Different patterns of breast cancer-related lymphedema according to body mass index

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Research Article

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Abstract

Purpose

This study aimed to clarify how body mass index (BMI) affects the development of breast cancer-related lymphedema (BCRL) and to improve the postoperative follow-up for BCRL.

Methods

In this prospective study, patients with operable breast cancer were registered in a single institute between November 2009 and July 2010. The incidence rates of lymphedema at 1, 3, and 5 years after surgery were assessed according to BMI, and the trend of newly developed BCRL was examined. The cut-off point of BMI was 25 kg/m^2 according to the definition of obesity by the Japan Society for the Study of Obesity.

Results

A total of 379 patients were analyzed in this study. The multivariate analysis of the whole population showed that high BMI, axillary dissection, and radiotherapy remained as risk factors for BCRL. Patients with high BMI showed a significantly higher incidence of lymphedema than those with low BMI at 1 year ($p < 0.0001$), regardless of axillary procedures (39.1% vs. 16.3% for axillary dissection, 15.6% vs. 1.5% for sentinel lymph node biopsy), but not at 3 and 5 years. Once BCRL was developed, patients with high BMI showed slow recovery, and 50.0% of the patients retained their lymphedema at 5 years. However, patients with low BMI showed rapid recovery, and 26.7% retained their lymphedema at 3 years ($p = 0.04$).

Conclusion

Preoperative BMI affected BCRL, regardless of axillary surgery or radiotherapy. Patients with high BMI should be provided appropriate information about BCRL before surgery and careful checkups after surgery.

Introduction

Although the survival of patients with breast cancer has remarkably improved, breast cancer-related lymphedema (BCRL) remains one of the most distressing and debilitating complications of breast cancer treatment [1, 2]. The incidence rate of lymphedema ranges from 6–50% after surgical treatment [3]. Previous studies have demonstrated that axillary lymph node dissection (ALND), regional lymph node irradiation, high preoperative body mass index (BMI), and docetaxel administration increase the risk of developing lymphedema [4–8]. Most of these risk factors are components of breast cancer treatment, but BMI is the only factor that is not associated with cancer treatment but with host physical characteristics.

The suggested BMI cut-off point used to define obesity (≥ 30 kg/m^2) was developed from observational studies, including exclusively Caucasian populations in Europe and the USA, and based on the association between BMI and mortality [9]. BMI ≥ 30 kg/m^2 is reported in less than 2–3% of Japanese individuals, in contrast to 10–20% observed in individuals originating from Europe and the USA [10, 11]. A World Health Organization expert consultation addressed the debate about the interpretation of recommended BMI cut-off points for determining overweight and obesity in Asian populations and considered that population-specific cut-off points for BMI are necessary [12]. They reviewed scientific evidence that suggests that Asian populations have different associations among BMI, percentage of body fat, and health risks from Caucasian populations. The consultation recommended lowering the BMI cut-off point for defining obesity in Asian populations. However, available data do not necessarily indicate a clear BMI cut-off point for all Asians for overweight or obesity. The Japan Society for the Study of Obesity examined the relationship between BMI and the prevalence of obesity-related disorders, assessed visceral fat accumulation by computed tomography scanning, and defined obesity as a BMI of 25 kg/m^2 or higher in the Japanese population [13].

Although the relationship between BCRL and BMI has been reported, there have been no reports examining the postoperative changes in BCRL over time in association with BMI. This study aimed to clarify how BMI affects the development of BCRL and to examine how BCRL changes over time according to BMI, to improve the postoperative follow-up scheme for BCRL.

Materials And Methods

Participants

This study prospectively registered patients with operable primary breast cancer who were scheduled to undergo curative surgery with either sentinel lymph node biopsy (SLNB) or ALND at the Cancer Institute Hospital of Japanese Foundation for Cancer Research between November 2009 and July 2010. The patients were treated with curative intent according to the guidelines by the Japanese Breast Cancer Society [14]. This study was approved by the institutional review board (# 2015 – 1085).

Measurements for lymphedema

One day prior to the surgery, the circumference of both upper extremities was measured using a tape as reference values at the following four sites: (1) 5 cm above the olecranon, (2) 5 cm below the olecranon, (3) ulnar head, and (4) dorsum of the hand. The same measurements were obtained 1, 3, and 5 years after the surgery. The change in ipsilateral upper-extremity circumference, corrected for any change in the contralateral upper extremity, was calculated using the following formula:

$$L = (If/u - Ib) - (Cf/u - Cb)$$

where I, C, f/u, and b indicates ipsilateral upper-extremity circumference, contralateral upper-extremity circumference, follow-up, and baseline, respectively [15–17]. L was calculated for all four sites. L ≥ 2 cm at one or more sites was defined as lymphedema. If the patient wore compression garments, it was also

defined as lymphedema. At the time of each measurement, patient's weight measurement and the doctors' physical inspection were performed. Lymphatic care nurses followed up and advised patients with BCRL to wear a compression garment.

Body mass index

Body height and weight were measured preoperatively to calculate BMI. In accordance with the definition of obesity by the Japan Society for the Study of Obesity, the cut-off was set at 25 for BMI.

Statistical analyses

The differences between the two groups were compared using the χ-squared and Wilcoxon tests. Logistic regression analysis was utilized to assess the relationship between risk factors and BCRL. All statistical analyses were performed using JMP Pro software version 13.0 (SAS Institute Japan, Tokyo). Two-sided $P < 0.05$ was considered statistically significant.

Results

A total of 421 patients were registered in this study. Among these patients, 38, 1, 2, and 1 having bilateral breast cancers, ipsilateral breast tumor recurrence (IBTR), stage IV disease, and arm injury (torn tendon), respectively, were excluded. Hence, 379 patients were included in the analysis (Fig. 1). Three years postoperatively, there was one case of IBTR, two cases of heterochronous bilateral breast cancer, two cases of additional dissection due to recurrence, and four cases of death, which were excluded from the analyses at 3 and 5 years.

Patients with BCRL who experienced lymphedema at least once in the first 5 years after surgery were compared with those without BCRL. The background characteristics of patients with and without BCRL are shown in Table 1. In the univariate analysis, the risk factors for BCRL included BMI ≥ 25 kg/m^2, ALND, hormonal therapy, chemotherapy (docetaxel included), and radiotherapy. The multivariate analysis including these risk factors showed that high BMI, ALND, and radiotherapy remained as the independent risk factors for BCRL (Table 2).

The patient background characteristics according to BMI are shown in Table 3. Patients with high BMI were significantly older (median age, 58 years) compared to those with low BMI (median age, 50 years). The percentages of breast-conserving surgery were 49.7% and 63.4% for low and high BMIs, respectively, indicating that breast-conserving surgery is more common in patients with high BMI than in those with low BMI. There was no difference in axillary procedure, postoperative systemic treatment, or radiation according to BMI.

The incidence rates of new lymphedema at 1, 3, and 5 years postoperatively according to BMI are shown in Fig. 2a. Patients with high BMI showed a significantly higher incidence rate of new lymphedema than those with low BMI at 1 year ($p < 0.0001$), but not at 3 and 5 years ($p = 0.94$ and $p = 0.47$, respectively). In patients with low BMI, the incidence rates of new lymphedema were persistent over time after surgery at approximately 7.0% ($p = 0.38$), whereas patients with high BMI showed decreased incidence rates of new

lymphedema over time after surgery, with 23.5% at 1 year to 9.4% at 5 years. BMI was significantly associated with the incidence of lymphedema at 1 year, even after adjusting for the type of axillary surgery, hormonal therapy, docetaxel administration, and radiotherapy (Table 4).

The incidence rate of new lymphedema was assessed based on the type of axillary surgery (Fig. 2b and 2c). In the ALND group, similar to the whole population, the incidence rate of new lymphedema was significantly higher in patients with high BMI at 1 year postoperatively ($p = 0.016$), but not at 3 and 5 years ($p = 0.21$ and $p = 0.21$, respectively; Fig. 2b), than in those with low BMI. Interestingly, even in patients undergoing SLNB, the incidence rate of lymphedema was high (15.6%) 1 year after surgery, but it was low after 3 years in patients with high BMI. However, the incidence rate was low persistently in patients with low BMI (Fig. 2c). To examine whether the lymphedema persists over time, patients who developed lymphedema 1 year after surgery were followed up at 3 and 5 years according to BMI (Fig. 3). Patients with low BMI who developed lymphedema at 1 year showed a rapid improvement of lymphedema at 3 years, whereas patients with high BMI showed a gradual improvement, indicating a significant difference of the improvement pattern according to BMI ($p = 0.04$). At 5 years, 26.7% and 50.0% of patients with low and high BMIs, respectively, had retained lymphedema.

We examined the detection rate of BCRL by physical inspection. In the whole population, 43.9% of the BCRL were detected by physical inspection. When sorted by BMI, 49.3% and 31.7% of the BCRL were detected in patients with low and high BMIs, respectively ($p = 0.07$).

Discussion

This study demonstrated that the incidence rate and time course of BCRL differed significantly depending on BMI. The incidence rate of newly developed BCRL was higher in patients with high BMI than in those with low BMI only in the first postoperative year and became similar after 3 years, regardless of BMI. In addition, once BCRL was developed, it was recovered slowly, and half of the patients with high BMI retained their lymphedema until 5 years. However, BCRL was alleviated rapidly, and only 26.7% of the patients with low BMI retained their lymphedema after 3 years. Notably, clinical factors relevant to BCRL, such as type of axillary surgery, chemotherapy use, and radiotherapy, were not different between patients with high and low BMIs, indicating that the different trends shown in this study are mainly derived from the differences in BMI.

To the best of our knowledge, this is the first report to examine a temporal trend of BCRL in association with BMI. The peak incidence of BCRL has been reported to be between 12 and 30 months postoperatively [3, 6]. In this study, BCRL was developed in the first postoperative year in 23.5% of patients with high BMI and only in 9.3% in the third year, which was similar to the previous reports. This study also examined the incidence rates of new lymphedema in the high and low BMI groups for different axillary procedures and found that the trends over time were different according to BMI. The patients with high BMI undergoing ALND still had a 28.6% incidence rate of new lymphedema at 5 years, indicating that long-term observation of lymphedema is necessary. In contrast, the patients with low BMI undergoing SLNB had a postoperative lymphedema frequency of less than 5% and did not appear to require close observation.

In this study, only approximately one-third (31.7%) of BCRL was detected by physical inspection in patients with high BMI, whereas approximately half (49.3%) was detected in those with low BMI. This may be due to plump body in patients with high BMI, which makes it difficult to make a gross assessment of body change. Lymphatic care intervention can improve lymphedema even in the absence of visible edema, and early diagnosis of lymphedema is important [4, 18, 19]. For patients with high BMI, healthcare providers should actively closely observe for lymphedema during regular checkups every 3–6 months until at least 3 years after surgery.

We showed that more than 15% of the patients with high BMI developed BCRL even with SLNB. Although the risk of lymphedema is carefully discussed with patients undergoing ALND during preoperative instructions, it is not intensively discussed with patients who are scheduled for SLNB. However, providing information and carefully discussing lymphedema in patients with high BMI even for SLNB are required. Thus, it is important to inform patients with high BMI, regardless of the axillary surgery procedure, regarding the peak incidence during the early years after surgery and a possibility of persistent BCRL once it is developed.

This study has some limitations. First, there is no standardized method for measuring lymphedema, and the National Lymphedema Network recommends the measurement of six anatomical landmarks (circumference at the mid-hand, wrist, elbow, upper arm just below the axilla, and at 10 cm distal to and proximal to the lateral epicondyle on both arms) [20]. In this study, we used the tape measure, which is the most commonly used method to assess lymphedema. The tape measure method does not specify how many points to measure, which parts of the body to measure, or how to define the presence of lymphedema. Previous studies using the tape measure have shown that the measurement points ranged from 1 to 10 [16, 21–25], and that the definition of lymphedema was mostly based on the increase by 2 cm in any of the body parts [6]. In this study, referring to the past literature, measurements were taken at four locations of both arms, and lymphedema was defined as having a circumference difference of ≥ 2 cm in any one location [15–17]. Although measurement using a tape measure has lower accuracy than perometry, bioimpedance spectroscopy, and lymphoscintigraphy [5, 26], tape measure's availability at any hospital is clinically advantageous and useful for daily use. Another limitation is lost to follow-up in some patients during 5 years mostly due to disease recurrence or death. One of the strengths of this study is a relatively large number of patients analyzed for lymphedema, who were followed up with the consistent method in a prospective study.

In conclusion, preoperative BMI was associated with postoperative lymphedema in patients with breast cancer, regardless of axillary surgery, chemotherapy, or radiotherapy. Patients with high BMI should be provided appropriate information and discussion about BCRL before surgery and careful checkups after surgery.

Declarations

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None

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Kiyomi Kimura, Takuji Iwase and Takayuki Ueno contributed to the study conception and design. Data collection and analysis were performed by Kiyomi Kimura and Akiko Ogiya. Akiko Ogiya wrote the manuscript, and all authors critically revised and approved the final manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Ethics Approval

This study was approved by the institutional review board (# 2015-1085).

Consent to Participate

Waiver for consent for this retrospective study was obtained from the Institutional Review Board at the Cancer Institute Hospital.

Consent to Publish

All authors have reviewed this version of the manuscript and provided consent for publication.

Abbreviations

ALND	axillary lymph node dissection
BCRL	breast cancer-related lymphedema
BMI	body mass index
IBTR	ipsilateral breast tumor recurrence
SLNB	sentinel lymph node biopsy

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Tables

Table 1. Patient characteristics

	No-BCRL				BCRL				
	(N = 289)				(N = 80)				
	N	%	Median	Range	N	%	Median	Range	p
Median age at the time of surgery			51	24–83			51	29–74	0.52
BMI at surgery									
< 25	242	83.7			56	70.0			
≥ 25	47	16.3			24	30.0			0.006
cT									
is	55	19.0			6	7.5			
1	174	60.2			29	36.3			
2	56	19.4			33	41.3			
3	2	0.7			7	8.8			
4	2	0.7			5	6.3			< 0.0001
Type of breast surgery									
Breast-conserving surgery	152	52.6			41	51.3			
Total mastectomy	137	47.4			39	48.8			0.83
Type of axillary surgery									
SLNB	224	77.5			28	35.0			
ALND	65	22.5			52	65.0			< .0001
Median total number of excisional nodes			3	1-33			14.5	1-30	< 0.0001
pN									
0	226	78.2			28	35.0			
1	58	20.1			40	50.0			

2	0	0.0	4	5.0	
3	5	1.7	8	10.0	< 0.0001
Tumor type					
DCIS	55	19.0	6	7.5	
IDC	210	72.7	62	77.5	
ILC	3	1.0	4	5.0	
Mucinous	7	2.4	1	1.3	
Others	14	4.8	7	8.8	0.01
Hormonal therapy					
Yes	169	58.5	59	73.8	
No	120	41.5	21	26.3	0.01
Chemotherapy					
Yes	81	28.0	56	70.0	
No	208	72.0	24	30.0	< 0.0001
Docetaxel included					
Yes	7	2.4	8	10.0	
No	282	97.6	72	90.0	0.002
Radiotherapy					
Yes	90	31.1	51	63.8	
No	199	68.9	29	36.3	< 0.0001

Abbreviations: BCRL, breast cancer-related lymphedema; BMI, body mass index; SLNB, sentinel lymph node biopsy;

ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; IDC, invasive ductal cancer; ILC, invasive lobular cancer.

Table 2. Multivariate analysis of lymphedema

	HR	95% CI	p
BMI ≥ 25 vs. BMI < 25	2.09	1.08–4.00	< .0001
ALND vs. SLNB	4.90	2.75–8.71	< .0001
Hormonal therapy yes vs. no	1.32	0.71–2.45	0.37
Docetaxel included vs. no docetaxel	2.64	0.84–8.28	0.1
Radiation yes vs. no	3.06	1.73–5.42	< .0001

Abbreviations: BMI, body mass index; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy

Table 3. Patient characteristics according to BMI

	BMI < 25				BMI ≥ 25				
	(N = 298)				(N = 71)				
	N	%	Median	Range	N	%	Median	Range	p
Median age at time of surgery			50	24–79			58	37–83	< 0.0001
cT									
is	52	17.5			9	12.7			
1	163	54.7			40	56.3			
2	71	23.8			18	25.4			
3	9	3.0			0	0.0			
4	3	1.0			4	5.6			0.05
Type of breast surgery									
Breast-conserving surgery	148	49.7			45	63.4			
Total mastectomy	150	50.3			26	36.6			0.04
Type of axillary surgery									
SLNB	205	68.8			47	66.2			
ALND	93	31.2			24	33.8			0.67
Median total number of excisional nodes			3	1-33			4	1-30	0.84
pN									
0	206	69.1			48	67.6			
1	79	26.5			19	26.8			
2	4	1.3			0	0.0			
3	9	3.0			4	5.6			0.55
Tumor type									
DCIS	52	17.5			9	12.7			
IDC	213	71.5			59	83.1			
ILC	7	2.4			0	0.0			
Mucinous	7	2.4			1	1.4			

Others	19	6.4	2	2.8	0.29
Hormonal therapy					
Yes	183	61.4	45	63.4	
No	115	38.6	26	36.6	0.76
Chemotherapy					
Yes	107	35.9	30	42.3	
No	191	64.1	41	57.8	0.32
Docetaxel included					
Yes	10	3.4	5	7.0	
No	288	96.6	66	93.0	0.16
Radiotherapy					
Yes	107	35.9	34	47.9	
No	191	64.1	37	52.1	0.06

Abbreviations: BMI, body mass index; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ;

IDC, invasive ductal cancer; ILC, invasive lobular cancer

Table 4. Multivariate analysis of lymphedema 1 year postoperatively

	HR	95% CI	p
BMI ≥ 25 vs. BMI < 25	4.57	2.03–10.26	0.0002
ALND vs. SLNB	4.79	2.03–11.27	0.0003
Hormonal therapy yes vs. no	1.45	0.59–3.55	0.42
Docetaxel included vs. no docetaxel	2.93	0.80–10.73	0.1
Radiation yes vs. no	1.92	0.85–4.4	0.12

Abbreviations: BMI, body mass index; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy

Figures

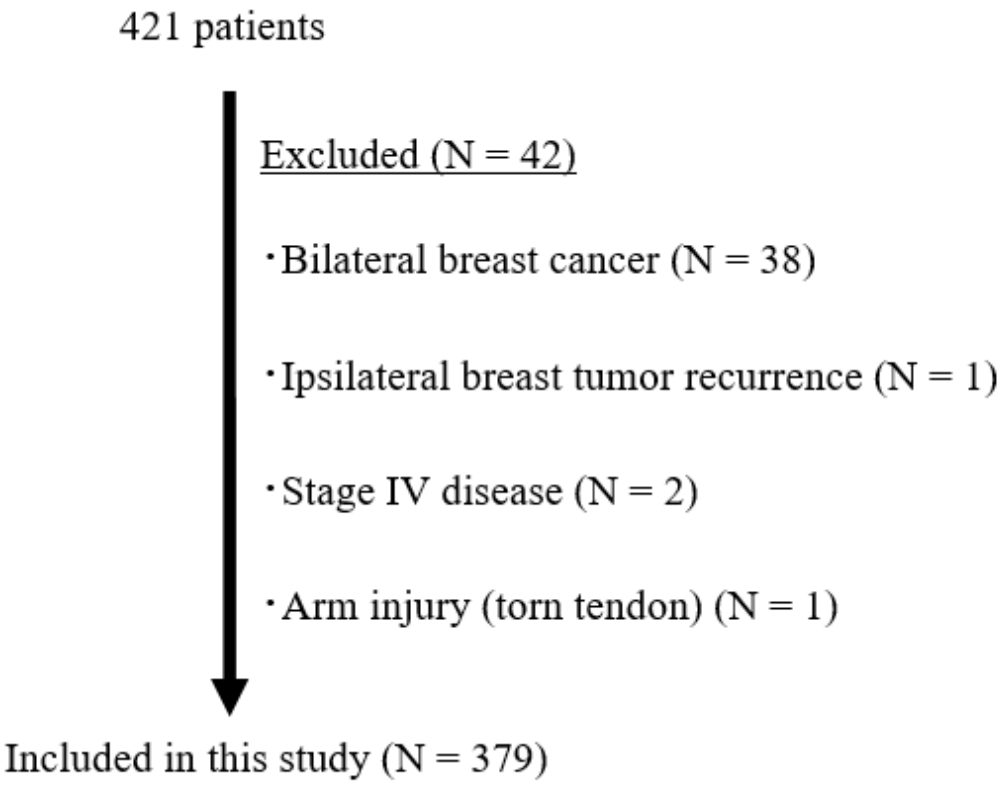

Figure 1

Consort diagram

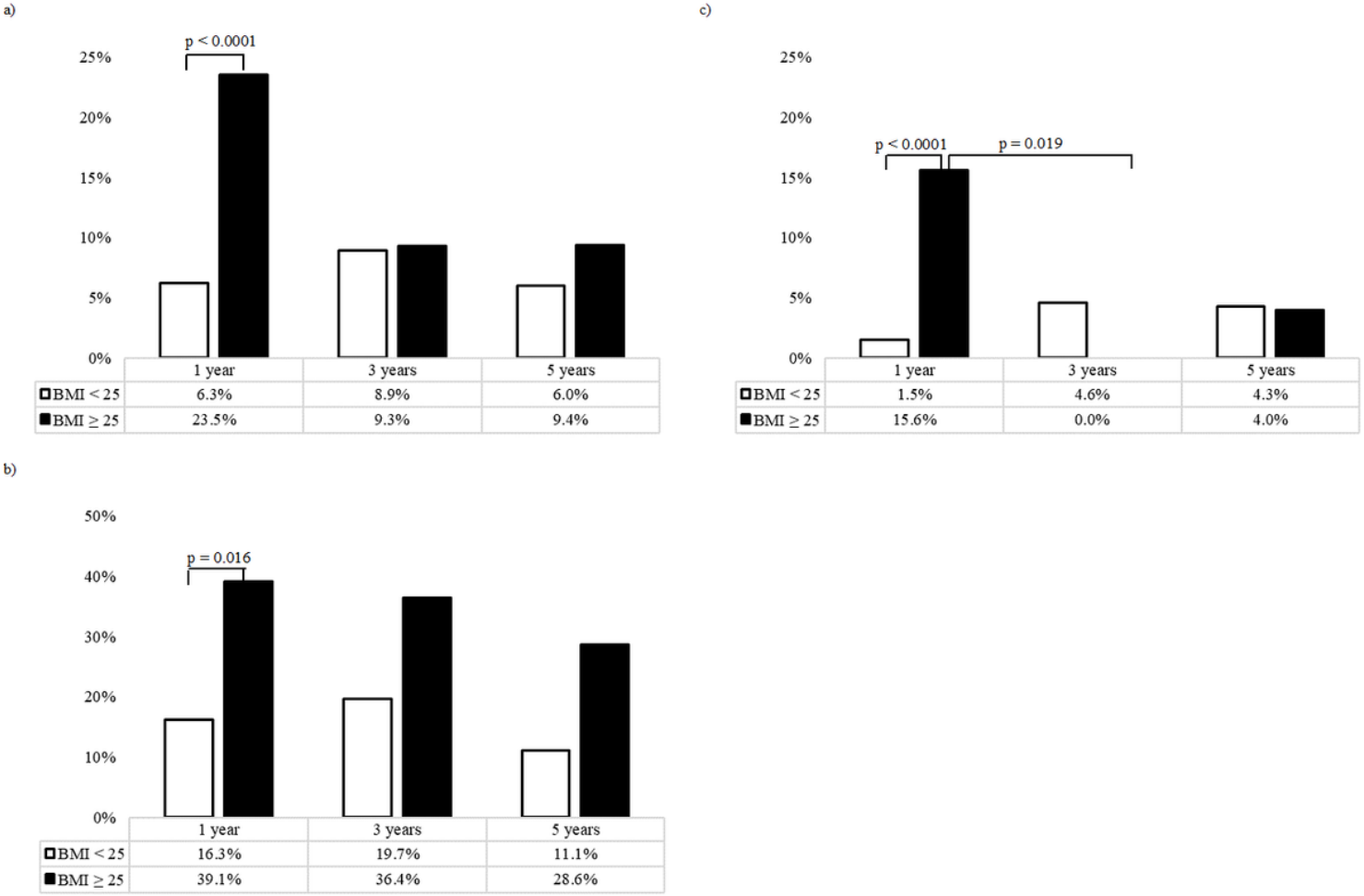

Figure 2

Incidence rate of new lymphedema according to body mass index. a) Whole population, b) axillary lymph node dissection, c) sentinel lymph node biopsy

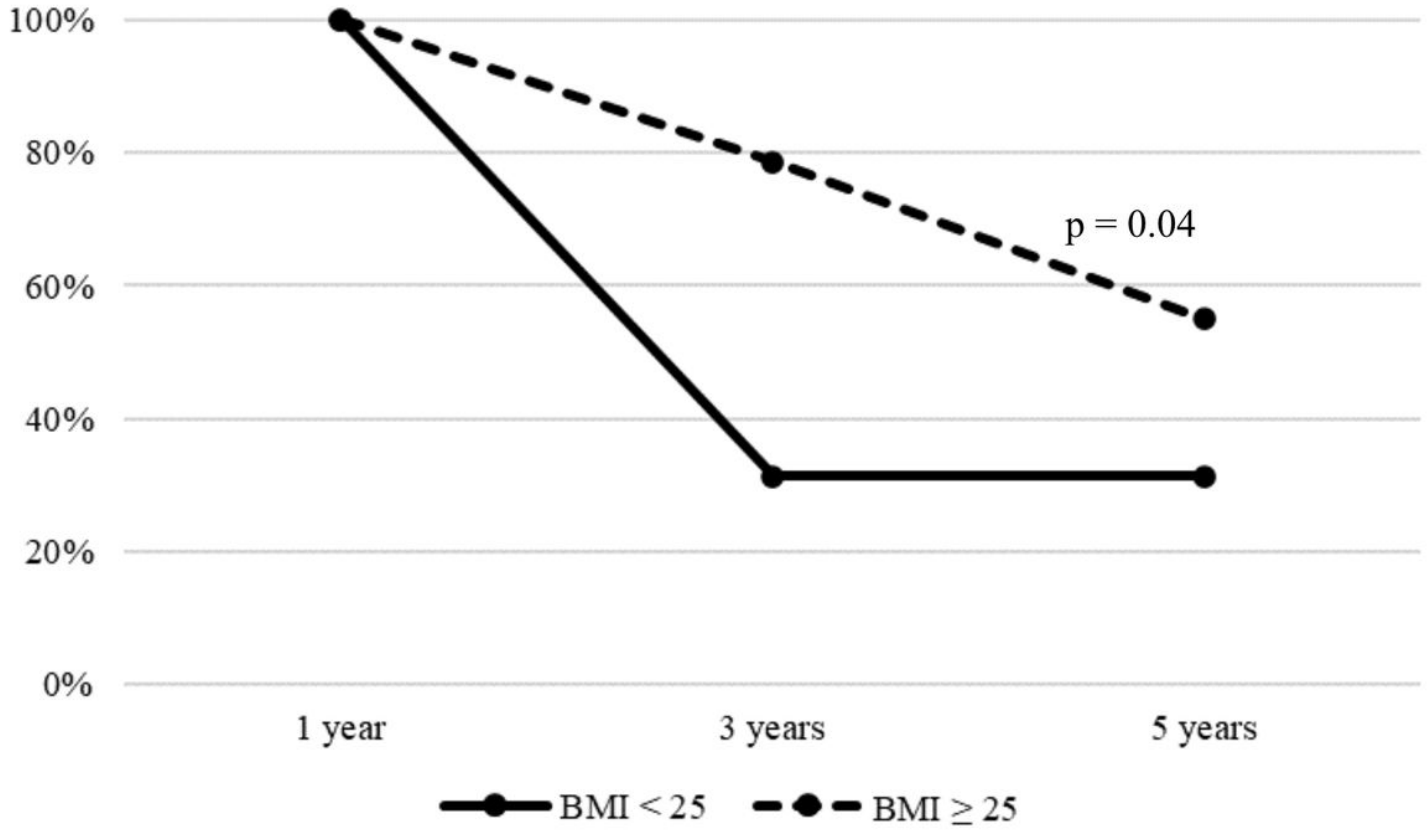

Figure 3

The time course of lymphedema in patients who developed lymphedema 1 year postoperatively according to body mass index