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Original Article

Clinical and cost outcomes of a polyethylene glycol (PEG)-coated patch *versus* drainage after axillary lymph node dissection in breast cancer: results from a multicentre randomized clinical trial

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Abstract

Background: The aim of this study was to compare the clinical outcomes between breast cancer patients who underwent axillary lymph node dissection with postoperative management using a polyethylene glycol-coated patch *versus* axillary drainage. The direct costs associated with both postoperative management strategies were also evaluated.

Methods: This was a multicentre RCT in women with breast cancer who underwent axillary lymph node dissection (ClinicalTrials.gov identifier: NCT04487561). Patients were randomly assigned (1 : 1) to receive either drainage or a polyethylene glycol-coated patch as postoperative management. The primary endpoints were the need for an emergency department visit for any event related to the surgery and the rate of seroma development.

Results: A total of 227 patients were included , 115 in the patch group (50.7 per cent) and 112 (29.4 per cent) in the drainage group. The incidence of emergency department visits was significantly greater for patients with drainage *versus* a polyethylene glycol-coated patch (incidence rate difference 26.1 per cent, 95 per cent c.i. 14.5 to 37.7 per cent; $P < 0.001$). Conversely, the seroma rate was significantly higher in the polyethylene glycol-coated patch group (incidence rate difference 22.8 per cent, 95 per cent c.i. 6.7 to 38.9 per cent; $P < 0.0055$). Compared with drainage, using a polyethylene glycol-coated patch resulted in cost savings of €100.41 per patient. An incremental cost-effectiveness ratio analysis found that drainage was associated with an incremental cost-effectiveness ratio of €7594.4 for no need for hospital admission and €491.7 for no need for an emergency department visit.

Conclusion: Compared with patients who received drainage after axillary lymph node dissection, the use of a polyethylene glycol-coated patch resulted in a higher rate of seroma, but a lower number of postoperative outpatient or emergency department visits and thus a reduction in overall costs.

Introduction

Breast cancer in women has surpassed lung cancer as the most common solid tumour in the world, with approximately 2.26 million new cases in 2020[1,2]. In Western Europe, its incidence and age-standardized mortality rates were 90.2 and 15.6 per 100 000 respectively[2]. Breast cancer represents a major public health challenge to national health systems. For instance, the mean total costs over a 5-year interval for breast cancer care in Spain were €160 642 per patient[3].

The introduction of novel targeted therapies has changed the treatment landscape, but surgery remains the most common treatment for breast cancer[3–5]. A greater number of breast cancer patients are, however, diagnosed with early-stage disease[2], and thus surgical treatment has become progressively less invasive[4,5].

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Although axillary lymph node dissection (ALND) remains important for staging and locoregional control[6], this procedure has been progressively replaced by the less invasive sentinel lymph node biopsy (SLNB). SNLB has led to a lower incidence of postoperative complications, with less effects on quality of life and delays of adjuvant treatment initiation[7,8]. SLNB is the main tool for assessing nodal involvement in breast cancer patients, particularly for patients where radiological examination fails and/or with a clinically negative nodal status[9].

Therefore, the current trend is to favour, whenever possible, a conservative surgical approach to the axilla[4,5,7,8]. The optimal management of the axilla remains a subject of debate[10], as there are clinical situations when ALND is still indicated[8]. Importantly, ALND provides accurate prognostic information that is crucial for achieving better clinical outcomes and greater survival rates, particularly in those patients with axillary disease[11].

ALND is, however, associated with increased morbidity and adverse events, such as lymphoedema, haematoma, decreased range of shoulder movement, and seroma[11,12]. Seroma is the most prevalent complication of breast cancer surgery, affecting between 15 and 81 per cent of patients after lymph node dissection[11,13–15].

Drain placement is common after ALND, and, while not a complication, a prolonged need for a drain can increase the incidence of other postoperative complications, such as infections, delayed wound healing, and a delay in initiation of adjuvant treatment[16,17].

Therefore, it is important to identify effective alternatives to drains that can reduce the incidence of complications and improve recovery before adjuvant treatment.

One alternative to drain placement is a polyethylene glycol (PEG)-coated patch (Hemopatch™, Sealing Hemostat, Baxter AG, Vienna, Austria) that has been associated with promising outcomes in a variety of surgical procedures[18,19].

Because national health systems face unlimited demand, with limited resources, the identification of interventions that reduce the costs associated with the postoperative management of patients is important. Several studies have analysed the overall cost of breast cancer treatment[3], the cost of imaging, such as MRI[20], and the economics of ambulatory breast cancer surgery[21].

The Spanish REDHEMOPACH network was established as a platform for the study of breast cancer treatment. Its main objectives were to collect clinical characteristics, intraoperative variables, and postoperative management strategies of patients undergoing ALND. An interim analysis of the REDHEMOPACH database revealed that the use of a PEG-coated patch was associated with improved postoperative management, as measured by a lower number of postoperative outpatient and emergency department (ED) visits. Its use did not reduce the incidence rate of seroma[22].

The aim of this study was to compare the clinical outcomes between breast cancer patients who received axillary drainage with those who received a PEG-coated patch after ALND. Direct costs associated with each postoperative management strategy were also evaluated.

Methods

Study design and participants

This was a multicentre, parallel RCT conducted in women with breast cancer who underwent ALND between 31 July 2019 and 15 July 2022.

The study protocol was approved by the Ethics Committee of the University Clinical Hospital of Valencia (register number: REDHEMOPACH V.6; 29 July 2020) and was registered in ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT04487561). The study was conducted in accordance with the Declaration of Helsinki and all the study participants provided written informed consent before starting the study. A detailed study protocol has been published elsewhere[16].

Inclusion/exclusion criteria

Women who were aged greater than or equal to 18 years and diagnosed with breast cancer, who were scheduled for surgical treatment by breast conservative surgery and ALND, and who were willing to comply with the investigators and protocol indications were included in the study.

Patients that were SLNB-negative, subsidiary mastectomy patients, and those who did not sign informed consent for axillary lymphadenectomy were excluded.

Study groups

Detailed information about the study protocol and procedures has been published elsewhere[22]. Patients were randomly assigned (1 : 1) to one of two study groups. In the patch group, before surgical closure of the axillary incision, a PEG-coated patch was placed. In the drainage group, a 12G (Needle gauge [G]) redon suction-drain tube was placed in the surgical wound before closure of the axillary incision.

Direct costs

A cost analysis was carried out from the perspective of the regional health systems involved in the study. Healthcare system costs were obtained for each regional health system. The median value of the costs was used in the analysis, as there were differences in costs between regional health system sites.

The cost-effectiveness ratio (CER) was calculated as a cost per outcome formula. CER was calculated once by considering the numerical difference in outcomes.

The incremental cost-effectiveness ratio (ICER) was calculated as the numerical difference in outcomes between early-switch and late-switch groups, using the following formula: ICER = (costs in patch group – costs in drainage group)/(effectiveness in patch group – effectiveness in drainage group).

Outcomes

The primary endpoints in this study were the need for an ED visit for the postoperative management of any event related to the surgery and the incidence rate of seroma.

Secondary endpoints included total seroma volume and the incidence of adverse events.

A combined secondary objective was also selected that considered both the incidence of seroma and the need for an ED visit. According to these criteria, the following assumptions were made: complete success was defined as patients in which the presence of seroma was not evident and there was no need for an ED visit; partial success was defined as patients that had evidence of seroma, but did not require an ED visit; and failure was defined as patients with seroma where an ED visit was required. Patients who visited the ED for any reason related to surgery, even if no seroma was present, were also considered failures.

Definitions

Seroma was defined as a palpable, uninfected, clear fluid collection (greater than or equal to 20 ml) under the wound, in the dead space of the axilla. BMI was stratified into normal weight (defined as BMI less than 25 kg/m^2), overweight (defined as BMI greater than or equal to 25 kg/m^2 to less than 30 kg/m^2), and obese (defined as BMI greater than or equal to 30 kg/m^2)[22].

Statistical analysis

A standard statistical analysis was performed using MedCalc® Statistical Software version 20.116 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

For sample size calculation, a difference in the incidence of seroma of 18 per cent was considered significant (using a two-tailed test). With an α of 0.05 and a power of 80 per cent, 111 patients per group were required. Based on previous experience (E Buch-Villa; E Muñoz- Sorsona; M Adrianzen; V López-Flor; J Ortega) the incidence rate of seroma in the patch group would be 29 per cent and according to a Cochrane Database systematic review[23] the incidence rate of seroma in conservative surgery with drainage would be 47 per cent.

Descriptive statistics (number (percentage), mean(s.d.), mean (95 per cent c.i.), mean(s.e.), median (interquartile range (i.q.r.)), or median (95 per cent c.i.)) were used, as appropriate.

Data were tested for normal distribution using a Shapiro–Wilk test.

The two-tailed unpaired Student's *t* test or the Mann–Whitney *U* test was used, as appropriate, to compare means between treatment groups for quantitative variables.

A logistic regression model was used to estimate and test factors for their association with seroma incidence and the need for an ED visit. A backward strategy was adopted, with a statistically significant cut-off for variable screening of ≤0.05. Factors associated with progression in the univariable analysis at $P \leq 0.1$ were included in the multivariable analysis.

Regarding the role of obesity, two different analyses were carried out. In the first analysis, groups were divided into normal weight (BMI less than 25 kg/m^2), overweight (BMI greater than or equal to 25 kg/m^2 to less than 30 kg/m^2), and obese (BMI greater than or equal to 30 kg/m^2). In the second analysis, groups were stratified into non-obese (BMI less than 30 kg/m^2) and obese (BMI greater than or equal to 30 kg/m^2).

Categorical variables were compared using the chi-squared test and Fisher's exact test, as required. $P < 0.05$ was considered significant.

Results

A total of 227 patients were included in the study, 115 (50.7 per cent) patients in the patch group and 112 (49.4 per cent) patients in the drain group.

Preoperative demographic and clinical characteristics

Table 1 shows the main baseline demographic and clinical characteristics of the study population. Except for BMI, in which significant differences between groups were observed, no other significant differences were detected in any of the variables analysed.

Surgical procedure

No differences were observed between groups with respect to characteristics of the surgical procedure (*Table 2*). The median number of patches used during the procedure was 1.0 (i.q.r. 1.0–2.0) patches, with 84 patients undergoing surgery with only a single patch.

Clinical outcomes

Table 3 summarizes the main clinical outcomes of the study. The incidence rate of ED visits was significantly greater in the drainage group (incidence rate 33.0 per cent, 95 per cent c.i. 26.1 to 51.0 per cent) than in the patch group (incidence rate 7.0 per cent, 95 per cent c.i. 3.5 to 15.8 per cent), with an incidence rate difference of 26.1 per cent (95 per cent c.i. 14.5 to 37.7 per cent; $P < 0.0001$). In the drainage group, the most frequent reason for attending the ED was problems related to the redon drain itself, followed by seroma. In the patch group, the most frequent reason was seroma.

In contrast, the rate of seroma was significantly higher in the patch group (incidence rate 49.6 per cent, 95 per cent c.i. 37.5 to 64.2 per cent) than in the drainage group (incidence rate 26.8 per cent, 95 per cent c.i. 18.1 to 38.2 per cent), with an incidence rate difference of 22.8 per cent (95 per cent c.i. 6.7 to 38.9 per cent; $P < 0.006$).

The time to first seroma puncture from surgery was significantly longer in the patch group than the drainage group (Hodges–Lehmann median difference 3.0 days, 95 per cent c.i. 0 to 5.0 days; $P = 0.025$).

In the drainage group, the mean(s.d.) number of days with drainage was 9.4(5.6) days. Patients in the drainage group required a significantly greater number of outpatient visits for seroma control than those in the patch group (Hodges–Lehmann median difference 2.0 visits, 95 per cent c.i. 1.0 to 2.0 visits; $P < 0.001$).

The overall predefined success rate was significantly greater in the patch group than in the drainage group, although this difference was mainly due to the rate of partial success.

Factors associated with the need for an emergency department visit and seroma incidence

Factors significantly associated with the need for an ED visit in the univariable analysis were the presence of diabetes mellitus, previous axillary surgery, and study group assignment (*Table 4*). In the univariable analysis, factors significantly associated with seroma incidence included study group assignment, age greater than 56 years, and the presence of preoperative co-morbidities (*Table 4*).

In the multivariable analysis, after adjusting for relevant factors, previous axillary surgery increased the probability of an ED visit by 4.8-fold, whereas assignment to the patch group significantly reduced the probability of an ED visit by 87 per cent. The patch group assignment increased the OR for seroma by 3.3-fold (*Table 4*).

Costs and cost-effectiveness

Compared with drainage, the use of a PEG-coated patch resulted in cost savings of €100.41 per patient (*Table 5*).

The CER of no need for an ED visit was €292.4 in the patch group and €605.6 in the drainage group. Similarly, the CER of no need for hospital admission and success of treatment were lower in the patch group (€284.8 and €308.9 respectively) than in the drainage group (€429.2 and €629.1 respectively) (*Table 5*).

Table 1 Baseline demographic and clinical characteristics of the study population*

	Overall ($n = 227$)	Patch ($n = 115$)	Drainage ($n = 112$)
Age (years)			
Mean(s.d.)	56.8 (12.5)	57.1 (12.7)	56.6 (12.3)
Median (i.q.r.)	56.0 (47.0–66.5)	58.0 (47.0–67.0)	55.5 (46.5–66.0)
BMI (kg/m^2)†			
Mean(s.d.)	27.3 (6.2)	26.7 (6.5)	28.0 (5.8)
Median (i.q.r.)	26.1 (23.1–29.7)	25.5 (22.9–28.7)	27.0 (23.4–30.3)
BMI (kg/m^2)†			
Normal weight	81	50	31
Overweight	88	43	45
Obese	52	22	30
Co-morbidities			
Yes	75	36	39
No	152	79	73
Diabetes mellitus			
Yes	25	8	17
No	201	107	94
Previous axillary surgery			
Yes	17	9	8
No	210	106	104
Breast cancer subtype			
Luminal A	72	37	35
Luminal B	93	46	47
Triple-negative	39	24	15
HER2 positive	18	6	12
Positive sentinel node			
Yes	153	83	70
No	74	32	42
Neoadjuvant therapy			
Yes	134	69	65
No	92	45	47
ASA grade			
I	46	21	25
II	139	70	69
III	41	24	17

Values are *n* (%) unless otherwise indicated. *Included all patients who underwent surgery and had at least one postoperative visit. †Missing information for six patients in the drainage group. i.q.r., interquartile range; HER2, human epidermal growth factor receptor 2.

Table 2 Clinical characteristics of the surgical procedure

	Overall ($n = 227$)	Patch ($n = 115$)	Drainage ($n = 112$)	*P*
Axillary incision				0.539*
TPM	102	53	49	
PPM	114	54	60	
U-shaped	5	3	2	
Others	6	5	1	
Single breast and axillary incision				1.000†
Yes	29	15	14	
No	197	100	97	
Ligasure®				0.889†
Yes	76	38	38	
No	151	77	74	
Harmonic®				0.790†
Yes	118	61	57	
No	108	53	55	
Number of patches				NA
1	84	84		
2	29	29		
3	2	2		
Removed lymph nodes				0.826‡
Mean(s.d.)	16.5 (6.1)	16.4 (5.9)	16.5 (6.3)	
Median (i.q.r.)	15.0 (13.0–20.0)	15.0 (13.0–19.8)	16.0 (12.0–20.8)	
Positive lymph nodes				0.260‡
Mean(s.d.)	3.4 (4.3)	3.8 (4.6)	3.1 (4.0)	
Median (i.q.r.)	2.0 (1.0–5.0)	2.0 (1.0–5.0)	2.0 (0.3–4.0)	
Intraoperative complications				0.618†
Yes	3	1	2	
No	224	114	110	

Values are *n* unless otherwise indicated. *Chi-squared for trend test. †Fisher's exact test. ‡Two-tailed unpaired Student's *t* test. Ligasure® - Medtronic, Minneapolis, MN, USA; Harmonic® - Ethicon Endo Surgery, Albuquerque, NM, USA. TPM, transverse to pectoralis major; PPM, parallel to pectoralis major; NA, not applicable; i.q.r., interquartile range.

Table 3 Overview of postoperative outcomes in the intent-to-treat study population

	Overall (*n* = 227)	Patch (*n* = 115)	Drainage (*n* = 112)	*P*
Seroma				0.006*
Yes	87	57	30	
POD of seroma onset				0.025†
Mean(s.d.)	11.6 (5.8)	11.1 (6.4)	13.0 (3.6)	
Median (i.q.r.)	11.0 (7.3–15.0)	10.0 (6.0–14.5)	14.0 (10.0–15.0)	
Seroma puncture				<0.001‡
Yes	68	50	18	
No	150	61	89	
Number of punctures				0.853†
Mean(s.d.)	3.1 (3.1)	2.9 (2.2)	3.5 (4.8)	
Median (i.q.r.)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	
Seroma volume (ml)				0.8190†
Mean(s.d.)	446.9 (511.1)	401.1 (359.0)	579.4 (805.5)	
Median (i.q.r.)	259.0 (140.0–660.0)	266.5 (145.0–590.0)	240.0 (105.0–750.0)	
ED visit§				<0.001*
Yes	45	8	37	
ED visit reason				<0.001¶
Seroma	12	7	5	
Redon	31	0	31	
Pain	1	1	0	
Haemorrhage	1	0	1	
Postoperative combined criteria				
Success	181	106	75	0.034*
Partial success#	67	49	18	<0.001*
Complete success#	114	57	57	0.888*
Seroma outpatient visits (*n*)**				<0.001†
Mean(s.d.)	3.3 (2.6)	2.5 (2.1)	4.1 (2.7)	
Median (i.q.r.)	3.0 (1.0–4.0)	2.0 (1.0–3.0)	4.0 (3.0–5.0)	
Axillary wound dehiscence				1.000‡
Yes	5	3	2	
No	222	112	110	
Axillary wound infection				1.000‡
Yes	6	3	3	
No	221	112	109	
Drainage complication††				NA
Haemorrhage	1		1	
Drain pipe extrusion	26		26	
Infection	7		7	
Pain	4		4	
Decubitus ulcer	4		4	
Redon bottles (*n*)				NA
Mean(s.d.)	2.8 (1.6)		2.8 (1.6)	
Median (i.q.r.)	3.0 (1.0–4.0)		3.0 (1.0–4.0)	

Values are *n* (%) unless otherwise indicated. *Chi-squared test. †Mann–Whitney *U* test. ‡Fisher's exact test. §Any emergency department visit event related to the surgery. ¶Chi-squared test for trend. #Among success subjects. **Number of outpatient visits necessary to control the seroma. ††Patients may have had more than one complication. The percentages were calculated according to the patients who had complications. POD, postoperative day; i.q.r., interquartile range; ED, emergency department; NA, not applicable.

Drainage was associated with an ICER of €7594.4 for no need for hospital admission, €491.7 for no need for an ED visit, and €542.5 for achieving treatment success (*Table 5*).

Discussion

Although breast cancer surgery is associated with low rates of surgical morbidity, it is not free of adverse events[24], and a common consequence of ALND is seroma. The incidence of seroma has been shown to be 30 per cent after an ALND, with even higher rates after adjuvant irradiation[13–15,25,26]. Different strategies focused on preventing and/or reducing the incidence of seroma have been previously assessed[16,17,23,27–30]. There is an increasing focus on post-surgical morbidity, as more patients survive breast cancer with the available therapies. Thus, the postoperative management of patients with breast cancer is a very important aspect of surgery[24].

The current study found that 45 (20.3 per cent) patients required an ED visit, with a significantly greater proportion seen in the drainage group compared with the patch group (incidence rate difference 26.1 per cent, 95 per cent c.i. 14.5 to 37.7 per cent; $P < 0.0001$). Additionally, the overall incidence of seroma was 38.3 per cent (87/227), with a significantly greater incidence in the patch group *versus* the drainage group (incidence rate difference 22.8 per cent, 95 per cent c.i. 6.7 to 38.9 per cent; $P < 0.0055$).

Except for preliminary results recently published by the authors in 2022[22], to the authors' knowledge, this is the first multicentre RCT evaluating the effect of a PEG-coated patch on reducing the incidence of seroma and other complications related to the postoperative management of breast cancer patients undergoing ALND.

There are no conclusive results that support the use of sealants to prevent the appearance of seroma after ALND. The different types of patients included in relevant studies, in addition to the differences in their surgical protocols, make it extremely difficult to make conclusions[18,31,32].

Although the incidence of seroma was greater in the patch group, the time between surgery and the first seroma puncture

Table 4 Univariable and multivariable analysis to evaluate risk factors for seroma and emergency department visits

Variable	Seroma				Emergency department visit			
	Univariable		Multivariable*		Univariable		Multivariable*	
	OR (95% c.i.)	P	OR (95% c.i.)	P	OR (95% c.i.)	P	OR (95% c.i.)	P
Age†								
>56 years	1.75 (1.02 to 3.00)	0.042	1.33 (0.73 to 2.42)	0.361	1.04 (0.54 to 1.99)	0.917		
BMI								
Normal weight	1				1			
Overweight	0.98 (0.53 to 1.83)	0.955			1.40 (0.65 to 3.04)	0.393		
Obese	1.67 (0.83 to 3.37)	0.149			1.83 (0.78 to 4.30)	0.163		
BMI								
Non-obese	1		1					
Obese	1.78 (0.96 to 3.32)	0.068	1.63 (0.81 to 3.279	0.171	1.71 (0.83 to 3.54)	0.149		
Co-morbidities								
No	1		1					
Yes	1.83 (1.04 to 3.22)	0.036	1.53 (0.76 to 3.08)	0.231	1.62 (0.83 to 3.17)	0.159		
DM								
No	1		1		1		1	
Yes	2.25 (0.97 to 5.21)	0.059	1.78 (0.63 to 5.00)	0.277	2.52 (1.03 to 6.15)	0.043	1.51 (0.52 to 4.34)	0.367
Previous axillary surgery								
No	1				1		1	
Yes	1.47 (0.55 to 3.98)	0.444			4.04 (1.46 to 11.16)	0.007	4.76 (1.41 to 16.10)	0.012
Breast cancer subtype								
Luminal A	1				1		1	
Luminal B	1.70 (0.90 to 3.21)	0.105			0.52 (0.25 to 1.10)	0.086	0.51 (0.22 to 1.18)	0.115
Triple-negative	2.01 (0.91 to 4.46)	0.085	1	0.108	0.58 (0.22 to 1.52)	0.269		
HER2 positive	1.49 (0.52 to 4.34)	0.460	2.02 (0.86 to 4.76)		0.53 (0.14 to 2.03)	0.354		
Positive lymph node								
No	1				1			
Yes	1.60 (0.89 to 2.87)	0.120			0.98 (0.49 to 1.95)	0.943		
Neoadjuvant therapy								
No	1				1			
Yes	1.05 (0.61 to 1.81)	0.858			0.68 (0.35 to 1.32)	0.258		
ASA grade								
I	1				1			
II	1.19 (0.60 to 2.39)	0.616			1.73 (0.67 to 4.49)	0.261		
III	1.52 (0.64 to 3.59)	0.344			2.53 (0.84 to 7.62)	0.099		
Study group								
Drainage	1				1			
Patch	2.69 (1.54 to 4.68)	<0.001	3.27 (1.78 to 6.00)	<0.001	0.16 (0.07 to 0.35)	<0.001	0.13 (0.05 to 0.32)	<0.001
Ligasure®								
No	1				1			
Yes	1.17 (0.67 to 2.059	0.588			1.67 (0.85 to 3.26)	0.138		
Harmonic®								
No	1				1			
Yes	0.63 (0.37 to 1.08)	0.090	0.58 (0.32 to 1.039)	0.065	0.85 (0.44 to 1.63)	0.613		
Removed lymph nodes†								
>15	1.12 (0.65 to 1.91)	0.691			1.82 (0.94 to 3.53)	0.075	1.68 (0.79 to 3.55)	0.176
Positive lymph nodes†								
>2	1.09 (0.63 to 1.88)	0.754			1.37 (0.71 to 2.65)	0.350		

*Factors associated with success in the univariable analysis at $P < 0.1$ were included in the multivariable analysis. †Reference group ≤median. Ligasure® - Medtronic, Minneapolis, MN, USA; Harmonic® - Ethicon Endo Surgery, Albuquerque, NM, USA. DM, diabetes mellitus; HER2, human epidermal growth factor receptor 2.

was significantly shorter in the drainage group (Hodges–Lehmann median difference −3.0 days, 95 per cent c.i. −5.0 to −0.0 days; $P = 0.025$). This may suggest that instances of seroma in the drainage group, although less frequent, were more difficult to manage. In support of this hypothesis is the fact that patients in the drainage group required a significantly greater number of outpatient visits to control the seroma than those in the patch group ($P < 0.001$).

In the multivariable analysis, previous axillary surgery was associated with a greater need for an ED visit ($P = 0.0122$), and the use of a PEG-coated patch was associated with a lower probability of an ED visit ($P < 0.001$). On the other hand, the patch group exhibited a greater incidence of seroma in the multivariable analysis ($P < 0.001$).

Obese patients are at increased risk of postoperative complications[33]. Additionally, increased body weight[18,34] and BMI[31,35–37] have both been associated with increased seroma formation. In the current study, obesity was, however, not significantly associated with either the incidence of seroma or the need for an ED visit.

Table 5 Comparative estimated postoperative costs of a polyethylene glycol-coated patch *versus* drainage

Postoperative requirement	Unit cost*	PEG-coated patch		Drainage		Cost savings using patch*
		Mean	Cost*	Mean	Cost*	
ED visits	193.01	0.026	5.02	0.49	94.58	89.56
Outpatient visits	10.78	2.46	26.52	4.09	44.09	17.57
PEG-coated patch	213.04†	1.29	240.00	0	0.00	−274.82
Consumables	3.44	0	0.00	2.85	9.80	9.80
Hospital admission	3637.79	0	0.00	0.071	258.3	258.3
Overall estimated cost savings per patient						100.41

	Direct postoperative costs						ICER§
	Hemopatch			Drainage			
	Cost*	Outcome (numerical)‡	CER§	Cost*	Outcome (numerical)‡	CER§	
No ED visit	284.8	0.974¶	292.4	421.5	0.696¶	605.6	491.7
No hospital admission	284.8	1.0	284.8	421.5	0.982	429.2	7594.4
Success	284.8	0.922	308.9	421.5	0.670	629.1	542.5

*Cost in Euros. †Mean value was calculated according to the price of the Hemopatch™ in Spain: €240.00 (large: 90 mm × 45 mm) and €140.00 (medium: 45 mm × 45 mm). ‡Proportion of patients who did not need to attend to the emergency department for any reason related to surgery. §CER and ICER analysis were based on total postoperative direct costs to the Spanish public health system. PEG, polyethylene glycol; ED, emergency department; CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio.

Public health services must cope with an unlimited demand for limited resources. Therefore, it is extremely important to identify cost-effective treatments. In the current study, although the incidence of seroma was greater in the patch group, their postoperative management appeared to be smoother. Cost and cost-effectiveness analyses support this assumption, as a PEG-coated patch resulted in a total mean cost savings of €100.41 per patient. Additionally, the use of drainage was associated with an ICER of €491.7, €7594.4, and €542.5 for no need for an ED visit, no need for hospital admission, and for achieving treatment success respectively.

This study has limitations that should be taken into consideration. Although this was a multicentre study, many patients were recruited in the Valencian community, and therefore the limited geographical distribution of the sample may limit the generalizability of the results, especially in terms of costs. The study protocol did not provide indications or collect information about the person responsible for the postoperative management of patients with drainage (either patient caregiver or nurse). This point was managed according to the specific protocols of each study centre. Additionally, this study did not evaluate direct non-medical costs (that is home healthcare and social services), patient transportation costs, or other incidental costs when establishing economic parameters. In view of the results, the inclusion of such costs would likely make the difference even more favourable with regard to the use of patches. Finally, this study has only considered direct costs associated with postoperative management. Therefore, the results of this analysis do not reflect the total costs of ALND. In patients who underwent axillary lymphadenectomy, a PEG-coated patch was associated with a lower number of postoperative outpatient visits and a lower number of ED visits, resulting in a reduction in costs. Although the incidence of seroma was significantly greater in patients who received the patch compared with those who received drainage, their postoperative management appeared to be smoother.

The clinical and economic value of using a PEG-coated patch in clinical practice, although promising, needs to be confirmed in future studies.

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Data availability

The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**:209–249
3. Bermejo de Las Heras B, Cortes Ramon y Cajal J, Galve Calvo E, de la Haba Rodriguez J, Garcia Mata J, Moreno Anton F *et al.* The economic burden of metastatic breast cancer in Spain. *Eur J Hosp Pharm* 2020;**27**:19–24
4. Keelan S, Flanagan M, Hill ADK. Evolving trends in surgical management of breast cancer: an analysis of 30 years of practice changing papers. *Front Oncol* 2021;**11**:622621
5. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;**347**:1227–1232
6. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE *et al.* Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;**15**:1303–1310
7. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002;**347**:567–575
8. Ling DC, Iarrobino NA, Champ CE, Soran A, Beriwal S. Regional recurrence rates with or without complete axillary dissection for breast cancer patients with node-positive disease on sentinel lymph node biopsy after neoadjuvant chemotherapy. *Adv Radiat Oncol* 2019;**5**:163–170
9. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP *et al.* Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010;**11**:927–933
10. Mamounas ETP. Optimal management of the axilla: a look at the evidence. *Adv Surg* 2016;**50**:29–40
11. Toomey A, Lewis CR. *Axillary Lymphadenectomy, 2021 Dec 16, StatPearls (Internet)*. Treasure Island: StatPearls Publishing, 2022
12. Gupta S, Gupta N, Kadayaprath G, Neha S. Use of sentinel lymph node biopsy and early physiotherapy to reduce incidence of lymphedema after breast cancer surgery: an institutional experience. *Indian J Surg Oncol* 2020;**11**:15–18
13. Montalto E, Mangraviti S, Costa G, Carrega P, Morandi B, Pezzino G *et al.* Seroma fluid subsequent to axillary lymph node dissection for breast cancer derives from an accumulation of afferent lymph. *Immunol Lett* 2010;**131**:67–72
14. van Bemmel AJ, van de Velde CJ, Schmitz RF, Liefers GJ. Prevention of seroma formation after axillary dissection in breast cancer: a systematic review. *Eur J Surg Oncol* 2011;**37**:829–835
15. Turner EJ, Benson JR, Winters ZE. Techniques in the prevention and management of seromas after breast surgery. *Future Oncol* 2014;**10**:1049–1463
16. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer* 2001;**92**:1368–1377
17. Puttawibul P, Sangthong B, Maipang T, Sampao S, Uttamakul P, Apakupakul N. Mastectomy without drain at pectoral area: a randomized controlled trial. *J Med Assoc Thai* 2003;**86**:325–331
18. Lewis KM, Ikeme S, Olubunmi T, Kuntze CE. Clinical effectiveness and versatility of a sealing hemostatic patch (HEMOPATCH) in multiple surgical specialties. *Expert Rev Med Devices* 2018;**15**:367–376
19. Nowak S, Schroeder HWS, Fleck S. Hemopatch as a new dural sealant: a clinical observation. *Clin Neurol Neurosurg* 2019;**176**:133–137
20. Onega T, Tosteson AN, Weiss J, Alford-Teaster J, Hubbard RA, Henderson LM *et al.* Costs of diagnostic and preoperative workup with and without breast MRI in older women with a breast cancer diagnosis. *BMC Health Serv Res* 2016;**16**:76
21. Susini T, Carriero C, Tani F, Mattioli G, Renda I, Biglia N *et al.* Day surgery management of early breast cancer: feasibility and psychological outcomes. *Anticancer Res* 2019;**39**:3141–3146
22. Buch-Villa E, Castañer-Puga C, Delgado-Garcia S, Fuster-Diana C, Vidal-Herrador B, Ripoll-Orts F *et al.* Polyethylene glycol-coated collagen patch (Hemopatchtm) versus axillar drainage. In patients undergoing axillary lymphadenectomy: interim analysis of a multicentre, prospective, randomized and controlled studys. *Br J Cancer Res* 2022;**5**:558–567
23. Thomson DR, Sadideen H, Furniss D. Wound drainage after axillary dissection for carcinoma of the breast. *Cochrane Database Syst Rev* 2013; (10)CD006823
24. Crystal J, Mella-Catinchi J, Xu K, Weingrad D. Current surgical innovations in the treatment of breast cancer. In: Mayrovitz HN (ed.), *Breast Cancer (Internet)*. Brisbane: Exon Publications, 2022
25. Schrenk P, Rieger R, Shamiyeh A, Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. *Cancer* 2000;**88**:608–614
26. Johnson AR, Kimball S, Epstein S, Recht A, Lin SJ, Lee BT *et al.* Lymphedema incidence after axillary lymph node dissection: quantifying the impact of radiation and the lymphatic microsurgical preventive healing approach. *Ann Plast Surg* 2019; **82**(Suppl 3): S234–S241
27. Lotze MT, Duncan MA, Gerber LH, Woltering EA, Rosenberg SA. Early versus delayed shoulder motion following axillary dissection: a randomized prospective study. *Ann Surg* 1981;**193**:288–295
28. Piñero-Madrona A, Castellanos-Escrig G, Abrisqueta-Carrión J, Canteras-Jordana M. Prospective randomized controlled study

to assess the value of a hemostatic and sealing agent for preventing seroma after axillary lymphadenectomy. *J Surg Oncol* 2016;**114**:423–427
29. Conversano A, Mazouni C, Thomin A, Gaudin A, Fournier M, Rimareix F *et al.* Use of low-thrombin fibrin sealant glue after axillary lymphadenectomy for breast cancer to reduce hospital length and seroma. *Clin Breast Cancer* 2017;**17**:293–297
30. Weber WP, Tausch C, Hayoz S, Fehr MK, Ribi K, Hawle H *et al.* Impact of a surgical sealing patch on lymphatic drainage after axillary dissection for breast cancer: the SAKK 23/13 multicenter randomized phase III trial. *Ann Surg Oncol* 2018;**25**:2632–2640
31. Benevento R, Santoriello A, Pellino G, Sciaudone G, Candilio G, De Fatico GS *et al.* The effects of low-thrombin fibrin sealant on wound serous drainage, seroma formation and length of postoperative stay in patients undergoing axillary node dissection for breast cancer. A randomized controlled trial. *Int J Surg* 2014;**12**:1210–1215
32. Chang YT, Shih SL, Loh EW, Tam KW. Effects of fibrin sealant on seroma reduction for patients with breast cancer undergoing axillary dissection: meta-analysis of randomized controlled trials. *Ann Surg Oncol* 2020;**27**:5286–5295
33. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The impact of obesity on breast cancer diagnosis and treatment. *Curr Oncol Rep* 2019;**21**:41
34. Kuroi K, Shimozuma K, Taguchi T, Imai H, Yamashiro H, Ohsumi S *et al.* Evidence-based risk factors for seroma formation in breast surgery. *Jpn J Clin Oncol* 2006;**36**:197–206
35. Woodworth PA, McBoyle MF, Helmer SD, Beamer RL. Seroma formation after breast cancer surgery: incidence and predicting factors. *Am Surg* 2000;**66**:444–450;discussion 450–451
36. Srivastava V, Basu S, Shukla VK. Seroma formation after breast cancer surgery: what we have learned in the last two decades. *J Breast Cancer* 2012;**15**:373–380
37. Zieliński J, Jaworski R, Irga N, Kruszewski JW, Jaskiewicz J. Analysis of selected factors influencing seroma formation in breast cancer patients undergoing mastectomy. *Arch Med Sci* 2013;**9**:86–92