A comprehensive approach for quality assessment of breast cancer care

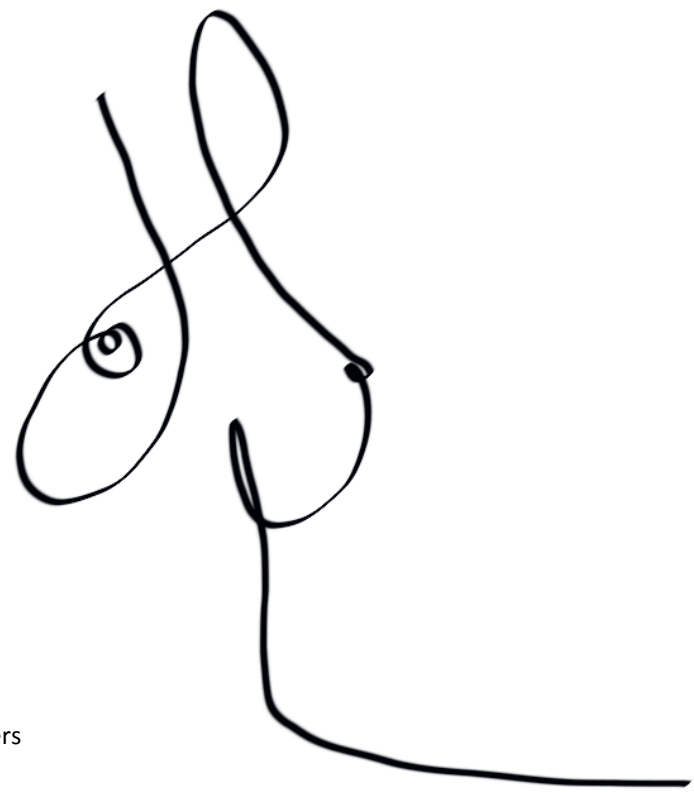
Heeg, E.

Part II

Continuity of the adjuvant chemotherapy pathway

Chapter 4

Nationwide population-based study of the impact of postmastectomy immediate breast reconstruction on the timing of adjuvant chemotherapy



Erik Heeg
Johan X. Harmeling
Babette E. Becherer
Perla J. Marang-van de Mheen
Marie-Jeanne T.F.D. Vrancken Peeters
Marc A.M. Mureau

British Journal of Surgery 2019;106(12):1640-1648

Abstract

Background

Initiation of adjuvant chemotherapy within 6–12 weeks after mastectomy is recommended by guidelines. The aim of this population-based study was to investigate whether immediate breast reconstruction (IBR) after mastectomy reduces the likelihood of timely initiation of adjuvant chemotherapy.

Methods

All patients with breast cancer who had undergone mastectomy and adjuvant chemotherapy between 2012 and 2016 in the Netherlands were identified. Time from surgery to adjuvant chemotherapy was categorized as within 6 weeks or after more than 6 weeks, within 9 weeks or after more than 9 weeks, and within 12 weeks or after more than 12 weeks. The impact of IBR on the initiation of adjuvant chemotherapy for these three scenarios was estimated using propensity score matching to adjust for treatment by indication bias.

Results

A total of 6,300 patients had undergone primary mastectomy and adjuvant chemotherapy, of whom 1,700 (27.0%) had received IBR. Multivariable analysis revealed that IBR reduced the likelihood of receiving adjuvant chemotherapy within 6 weeks (odds ratio (OR) 0.76, 95T%-CI 0.66-0.87) and 9 weeks (0.69, 95%-CI 0.54-0.87), but not within 12 weeks (OR 0.75, 95%-CI 0.48-1.17). Following propensity score matching, IBR only reduced the likelihood of receiving adjuvant chemotherapy within 6 weeks (OR 0.95, 95%-CI 0.90-0.99), but not within 9 weeks (OR 0·97, 95%-CI 0.95-1.00) or 12 weeks (OR 1.00, 95%-CI 0.99-1.01).

Conclusion

Postmastectomy IBR marginally reduced the likelihood of receiving adjuvant chemotherapy within 6 weeks, but not within 9 or 12 weeks. Thus, IBR is not contraindicated in patients who need adjuvant chemotherapy after mastectomy

Introduction

Breast cancer is the most commonly diagnosed malignant cancer among women.[1] Despite advancements in diagnostics and systemic treatment, up to one-third of patients with breast cancer undergo mastectomy as the first surgical treatment to achieve local control.[2] Adjuvant systemic treatment, including chemotherapy, reduces the risk of distant recurrence and breast cancer mortality.[3] In the Netherlands, 6 weeks is the maximum time limit aimed for between surgery and initiation of adjuvant chemotherapy, as recommended by the European Society for Medical Oncology (ESMO)[4] and the Netherlands Society for Plastic Surgery.[5,6]

Several studies have reported that delayed initiation of adjuvant chemotherapy is associated with lower overall and recurrence-free survival.[7-12] The recommended acceptable maximum delay, however, varies from 7 to 12 weeks. There still is no international consensus on the definition of an unacceptable delay, but all guidelines advocate that initiation of adjuvant chemotherapy should not be delayed unnecessarily, as this may have a negative impact on survival, specifically in patients at higher risk of recurrence.[9,10,12]

The addition of immediate breast reconstruction (IBR) to mastectomy could result in preoperative delay owing to more complex logistic coordination of the operation. After surgery, a delay could be the result of longer recovery, as IBR may increase the risk of postoperative complications, even though reports on the risk of adverse events are contradicting.[13-16]

In the past decade, an increasing number of women have undergone IBR after mastectomy.[2,17,18] IBR is generally associated with good aesthetic results and less negative psychological impact on the patient, as it involves fewer operations and hospital admissions compared with breast reconstruction at a later time.[19-21] Owing to the lack of consensus on timing of adjuvant chemotherapy, physicians remain cautious in recommending IBR when adjuvant chemotherapy is part of the preoperative treatment plan.[22]

Most previous studies on the possible delaying impact of post mastectomy IBR have been single-centre studies with weak methodology and no adjustment for treatment by indication bias.[16,23,24] A systematic review from 2015 concluded that IBR does not delay time from surgery to adjuvant chemotherapy to a clinically relevant extent,[24] although the included studies showed strongly contradictory results. Moreover, a cut-off point of 12 weeks to initiation of adjuvant treatment was used, whereas current European guidelines recommend 6 weeks.[4] Furthermore, it seems likely that there may be an underlying reason why some patients have IBR and others do not, giving rise to treatment by indication bias when comparing the outcomes of these two groups. The

aim of the present nationwide population-based study was to investigate the extent to which post mastectomy IBR reduces the likelihood of timely initiation of adjuvant chemotherapy compared with mastectomy alone, while also adjusting for confounding by indication.

Methods

Prospectively collected data from the NABON Breast Cancer Audit (NBCA) database were used. The NBCA was started in 2011 and is an initiative from the National Breast Cancer Organization Netherlands (NABON), the Netherlands Comprehensive Cancer Organization and the Dutch Institute for Clinical Auditing. The NBCA collects anonymized data on clinicopathological characteristics, diagnostics and treatment modalities in a database from all hospitals in the Netherlands. It includes all patients diagnosed with ductal carcinoma in situ (DCIS) or invasive breast cancer treated surgically since 2012. The NBCA aims to monitor the quality of breast cancer care and to provide feedback to participating hospitals to stimulate and facilitate quality improvement.[25] No formal consent is required for this type of study from an ethics committee in the Netherlands according to Central Committee on Research involving Human Subjects.

Patient population

All women diagnosed with invasive breast cancer between 2012 and 2016 who had undergone primary mastectomy with or without IBR followed by adjuvant chemotherapy were identified from the NBCA database. IBR was defined as a reconstruction performed by a plastic surgeon on the same day as the mastectomy. Women who had received systemic neoadjuvant treatment, had undergone lumpectomy as initial surgery or had a re-excision were excluded from the analysis. Patients who had received another adjuvant therapy before the initiation of adjuvant chemotherapy, and those with a missing date of operation or adjuvant chemotherapy were also excluded.

Outcomes

The primary outcome was whether the patient received adjuvant chemotherapy within a specific time interval after surgery. Time to adjuvant chemotherapy was analysed with three different cut-off values: within 6 weeks or after more than 6 weeks, within 9 weeks or after more than 9 weeks, and within 12 weeks or after more than 12 weeks. These cut-offs were chosen based on the currently recommended starting point

according to Dutch and ESMO guidelines,[4,5] and on previous literature demonstrating that a clinical impact is found when adjuvant chemotherapy is started later than 7-12 weeks, indicating the importance of initiating adjuvant chemotherapy at least within this time period.[7-12]

Confounders

Potential confounders included in analyses were year of diagnosis, age, WHO performance status,[26] presence of DCIS, histological type, receptor status, tumour stage according to the seventh edition of AJCC,[27] sentinel node biopsy, axillary lymph node dissection (ALND), hospital transfer between site for surgery and that for adjuvant chemotherapy, and annual number of patients operated on for breast cancer at the hospital (hospital volume). Data regarding reconstruction at a later time, rather than IBR, are not registered in the NBCA and could therefore not be included.

Statistical analysis

Statistical differences for all possible confounders between women who had mastectomy alone and those who had mastectomy plus IBR were determined using χ^2tests. All tests were two-sided, and $p<0.050$ was considered statistically significant. Multivariable logistic regression analysis was used to determine the likelihood that women who had undergone IBR received adjuvant chemotherapy within6, 9 and 12 weeks, when adjusted for the confounders. There may, however, be an underlying reason why patient shave IBR, so that not all women are equally likely to receive IBR, for example because of a different type of tumour or age of the patient, introducing a treatment by indication bias. Thus, propensity score matching (PSM) was performed, including all available patient and tumour characteristics to adjust for treatment by indication bias. Use of PSM ensures that patients from both cohorts are matched and have the same likelihood of receiving IBR, given certain patient and tumour characteristics. For each pair, one patient did and one did not undergo IBR; this is essential to estimate the true treatment effect on an out-come in observational studies.[28,29] Statistical analyses were performed with SPSS® version 24 (IBM, Armonk, New York, USA).

Results

In the selected time interval, 6,300 women were diagnosed with invasive breast cancer and met the eligibility criteria. Of these, 4,600 patients (73.0%) underwent mastectomy

alone and 1,700 patients (27.0%) had postmastectomy IBR. Of the women who had IBR, 91.2% had received an implant-based reconstruction (including tissue expanders).The proportion of women who had postmastectomy IBR decreased with patient age and increased over time (Figure 4.1).Patients who underwent IBR were younger at diagnosis, more often had a WHO status of 0, or were diagnosed with no special type of histology, DCIS component and tumour stage I than women who had mastectomy alone (Table 4.1). There was no difference in receptor status or differentiation grade between the two groups. Of women who had postmastectomy IBR, the proportions that underwent sentinel node biopsy, transferred hospital between surgery and adjuvant chemotherapy, or were treated in a hospital with surgical volume exceeding 250 patients annually were also higher compared with those of women who had mastectomy alone. However, the proportion that had ALND was lower in women who underwent postmastectomy IBR (Table 4.1).

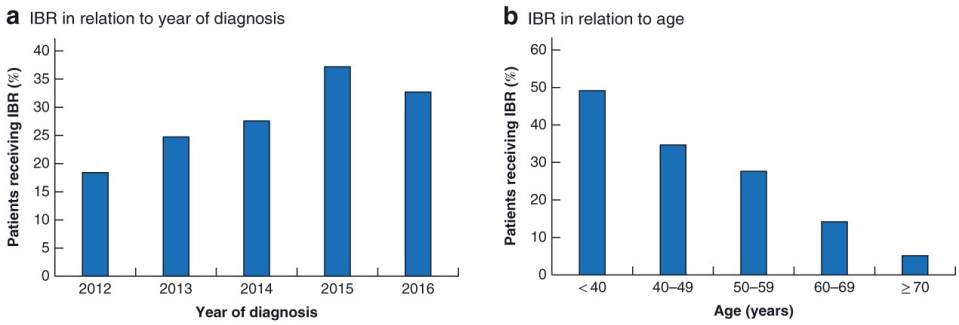


Figure 4.1. Proportion of patients having immediate breast reconstruction in relation to (a) year of diagnosis and (b) age.

Time to adjuvant chemotherapy

The median (i.q.r.) time from surgery to adjuvant chemotherapy in women who had postmastectomy IBR was 36 (29–47) days, compared with 34 (28–44) days in those who had mastectomy alone (Table 4.2). Adjuvant chemotherapy was initiated within 6 weeks in more than two-thirds of patients, and the vast majority received adjuvant chemotherapy within 9 and 12 weeks. The total proportion of patients who received adjuvant chemotherapy within 6, 9 and 12 weeks did not differ over time (2012–2016: p=0.282, p=0.128 and p=0.052 respectively) (Figure 4.2).

Table 4.1. Baseline characteristics of patients who had mastectomy alone or immediate breast reconstruction after mastectomy and received adjuvant chemotherapy.

	Mastectomy alone (n=4,600)	IBR after mastectomy (n=1,700)	p-value*
Year of diagnosis			<0.001
2012	1,282 (27.9)	290 (17.1)	
2013	1,113 (23.4)	365 (21.5)	
2014	987 (21.5)	378 (22.2)	
2015	690 (15.0)	411 (24.2)	
2016	528 (11.5)	256 (15.1)	
Age (years)			<0.001
<40	304 (6.6)	295 (17.4)	
40-49	1,081 (23.5)	578 (34.0)	
50-59	1,506 (32.7)	578 (34.0)	
60-69	1,409 (30.6)	233 (13.7)	
≥70	300 (6.5)	16 (0.9)	
WHO performance status			0.001
0	4,126 (89.7)	1572 (92.5)	
1	450 (9.8)	116 (6.8)	
≥2	24 (0.5)	12 (0.7)	
Histology			<0.001
No special type	3,580 (77.8)	1414 (83.2)	
Lobular	731 (15.9)	168 (9.9)	
Both/other	289 (6.3)	118 (6.9)	
DCIS component			<0.001
No	2,241 (48.7)	623 (36.6)	
Yes	2,359 (51.3)	1077 (63.4)	
Receptor status			0.071
Triple negative	695 (15.1)	223 (13.1)	
HER2-neu+	1,053 (22.9)	405 (23.8)	
HR + and HER2 -	2,727 (59.3)	1038 (61.1)	
Unknown	125 (2.7)	34 (2.0)	
Differentiation grade			0.987
Well	431 (9.4)	161 (9.5)	
Moderate	2,136 (46.4)	791 (46.5)	
Poor	2,033 (44.2)	748 (44.0)	
Tumour stage			<0.001
I	1,036 (22.5)	735 (43.2)	
IIa	1,542 (33.5)	632 (37.2)	
IIb	856 (18.6)	200 (11.8)	
III	1,128 (24.5)	128 (7.5)	
IV	38 (0.8)	5 (0.3)	
Sentinel node biopsy			<0.001
No	1,439 (31.3)	131 (7.7)	
Yes	3,161 (68.7)	1569 (92.3)	
ALND			<0.001
No	2,303 (50.1)	1265 (74.4)	
Yes	2,297 (49.9)	435 (25.6)	
Hospital transfer			0.030
No	4,466 (97.1)	1632 (96.0)	
Yes	134 (2.9)	68 (4.0)	
Hospital volume of surgery (no. of patients)			<0.001
1-99	223 (4.8)	29 (1.7)	
100-149	1,036 (22.5)	263 (15.5)	
150-199	978 (21.3)	253 (14.9)	
200-249	478 (10.4)	236 (13.9)	
≥250	1,885 (41.0)	919 (54.1)	

Values in parentheses are percentages. IBR, immediate breast reconstruction; DCIS, ductal carcinoma in situ; HR+, hormone receptor-positive; ALND, axillary lymph node dissection. *χ^2 test.

Table 4.1. (continued)

	Mastectomy alone (n=4,600)	IBR after mastectomy (n=1,700)	p-value*
Hospital volume of surgery (no. of patients)			<0.001
1-99	223 (4.8)	29 (1.7)	
100-149	1,036 (22.5)	263 (15.5)	
150-199	978 (21.3)	253 (14.9)	
200-249	478 (10.4)	236 (13.9)	
≥250	1,885 (41.0)	919 (54.1)	

Values in parentheses are percentages. IBR, immediate breast reconstruction; DCIS, ductal carcinoma in situ; HR+, hormone receptor-positive; ALND, axillary lymph node dissection. *χ^2 test.

Table 4.2. Time from surgery to adjuvant chemotherapy, and proportion of patients receiving adjuvant chemotherapy within 6, 9 and 12 weeks.

	Mastectomy alone (n=4,600)	IBR after mastectomy (n=1,700)
Time from surgery to adjuvant chemotherapy (days)*	34 (28 to 44)	36 (29 to 47)
No. of patients receiving adjuvant chemotherapy		
Within 6 weeks	3,297 (71.7)	1,145 (67.4)
Within 9 weeks	4,304 (93.6)	1,564 (92.0)
Within 12 weeks	4,509 (98.0)	1,669 (98.2)

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). IBR, immediate breast reconstruction.

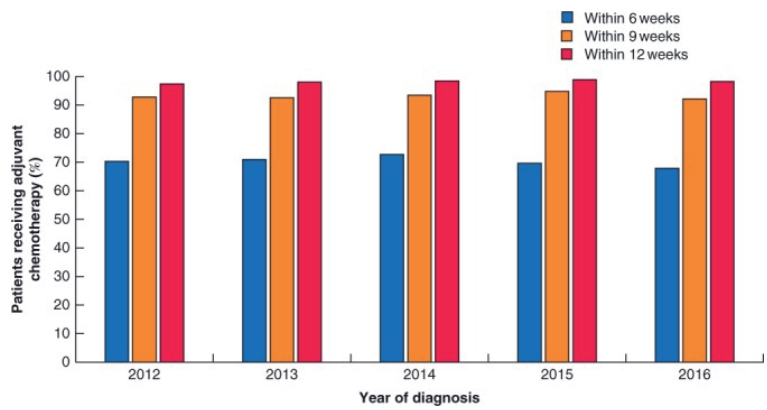


Figure 4.2. Proportion of women receiving adjuvant chemotherapy within 6, 9 and 12 weeks in relation to year of diagnosis.

Unmatched multivariable analyses

Multivariable analysis revealed that patients who had undergone IBR were less likely than those having mastectomy alone to receive adjuvant chemotherapy within6 weeks (odds ratio (OR) 0.76, 95%-CI 0.66-0.87; p<0.001) or 9 weeks (OR 0.69, 95%-CI 0.54-0.87; p=0.002) of surgery (Table 4.3). However, IBR had no association with receiving adjuvant chemotherapy within 12 weeks (OR 0.75, 95%-CI 0.48-1.17; p=0.205).

Table 4.3. Univariable and multivariable analyses without propensity score matching of characteristics associated with time to adjuvant chemotherapy within 6, 9 and 12 weeks.

	No. of patients (n=6,300)*	Time to adjuvant chemotherapy					
		≤6 weeks		≤9 weeks		≤12 weeks	
		OR (univariable)	OR (multivariable)	OR (univariable)	OR (multivariable)	OR (univariable)	OR (multivariable)
IBR after mastectomy							
No	4,600 (73.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	1,700 (27.0)	0.82 (0.72-0.92)	0.76 (0.66-0.87)	0.79 (0.64-0.98)	0.69 (0.54-0.87)	1.09 (0·72-1·64)	0.75 (0.48-1.17)
Year of diagnosis							
2012	1,572 (25.0)	1.00 (reference)	-	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2013	1,478 (23.5)	1.03 (0.88-1.21)	-	0.96 (0.73-1.26)	0.95 (0.72-1.25)	1.28 (0.80-2.05)	1.30 (0.81-2.08)
2014	1,365 (21.7)	1.12 (0.95-1.31)	-	1.11 (0.83-1.48)	1.05 (0.78-1.42)	1.53 (0.92-2.55)	1.50 (0.90-2.50)
2015	1,101 (17.5)	0.99 (0.83-1.17)	-	1.43 (1.03-1.99)	1.47 (1.04-2.07)	2.49 (1.31-4.75)	2.44 (1.26-4.70)
2016	784 (12.4)	0.91 (0.76-1.09)	-	0.94 (0.68-1.31)	0.85 (0.60-1.20)	1.63 (0.87-3.05)	1.52 (0.80-2.89)
Age (years)							
<40	599 (9.5)	1.13 (0.92-1.39)	1.17 (0.94-1.46)	1.17 (0.79-1.72)	1.17 (0.78-1.75)	1.23 (0.56-2.66)	1.28 (0.59-2.79)
40-49	1,659 (26.3)	1.18 (1.02-1.37)	1.20 (1.03-1.40)	1.24 (0.94-1.63)	1.21 (0.92-1.60)	0.93 (0.57-1.54)	0.94 (0.57-1.55)
50-59	2,084 (33.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
60-69	1,642 (26.1)	0.78 (0.68-0.93)	0.68 (0.59-0.79)	0.72 (0.56-0.91)	0.64 (0.49-0.82)	0.60 (0.38-0.95)	0.57 (0.36-0.89)
≥70	316 (5.0)	0.71 (0.55-0.91)	0.51 (0.39-0.67)	0.82 (0.53-1.28)	0.62 (0.39-0.99)	0.73 (0.32-1.67)	0.68 (0.30-1.56)
WHO performance status							
0	5,698 (90.4)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
1	566 (9.0)	0.62 (0.52-0.74)	0.62 (0.51-0.75)	0.63 (0.47-0.85)	0.63 (0.46-0.85)	0.75 (0.43-1.31)	-
≥2	36 (0.6)	0.44 (0.23-0.86)	0.51 (0.25-1.02)	0.35 (0.14-0.84)	0.39 (0.15-0.98)	0.32 (0.08-1.36)	-
Histology							
No special type	4,994 (79.3)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Lobular	899 (14.3)	0.96 (0.82-1.12)	-	1.04 (0.78-1.38)	-	1.67 (0.89-3.12)	-
Both/other	407 (6.5)	0.86 (0.69-1.06)	-	0.80 (0.55-1.15)	-	0.82 (0.42-1.58)	-
DCIS component							
No	2,864 (45.5)	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Yes	3,436 (54.5)	0.99 (0.89-1.11)	-	0.90 (0.74-1.10)	-	0.89 (0.62-1.28)	-
Receptor status							
Triple negative	918 (14.6)	1.34 (1.14-1.58)	1.12 (1.03-1.22)	1.33 (0.99-1.80)	0.96 (0.69-1.35)	0.79 (0.49-1.29)	-
HER2-neu+	1,458 (23.1)	1.34 (1.17-1.53)	1.17 (1.09-1.26)	1.43 (1.11-1.85)	1.19 (0.91-1.57)	1.12 (0.71-1.77)	-
HR + and HER2 -	3,765 (59.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
Unknown	159 (2.5)	1.50 (1.03-2.17)	1.94 (1.70-2.22)	1.39 (0.70-2.74)	1.51 (0.75-3.06)	1.01 (0.32-3.25)	-

Table 4.3 (continued)

	No. of patients (n=6,300)*	Time to adjuvant chemotherapy					
		≤6 weeks		≤9 weeks		≤12 weeks	
		OR (univariable)	OR (multivariable)	OR (univariable)	OR (multivariable)	OR (univariable)	OR (multivariable)
Receptor status							
Triple negative	918 (14.6)	1.34 (1.14-1.58)	1.12 (1.03-1.22)	1.33 (0.99-1.80)	0.96 (0.69-1.35)	0.79 (0.49-1.29)	-
HER2-neu+	1,458 (23.1)	1.34 (1.17-1.53)	1.17 (1.09-1.26)	1.43 (1.11-1.85)	1.19 (0.91-1.57)	1.12 (0.71-1.77)	-
HR + and HER2 -	3,765 (59.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
Unknown	159 (2.5)	1.50 (1.03-2.17)	1.94 (1.70-2.22)	1.39 (0.70-2.74)	1.51 (0.75-3.06)	1.01 (0.32-3.25)	-
Differentiation grade							
Well	592 (9.4)	0.70 (0·58-0.84)	0.90 (0.73-1.11)	0.55 (0.40-0.75)	0.68 (0.48-0.96)	0.61 (0.35-1.05)	-
Moderate	2,927 (46.5)	0.83 (0·74-0.93)	0.94 (0.85-1.11)	0.71 (0.57-0.88)	0.81 (0.64-1.03)	1.05 (0.72-1.55)	-
Poor	2,781 (44.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
Tumour stage							
I	1,771 (28.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
IIa	2,174 (34.5)	1.08 (0.94-1.24)	1.44 (1.24-1.68)	1.12 (0.87-1.45)	1.51 (1.14-2.00)	1.38 (0.87-2.20)	-
IIb	1,056 (16.8)	0.72 (0.61-0.84)	1.30 (1.06-1.60)	0.73 (0.55-0.97)	1.34 (0.94-1.90)	0.99 (0.58-1.66)	-
III	1,256 (19.9)	1.11 (0.94-1.30)	1.72 (1.37-2.15)	0.90 (0.67-1.19)	1.43 (0.98-2.09)	1.03 (0.63-1.70)	-
IV	43 (0.7)	0.52 (0.28-0.95)	0.65 (0.34-1.25)	2.97 (0.41-21.78)	3.76 (0.50-28.18)	-	-
Sentinel node biopsy							
No	1,570 (24.9)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
Yes	4,730 (75.1)	0.51 (0.44-0.58)	0.23 (0.19-0.27)	0.59 (0.46-0.77)	0.33 (0.24-0.45)	0.85 (0.56-1.31)	-
ALND							
No	3,568 (56.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	2,732 (43.4)	0.57 (0.51-0.63)	0.23 (0.19-0.27)	0.53 (0.44-0.65)	0.30 (0.23-0.39)	0.56 (0.39-0.81)	0.58 (0.40-0.85)
Hospital transfer							
No	6,098 (96.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-	Ref	-
Yes	202 (3.2)	0.55 (0.42-0.73)	0.48 (0.36-0.66)	0.75 (0.45-1.22)	-	0.98 (0.36-2.67)	-
Hospital volume of surgery (no. of patients)							
1-99	252 (4.0)	0.91 (0.67-1.23)	0.94 (0.68-1.30)	1.37 (0.70-2.70)	1.40 (0.70-2.79)	1.37 (0.40-4.65)	-
100-149	1,299 (20.6)	0.88 (0.74-1.04)	0.87 (0.72-1.04)	0.70 (0.51-0.97)	0.71 (0.51-0.99)	0.70 (0.40-1.24)	-
150-199	1,231 (19.5)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	-
200-249	714 (11.3)	0.96 (0.78-1.20)	0.61 (0.76-1.18)	0.68 (0.47-0.98)	0.69 (0.47-1.00)	0.60 (0.32-1.14)	-
≥250	2,804 (44.5)	0.76 (0.66-0.89(	0.75 (0.66-0.87)	0.72 (0.54-0.96)	0.76 (0.57-1.02)	0.91 (0.54-1.54)	-

Values in parentheses are 95 per cent confidence intervals unless indicated otherwise; *values are number (per cent). †Between surgery and adjuvant chemotherapy. IBR, immediate breast reconstruction; DCIS, ductal carcinoma in situ; HR+, hormone receptor-positive; ALND, axillary lymph node dissection.

Although not the focus of this study, analyses of predictive confounders demonstrated that, amongst other factors, patients who had a sentinel node biopsy or ALND were less likely to receive adjuvant chemotherapy within6 and 9 weeks, as well as within 12 weeks for ALND (Table 4.3).

Matched comparison of the two groups

Following PSM of patients with an equal likelihood of receiving IBR based on patient and tumour characteristics, women who had IBR were still less likely to receive adjuvant chemotherapy within 6 weeks (OR 0.95, 95%-CI 0.90-0.99; p=0.035), but not within 9 weeks (OR 0.97, 95%-CI 0.95-1.00; p=0.050) or 12 weeks (OR 1.00, 95%-CI 0.99-1.01; p=0.894).

Discussion

This large population-based study, analysing patients from all hospitals treating breast cancer in the Nether-lands, found that, compared with mastectomy alone, IBR after mastectomy reduced the likelihood of receiving adjuvant chemotherapy within 6 weeks of surgery, as recommended by Dutch and European guidelines,[4-6] but not within 9 or 12 weeks. This suggests that postmastectomy IBR is not necessarily contraindicated inpatients who need adjuvant chemotherapy, because in general IBR does not delay its initiation to a clinically relevant extent.

Previous studies on the impact of IBR on time to adjuvant chemotherapy reported a large variation in time to adjuvant chemotherapy, ranging from 21 to 80 days for those who had mastectomy alone and from 31 to 97 days for patients who received IBR,[30-34] with reported differences between these cohorts of 14–27 days.[24] However, this large variation may have been the result of the small single-centre studies, weak methodology and biases, such as the lack of adjusting for treatment by indication bias. The findings of the present study are not in line with the recently published results from a large multicentre study of Jabo and colleagues in the USA,[35] which suggested that IBR delays time from diagnosis to treatment but not from surgery to adjuvant chemotherapy. This discrepancy may be explained by differences in the statistical approach, as these authors used time as a continuous value, compared with a categorical value in the present study. Moreover, Jabo and co-workers compared time from surgery to adjuvant chemotherapy with non-parametric tests with-out adjusting for confounders,[35] because the latter was not the main focus of their study. It is noteworthy that their reported time from surgery to adjuvant chemotherapy was

considerably longer than that found in the present study, both for patients who had mastectomy alone (40 versus34 days respectively) and those who underwent IBR (42 versus 36 days).[35]

The present study suggests that patients who had sentinel node biopsy or ALND were less likely to receive adjuvant chemotherapy within the predefined cut-off points, confirming the previously reported delaying impact of ALND.[34] In the present study, postoperative complications may have occurred more frequently in patients who under-went ALND combined with postmastectomy IBR, and thereby potentially could have delayed chemotherapy.

Postoperative complications, such as axillary seroma, are common after mastectomy combined with ALND.[36-38] The present study suggests that the associated risk of postoperative complications after sentinel node biopsy and ALND may increase the likelihood of delay. The risk of seroma formation can be reduced by minimizing dead space through quilting sutures or an axillary drain.[39] Complications, and strategies to prevent their occurrence, are not collected in the NBCA database and could therefore not be studied as a potential explanatory factor.

The present study has shown that patients diagnosed with triple-negative breast cancer, human epidermal growth factor receptor 2-positive breast cancer and higher stage disease were more likely to receive adjuvant chemotherapy within 6 weeks. It is reassuring that these tumour characteristics were predictive of timely initiation of adjuvant chemotherapy, as previous studies have shown that delay is of particular relevance in women with these more aggressive types of cancer.[7,10]

It was expected that the impact of IBR on time to adjuvant chemotherapy would change after adjusting for treatment by indication bias, as the present results and a previous Dutch study both showed that patients undergoing IBR differ in many characteristics from those undergoing mastectomy alone.[40]

The majority of patients in the present study underwent a two-stage implant IBR with a tissue expander. This type of IBR is the most common approach in patients eligible for postoperative radiotherapy in most industrialized countries.[41] Despite autologous reconstructions being used increasingly in the last decade,[18] the proportions of different types of IBR were comparable between the predefined cut-off points (data not shown). Nonetheless, the number of women who had IBR using autologous tissue with or without a prosthesis was low (less than 8 per cent), reflecting practice in the past. Therefore, a future study with more patients receiving IBR using autologous tissue could investigate whether this will affect the results.

Patients who changed hospital after surgery were less likely to receive adjuvant chemotherapy within 6 weeks, but not within 9 or 12 weeks. Although this concerned

only 3.2% of all patients, the association corroborates the theory that hospital transfer delays treatment, as shown by previous studies.[34,42,43]

The present results are inconclusive regarding the association between hospital volume and time to adjuvant chemotherapy. On the one hand, higher volume reduced the likelihood of receiving adjuvant chemotherapy within6 weeks, but on the other hand, lower volume reduced the likelihood of receiving adjuvant chemotherapy within9 weeks. A recent study by Schreuder and co-workers demonstrated that hospital volume only partly explains the use of IBR in the Netherlands.[44] Presumably, other hospital related factors such as theatre availability or number of medical specialists have more impact on time to adjuvant chemotherapy after IBR than just hospital volume.

The number of patients aged 70 years or above seems lower in the present study than in previous studies. This might be explained by the fact that adjuvant chemotherapy is used less frequently in these older women in the Netherlands.[45] Furthermore, postmastectomy IBR is used less frequently in this patient group in the Netherlands.[40]

There were several limitations to the present study. First, it was observational, using PSM to adjust for confounding as best as possible. However, matching may be improved by adding other factors potentially associated with delay of adjuvant chemotherapy or the type of surgery (such as radiotherapy, BMI, travel distance). Unfortunately, it was not possible to include these factors as these are not registered in the NBCA database. Insurance coverage was probably not important in the present study, in contrast to studies from the USA, because all Dutch patients are obliged to have basic insurance coverage, providing equal access to breast cancer treatment and breast reconstruction. Second, treatment delay or choice for a specific type of surgery can also be the result of patient preference, such as seeking a second opinion or personal scheduling limitations. Third, this study focused on the time between surgery and initiation of adjuvant chemotherapy, and was therefore not able to assess the potential delaying impact of IBR in the preoperative phase owing to organizational factors such as planning.

The results of the present study in a population-based setting, which were adjusted for confounding and treatment by indication bias, add to the evidence in current literature that IBR is not contraindicated in patients who require a mastectomy and adjuvant chemotherapy, because it does not generally delay time to adjuvant chemotherapy to a clinically relevant extent.

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.
2. DICA. Jaarrapportage 2017. Dutch Institute for Clinical Auditing. http://dica.nl/jaarrapportage-2017. Published 2018. Accessed August 1th, 2018.
3. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. *BMC Med.* 2015;13:195.
4. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v8-30.
5. Mureau MAM, Group BRGW. Dutch breast reconstruction guideline. *J Plast Reconstr Aesthet Surg.* 2018;71(3):290-304.
6. Surgery NSfP. Dutch Guideline Breast Reconstruction. © 2018 Nederlandse Vereniging voor Plastische Chirurgie https://richtlijnendatabase.nl/en/richtlijn/breast_reconstruction/breast_reconstruction_after_mastectomy.html. Published 2018. Accessed September 1th 2018.
7. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, Giordano SH. Delayed Initiation of Adjuvant Chemotherapy Among Patients With Breast Cancer. *JAMA Oncol.* 2016;2(3):322-9.
8. Cold S, Düring M, Ewertz M, Knoop A, Møller S. Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG). *Br J Cancer.* 2005;93(6):627-32.
9. Farolfi A, Scarpi E, Rocca A, et al. Time to initiation of adjuvant chemotherapy in patients with rapidly proliferating early breast cancer. *Eur J Cancer.* 2015;51(14):1874-81.
10. Gagliato DeM, Gonzalez-Angulo AM, Lei X, et al. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. *J Clin Oncol.* 2014;32(8):735-44.
11. Lohrisch C, Paltiel C, Gelmon K, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol.* 2006;24(30):4888-94.
12. Zhan QH, Fu JQ, Fu FM, Zhang J, Wang C. Survival and time to initiation of adjuvant chemotherapy among breast cancer patients: a systematic review and meta-analysis. *Oncotarget.* 2018;9(2):2739-51.
13. Cohen O, Lam G, Choi M, Ceradini D, Karp N. Risk Factors for Delays in Adjuvant Chemotherapy following Immediate Breast Reconstruction. *Plast Reconstr Surg.* 2018;142(2):299-305.
14. El-Sabawi B, Sosin M, Carey JN, Nahabedian MY, Patel KM. Breast reconstruction and adjuvant therapy: A systematic review of surgical outcomes. *J Surg Oncol.* 2015;112(5):458-64.
15. Tanaka S, Hayek G, Jayapratap P, et al. The Impact of Chemotherapy on Complications Associated with Mastectomy and Immediate Autologous Tissue Reconstruction. *Am Surg.* 2016;82(8):713-7.
16. Zhong T, Hofer SO, McCready DR, Jacks LM, Cook FE, Baxter N. A comparison of surgical complications between immediate breast reconstruction and mastectomy: the impact on delivery of chemotherapy--an analysis of 391 procedures. *Ann Surg Oncol.* 2012;19(2):560-6.
17. Liederbach E, Sisco M, Wang C, et al. Wait times for breast surgical operations, 2003-2011: a report from the National Cancer Data Base. *Ann Surg Oncol.* 2015;22(3):899-907.
18. Albornoz CR, Bach PB, Mehrara BJ, et al. A paradigm shift in U.S. Breast reconstruction: increasing implant rates. *Plast Reconstr Surg.* 2013;131(1):15-23.
19. Gerber B, Marx M, Untch M, Faridi A. Breast Reconstruction Following Cancer Treatment. *Dtsch Arztebl Int.* 2015;112(35-36):593-600.
20. Agrawal A, Sibbering DM, Courtney CA. Skin sparing mastectomy and immediate breast reconstruction: a review. *Eur J Surg Oncol.* 2013;39(4):320-8.
21. Jagsi R, Li Y, Morrow M, et al. Patient-reported Quality of Life and Satisfaction With Cosmetic Outcomes After Breast Conservation and Mastectomy With and Without Reconstruction: Results of a Survey of Breast Cancer Survivors. *Ann Surg.* 2015;261(6):1198-206.
22. Wanzel KR, Brown MH, Anastakis DJ, Regehr G. Reconstructive breast surgery: referring physician knowledge and learning needs. *Plast Reconstr Surg.* 2002;110(6):1441-50.
23. Eriksen C, Frisell J, Wickman M, Lidbrink E, Krawiec K, Sandelin K. Immediate reconstruction with implants in women with invasive breast cancer does not affect oncological safety in a matched cohort study. *Breast Cancer Res Treat.* 2011;127(2):439-46.

24. Xavier Harmeling J, Kouwenberg CA, Bijlard E, Burger KN, Jager A, Mureau MA. The effect of immediate breast reconstruction on the timing of adjuvant chemotherapy: a systematic review. *Breast Cancer Res Treat.* 2015;153(2):241-51.
25. van Bommel AC, Spronk PE, Vrancken Peeters MT, et al. Clinical auditing as an instrument for quality improvement in breast cancer care in the Netherlands: The national NABON Breast Cancer Audit. *J Surg Oncol.* 2017;115(3):243-9.
26. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-55.
27. Stephen Edge DRB, Carolyn C. Compton, April G. Fritz, Frederick Greene, Andrew Trotti. *AJCC Cancer Staging Handbook.* 7 ed: Springer-Verlag New York; 2010.
28. Groenwold RH. [Propensity scores in observational research]. *Ned Tijdschr Geneeskd.* 2013;157(29):A6179.
29. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Stat Med.* 2004;23(19):2937-60.
30. Alderman AK, Collins ED, Schott A, et al. The impact of breast reconstruction on the delivery of chemotherapy. *Cancer.* 2010;116(7):1791-800.
31. Allweis TM, Boisvert ME, Otero SE, Perry DJ, Dubin NH, Priebat DA. Immediate reconstruction after mastectomy for breast cancer does not prolong the time to starting adjuvant chemotherapy. *Am J Surg.* 2002;183(3):218-21.
32. Henry LR, Morris LL, Downs R, Schwarz RE. The impact of immediate breast reconstruction after mastectomy on time to first adjuvant treatment in women with breast cancer in a community setting. *Am J Surg.* 2017;213(3):534-8.
33. Losk K, Vaz-Luis I, Camuso K, et al. Factors Associated With Delays in Chemotherapy Initiation Among Patients With Breast Cancer at a Comprehensive Cancer Center. *J Natl Compr Canc Netw.* 2016;14(12): 1519-26.
34. Vandergrift JL, Niland JC, Theriault RL, et al. Time to adjuvant chemotherapy for breast cancer in National Comprehensive Cancer Network institutions. *J Natl Cancer Inst.* 2013;105(2):104-12.
35. Jabo B, Lin AC, Aljehani MA, et al. Impact of Breast Reconstruction on Time to Definitive Surgical Treatment, Adjuvant Therapy, and Breast Cancer Outcomes. *Ann Surg Oncol.* 2018;25(10):3096-105.
36. Kell MR, Burke JP, Barry M, Morrow M. Outcome of axillary staging in early breast cancer: a meta-analysis. *Breast Cancer Res Treat.* 2010;120(2):441-7.
37. Kootstra J, Hoekstra-Weebers JE, Rietman H, et al. Quality of life after sentinel lymph node biopsy or axillary lymph node dissection in stage I/II breast cancer patients: a prospective longitudinal study. *Ann Surg Oncol.* 2008;15(9):2533-41.
38. Madsen RJ, Esmonde NO, Ramsey KL, Hansen JE. Axillary Lymph Node Dissection Is a Risk Factor for Major Complications After Immediate Breast Reconstruction. *Ann Plast Surg.* 2016;77(5):513-6.
39. 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(10):829-35.
40. van Bommel AC, Mureau MA, Schreuder K, et al. Large variation between hospitals in immediate breast reconstruction rates after mastectomy for breast cancer in the Netherlands. *J Plast Reconstr Aesthet Surg.* 2017;70(2):215-21.
41. Kronowitz SJ. Current status of implant-based breast reconstruction in patients receiving postmastectomy radiation therapy. *Plast Reconstr Surg.* 2012;130(4):513e-23e.
42. Heeg E, Schreuder K, Spronk PER, et al. Hospital transfer after a breast cancer diagnosis: A population-based study in the Netherlands of the extent, predictive characteristics and its impact on time to treatment. *Eur J Surg Oncol.* 2019;45(4):560-6.
43. Bleicher RJ, Chang C, Wang CE, et al. Treatment delays from transfers of care and their impact on breast cancer quality measures. *Breast Cancer Res Treat.* 2019;173(3):603-17.
44. Schreuder K, van Bommel ACM, de Ligt KM, et al. Hospital organizational factors affect the use of immediate breast reconstruction after mastectomy for breast cancer in the Netherlands. *Breast.* 2017;34:96-102.
45. Poodt IGM, Spronk PER, Vugts G, et al. Trends on Axillary Surgery in Nondistant Metastatic Breast Cancer Patients Treated Between 2011 and 2015: A Dutch Population-based Study in the ACOSOG-Z0011 and AMAROS Era. *Ann Surg.* 2018;268(6):1084-90.