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Necrotic Complications in Nipple-Sparing Mastectomy Followed by Immediate Breast Reconstruction: Systematic Review with Pooled Analysis

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This study provides a systematic review of the literature on nipple-sparing mastectomy and necrotic complications in order to estimate the prevalence of necrotic complications and to investigate their significant predictors. A literature search was conducted using the MEDLINE and Ovid databases. A pooled analysis was performed for calculation of the prevalence of nipple-areolar complex (NAC) necrosis, mastectomy flap necrosis, and overall necrotic complications and to evaluate the relationships between necrotic complications and potential risk factors. A total of 44 papers were analyzed. The prevalence of overall necrotic complications was 13.7%, including 7.5% for NAC necrosis and 7.8% for mastectomy flap necrosis. Types of incisions showed significant association with the rates of NAC necrosis and mastectomy flap necrosis. Incisions involving the NAC showed a significantly higher rate of NAC necrosis than those not involving it. The prevalence of NAC necrosis was higher in the autologous tissue reconstruction group than in the prosthesis group. Active smoking and diathermy dissection were significant predictors of both NAC necrosis and mastectomy flap necrosis. The findings of this review suggest that there are several predictors of necrotic complications in nipple-sparing mastectomy. Appropriate patient selection, careful operative planning, and surgical technique refinements may reduce the risk of necrotic complications.

Key Words: Mastectomy, Postoperative complication, Necrosis

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INTRODUCTION

Recently, nipple-sparing mastectomy (NSM) has received increased attention for the treatment of early-stage breast cancer patients. Several studies have demonstrated that NSM can produce satisfactory oncological outcomes when it is performed in select patients.[1-6] In addition, NSM provides superior aesthetic outcomes by preserving the whole skin envelope, including the nipple-areolar complex (NAC), and facilitates the reconstruction of more symmetric and natural breasts.[7-9]

Necrotic complications including necrosis of the NAC region or the mastectomy flap remain a major problem in NSM. These complications can delay and disturb oncological treatment[10] and produce less satisfactory aesthetic outcomes,[11-13] eventually obviating the main advantage of NSM.

The reported prevalence of necrotic complications ranges from 0.0% to 41.2%.[6,14-19] With careful patient selection and technical advances, the rate of necrotic complications have been reduced, but remains still relatively high, compared with that of other mastectomy procedures. Although some factors have been reported to influence the development of

necrotic complications, including the type of incision,[8,19,20] the reconstruction method,[19,21,22] age,[20,23] and smoking,[7] there is no general consensus as to which factors are important and the debate is ongoing. These differences in reported outcomes and the resulting debate over risk factors can be attributed to differences in patient demographics, operative techniques (e.g., the choice of incision placement, reconstruction methods, and dissection tools), and different skill levels and experience of surgeons. In this regard, a systematic literature review should provide a more comprehensive overview of necrotic complications in NSM cases.

Several studies have provided systematic reviews of NSM[4,24] but focused mainly on its oncological aspects, paying little attention to necrotic complications. Although there was one recent review comparing the prevalence of postoperative complications after NSM procedures, including nipple necrosis, based on the type of mastectomy incision and the reconstruction method,[25] it evaluated only two risk factors for these complications and ignored the necrotic complications that developed in the areola and the mastectomy skin flap, which can also present serious challenges.[23,26,27] The present systematic review estimates the overall prevalence of each necrotic complication in the NAC and the mastectomy flap and identifies the relationships between the development of necrotic complications and their potential risk factors.

PATIENTS AND METHODS

Literature review

A literature search of the Medline and Ovid database was conducted in November 2013 by using the search terms 'nipple-sparing mastectomy' and 'total skin-sparing mastectomy' as keywords. A manual search was also conducted for additional papers relevant to the topic. A total of 296 papers were obtained through this search. After excluding the articles that were not related to surgical outcomes of NSM in title review, 221 abstracts were reviewed. Basically, all papers presenting the prevalence of necrotic complications in NSM procedures were included, regardless of their publication types and languages. Then, following studies were excluded by predefined exclusion criteria; systematic reviews and meta-analyses, case reports and series with fewer than 10 cases, studies in languages other than English, studies not concerning NSM procedures, and studies lacking extractable data on necrotic complications of NSM because it was hard to distinguish NSM outcomes from those of other mastectomy procedures. Not only total necrosis requiring surgical intervention but also partial necrosis that could be healed only by conservative treatment was regarded as a necrotic complication. Two authors independently identified the relevant studies for inclusion and extracted data related to the outcomes. Disagreements were resolved by consensus discussion between authors. Based on these criteria, 203 papers were excluded,

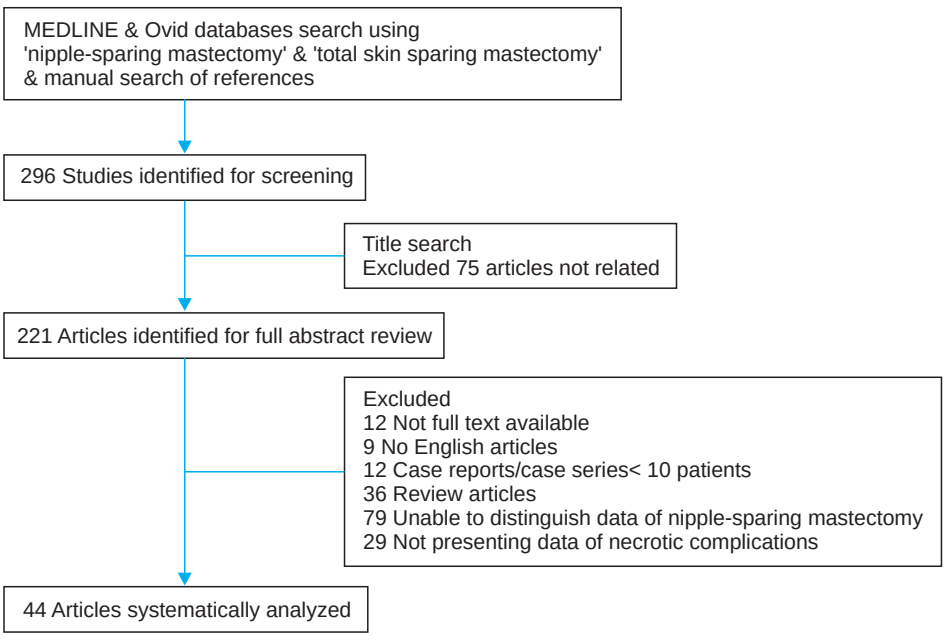

Fig. 1. Study attrition diagram.

eventually yielding 44 for the final analysis (Fig. 1).

Data extraction and analysis

Full-text reviews were conducted for all 44 papers. The following data were extracted using a standardized data extraction form (Table 1): study characteristics including the first author, the publication year, the study institution, the number of patients, the number of NSM procedures, the

Table 1. Data extraction form

Study characteristics		
Study name		
First author		
Institution		
Study period		
Patients number		
NSM case number		
Potential risk factors	Total No. of cases	Number of necrotic complication development (NAC/mastectomy skin flap/overall)
Active smoker		
Purpose of mastectomy		
Therapeutic		
Diagnostic		
Dissection method		
NAC dissection		
Sharp		
Diathermy		
Other breast region dissection		
Sharp		
Diathermy		
Mastectomy incision type		
Transareolar		
Periareolar		
Periareolar with radial extension		
Radial incision only		
Vertical incision		
Lateral incision		
Inframammary fold incision		
Others		
Reconstruction methods		
Autologous tissue reconstruction		
Pedicled flap		
Free flap		
Prosthesis reconstruction		
Two stage with tissue expander		
One stage with direct insertion		
Combined method		
Previous radiation history		
Other risk or protective factors mentioned		

NAC: nipple-areolar complex.

number of NAC necrosis cases, mastectomy flap necrosis and overall complications, the type of incision, the NAC involvement of incisions, the type of reconstruction, the dissection method for mastectomy, the purpose of NSM procedures (therapeutic or prophylactic), and the patient history of irradiation. Necrotic complications were classified into two categories, namely NAC necrosis and mastectomy flap necrosis, and were analyzed separately. Necrosis of the nipple or areolar region was regarded as NAC necrosis. Necrosis of other breast skin envelopes was regarded as mastectomy flap necrosis. Not all data were available in every paper. In the calculation of the prevalence of overall necrotic complications, papers that demonstrated the prevalence of only NAC or mastectomy skin flap necrosis but did not present the rate of overall necrotic complications were excluded. Those papers presenting only overall necrotic complication rates were also excluded in analyzing the prevalence of each necrotic complication.

When more than one paper was reported from the same institution with overlapping data collection periods, they were regarded as the same cohort. To evaluate the prevalence of necrotic complications, papers with the largest number of cases were chosen. In the analysis of risk factors, those papers demonstrating data on these factors were included regardless of the number of cases.

A pooled analysis of the prevalence of necrotic complications was conducted. The number of cases with necrotic complications was calculated in the presence and absence of risk factors. A chi-square test was conducted and $p<0.05$ was considered significant. PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA) was used for the statistical analysis.

RESULTS

Overall prevalence of necrotic complications

Forty-four articles[1-3,7-9,14-16,18,20-23,28-57] were included in the calculation of the prevalence of necrotic complications, representing a total of 6,722 NSM cases in 5,432 patients (Table 2). The prevalence of NAC necrosis was described in 38 arti cles,[1,3,7-9,14-16,20,22,23,28-31,33-57] that of mastectomy flap necrosis in 29 articles,[3,7-9,14,15,18,20,22,23,29,31-33,35,37,38,40-42,45-48,52-54,56,57] and that of overall necrotic complications in 18.[2,7,8,15,18,20-23,29,31,33,35,37,38,45,52,57] NAC necrosis developed in 445 out of 5,965 cases (7.5%), and mastectomy flap necrosis in 239 out of 3,049 (7.8%). The overall necrotic complications prevalence was 13.7% (222 out of 1,620 cases).

Incision type

Twenty-five papers[8,9,14,18,20-22,29-35,38,39,41,42,45,47,48,51,53,56,57] representing 2,570 NSM cases described the prevalence of necrotic complications by incision type. Here, 15 different incisions were used and could be classified into eight categories: transareolar incisions, periareolar incisions, periareolar incisions with a radial extension, radial incisions only, vertical incisions, lateral incisions, inframammary fold incisions, and others. The effect of incision type on the development of NAC necrosis was demonstrated in 22 papers.[8,9,14,18,22,30-35,38,39,41,42,45,47,48,51,53,56,57] NAC necrosis developed most frequently in transareolar incisions (81.8%), followed by periareolar incisions (38.3%), inframammary fold incisions (13.8%), periareolar incisions with a radial extension (13.4%), radial incisions only (11.0%), lateral incisions (5.6%), and vertical incisions (3.9%), and differences were significant ($p<0.001$) (Table 3). An additional analysis of 20 of the papers was conducted with classifying all incision types into two groups based on whether they involved NAC regions or not, regardless of the incision su btype.[8,9,14,18,30,32-35,38,39,41,42,45,47,48,51,53,56,57] Cases with incisions involving the NAC showed significantly higher rates of NAC necrosis than those with incisions not involving this region (23.6% vs. 10.6%, $p<0.001$) (Table 4).

Seventeen papers[8,9,14,18,22,32,33,37,38,40,42,45,47,48,53,56,57] representing 1,008 cases described the prevalence of mastectomy flap necrosis depending on the type of incision. Transareolar incisions had the highest prevalence of mastectomy flap necrosis (36.4%), followed by periareolar incisions with a radial extension, radial incisions only, lateral, inframammary incisions, vertical incisions, and periareolar incisions. In contrast to its relationship with NAC necrosis, surgeries that included an incision with NAC involvement did not show asignificantly higher rate of mastectomy flap necrosis than surgeries without NAC involvement (7.7% vs. 5.6%, $p=0.261$).

Overall necrotic complications were described in 11 papers, including 733 cases.[8,18,20-22,29,33,35,38,45,57] No significant differences were observed across the incision types. Furthermore, NAC involvement in incisions had no effect on the development of overall necrotic complications.

Table 2. Characteristics of 44 included studies

Study (year)	Design	No. of patients	No. of cases	Mean age (yr)	Active smoker (%)	Type of incision used	Type of reconstruction	Necrotic complication rate (%)		
								Overall	NAC necrosis	Mastectomy flap necrosis
Sufi et al.[57] (2000)	Retrospective	12	12	40	N/A	Lateral	Combined	16.7	8.3	8.3
Margulies et al.[56] (2005)	Retrospective	31	50	46	25.8	IMF, others	Prosthesis	N/A	14.0	2.0
Caruso et al.[55] (2006)	Prospective	50	51	42	N/A	Radial, IMF, others	Prosthesis	N/A	2.0	N/A
Komorowski et al.[23] (2006)	Retrospective	38	38	44.5	N/A	Periareolar, lateral, others	Prosthesis	15.8	13.2	2.6
Sacchini et al.[54] (2006)	Retrospective	123	192	45	N/A	Periareolar with radial extension, transareolar, IMF, others	Prosthesis, autologous	N/A	11.5	9.9
Denewer and Farouk[53] (2007)	Retrospective	41	41	41.5	N/A	Periareolar with radial extension	Autologous	N/A	2.4	7.3
Crowe et al.[34] (2008)	Prospective	110	149	43	N/A	Radial	Prosthesis, autologous	N/A	1.3	N/A
Regolo et al.[51] (2008)	Retrospective	70	102	42.3	N/A	Periareolar, lateral	Prosthesis	N/A	20.6	N/A
Sookhan et al.[52] (2008)	Retrospective	18	18	44	11.1	IMF, periareolar	Prosthesis	11.1	11.1	0.0
Stolier et al.[18] (2008)	Prospective	58	82	48.6	0.0	Vertical, radial	Prosthesis, autologous	2.4	0.0	2.4
Wijayanayagam et al.[32] (2008)	Prospective	43	64	43.7	11.6	Periareolar, transareolar, IMF, radial	Prosthesis, autologous, combined	N/A	2.0	17.2
Garwood et al.[21] (2009)	Prospective	115	170	44	7.0	IMF, radial, lateral, transareolar, periareolar, others	Prosthesis, autologous	19.4	10.6	12.9
Paepke et al.[50] (2009)	Prospective	96	96	N/A	N/A	Periareolar, IMF, lateral, others	Prosthesis, autologous	N/A	28.1	N/A
Petit et al.[36] (2009)	Prospective	976	1,001	46	N/A	Others	Prosthesis, autologous	N/A	9.0	N/A
Yueh et al.[14] (2009)	Prospective	10	17	44	N/A	IMF	Prosthesis, autologous	N/A	41.2	11.8
Colwell et al.[38] (2010)	Retrospective	8	14	43	0.0	IMF	Prosthesis	7.1	0.0	7.1
Kim et al.[49] (2010)	Prospective	115	115	41.5	N/A	Periareolar with radial extension, radial	Autologous	N/A	22.6	N/A
Radovanovic et al.[35] (2010)	Prospective	205	214	47	N/A	Radial	Prosthesis	7.5	2.3	6.5
Salgarello et al.[48] (2010)	Retrospective	33	42	45.8	9.1	Periareolar, periareolar with radial extension, radial, others	Prosthesis	N/A	9.5	2.4
Boneti et al.[47] (2011)	Retrospective	N/A	281	51.2	3.6	Periareolar, IMF, others	Prosthesis	N/A	0.7	4.6
de Alcantara et al.[2] (2011)	Retrospective	200	353	44	0.0	Periareolar, lateral	Prosthesis, autologous	19.5	0.3	N/A
Harness et al.[37] (2011)	Retrospective	43	60	48.7	9.3	IMF, radial, others	Prosthesis	15.0	15.0	0.0
Jensen et al.[1] (2011)	Prospective	99	149	51	5.1	Periareolar, radial, IMF	Prosthesis, autologous	N/A	5.4	N/A
Rawlani et al.[33] (2011)	Retrospective	20	37	44.4	N/A	Periareolar, lateral, IMF	Prosthesis	24.3	24.3	0.0
Spear et al.[46] (2011)	Retrospective	101	162	43	14.9	Lateral, IMF, vertical, periareolar	Prosthesis, autologous	N/A	7.0	1.9

Table 2. Continued

Study (year)	Design	No. of patients	No. of cases	Mean age (yr)	Active smoker (%)	Type of incision used	Type of reconstruction	Necrotic complication rate (%)		
								Overall	NAC necrosis	Mastectomy flap necrosis
Algaithy et al.[20] (2012)	Prospective	45	50	42	26.7	Periareolar, radial	Prosthesis	26.0	24.0	14.0
Folli et al.[39] (2012)	Non-concurrent cohort	115	115	N/A	0.0	Radial	Prosthesis	N/A	40.0	N/A
Moyer et al.[41] (2012)	Retrospective	26	40	42.9	N/A	Periareolar with radial extension, radial, vertical, IMF	Prosthesis, autologous	N/A	37.5	2.5
Peled et al.[9] (2012)	Prospective	428	657	46.9	1.6	IMF, periareolar, radial, lateral, transareolar, others	Prosthesis, autologous	N/A	3.5	11.9
Schneider et al.[43] (2012)	Retrospective	19	34	47.4	0.0	Vertical, radial	Autologous	N/A	2.9	N/A
Wagner et al.[40] (2012)	Prospective	33	54	45.4	24.2	Lateral	Prosthesis, autologous	N/A	29.6	9.3
Warren Peled et al.[3] (2012)	Prospective	160	260	46.5	N/A	IMF, periareolar, radial, lateral	Prosthesis	N/A	1.2	6.2
Yang et al.[42] (2012)	Prospective	92	92	43.2	N/A	Radial	Autologous	N/A	13.0	9.8
Alperovich et al.[15] (2013)	Retrospective	8	13	46.6	12.5	Others	Prosthesis, autologous, combined	0.0	0.0	0.0
Blechman et al.[8] (2013)	Retrospective	29	55	46	0.0	IMF	Prosthesis	5.5	5.5	3.6
Gould et al.[30] (2013)	Retrospective	73	113	47	30.1	Periareolar, radial, vertical, lateral, IMF	Prosthesis, autologous, combined	N/A	20.4	N/A
Lee et al.[22] (2013)	Retrospective	125	130	40.6	1.6	Radial	Prosthesis, autologous	16.2	11.5	8.5
Levine et al.[31] (2013)	Retrospective	84	134	N/A	0.0	Vertical, lateral, IMF	Autologous	3.7	0.0	3.7
Munhoz et al.[29] (2013)	Retrospective	158	158	51.4	19.6	Periareolar, IMF	Prosthesis	7.6	5.1	2.5
Rulli et al.[28] (2013)	Retrospective	60	73	50	N/A	Periareolar with radial extension, radial	Prosthesis	N/A	5.5	N/A
Sakurai et al.[16] (2013)	Retrospective	788	788	51	N/A	Periareolar with radial extension, IMF	Prosthesis	N/A	0.0	N/A
Stolier and Levine[44] (2013)	Retrospective	231	340	N/A	0.0	Vertical, lateral, IMF	Prosthesis, autologous	N/A	2.6	N/A
Tanna et al.[7] (2013)	Retrospective	51	85	47.8	0.0	Vertical, radial, IMF, others	Autologous	20.0	12.9	12.9
Vaughn et al.[45] (2013)	Retrospective	11	21	43	0.0	IMF	Prosthesis	9.5	0.0	9.5

NAC: nipple-areolar complex, N/A: not applicable, IMF: inframammary fold.

Table 3. Incision types as a predictor of necrotic complications

Incision type	Nipple-areolar complex		Mastectomy flap		Overall	
	Total cases	Necrosis cases	Total cases	Necrosis cases	Total cases	Necrosis cases
Total	1,507	180 (11.9)	961	65 (6.8)	733	80 (10.9)
Transareolar	11	9 (81.8)	11	4 (36.4)		
Periareolar	81	31 (38.3)	49	1 (2.0)	92	14 (15.2)
Periareolar with radial extension	112	15 (13.4)	45	4 (8.9)	39	4 (10.3)
Radial incision only	857	94 (11.0)	500	38 (7.6)	390	43 (11.0)
Vertical	128	5 (3.9)	54	2 (3.7)	51	2 (3.9)
Lateral	198	11 (5.6)	135	8 (5.9)	67	5 (7.5)
Inframammary fold	109	15 (13.8)	147	8 (5.4)	35	3 (8.6)
Others	11	0 (0.0)	20	0 (0.0)	59	9 (15.3)
p-value		<0.001		0.004		0.369

Values are presented as number or number (%).

Table 4. Association between incision with NAC involvement and necrotic complications

Incision type	NAC		Mastectomy flap		Overall	
	Total cases	Necrosis cases	Total cases	Necrosis cases	Total cases	Necrosis cases
Total	1,220	168 (13.8)	878	53 (6.0)	398	44 (11.1)
Incision with NAC involvement	301	71 (23.6)	194	15 (7.7)	185	24 (13.0)
Incision without NAC involvement	919	97 (10.6)	684	38 (5.6)	213	20 (9.4)
p-value		<0.001		0.261		0.256

Values are presented as number or number (%).
NAC: nipple-areolar complex.

Table 5. Reconstruction method as a predictor of necrotic complications

Reconstruction methods	Nipple-areolar complex		Mastectomy flap		Overall	
	Total cases	Necrosis cases	Total cases	Necrosis cases	Total cases	Necrosis cases
Total	2,641	233 (8.8)	2,110	146 (6.9)	1,051	139 (13.2)
Autologous tissue reconstruction	644	71 (11.0)	491	43 (8.8)	354	53 (15.0)
Prosthesis reconstruction	1,982	159 (8.0)	1,600	102 (6.4)	678	84 (12.4)
Combined method	15	3 (20.0)	19	1 (5.3)	19	2 (10.5)
p-value		0.020		0.183		0.478

Values are presented as number or number (%).

Reconstruction methods

Twenty-nine papers[7-9,14,15,18,20-23,30,31,33,35,37-39,42,43,45,47-49,52-57] representing 2,765 cases demonstrated the prevalence of necrotic complications depending on reconstruction method used. The relationship between NAC necrosis and reconstruction method was analyzed for 2,641 cases from 28 papers.[7-9,14,15,18,20,22,23,30,31,33,35,37-39,42,43,45,47-49,52-57] The NAC necrosis rate was significantly different between three reconstruction groups, namely the autologous reconstruction group, the prosthesis reconstruction group, and the combined-method group (p=0.020) (Table 5). In a separate comparison between just the autologous reconstruction group and the prosthesis reconstruction group, excluding the combined-method group, a significant difference was observed and autologous reconstruction showed a significantly higher rate of NAC necrosis than did prosthesis reconstruction (p=0.019).

In the subgroup analysis for the prosthesis reconstruction group, two methods (two-stage reconstruction with a tissue expander and one-stage reconstruction with the direct insertion of an implant) demonstrated similar NAC necrosis rates (p=0.319). In the subgroup analysis within the autologous group, cases of free flaps showed significantly lower rates of NAC necrosis than those of pedicled flaps (p=0.001) (Table 6).

Mastectomy flap necrosis with different reconstruction methods was described in 23 papers.[7-9,14,15,20,22,23,31-33,35,37,38,42,45,47,48,52-54,56,57] No significant differences were observed between the three types of reconstruction methods. In the analysis after excluding cases of the combined method, mastectomy flap necrosis in the autologous tissue group was higher than that in the prosthesis group with marginal significance (8.8% vs. 6.4%, p=0.069). In terms of overall necrotic complications, 1,051 cases from 15 pa pers[7,8,15,20-23,31,33,35,37,38,45,52,57] were analyzed, but no significant differences were found between the three groups. No subgroup analysis for each reconstruction method group showed any significant differences between the groups, either in the prevalence of mastectomy flap necrosis or overall necrotic complications.

Active smoking

Eighteen papers[7,8,15,18,20-22,30-32,37,38,43,45-47,52,56] representing 1,536 cases demonstrated the prevalence of necrotic complications by smoking status. The prevalence of NAC necrosis was described in 14 papers[7,8,15,18,22,30-32,38,43,45-47,56] and was significantly higher in active smokers (28.6%) than in non-active ones (6.0%) (p<0.001). In the analysis of mastectomy flap necrosis from 12 papers,[7,15,18,22,31,32,37,38,45,47,52,56] active smokers also showed a significantly higher rate of mastectomy flap necrosis than did non-active ones (16.1% vs. 5.4%, p=0.012). Overall necrotic complications depending on active smoking were computed in 672 cases found in nine papers,[7,8,15,20-22,31,38,45] and similar results were found (Table 7).

Mastectomy dissection methods

A total of 16 papers[8,9,14,15,18,32,37-39,45-47,49,51,52,56] representing 1,595 cases described the prevalence of necrotic complications depending on dissection methods, which were classified into two groups: sharp and diathermy dissection groups. Cases in which sharp dissection was mainly used and the use of electrocautery was limited only to vessel cauterization were assigned to the sharp dissection group. The prevalence of NAC necrosis in the diathermy dissection group was significantly higher than that in the sharp dissection group (20.8% vs. 7.9%, p<0.001). The prevalence of mastectomy flap necrosis

Table 6. Subgroup analysis in each reconstruction method group

Reconstruction methods	Nipple-areolar complex		Mastectomy flap		Overall	
	Necrotic complication rate (%)	p-value	Necrotic complication rate (%)	p-value	Necrotic complication rate (%)	p-value
Autologous tissue reconstruction		0.001		0.740		0.360
Pedicled flap	17.7		9.1		16.7	
Free flap	7.9		8.0		9.9	
Prosthesis reconstruction		0.319		0.947		
Tissue expander insertion	5.6		6.5		14.5	
Direct implant insertion	4.5		6.6		11.0	0.225

Table 7. Active smoking as a predictor of necrotic complications

Smoking status	Nipple-areolar complex		Mastectomy flap		Overall	
	Total cases	Necrosis cases	Total cases	Necrosis cases	Total cases	Necrosis cases
Total	1,180	85 (7.2)	868	50 (5.8)	672	95 (14.1)
Active smoker	63	18 (28.6)	31	5 (16.1)	23	13 (56.5)
Non-active smoker	1,117	67 (6.0)	837	45 (5.4)	649	82 (12.6)
p-value		<0.001		0.012		<0.001

Values are presented as number or number (%).

described in 813 cases from 12 papers[8,14,15,18,32,37,38,45-47,52,56] was also significantly higher in the diathermy dissection group than in the sharp dissection group (7.6% vs. 3.4%, p=0.011). Four papers[8,15,37,52] described overall necrotic complications depending on dissection methods, and a higher prevalence was shown in the diathermy dissection group, although it was not significant (Table 8).

Mastectomy purpose

Sixteen papers[8,15,20,30,33,36-38,42,45,46,48,49,52,53,55] representing 1,916 NSM cases described the prevalence of necrotic complications with respect to the purpose of mastectomy, including therapeutic or prophylactic purposes. The prevalence of NAC necrosis for therapeutic purposes was 9.9%, similar to that for prophylactic purposes (8.8%). By contrast, the prevalence of mastectomy flap necrosis computed from eight papers[15,33,37,38,42,46,52,53] was significantly different between the groups, and surgeries performed for therapeutic purposes showed a higher rate of complications than when performed for prophylactic purposes (5.3% vs. 1.2%, p=0.026). The prevalence of overall necrotic complications depending on mastectomy purposes was mentioned in four papers,[8,15,20,38] and there was no significant difference between the groups (Table 9).

Breast irradiation history

Ten papers[1,21,22,31,33,38,40,45,56,57] representing 771 NSM procedures were included in our review of breast irradiation. The prevalence of NAC necrosis in the cases of prior radiation was 18.8%, which was significantly higher than that in the cases of no prior irradiation (6.6%, p=0.010). However, the

Table 8. Dissection method of mastectomy as a predictor of necrotic complications

Dissection methods	Nipple-areolar complex		Mastectomy flap		Overall	
	Total cases	Necrosis cases	Total cases	Necrosis cases	Total cases	Necrosis cases
Total	1,595	151 (9.5)	813	37 (4.6)	146	14 (9.6)
Sharp dissection	1,398	110 (7.9)	588	20 (3.4)	128	12 (9.4)
Diathermy dissection	197	41 (20.8)	225	17 (7.6)	18	2 (11.1)
p-value		<0.001		0.011		0.815

Values are presented as number or number (%).

Table 9. Association between purpose of mastectomy and necrotic complications

Purpose of mastectomy	Nipple-areolar complex		Mastectomy flap		Overall	
	Total cases	Necrosis cases	Total cases	Necrosis cases	Total cases	Necrosis cases
Total	1,751	171 (9.8)	437	16 (3.7)	132	17 (12.9)
Therapeutic purpose	1,502	149 (9.9)	266	14 (5.3)	71	10 (14.1)
Prophylactic purpose	249	22 (8.8)	171	2 (1.2)	61	7 (11.5)
p-value		0.593		0.026		0.655

Values are presented as number or number (%).

Table 10. Prior radiation history as a predictor of necrotic complications

Preoperative radiotherapy	Nipple-areolar complex		Mastectomy flap		Overall	
	Total cases	Necrosis cases	Total cases	Necrosis cases	Total cases	Necrosis cases
Total	547	40 (7.3)	417	23 (5.5)	483	70 (14.5)
With prior radiation history	32	6 (18.8)	11	0 (0.0)	26	10 (38.5)
Without prior radiation history	515	34 (6.6)	406	23 (5.7)	457	60 (13.1)
p-value		0.010		0.417		<0.001

Values are presented as number or number (%).

prevalence of mastectomy flap necrosis was not significantly different between the two groups. In terms of overall necrotic complications, five papers[21,22,31,33,57] were analyzed, and the prior irradiation group had a significantly higher rate of overall necrotic complications than did the group with no prior irradiation (38.5% vs. 13.1%, p<0.001) (Table 10).

DISCUSSION

This systematic review documented a computed prevalence of overall necrotic complications of 13.7%, including 7.5% for the prevalence of NAC necrosis and 7.8% for that of mastectomy flap necrosis. Although this study included partial necrosis events that could be healed with conservative management, the fact that some sort of necrotic complication developed in every 7.5 NSM case is noteworthy and indicates a need to reduce this rate. In addition, some patients and operation-related factors were significantly related to the development of necrotic complications after NSM procedures. This finding suggests that the avoidance or reduction of risk factors could reduce the risk of necrotic complications.

The type of mastectomy incision was significantly related to the development of necrotic complications, especially NAC necrosis, which is consistent with the findings of several other studies.[33,41] Noteworthy is that the cases where incisions involving the NAC regions showed a significantly higher rate of NAC necrosis than those not involving these regions across all incision subtypes. Previous studies have provided similar findings that incisions involving more than a third[20] or 30% of the NAC[21] are significantly related to the development of NAC necrosis. In NSM, the perfusion of the mastectomy flap relies only on the subdermal plexus from adjacent vessels.[58] The perfusion of NAC regions placed furthest away from the vascular source becomes most vulnerable to ischemia. Therefore, it can be assumed that placement of the incision along the areolar margin or crossing the NAC can seriously interrupt blood supply through the subdermal plexus to NAC regions, eventually increasing the risk of necrosis.

The rate of mastectomy flap necrosis was not significantly associated with whether incisions involved the NAC region or not. As a matter of fact, although the rate of mastectomy flap necrosis was significantly different among the eight different incision groups (p=0.004), the significant difference did not remain in the further analysis after excluding 11 cases of transareolar incisions (p=0.481). Considering that mastectomy flap after NSM is a random flap perfused by subdermal plexus, the length and size of incision that can break down subdermal plexus, rather than location of incision, may be more important to perfusion of mastectomy flap. Actually, periareolar incision allows only a small size of skin break down, leading to a relatively low rate of necrosis (2.0%). However, a periareolar incision with radial extension, which elongated the total length of incision, showed the second largest rate of mastectomy flap necrosis (8.9%). Thus, if possible, shorter incision may be recommendable for reducing the risk of mastectomy flap necrosis.

The literature is not conclusive about whether reconstruction methods are actually associated with the development of necrotic complications and which reconstructive methods are better for reducing those risks. Some studies have demonstrated a significant relationship between reconstruction methods and necrotic complications, reporting a significantly lower prevalence of necrotic complications with autologous reconstruction.[19,22] In contrast, another study demonstrated that autologous tissue reconstruction was an independent risk factor for necrotic complications.[21] In the present review, cases of autologous tissue reconstruction showed higher prevalence of all types of necrotic complications. Generally, autologous tissue reconstruction methods are more often chosen for the reconstruction of large ptotic breasts or in obese patients.[59] Although some studies have reported successful outcomes and low complication rates after performing NSM for large ptotic breasts,[43] it is generally considered that necrotic complications can develop more frequently in large and ptotic breasts.[46,60,61] In addition, several studies have demonstrated a relationship between obesity and complications such as wound problems after breast surgery.[62-64] Although potential detrimental effects associated with those characteristics were not evaluated in this review because of a lack of data, they might have contributed to the high prevalence of necrotic complications in autologous tissue reconstruction. In this regard, further prospective well-designed studies would be helpful to increase the validity of these findings.

Interestingly, cases of pedicled flaps showed a significantly higher prevalence of NAC necrosis than that of free flaps. In general, breast reconstruction procedures using pedicled

flaps require some additional undermining beneath the breast envelope to acquire a window for flap transposition. It is likely that this wider dissection may result in some disturbance of the perfusion in the mastectomy flap, leading to a high prevalence of necrosis.

The relationship between active smoking and the development of necrotic complications has been reported in several studies,[7,20,21] which is consistent with the results of the present study. The adverse effect of smoking on micro- and macrocirculation is well known.[4,65,66] The mastectomy flap after NSM in active smokers may be more vulnerable to ischemia than that in non-active smokers. Given that NSM showed higher prevalence of necrotic complications than other mastectomy procedures, patients should cease smoking before surgery to reduce the risk of necrotic complications.

In the present review, diathermy dissection showed almost twice the prevalence of NAC necrosis and mastectomy flap necrosis in comparison to sharp dissection. Electrocautery can easily cause collateral thermal damage to dermal vessels and adjacent tissue, disturbing the mastectomy flap perfusion.[21] To reduce the risk of necrotic complications, sharp dissection with the limited use of electrocautery would be beneficial, as also recommended by previous research.[21,43]

The debate over the relationship between the purpose of mastectomy and the development of necrotic complications continues. Although therapeutic NSM showed higher prevalence for all types of necrotic complications, the differences between the groups were relatively small and were significant only in mastectomy flap necrosis. Actually, for some therapeutic purposes, taking additional tissue for a safety margin clearance would be necessary depending on the size and location of the tumor, and therefore higher rates of necrosis would be expected for the therapeutic group. Unexpectedly, however, no significant difference was observed in this review, which is consistent with the findings of previous studies.[8,46] This lack of significance suggests that therapeutic NSM is also safe, even from necrotic complications, as long as it is performed in selected patients such as those with small tumors or tumors far removed from the breast skin.

Previous studies of potential effects of prior irradiation history on necrotic complications have produced mixed results,[1,21] and a similar phenomenon was observed in this review. It is well known that wound healing can be impaired in irradiated tissue because of the inhibition of fibroblast function[67] and increase in microvascular disease,[68] which can increase the rate of necrotic complications. In this review, the prevalence of NAC necrosis and overall necrotic complications were significantly higher in irradiated cases, while that of mastectomy flap necrosis was not. This mixed result may be explained by a lack of concrete data on prior irradiation, including the period of time between radiation and subsequent NSM and the dose of radiation, and the small number of cases included in this analysis. Future research should consider a larger cohort for clearer conclusions.

Despite the strengths of this review including a large number of cases and analysis of multiple risk factors for necrotic complications, there are some limitations. A majority of the studies included were retrospective and observational, and it was difficult to exclude all confounding biases. Most studies did not present specific data for each subgroup, such as reconstruction methods used in each incision group. Therefore, a subgroup or multiple logistic regression analysis for evaluating independent effects of each risk factor could not be conducted. The effects of other potential risk factors for necrotic complications, including the thickness of mastectomy skin flap and different levels of experience among surgeons, could not be analyzed because of a lack of data. Additionally, it may not be straight forward to assess publication bias by statistical tests in this design of pooled analysis. In spite of our thorough efforts for including all relevant studies using two large databases, slight possibility of publication bias could not be excluded totally in the present review.

CONCLUSIONS

The development of necrotic complications in NSM patients, including NAC necrosis and mastectomy flap necrosis, may be influenced by patient characteristics like smoking status or prior irradiation history and operation-related factors such as the type of mastectomy incision, the reconstruction method, the dissection method, and the purpose of the mastectomy. Although randomized prospective studies or their systematic reviews are required for definitive conclusions, the results of the present review provide helpful insights for patient counseling and preoperative planning to minimize the risk of necrotic complications in NSM followed by immediate breast reconstruction.

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