BRÖSTCANCER FÖRBUNDET

Forskningsrapport

Huvudsökande:
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Frågeställning:
Att utvärdera om det är säkert att avstå från kompletterande axillutrymning vid mikrometastas i sentinel node vid bröstcancer.

Tre frågor till Yvette:

Hur kan resultatet av er forskning hjälpa patienterna, rent konkret?
Att göra axillutrymning ökar risken för besvär från armen, både i form av svullnad, värk och nedsatt rörlighet.

Om man kan se att det är säkert att avstå från detta kan många patienter besparas värk och andra besvär och få en bättre livskvalitet.

Att avstå från axillutrymning har redan införts till stor del, men i vissa fall saknas ännu evidens.

Hur viktigt har stödet från Bröstcancerförbundet varit för er forskning?
Stödet har möjliggjort att vi har kunnat fortsätta arbeta med detta långsiktiga projekt och följa upp patienterna på ett bra sätt.

Vad vill du hälsa alla Bröstcancerförbundets givare?
Jag vill tacka för att ni bidrar till att öka kunskapen och att vi, steg för steg, kan förbättra och anpassa behandlingen så att överlevnaden ökar, men också så att vi kan ta bort onödig behandling och minska biverkningar.

Yvettes populärvetenskapliga sammanfattning, samt publikation finns att läsa på efterföljande sidor för dig som vill läsa mer.

Populärvetenskaplig sammanfattning

SENOMIC: en nationell kohortstudie på överlevnad och axillrecidiv hos bröstcancerpatienter med mikrometastas i sentinel node som inte genomgår kompletterande axillutrymning

Eventuell spridning (metastasering) till lymfkörtlarna är en av de faktorer som har störst betydelse för prognosen vid bröstcancer. I den kirurgiska behandlingen har det rutinmässigt, utöver ingreppet i bröstet, även ingått borttagande av flera lymfkörtlar i armhålan (axillutrymning). Detta ingrepp medför stor risk för besvär med bland annat svullnad i armen.

I början av 2000-talet infördes sentinel node-metoden i Sverige. Sentinel node, eller portvaktskörteln, är den körtel dit lymfvätska från tumörområdet dräneras och om en bröstcancer sprider sig är det denna körtel som i de allra flesta fall drabbas först. Om sentinel node är frisk är de andra lymfkörtlarna med största sannolikhet inte heller drabbade och man behöver inte göra någon axillutrymning. Flera studier talar också för att man kan avstå från axillutrymning även vid metastasering till sentinel node utan att det försämrar prognosen.

Tidigare studier har dock en del svagheter, och de patienter som är inkluderade är sannolikt selekterade till mer gynnsamma prognostiska faktorer. Dessutom är patienter som genomgår mastektomi (opererar bort hela bröstet) underrepresenterade. För 6-7 år sedan ansåg man i Sverige inte att det fanns tillräcklig evidens för att rutinmässigt avstå från kompletterande axillutrymning, och vi startade därför svenska multicenterstudier.

SENOMIC startade oktober 2013 och är en kohortstudie där vi inkluderar bröstcancerpatienter med metastaser i sentinel node som är större än 0,2 men max 2 mm stora (mikrometastaser). Patienterna genomgår ingen ytterligare kirurgi i armhålan och följs sedan med extra kliniska kontroller årligen i fem år för att kunna upptäcka eventuella återfall. Kontroller planeras också efter 10 och 15 år.

Vi har nu gjort en 3-årsuppföljning på 566 patienter från 23 svenska sjukhus. Överlevnaden utan återfall var hög (96%). Av de 217 patienter som opererats med mastektomi, hade 4 patienter fått ett återfall i lymfkörtlarna i armhålan utan återfall i bröstet, och av de 349 patienter som genomgick bröstbevarande kirurgi var det bara en patient som fick återfall i lymfkörtlarna.

Slutsatsen var att det verkar vara säkert att avstå från axillutrymning vid mikrometastas i sentinel node.

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Original Article

Omitting completion axillary lymph node dissection after detection of sentinel node micrometastases in breast cancer: first results from the prospective SENOMIC trial

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Abstract

Background: Completion axillary lymph node dissection has been abandoned widely among patients with breast cancer and sentinel lymph node micrometastases, based on evidence from prospective RCTs. Inclusion in these trials has been subject to selection bias, with patients undergoing mastectomy being under-represented. The aim of the SENOMIC (omission of axillary lymph node dissection in SENtinel NOde MICrometases) trial was to confirm the safety of omission of axillary lymph node dissection in patients with breast cancer and sentinel lymph node micrometastases, and including patients undergoing mastectomy.

Methods: The prospective SENOMIC multicentre cohort trial enrolled patients with breast cancer and sentinel lymph node micrometastases who had breast-conserving surgery or mastectomy at one of 23 Swedish hospitals between October 2013 and March 2017. No completion axillary lymph node dissection was performed. The primary endpoint was event-free survival, with a trial accrual target of 452 patients. Survival proportions were based on Kaplan–Meier survival estimates.

Results: The trial included 566 patients. Median follow-up was 38 (range 7–67) months. The 3-year event-free survival rate was 96.2 per cent, based on 26 reported breast cancer recurrences, including five isolated axillary recurrences. The unadjusted 3-year event-free survival rate was higher than anticipated, but differed between patients who had mastectomy and those who underwent breast-conserving surgery (93.8 *versus* 97.8 per cent respectively; $P = 0.011$). Patients who underwent mastectomy had significantly worse tumour characteristics. On univariable Cox proportional hazards regression analysis, patients who had mastectomy without adjuvant radiotherapy had a significantly higher risk of recurrence than those who underwent breast-conserving surgery (hazard ratio 2.91, 95 per cent c.i. 1.25 to 6.75).

Conclusion: After 3 years, event-free survival was excellent in patients with breast cancer and sentinel node micrometastases despite omission of axillary lymph node dissection. Long-term follow-up and continued enrolment of patients having mastectomy, especially those not receiving adjuvant radiotherapy, are of utmost importance.

Introduction

Sentinel lymph node biopsy (SLNB) is used for routine axillary staging in clinically node-negative breast cancer, and has replaced axillary lymph node dissection (ALND)[1]. Until publication of ACOSOG Z0011, AMAROS, and IBCSG 23–01 trial results[2–4], ALND was regarded as being not only diagnostic but also therapeutic in patients with a positive SLNB. Increasing evidence suggests, however, that completion ALND may be omitted in patients with limited nodal metastases[5–12], but key randomized trials[13–16] have been underpowered and selective, and their generalizability has been questioned. In these trials, many patients had favourable prognostic tumour characteristics and, importantly, very few patients underwent mastectomy.

The Swedish prospective multicentre cohort study SENOMIC was initiated with the aim of confirming the oncological safety of omitting completion ALND in patients with sentinel lymph node (SLN) micrometastases, and also in those with less favourable prognostic characteristics or who underwent mastectomy. A recent analysis[17] compared patients included in this trial with the background population reported to the Swedish National Breast Cancer Register, and demonstrated high external validity. This report presents the first outcome data on axillary recurrence and survival after a median follow-up of 38 months.

Methods

Between October 2013 and March 2017, patients with clinically node-negative invasive breast cancer and SLN micrometastases (pN1mi) were included in the prospective SENOMIC trial (NCT02049632) at 23 Swedish hospitals. Both patients who had

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breast-conserving surgery (BCS) and those who underwent mastectomy were eligible for inclusion. Use of double-tracer and frozen-section analysis of SNLBs was optional. There was no maximum number of SLN micrometastases.

Exclusion criteria were: preoperative diagnosis of axillary lymph node metastasis, history of a previous invasive breast cancer, metastasis outside the ipsilateral axilla, SLN metastasis larger than 2 mm in size, pregnancy, and medical contraindications to adjuvant systemic treatment. At trial initiation, tumour size over 5 cm and neoadjuvant treatment were further exclusion criteria. Following a protocol amendment, the inclusion of patients with T3 tumours and/or neoadjuvant treatment following upfront SLNB was allowed from January 2017; however, as very few patients with neoadjuvant treatment were enrolled before March 2017, these patients were excluded from the present analysis.

The trial was approved by the respective regional ethical committees and the Central Ethical Committee in Stockholm (2013/1258–31/4). Data management followed the respective applicable Swedish and European legislation. Informed consent was obtained from all individuals included in the study.

Pathology

For definitive pathology, each SLNB specimen was cut into sections with a maximum thickness of 2 mm, and stained with haematoxylin and eosin. Immunohistochemical (IHC) analysis was recommended but not mandatory, and was performed in 504 patients (89.0 per cent). The limit for oestrogen (ER) and progesterone (PR) receptor positivity was set at 10 per cent. Tumours were classified into three surrogate molecular subtypes: luminal-like (ER-positive), human epidermal growth factor receptor 2 (HER2)-enriched (HER2/neu-positive) and basal-like (ER-, PR- and HER2/neu-negative). Micrometastases were defined as metastases over 0.2 to 2 mm in size according to the AJCC staging system for breast cancer[18].

Adjuvant therapy and follow-up

Included patients did not receive completion ALND, and adjuvant treatment was given according to national and regional treatment guidelines[19]. Trastuzumab was recommended for patients with HER-2-positive breast cancer, and this was reported to the study centre. Other HER-2-targeted agents were not specified.

The Swedish national treatment guidelines did not recommend regional nodal irradiation in patients with micrometastases. If nodal irradiation was given, however, the target area included ipsilateral axillary levels 2 and 3, as well as supraclavicular/infraclavicular nodal basins. Parasternal lymph nodes were not routinely included in the regional radiotherapy target in Sweden at that time. Furthermore, the guidelines recommended whole-breast irradiation after all BCS, and irradiation to the thoracic wall after mastectomy if the tumour was larger than 5 cm, or if there was extensive multifocal disease.

Patient and tumour characteristics were validated by scrutinizing pathology reports and recorded together with data on adjuvant treatment. Trial participants were followed by annual clinical examinations and mammography.

Statistical analysis

In a previously described Swedish cohort of patients with breast cancer and SLN micrometastases, the 5-year event-free survival rate was 80 per cent[20]. The aim of the present trial was to show that event-free survival would not be lower than this, despite the omission of ALND. Based on 80 per cent power and statistical significance at the 0.05 level, the primary accrual target was set at 452 patients without regional nodal irradiation.

Patient and tumour characteristics are presented as numbers with percentages for categorical data, and median (range) for continuous data.

The primary endpoint was 5-year event-free survival. Secondary endpoints were axillary recurrence, and cancer-specific and overall survival rates. Measured from the date of SLNB, event-free survival was calculated to the date of recurrence in the ipsilateral breast or chest (local), ipsilateral axilla or non-axillary lymph nodes, distant metastasis or death from any cause. Cancer-specific survival was calculated to the date of death from breast cancer, and overall survival was calculated to the date of death from any cause. In the absence of any event, survival time was censored and calculated from the date of SLNB to the date of last follow-up. Contralateral breast cancer was not considered an event.

Event-free, overall and breast cancer-specific survival rates were calculated from Kaplan–Meier estimates, and group differences tested by means of the log rank test. Univariable Cox proportional hazards regression was used to investigate whether the type of locoregional treatment (type of breast surgery with or without adjuvant radiotherapy) was associated with the outcome. Owing to a low number of events, multivariable analyses were not performed.

In a subgroup analysis that was not prespecified, patients with BCS were compared with those undergoing mastectomy. The χ^2 test was used to analyse the distribution of categorical data and Student's *t* test for continuous data.

Statistical significance was set at $P < 0.050$ for all tests. Statistical analysis was performed using SPSS® version 24 (IBM, Armonk, New York, USA).

Results

Of 610 patients with breast cancer included in the SENOMIC trial, 44 were excluded (*Fig. 1*). In one patient with bilateral breast cancer and bilateral SLN micrometastases, the side with the most favourable tumour characteristics was excluded. Thus, 566 patients were included in the present analysis. Although 36 patients who underwent mastectomy (16.6 per cent) and 42 who had BCS (12.0 per cent) had received radiotherapy to regional lymph nodes, target accrual was reached with 488 participants who had not received nodal irradiation.

Patient, treatment, and tumour characteristics are shown in *Table 1*. The median number of excised SLNs was 2 (range 1–10). During a median follow-up of 38 (7–67) months, there were 26 recurrences among 17 patients (3.0 per cent), resulting in a 3-year event-free survival rate of 96.2 per cent (*Table 2*). The estimated 5-year event-free survival rate was 93.2 per cent, well above the limit of 80 per cent proposed in the power calculation. Five isolated axillary recurrences were diagnosed: in 4 of 217 patients after mastectomy (1.8 per cent), of whom one had locoregional irradiation and another had irradiation to the thoracic wall only, and in 1 of 349 after BCS (0.3 per cent) ($P = 0.054$).

Overall, 15 deaths were reported (2.6 per cent), four (0.7 per cent) of which were caused by breast cancer. The 3-year cancer-specific survival rate was 99.3 per cent and the overall survival rate was 97.6 per cent (*Fig. 2a*).

Mastectomy was performed in 217 patients (38.3 per cent), and more often in the youngest and oldest age groups. Patients who had mastectomy had significantly larger and higher-grade tumours than those operated with BCS (*Table 1*). Furthermore,

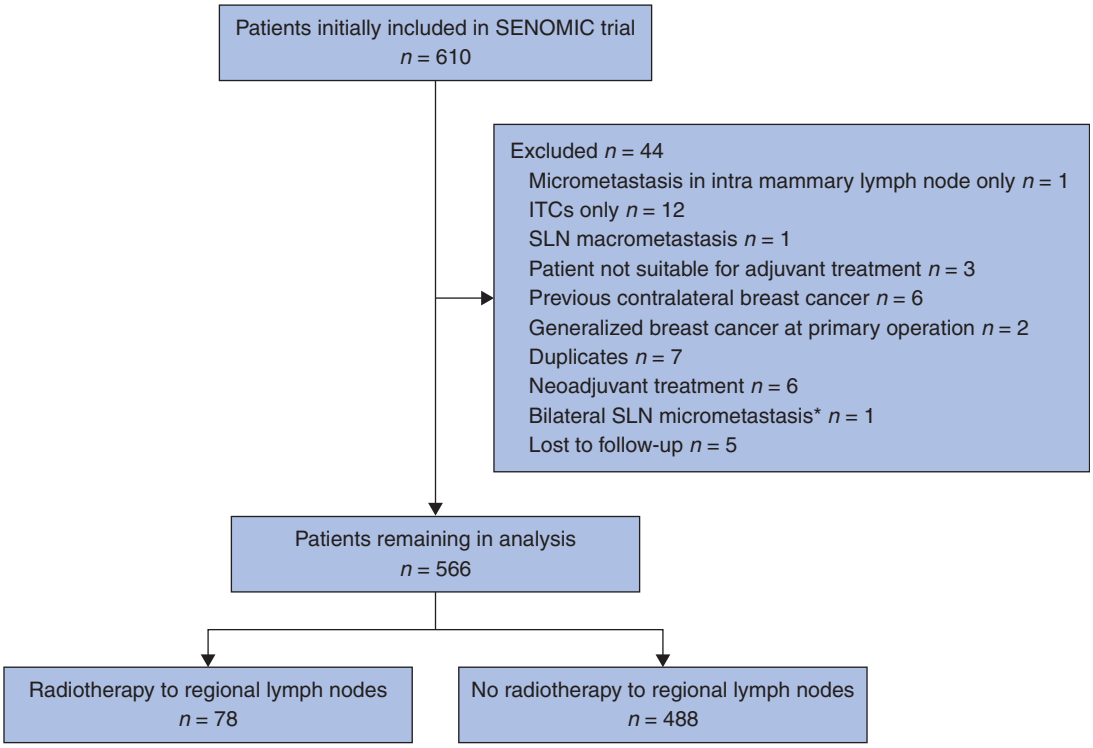

Fig. 1 Flow chart for inclusion and exclusion of patients with breast cancer and sentinel lymph node micrometastases in the SENOMIC trial

*The cancer with lowest lymph node category, smallest tumour size or lowest tumour grade was excluded. ITCs, isolated tumour cells (0.2 mm or smaller); SLN, sentinel lymph node.

their tumours were more often lobular, multifocal, and ER-negative. Even though patients who underwent mastectomy had a lower crude 3-year event-free survival rate than those who had BCS (93.8 *versus* 97.8 per cent; $P = 0.011$) (*Fig. 2b*), their estimated 5-year event-free survival rate of 88.9 per cent was still well above the anticipated proportion of 80 per cent. On univariable Cox proportional hazards regression analysis, patients who had mastectomy without adjuvant radiotherapy had a significantly higher risk of recurrence than those who had BCS (hazard ratio 2.91, 95 per cent c.i. 1.25 to 6.75). Excluding patients who had received nodal irradiation did not change the results.

Discussion

The present 3-year follow-up of the prospective SENOMIC trial has shown an excellent event-free survival rate and low isolated axillary recurrence rate when ALND is omitted in patients with SLN micrometastasis. This trial specifically included a substantial proportion of patients selected for mastectomy. Even though event-free survival for patients who underwent mastectomy was inferior to that of patients operated with BCS, most likely because of their worse prognostic tumour characteristics, it was still higher than that initially estimated. This report, however, raises some concern about the safety of omitting ALND in patients who have mastectomy without receiving adjuvant radiotherapy. The number of events was still low and did not allow subgroup analysis. The SENOMIC trial is therefore currently continuing to enrol mastectomy patients with or without adjuvant radiotherapy.

Several nomograms and scoring systems have been created with the aim of identifying patients with a negligible risk of non-SLN metastases[21–27]. The prediction accuracy varies, but is moderate at best. Previous studies[5–9,28] have also suggested that, even if metastatic lymph nodes are left behind, the therapeutic benefit of axillary dissection is limited, and especially so in patients with SLN micrometastases. Accordingly, in a propensity score-matched analysis of patients with breast cancer and SLN micrometastases in the American Surveillance, Epidemiology, and End Results database[29], there was no difference in survival between patients who underwent axillary dissection and those who had SLNB alone. Three trials randomizing patients with breast cancer and SLN metastases to either completion axillary dissection or no further axillary surgery have been published so far. In 2011 and 2017, Giuliano and colleagues published results from the ACOSOG Z0011 trial, in which only 301 of 891 patients had SLN micrometastases. After a median follow-up of 9 years, there was no statistical difference in axillary recurrence or survival[4,11,30]. Even though ACOSOG Z0011 included mostly patients with SLN macrometastases, recruited patients had smaller and lower-grade tumours than patients in the SENOMIC trial, most likely because mastectomy was an exclusion criterion. The 5-year disease-free survival rate was 83.9 per cent for the group in which axillary dissection was omitted, and thus significantly lower than that estimated in the SENOMIC trial.

In 2012, Solá and co-workers[12] reported the results from the small AATRM trial, which randomized 233 patients with SLN micrometastases to axillary dissection or observation. All patients had BCS and whole-breast irradiation. After 5 years, the disease-free survival rate was 98.2 per cent for all included patients, and no statistically significant difference between the groups was reported. In 2013, Galimberti *et al.*[3] published 5-year follow-up from the randomized IBSCG 23-01 trial, showing a 5-year disease-free survival rate of 87.8 (95 per cent c.i. 84.4 to 91.2) per cent in the group without axillary dissection, and no statistical difference in survival between the groups. The latter was later confirmed with 10-year data from the same population[10]. This trial, however, also enrolled patients with smaller and

Table 1 Patient, treatment, and tumour characteristics in SENOMIC trial participants

	Mastectomy ($n = 217$)	Breast-conserving surgery ($n = 349$)	P[§]
Age (years)*	63 (23–90)	61 (37–89)	0.168[¶]
<41	19 (8.7)	11 (3.1)	<0.001
41–50	38 (17.5)	68 (19.5)	
51–65	62 (28.6)	149 (42.7)	
>65	98 (45.2)	121 (34.7)	
Tumour size (mm)*	21 (1–95)	16 (1–60)	<0.001[¶]
<20	96 (44.2)	251 (71.9)	<0.001
20–29	66 (30.4)	82 (23.5)	
30–50	55 (25.4)	16 (4.6)	
No. of SLN micrometastases			0.563[#]
1	204 (94.0)	332 (95.1)	
2	12 (5.5)	17 (4.9)	
3	1 (0.5)	0 (0)	
Multifocality	70 (32.3)	54 (15.5)	<0.001
Histological tumour type			0.001
Ductal	160 (73.7)	301 (86.3)	
Lobular	40 (18.5)	27 (7.7)	
Mixed	5 (2.3)	6 (1.7)	
Other	12 (5.5)	15 (4.3)	
Tumour grade (NHG)			0.002
1	21 (9.7)	73 (20.9)	
2	129 (59.4)	191 (54.7)	
3	65 (30.0)	83 (23.8)	
Missing	2 (0.9)	2 (0.6)	
Oestrogen receptor status			0.037
Positive	191 (88.0)	325 (93.1)	
Negative	26 (12.0)	24 (6.9)	
Missing	0 (0)	0 (0)	
Progesterone receptor status			0.570
Positive	169 (77.9)	280 (80.2)	
Negative	47 (21.7)	69 (19.8)	
Missing	1 (0.4)	0 (0)	
HER2/neu status			0.076
Amplified[†]	30 (13.8)	32 (9.2)	
Not amplified	182 (83.9)	313 (89.7)	
Missing	5 (2.3)	4 (1.1)	
Tumour molecular subtype			0.135
Luminal-like	169 (77.9)	297 (85.1)	
HER2-enriched	30 (13.8)	32 (9.2)	
Basal-like	13 (6.0)	16 (4.6)	
Missing	5 (2.3)	4(1.1)	
Lymphovascular invasion			0.310
Yes	60 (27.7)	83 (23.8)	
No	155 (71.4)	262 (75.1)	
Missing	2 (0.9)	4 (1.1)	
Radiotherapy[‡]	67 (30.9)	344 (98.6)	<0.001
Endocrine therapy	191 (88.0)	325 (93.1)	0.037
Chemotherapy	121 (55.8)	178 (51.0)	0.270
Trastuzumab	27 (12.4)	30 (8.6)	0.139

Values in parentheses are percentages unless indicated otherwise;*values are median (range). [†]Human epidermal growth factor receptor 2 (HER2) 3+ and/or *in situ* hybridization-positive. [‡]Radiation to remaining breast/chest wall and/or regional lymph nodes. SLN, sentinel lymph node; NHG, Nottingham histological grade. [§]χ^2 test, except [¶]Student's *t* test; missing values were excluded from the statistical analysis. [#]Analysis of one *versus* more than one micrometastasis.

Table 2 Recurrences and deaths among SENOMIC trial participants

	Mastectomy ($n = 217$)	Breast-conserving surgery ($n = 349$)
Death	10	5
From breast cancer	2	2
Local recurrence	3	4
Ipsilateral axillary recurrence	6*	1
Extra-axillary lymph recurrence	3[†]	0
Distant recurrence	5	4

*Two patients had synchronous local recurrence.[†]One patient had synchronous distant metastasis.

lower-grade tumours than SENOMIC, and only 9 per cent of patients had a mastectomy. Considering such signs of potential selection bias, and the fact that both ACOSOG Z0011 and IBCSG 23-01 were statistically underpowered owing to low event rates, interpretation of the results requires some caution. Still, many countries omit completion axillary dissection not only in patients who have BCS but also in those who undergo mastectomy[31], risking undertreatment of these patients. The early results of the

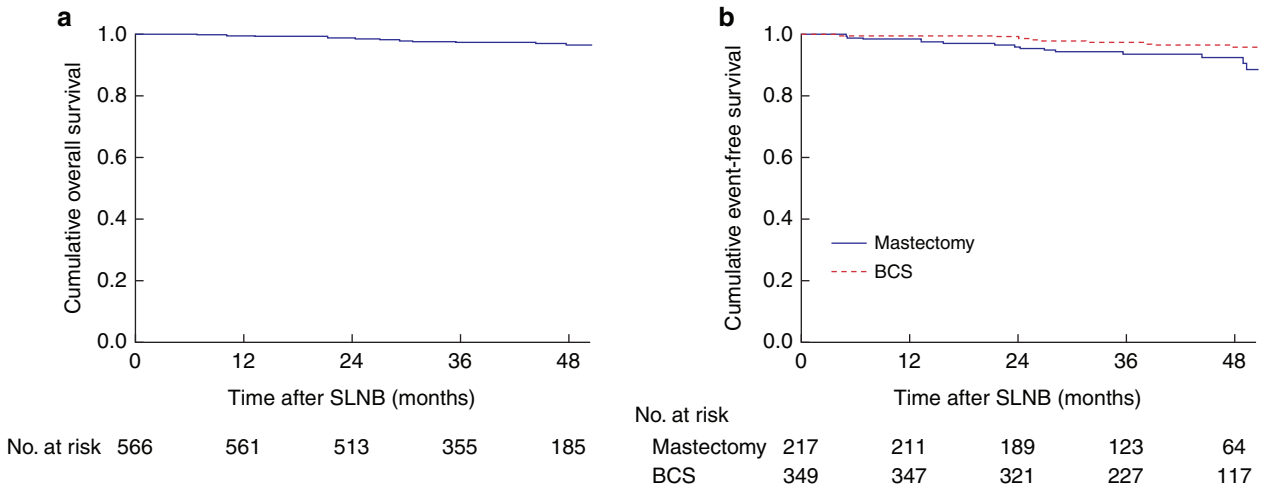

Fig. 2 Overall survival for all patients in SENOMIC, and unadjusted event-free survival according to type of surgery

a Overall survival in all patients, and **b** unadjusted event-free survival among patients who had mastectomy or breast-conserving surgery (BCS) after sentinel lymph node biopsy (SLNB). $P = 0.011$ (log rank test).

SENOMIC trial indicate that the omission of axillary dissection may also be safe in patients undergoing mastectomy, but the present results raise some concern about the subgroup of patients having mastectomy but not receiving any adjuvant radiotherapy.

The strength of this report lies in the prospective enrolment of a well defined patient cohort, with target accrual reached within the prespecified time frame. In addition, the SENOMIC trial was validated against the Swedish National Breast Cancer Register, and the concordance was high[17]. Some differences between breast cancer cohorts are of course inevitable. A comparison between patients in the French multicentre trial SERC, the Multicentre French Cohort, and the SENOMIC trial demonstrated a higher rate of grade 1 tumours in the French cohorts than in the SENOMIC population[32]. Furthermore, IHC analysis of SLNs was performed for the vast majority of patients in SENOMIC, reflecting widespread use of this procedure in Sweden. IHC analysis allows detection of smaller metastases and may upgrade some patients who otherwise would have been classified as SLN-negative[33]. This could imply that patients in SENOMIC may have a better prognosis than populations in which IHC analysis is performed more rarely. Bearing this in mind, the external validity of the SENOMIC trial is high, and the present results may therefore be generalized to patients in clinical practice. This is crucial to ensure the representativeness of trial patients for the clinical population in which the research results are subsequently implemented.

Inclusion of only patients with SLN micrometastases may be seen as a limitation of the SENOMIC trial; the distinction between micrometastases and macrometastases, however, is clinically relevant. Therefore, SENOMIC was initiated as a prospective single-arm cohort study dedicated to SLN micrometastases; at the same time, the randomized SENOMAC trial was started, which includes only SLN macrometastases[13].

Of note, the proportion of ER-negative breast cancer was low in the SENOMIC population (9.4 per cent), but several other publications on micrometastatic breast cancer have reported similar rates. In both the IBSCG 23-01 trial[3] and the Swedish Multicentre Sentinel Node Cohort[20], the proportion of ER-negative cancer was 9.8 per cent. Furthermore, among patients with micrometastases reported to the Swedish National Breast Cancer Register between January 2014 and March 2017, 9.0 per cent had ER-negative breast cancer[17].

The major limitation of the present study is that the follow-up time is still limited and, because there were fewer events than anticipated, no adjusted analyses could be performed. Even though the early results are promising, breast cancer shows indolent behaviour and recurrence may develop after a very long time[34,35], which is probably especially relevant in micrometastatic disease[36]. Hence, longer follow-up is of utmost importance, and an updated follow-up of the SENOMIC trial is scheduled after 5 years. Further evaluation is particularly important for patients undergoing mastectomy, and so the SENOMIC trial is continuing to enrol this patient subgroup.

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