

# Influence of complications following immediate breast reconstruction on breast cancer recurrence rates

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**Background:** The rate of immediate breast reconstruction is rising. Postoperative infections are more frequent in patients who undergo reconstruction. The inflammatory response to a postoperative infection can increase the risk of tumour recurrence in other forms of cancer through the release of proinflammatory mediators. The aim of this study was to assess the relationship between complications and breast cancer recurrence in patients undergoing immediate reconstruction.

**Methods:** This was a review of a prospectively maintained database of all patients who had immediate breast reconstruction between 2004 and 2009 at Galway University Hospital, a tertiary breast cancer referral centre serving the west of Ireland. All patients had a minimum follow-up of 5 years. Outcomes assessed included the development of wound complications and breast cancer recurrence. The data were evaluated by univariable and multivariable Cox regression analysis.

**Results:** A total of 229 patients who underwent immediate reconstruction were identified. The overall 5-year recurrence-free survival rate was 85.6 per cent. Fifty-three patients (23.1 per cent) had wound complications, of whom 44 (19.2 per cent) developed a wound infection. There was a significantly greater risk of developing systemic recurrence among patients who experienced a postoperative wound complication compared with those without a complication (hazard ratio 4.94, 95 per cent c.i. 2.72 to 8.95;  $P < 0.001$ ). This remained significant after adjusting for Nottingham Prognostic Index group in the multivariable analysis. The 5-year recurrence-free survival rate for patients who had a wound complication was 64 per cent, compared with 89.2 per cent in patients without a complication ( $P < 0.001$ ).

**Conclusion:** This study has demonstrated that wound complications after immediate breast reconstructive surgery have significant implications for patients with breast cancer. Strategies are required to minimize the risk of postoperative wound complications in patients with breast cancer undergoing immediate reconstruction.

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## Introduction

Breast cancer is the most common cancer in women worldwide, with 1.7 million women diagnosed each year<sup>1</sup>. Over recent years, immediate breast reconstruction has been incorporated into treatment strategies for breast cancer. The rates of reconstruction are increasing internationally; for example, in the UK the proportion of women having immediate reconstruction increased from approximately 11 per cent in 2006 to 21 per cent in 2009<sup>2,3</sup>. Concerns continue to exist surrounding the oncological safety of breast reconstructive methods. However, recent data have demonstrated no survival disadvantage

for patients undergoing either immediate or delayed reconstruction<sup>4-6</sup>.

The incidence of surgical-site infection varies between types of surgery for breast cancer. For breast cancer surgery in general, it ranges between 0.8 and 26 per cent<sup>7</sup>. However, patients who undergo immediate breast reconstruction have a higher incidence of surgical-site complications than those who have mastectomy alone<sup>8</sup>. Wound complications associated with breast cancer surgery can result in delays to adjuvant therapy, increased costs and failed reconstructions.

There is strong evidence of survival implications for patients who develop postoperative complications,

**Table 1** Patient demographics, tumour characteristics and treatment received

	All patients (n = 229)	No recurrence (n = 185)	Recurrence (n = 44)
<b>Patient demographics</b>			
Age at diagnosis (years)*	48 (26–82)	47 (26–70)	48 (27–82)
Smoker	80 (34.9)	63 (34.1)	17 (39)
Diabetic	4 (1.7)	4 (2.2)	0 (0)
<b>Tumour characteristics</b>			
Ductal	180 (78.6)	149 (80.5)	31 (70)
Lobular	41 (17.9)	30 (16.2)	11 (25)
Mixed	8 (3.5)	6 (3.2)	2 (5)
Node-positive	134 (58.5)	98 (53.0)	36 (82)
<b>Treatment</b>			
Neoadjuvant chemotherapy	44 (19.2)	30 (16.2)	14 (32)
Adjuvant chemotherapy	148 (64.6)	120 (64.9)	28 (64)
Hormone therapy	183 (79.9)	151 (81.6)	32 (73)
Radiotherapy	133 (58.1)	100 (54.1)	33 (75)

Values in parentheses are percentages unless indicated otherwise; \*values are mean (range).

including wound infection, in other forms of cancer<sup>9</sup>. In colonic cancer, for example, anastomotic leaks, with resulting peritoneal infection, affect survival<sup>10</sup>. The mechanism responsible for this association is thought to relate to the release of local and systemic inflammatory mediators, which interact with residual tumour cells locally and with dormant distant metastatic deposits. These stimulate tumour growth leading to adverse outcomes. Similar evidence in breast cancer is limited; however, one study<sup>11</sup> has suggested that delayed wound healing is associated with an increased rate of systemic recurrence after primary breast cancer surgery. In addition, patients who experience fever in the postoperative period are also more likely to develop breast cancer recurrence<sup>12</sup>.

To date, the association between immediate breast reconstruction-related complications and survival has not been assessed. The hypothesis for the present study was that complications, including infection, would have survival implications for patients with breast cancer owing to the effects of the inflammatory response, as previously reported for other cancers. Therefore, the aim of this study was to assess the relationship between postoperative complications and breast cancer recurrence in patients undergoing immediate breast reconstructive surgery.

## Methods

The study was undertaken in Galway University Hospital, a tertiary breast cancer referral centre serving the west

of Ireland. The number of patients diagnosed with breast cancer annually in the unit increased from 130 in 2004 to 249 in 2008<sup>13</sup>. Patients who underwent immediate breast reconstructive surgery for breast cancer between 2004 and 2009 were identified from theatre registers for inclusion in the present study. All patients were followed up annually in the surveillance breast clinic and those included in the study had a minimum of 5 years' follow-up. Patients who died during the study were identified by chart review. Exclusion criteria were: metastatic disease at diagnosis, moving away from the referral catchment area and unavailability of case notes. Ethical approval for the study was granted by the local ethics committee.

## Data collection

A single abstractor reviewed all patients' paper-based medical notes retrospectively, and retrieved information from electronic pathology and radiology databases. Data gathered included: patient demographics, co-morbidities, surgery performed, histology results, chemoradiotherapy received, complication details and information on tumour recurrence. Patients were designated as smokers if they were active smokers at the time of surgery. Diabetics included patients with either type 1 or type 2 diabetes at the time of surgery. The Nottingham Prognostic Index (NPI) was calculated using the formula:  $0.2 \times (\text{tumour size in cm}) + (\text{tumour grade}) + (\text{lymph node status})$ . The resulting NPI value was categorized into prognostic groups: good, intermediate and poor<sup>14</sup>. Oestrogen receptor and progesterone receptor status was established by routine immunohistochemical techniques. The histological grade was based on the Allred scoring system<sup>15</sup>. Human epidermal growth factor receptor 2 status was established using standard immunohistochemical protocols. Equivocal results were further analysed by means of fluorescence *in situ* hybridization.

## Definition of complications

Complications considered for the present analysis were those that developed within 30 days after surgery at the surgical incision site following immediate breast reconstruction. These included wound infection, haematoma formation, flap dehiscence or skin necrosis. The incidence of a wound complication was recorded in the patient's medical notes during the hospital stay or at the clinic review. A wound infection was defined by the presence of cellulitis, purulent discharge or abscess formation at the surgical site on clinical examination. All patients who developed an infection received antibiotics.

**Table 2** Factors associated with breast cancer recurrence

	All patients (n = 229)	No recurrence (n = 185)	Recurrence (n = 44)	P‡
Complication				< 0.001
Yes	53 (23.1)	29 (15.7)	24 (55)	
No	176 (76.9)	156 (84.3)	20 (45)	
Infection				< 0.001
Yes	44 (19.2)	20 (10.8)	24 (55)	
No	185 (80.8)	165 (89.2)	20 (45)	
Haematoma				0.107
Yes	7 (3.1)	4 (2.2)	3 (7)	
No	222 (96.9)	181 (97.8)	41 (93)	
Hormone receptor status				0.307
Positive	189 (82.5)	155 (83.8)	34 (77)	
Negative	40 (17.5)	30 (16.2)	10 (23)	
HER2 status				0.816
Positive	44 (19.2)	35 (18.9)	9 (20)	
Negative	185 (80.8)	150 (81.1)	35 (80)	
Triple-negative				0.153
Yes	19 (7.9)	13 (6.5)	6 (14)	
No	210 (92.1)	172 (93.5)	38 (86)	
Node status				< 0.001
Positive	134 (58.5)	98 (53.0)	36 (82)	
Negative	95 (41.5)	87 (47.0)	8 (18)	
NPI status				< 0.001
Good	30 (13.1)	28 (15.1)	2 (5)	
Intermediate	119 (52.0)	105 (56.8)	14 (32)	
Poor	80 (34.9)	52 (28.1)	28 (64)	
Lymphovascular invasion				0.002
Yes	80 (34.9)	56 (30.3)	24 (55)	
No	149 (65.1)	129 (69.7)	20 (45)	
Chemotherapy*				0.020
Yes	192 (83.8)	150 (81.1)	42 (95)	
No	37 (16.2)	35 (8.9)	2 (5)	
Radiotherapy†				0.011
Yes	133 (58.1)	100 (54.1)	33 (75)	
No	96 (41.9)	85 (45.9)	11 (25)	

Values in parentheses are percentages. \*Both neoadjuvant and adjuvant. †No women received radiotherapy before surgery. HER, human epidermal growth factor receptor; NPI, Nottingham Prognostic Index. ‡ $\chi^2$  test.

## Statistical analysis

The association between categorical factors of interest and disease recurrence was analysed using Pearson's  $\chi^2$  test of association. Continuous variables were analysed by means of independent *t* test.  $P < 0.050$  was considered statistically significant. Factors that proved significant on  $\chi^2$  analysis were then included in multivariable Cox regression analysis. The extent of disease also has implications for breast cancer recurrence. As this may be a confounding factor, the multivariable analysis was adjusted for NPI groups. Recurrence-free survival was calculated using the Kaplan–Meier method. Endpoints analysed included breast cancer recurrence and death from breast cancer during follow-up. All analyses were performed using SPSS® version 21 (IBM, Armonk, New York, USA).

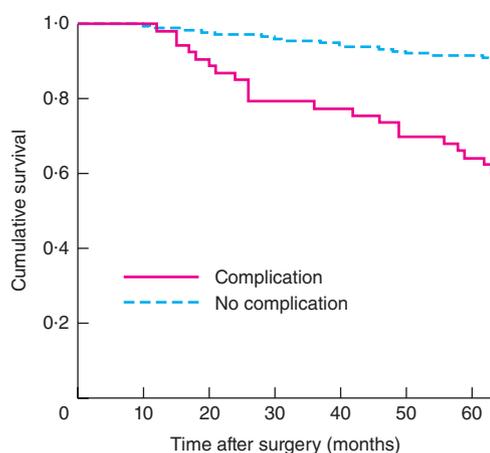
## Results

A total of 268 patients who underwent immediate breast reconstruction for breast cancer between 2004 and 2009 were identified. Patients with lack of follow-up (27), inaccessible case notes (5) or metastatic disease at diagnosis (7) were excluded. Therefore, 229 patients who had immediate breast reconstruction were included in the study. Patient demographics, tumour characteristics and other treatments received are shown in *Table 1*. Seventy-one patients (31.0 per cent) had previously undergone breast-conserving surgery before definitive resection with mastectomy and reconstruction. No patient had radiotherapy before breast reconstruction. Ninety-four patients (41.0 per cent) had a sentinel node biopsy and 135 (59.0 per cent) underwent axillary node clearance (ANC). Patients were followed up for a

**Table 3** Univariable and multivariable Cox regression analysis of factors associated with breast cancer recurrence

	No. of patients	Univariable analysis		Multivariable analysis	
		Hazard ratio	<i>P</i>	Hazard ratio	<i>P</i>
Wound complication			< 0.001		< 0.001
Yes	53	4.94 (2.72, 8.95)		4.61 (2.47, 8.61)	
No	176	1.00 (reference)		1.00 (reference)	
Infection			< 0.001		< 0.001
Yes	44	6.64 (3.66, 12.04)		6.15 (3.33, 11.33)	
No	185	1.00 (reference)		1.00 (reference)	
NPI status			< 0.001		0.003
Good	30	1.00 (reference)		1.00 (reference)	
Intermediate	119	1.81 (0.41, 7.94)		1.05 (0.22, 5.03)	
Poor	80	6.09 (1.45, 25.57)		3.59 (0.73, 17.71)	
Lymphovascular invasion			0.002		0.223
Yes	80	2.57 (1.42, 4.66)		1.48 (0.79, 2.79)	
No	149	1.00 (reference)		1.00 (reference)	
Chemotherapy			0.042		0.243
Yes	192	4.35 (1.05, 17.98)		2.49 (0.54, 11.51)	
No	37	1.00 (reference)		1.00 (reference)	
Radiotherapy			0.018		0.493
Yes	133	2.28 (1.15, 4.52)		0.75 (0.34, 1.69)	
No	96	1.00 (reference)		1.00 (reference)	

Values in parentheses are 95 per cent c.i. NPI, Nottingham Prognostic Index.



No. at risk	0	10	20	30	40	50	60
Complication	53	53	47	42	41	37	34
No complication	176	175	172	169	165	162	157

**Fig. 1** Kaplan–Meier analysis of systemic recurrence-free survival in patients with and without complications.  $P < 0.001$  (log rank test)

minimum of 5 years from the date of diagnosis (median 80 months).

### Type of reconstruction

The method of reconstruction varied according surgeon preference, preoperative breast size and patient preference. Latissimus dorsi (LD) flap reconstruction with

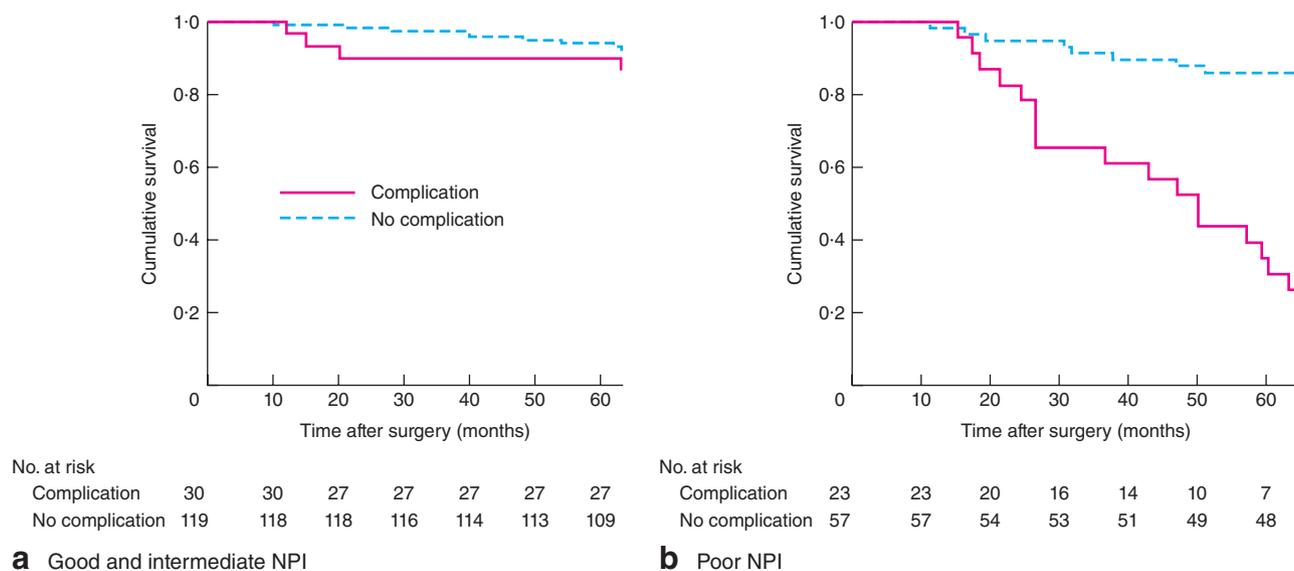
implant insertion was the reconstruction type used in 101 women (44.1 per cent) and 45 patients (19.7 per cent) had implant-only reconstruction. Reconstruction with LD flaps alone was used in 66 patients (28.8 per cent). Thirteen (5.7 per cent) underwent reconstruction with a transverse rectus abdominis muscle (TRAM) flap and four (1.7 per cent) had reconstruction with a deep inferior epigastric perforator (DIEP) flap.

### Complication rates

Overall, 53 patients (23.1 per cent) had wound complications, of whom 44 had a wound infection. Other complications included wound dehiscence (7), skin necrosis (6) and haematoma formation (7). Of the 53 wound complications, 21 involved LD flap and implant reconstruction, 13 LD flap only, 12 implant only, six TRAM flap and one DIEP flap reconstruction. There was no association between the use of an implant and development of a post-operative infection ( $P = 0.539$ ). Thirty-six patients with a wound infection underwent ANC. Twenty-four patients who had complications were smokers, and smoking was associated with developing a wound infection ( $P = 0.048$ ). However, neoadjuvant chemotherapy, diabetes and ANC were not ( $P = 0.847$ ,  $P = 0.335$  and  $P = 0.140$  respectively).

### Breast cancer recurrence

Forty-four patients (19.2 per cent) were diagnosed with breast cancer recurrence (local and/or systemic) by 31



**Fig. 2** Kaplan–Meier analysis of systemic recurrence-free survival in patients with and without complications according to Nottingham Prognostic Index (NPI): **a** good and intermediate NPI and **b** poor NPI. **a**  $P = 0.063$ , **b**  $P = 0.001$  (log rank test)

December 2014, and 29 women (12.7 per cent) had died from disease recurrence. Of these 44 patients, six had local recurrence alone and 30 had systemic recurrence. A further eight patients had both local and distant recurrence. In 33 patients the recurrence developed during the first 5 years of follow-up. The overall 5-year systemic recurrence-free survival rate was 85.6 per cent. Twenty-four patients with breast cancer recurrence had experienced a wound complication in the postoperative period. Sixteen of these patients had distant recurrence alone, two had locoregional recurrence alone and four patients developed both. There was no association between the method of reconstruction and the development of breast cancer recurrence ( $P = 0.845$ ). There was also no association between the time to recurrence for patients with and without a postoperative complication (24 versus 20 months;  $P = 0.799$ ).

### Factors associated with recurrence

On  $\chi^2$  analysis, factors significantly associated with breast cancer recurrence were wound complication, wound infection, node status and lymphovascular invasion (Table 2). Postoperative haematoma and tumour subtype were not associated with breast cancer recurrence. In addition, there was no association between patient age or smoking status and breast cancer recurrence or overall survival. Factors significantly associated with disease recurrence were further analysed using multivariable Cox

regression (Table 3). The relationship between wound complications, particularly wound infection, and breast cancer recurrence remained significant on multivariable analysis even after adjustment for NPI. Furthermore, the multivariable analysis showed that NPI status was independently and significantly associated with breast cancer recurrence.

### Recurrence-free survival

The occurrence of a wound complication in the postoperative period had a significant effect on recurrence-free survival. The 5-year recurrence-free survival rate was 64 and 89.2 per cent respectively in patients with and without a wound complication (Fig. 1). Analysis according to NPI (good/intermediate or poor) showed that postoperative complications affected recurrence-free survival in both groups, with particularly strong implications for patients with a poor NPI value ( $P = 0.001$ ) (Fig. 2).

### Discussion

Factors associated with tumour recurrence are complex. There is increasing evidence to suggest that the systemic inflammatory consequences of postoperative complications may have a secondary deleterious influence on survival by increasing the risk of cancer recurrence. The association between wound complications and numerous types of cancer has been well documented. It has been demonstrated,

both *in vitro* and *in vivo*, that anastomotic leakage, with resulting peritoneal infection, can increase the risk of tumour recurrence in colorectal cancer<sup>16,17</sup>. It has also been suggested that infection in the postoperative period leads to worse outcome in head and neck cancer<sup>18</sup>. Recently, this association has also been suggested for gastric cancer<sup>19</sup>. For breast cancer, however, the association between complications and cancer recurrence after immediate breast reconstructive surgery had yet to be confirmed<sup>11</sup>.

Tissue factors associated with wound healing can stimulate tumour growth. New cancers can develop in wounds after a long period of time<sup>20</sup>. Growth factors released in wounds are mitogenic to tumour cells, which leads to accelerated tumour growth<sup>21,22</sup>. These growth factors can be released into the bloodstream, and stimulate the proliferation of metastases distant from the surgical incision site<sup>23,24</sup>. Further to this, it has been demonstrated that the inflammatory response and postoperative angiogenesis, as well as tumour growth, are proportional to the severity of operative trauma<sup>25</sup>. Infection results in a greater inflammatory response in the process of incision-site healing, and animal models have shown that postoperative infection increases angiogenesis and tumour recurrence after operative excision of cancer<sup>16</sup>. The extent of surgical trauma is also thought to influence the rate of tumour recurrence<sup>26</sup>. Methods of reconstruction vary in their extent of surgical trauma. However, in the present study no correlation was found between the method of reconstruction and breast cancer recurrence; however, the numbers were limited.

Postoperative infection is not uncommon after breast reconstructive surgery<sup>27</sup>, affecting 19.2 per cent of the patients studied here. This results in increased morbidity, a longer hospital stay and ultimately increased costs<sup>28</sup>. Furthermore, the present study demonstrated a statistically significant relationship between wound infection after immediate breast reconstructive surgery and the development of systemic recurrent breast cancer. The 5-year recurrence-free survival rate in this cohort was reduced by 25 per cent in those who experienced a surgical-site complication. This association with a complication was seen for both local and distant recurrence, with a particularly strong association with distant disease.

The number of patients undergoing breast reconstructive surgery is increasing. Patients should be informed about all possibilities for breast reconstruction, including the advantages and disadvantages of each technique. Overall, whether or not a woman chooses breast reconstructive surgery has not been demonstrated to affect the risk of breast cancer recurrence<sup>29</sup>. However, the incidence of surgical-site infection can vary with different methods

of reconstruction<sup>30,31</sup>. Patients should take into account the potential association between complications and disease recurrence when choosing the method of breast reconstruction.

The present study also showed that the risk of infection was greater in patients who smoked. The association between smoking and postoperative breast infection has also been demonstrated in other studies<sup>32</sup>. Other factors that have been shown previously to be associated with wound infection include obesity, neoadjuvant chemotherapy and ANC<sup>33</sup>, but none of these factors was significantly associated with a complication in the present study.

The limitations of the present study include its retrospective nature and small cohort. Different techniques of breast reconstruction lead to different amounts of surgical trauma that may have further implications for survival. The numbers in each category of breast reconstruction were relatively small here, which may account for the lack of significant association between the reconstructive method and recurrence. In addition, there may be a group of patients who are primed immunologically to develop a wound infection and recurrence regardless of whether they have a breast reconstruction; the causative link to the breast reconstruction is not established.

However, as wound infection following breast reconstruction appears to result in an increase in breast cancer recurrence rates, every effort should be taken to minimize this risk. Factors associated with wound complications can be identified, and methods should be put in place to reduce these potential risks<sup>34</sup>. In one study<sup>33</sup> risk-reducing protocols, with measures including showering with chlorhexidine the day before surgery, immersing implants in antibiotic solutions and irrigation of the insertion site with antibiotic solution before implant insertion, reduced the rate of infection by 55 per cent. Continuing antibiotic prophylaxis into the postoperative period may also be beneficial in reducing wound infection<sup>35</sup>. Other studies have suggested that obese patients or those who continue to smoke have increased rates of wound complications, and reconstructive surgery should be avoided in these patients<sup>36</sup>.

Wound complications after immediate breast reconstructive surgery have survival implications. Therefore, strategies are required to minimize the risk of postoperative wound complications in patients undergoing reconstruction after breast cancer surgery.

## Disclosure

The authors declare no conflict of interest.

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### Editor's comments

These findings add to the increasing evidence of the deleterious effect of a postoperative infection on the long-term outcome for patients with cancer. Although well studied for many other cancers, few data are available on breast cancer, especially in the setting of breast reconstruction. The association between postoperative infection and adverse cancer outcome appears clear, but the cellular link between these remains elusive. Perhaps postoperative infection is an effective growth medium for residual cancer cells, or maybe sepsis affects tumour immunity in a deleterious way. As shown here, patient-related risk factors such as smoking and obesity should be considered before planning breast reconstruction, and patients advised accordingly. More effort should be put into establishing a solid evidence base on how best to prevent postoperative infection.

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