 33%), endocrine and chemotherapy in 11% (endocrine therapy: 40%, chemotherapy: 45%), local and systemic therapy in 26% (systemic therapy only: 49%, no systemic therapy: 25%). The 5-year progression free survival (PFS) rate was 15%, median PFS was 18 months, 5-year OS was 24%, and median OS was 29 months. As to prognostic factors, complete remission was related to better outcomes (P<0.0001), and systemic therapy prolonged PFS. Most notably, a combination of systemic and loco-regional treatment reduced progression. All of these factors were identified by univariate analysis. On multivariate analysis, combination therapy was an independent factor associated with improved PFS, as compared to local therapy only, and negative lymph node status and low tumor grade at the diagnosis of the primary disease were also independent factors related to PFS. Salvage treatment and tumor grade were significantly associated with OS.

In summary, we have reviewed a small number of retrospective and non-randomized studies. The outcomes of patients with isolated SR are better than those of patients with distant metastases. The effectiveness of surgical resection for improving the OS of patients with isolated SR remains controversial, while regimens combining systemic treatments and radiotherapy with surgery might contribute to good neck control, better PFS, and longer OS. The treatment decisions must be made by cancer board, and the risks of surgical treatment must be taken into consideration. The results of further investigations are thus needed.

Future perspectives

There is a report describing recurrence risk according to receptor phenotypes (22). Lowery *et al.* investigated the relationship between locoregional recurrence and the primary cancer subtype. Estrogen receptor and/or progesterone receptor positive patients had a lower risk of locoregional recurrence than those with triple negative and HER2/neu-over-expressing tumors after breast conserving surgery (RR 0.38; 95% CI: 0.23–0.61, RR 0.34; 95% CI: 0.26–0.45, respectively) Mastectomy patients had results very similar to those of patients receiving breast conserving surgery. HER2/neu-over-expressing tumors carried a higher risk of locoregional recurrence than triple negative tumors after breast conserving surgery (RR 1.44; 95% CI: 1.06–1.95). However, after mastectomy, these two groups showed no difference in locoregional recurrence rates. HER2/neu-over-expressing and triple negative tumors tended to have a high risk of locoregional recurrence, regardless of whether breast conserving surgery or mastectomy had been performed, suggesting that local and systemic treatments should be tailored to each subtype. Michel *et al.* (23) also reported risk prediction based on locoregional recurrence by using the CPS + EG score which predicts distant metastases. The score is calculated based on clinical stage, post-treatment pathological stage, estrogen receptor status, and tumor grade. They divided patients into 6 prognostic groups with 5-year locoregional recurrence free survival and 5-year distant metastasis free survival, which ranged from 100–41% (P=0.02), and 96–35% (P<0.0001, respectively). If risks of locoregional recurrence can be reliably assessed, tailored adjuvant treatment for primary breast cancer might this type of recurrence and thereby improve the outcomes of patients with isolated AR, SR, and other forms of locoregional recurrence.

Surgical treatment for locoregional recurrence aims not only to cure but also diagnose metastatic lymph nodes. Thangarajah *et al.* (24) reported discordance of receptor status between primary and metastatic sites of SR. Discordance rates between primary tumor and metastatic sites in terms of estrogen, progesterone, and Her2 receptor status were 20.0%, 36.8%, and 29.4%, respectively. When treating SR, combination therapy achieves better local control, longer DFS, improved rates of being distant metastases free and better OS, such that optimal selection of systemic therapy is crucial. Surgical treatment of SR is also contributes to improved outcomes.

In terms of systemic therapy, we now have a wider range of novel drugs for breast cancer. Molecularly-targeted therapies such as anti- HER2 agents, including trastuzumab, pertuzumab and T-DM1 (25,26), immune

checkpoint inhibitors (ICI) such as humanized monoclonal anti–PD-L1 antibody (Atezolizumab) (27), and PARP inhibitors have shown efficacy for BRCA (BReast CAncer gene)-positive HER2 negative metastatic breast cancers (28) and are thereby contributing to better outcomes not only for metastatic breast cancer patients but also those receiving adjuvant therapy for primary breast cancer. Regimens combining local treatment and systemic therapy appear to be highly effective, even potentially curative, and further investigations are thus needed.

Conclusions

We reviewed clinical outcomes of combining surgery with other treatments for AR, and examined the role of surgery for isolated SR. Although further investigation employing a prospective randomized clinical study design is needed, appropriate surgical therapy with minimum morbidity combined with radiotherapy and/or the newer, effective systemic agents improves the clinical outcomes of breast cancer patients with locoregional lymph node metastases.

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Footnote

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