Breast Cancer: Current Research

Chan et al., Breast Can Curr Res 2017, 2:1

Research Article OMICS International

Immediate Breast Reconstruction does not Delay Adjuvant Chemotherapy nor affect Clinical Outcome

Chan MYP, Ho SYM, Thambiah M, Seah DW, Chen JC, Lu QS, Cheong EC and Tan EY*

Department of General Surgery, Tan Tock Seng Hospital, Singapore

***Corresponding author:** Tan EY, Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore, Tel: +65 6357 7807; E-mail: Ern_Yu_Tan@ttsh.com.sg

Received date: March 07, 2017; **Accepted date:** March 15, 2017; **Published date:** March 20, 2017

Abstract

Background: Post-operative complications are more frequent after immediate breast reconstruction and there are concerns that it adversely affects clinical outcome.

Objectives: We reviewed the rate of early and late complications after immediate breast reconstruction and evaluated their impact on adjuvant treatments and outcome.

Methods: Retrospective review was performed of 146 women who underwent immediate breast reconstruction after mastectomy for breast cancer from 1st January 2001 to 31st December 2010.

Results: Median patient age was 46 years and all women had no major co-morbidities. More than half the women had early-stage cancers. Reconstruction was performed with a pedicled transrectus abdominis myocutaneous flap in 109 patients, a latissimus dorsi flap in 29, a free deep inferior epigastric perforator flap in 4 and implants were inserted in 4 patients. Two patients suffered a cerebrovascular accident and one a cardiac event but all recovered fully. Early post-operative wound complications within 30 days of surgery occurred in 25 patients (17%). All, except one, were managed conservatively. Late complications occurred in 18 patients and 7 patients underwent further surgery, which most often involved abdominal hernia repair. Complications were more frequent in older patients, diabetics and those with implants inserted ($P<0.01$, $P=0.05$, $P=0.01$ respectively). Adjuvant treatments proceeded as planned in most cases, with wound complications delaying initiation of chemotherapy for longer than 3 months in only 3 patients. We observed no correlation between post-operative complications and disease recurrence, whether local or distant ($P=0.39$, $P=1.00$ respectively) and reconstruction together with cancer surgery did not increase the likelihood of disease recurrence ($P=0.08$).

Conclusions: Post-operative complications after immediate breast reconstruction did not delay planned adjuvant treatments nor did it increase the risk of disease recurrence. This study affirms the oncological safety of immediate reconstruction following mastectomy for breast cancer.

Keywords: Breast reconstruction; Adjuvant chemotherapy; Disease recurrence

Introduction

It has become routine for most tertiary breast cancer units to offer women the option of breast reconstruction. At our unit, breast reconstruction is offered after a mastectomy and is done in the same setting. Some women request for reconstruction only later, after the mastectomy has already been done, and reconstruction is then delayed until adjuvant treatments are completed. Breast conserving surgery (BCS) is an option for women with small tumors without any contraindications to post-operative radiation, but many women at our unit still opt for a mastectomy [1]. Many women would rather compromise on the post-operative cosmesis than undergo radiation and some perceive mastectomy as a 'more complete cure'. Breast reconstruction hence becomes a means by which these women can preserve their body image even after a mastectomy.

It is often said that Asian women are less concerned with body image issues and so are less likely to opt for reconstruction. This may not necessarily be true. In the past, there were fewer options for reconstruction and many women deemed it unaffordable and felt it frivolous to discuss body image issues when discussing cancer treatment. Many women therefore accepted that the loss of the breast was an inevitable, or even necessary, consequence of treatment. Even surgeons seldom offered reconstruction unless in very young women. This has changed with greater subspecialisation, growing affluence and changing patient expectations. Women are now more educated and better informed and have become more forthcoming about femininity issues and the desire to preserve their body image. It is not uncommon for the women themselves to initiate the discussion about breast reconstruction, having learnt of this option from friends or the media. Breast surgeons, too, now routinely offer the option of reconstruction, reassured by studies that have consistently shown that immediate breast reconstruction is not associated with serious complications [2] and importantly, that reconstruction does not compromise oncologic outcomes [3]. However, post-operative complications are indeed more frequent after breast reconstruction than with mastectomy or BCS and recent reports of a link between post-operative complications and disease recurrence has once again renewed concerns about the

oncologic safety of reconstruction, which essentially is a cosmetic procedure that is not essential to breast cancer management [4].

In this study, we reviewed our experience with immediate breast reconstruction in women undergoing mastectomy for breast cancer over a period of 10 years, from 2001 to 2010; all patients were followed-up for at least 5 years. Specifically, post-operative recovery and the incidence of complications were evaluated to determine whether these had any impact on subsequent adjuvant treatments and clinical outcome.

Materials and Methods

Retrospective review was performed of 146 women who were diagnosed with either non-metastatic invasive breast cancer or ductal carcinoma-in-situ (DCIS) and who underwent immediate breast reconstruction at our institute from 1st January 2001 to 31st December 2010. None of the women in this study had undergone a prophylactic mastectomy, and flaps done primarily for chest wall cover rather than for cosmetic reconstruction were excluded. This study has ethics committee approval (2011/00409). The option of reconstruction was discussed if the woman was deemed a suitable candidate, and included those without serious co-morbidities, such as ischaemic heart disease with poor residual cardiac function, severe respiratory disease, morbid obesity (BMI>40) and who were not on long term anti-coagulation therapy; age per se was not a determining factor as long as the patient desired reconstruction and was surgically fit to receive one. Women keen to consider reconstruction were referred to a Plastic surgeon who would discuss the various options available and potential complications. To facilitate the reconstruction, either a skin sparing or nipple-areolar complex (NAC)-sparing mastectomy was done. In a skin-sparing mastectomy, the breast was removed through an incision made around the NAC while preserving the skin overlying the breast and the infra-mammary fold; the NAC was removed together with the breast. Preservation of the NAC was considered in instances where there was no clinical or radiological evidence of NAC involvement and when the tumour was away from the NAC (zone 2 or 3) [5]. Pre-operative chemotherapy was not a contraindication, though pre-operative radiation may influence the choice of reconstructive procedure.

The choice of reconstructive procedure was made after a discussion involving the breast surgeon, plastic surgeon and the patient. Depending on several factors, including the need for post-operative radiation, patient willingness to accept a donor site and its accompanying morbidity, the possibility of secondary surgery for implant exchange, as well as breast size and ptosis grade, patients were offered either autologous or implant-based reconstruction. Implant-based reconstruction would be either with the Becker implant-expander type (which required patient commitment to regular sessions of tissue expansion) or the direct-to-implant type using Allergan or Mentor textured breast implants, with or without a concomitant Latissimus dorsi (LD) myocutaneous flap. Implants were selected based on the ipsilateral breast base width and height and were placed in a subpectoral fashion. In the case of the Becker implant-expander, the port was situated at a subcutaneous site remote from the implant, allowing for easy identification and access. All patients were counselled on the possibility of secondary implant exchange in the future, for reasons such as capsular contracture, infection, implant rupture or exposure. Autologous breast reconstruction, whether in the form of pedicled or free flaps, would offered to patients willing to accept the morbidity of a flap donor site, or who were likely to require post-operative radiation. Patients with large breast volumes and Regnault breast ptosis grade 3 were preferentially offered autologous reconstruction. In our centre, an autologous flap was the preferred choice of breast reconstruction, and the pedicled transverse rectus abdominis myocutaneous (TRAM) flap was the preferred autologous flap because it allowed for reliable harvest of a large amount of donor tissue, a well-concealed donor scar, a two-teamed approach which significantly reduced operative times, did not require intra-operative turning of the patient and resulted in significant improvement in abdominal wall aesthetics. The abdominal flap, either ipsilateral or contralateral-based, would be harvested through a transverse lower elliptical incision, with preservation of the respective perforators. In the case of a pedicled TRAM flap, the entire rectus abdominis muscle would be harvested, sparing the rectus fascia and preserving the medial or lateral, or at times both, row perforators. The flap was tunneled suprafascially to the mastectomy pocket and anchored. The rectus fascia was closed with PDS1 suture, with or without a Prolene mesh, depending on the degree of fascia and muscle sacrifice. In the DIEP flap, only the largest perforator would be used with resultant maximal rectus fascia and muscle preservation. A recipient vessel system, either the thoracodorsal vessels or internal mammary vessels, would be prepared for microsurgical anastomosis.

Patients usually remained in hospital for a week and were discharged when the surgical drains were removed. Post-operative pain was well controlled with oral analgesics, such as paracetamol, non-steroid anti-inflammatory agents, tramadol; with intravenous opiates via patient controlled devices being generally required in the first post-operative day only. Adjuvant treatments were recommended according to existing NCCN guidelines. Systemic chemotherapy was indicated for node-positive disease, and in node-negative disease if the tumour is larger than 1cm and if high risk factors were present; Oncotype DX was discussed if indicated. Trastuzumab was indicated for HER2-positive tumors, and hormonal therapy for hormone-responsive tumors. Radiation was recommended in pre-menopausal women with nodal involvement, in post-menopausal women with more than 4 nodes involved, when tumour is more than 5 cm in diameter and where there was chest wall involvement; post-menopausal women with 1 to 3 nodes involved were considered to be at borderline risk and radiation was discussed on a case-by-case basis. Other than hormonal therapy, all other treatments were started after the surgical wounds healed. Chemotherapy, if indicated, was the first adjuvant therapy given, followed by radiation after its completion. Tamoxifen was started only after radiation was completed, though aromatase inhibitors were started together with radiation.

Univariate correlation analyses to determine the association of complications with outcome, and the association of ethnicity, co-morbidities, disease stage and type of reconstructive procedure with complications were performed with Chi square test, or with Fisher's exact test where appropriate, with GraphPadPrism version 6 (GraphPad software Inc., San Diego CA). The association of patient age and operative time with complications was analysed with Mann Whitney test. Logistic regression model was used to identify independent risk factors for mortality, using the Stata/SE version 11.2 (Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845, USA). A 2-tailed P value test was used in all analyses and a P value of less than 0.05 was considered statistically significant.

Results

Over the 10-year period, 146 women underwent immediate breast reconstruction after mastectomy for breast cancer. Details are in Table 1.

Parameter	Number of Patients (%)
Ethnicity	
Chinese	120 (82)
Malay	17 (12)
Indian	5 (3)
Others	4 (3)
Co-morbidities	77 (53)
Obesity	25
Obstructive sleep apnoea	5
Hypertension	16
Hyperlipidaemia	16
Diabetes mellitus	10
Ischaemic heart disease	4
Valvular heart disease	4
Congential heart disease	1
Asthma	9
Hyperthyroidism	9
Gastro-esophageal reflux	1
Thrombocytopenia	1
Thalaessmia minor	1
Systemic lupus erythematosus	2
Sjorgen's syndrome	1
Hepatitis B carrier	2
Previous abdominal surgery	45 (31)
LSCS	24
Hysterectomy	9 (1 laparoscopic)
Salphingo-oophrectomy	2
Myomectomy	1
Appendiectomy	4
Anterior resection	1
Laparoscopic cholecystectomy	3
Splenectomy	1
Neoadjuvant chemotherapy	4 (3)
Mastectomy procedure	
Skin-sparing	139 (95)
Nipple areolar-complex sparing	7 (5)
Reconstructive procedure	
Pedicled TRAM flap	109 (75)
LD flap	29 (20)
DIEP (free) flap	4 (3)
Implant	4 (3)
Tumour histology	
DCIS	24 (16)
Invasive ductal carcinoma	98 (67)
Invasive lobular carcinoma	12 (8)
Others	12 (8)
Disease stage	
DCIS	21 (14)
I	40 (27)
II	30 (21)
III	54 (37)
IV	1 (1)
Oestrogen Receptor status	
Positive	94 (64)
Negative	39 (27)
Unknown	13 (9)
Progesterone Receptor status	
Positive	80 (55)
Negative	53 (36)
Unknown	13 (9)
Human Epidermal Receptor (HER)-2 status	
Positive	26 (18)
Negative	65 (45)
Equivocal	11 (8)
Unknown	44 (30)

Table 1: Clinical details of 146 patients undergoing breast reconstruction following mastectomy. TRAM: Transrectus Abdominis

Myocutaneous; LD: Latissimus Dorsi, DIEP; Deep Inferior Epigastric Perforator; DCIS: Ductal Carcinoma in situ.

Median patient age was 46 years (ranging from 23 to 72 years) and most women (123 of 146, 84.3%) were pre-menopausal. Half the patients had no co-morbidities (American Society of Anaesthesiology, ASA, score 1), while 22 patients had more than 1 co-morbidity; all were ASA 2. Being overweight (BMI more than 23.0) was the most common co-morbidity, followed by hypertension and hyperlipidaemia; 10 patients had diabetes mellitus that was adequately controlled with oral hypoglycaemics. Two patients had a history of systemic lupus erythematosus (SLE) and 1 patient a history of Sjogren's syndrome. Two patients were smokers. Forty-five women (31%) had previous abdominal surgery, which in most cases was a lower segment Caesarean section (LSCS). Ductal carcinoma in situ (DCIS) was diagnosed in 21 women (14%) and 70 women (48%) had early-stage Stage I or II cancers. Median tumour size was 22 mm (ranging from 1 to 110mm); 92 patients (63%) had tumors 3 cm or smaller and would have been eligible for BCS. Four patients received prior neoadjuvant chemotherapy but none had pre-operative radiation. Median follow-up period was 103 months (ranging from 59 to 179 months).

In all 146 patients, reconstruction was done at the same setting as the mastectomy. Most women underwent skin-sparing mastectomy and a pedicled TRAM flap was the most commonly performed reconstructive procedure. A free flap was performed in 4 patients and an expander implant was inserted in another 4 patients. Median weight of the resected breast tissue was 438 grams (ranging from 138 to 1180 grams). In those who underwent TRAM flap reconstruction, the donor site defect was closed primarily in 78 patients, supplemented with a TI mesh in 26 patients and with a prolene mesh in 5 patients. Median duration of surgery, including both the mastectomy and reconstruction, was 395 minutes (ranging from 90 to 935 minutes); 380 minutes for TRAM flap (ranging from 195 to 935 min), 440 minutes for LD flap (ranging from 90 to 660 min), 640 minutes for DIEP flap (ranging from 425 to 720 minutes), and 155 minutes for implant (ranging from 90 to 180 min). Despite the variation in the operative times, median length of hospital stay was similar regardless of the type of autologous flap reconstruction (9 days), while the median length of stay was shorter after an implant (4 days).

Major post-operative events occurred in 3 patients. Surgery had been uneventful in all 3 patients, with no major blood loss or haemodynamic instability recorded throughout the peri-operative period. Two patients suffered a cerebrovascular accident (CVA) in the immediate post-operative period. One patient was a 50-year-old Chinese lady, with a history of well-controlled hypertension, who had undergone skin-sparing mastectomy with TRAM flap reconstruction. Right-sided weakness and slurred speech developed on the second post-operative day and she diagnosed with an acute infarct in the left frontal lobe and cortical region in the middle cerebral artery territory. Another was a 72-year-old Chinese lady, with a history of hypertension and diabetes, also adequately controlled, who developed left-sided weakness, slurred speech and vertiginous giddiness 2 days after mastectomy and implant insertion. MRI scan confirmed an acute infarct in the right corona radiata. Both patients received inpatient rehabilitation, were discharged within 2 weeks and subsequently made full functional recovery. The third patient was a 51-year-old Malay lady, with no prior medial history, who developed an inferior ST-elevated acute myocardial infarction on the first post-operative day after a skin-sparing mastectomy and LD flap reconstruction. She was managed conservatively and discharged after 8 days.

Early post-operative complications, occurring within the first month of the surgery, occurred in 25 patients (17%) (Table 2).

Complications	Number of Patients (%)	Numbers Requiring Further Surgery	Secondary Surgical Procedure Performed
Major complications			
Acute moyocardial infarction	1 (1)		
Cerebrovascular Accident	2 (1)		
Immediate complications*	25 (17)	1	
Epidermolysis	12		
Superficial wound dehiscence	3		
Cellulitis	5		
Haematoma	3	1	Evacuation of infected haematoma
Fat necrosis	2		
Late complications*	18 (12)	7	
Abdominal bulge	1		
Abdominal hernia	4	3	Hernia repair
Superficial wound dehiscence	1		
Cellulitis	1		
Haematoma / Seroma	2		

Fat necrosis	6	2	Excision of fat necrosis
Implant related issues	3		
Capsular contracture	2	1	Capsulotomy
Rupture	1	1	Implant exchange
Size mismatch	20 (14)	8	
		4	Fat grafting
		2	Flap liposuction
		1	Augmentation (contralateral breast)
		1	Reduction mammoplasty and mastopexy (contralateral breast)

Table 2: Details of post-operative complications. *Immediate complications refer to events occurring within 30 days of surgery; late complications refer to events occurring more than 30 days after surgery.

Epidermolysis was the most common, occurring in 12 patients and resolved in all cases without the need for secondary skin grafting. Secondary suturing was done under local anaesthesia in 2 patients with superficial wound dehiscence. One patient underwent an unplanned re-operation to evacuate an infected haematoma. Complications occurring after 30 days were recorded in 18 patients (12%); 9 of these patients had earlier developed complications within the first month. Fat necrosis was the most common complication recorded and 2 of these 6 patients underwent excision of the necrotic masses with flap revision. Abdominal herniation at the TRAM donor site occurred in 4 patients and was surgically repaired in 3. Implant related complications occurred in 3 of the 4 patients who had implants inserted. One patient required capsulotomy for capsule contractions following radiation therapy and another required an exchange after spontaneous implant rupture. Complications were more frequent among older women ($P<0.01$), those with diabetes ($P=0.05$, or 3.69, 95% CI 0.07-1.00) and in those receiving implants ($P<0.01$) (Table 3).

The shorter operative times observed among those who developed complications was because of the inclusion of 3 patients who had implant insertion, which was a quicker procedure compared to autologous flap reconstruction. Two of the 4 patients who had received neoadjuvant chemotherapy developed minor complications within the first month. One developed a superficial wound infection and the other superficial wound dehiscence; both resolved without surgery. Size mismatch was documented in 20 patients (14%), 8 of whom later underwent a secondary procedure either on the reconstructed or the contralateral breast.

Most patients (82%) received further treatments after surgery, with only 2 patients declining recommended treatments (1 chemotherapy and 1 hormonal therapy). Chemotherapy was started in 93 patients (64%), after a median interval of 1.30 months (ranging from 0.77 to 3.87 months). Chemotherapy was started more than 3 months after surgery in 6 patients (ranging from 3.07 to 4.47 months) and was directly related to early complications (epidermolysis and wound infection) in 3 patients. Metastatic disease recurrence developed in 3 of these 6 patients; 1 of whom also had concurrent locoregional recurrence. Another 25 patients did not receive chemotherapy but started on hormonal therapy after surgery, after a median interval of 1.37 months (ranging from 0.43 to 3.27 months). Fifty-nine patients (40%) received whole breast radiation following the completion of chemotherapy. In one patient, histological analysis of the surgical specimen revealed the breast tumour to be in fact a metastatic deposit from a lung primary and the patient was treated as for Stage IV non-small cell lung carcinoma with tyrosine kinase inhibitors starting 2.43 months after surgery.

Recurrence occurred in 22 patients, of whom 4 had started systemic treatments more than 3 months after surgery. Local recurrence over the reconstructed breast developed in 8 patients, after a median interval of 22 months (ranging from 9 to 77 months) (Table 3). One patient had initially been diagnosed with DCIS, 2 with Stage I disease, 3 with Stage II and 2 with Stage III disease. Of these 8 patients, 3 patients had no further adjuvant treatments (2 declined recommended treatments and 1 had a T1aN0 ER-negative tumour). Four of the other 5 patients had started chemotherapy within 3 months of surgery. Chemotherapy was started 3.87 months after surgery because of epidermolysis and wound infection in the remaining patient; this patient had a T2N0 triple negative tumour (negative for ER, PR and HER2) and developed metastatic disease in the lungs and liver another 5 months later. Another 14 patients developed distant recurrence, after a median interval of 31 months (ranging from 8 to 104 months); 1 patient was initially diagnosed with Stage I disease, 2 with Stage II cancer and the remaining 11 with Stage III cancer. Three of these 14 patients had started systemic therapy more than 3 months from the surgery. One patient started chemotherapy 3.57 months later because of post-operative complications, another started chemotherapy 3.40 months later (not related to post-operative complications) and the third patient with Stage I disease started hormonal therapy 3.27 months after surgery. Median time to commencing adjuvant treatments was statistically longer in those who developed post-operative complications ($P=0.01$), but the difference (median of 1.60 months in those who developed complications compared to a median of 1.20 months in those without) was not likely clinically significant. Post-operative complications were not found significantly associated with disease recurrence or with contralateral cancer ($P>0.05$) (Table 3).

	Patients with Post-Operative Complications	**Patients without Post-Operative Complications**	**P value**
	(n=34)	(n=112)	
Median age (years)	53 (25–72)	45 (23–63)	<0.01
Ethnicity			
Chinese	23	97	
Malay	7	10	0.09
Indian	2	3	
Others	2	2	
Co-morbidities			
Yes	21	56	0.23
No	13	56	
Diabetes mellitus			
Yes	5	5	0.05
No	29	107	
Disease stage			
DCIS	5	16	
Stage I	9	31	
Stage II	7	23	0.99
Stage III	13	41	
Stage IV	0	1	
Type of reconstruction			
Pedicled TRAM	31	77	
LD	1	29	0.01
DIEP	0	4	
Implant	2	2	
Median duration of surgery (min)	335 (90–690)	410 (90–935)	<0.01
Length of stay (days)	9 (3–22)	9 (2–17)	0.39
Local recurrence			
Yes	3	5	0.39
No	31	107	
Distant recurrence			
Yes	3	12	1
No	31	100	
Contralateral cancer			
Yes	1	2	0.55
No	33	110	

Median time to adjuvant treatment (months)	1.60 (0.43–3.87)	1.20 (0.33–3.57)	0.01

Table 3: Correlation analyses of post-operative complications with disease, operative factors, and clinical outcome (n=146).

Outcomes were compared with 2125 women with non-metastatic breast cancer who had either undergone mastectomy or BCS without reconstruction during the same period at our institute. Disease recurrence, whether local or distant, was no different among those who had reconstruction compared to those who had undergone either mastectomy alone or BCS (P>0.05) (Table 4a).

	Patients undergoing Reconstruction	**Patients undergoing Mastectomy or BCS**	P value
	(n=146)	(n=2125)	
Local recurrence			0.91
Yes	12	188	
No	134	1937	
Distant recurrence			0.81
Yes	22	297	
No	124	1828	
Death			<0.01
Yes	10	353	
No	136	1772	

Table 4a: Comparison of outcomes between those treated with mastectomy and reconstruction, those treated with breast conserving surgery (BCS) and those treated with mastectomy without reconstruction over the same 10-year period (n=2271).

Recurrence was also no different between those who had reconstruction compared to those treated with mastectomy alone (Table 4b). There were significantly less deaths among those who underwent reconstruction (P<0.01) (Tables 4a and 4b), but this association was no longer found after adjusting for age (Table 4b).

Parameter	**Odds ratio**	**Standard error**	**P value**	**95% CI**
Surgery type*	0.57	0.18	0.08	0.30–1.08
Age	1.03	<0.01	<0.01	1.02–1.04

Table 4b: Logistic regression of mortality stratified by surgery type* (mastectomy with reconstruction compared against mastectomy alone and breast conserving surgery) and age (n=2271).

Discussion

Immediate breast reconstruction helps restore the body image and can lessen the psychological impact of a mastectomy [6]. Many of our patients eligible for breast conservation opt for mastectomy to avoid post-operative radiation, but this 'advantage' is decreasing with radiation now being increasingly recommended for women with N1 disease [7]. In addition, oncoplastic techniques, including local tissue re-arrangement and pedicled locoregional flaps, can reduce the post-operative deformity and contralateral asymmetry even after extensive local resections, and have expanded the criteria for BCS [8]. However, such oncoplastic techniques are rarely performed at our unit as Asian women generally have much smaller breast volumes and extensive local resection often leaves a defect too large to be remodeled with local tissue re-arrangement alone, necessitating local pedicled flap transfer to prevent the contour deformity that will often be exacerbated by radiation. There is then little advantage over a mastectomy and reconstruction, since surgery is not less extensive and post-operative radiation is still necessary.

When skin-sparing mastectomy was first introduced, there were concerns over the oncologic safety of leaving behind much more skin and subcutaneous tissue than in a conventional mastectomy. Theoretically, the more tissue left behind, the higher the likelihood of local recurrence. This has, however, been consistently disproven in large studies and it is now widely accepted that breast cancer specific survival is no different after a reconstruction [9-11]. We have also found no difference in survival outcomes in women undergoing reconstruction, with both locoregional and distant recurrence rates being similar regardless of whether reconstruction is or is not performed. Likewise, in properly selected cases, preservation of the nipple-areolar complex does not compromise oncologic outcomes

either [12] Our study, as well as several others, found reconstruction to correlate with better overall survival, and socioeconomic factors were thought to be the underlying factor [10,11]. Affordability and access to healthcare is seldom an issue in our context, and the apparent survival advantage observed in our study reflects the selection bias towards younger patients, in line with our practice of offering reconstruction to younger patients with no or minimal pre-existing co-morbidities.

While the reconstruction procedure itself has not been shown to adversely affect clinical outcomes, post-operative complications are indeed more frequent after a reconstruction compared to after a mastectomy alone [13,14]. Wound complications can potentially delay the initiation of adjuvant chemotherapy and may consequently predispose to a higher risk of disease recurrence. Furthermore, some evidence has suggested that wound complications can induce systemic effects that directly potentiate systemic recurrence. In the case of colorectal cancer, anastomotic leaks and intra-abdominal infection were associated with poorer survival, [15-17] and one study reported a similar positive correlation between breast cancer recurrence and post-operative wound complications [18]. In that study, patients with wound complications, defined as wound breakdown requiring dressing, packing or debridement, or persistent wound discharge had a 2.5-fold increase in systemic recurrence, independent of tumour ER status and Nottingham Prognostic Index score. Local wound infection and inflammation trigger an augmented and prolonged cytokine response, involving transforming growth factor (TGF)-, tumour necrosis factor (TNF) and interleukins (IL)-6 and (IL)-8, which are implicated in epithelial-mesenchymal transition, metastasis and chemo-resistance [19-22]. While the more recent studies have focused on systemic recurrence, an older study also reported an association with local recurrence, suggesting that cytokine and growth factor induction at the surgical site may activate residual tumour cells which would have otherwise been non-viable [23]. Overall, data on post-operative wound complications and clinical outcome remains inconclusive.

Apart from direct systemic effects, post-operative complications can also potentially delay the initiation of adjuvant treatments. Many patients are recommended adjuvant chemotherapy and guidelines caution that it is significantly less effective if initiated more than 12 weeks after surgery [24]. A 10-year review found equivalent efficacy regardless of whether anthracycline-based chemotherapy was started within the first 4 weeks or in 8 to 12 weeks after surgery [25]. However, a recent study reported that the initiation of chemotherapy impacted clinical outcome in specific tumour subtypes; early initiation within 2 months of surgery appeared particularly important for Stage III, triple negative and HER2-overexpressing breast cancers, where the risk of relapse is high, while it had no effect on outcome in hormone-responsive tumors [26]. It has been postulated that surgical resection of the primary tumour increases circulating tumour cell burden, induces cytokines and growth factors and depresses cell-mediate immunity; factors that may be particularly significant in high-risk disease [27,28]. Post-operative complications occurred in 17% of our patients undergoing reconstruction and was comparable to published rates [14-29]. Most complications were minor and resolved with non-surgical management. Median time to initiating adjuvant chemotherapy was slightly longer in those with post-operative complications (1.60 months compared to 1.20 months), but was still well within 3 months from surgery. Chemotherapy was started more than 3 months after surgery in only 6 patients (4.1%) and this was directly related to delayed wound healing in only 3. Several studies have also reported that reconstruction did not significantly delay the initiation of chemotherapy [13,29-31]. Furthermore, reconstruction was not associated with dose reductions, delays in completing the planned regimens or premature discontinuation [13,32-34]. Taken together, these suggest that adjuvant treatments proceed as planned in most instances after immediate reconstruction, and need not be a reason for delayed reconstruction. Coordination between the surgical and oncology teams can avoid unnecessary delays when delayed wound healing does occur. Many oncologists are hesitant to start doxorubicin, a component of many first-line regimens, because wound healing may be further impaired since doxorubicin interferes with collagen synthesis and causes myelosuppression [35,36]. However, other first-line agents like taxanes and trastuzumab are not known to interfere with wound healing and can be initiated first to allow time for wound healing before anthracyclines are started [37].

Our study found no clear association between breast reconstruction, post-operative complications and disease recurrence. Recurrence is multi-factorial and is determined by disease stage, inherent molecular characteristics, the adequacy of treatment regimens and also patient factors. Adding to the complexity is the recent hypothesis that general anaesthetics and opioid use in the peri-operative period can inhibit cellular and humoral immunity and suppress critical anti-tumour immune functions to increase the risk of metastasis [38]. There is currently no strong evidence to suggest that immediate breast reconstruction or post-operative complications compromise clinical outcome. Women who receive immediate reconstruction are generally young and healthy and are unlikely to suffer serious complications or have problems with wound healing. Mastectomy and immediate reconstruction remains a viable option for women who either need or opt for a mastectomy; in our study, 63% (58 of 92) of those eligible for breast conservation did not need adjuvant radiation after mastectomy and reconstruction.

Conclusions

Post-operative complications occurred in 17% of patients undergoing immediate breast reconstruction after mastectomy for breast cancer. Most were minor wound problems and resolved with conservative treatment. We found no evidence that immediate reconstruction or post-operative complications adversely affected clinical outcomes. Adjuvant treatments, in particular chemotherapy, were not significantly delayed even when wound problems had occurred. Our study thus suggests that immediate breast reconstruction is a reasonable option for women who feel psychologically uncomfortable with their body image after a mastectomy.

References

1. Chan PM, Choo BA, Zhang T, Seah MD, Chen JJ, et al. (2015) Mastectomy rates remain high in Singapore and are not associated with poorer survival after adjusting for age. Springerplus 4: 685.
2. Delgado JF, Garcia-Guilarte RF, Palazuelo MR, Mendez JI, Perez CC (2010) Immediate breast reconstruction with direct, anatomic, gel-cohesive, extra-projection prosthesis: 400 cases. Plast Reconstr Surg 125: 1599-1605.
3. Yang X, Zhu C, Gu Y (2015) The prognosis of breast cancer patients after mastectomy and immediate breast reconstruction: a meta-analysis. PLoS One 10: e0125655.
4. Espin E, Ciga MA, Pera M, Ortiz H, Spanish Rectal Cancer P (2015) Oncological outcome following anastomotic leak in rectal surgery. Br J Surg 102: 416-422.

5. Lohsiriwat V, Petit J (2012) Nipple Sparing Mastectomy: from prophylactic to therapeutic standard. Gland Surg 1: 75-79.
6. Al-Ghazal SK, Fallowfield L, Blamey RW (2000) Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. Eur J Cancer 36: 1938-1943.
7. Jagsi R (2013) Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg 2013: 212979.
8. Piper M, Peled AW, Sbitany H (2015) Oncoplastic breast surgery: current strategies. Gland Surg, 4(2):154-163.
9. Agarwal S, Liu JH, Crisera CA, Buys S, Agarwal JP (2010) Survival in breast cancer patients undergoing immediate breast reconstruction. Breast J 16: 503-509.
10. Agarwal J, Agarwal S, Pappas L, Neumayer L (2012) A population-based study of breast cancer-specific survival following mastectomy and immediate or early-delayed breast reconstruction. Breast J 18: 226-232.
11. Bezuhly M, Temple C, Sigurdson LJ, Davis RB, Flowerdew G, et al. (2009) Immediate postmastectomy reconstruction is associated with improved breast cancer-specific survival: evidence and new challenges from the Surveillance, Epidemiology, and End Results database. Cancer 115: 4648-4654.
12. Stanec Z, Zic R, Budi S, Stanec S, Milanovic R, et al. (2014) Skin and nipple-areola complex sparing mastectomy in breast cancer patients: 15-year experience. Ann Plast Surg, 73: 485-491.
13. Mortenson MM, Schneider PD, Khatri VP, Stevenson TR, Whetzel TP, et al. (2004) Immediate breast reconstruction after mastectomy increases wound complications: however, initiation of adjuvant chemotherapy is not delayed. Arch Surg 139: 988-991.
14. Beecher SM, O'Leary DP, McLaughlin R, Sweeney KJ, Kerin MJ (2016) Influence of complications following immediate breast reconstruction on breast cancer recurrence rates. Br J Surg 103: 391-398.
15. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, Harling H (2014) Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer: a nationwide cohort study. Ann Surg 259: 930-938.
16. Bohle B, Pera M, Pascual M, Alonso S, Mayol X, et al. (2010) Postoperative intra-abdominal infection increases angiogenesis and tumor recurrence after surgical excision of colon cancer in mice. Surgery 147: 120-126.
17. Salvans S, Mayol X, Alonso S, Messeguer R, Pascual M, et al. (2014) Postoperative peritoneal infection enhances migration and invasion capacities of tumor cells in vitro: an insight into the association between anastomotic leak and recurrence after surgery for colorectal cancer. Ann Surg 260: 939-943.
18. Murthy BL, Thomson CS, Dodwell D, Shenoy H, Mikeljevic JS, et al. (2007) Postoperative wound complications and systemic recurrence in breast cancer. Br J Cancer, 97:1211-1217.
19. Yu Y, Wang Y, Ren X, Tsuyada A, Li A, et al. (2010) Context-dependent bidirectional regulation of the MutS homolog 2 by transforming growth factor beta contributes to chemoresistance in breast cancer cells. Mol Cancer Res 8: 1633-1642.
20. Yilmaz M, Christofori G (2009) Emt, the cytoskeleton, and cancer cell invasion. Cancer Metastasis Rev 28: 15-33.
21. Allavena P, Sica A, Solinas G, Porta C, Mantovani A (2008) The inflammatory micro-environment in tumor progression: the role of tumor-associated macrophages. Crit Rev Oncol Hematol 66: 1-9.
22. Guo Y, Xu F, Lu T, Duan Z, Zhang Z (2012) Interleukin-6 signaling pathway in targeted therapy for cancer. Cancer Treat Rev 38: 904-910.
23. Reid SE, Scanlon EF, Kaufman MW, Murthy MS (1996) Role of cytokines and growth factors in promoting the local recurrence of breast cancer. Br J Surg 83: 313-320.
24. Senkus E, Kyriakides S, Penault-Llorca F, Poortmans P, Thompson A, et al. (2013) Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24: 7-23.
25. Lohrisch C, Paltiel C, Gelmon K, Speers C, Taylor S, et al. (2006) Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 24: 4888-4894.
26. Gagliato Dde M, Gonzalez-Angulo AM, Lei X, Theriault RL, Giordano SH, et al. (2014) Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. J Clin Oncol 32: 735-744.
27. Bar-Yosef S, Melamed R, Page GG, Shakhar G, Shakhar K, et al. (2001) Attenuation of the tumor-promoting effect of surgery by spinal blockade in rats. Anesthesiology 94: 1066-1073.
28. Shakhar G, Ben-Eliyahu S (2003) Potential prophylactic measures against postoperative immunosuppression: could they reduce recurrence rates in oncological patients? Ann Surg Oncol 10: 972-992.
29. Lee J, Lee SK, Kim S, Koo MY, Choi MY, et al. (2011) Does Immediate Breast Reconstruction after Mastectomy affect the Initiation of Adjuvant Chemotherapy? J Breast Cancer 14: 322-327.
30. Xavier Harmeling J, Kouwenberg CA, Bijlard E, Burger KN, Jager A, et al. (2015) The effect of immediate breast reconstruction on the timing of adjuvant chemotherapy: a systematic review. Breast Cancer Res Treat 153: 241-251.
31. Hamahata A, Kubo K, Takei H, Saitou T, Hayashi Y, et al. (2015) Impact of immediate breast reconstruction on postoperative adjuvant chemotherapy: a single center study. Breast Cancer 22: 287-291.
32. Chang RJ, Kirkpatrick K, De Boer RH, Bruce Mann G (2013) Does immediate breast reconstruction compromise the delivery of adjuvant chemotherapy? Breast 22: 64-69.
33. Eriksen C, Frisell J, Wickman M, Lidbrink E, Krawiec K, et al. (2011) Immediate reconstruction with implants in women with invasive breast cancer does not affect oncological safety in a matched cohort study. Breast Cancer Res Treat 127: 439-446.
34. Taylor CW, Kumar S (2005) The effect of immediate breast reconstruction on adjuvant chemotherapy. Breast 14: 18-21.
35. Noh R, Karp GI, Devereux DF (1991) The effects of doxorubicin and mitoxantrone on wound healing. Cancer Chemother Pharmacol 29: 141-144.
36. Lawrence WT, Norton JA, Harvey AK, Gorschboth CM, Talbot TL, et al. (1986) Doxorubicin-induced impairment of wound healing in rats. J Natl Cancer Inst 76: 119-126.
37. Yoo GH, Subramanian G, Piechocki MP, Ensley JF, Kucuk O, et al. (2008) Effect of docetaxel on the surgical tumor microenvironment of head and neck cancer in murine models. Arch Otolaryngol Head Neck Surg 134: 735-742.
38. Shavit Y, Ben-Eliyahu S, Zeidel A, Beilin B (2004) Effects of fentanyl on natural killer cell activity and on resistance to tumor metastasis in rats. Dose and timing study. Neuroimmunomodulation 11: 255-260.