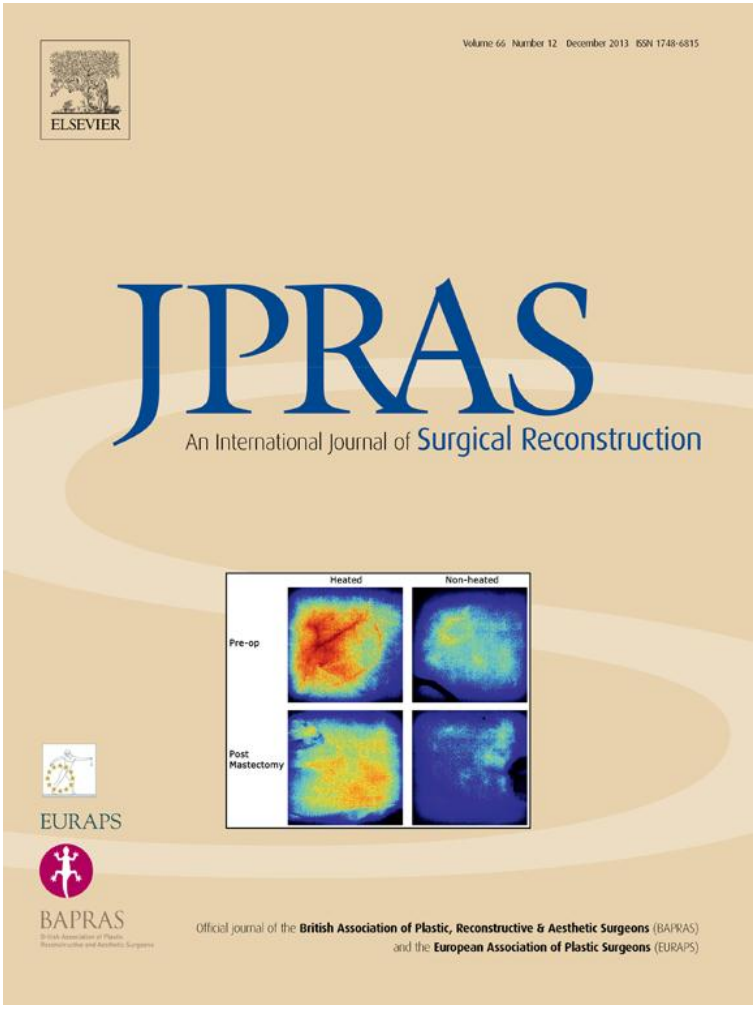

Journal of Plastic, Reconstructive & Aesthetic Surgery (2013) 66, 1676–1682

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Local heat preconditioning in skin sparing mastectomy: A pilot study☆

Saahil Mehta [a,*], Rachel Rolph [a], Victoria Cornelius [b], Yves Harder [a,c], Jian Farhadi [a]

[a] *Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, United Kingdom*
[b] *RDS London, Department of Primary Care and Public Health Sciences, King's College London, 42 Weston Street, London SE1 3QD, United Kingdom*
[c] *Department of Plastic Surgery and Handsurgery, Klinikum rechts der Isar, Technische Universität München, Ismaningerstrasse 22, D-81675 Munich, Germany*

Received 6 March 2013; accepted 30 July 2013

KEYWORDS
Preconditioning;
Skin sparing mastectomy;
Complications;
Skin necrosis;
Prevention

Summary *Background:* Experimental data has shown an association with a reduction of flap necrosis after local heat-application to a supraphysiological level resulting from the up-regulation of heat shock proteins, such as HSP-32. The proteins maintained capillary perfusion and increased tissue tolerance to ischaemia. The purpose of this translational study was to evaluate the effect of local heat preconditioning before skin sparing mastectomy and immediate breast reconstruction.
Methods: A prospective non-randomised trial was performed from July 2009–April 2010. 50 consecutive patients at risk of skin flap necrosis (BMI >30, sternal-to-nipple distance >26 cm or breast size >C-cup) were included. Twenty-five patients were asked to heat-precondition their breast 24-h prior to surgery using a hot water bottle with a water temperature of 43 °C (thermometers provided), in three 30-min cycles interrupted by spontaneous cooling to room temperature. Skin flap necrosis was defined by the need for surgical debridement. LDI images were taken pre- and post-mastectomy to demonstrate an increase in tissue vascularity.
Results: 36% of women ($n = 25$) without local heat-treatment developed skin flap necrosis, 12% developed skin flap necrosis in the treatment group, resulting in a 24% difference ($n = 25$; $p = 0.047$ (95%CI 1%–47%)). LDI scanning of the heated breast demonstrated an increase in vascularity compared to the contralateral non-heated breast. Median length of inpatient stay for

☆ This work has been presented at: (1) EURAPS, Munich, Germany, 23rd–24th May 2012. (2) American Society of Reconstructive Microsurgery, Las Vegas, USA, 14–17th January 2012. (3) EPSRC, Hamburg, Germany, 23rd–27th September 2011.

* Corresponding author.
E-mail address: saahil47@gmail.com (S. Mehta).

http://dx.doi.org/10.1016/j.bjps.2013.07.034

treatment group was 4 days (95%CI(4, 7)), controls 8 days (95%CI(8, 9) ($p = <0.001$)).
Conclusions: The data suggests that in selected cases, local heat preconditioning is a simple and non-invasive method of reducing skin necrosis and length of hospital stay following skin sparing mastectomy.
Clinical Trial Registration Number: ACTRN12612001197820.
Level of evidence: II.

Introduction

Skin sparing mastectomy (SSM) has become a commonly used method of surgical treatment for breast cancer and allows immediate breast reconstruction. Preservation of the breast skin envelope provides excellent cosmetic results and the overall sensation is largely maintained.[1,2] However, skin necrosis of the mastectomy envelope due to ischaemia remains a serious complication that can result in further operations, prolonged hospital stay and increased patient morbidity. In a survey of oncoplastic units in the UK, 68% of respondents reported skin necrosis as a complication in skin sparing mastectomy with rates of up to 54% being seen.[1,3–7]

Various preconditioning strategies have been explored to protect the musculocutaneous tissues from ischaemia-induced wound complications. To date, surgical delay, i.e. the stepwise cut down and dissection of a flap, has proven to be the forerunner and gold standard of tissue conditioning. Hypoxic conditions of the flap induce angio- and arteriogenesis and so increase the perfusion of the tissue to be transferred. The procedure however is invasive and time-consuming. Alternative methods of preconditioning that have been used remote preconditioning, hypo-& hyperthermic application, as well as administrations of pharmacological and biological.[8–12] All these modalities remain in the experimental phase of animal studies. Consequently, there is a lack of clinical data.

Local heat preconditioning has been shown to exert a protective effect on ischaemically challenged tissues in experimental models. The protective mechanism has been associated with so-called stress- or heat shock proteins (HSP's) such as HSP-32.[13–15]

Therefore the aim of this translational pilot study was to evaluate the effect of local heat preconditioning in the clinical setting on the mastectomy skin flap following skin sparing mastectomy.

Methods

Ethical approval was obtained from the Guy's and St. Thomas' Research Ethical Committee (Ethics number: 09/H0804/035) to perform a prospective, non-randomised study between July 2009 to April 2010. Patients that were identified as being at increased risk of developing skin necrosis of the mastectomy skin flap were included in the study.[16] Inclusion criteria were:

- A body mass index (BMI) between 26 and 36 kg/m^2
- A sternal notch-to-nipple distance (SN-N) of equal to or over 26 cm
- Bra cup size C to J.

Patients could present with one or more of the above risk factors and needed at least one to be included. All active smokers were excluded. The treatment group was matched to a patient population treated 12-months previously. The control group consisted of a consecutive selection of patients who met the inclusion criteria for this study.

Procedure of preconditioning: patients were then given a hot water bottle and an underwater thermometer and asked to perform the heat preconditioning procedure, at home, starting 24 h before they were due to attend for surgery. Patients were asked to heat water up to 43 °C in a saucepan and pour it into the hot water bottle. The bottle was then placed on the breast to be operated on. The heating protocol was arranged into three thirty-minute cycles interrupted by thirty-minute breaks when the breast was allowed to cool spontaneously to room temperature. Patients undergoing bilateral prophylactic SSM were asked to heat only the right breast. This heating procedure was based on the protocol used in an experimental animal model investigating the effect of local heat preconditioning.[13]

The patients' BMI, SN-N distance and bra size, type of incision and reconstruction performed was recorded. Each mastectomy was performed by one of four Consultant Breast Surgeons. Autologous reconstructions included the deep inferior epigastric perforator flap (DIEP), transverse myocutaneous gracilis flap (TMG), and superior gluteal artery perforator flap (SGAP). Patients were seen by clinical staff everyday postoperatively to monitor for skin necrosis. Necrosis was characterised by a circumscribed full thickness loss of skin and subcutaneous tissue needing surgical intervention. Patients were followed up until either they developed a fully demarcated necrosis or for 10 days as inpatients. The duration of inpatient stay for both treatment group and controls was recorded.

Skin perfusion was measured using a real time aïmago laser Doppler imaging (LDI) (Figure 1). The non-heated breast was used as a control and compared to the heated breast. Images were taken immediately before surgery i.e. 24 h after heating and also after the mastectomy had been performed.

A patient participation focus group meeting was held after the study to gather opinion on the user friendliness of the heating protocol. In attendance were patients who took part in this study.

Data were analysed by treatment group. Continuous data were assessed for normality and where appropriate the mean and standard deviation or the median value and

Figure 1 äimago Laser Doppler Imager.

inter-quartile range were presented. Percentages were calculated for binary data and the groups were compared by calculating the difference in proportion between the two treatment groups. Results are presented with 95% confidence intervals (CI). All patients in the treatment group were included in the analysis regardless of their adherence to the heating protocol. Kaplan–Meier estimates were calculated to examine differences in length of stay after surgery. A logrank test was performed to test if there was a difference in length of stay curves. Analyses were performed using Stata version 11.

Results

There were twenty-five participants in each group (local heat preconditioning and control group). Two of the participants in the heat preconditioning group did not successfully complete the heating protocol. All patients in the treatment group were included in the analysis regardless of their adherence to the heating protocol.

One patient in the intervention group suffered from diabetes and had previous adjuvant radiotherapy to the chest wall developed a superficial burn (less than 1%) on the heated breast. The burn was managed conservatively.

Table 1 Patient demographics, types of incision and reconstruction used by group.

Patient demographics	Heated ($N = 25$)	Non-Heated ($N = 25$)
BMI (kg/m^2), mean (SD)	30.0 (3.8)	30.0 (4.0)
SN-N distance (cm), mean (SD)	26.8 (4.4)	26.4 (3.7)
Cup size, mode (min, max)	DD (B, J)	DD (C, FF)
Chest size, median (min, max)	36 (34, 38)	38 (32, 40)
Reconstruction		
DIEP, *n*	17	19
SGAP, *n*	1	2
TMG, *n*	2	0
Implant, *n*	2	4
Expander, *n*	3	0
Incision		
Wise, *n*	3	6
Round, *n*	18	15
Elliptical, *n*	3	4
Nipple-sparing, *n*	1	0

The average breast size, SN-N distance and BMI were comparable between groups (Table 1). DIEP flap re construction and the "round" (peri-areolar) incision were the most common techniques used. Only the nipple–areola complex was excised using the round technique and no breast skin. Table 2 compares the characteristics of patients who developed skin necrosis needing surgical intervention in both the non-heated and heated group.

Skin necrosis was observed in 36% ($n = 9$) of the patients without local heat-application compared to 12% ($n = 3$) in the heated group, resulting in an estimated difference of 24% (95%CI (1%, 47%) p value $= 0.047$). Patients with necrosis underwent a combination of surgical debridement and dressings.

Laser Doppler Imaging showed an overall increase in perfusion (Figure 2) in the heated breast both pre-operatively and also immediately post-mastectomy.

The median length of inpatient stay for the heated group was 4 days 95%CI, range 3–10 days, and 8 days 95%CI, range 5–10 days, for the non-heated group, logrank test p value <0.001 (Figure 3).

A patient participation focus group meeting was held after the study to obtain patients' views on the heating protocol. The general feeling amongst patients was that the heat preconditioning was easy to do. More than one patient commented that it made them feel more involved with the surgery and that they were doing everything they could do to optimise their outcome. Another said that the protocol forced her to relax and focus her mind on the surgery.

Discussion

Skin sparing mastectomy (SSM) is a relatively new technique based on the fascial anatomy of the breast. Classically, SSM has been defined as the resection of the glandular tissue of the breast, including the skin of the nipple, the areola, and the original biopsy scar. At the same time it is recommended to preserve as much of the breast's skin as possible, including the inframammary fold, in order to enhance the aesthetic result of breast reconstruction.[17,18]

The principal observation in this study is that local heat preconditioning, at a supraphysiological temperature, reduces the rate of skin necrosis after skin sparing mastectomy in selected patients. The suggested mechanism is by the up-regulation of heat shock proteins (HSP's).

In an experimental animal model, mice were heated to 43 °C 24 h before flap surgery i.e. the induction of acute persistent ischaemia.[13] Heat was applied locally in three, thirty-minute cycles interrupted by 30-min breaks where the skin was allowed to cool spontaneously. A random pattern myocutaneous pedicled flap was then elevated on the back of the animals and was fixed into a dorsal skinfold chamber. The rate of necrosis in heated mice was 4% ± 1% versus 53% ± 5% in untreated controls. Immunohistological tissue analysis revealed a significant increase in the expression of heat shock proteins (HSP), particularly HSP-32, which was thought to play a crucial role in protecting the skin from necrosis and promoting tissue vascularity.

Table 2 Comparison of details of non-heated and heated groups of patients that developed skin necrosis. IDC — invasive ductal carcinoma; DCIS — ductal carcinoma in situ; LCIS — lobular carcinoma in situ.

Age	BMI	SN-N Left (cm)	SN-N Right (cm)	Cup size	Reconstruction	Incision	Diagnosis
Heated group							
68	35	28	27	38C	L SSM + expander	Round	IDC
52	32	30	30	38DD	L SSM + DIEP	Round	Low Grade DCIS
49	30	27	26	34C	Bilateral TMG	Round	BRCA Carrier
Non-heated group							
51	34	26	26	34B	L SSM + DIEP	Round	IDC II
48	31	27	27		Bilateral SSM + DIEP	Round	BRCA Carrier
65	28	36	36	38E	Bilateral SSM + DIEP	Wise	BRCA Carrier
34	33	31	31	34D	R SSM + SGAP	Wise	Low Grade DCIS
60	31	28	29	38DD	R SSM + DIEP	Wise	High Grade DCIS
48	26	29	30	26DD	Bilateral SSM + DIEP	Wise	BRCA Carrier
60	26	31	31	28DD	R SSM + DIEP	Round	LCIS II
50	28	22	23	38DD	L SSM + TRAM	Round	DCIS
51	26	28	28	34D	L SSM + TRAM	Round	DCIS

HSP-32 has been identified as haem-oxygenase-1 (HO-1) and is known to be the rate-limiting enzyme in the catabolism of haem to bilirubin.[19] One of the metabolites produced in this process is carbon monoxide, a potent vasodilator, which is able to maintain perfusion within ischaemically jeopardised tissues. HSP-32 has been shown to be expressed in heat preconditioned tissue and is thought to have a protective role against tissue ischaemia.[13]

The protective effects of heat shock proteins expressed after preconditioning have been demonstrated in various organs such as the kidney, the bone, the heart, and the liver, as well as in tendons and after burns.[20–25] Koenig et al. were the first group to beneficially use local supraphysiological heat preconditioning in experimental flap surgery and reported an improvement in flap survival.[9]

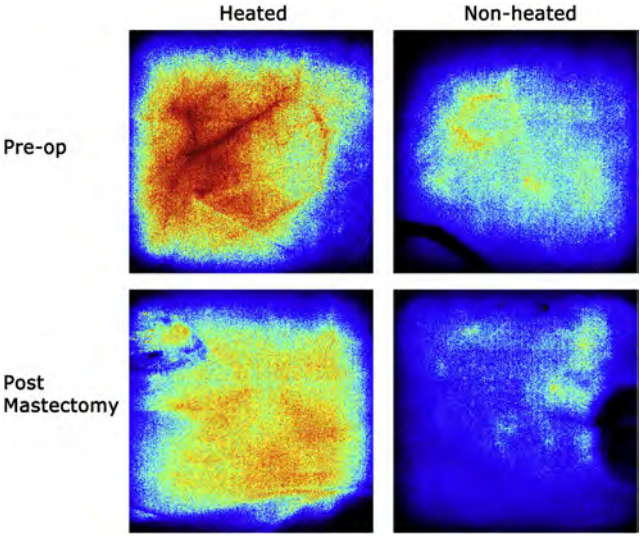

Figure 2 LDI images showing difference in perfusion in the heated and non-heated breast.

Locally applied heat has the advantage of being relatively simple to apply unlike other methods of preconditioning. One of the study aims was to describe a method of applying the heat therapy that was simple, inexpensive and did not require any extra admissions to hospital. Hot water bottles were chosen as the heating modality as they are readily available and cost-effective. Each patient was provided with a hot water bottle and a commercially available underwater thermometer. The hot water bottle was applied to the breast for three, thirty-minute cycles interrupted with thirty-minute breaks to compensate for the cooling of the device during the application.

The comments from the patient participation focus group meeting were very promising. The general feeling amongst patients was that the heat preconditioning was easy to do and allowed the patient to focus and relax before the surgery. This shows that the current heating protocol is acceptable to patients and will be suitable for further trials.

One patient experienced a superficial burn from the heating procedure that healed without any scars by conservative means. This patient had previously undergone adjuvant chemo-radiotherapy. This left her with an area of paraesthesia of the skin of the breast that was preconditioned. Reduced sensation of the skin is commonly reported following radiotherapy and this could be the reason for the burn.[26,27] It is possible that the hot water bottle was either too hot or left on the skin for too long or a combination of both mechanisms. This issue was brought up at the patient participation focus group and whilst none of the patients in attendance experienced this complication it was decided that patients who have had radiotherapy will be excluded from future trials.

Demographics did not differ between both groups. The majority of reconstructions were performed using abdominal fasciocutaneous tissue i.e. a DIEP flap. DIEP flap reconstructions have been shown to have an overall increase in complications however, this would not appear to be the case in our study. In addition, the majority of incisions

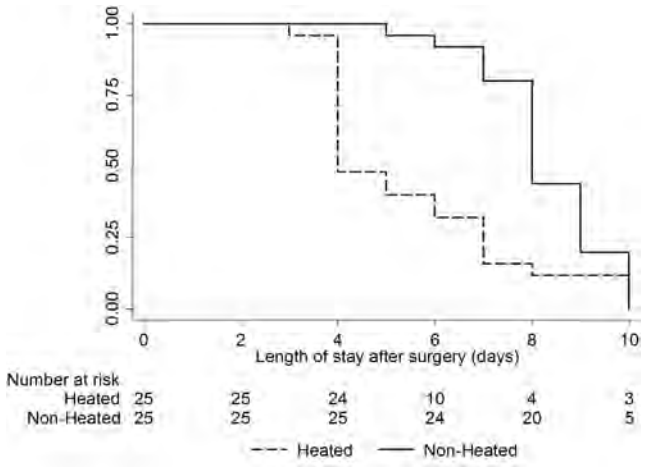

Figure 3 Kaplan—Meier estimates of the proportion in hospital by length in stay. Median length of stay 4 days 95%CI (4, 7) in heated group, 8 days 95%CI (8, 9) in the non-heated group, logrank test $p < 0.001$.

made to perform the skin sparing mastectomy were round-type. Wise pattern incisions have been shown to be associated with an increase of complications particularly skin necrosis however our data suggests that the Wise pattern can be used with heat preconditioning.[16,28]

There was a 24% reduction in skin necrosis between the heated and non-heated groups. The rate of skin necrosis in the non-heated group was 36%. This may seem high however these patients were already at risk of developing skin necrosis for reasons previously discussed. Further, it is worth pointing out that skin necrosis is multifactorial however it is not possible to differentiate between these due to the small size of this study. Despite this, similar rates of necrosis in other groups have been reported.[7,29] These results suggest that there is a clinical correlation between local heat preconditioning and the reduction of skin necrosis. A larger multi-centred randomised trial performed in several centres is required to determine if the observations we found are generalisable and to provide the opportunity to estimate the true treatment effect with greater precision.

An overall all increase of vascularity to the skin of the heated breast compared to the non-heated breast was shown on LDI imaging. Interestingly, this increase was visible 24-h after the preconditioning procedure and even post-mastectomy. This further supports the hypothesis that local heat preconditioning induces an increase in blood flow that is able to maintain perfusion within critically perfused skin i.e. to the mastectomy skin flap. An interesting question to answer is whether LDI imaging can be used intra-operatively to predict skin necrosis. SPY Intraoperative Perfusion Assessment and indocyanin green staining have both been shown to help predict skin ischaemia intra-operatively in pilot studies and would be a useful adjunct to further work in local heat preconditioning.[30,31]

The length of stay in the treatment group was approximately half that of controls. This indicates that heat preconditioning could help to reduce the duration of hospital stay and therefore allow quicker progression to essential adjuvant therapy and reduce healthcare costs.

According to the NHS' Institute for Innovation and Improvement, reducing the length of hospital stay is ranked as a level 1 priority.[32] An economic study into autologous breast surgery at another UK centre, the average length of stay (LOS) following a DIEP flap was 8 days and this is comparable to the LOS at Guy's and St. Thomas' Hospital.[33] In the USA, the LOS is much shorter however this is mainly due to the restrictions of private funding from insurance companies for the same procedure.[34,35] LOS is the most influential factor in the reducing the cost of autologous breast reconstruction.[35] This reduction in LOS potentially indicates a saving of 4 hospital inpatient bed days in one hospital per patient. Last year a total of 151 skin sparing mastectomies were performed at Guy's & St. Thomas' Hospital which could equal a total saving of 604 inpatient bed days per year.

Breast reconstruction is an expensive procedure and essential strategies are needed to help reduce its costs. A bilateral mastectomy and immediate breast reconstruction can last an entire day of operating theatre time. The average cost of a free flap breast reconstruction is estimated at £10,910.[33] There is little data on the cost implications of specifically skin necrosis however, the incidence is between 20 and 40% and the cost of surgical treatment (debridement and skin graft) is approximately £1782 plus extra theatre time (£3840 for half a day in theatre[36]). Extra hospital stay means that the costs can spiral into the thousands. In a modern NHS with increasing financial constraints heat preconditioning could help to reduce the costs of breast reconstruction.

Other benefits to patients aside from financial that come with reduced LOS are improved wound healing and therefore quicker recovery and progression to adjuvant therapy. This means a quicker return to normal life but more importantly, earlier discharge improves recovery, reduces the risks of hospital-acquired infections and venous thromboembolism.[32]

There are several limitations in this study namely that it has small numbers and was not randomised. We are currently planning a larger, randomised, single-blinded single centre trial to investigate the true effect of local heat preconditioning in skin sparing mastectomy. We will also analyse our results based on a per-surgeon basis. The results from this larger trial will provide data to set-up a multi-centred definitive study in the future.

SSM is an excellent model to test heat preconditioning for several reasons: the breast is easy for a patient heat; the patients tend to be healthy with few co-morbidities and are highly motivated. There is scope to use heat preconditioning in other procedures, such as breast reduction and abdominoplasty in the obese population where there is a risk of developing wound-healing problems.[37—39]

Conclusions

The data from this preliminary study suggest that there is a clinical correlation between the reduction of skin necrosis of the mastectomy flaps following SSM with the use of local heat preconditioning in a selected group of patients at risk of this complication. Heat preconditioning is a safe, simple

and cost-effective intervention that can be performed at home and requires no extra admissions to hospital.

Financial disclosures

Part of this project was supported by an Enabling Involvement Grant from the Research Design Service, Kings College London, UK, to support patient participation. There are no other financial disclosures or commercial interests to declare.

Authors contributions

Saahil Mehta — 1st author and principal clinical researcher.

Rachel Rolph — 2nd author and clinical researcher.

Victoria Cornelius — 3rd author and consultant for statistics and preparation of results.

Yves Harder — 4th author, scientific consultant and clinical researcher.

Jian Farhadi — senior author, clinical researcher.

Acknowledgements

The authors wish to thank the Research Design Service, Kings College London, UK, for an Enabling Involvement grant to help with patient participation in this project.

References

1. Meretoja TJ, von Smitten KAJ, Kuokkanen HOM, Suominen SHH, Jahkola TA. Complications of skin-sparing mastectomy followed by immediate breast reconstruction: a prospective randomized study comparing high-frequency radiosurgery with conventional diathermy. *Ann Plast Surg* 2008 Jan;**60**(1):24—8.
2. Munhoz AM, Aldrighi C, Montag E, et al. Periareolar skin-sparing mastectomy and latissimus dorsi flap with biodimensional expander implant reconstruction: surgical planning, outcome, and complications. *Plast Reconstr Surg* 2007 May;**119**(6): 1637—49 [discussion 1650—2].
3. Sotheran WJ, Rainsbury RM. Skin-sparing mastectomy in the UK — a review of current practice. *Ann R Coll Surg Engl* 2004 Mar; **86**(2):82—6.
4. Garwood ER, Moore D, Ewing C, et al. Total skin-sparing mastectomy: complications and local recurrence rates in 2 cohorts of patients. *Ann Surg* 2009 Jan;**249**(1):26—32.
5. Rainsbury RM. Skin-sparing mastectomy. *Br J Surg* 2006 Mar; **93**(3):276—81.
6. Di Candia M, Lie KH, Forouhi P, Malata CM. Experience with the Wise mammaplasty skin resection pattern in skin-sparing mastectomy and immediate breast reconstruction for large breast volumes. *Int J Surg* 2011;**9**(1):41—5.
7. Nava MB, Cortinovis U, Ottolenghi J, et al. Skin-reducing mastectomy. *Plast Reconstr Surg* 2006 Sep;**118**(3):603—10 [discussion 611—3].
8. Bastiaanse J, Nanhekhan LV, Slaaf DW, Boeckx WD, oude Egbrink MGA. Preservation of rat cremaster muscle microcirculation after prolonged cold storage and transplantation. *J Surg Res* 2006 Mar;**131**(1):41—8.
9. Koenig WJ, Lohner RA, Perdrizet GA, Lohner ME, Schweitzer RT, Lewis VL. Improving acute skin-flap survival through stress conditioning using heat shock and recovery. *Plast Reconstr Surg* 1992 Oct;**90**(4):659—64.
10. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993 Mar;**87**(3):893—9.
11. Reinisch JF. The pathophysiology of skin flap circulation. The delay phenomenon. *Plast Reconstr Surg* 1974 Nov;**54**(5): 585—98.
12. Harder Y, Amon M, Laschke MW, et al. An old dream revitalised: preconditioning strategies to protect surgical flaps from critical ischaemia and ischaemia-reperfusion injury. *J Plast Reconstr Aesthet Surg* 2008;**61**(5):503—11.
13. Harder Y, Amon M, Schramm R, et al. Heat shock preconditioning reduces ischemic tissue necrosis by heat shock protein (HSP)-32-mediated improvement of the microcirculation rather than induction of ischemic tolerance. *Ann Surg* 2005 Dec;**242**(6):869—78 [discussion 878—9].
14. Contaldo C, Harder Y, Plock J, Banic A, Jakob SM, Erni D. The influence of local and systemic preconditioning on oxygenation, metabolism and survival in critically ischaemic skin flaps in pigs. *J Plast Reconstr Aesthet Surg* 2007;**60**(11): 1182—92.
15. Harder Y, Contaldo C, Klenk J, Banic A, Jakob SM, Erni D. Improved skin flap survival after local heat preconditioning in pigs. *J Surg Res* 2004 Jun 6;**119**(1):100—5.
16. Davies K, Allan L, Roblin P, Ross D, Farhadi J. Factors affecting post-operative complications following skin sparing mastectomy with immediate breast reconstruction. *Breast* 2011 Feb; **20**(1):21—5.
17. Toth BA, Lappert P. Modified skin incisions for mastectomy: the need for plastic surgical input in preoperative planning. *Plast Reconstr Surg* 1991 Jun;**87**(6):1048—53.
18. Carlson GW. Skin sparing mastectomy: anatomic and technical considerations. *Am Surg* 1996 Feb;**62**(2):151—5.
19. Maines MD, Gibbs PEM. 30 some years of heme oxygenase: from a "molecular wrecking ball" to a "mesmerizing" trigger of cellular events. *Biochem Biophys Res Commun* 2005 Dec 12; **338**(1):568—77.
20. Salom MG, Cerón SN, Rodriguez F, et al. Heme oxygenase-1 induction improves ischemic renal failure: role of nitric oxide and peroxynitrite. *Am J Physiol Heart Circ Physiol* 2007 Dec; **293**(6):H3542—9.
21. Desmons SO, Delfosse CJ, Rochon P, Buys B, Penel G, Mordon S. Laser preconditioning of calvarial bone prior to an X-ray radiation injury: a preliminary in vivo study of the vascular response. *Lasers Surg Med* 2008 Jan;**40**(1):28—37.
22. Clark JE, Foresti R, Sarathchandra P, Kaur H, Green CJ, Motterlini R. Heme oxygenase-1-derived bilirubin ameliorates postischemic myocardial dysfunction. *Am J Physiol Heart Circ Physiol* 2000 Feb;**278**(2):H643—51.
23. Yang ZF, Tsui TY, Ho DW, Tang TC, Fan S-T. Heme oxygenase-1 potentiates the survival of small-for-size liver graft. *Liver Transpl* 2004;**10**(6):784—93.
24. Healy C, Mulhall KJ, Fitz Patrick D, Kay EW, Bouchier-Hayes D. The effect of thermal preconditioning of the limb on flexor tendon healing. *J Hand Surg Eur Vol* 2007 Jun;**32**(3):289—95.
25. Meyer TN, Silva ALD, Vieira C, Alves ACV. Heat shock response reduces mortality after severe experimental burns. *Burns* 2000;**26**(3):233—8.
26. Wernicke AG, Shamis M, Sidhu KK, et al. Complication rates in patients with negative axillary nodes 10 years after local breast radiotherapy after either sentinel lymph node dissection or axillary clearance. *Am J Clin Oncol* 2011 Nov 11.
27. Bani HA, Fasching PA, Lux MM, et al. Lymphedema in breast cancer survivors: assessment and information provision in a specialized breast unit. *Patient Educ Couns* 2007 Jun;**66**(3): 311—8.

28. Santanelli F, Longo B, Sorotos M, Farcomeni A, Paolini G. Flap survival of skin-sparing mastectomy type IV: a retrospective cohort study of 75 consecutive cases. *Ann Surg Oncol* 2013 Mar; **20**(3):981—9.
29. Skoll PJ, Hudson DA. Skin-sparing mastectomy using a modified Wise pattern. *Plast Reconstr Surg* 2002 Jul;**110**(1): 214—7.
30. Newman MI, Jack MC, Samson MC. SPY-Q analysis toolkit values potentially predict mastectomy flap necrosis. *Ann Plast Surg* 2013 May;**70**(5):595—8.
31. Piwkowski C, Gabryel P, Gasiorowski L, et al. Indocyanine green fluorescence in the assessment of the quality of the pedicled intercostal muscle flap: a pilot study. *Eur J Cardiothorac Surg* 2013 Mar 20.
32. Length of stay — reducing length of stay — NHS Institute for Innovation and Improvement. [cited 2012, Jan 1].
33. Atherton DD, Hills AJ, Moradi P, Muirhead N, Wood SH. The economic viability of breast reconstruction in the UK: comparison of a single surgeon's experience of implant; LD; TRAM and DIEP based reconstructions in 274 patients. *J Plast Reconstr Aesthet Surg* 2011 Jun;**64**(6):710—5.
34. Serletti JM, Moran SL. Free versus the pedicled TRAM flap: a cost comparison and outcome analysis. *Plast Reconstr Surg* 1997 Nov;**100**(6):1418—24 [discussion 1425—7].
35. Kaplan JL, Allen RJ. Cost-based comparison between perforator flaps and TRAM flaps for breast reconstruction. *Plast Reconstr Surg* 2000 Mar;**105**(3):943—8.
36. Abbott T, White SM, Pandit JJ. Factors affecting the profitability of surgical procedures under 'payment by results'. *Anaesthesia* 2011 Apr;**66**(4):283—92.
37. Setälä L, Papp A, Joukainen S, et al. Obesity and complications in breast reduction surgery: are restrictions justified? *J Plast Reconstr Aesthet Surg* 2009 Feb;**62**(2):195—9.
38. Gusenoff JA, Rubin JP. Plastic surgery after weight loss: current concepts in massive weight loss surgery. *Aesthet Surg J* 2008;**28**(4):452—5.
39. Sozer SO, Agullo FJ, Santillan AA, Wolf C. Decision making in abdominoplasty. *Aesthetic Plast Surg* 2007;**31**(2):117—27.