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Wide local extension and higher proliferation indices are characteristic features of symptomatic lobular neoplasias (LNs) and LNs with an early invasive component

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Wide local extension and higher proliferation indices are characteristic features of symptomatic lobular neoplasias and LNs with an early invasive component

Aims: Lobular neoplasias (LNs) are typically small, clinically undetectable breast lesions, but some LNs are of clinical significance. The aim of this study was to clarify the histopathological characteristics of clinically overt (symptomatic) LNs and early invasive LNs.

Methods and results: Sixty-two surgically resected LNs, including eight with early invasion (≤10 mm), were classified into the following groups: (i) symptomatic and occult; and (ii) early invasive and non-invasive. Six histopathological factors, including the Ki67 labelling index (LI), were assessed and analysed by logistic regression models. On multivariate analysis, tumour size ($P = 0.008$), mitotic counts ($P = 0.006$) and Ki67 LI ($P = 0.035$) were risk factors for symptomatic features, and tumour size ($P = 0.009$) and Ki67 LI ($P = 0.015$) were risk factors for early invasive lesions. In the eight LNs with invasion, the symptomatic and occult subgroups showed differing nuclear atypia and structural patterns, but both lesions extended widely (22–96 mm).

Conclusions: Wide extension and higher proliferation activity were characteristic features of symptomatic LNs and LNs with early invasion.

Keywords: clinical presentation, early invasion, Ki67, lobular neoplasia, tumour size

Introduction

Lobular neoplasias (LNs) are typically small, clinically undetectable lesions incidentally discovered through microscopic examination of background mammary glands during histological examination of resected specimens of breast cancer.[1–4] The term LN is used to refer to both lobular carcinoma *in situ* (LCIS) and atypical lobular hyperplasia (ALH).[3] LCIS of the breast is a non-invasive neoplastic lesion characterized by monotonous proliferation of small and poorly cohesive cells that both fill and distend >50% of the acini of the involved lobular units, with or without pagetoid involvement of terminal ducts.[5,6] ALH is similar to LCIS, but shows less acinar involvement, with <50% of the acini being filled and distended. However, differentiation of LCIS and ALH is based only on differences in the extent of involved lobules and acinar distension, and these two lesions may overlap in cellular and structural findings.[5,6]

In the current consensus, LNs constitute both a risk factor for concurrent breast cancers, ipsilateral

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and/or contralateral, and a non-obligate precursor for the subsequent development of invasive carcinoma in either breast.[2,4,7,8] Such tumour progression is considered to occur usually only in a minority of women after long-term follow-up.[4] However, cases of widespread LN are sometimes encountered, some of which are detected clinically or with imaging diagnostic tools, and LNs can be accompanied by early invasive foci detectable only by histological examination. Additionally, it has been reported that ~50% of invasive cancers developing on a background of LN are of the lobular type,[9,10] and that coexistent LN and invasive lobular carcinoma (ILC) often show similar genetic alterations.[11,12] In LN cases, it appears that clinically overt LN and/or LN with early invasive foci should be treated as invasive carcinoma. The aim of the present study was to clarify the histopathological features correlated with clinically overt (symptomatic) LNs and LNs accompanied by an early invasive component, by examining surgically resected specimens of LNs.

Materials and methods

PATIENTS

This study was approved by the internal review board of National Cancer Centre, Tokyo, Japan (2010-077). By a search of the database of the Department of Pathology, National Cancer Centre Hospital, 88 consecutive lesions of LN or early invasive LN were identified out of a total of 4811 surgically resected breast cancer specimens between January 2002 and July 2012. Twenty-six of the 88 lesions were excluded from the study because of the coexistence of ductal carcinoma *in situ* (DCIS) and LN components in a single lesion, or positive E-cadherin expression. A total of 62 eligible LNs were reviewed by two pathologists (Y.K. and H.T.): 54 lesions were confirmed to be LNs (seven ALHs and 47 cases of LCIS), and the remaining eight lesions were LNs (LCIS) with early invasive components (which were defined as ILC with an invasive component of ≤10 mm at the largest diameter, associated with an overwhelming LN component). The former larger group was defined as LN without invasion, and the latter smaller group as LN with invasion.

We included pure LNs and pure LNs with invasion. Therefore, if these LNs and LNs with invasion were confirmed not to have coexistent DCIS or invasive carcinoma in the ipsilateral breast by histological examination, these cases were judged as independent primary lesions and included in the study. Forty-six LNs (41 LNs without invasion and five LNs with invasion) had coexistent and separate ipsilateral carcinomas, the histological types of which were invasive ductal carcinoma (IDC) in 32, DCIS in nine, ILC in three, mucinous carcinoma in one, and tubular carcinoma in one. These lesions were judged to be 3–57 mm in size (median, 14 mm; mean, 18.2 mm), excluding the LNs.

Twenty LNs with or without invasion were suspected clinically or by imaging diagnosis. The lesion was identified by: health examination in nine cases, comprising mammography in eight (calcification in six and distortion in two) and tumour palpation in one; tumour palpation by the patient in six; mammographic detection of calcification during preoperative or follow-up examination of contralateral breast cancer in four; and ultrasound detection of a tumour during preoperative examination of another ipsilateral breast cancer in one. Therefore, the modality that initially detected the lesion was mammography in 12 (calcification in 10; distortion in two), tumour palpation in seven, and ultrasound in one. Among these three modalities, mammography detected nine cases of LN, US detected one case of LN, and multiple modalities detected another 10 LNs during the process of detailed examination. Magnetic resonance imaging and computed tomography identified one and two lesions corresponding to the LNs, respectively, although these modalities were not used for all patients.

These 20 lesions were defined as the symptomatic group, and surgery was performed for these lesions after histological diagnosis of LCIS or non-invasive carcinoma by core biopsy.

For the remaining 42 LN lesions, surgery was performed for clinically detected carcinoma (41 cases) or a benign tumour (one intraductal papilloma) after histological diagnosis of these tumours by core biopsy. The former 41 LNs were confirmed to be separate from the clinically detected cancer lesions by histological examination. Because these 42 LN lesions were not clinically identified and were only found incidentally in surgically resected specimens on histological examination, they were defined as the occult group.

Of the 62 LNs, 39 were occult without invasion, 15 were symptomatic without invasion, five were symptomatic with invasion, and three were occult with invasion. Because most patients who consulted the National Cancer Centre had been referred from another general hospital after receiving a diagnosis of breast cancer or with high suspicion of cancer, almost all incidental LN cases were found with malignant lesions.

HISTOPATHOLOGICAL EXAMINATION

Surgically resected specimens were fixed in 10% formalin overnight, and cut into slices at 10–15-mm intervals. Almost the entire area of the LN lesions was histologically examined for all cases. On average, 25 tissue blocks (7–64) per patient were routinely prepared and paraffin-embedded. Histological sections were reviewed for tumour size, nuclear atypia (score 1–3), the number of mitoses [per 10 high-power-fields (HPFs)], the presence of synchronous separate ipsilateral breast cancers, and the Ki67 labelling index (Ki67 LI).[4–6]

Microscopically, tumours were also classified into four structural patterns—nodular, solid, displacement, and pagetoid—according to the predominant features (Figure 1).[13] The nodular patterns showed maximally distended lobules, forming a distinct nodule. The solid pattern was primarily composed of a typical histopathological appearance of LCIS, in which distended lobular glands were filled with tumour cells, but did not form grossly identifiable nodules. The displacement patterns showed glandular epithelia mostly replaced by LN cells without glandular distension. The pagetoid pattern was characterized by pagetoid spread of tumour cells without glandular distension.

The histological characteristics listed above were compared between subgroups of LN. Detailed histopathological examination and mapping of the area of tumour spread were performed to confirm the continuity of potentially multicentric lesions (Figure 2).

When LNs were observed in multiple sections from a resected breast and were microscopically judged to be continuous by the mapping of tumour extension

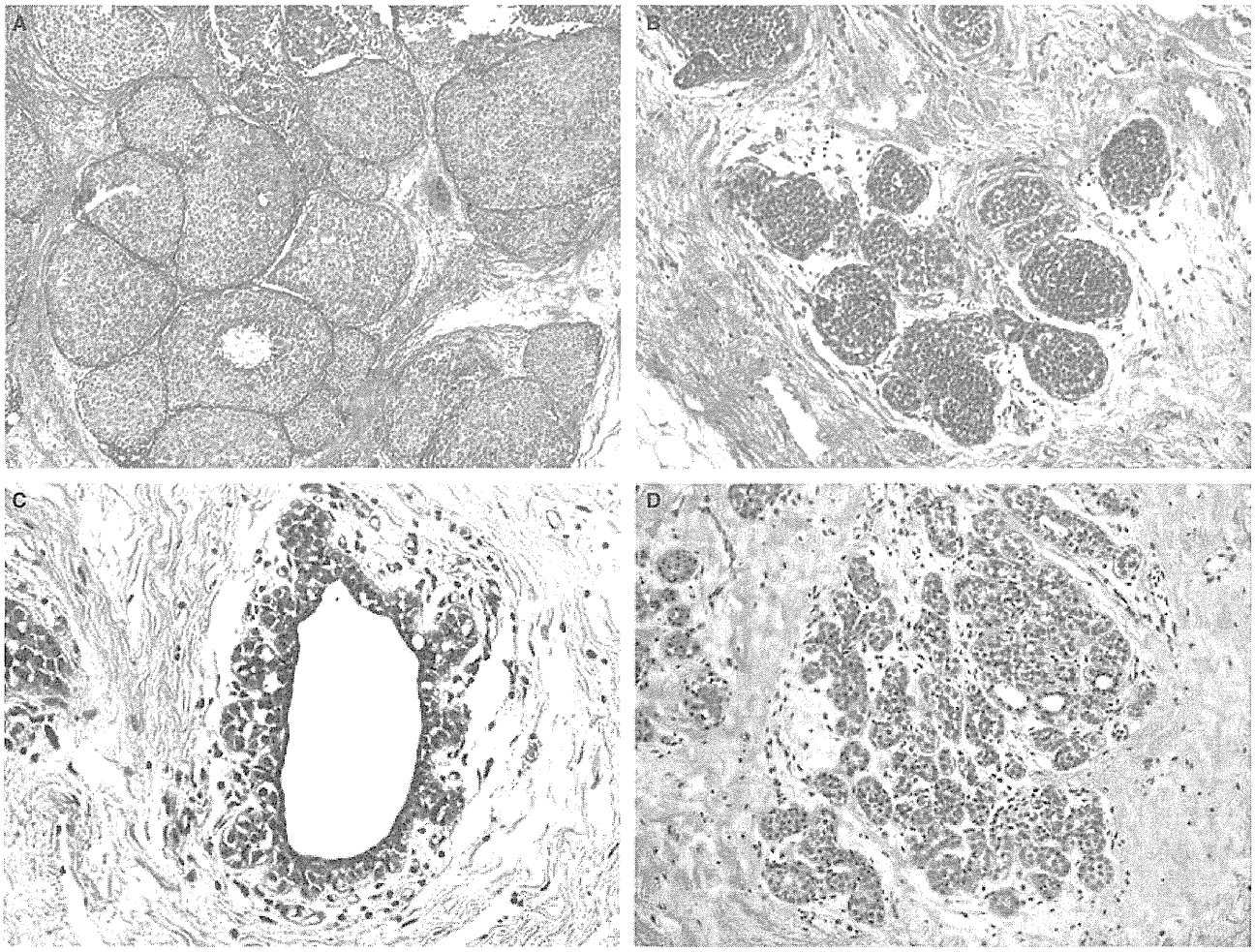

Figure 1. Four typical microscopic structural patterns of lobular neoplasia. **A**, Nodular pattern; tumour cells maximally distend the acini and form a distinct nodule. **B**, Solid pattern; tumour cells fill and distend the acini but do not form grossly identifiable nodules. **C**, Pagetoid pattern; tumour cells show pagetoid spread in a duct. **D**, Displacement pattern; atypical cells replace glandular epithelia without glandular distension.

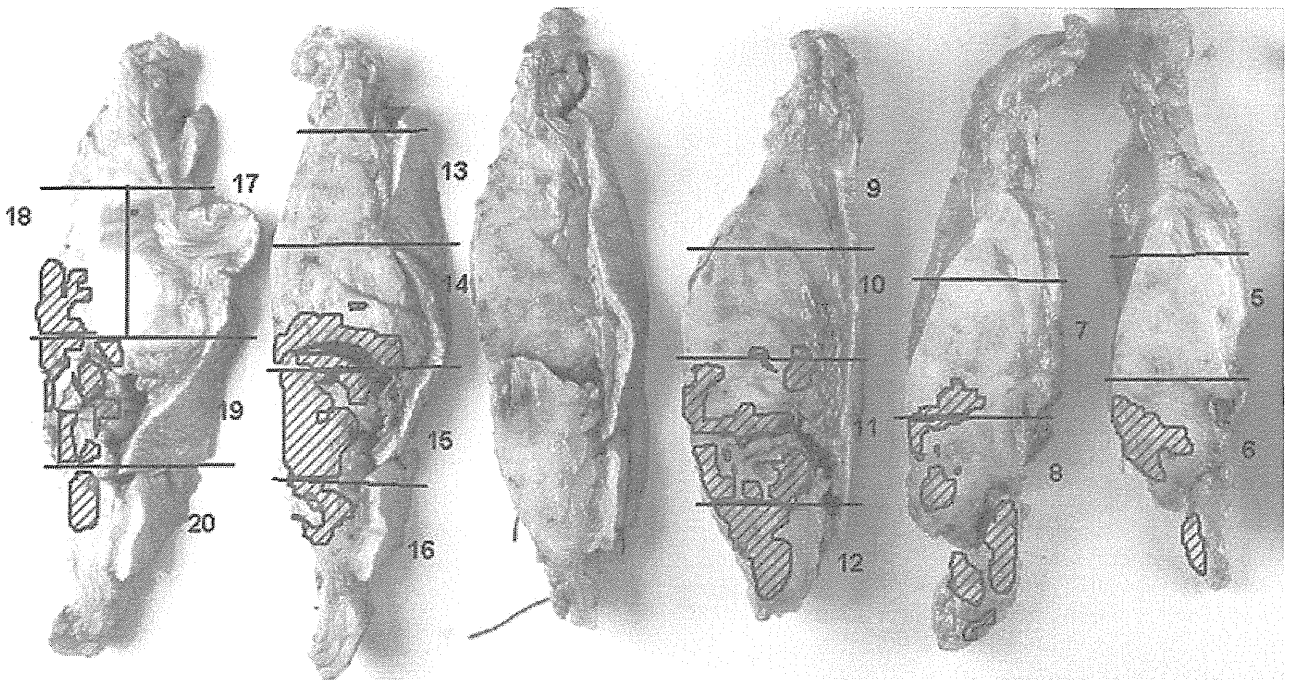

Figure 2. Mapping figure of a case of lobular neoplasia with an early invasive carcinoma component (case 7 in Table 5). Blue and red areas represent the lobular carcinoma *in situ* component and the invasive lobular carcinoma component, respectively. There are three foci of the invasive carcinoma, with a diameter of <7 mm.

area, we defined these lesions as being derived from a single LN. In contrast, when LNs were observed in multiple sections in a resected unilateral breast but were judged not to be continuous, these LNs were defined as multicentric in origin.

IMMUNOHISTOCHEMISTRY

Four-micrometre-thick tissue sections of the representative and best-preserved tumour areas were subjected to immunohistochemical analysis. The primary antibodies used included mouse anti-human E-cadherin antibody (clone NCN-38, 1:100; Dako, Glostrup, Denmark) and mouse anti-human Ki67 antibody (clone MIB-1, 1:100; Dako). Antigen retrieval for E-cadherin and Ki67 was performed by autoclaving for 10 min at 121°C in TRS buffer (Dako) and in citrate buffer (pH 6.0), respectively. The primary and secondary antibody reactions with Envision (Dako) were performed using a Dako autostainer, according to the manufacturer's protocol.

The Ki67 LI, defined as the percentage of LN nuclei in a HPF showing immunopositivity, was determined by analysing the most intensively stained area of the slide. Nineteen LN lesions were re-examined with a double-stain method for E-cadherin and Ki67 using the EnVision G/2 Doublestain System, Rabbit/Mouse (Dako), according to the manufacturer's protocol. For these 19 cases, the ratio of nuclear Ki67-positive and E-cadherin-negative cells to all E-cadherin-negative cells was calculated for estimation of the Ki67 LI (Figure 3).

STATISTICAL ANALYSIS

Statistical analyses were performed with STATVIEW software. Correlation analyses were performed using the chi-square test or Fisher's exact test for categorical variables. Comparison of mean values between two groups was performed using the Welch *t*-test. Logistic regression model analyses were used to estimate the impact of clinicopathological parameters on symptomatic lesions and on early invasive lesions. Differences were considered to be significant at $P < 0.05$.

Results

CLINICAL PARAMETERS

Of 20 symptomatic cases, 12 lesions were found by mammography (calcification in 10; distortion in two). In the 10 cases presenting with calcification, the LN component had a nodular or solid pattern in six, and

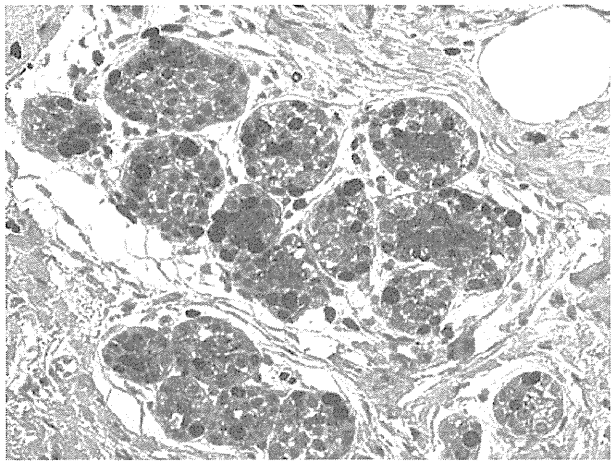

Figure 3. Double staining for E-cadherin and Ki67. Tumour cells show membranous E-cadherin staining (red) and nuclear Ki67 staining (brown). For correct counting of the Ki67 labeling index in lobular neoplasia (LN) cells, we calculated the ratio of Ki67-positive and E-cadherin-negative LN cells to all E-cadherin-negative LN cells.

nuclear grade 2 or 3 in seven, which included two cases with an obvious comedo pattern.

Partial resection was performed for 42 patients. The remaining 20 patients underwent mastectomy, including four for whom partial resection was planned but the procedure was changed to mastectomy because of positive tumour cells at surgical margins, as determined by intraoperative histopathological examination. Among the 20 patients in the symptomatic group, 18 underwent sentinel lymph node biopsy or axillary lymph node dissection, and did not have metastasis. The other two did not undergo examination of regional lymph nodes.

Only five of the 62 LNs were multicentric. Most LNs were not multicentric, but instead were single lesions that encompassed multiple tissue blocks.

CLINICOPATHOLOGICAL PARAMETERS CORRELATED WITH CLINICALLY OVERT LNs

The results of comparison between the symptomatic and occult groups are shown in Table 1. The mean age of patients did not differ between the two groups. Mean tumour sizes (ranges) were 41.5 mm (10–100) and 18.7 mm (0.7–96) in the symptomatic and occult groups, respectively. The incidence of tumours with an LN component of ≥30 mm was significantly higher in the symptomatic group (65%, 13/20) than in the occult group (17%, 7/42) ($P < 0.001$).

Mean Ki67 LIs were 10.5% (1–38%) and 3.7% (0–26.1%) in the symptomatic and occult groups, respectively, and the Ki67 LI in the symptomatic group was significantly higher than that in the occult group ($P < 0.05$). Similarly, the symptomatic group tended to show higher nuclear atypia (scores of 2 or 3) and higher mitotic counts than the occult group ($P < 0.001$ for each), and nodular or solid patterns. In the occult group, there was no case with nuclear atypia grade 3, a nodular pattern, or ≥2 mitotic counts per 10 HPFs. Four (20%) of the symptomatic lesions and 41 (98%) of the occult lesions had synchronous ipsilateral breast cancers, which were mostly low-grade conventional ductal carcinomas.

Five (25%) lesions in the symptomatic group and three (7%) in the occult group possessed components of early invasion. All early invasive cases in the occult group possessed widespread LNs, and 43% of the seven occult lesions that were >30 mm showed components of early invasion.

On the basis of univariate logistic regression models, larger size, higher nuclear atypia, a nodular or solid microscopic structural pattern, a higher mitotic count and a higher Ki67 LI were significant risk factors for symptomatic lesions (Table 2). In addition, on the basis of multivariate analysis including these five parameters, tumour size ≥30 mm [odds ratio (OR) 22.8, 95% confidence interval (CI) 2.29–227, $P = 0.008$], mitotic count ≥1 per 10 HPF (OR 34.4, 95% CI 2.78–425, $P = 0.006$) and Ki67 LI ≥10% (OR 10.2, 95% CI 1.18–88.7, $P = 0.035$) were independent risk factors for symptomatic lesions (Table 2).

CLINICOPATHOLOGICAL PARAMETERS CORRELATED WITH EARLY INVASION IN LNs

Among 62 surgically resected LN specimens, eight and 54 were classified as LN with invasion and LN without invasion, respectively (Table 3). The mean patient ages were 57.1 years (range 38–77) and 53.0 years (range 33–80) in the LN with invasion group and the LN without invasion group, respectively. Mean tumour sizes were 21.1 mm (0.7–100) in the LN without invasion group and 59.0 mm (22–96) in the LN with invasion group ($P < 0.05$). The incidence of lesions with an LN component of ≥30 mm was significantly higher in the latter group (87%, 7/8) than in the former group (24%, 13/54) ($P = 0.001$). Mean Ki67 LIs were 4.8% (0–26.1%) in the LN without invasion group and 13.4% (1.2–38.0%) in the LN with invasion group ($P < 0.05$), and the latter group had a higher Ki67 LI than the former group ($P < 0.005$).

Table 1. Comparison between symptomatic and occult groups of lobular neoplasias

Parameter	Total	Number of cases (%)		*P*-value
		Symptomatic group (n = 20)	Occult group (n = 42)	
Age (years)		52.6 (38–71)*	54.0 (33–80)*	NS
Mean tumour size (mm)		41.5 (10–100)*	18.7 (0.7–96)*	<0.05
Mean Ki67 LI (%)		10.5 (1–38)*	3.7 (0–26.1)*	<0.05
Early invasion				
Present	8	5 (25)	3 (7)	NS
Absent	54	15 (75)	39 (93)	
Size of lesion (mm)				
≥30	20	13 (65)	7 (17)	<0.001
<30	42	7 (35)	35 (83)	
Nuclear atypia				
1	41	7 (35)	34 (81)	<0.001
2	14	6 (30)	8 (19)	
3	7	7 (35)	0 (0)	
ALH/LCIS				
ALH	7	0 (0)	7 (17)	NS
LCIS	55	20 (100)	35 (83)	
Microscopic structural pattern				
Nodular	7	7 (35)	0 (0)	<0.001
Solid	18	7 (35)	11 (26)	
Displacement	20	4 (20)	16 (39)	
Pagetoid	17	2 (10)	15 (33)	
Mitotic count/10 HPFs				
0	42	5 (25)	37 (88)	<0.001
1	12	7 (35)	5 (12)	
≥2	8	8 (40)	0 (0)	
Synchronous ipsilateral breast cancer				
Present	46	5 (25)	41 (98)	<0.001
Absent	16	15 (75)	1 (2)	
Ki67 LI (%)				
≥10	12	9 (45)	3 (7)	<0.005
<10	50	11 (55)	39 (93)	

HPF, high-power field; LI, labelling index; NS, not significant; ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma *in situ*.
*Mean (range).

Table 2. Parameters correlated with risk of symptomatic lesion in lobular neoplasias computed by univariate and multivariate logistic regression model analyses ($n = 62$)

	Univariate			Multivariate		
Parameter	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Early invasion (present versus absent)	4.33	0.92–20.4	0.063			
Size of LN (≥30 versus <30 mm)	9.29	2.73–31.6	0.0004	22.8	2.29–227	0.008
Nuclear atypia (2, 3 versus 1)	7.89	2.38–26.2	0.0007	2.42	0.29–20	0.41
Microscopic structural pattern (solid/nodular versus others)	7.47	2.27–24.6	0.0009	0.9	0.11–7.23	0.91
Mitotic count/10 HPFs (≥1 versus 0)	22.2	5.60–88.0	<0.0001	34.4	2.78–425	0.006
Ki67 LI (≥10% versus <10%)	10.6	2.45–46.2	0.0016	10.2	1.18–88.7	0.035

CI, confidence interval; HPF, high-power field; LI, labelling index; OR, odds ratio.

Univariate logistic regression models showed that the size of the LN lesion and Ki67 LI were significant risk factors for a coexistent early invasive component (Table 4). On the basis of multivariate analysis including these two parameters, both LN size ≥30 mm (OR 22.6, 95% CI 2.15–237, $P = 0.009$) and Ki67 LI ≥10% (OR 11.5, 95% CI 1.60–83.0, $P = 0.015$) were independent risk factors for early invasion (Table 4).

All early invasive components of the LN with invasion group were classic ILC, although the LN component in five of the eight LN with invasion group cases was diagnosed as non-classic LCIS, i.e. high nuclear grade, central necrosis, and/or apocrine features. Five lesions in the LN with invasion group (62.5%) coexisted with another separate lesion of breast cancer in the ipsilateral breast (four IDCs and one DCIS). The eight LN with invasion cases were subclassified into symptomatic and occult subgroups (Table 5). Of the five lesions in the symptomatic subgroup, the LN component was always non-classic LCIS. In contrast, of the three lesions in the occult subgroup, the LN component was always classic LCIS, although all three lesions showed large sizes, ranging from 45 to 96 mm (Table 5).

Discussion

The concepts of LCIS and ALH were first introduced by Foote and Stewart in 1941,[14] and the term LN, including both LCIS and ALH, was coined by Haagensen *et al.*[1] In the present study, we clarified the histopathological characteristics of LNs that were detected clinically or that may have progressed to ILC. Statistical comparative analyses between the symptomatic and occult groups demonstrated that symptomatic LNs were larger, had greater nuclear atypia and more active proliferation than incidental LNs, and had a distended or solid structural pattern. In particular, tumour size (≥30 mm), mitotic count (≥1 per 10 HPFs) and Ki67 LI (≥10%) appeared to be important predictors for the symptomatic group, as determined using multivariate analysis. All symptomatic group LNs were >10 mm in diameter, and all of the LNs forming the nodular pattern belonged to the symptomatic group. These could be the reasons why the LNs of the symptomatic group were clinically identified relatively easily.

Szyglarewicz *et al.* found that 64% of LNs ($n = 24$) diagnosed on the basis of radiologically significant findings had ILC components in the subsequent excisional biopsy specimens.[15] However, in the present study, no significant differences were observed between the symptomatic and occult groups with regard to the presence of foci of early ILC.

An LN often coexists with another breast cancer. Recently, there have been a number of studies estimating the upgrade rate of the LNs on core biopsies.[16–21] Chaudhary *et al.* reported that 0–35% of patients diagnosed as having LN on core biopsy had coexistent DCIS or invasive cancer at or near the biopsy site.[21] In these studies, the upgraded lesions were assumed to be independent of the LN. In the present study, we confirmed that 20% (4/20) of symptomatic lesions had another synchronous ipsilateral breast cancer.

On the other hand, there are few descriptions of LN status in the excisional biopsy specimens in these reports.[16–21] Murray *et al.* reported that, in eight cases of classic LCIS that were diagnosed on core

Table 3. Comparison between non-invasive and early invasive groups of lobular neoplasias

Parameter	Total	Number of cases (%)		*P*-value
		With invasion (n = 8)	Without invasion (n = 54)	
Mean age (years)		57.1 (38–77)*	53.0 (33–80)*	NS
Mean tumour size (mm)		59.0 (22–96)*	21.1 (0.7–100)*	<0.05
Mean Ki67 LI (%)		13.4 (1.2–38)*	4.8 (0–26.1)*	<0.05
Clinically detectable				
Yes	20	5 (62)	15 (34)	NS
No	42	3 (38)	39 (66)	
Size of lesion (mm)				
≥30	20	7 (87)	13 (24)	0.001
<30	42	1 (13)	41 (76)	
Nuclear atypia				
1	41	3 (37.5)	38 (70)	NS
2	14	2 (25)	12 (22)	
3	7	3 (37.5)	4 (8)	
ALH/LCIS				
ALH	7	0 (0)	7 (13)	NS
LCIS	55	8 (100)	47 (87)	
Microscopic structural pattern				
Nodular	7	4 (50)	3 (6)	NS
Solid	18	1 (12.5)	17 (31)	
Displacement	20	1 (12.5)	19 (35)	
Pagetoid	17	2 (25)	15 (28)	
Mitotic count/10 HPFs				
0	42	4 (50)	38 (71)	NS
1	12	1 (13)	11 (20)	
≥2	8	3 (37)	5 (9)	
Synchronous ipsilateral breast cancer				
Presence	46	5 (62)	41 (76)	NS
Absence	16	3 (38)	13 (24)	
Ki67 LI (%)				
≥10	12	5 (38)	7 (13)	<0.005
<10	50	3 (62)	47 (87)	

HPF, high-power field; LI, labelling index; NS, not significant; ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma *in situ*.
*Mean (range).

Table 4. Parameters correlated with risk of a coexistent early invasive carcinoma component in lobular neoplasias computed by univariate and multivariate logistic regression model analyses

	Univariate			Multivariate		
Parameter	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Clinically detectable (yes or no)	4.33	0.92–20.4	0.064			
Size of lesion (≥30 mm versus <30 mm)	22.1	2.48–197	0.006	22.6	2.15–237	0.009
Nuclear atypia (2, 3 versus 1)	3.96	0.84–18.6	0.081			
Microscopic structural pattern (solid/nodular versus others)	3.07	0.66–14.3	0.153			
Mitotic count/10 HPFs (≥1 versus 0)	2.38	0.53–10.7	0.260			
Ki67 LI (≥10% versus <10%)	11.2	2.18–57.5	0.004	11.5	1.60–83.0	0.015

CI, confidence interval; HPF, high-power field; LI, labelling index; OR, odds ratio.

Table 5. Details of eight cases of lobular neoplasia with an early invasive carcinoma component

Case no.	Clinical presentation	Tumour size (mm)	Size of invasive component (mm)	Nuclear atypia	Microscopic structural pattern
1	Occult	96	0.5	1	Pagetoid
2	Occult	88	3.0	1	Pagetoid
3	Occult	45	2.0	1	Displacement
4	Symptomatic	50	5.0	3	Nodular
5	Symptomatic	40	1.0	2	Nodular
6	Symptomatic	22	8.0	3	Nodular
7	Symptomatic	96	7.0	3	Solid
8	Symptomatic	35	10.0	2	Nodular

biopsy and were sufficiently explained by imaging diagnoses, four still showed LCIS or ALH in excisional biopsy specimens, whereas three were upgraded.[20] In the study of Lewis *et al.*, the pathological diagnosis of surgical excision specimens was ILC in nine of the 144 patients who were diagnosed as having LN on core biopsy.[19] However, the relationship between the LN and ILC components and the extent of the LN in excisional biopsy specimens were not described in their paper.

Comparisons between the LN with invasion and LN without invasion groups using both univariate and multivariate logistic regression models revealed that larger tumour size (≥30 mm) and higher Ki67 LI (≥10%) were significant predictors of early invasion. All LN lesions with invasion were >20 mm in diameter.

Esserman *et al.* reported that ILCs diagnosed after the excision of LNs were associated with diffuse LNs, using core needle biopsy.[22] Their study showed that widespread LNs progressed to ILC. The present study confirmed these results, and also found that parameters of proliferative activity, e.g. Ki67 LI, of constituent LN cells are indicators of risk of early invasion. Because all lesions with a Ki67 LI of >10% showed a nuclear atypia score of 2 or 3, Ki67 LI was suggested to be associated with nuclear atypia (data not presented).

LNs are known to have a high incidence of multicentricity and bilaterality, being multicentric in as many as 85% of patients and bilateral in 30–67%.[4,23] However, the incidence of multicentricity of LNs in our study was only 8.1% (5/62). These data might be related to detailed histological mapping

of the extent of the LN in the resected specimens. Through detailed mapping, involved multiple lobules were frequently found to be continuous with each other, and most of the LNs in this study were considered to be single LN lesions.

In conclusion, wide local extension and higher proliferation indices, i.e. higher mitotic counts or a higher Ki67 LI, were characteristic features of symptomatic LNs and LNs with early invasive components. Further studies involving immunohistochemical and molecular biological analyses, and examining a larger number of cases, should be conducted to identify which LNs are at risk of progression to invasive disease.

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Conflict of interests

None to declare.

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Japan Breast Cancer Society clinical practice guideline for surgical treatment of breast cancer

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Breast-conserving therapy

From 1972 to 1989, 6 randomized controlled trials (RCT) of breast-conserving surgery followed by radiotherapy and radical mastectomy were performed. The two groups did not significantly differ in long-term survival rate after 20 years [1, 2]. Breast-conserving therapy is now a standard of care for Stage I and II breast cancer. As for ductal carcinoma in situ (DCIS), no RCTs compared breast-conserving therapy with mastectomy, but many published case series, reviews and meta-analyses showed good local control rates and high overall survival (OS) results [3]. Most Stage 0–II breast cancers are candidates for breast-conserving therapy, but as the EBCTCG's meta-analysis showed that local recurrence adversely affected survival rates [4], caution is warranted regarding indication or contraindication for breast-conservation therapy and extent of resection.

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Contraindications for breast-conserving therapy

1.	Multiple cancer lesions are found in different quadrants.
2.	Breast cancer is widely extensive (e.g., extensive mammary gland micro calcifications in mammography)
3.	Radiotherapy cannot be provided (cf. radiotherapy CQ8)
4.	Inadequate cosmetic outcome is predicted because of tumor size.
5.	No wish for breast-conserving therapy by patient.

CQ1. Is breast-conserving therapy recommended for DCIS?

Recommendation

Breast-conserving therapy for DCIS is strongly recommended according to the indication of breast-conserving therapy for invasive cancer (Grade A).

Breast-conserving therapy is the standard of care for DCIS if we can retain histologically negative resection margins and expect good cosmetic outcome. Some risk factors must be considered, including omission of postoperative irradiation, positive margins, negative estrogen receptor (ER) status, high proliferative ability, HER2 overexpression, and young age. The Van Nuys prognostic index is proposed as a risk prediction tool for local recurrence [5].

CQ2. Is breast-conserving therapy recommended as a local therapy for Stage I and II invasive breast cancers?

Recommendation

Breast-conserving therapy for Stage I and II invasive breast cancer is strongly recommended as a primary treatment, because it provides a similar survival rate to that of mastectomy (Grade A).

CQ3. Is re-excision recommended for cases with positive surgical margins detected in breast-conserving surgery?

Recommendation

If a large volume of residual tumor is predicted [exposure of cancer cells to the margin of resection (invasive or non-invasive lesion), etc.], surgical resection is recommended (Grade B).

If a small volume of residual tumor is predicted (the presence of cancer cells close to the margin of resection, etc.), appropriate postoperative therapy may be able to control residual disease locally (Grade C1).

Many RCTs and meta-analyses indicate that microscopic positive resection margins are the major risk factor for ipsilateral breast tumor recurrence (IBTR) [6, 7], but no widely adopted pathological definition of an adequate negative margin exists. Houssami et al. [7] showed that IBTR probability is associated with margin status (odds ratios are 2.42, 2.02 and 1.90, respectively, for positive, positive/close and close versus negative). However, adjustment for covariates (adjuvant therapy) removes the significance of the threshold distance. Patients at high risk for IBTR (i.e., in situ/invasive carcinoma at inked margins and many carcinoma foci at the closed margins) are recommended to have re-excisions.

CQ4. Is breast-conserving surgery recommended for patients with invasive breast cancer whose tumor size has been reduced enough by neoadjuvant chemotherapy (NAC)?

Recommendation

Breast-conserving therapy is recommended for patients with invasive breast cancer whose tumor size has been reduced enough by NAC (Grade B).

Although a meta-analysis has shown improved rates of breast conservation after NAC [8], local recurrence was slightly higher in patients with NAC compared with adjuvant chemotherapy (HR = 1.22; 95 % CI: 1.04–1.43) and data on long-term outcomes are limited [9]. Japanese data indicate that pre- and post-chemotherapy magnetic

resonance imaging (MRI) or computed tomography (CT) is a useful modality for evaluating treatment effect [10, 11]. Patients with a concentric shrinkage pattern of the primary tumor are good candidates for breast-conserving surgery, while breast-conserving surgery should be cautiously applied to those with dendritic or mosaic shrinkage patterns.

CQ5. Is repeat lumpectomy recommended for IBTR after the breast-conserving therapy?

Recommendation

Clear evidence for repeat lumpectomy for IBTR after breast-conserving therapy does not currently exist; its use should be considered with the utmost caution (Grade C1).

Many reports show no difference in survival between repeat lumpectomy and mastectomy; however, the 5-year rate of second local relapse is reportedly 6.7–38 %. Ishitobi et al. [12] reported ER positivity and longer disease-free survival (DFS) (over 2 years) are correlated with good local control, but no current consensus on these risk factors for second local relapse exists, and risk factors for second local relapse after repeat lumpectomy are not clear. Therefore, salvage mastectomy is the standard surgery for IBTR at this time.

CQ6. Is skin-sparing or nipple-sparing mastectomy feasible for patients with early-stage breast cancer planned for mastectomy?

Recommendation

Skin-sparing mastectomy (SSM) is useful a procedure with providing both curability and a good cosmetic outcome. Especially, early breast cancer including extensive DCIS is an ideal indication of this surgery (Grade B).

Nipple-sparing mastectomy (NSM) should be performed on carefully selected patients who meet the criteria such as early breast cancer and a wide nipple tumor distance after fully informing patients about a major complication of nipple necrosis and local recurrence in the nipple–areolar complex (Grade C1).

SSM involves resection of the mammary gland including the nipple–areola complex, but preserves the breast skin. NSM preserves breast skin and the nipple–areola complex. SSM and NSM allows immediate (or primary) and one-stage breast reconstruction and have the great advantage of both good oncologic outcome and improved cosmetic outcome. Many studies have reported that its therapeutic result is similar to that of conventional mastectomy [13, 14]. However, SSM and NSM should be applied with caution to patients with locally advanced breast cancer or with tumors close to the nipple, only after full explanation given to the patients [14].

Axillary dissection, sentinel lymph node biopsy and some problems associated with them

Surgical management of breast cancer has traditionally been primary tumor resection and axillary lymph node dissection (ALND). ALND provides staging information and guidance for treatment options. Although ALND has long been considered the standard procedure for management of early-stage breast cancer, its survival advantage is unclear. Even after a long follow-up period (25 years), the NSABP B-04 study, which compared ALND, postoperative regional radiation and delayed dissection among those who subsequently develop axillary recurrence for clinically node-negative breast cancers, and compared ALND and postoperative regional radiation for clinically node-positive breast cancers, found no significant difference in OS among the three node-negative groups, or between the two node-positive groups [15]. Conversely, a Bayesian meta-analysis showed that prophylactic ALND improved survival from 4 to 16 % [16]. Therefore, only the result of the NSABP B-04 is not sufficient to conclude that ALND does not improve survival rates.

Sentinel node biopsy (SNB) is an alternative to ALND in detection of lymph node metastases, and avoiding unnecessary complications of ALND. Results from three studies on omitting ALND based on negative SNBs suggest that omission of ALND for negative sentinel lymph node (SLN) should become the new standard of care [17–19].

CQ7. Should patients with clinically positive axillary lymph nodes undergo ALND to improve their survival rate?

Recommendation

Given the improvement in survival rate and local control, ALND is recommended for patients with clinically positive axillary lymph nodes (Grade B).

No RCT has directly compared the significance of ALND for patients with clinically positive axillary lymph nodes. Local control by ALND and postoperative treatment guided by exact staging are very important. A patient with a clinically positive lymph node is recommended to undergo ALND.

CQ8. Should patients with clinically positive axillary lymph nodes undergo level I and II axillary lymph node dissection?

Recommendation

Level I and II ALND is recommended for patients with clinically positive axillary lymph nodes (Grade A).

According to reports investigating the extent of lymph node metastases in patients who had clinically positive axillary lymph nodes, only level I nodes were involved in 20–58 % of patients, but levels I + II and I + II + III nodes were involved in 20–29 % and 16–32 % of patients, respectively. Approximately 20 % of patients had pathologically confirmed metastases involving up to level III nodes. [20–22]. Another article reported that regional node failure was related to the number of axillary nodes removed [23]. This study shows that inappropriate dissection raises the risk of an axillary lymph node recurrence. A meta-analysis conducted by EBCTCG showed that an increase in local recurrence was associated with a reduction in 15-year survival rate. [4]. Especially in patients with positive lymph node metastases, appropriate surgery combined with radiotherapy is highly effective in improving survival.

Subclinical lymph node metastasis is not thought to influence prognoses of patients treated with appropriate post-surgical adjuvant treatment, but level I–II axillary dissection is a standard treatment for node-positive patients. When level III lymph nodes metastases appear in surgery, dissection should include level III nodes and their surroundings.

CQ9. Is omission of ALND based on negative SNB recommended for patients with node-negative breast cancer?

Recommendation

SNB alone is considered to be a current standard of care (Grade A).

Three studies have reported on omission of ALND based on negative SNB. In the first study (516 patients with T1N0 breast cancer; median follow-up period, 79 months), DFS and OS were similar between the SNB and ALND groups [17]. In the second (697 patients with breast cancer $\leq$3 cm; median follow-up period, 56 months), the SNB group had more local recurrences, although the study had a high false-negative rate (FNR) of approximately 17.0 % [18]. In the third study (3,986 patients; mean follow-up period, 95.6 months), 8-year OS rates were 90.3 and 91.8 % in the SNB and ALND groups, respectively, and 8-year DFS rates were 81.5 and 82.4 % in the SNB and ALND groups, respectively, which showed no significant difference [19].

These results indicate that SNB performed by teams of skilled surgeons, pathologists, radiologists and other professionals allows almost exact diagnosis of axillary lymph node metastasis in early breast cancer with clinically negative nodes. Thus, SNB alone is considered to be a current standard of care.

CQ10. Is SNB preferred to ALND for improvement of postoperative quality of life (QOL)?

Recommendation

SNB is strongly recommended because of fewer postoperative complications and upper-limb morbidity and significant improvement in QOL compared with ALND (Grade A).

RCTs that compared upper-limb morbidity and QOL between SNB alone and ALND have consistently demonstrated superiority of SNB alone compared with ALND in terms of upper-limb/shoulder morbidity (range of motion, edema, paresthesia and pain), QOL, axillary operative time, drain usage, length of hospital stay and time to resume normal daily activities [24]. Omission of ALND based on the SNB result can significantly contribute to improvement of QOL.

CQ11. Should SLNs be identified by a combination of blue dye and radioisotope (RI)?

Recommendation

If the RI is available for identifying SLNs, the combination of RI and blue dye is recommended because it is superior to either method alone (Grade B).

Although some studies reported that high identification rates can be achieved with either blue dye alone or RI alone, the demonstration that $\sim$10 % of SLNs were identified only by blue dye plus RI suggests that the combination method increases the identification rate [25].

CQ12. Are SNBs recommended for patients who are preoperatively diagnosed with DCIS?

Recommendation

SNB with primary tumor excision is recommended for patients who are diagnosed with DCIS on biopsy if invasive cancer is suspected or if enforcement of the two-stage SNB is difficult (Grade B).

In a patient who is diagnosed with DCIS through a detailed pathological examination following an excision biopsy, an additional SNB is unnecessary (Grade D).

Approximately 8–38 % of DCIS diagnosed by biopsy proves to be invasive cancer in the final pathological examination [26]. Factors associated with the infiltration are large size, palpable tumor, high-grade tumor, presence of comedo necrosis, mass shadow in mammography, extending more than 2 cm by MRI, young age, and diagnosis by core needle biopsy. When conducting breast-conserving surgery in patients with a biopsy-proven diagnosis of DCIS following image findings suggestive of a localized tumor in a narrow area, SNB may be omitted because SNB can be conducted in two stages. In the case of mastectomy, immediate reconstruction or tumor near the axilla, SNB with primary tumor excision is desirable.

CQ13. Is omission of ALND recommended for patients with metastasis to the SLN?

Recommendation

Omission of ALND is recommended for patients with early breast cancer with micrometastases to the SLN (Grade B).

If macrometastasis is found in the SLN, basically omission of ALND is not recommended. However, the possibility of its omission should be assessed in individual patients. Appropriate postoperative treatment is essential (Grade C1).

As the ACOSOG Z0011 trial demonstrated that SNB and ALND result in similar prognosis [27], the appropriateness of changing practice on the basis of this study has aroused the argument. In the ASOCOG Z0011 trial, 5-year OS was 91.8 % with ALND and 92.5 % with SNB alone at a median follow-up of 6.3 years. Five-year DFS was 82.2 % with ALND and 83.9 % with SNB alone. Non-inferiority was achieved with high statistical significance ($P < 0.008$). These findings from Z0011 indicated that a high rate of locoregional control can be achieved with multidisciplinary therapy, even without ALND. One criticism is that the women included in Z0011 were highly selected and had favorable prognoses; the majority were postmenopausal with ER-positive T1 tumors, and many had micrometastatic disease in the SLNs. This study also closed before recruitment reached the planned accrual size and its event rate was much lower than anticipated for both arms. Therefore, the appropriateness of applying these findings to the general population of women with breast cancer who undergo breast-conserving therapy has been questioned.

In the IBCSG23-01 trial, which randomized patients with SLN micrometastases to ALND or no further surgery, no difference for the primary endpoint of DFS was noted [28]. However, most patients in this trial had tumors <3 cm (92 %), received breast conservation (91 %) and adjuvant systemic therapy (96 %). These results suggested that ALND could be avoided in early breast cancer patients with limited SLN involvement who had appropriate systemic therapy.

Together, these results indicate that ALND has little therapeutic advantage for patients with micrometastatic disease in the SLNs. For macrometastases in the SLNs, especially in patient's who meet the Z0011 eligibility criteria, patients should be informed of the indications that an axilla might need ALND, and to be involved in the decision-making process for their treatment.

Adaptation of omission of ALND for positive sentinel node

1.	Clinical stage of T0-2N0
2.	No more than two metastatic SLN detected by H&E
3.	Planned breast irradiation following breast-conserving surgery
4.	Appropriate drug therapy after surgery

CQ14. Is SNB after NAC both feasible and accurate in clinically node-negative patients at presentation?

Recommendation

SNB after NAC is both feasible and accurate in clinically node-negative patients at presentation (Grade C1).

SNB is not recommended after NAC in clinically node-positive patients before chemotherapy (Grade C2).

Accuracy of SNB in breast cancer patients who receive NAC remains open to debate. A systematic review of 27 studies with a total study population of 2,148 patients had a pooled SLN identification rate of 90.9 % and a FNR of 10.5 % after NAC [29]. The initial positive clinical nodal status was reportedly associated with decreased accuracy

of SNB. In the SENTINA trial [30], FNR was 14.2 % in patients who converted after NAC from cN+ to ycN0. A similar FNR of 12.6 % was reported from the ACOSOG Z1071 trial [31]. Although SNB is a reliable diagnostic method after NAC in clinically node-negative patients, it is not accurate enough to spare ALND in clinically node-positive patients.

CQ15. Are internal mammary SNBs practical?

Recommendation

Internal mammary (IM) SNB has not proven to be practical because data were insufficient (Grade C2).

SNB in IM resulted in 13–26.8 % of nodal involvement. Evaluation of IM SLN status may provide more precise staging and identify patient subgroups who benefit from altered adjuvant therapy, leading to better survival. IM SNB, however, should be regarded as still in the investigative stage because of insufficient data. Further studies are necessary to fully access its relevance.

CQ16. Is a SNB recommended for IBTR after breast-conserving surgery?

Recommendation

If ALND is not performed during initial surgery, the percentage of identifying ipsilateral axillary SLNs is high. Since identification of SLNs can be useful in predicting prognosis for local recurrence and determining treatment strategy, it might be appropriate to carefully conduct the sentinel node procedure (Grade C1).

If ALND is performed during initial surgery, sentinel nodes other than the ipsilateral axillary may be identified. Lymphoscintigraphy is essential, but therapeutic significance of SLN sampling and its impact on prognosis are not clear. Therefore, basically its sampling is not recommended in routine clinical practice (Grade C2).

CQ17. Is preservation of the intercostobrachial nerve (ICBN) recommended to prevent sensory loss of axilla and upper arm?

Recommendation

Sparing of the ICBN is useful in reducing axillary/brachiomedial sensory deficits. However, since the long-term outcome of ICBN sparing in patients with positive lymph node metastasis is not clear, it may be appropriate to perform such a surgery with extreme caution (Grade C1).

Sparing of the ICBN have been identified in several randomized and non-randomized studies. Preservation of the ICBN improves patient sensory deficit [32]. However, most of these studies were performed with node-negative patients; the long-term result of preserving the ICBN in node-positive patient who undergo axillary dissection currently is unclear. Sparing of the ICBN should be performed cautiously.

CQ18. Is upper extremity rehabilitation after ANLD recommended?

Recommendation

We recommended upper extremity rehabilitation after ALND. The need for structured exercise program, such as physical therapy can be individually assessed (Grade B).

A Cochrane review of 10 studies evaluated the effectiveness of exercise interventions in improving upper-limb dysfunction due to breast cancer treatment [33]. Implementing early exercise was more effective than delayed exercise in short-term recovery of shoulder flexion range of motion. The need for structured exercise program by a physical therapist should be individually decided.

CQ19. Is management of lymphedema recommended?

Recommendation

Appropriate preventive education of patients for postoperative lymphedema reduces its incidence. Once it occurs, an early intervention with composite therapy including compression therapy wearing an elastic bandage and well-controlled exercise under compression therapy is effective in halting the progression of lymphedema and is expected to be effective to a certain extent even in severe cases (Grade B).

Surgical options such as lymphatic–venous anastomosis alone are not well standardized (Grade C2).

According to the field survey granted by Japan Society of Breast Cancer, onset incidence was 50.9 % when laterality of circumference of 5 sites of each arm $\geq$1 cm is regarded as significantly different. Daily prophylactic care and early intervention against early detection are important in management of lymphedema [34]. As few RCTs of surgical interventions have yet been performed, their efficacy cannot be conclusively assessed.

Less invasive treatment (endoscopic surgery and non-surgical ablation)

Breast cancer therapy continues to improve, and patients' QOL improves with it. Endoscopic breast surgery techniques

that use small incisions from extra-mammary sites have been developed especially in Japan. As progress in diagnostic imaging improves the detection rate for early breast cancers, non-surgical ablation such as radio-frequency ablation (RFA), cryotherapy and percutaneous ethanol injection therapy are becoming important treatment modalities.

CQ20. Is endoscopic surgery for breast cancer acceptable?

Recommendation

When performed by skillful experts, endoscopic breast surgery has a great advantage in cosmetic outcome over traditional direct incision. These procedures and techniques are expected to become standardized in the near future (Grade C1).

Nakajima reported on long-term results of endoscopic surgery for Stage I and II breast cancer and found no statistical difference in survival rates between the endoscopic surgery group and direct incision group [35]. Thus endoscopic surgery is acceptable as an option for early-stage breast cancer, despite the absence of much RCT-based evidence.

CQ21. Is non-surgical ablation recommended as a local standard therapy for early-stage breast cancer?

Recommendation

Non-surgical ablation is not recommended because of the absence of sufficient data of a local therapeutic effect (Grade C2).

A retrospective study of RFA for 497 patients with early breast cancer was performed in 10 institutions in Japan; the study data were reported in ASCO 2012 [36]. Mean tumor size was 1.6 cm and median follow-up period was 50 months (range 3–92 months). The local recurrence rate after RFA was higher in tumors of >2 cm (13 of 72, 18 %). Non-surgical ablation for early breast cancer could control a local site for limited indications. Currently, it should be performed as part of a clinical trial.

Breast reconstruction

Currently in Japan, breast reconstructions are increasing. One-stage and two-stage reconstructions are performed after mastectomies. The former uses autologous tissue and implants directly without the additional procedures for skin extension. The latter is reconstructed at a later date after first extending the skin, using a tissue expander. A primary reconstruction involves skin extension performed at the time of mastectomy; a secondary reconstruction involves a breast that is rebuilt following mastectomy. In this part, basic aspects of breast reconstruction are summarized.

CQ22. Is immediate breast reconstruction recommended for patients who undergo mastectomy?

Recommendation

For early-stage breast cancer, immediate breast reconstruction by a skilled surgeon is a useful method to improve the cosmetic outcome without impairing the curability. Immediate (or primary) breast reconstruction should be presented as an option to patients who undergo mastectomy (Grade B).

Sharma compared outcomes of 495 patients with T1/T2 tumors and 0–3 positive lymph nodes who received immediate breast reconstruction with 524 patients who did not receive breast reconstruction [37]. Local recurrence occurred in 3.2 and 1.3 % of the patients with and without reconstruction, respectively ($P = 0.061$). The 10-year OS rate for patients with isolated local recurrences (87.5 vs. 90.3 %; $P = 0.234$) was not significantly different. Venus evaluated immediate breast reconstructions using the latissimus dorsi flap and concluded that this procedure gives the majority of patients a satisfying cosmetic outcome while minimizing postoperative complications [38].

CQ23. Is breast reconstruction recommended after NAC?

Recommendation

Most reports have indicated that regardless of the reconstruction procedure used, breast reconstruction after NAC is not associated with an increase in the incidence of adverse events or a delay in starting postoperative treatment. However, due to the lack of high-quality evidence, caution must be exercised in its application (Grade C1).

Especially in patients requiring postoperative radiotherapy, breast reconstruction should be conducted carefully regardless of the type of reconstruction material used (Grade C2).

Breast reconstruction after NAC often requires postoperative radiotherapy and is not supported by adequate evidence. Prabhu et al. [39] evaluated outcomes of 100 patients with Stage III breast cancer who each received NAC and mastectomy. The time from initial biopsy to adjuvant radiotherapy was prolonged and the rate of complications requiring surgical intervention was significantly higher. However, other case–control studies show no

concern for breast reconstruction after NAC in terms of either safety or oncologic outcome [40]. Thus breast reconstruction after NAC should be carefully performed after full explanation to patients and taking patients' wishes into account.

CQ24. Is breast reconstruction recommended for patients with histories of chest wall irradiation?

Recommendation

Insufficient evidence exists of good outcomes for breast reconstruction in patients who have had chest wall irradiation. As risk of postoperative complication is higher, breast reconstruction for such patients is not recommended (Grade C2).

Few studies have investigated breast reconstruction after chest wall irradiation. Therefore, patients should be informed of the increased risk of complications and the potential disfigurement. Rebuilding with autologous tissue can be accomplished with relative safety.

Surgical treatment for advanced and metastatic breast cancer

Although the role of surgery for advanced and metastatic breast cancer is not large, it can improve local control and QOL in some cases. However, evidence that surgery contributes to the survival rate for Stage IV disease or oligometastases is insufficient.

CQ25. Are primary tumor resections recommended for Stage IV breast cancer?

Recommendation

Surgical resection of primary tumor for patients with distant metastasis may provide local control over the long term. However, resection of the primary tumor for Stage IV breast cancer may be conducted with utmost care, as its survival advantage is unclear (Grade C1).

An analysis from the National Cancer Data Base of the American College of Surgeons reported on the relationship between the use of surgical procedures for the primary tumor and duration of survival for a total of 16,023 patients with Stage IV breast cancer [41]. Women treated with surgical resection compared with those not surgically treated, had superior prognosis with a hazard ratio of 0.61. A retrospective study in Japan also demonstrated that local surgery improved OS of patients with Stage IV, especially local surgery in younger patients [42].

Some RCTs are now evaluating whether surgical excision of primary tumor is effective for Stage IV breast cancer [43]. The limited data available at this time indicate that patients with Stage IV disease should be carefully selected for primary tumor resection, taking the status of metastatic sites into consideration.

CQ26. Is resection of metastatic lymph nodes recommended for breast cancer with regional lymph node recurrence?

Recommendation

Ipsilateral supraclavicular lymph node recurrence alone requires systemic treatment and radiation. In principle, surgical resection to obtain complete cure is not recommended (Grade C2).

After ALND or preserving axillary lymph node with negative sentinel node, axillary dissection is recommended for patients with ipsilateral axillary lymph node recurrence alone, to obtain complete cure (Grade B).

Some articles report that patients with ipsilateral supraclavicular lymph node recurrence who derive good local control or complete response from combined systemic and local treatments have improved prognoses [44].

For ipsilateral axillary lymph node recurrence after axillary dissection, the group treated with additional dissection had significant better prognosis than the group without it [45]. There have been no reports comparing treatment methods and prognosis among patients with an isolated axillary lymph node recurrence after SNB. Because initial axillary dissection and delayed dissection did not show different prognoses in the NSABP B-04 study [15], we expect that additional axillary dissection provide good local control and prognosis for axillary lymph node recurrence alone after negative SNB.

CQ27. Is surgical excision of a relapsed chest wall lesion after mastectomy recommended?

Recommendation

It may be appropriate to carefully perform minimal excision of a local chest wall recurrence for examination of biological characteristics of tumor and in view of significance of local control (Grade C1).

However, there is no evidence to support the claim that it would contribute to improvement in survival and also given deterioration of QOL by surgery, an extensive chest wall recurrence should not be treated by excision of a lesion together with the chest wall (Grade D).

CQ28. Is resection of lungs, bone or liver recommended when metastasis has occurred?

Recommendation

For multiple metastases and numerous metastases involving multiple organs, surgical excision is not recommended with an exception of selected cases, because there is no evidence to support the claim that it would contribute to prolongation of survival (Grade C2).

Although there are data to show that lung resection in Stage IV breast cancer with isolated lung metastasis can provide long-term survival, the selection of these data is biased. [46]. Excisions might be considered for solitary lung tumors whose primary (as opposed to metastatic) status is unclear. Surgery for metastatic thigh bone is typically performed as palliative treatment to protect against fracture or reduce pain and vertebral to reduce nerve symptoms due to spinal cord compression [47]. Even if patients are considered to have surgically treatable liver metastases, more than 50 % have diffuse hepatic and peritoneal metastases and surgery is not indicated in most patients [48]. Surgery may be effective in limited cases of distant metastasis, but treatment should be carefully considered by an experienced medical care team.

CQ29. Is the surgical resection for the brain metastases recommended?

Recommendation

Surgical resection for brain metastases is not recommended, although surgery and radiation may improve local control and QOL (Grade C2).

Median survival for patients with brain metastases is 1–2 months without treatment [49]. Whole brain irradiation relieves symptoms and extends survival period for 4–6 months longer, but symptom returns in several months. The 1-year survival rate is <20 % [50]. Surgery can improve symptoms of single brain metastases faster than can whole brain radiotherapy (WBRT). Long-term outcomes do not differ between surgery and stereotactic radiosurgery, but surgery can effect earlier improvement for operable, localized, symptomatic tumors ≥3 cm [51]. Use of surgery to treat multiple brain metastases is controversial.

Surgery is effective as local treatment in limited cases (isolated tumor, good performance status, no active metastasis to another organ, operable localization, ≥3 cm, and symptomatic tumor) [51], but radiotherapy (WBRT, stereotactic radiosurgery) should be generally preferred.

CQ30. Is surgery for breast cancer during pregnancy recommended?

Recommendation

Surgery is recommended for pregnant patients with breast carcinoma, because surgery is relatively safe, even in the third trimester. However, gestational period may affect choice of procedure (Grade B).

Others

CQ31. Is surgery recommended for breast cancer in elderly women?

Recommendation

Surgery is recommended for breast cancer in elderly women (Grade A).

In the systematic review of the Cochrane Database of 2006, a meta-analysis of six RCTs found no difference in survival for surgery versus tamoxifen alone for breast cancer in women 70 years or older, [52]. But time to progression was significantly shorter in the tamoxifen-only group. Therefore, surgical treatment is considered to be standard, even in elderly patients. However, for those with ER-positive breast cancer and serious comorbidities, endocrine therapy is considered better.

For elderly patients, treatment should be individually decided, not only by age but also by survival expectancy, comorbidities and wishes of the patient and her family.

CQ32. Is routine use of antibiotic prophylaxis for breast operations recommended?

Recommendation

We recommended routine use of antibiotic prophylaxis for breast operations at present. However, the benefit of antibiotic prophylaxis might become less significant as use of limited breast surgery increases in the near future. In any case, antibiotic prophylaxis for high-risk patients is recommended (Grade B).

A systematic review of 5 RCTs, including 1,307 patients, revealed a statistically significant risk ratio (RR) of 0.60 favoring antibiotics [53]. The Cochrane Library analysis, which was reprinted in 2012, demonstrated that prophylactic antibiotics administered preoperatively significantly reduce the incidence of surgical site infection for patients who undergo breast cancer surgery without reconstruction (pooled RR: 0.71) [54].