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Impact of sentinel node biopsy on long-term quality of life in breast cancer patients

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Background: The aim of this study was to assess long-term quality of life (QoL) over a period of 6 years in women with breast cancer (BC) who underwent sentinel lymph node biopsy (SLNB), axillary lymph node dissection (ALND), or SLNB followed by ALND.

Methods: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)-C30 and the EORTC-QLQ-BR-23 questionnaires were used to assess QoL before surgery, just after surgery, 6, 12 and 72 months later. The longitudinal effect of surgical modalities on QoL was assessed with a mixed model analysis of variance for repeated measurements.

Results: Five hundred and eighteen BC patients were initially included. The median follow-up was 6 years. During the follow-up, 61 patients died. None of the patients of the SLNB group developed lymphedema during follow-up and the relapse rate was similar in the different groups ($P=0.62$). Before surgery, global health status ($P=0.52$) and arm symptoms (BRAS) ($P=0.99$) QoL scores were similar whatever the surgical procedure. The BRAS score ($P=0.0001$) was better in the SLNB group 72 months after surgery. Moreover, during follow-up, patients treated with SLNB had lower arm symptoms scores than ALND patients and there was no difference for arm symptoms between patients treated with ALND and those treated with SLNB followed by complementary ALND.

Conclusion: Long-term follow-up showed that SLNB was associated with less morbidity than ALND.

Breast cancer (BC) is the most common malignancy in women worldwide. At present, the incidence of BC in Europe is 94.3 per 100 000 with a mortality of 26 per 100 000 (Ferlay *et al*, 2007). Owing to BC screening and new adjuvant systemic and/or hormone therapies, survival after BC has improved by 7–11% over the past few years (Vervoort *et al*, 2004). Five-year survival in

France is about 80% (Sant *et al*, 2009). As overall survival is good for patients with BC, it is important to assess the impact of BC management (that is, treatment advances) on health-related quality of life (QoL) in patients with BC. Indeed, QoL issues are of interest in BC, because effective methods for detection and treatment have led to an increase in the number of long-term survivors.

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Surgical procedures for BC have improved according to the results of randomised trials testing new procedures (Lacour *et al*, 1983; Maddox *et al*, 1983; Jacobson *et al*, 1995; Fisher *et al*, 2002; McCready *et al*, 2005). Breast-conserving treatment is now regarded as a standard treatment for early BC and sentinel lymph node biopsy (SLNB) became an alternative to axillary lymph node dissection (ALND) in the 1990s (McCready *et al*, 2005). Sentinel lymph node biopsy is a proven safe surgical method and causes less morbidity than ALND (Krag *et al*, 1993; Burak *et al*, 2002) with a smaller impact on QoL (Veronesi *et al*, 2003; Purushotham *et al*, 2005; Mansel *et al*, 2006; Del Bianco *et al*, 2008; Dabakuyo *et al*, 2009; Gill, 2009; Wang *et al*, 2011). Moreover, ALND may result in significant arm morbidity (Kuehn *et al*, 2000), including wound infections, seroma formation, damage to sensory and motor nerves, pain, loss of strength, impaired range of shoulder motion (Kissin *et al*, 1986), and lymphedema, which is of particular concern for women undergoing axillary surgery. Lymphedema is the most common long-term morbidity following axillary surgery and it may be associated with decreased limb mobility and functional problems, pain, sleep disturbance, anxiety, depression, poor wound healing and increased risk of infection (Erickson *et al*, 2001). To our knowledge, no prospective study has assessed QoL after axillary surgery for BC with a long follow-up.

The aim of this study was to assess long-term QoL over a period of 6 years in women with BC who underwent ALND, SLNB or SLNB followed by ALND.

PATIENTS AND METHODS

Patients. The design of this study has been described elsewhere (Dabakuyo *et al*, 2009). Briefly, it was a prospective multicentre study that include all women operated on for BC as the primary treatment in five hospitals of the Côte d'Or and Saône et Loire (French counties). Cases were registered from January 2005 to January 2006. Since the American Society of Clinical Oncology (ASCO) published recommendations for sentinel lymph node biopsy in early-stage BC in 2005 (Lyman *et al*, 2005), it was therefore impossible to conduct a randomised trial. The study was thus designed to assess routine surgical procedures, and the choice between ALND and SLNB was made by surgeons according to ASCO recommendations and according to their usual practice in their centre. A third group was defined for patients who underwent SLNB with additional lymphadenectomy.

Written informed consent was obtained from every participant in accordance with a protocol approved by local ethics committees ('Comité de Protection des Personnes' de Bourgogne).

Studied variables and end points. QoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)-C30 and the EORTC-QLQ-BR23 (Aaronson *et al*, 1993). QoL scores vary from 0 (worst) to 100 (best) for the functional and global health status (GHS) parameters and from 0 (best) to 100 (worst) for symptoms parameters. A five-point difference in QoL scores is considered the minimum clinically significant difference (Osoba *et al*, 1998). The GHS, the arm (BRAS) and breast (BRBS) symptoms scores were targeted for analyses.

Follow-up. The QoL was assessed by the patients according to a time-driven design: before surgery, just after surgery and 6 and 12 months later. In addition, a final assessment of QoL was done in summer 2011 (about 6 years after the surgery).

Clinical variables such as age, administration and duration of the hormone replacement therapy, tumour size (categorised into three classes: ≤ 10 mm (T1mic, T1a and T1b), 11–20 mm (T1c), > 20 mm ($\geq T2$)), tumour histology, c-erb-2 status, the Scarff Bloom and Richardson (SBR) grade and hormone receptor status

(either oestrogen or progesterone) were recorded at the time of surgery. At the time the QoL data were updated, information about treatments (chemotherapy, radiotherapy and hormone therapy), the occurrence of lymphedema or breast tumour recurrence, the type of recurrence, as well as the type of surveillance since the diagnosis (regular with one consultation with a mammogram every year or irregular, with less than one consultation with a mammogram every year) were also retrospectively collected.

Statistical methods. Continuous variables were described by means, standard deviations (s.d.), medians and ranges, while qualitative variables were given as percentages. The characteristics of patients who answered the questionnaire during summer 2011 and those who did not were compared using the Pearson's χ^2 -test for qualitative variables and the Student's *t*-test or Mann-Whitney test for quantitative variables. For these patients, the QoL before updating was also compared using Mann-Whitney tests.

At baseline, patients' clinical characteristics were compared according to the surgical procedure used. The Kruskal-Wallis non-parametric test was used for quantitative variables and the Pearson's χ^2 -test for qualitative variables.

For each surgical procedure, QoL scores were described at each follow-up time by means, s.d., medians and ranges. The Kruskal-Wallis test was used to compare scores according to the surgical procedure using the Bonferroni correction for multiple comparisons ($\alpha' = \alpha/n$ with n = number of comparisons made). QoL scores were also described at each follow-up time in the subset of patients with the same favourable prognostic characteristics (T1–T2 and positive hormone receptor status).

Patients' missing-score profiles were then generated to study their impact on QoL scores. Four profiles were studied according to missing-score patterns:

- Patients without missing scores
- Patients with drop-out scores: when a score was missing at one time of the follow-up, all following scores were inevitably missing (patients lost to follow-up or dead)
- Patients with intermittent missing scores: missing score occurring at any time of the follow-up between two existing scores
- Patients with all scores missing

Patients' missing-score profiles were compared according to the type of surgery to determine whether the patterns of missing data were different depending on the type of surgery. Finally, a mixed model analysis of variance for repeated measurements was applied for each score to assess the impact of the surgical procedure on QoL whatever the follow-up and to test longitudinal change of QoL whatever the surgical procedure. Co-variables were entered as classification variables in the model. Based on the Akaike's information criterion (AIC) (Akaike and Hirotugu, 1974), a compound symmetry covariance structure was chosen in all analyses. Analyses were adjusted on the variables distributed differently depending on the type of surgical procedure as these may confound the results. The interaction between the surgical procedure and the follow-up time and the effect of the patient's profile on QoL were also checked.

All reported *P*-values are two sided. The statistical significance level was set at $P < 0.05$. Analyses were done using SAS (version 9.3).

RESULTS

Population. A pragmatic prospective multicentre study was conducted in five hospitals of the Côte d'Or and Saône et Loire (French counties). All of the women undergoing breast surgery as

Table 1. Clinical and pathological features according to surgery modalities

Variables	ALND		SLNB		SLNB + ALND ^a		P-value
	N	%	N	%	N	%	
Hospital							<0.0001
CGFL	143	86.7	103	59.5	37	86.0	
Private hospital of Dijon	17	10.3	24	13.9	5	11.6	
Le Creusot	0	0.0	17	9.8	0	0.0	
Chalon sur Saône	4	2.4	14	8.1	1	2.3	
Macon	1	0.6	15	8.7	0	0.0	
Hormone status							0.04
Premenopausal	43	26.1	26	15.0	9	20.9	
Postmenopausal	122	73.9	146	84.4	34	79.1	
Unknown	0	0.0	1	0.6	0	0.0	
HRT							0.08
Yes	34	20.6	45	26.0	6	14.0	
No	106	64.2	96	55.5	33	76.7	
Unknown	25	15.2	32	18.5	4	9.3	
Tumour histology							0.001
Invasive ductal	134	81.2	133	76.9	37	86.0	
Invasive lobular	17	10.3	9	5.2	3	7.0	
<i>In situ</i>	6	3.6	23	13.3	0	0.0	
Medullary cancer	1	0.6	0	0	1	2.3	
micro-invasive cancer	1	0.6	1	0.6	1	2.3	
Unknown	6	3.6	7	4.0	1	2.3	
SBR Grade							<0.0001
1	32	19.4	69	39.9	10	23.3	
2	64	38.8	56	32.4	21	48.8	
3	52	31.5	19	11.0	10	23.3	
Unknown	17	10.3	29	16.8	2	4.7	
C-erb-2 status		0.0		0.0		0.0	0.34
Positive	25	15.2	14	8.1	4	9.3	
Negative	121	73.3	104	60.1	36	83.7	
Unknown	19	11.5	55	31.8	3	7.0	
Hormone receptor status							0.95
Positive	120	72.7	113	65.3	33	76.7	
Negative	25	15.2	22	12.7	6	14.0	
Unknown	20	12.1	38	22.0	4	9.3	
Treatments		0.0		0.0		0.0	
Surgery							<0.0001
Lumpectomy	88	53.3	155	89.6	42	97.7	
Mastectomy	77	46.7	17	9.8	1	2.3	
Unknown	0	0.0	1	0.6	0	0.0	
Adjuvant chemotherapy							<0.0001
Yes	111	67.3	28	16.2	28	65.1	
No	54	32.7	141	81.5	15	34.9	
Unknown	0	0.0	4	2.3	0	0.0	
Radiotherapy							0.16
Yes	139	84.2	149	86.1	41	95.3	
No	26	15.8	23	13.3	2	4.7	
Unknown	0	0.0	1	0.6	0	0.0	

Table 1. (Continued)

Variables	ALND		SLNB		SLNB + ALND ^a		P-value
	N	%	N	%	N	%	
Hormone therapy							<0.0001
Yes	135	81.8	108	62.4	34	79.1	
No	29	17.6	65	37.6	8	18.6	
Unknown	1	0.6	0	0.0	1	2.3	
Breast reconstruction							0.07
Yes	22	13.3	12	6.9	2	4.7	
No	140	84.8	158	91.3	40	93.0	
Unknown	3	1.8	3	1.7	1	2.3	
Lymphedema							<0.0001
Yes	17	10.3	0	0.0	3	7.0	
No	143	86.7	170	98.3	39	90.7	
Unknown	5	3.0	3	1.7	1	2.3	
Type of monitoring							0.91
Regular	154	93.3	160	92.5	41	95.3	
Irregular	8	4.8	10	5.8	2	4.7	
Unknown	3	1.8	3	1.7	0	0.0	
Recurrence							0.62
Yes	10	6.1	9	5.2	4	9.3	
No	150	90.9	161	93.1	39	90.7	
Unknown	5	3.0	3	1.7	0	0.0	
Tumour size (mm)							0.0001
≤10 mm	35	21.2	91	52.6	10	23.3	
10–20 mm	54	32.7	71	41.0	28	65.1	
>10 mm	72	43.6	5	2.9	5	11.6	
Unknown	4	2.4	6	3.5	0	0.0	

Abbreviations: ALND = axillary lymph node dissection; CGFL = Centre Georges François Leclerc; HRT = hormone replacement therapy; SBR = Scarff Bloom and Richardson; SLNB = sentinel lymph node biopsy. Kruskal–Wallis test was used to test the homogeneity of the different groups for quantitative variables; Pearson's χ^2 -test was used to test the homogeneity of the different groups for qualitative variables.

^aForty patients had SLNB + ALND at the same time.

the primary treatment were eligible. Patients with synchronous bilateral BC were excluded. Cases were registered from January 2005 to January 2006. From 1 January 2005 to 1 January 2006, 518 BC patients were initially included. In July 2011, when the QoL data were updated, 61 (11.8%) patients had died, 9 (1.7%) were lost to follow-up. For patients who had died, 44 (72.1%), 8 (13.1%) and 9 (14.8%) had been treated by ALND, SLNB and SLNB + ALND, respectively.

QoL questionnaires were sent to 448 patients. Of these, 381 (85%) answered and were thus retained for the analyses. For this population, the median follow-up was 6 years (1.7; 6.6), 365 patients (95.8%) had small tumours (≤ 50 mm), 6 patients had tumours larger than 50 mm (1.6%) and for 10 patients (2.6%) the information about the tumour size was missing. The mean tumour size ($P < 0.0001$) was: 21 mm (s.d. = 14), 11 mm (s.d. = 10) and 15 mm (s.d. = 6) for the ALND, SLNB and SLNB + ALND groups, respectively, while the mean age at diagnosis ($P = 0.18$) was 58 (s.d. = 12), 60 (s.d. = 11) and 59 (s.d. = 11), respectively. Among the study population, 165 patients (43%) underwent ALND, 173 patients (45%) had SLNB and 43 (11%) patients had SLNB + ALND. For 40 (93%) of these 43 patients, SLNB was followed by immediate complementary ALND. The clinical and pathological features of the three groups of patients are presented in Table 1. Sentinel lymph node biopsy was more often performed in patients

with small tumours, and none of the patients of the SLNB group had lymphedema. Patients who underwent SLNB were also more often treated with conservative surgery ($P < 0.0001$), without adjuvant chemotherapy ($P < 0.0001$) and without adjuvant hormone therapy ($P < 0.0001$).

Comparison of the features of the patients who completed and those who did not complete the questionnaire at 72 months.

The responders and the non-responders were different only for the hospital ($P = 0.007$). All other characteristics were similar: type of axillary surgery (ALND, SLNB, SLNB + ALND) ($P = 0.579$), the occurrence of lymphedema ($P = 0.41$), breast reconstruction ($P = 0.18$), the type of surveillance ($P = 0.81$), the tumour recurrence ($P = 0.08$), age ($P = 0.93$), the treatments: surgery (lumpectomy, mastectomy) ($P = 0.95$), adjuvant chemotherapy ($P = 0.27$), radiotherapy ($P = 0.31$), hormone therapy ($P = 0.65$). In addition, the QoL scores before, after, at 6 and 12 months after the surgery in the two groups were comparable.

QoL scores according to the surgical procedure. Patients' missing-score profiles were not different according to the surgical procedure. Indeed, there was no difference between the types of surgery for the proportions of patients without missing scores, with drop-out scores, with intermittent missing scores, with all scores

Table 2. Patient's missing-score profiles according to axillary dissection type

	ALND group (N = 165)		SLNB group (N = 173)		SLNB + ALND group ^a (N = 43)		Fisher's exact P-value
	N	%	N	%	N	%	
GHS							0.8
No missing scores	67	41	76	44	16	37	
Drop-out scores	3	2	2	1	1	2	
Intermittent missing scores	95	58	95	55	26	60	
No values	0	0	0	0	0	0	
BRAS							0.81
No missing scores	67	41	77	45	16	37	
Drop-out scores	2	1	1	1	0	0	
Intermittent missing scores	96	58	94	54	27	63	
No values	0	0	1	1	0	0	
BRBS							0.51
No missing scores	85	52	87	50	26	60	
Drop-out scores	2	1	0	0	0	0	
Intermittent missing scores	77	47	86	50	17	40	
No values	1	1	0	0	0	0	

Abbreviations: ALND = axillary lymph node dissection; BRAS = BR23 arm symptom; BRBS = BR23 breast symptom; GHS = global health status; SLNB = sentinel lymph node biopsy.
^aForty patients had SLNB + ALND at the same time.

missing for GHS ($P=0.8$), BRAS ($P=0.81$) and BRBS ($P=0.51$) scores (Table 2).

Before surgery, GHS ($P=0.52$) and BRAS ($P=0.99$) QoL scores were similar whatever the surgical procedure (Table 3). There were no differences for GHS and BRBS according to the surgical procedure just after surgery, 6 months later, 12 months later or 72 months later (Table 3, Figures 1a and c). However, BRAS scores were better in the SLNB group after the surgery ($P=0.004$), 6 months later ($P=0.001$), 12 months later (0.0001) and 72 months later ($P=0.0001$) (Figure 1b). Two-by-two comparison with the Bonferroni correction (statistical significance level $P<0.02$) showed significantly better BRAS scores in the SLNB group than in the ALND and SLNB + ALND groups at 6 months ($P=0.0003$ and $P=0.01$, respectively) and 12 months ($P<0.0001$ and $P=0.002$, respectively). After the surgery ($P=0.0006$) and at 72 months ($P<0.0001$), BRAS scores were significantly different only between the SLNB and ALND groups.

At 72 months, the body image (BRBI) score was different according to the surgical procedure ($P=0.0005$). Two-by-two comparison with the Bonferroni correction confirmed that the BRBI score was better in the SLNB group than in the ALND group ($P=0.0001$). Moreover, at 72 months, two-by-two comparison with the Bonferroni correction showed that the future perspectives ($P=0.0096$), the systemic therapy side effects ($P=0.0097$) and upset by hair loss ($P=0.0008$) QoL scores were better in the SLNB group than in the ALND group.

Of the studied population, 258 (68%) had the most favourable prognostic characteristics (tumour size smaller than 50 mm (T1–T2) and positive hormone receptor status). Comparisons of QoL scores in these patients according to the surgical procedure showed similar results to those obtained in the whole population. Indeed, BRAS scores were also better in the SLNB group after the surgery ($P=0.006$), 12 ($P=0.007$) and 72 months later ($P=0.0001$). Scores for body image ($P=0.002$) and upset by hair loss ($P=0.002$) were also better in SLNB group 72 months after surgery.

Longitudinal GHS QoL scores. There was no significant effect of the patients' profiles ($P=0.15$) on the GHS scores and there was no interaction between the follow-up and the type of surgery ($P=0.22$). In addition, the hospital ($P=0.92$), the hormone status ($P=0.75$), the SBR grade ($P=0.28$), the treatments: type of surgery (lumpectomy, mastectomy) ($P=0.26$), adjuvant chemotherapy ($P=0.36$), hormone therapy ($P=0.20$), the occurrence of lymphedema ($P=0.55$), which were different depending on the type of axillary surgery, had no independent effect on the GHS scores. Only the tumour size ($P=0.04$) affected GHS scores. Indeed, women with tumour smaller than 10 mm had higher GHS scores (MD = 7.2) than did women with tumours larger than 20 mm ($P=0.01$).

Whatever the surgical procedure, GHS scores decreased after surgery, started increasing 6 months later until 12 months but decreased again 72 months later. Whatever the follow-up, the surgical procedure had no impact on GHS scores ($P=0.0726$) (Table 4).

Longitudinal BRAS QoL scores. There was no significant effect of the patients' profiles ($P=0.16$) on the BRAS scores. In addition, the hospital ($P=0.92$), the hormone status ($P=0.32$), the SBR grade ($P=0.38$), the treatments: type of surgery (lumpectomy, mastectomy) ($P=0.55$), adjuvant chemotherapy ($P=0.35$), the tumour size ($P=0.81$), which were different depending on the type of axillary surgery, had no independent effect on the BRAS scores. Patients treated without hormone therapy had lower scores for arms symptoms than those treated with hormone therapy MD = -3.91 ($P=0.049$). The occurrence of lymphedema ($P<0.0001$) also affected BRAS scores. Indeed, in women without lymphedema during follow-up, arms symptoms scores were lower (MD = -13.4, $P<0.0001$).

Whatever the surgical procedure, BRAS scores increased after the surgery (MD = 12.6, s.d. = 2.2, $P<0.0001$), 6 months later (MD = 12.6, s.d. = 2.1, $P<0.0001$), 12 months later (MD = 13.2, s.d. = 2.1, $P<0.0001$) and 72 months later (MD = 15.5, s.d. = 2.1, $P<0.0001$).

Table 3. QoL scores according to the axillary surgery modalities

Variables	ALND (N= 165)			SLNB (N= 173)			SLNB + ALND ^a (N= 43)			P-value
	N	Mean (s.d.)	Median (Min–Max)	N	Mean (s.d.)	Median (Min–Max)	N	Mean (s.d.)	Median (Min–Max)	
GHS										
Before surgery	93	74 (19)	75 (17–100)	119	76 (17)	83 (33–100)	25	79 (19)	83 (33–100)	0.52
After surgery	114	68 (19)	67 (8–100)	126	72 (18)	71 (17–100)	28	65 (23)	67 (0–100)	0.27
6 Months after surgery	147	72 (18)	75 (17–100)	137	73 (19)	75 (0–100)	39	69 (19)	67 (33–100)	0.36
12 Months after surgery	144	75 (18)	83 (25–100)	136	77 (18)	83 (25–100)	36	70 (19)	67 (25–100)	0.1
72 Months after surgery	160	72 (22)	75 (0–100)	170	70 (20)	67 (0–100)	41	65 (22)	67 (17–100)	0.15
BRAS										
Before surgery	93	6 (9)	0 (0–33)	120	7 (12)	0 (0–67)	25	7 (13)	0 (0–56)	0.99
After surgery	115	19 (18)	11 (0–89)	125	12 (15)	11 (0–67)	28	15 (17)	11 (0–67)	0.004
6 Months after surgery	146	20 (20)	11 (0–100)	138	13 (16)	11 (0–100)	39	21 (20)	11 (0–78)	0.001
12 Months after surgery	145	20 (20)	11 (0–100)	136	11 (15)	0 (0–78)	36	19 (17)	17 (0–56)	0.0001
72 Months after surgery	159	23 (26)	11 (0–100)	171	12 (19)	0 (0–100)	42	17 (24)	11 (0–100)	0.0001
BRBS										
After surgery	102	19 (15)	17 (0–67)	116	21 (17)	17 (0–83)	28	17 (17)	17 (28–58)	0.33
6 Months after surgery	146	22 (20)	17 (0–92)	138	22 (16)	17 (0–89)	40	26 (23)	17 (0–100)	0.64
12 Months after surgery	144	19 (18)	17 (0–100)	136	19 (16)	17 (0–92)	37	19 (16)	17 (0–58)	0.91
72 Months after surgery	160	19 (20)	17 (0–92)	173	16 (18)	8 (0–92)	42	17 (20)	17 (0–92)	0.63
Other scores at 72 months										
Physical functioning	164	83 (17)	87 (27–100)	172	86 (16)	93 (27–100)	43	82 (19)	87 (0–100)	0.11
Role functioning	164	80 (26)	83 (0–100)	173	85 (22)	100 (0–100)	42	82 (22)	83 (0–100)	0.13
Emotional functioning	161	75(24)	75 (0–100)	170	76 (23)	83 (0–100)	42	73 (22)	75 (8–100)	0.53
Cognitive functioning	161	84 (21)	83 (0–100)	172	84 (21)	100 (0–100)	42	77 (26)	83 (0–100)	0.27
Social functioning	159	85 (26)	100 (0–100)	170	89 (21)	100 (0–100)	42	83 (24)	100 (17–100)	0.33
Fatigue	162	28 (25)	22 (0–100)	172	27 (23)	22 (0–100)	42	31 (24)	33 (0–100)	0.51
Nausea and vomiting	162	6 (15)	0 (0–100)	171	3 (10)	0 (0–67)	42	3 (16)	0 (0–100)	0.51
Pain	164	21 (26)	17 (0–100)	172	18 (24)	33 (0–100)	42	20 (22)	17 (0–67)	0.5
Dyspnoea	160	19 (26)	0 (0–100)	171	20 (27)	0 (0–100)	41	21 (29)	0 (0–100)	0.96
Insomnia	158	28 (29)	33 (0–100)	169	31 (33)	33 (0–100)	41	41 (33)	33 (0–100)	0.12
Appetite loss	160	10 (23)	0 (0–100)	171	6 (17)	0 (0–100)	40	5 (16)	0 (0–67)	0.38
Constipation	162	17 (28)	0 (0–100)	170	16 (25)	0 (0–100)	42	13 (21)	0 (0–67)	0.96
Diarrhoea	159	8 (16)	0 (0–67)	169	7 (15)	0 (0–67)	40	9 (18)	0 (0–67)	0.95
Financial difficulties	159	7 (20)	0 (0–100)	169	7 (18)	0 (0–100)	42	6 (15)	0 (0–67)	0.97
QLQ-BR23										
Body image	159	71 (32)	83 (0–100)	168	83 (25)	92 (0–100)	40	76 (27)	83 (0–100)	0.0005
Sexual functioning	145	19 (24)	0 (0–100)	152	18 (23)	0 (0–83)	38	16 (20)	0 (0–67)	0.77
Sexual enjoyment	68	46(33)	33 (0–100)	65	53 (33)	67 (0–100)	17	45 (29)	33 (0–100)	0.44
Future perspectives	156	57 (35)	67 (0–100)	166	67 (30)	67 (0–100)	37	66 (33)	67 (0–100)	0.04
Systemic therapy side effects	162	19 (20)	14 (0–95)	170	13 (14)	10 (0–81)	41	18 (15)	14 (0–81)	0.01
Upset by hair loss	63	56 (41)	67 (0–100)	45	30 (34)	33 (0–100)	21	38 (41)	33 (0–100)	0.004

Abbreviations: ALND = axillary lymph node dissection; BRAS = BR23 arm symptom; BRBS = BR23 breast symptom; GHS = global health status; QoL = quality of life; SLNB = sentinel lymph node biopsy.

^aForty patients had SLNB + ALND at the same time.

A quantitative interaction was seen between the follow-up and the type of surgery ($P = 0.04$). In fact, patients treated with SLNB had lower symptoms scores during the follow-up than patients treated with ALND. BRAS scores were lower in the SLNB group than in the ALND group after the surgery (MD = -7.6 , s.d. = 3.1 , $P = 0.01$), 6 months later (MD = -6.1 , s.d. = 3 , $P = 0.04$), 12 months later (MD = -9 , s.d. = 3 , $P = 0.003$) and 72 months later (MD = -10.8 , s.d. = 2.9 , $P = 0.0002$). However, BRAS scores were not significantly different between ALND and SLNB + ALND whatever the follow-up time (Table 5).

Longitudinal BRBS QoL scores. There was no significant effect of the patients' profiles ($P = 0.51$) on the BRBS scores and there was no interaction between the follow-up and the type of surgery ($P = 0.2$). In addition, the hospital ($P = 0.86$), the SBR grade ($P = 0.75$), the treatments: type of surgery (lumpectomy, mastectomy) ($P = 0.78$), adjuvant chemotherapy ($P = 0.51$), hormone therapy ($P = 0.54$), the occurrence of lymphedema ($P = 0.56$), the tumour size ($P = 0.45$) had no independent effect on the GHS scores. Only the hormone status ($P = 0.03$) affected BRBS scores.

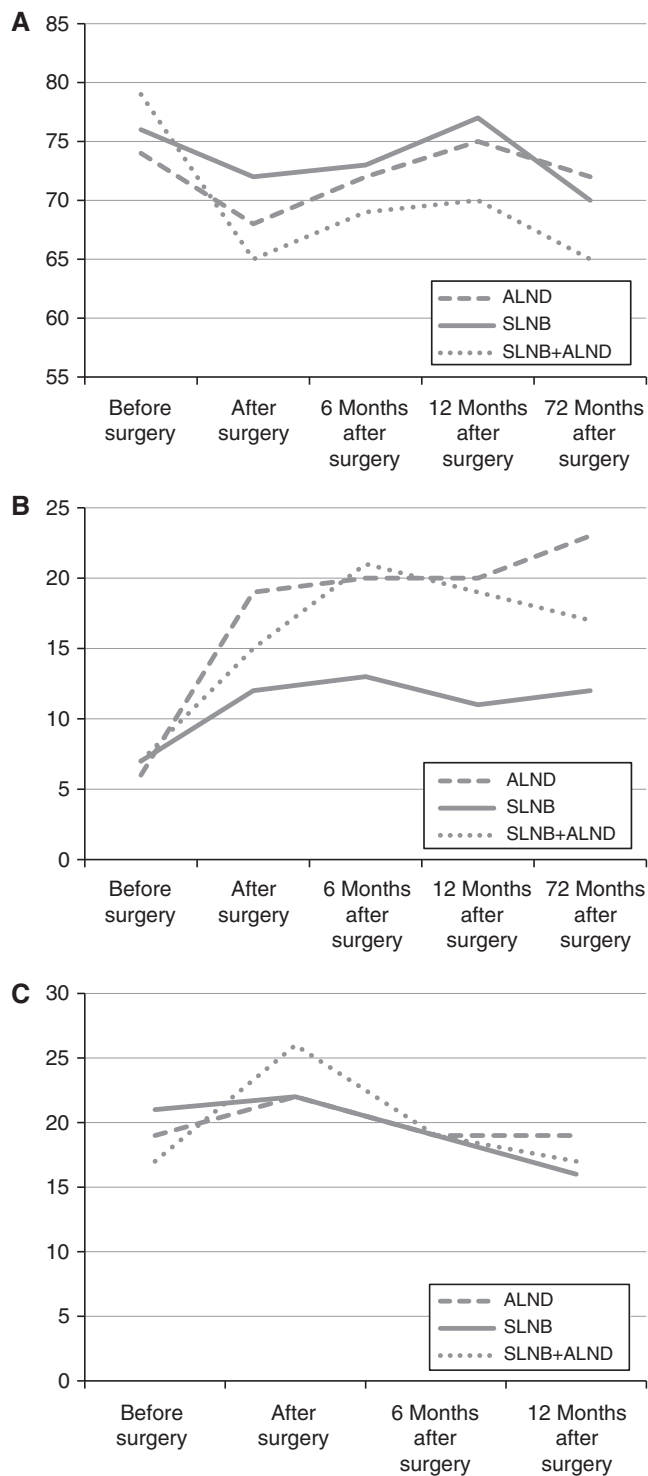


Figure 1. Mean quality of life scores according to the follow-up time and the type of surgery: (A) global health; (B) arm symptoms; (C) breast symptoms.

Whatever the surgical procedure, BRBS scores were higher 6 months than immediately after the surgery ($P=0.001$). However, BRBS scores 12 months after surgery ($P=0.52$) and 72 months after surgery ($P=0.41$) were not different to post-surgery scores (Table 4).

Whatever the follow-up, the axillary surgical procedure had no impact on BRBS QoL scores ($P=0.84$) (Table 4), and premenopausal women were more likely than postmenopausal women to have high breast symptoms scores (MD = 4.4, $P=0.03$).

Table 4. Long-term effect of surgical procedure and factors affecting global health and breast symptoms in breast cancer patient

	Global health		Breast symptoms	
	Beta (s.e.)	P	Beta (s.e.)	P
Constant	74 (6.4)	<0.0001	19.8 (6.4)	0.002
Follow-up		<0.0001 ^a		<0.0001 ^a
Before surgery	Reference			
After surgery	- 6.7 (1.5)	<0.0001	Reference	
6 Months after surgery	- 4 (1.4)	0.005	4.4 (1.4)	0.0012
12 Months after surgery	- 1.2 (1.4)	0.4	0.9 (1.4)	0.52
72 Months after surgery	- 5.3 (1.4)	0.0002	- 1.1 (1.3)	0.41
Axillary dissection type		0.0726 ^a		0.84 ^a
ALND	Reference		Reference	
SLNB	- 1.8 (2.5)	0.48	- 1.1 (2.4)	0.6323
SLNB + ALND	- 6.4 (2.8)	0.02	0.3 (2.7)	0.9075
Tumour size		0.0371 ^a		
> 20 mm	Reference			
10–20 mm	3.4 (2.4)	0.16		
≤ 0 mm	7.2 (2.8)	0.01		
Hormone status				0.03
Postmenopausal			Reference	
Premenopausal			4.4 (2)	

Abbreviations: ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy; s.e. = standard error. NB: Multivariable analyses were adjusted for hospitals, hormonal status, the Scarff Bloom and Richardson grade, treatments: the type of surgery, adjuvant chemotherapy, hormone therapy, the occurrence of lymphedema and tumour size.
^aOverall effect.

DISCUSSION

The results of previous studies suggest that SLNB is associated with less morbidity than ALND (Kissin *et al*, 1986; Kuehn *et al*, 2000; Erickson *et al*, 2001; Burak *et al*, 2002; Veronesi U *et al*, 2003; Purushotham *et al*, 2005; Mansel *et al*, 2006; Del Bianco *et al*, 2008; Dabakuyo *et al*, 2009; Gill, 2009; Wang *et al*, 2011), but the comparative effects of these two approaches on tumour recurrence, patient survival and QoL with long follow-up data are still unclear. To our knowledge, no prospective study has assessed QoL after axillary surgery for BC with a long follow-up. Published studies with long-term follow-up stopped monitoring patients 3 years after surgery (Kootstra *et al*, 2008; Kootstra *et al*, 2010; Land *et al*, 2010). The aim of this pragmatic prospective multicentre study was to assess long-term QoL over a period of 6 years in women with BC who underwent ALND, SLNB or SLNB followed by ALND.

During follow-up, 12% of patients died, with a greater proportion of deaths among those treated with ALND (72%). The higher mortality in the ALND group may be related to the larger tumour size seen in this group at baseline. It is well known that tumour size is an important prognostic factor in BC. Our study was designed to assess routine surgical procedures. The choice between ALND and SLNB was made by surgeons according to ASCO recommendations and according to their usual practice in their centre. Differences between surgical groups may result from the indication for SLNB for small tumours. Despite these differences, QoL scores at baseline were similar.

Table 5. Long-term effect of surgical procedure and factors affecting arm symptoms in breast cancer patients

	Arm symptoms	
	Beta (s.e.)	P
Constant	19.8 (6)	0.0011
Follow-up		<0.0001
Before surgery	Reference	
After surgery	12.6 (2.2)	<0.0001
6 Months after surgery	12.6 (2.1)	<0.0001
12 Months after surgery	13.2 (2.1)	<0.0001
72 Months after surgery	15.5 (2.1)	<0.0001
Axillary dissection type		0.22 ^a
ALND	Reference	
SLNB	3.1 (3.1)	0.32
SLNB + ALND	2.4 (4.2)	0.56
Interaction follow-up time and surgical procedure		0.04 ^a
After surgery and SLNB	-7.6 (3.1)	0.01
After surgery and (SLNB + ALND)	-5.1 (4.9)	0.29
After surgery and ALND	Reference	
6 Months after surgery and SLNB	-6.1 (3)	0.04
6 Months after surgery and (SLNB + ALND)	-2.2 (4.6)	0.63
6 Months after surgery and ALND	Reference	
12 Months after surgery and SLNB	-9 (3)	0.003
12 Months after surgery and (SLNB + ALND)	-0.7 (4.6)	0.88
12 Months after surgery and ALND	Reference	
72 Months after surgery and SLNB	-10.8 (2.9)	0.0002
72 Months after surgery and (SLNB + ALND)	-5.3 (4.5)	0.24
72 Months after surgery and ALND	Reference	
Lymphedema		<0.0001
Yes	Reference	
No	-13.4 (3.2)	<0.0001
Hormone therapy		
Yes	Reference	
No	-3.9 (2)	0.049

Abbreviations: ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy.
 NB: Multivariable analyses were adjusted for hospitals, hormone status, the Scarff Bloom and Richardson grade, treatments (the type of surgery, adjuvant chemotherapy, hormone therapy), the occurrence of lymphedema and tumour size.
^aOverall effect.

As regards the treatments, the frequencies of radiotherapy and breast reconstruction were not statistically different whatever the surgical treatment groups. However, patients who underwent SLNB were more often treated with conservative surgery, without adjuvant chemotherapy and without adjuvant hormone therapy. Differences between treatments may also be due to the difference in tumour size seen between treatment groups at baseline. Moreover, whatever the surgical procedure, patients with tumour smaller than 10 mm had better global health than those with tumours larger than 20 mm. Taking into account Osoba *et al*'s (1998) conclusion about clinical difference, namely that a five-point difference in QoL scores is considered the minimum clinically important difference, this statistical difference (MD = 7) should have clinical repercussions. Patients with larger tumours

were probably treated more aggressively than those with smaller tumours and this can have a negative effect on their overall health.

The results of this study also showed that, whatever the surgical procedure, premenopausal patients had higher breast symptoms scores than postmenopausal women (MD = 4) and patients treated without hormone therapy had lower arm symptoms scores than those treated with hormone therapy (MD = -3.9). However, these differences were too small to have a significant clinical impact (Osoba *et al*, 1998). One striking finding was the beneficial effects of SLNB in comparison with ALND for arm symptoms in patients with BC 5 to 6 years after diagnosis. Moreover, compared with ALND patients, SLNB patients gradually had less pain as time passed. Although the beneficial effect of SLNB in reducing arm morbidity after surgery is well known, this is the first study to report the outcomes after SLNB or ALND with such a long follow-up. These results also confirmed our previous findings (Dabakuyo *et al*, 2009) that there was no difference for arm symptoms, between patients treated with ALND and those treated with SLNB followed by complementary ALND. This result remained 5 to 6 years after diagnosis.

In this study, the occurrence of lymphedema was responsible for arm morbidity, which affected the arm dimension of QoL. Indeed, patients with lymphedema had very high scores for arm symptoms in comparison with those without lymphedema. None of the patients of the SLNB group developed lymphedema during follow-up. In comparison, 10.3% of the ALND group and 7% of the ALND + SLNB group developed lymphedema. This could explain the better QoL in the SLNB group for arm symptoms.

Another finding was that body image was better 5 to 6 years after diagnosis in patients treated with SLNB. One explanation could be that, in this study, patients who underwent SLNB were more often treated with conservative surgery due to the smaller tumour size in this group than were patients in the ALND and SLNB + ALND groups. Systemic therapy side effects and upset by hair loss QoL dimensions were also better in patients in the SLNB group, who were less often treated with adjuvant chemotherapy and with adjuvant hormone therapy, which may cause side effects and hair loss. Finally, the smaller tumour size and the less aggressive treatment led to better future perspectives in the SLNB group.

The relapse rate in the different surgical groups was similar 5 to 6 years after surgery. As pointed out by Wang *et al* (2011) in a recent meta-analysis of randomised controlled trials that compared the effectiveness and safety of SLNB with ALND, there was no significant difference between the SLNB and ALND groups for regional recurrence whether the SLNB was positive or negative. Therefore, SLNB can thus be recommended as a safe and acceptable method for the accurate identification of early-stage BC without involvement of the axillary lymph nodes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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