



# Short-Term Surgical Complications of Skin-Sparing Mastectomy and Direct-to-Implant Immediate Breast Reconstruction in Women Concurrently Treated with Adjuvant Radiotherapy for Breast Cancer

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## Abstract

**Background** Postmastectomy radiotherapy (PMRT) is allegedly associated with a higher risk of complications of combined nipple-sparing or skin-sparing mastectomy and subpectoral direct-to-implant immediate breast reconstruction ([N]SSM/SDTI-IBR). For this reason, this combination is usually advised against or, even, refused in women who need to undergo PMRT. Because this advice has never been justified, we assessed the short-term complications that may potentially be associated with PMRT after [N]SSM/SDTI-IBR.

**Methods** We compared the complications requiring reintervention and implant loss occurring after 273 [N]SSM/SDTI-IBR that were exposed to PMRT within the first 16 postoperative weeks (interventional group) to those occurring in 739 similarly operated breasts that were not (control group). Additionally, we compared the fraction of complications requiring reintervention occurring after the onset of radiotherapy in the interventional group to that occurring after a comparable postoperative period in the control group.

**Results** The fraction of breasts requiring unscheduled surgical reinterventions for complications and the loss of implants did not differ significantly between both groups but significantly more reinterventions were needed among the controls ( $p = 0.00$ ). The fraction of events after the onset of radiotherapy in the interventional group was higher than the fraction of events after 6.2 weeks in the control group, but not significantly so.

**Conclusion** We found no prove for the alleged increase of short-term complications of adjuvant radiotherapy. Therefore, we advise that these should not be considered valid arguments to advice against [N]SSM/SDTI-IBR.

## Keywords

- breast reconstruction
- breast implant
- radiotherapy

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Combined nipple-sparing or skin-sparing mastectomy and immediate breast reconstruction is oncologically safe and benefits the patient's postoperative self-esteem and sexuality.<sup>1-3</sup> Preservation of the mammary skin and inframammary fold optimizes the overall aesthetic outcome and allows for immediate replacement of the breast volume by autologous tissue, an implant, or a combination of both.<sup>1,2</sup> Of these, implant-based immediate reconstruction has become the most common method for technical, financial, and logistic reasons.<sup>1,4,5</sup> A permanent implant is increasingly being used immediately (the so-called *direct-to-implant* [DTI] approach),<sup>6</sup> likely as a result of the increasing popularity of the nipple-sparing technique of mastectomy and the addition of an acellular dermal matrix (ADM) or mesh to the reconstruction.<sup>5,7</sup>

In parallel, an increasing proportion of women with breast cancer undergo postmastectomy radiotherapy (PMRT) to improve local control, disease-free survival, and long-term survival.<sup>4</sup> Although favorable for the oncological outcome, PMRT has been associated with a significant higher risk of short- and long-term drawbacks that may negatively influence the aesthetic outcome of combined nipple- or skin-sparing mastectomy and implant-based immediate breast reconstruction ([N]SSM/IIBR).<sup>3,5,8</sup> The short-term drawbacks of radiotherapy include skin burn, subcutaneous edema, and wound breakdown, which may result in early infection or, even, loss of the implant.<sup>9,10</sup> The long-term drawbacks usually are the result of radiation-induced increased thickening and subsequent contraction of the physiologic fibrose layer that will encapsulate any implant.<sup>2,11,12</sup> Such capsular contraction causes the reconstructed breast to become firm, distorted, and painful. For these reasons, [N]SSM/IIBR is preoperatively being advised against or, even, refused in patients who might need to undergo PMRT.<sup>4,5,10</sup>

Still, the psychological, aesthetic, and cost-effective advantages of combined [N]SSM/IIBR seem to outweigh the radiation-induced increase of risk of the long-term drawbacks.<sup>9,11,13</sup> This holds true even more for a DTI-IBR.<sup>5</sup> Furthermore, the long-term drawbacks are predictable and can be dealt with. Because they do not result in unscheduled implant loss, these drawbacks should no longer be considered as contraindications for [N]SSM/IIBR in cases where PMRT is indicated.<sup>3,13-15</sup>

The short-term complications that occur in the vulnerable early postoperative period may be considered to feature more psychological impact to the patients. Even though combined nipple- or skin-sparing mastectomy and ADM-assisted DTI-IBR has received ample attention recently, relevant up-to-date information on short-term complications and implant loss resulting from PMRT after conventional combined [N]SSM/SDTI-IBR is lacking to date. There is no univocal evidence that concurrent PMRT causes short-term complications after such [N]SSM/SDTI-IBR and, consequently, the advice against this procedure in women who need to undergo PMRT has so far never been substantiated by clinical study.<sup>15</sup> Therefore, we aimed to assess short-term complications that may potentially be associated with PMRT after [N]SSM/SDTI-IBR.

In this study, we compared the prevalence of these complications after combined conventional [N]SSM/SDTI-IBR that were exposed to PMRT within the first 16 postoperative weeks (interventional group) to that occurring in similarly operated breasts that were not (control group).

## Methods

### Patients

From January 1, 2013, through December 31, 2018, 1,762 combined [N]SSM/SDTI-IBR were performed in the Netherlands Cancer Institute for 1,364 women. Of these, 672 prophylactic procedures were not included for this study. The other 1,090 breasts were therapeutically operated for carcinoma or ductal carcinoma in situ (DCIS). Data on 72 of these 1,090 breasts were excluded because a two-staged tissue expander/implant approach was used rather than a DTI approach. Additionally, data on another five breasts (four women) was excluded because the prosthesis differed from the implant routinely used in our patients. Finally, data on one breast (one woman) was excluded because she underwent radiotherapy prior to her therapeutic mastectomy and reconstruction.

Of the 1,012 operated breasts (965 women) included for further assessment, 273 breasts (271 women) underwent PMRT within the first 16 postmastectomy weeks. Two women in this interventional group bilaterally underwent the therapeutically applied combined breast procedure and concurrent PMRT (►Table 1). The remaining 739 breasts (706 women) did not receive radiotherapy within the first 16 weeks after surgery.

In 12 of the 965 women, both breasts were therapeutically treated while only one of both was subjected to adjuvant radiotherapy. Consequently, the data on the one breast of these 12 women were included in the interventional group, whereas the data on the contralateral breast were included in the control group. The study was approved by the Institutional Review Board.

### Treatment

#### Preoperative Therapy

Neoadjuvant chemotherapy was provided to 210 of the 271 women (210/273 breasts) of the interventional group and to 210 of the 706 women (215/739 breasts) of the control group. None of them underwent neoadjuvant radiotherapy or previous radiotherapy as part of breast conserving therapy.

#### Mastectomy and Subpectoral Direct-to-Implant Immediate Breast Reconstruction

All women were operated on by one of five dedicated oncologic breast surgeons and one of five dedicated plastic surgeons in the standardized fashion previously reported.<sup>16</sup> In 535 of the 1,012 mastectomies the areolar complex was resected, whereas a nipple-sparing mastectomy was performed in the other 477 breasts (►Table 1).

Immediately following nipple- or skin-sparing mastectomy, a textured, high-cohesive gel-filled permanent

**Table 1** Means (range and standard deviation) or number (percentages) of patient-related and procedure-related characteristics occurring among our study groups

Factor	Interventional group (273 breasts)	Control group (739 breasts)	p-Value
Age [y] <sup>a</sup>	44.1 (25–72; SD 11.57)	48.4 (19–76, SD 10.91)	<b>0.00</b>
BMI [kg/m <sup>2</sup> ] <sup>a</sup>	24.0 (16.7–43.4; SD 3.72)	23.5 (16.5–40.4; SD 3.90)	0.07
General health factors <sup>b</sup>	26 (9.5)	95 (12.9)	0.15
Tobacco abuse <sup>c</sup>	16 (5.9)	102 (13.8)	<b>0.00</b>
Previous BCS <sup>d</sup>	29 (10.6)	83 (11.2)	0.79
Carcinoma	270 (98.9)	537 (72.7)	<b>0.00</b>
Contralateral surgery <sup>e</sup>	52 (19.0)	199 (26.9)	<b>0.01</b>
Specimen weight [g]	499 (100–1,545; SD 268.2)	485 (68–1,750; SD 265.3)	0.46
Implant volume [mL] <sup>f</sup>	433 (110–775; SD 142.8)	425 (125–775; SD 136.5)	0.41
Nipple-sparing mastectomy	116 (42.5)	361 (48.8)	0.07

Abbreviations: BCS, breast conserving surgery; BMI, body mass index; SD, standard deviation.

Note: Statistically significant p-values are provided in bold.

<sup>a</sup>Means or fractions in women instead of in breasts.

<sup>b</sup>General health factors = preexistent diabetes mellitus, cardiovascular or pulmonary disease, rheumatoid arthritis, and/or hematologic disorders.

<sup>c</sup>Tobacco abuse = negative if patient quit smoking  $\geq 6$  months ago.

<sup>d</sup>Breast conserving surgery (not followed by adjuvant radiotherapy).

<sup>e</sup>Skin-sparing mastectomy combined with any simultaneous contralateral breast surgery.

<sup>f</sup>Intraoperative implant volume.

implant (Natrelle Style 410; Allergan, Marlow, Buckinghamshire, United Kingdom) was implanted subpectorally. For this, the costal and lower sternal attachment of the pectoral major muscle to the lower costal arch and the caudal part of the sternum was released.<sup>16</sup> Subsequently, the released origin of the major pectoral muscle was sutured subcutaneously to the inferior mammary flap. Because no biological or synthetic matrix was applied in any of the operated women, the lower pole of the implant was situated subcutaneously and the upper pole, subpectorally.

After the combined surgical procedure, 23 of the 273 breasts in the interventional group and 167 of the 739 breasts in the control group were exposed to adjuvant chemotherapy.

### Postmastectomy Radiotherapy

PMRT started a mean of 6.2 weeks (standard deviation [SD] 2.30) postmastectomy in women of the interventional group. In general, a mean radiation dose of 5080 cGy (range, 4256–7000) was given in 16 to 28 fractions, resulting in a total of 4 to 6 weeks of daily sessions of radiotherapy.

The control group either received no PMRT (655 breasts of 626 women), or PMRT started more than 16 weeks after surgery (84 breasts of 80 women).

## Data Gathering and Analysis

### Patient-Related and Procedure-Related Data

Demographics and data on characteristics of the patients and procedures that may possibly have acted as surgical risk factors for postoperative complications were retrieved from a prospectively maintained database, for both groups (►Table 1). Apart from advanced age, tobacco abuse, and

overweight, we scored previous lumpectomy, the type of malignancy (carcinoma or DCIS), and various health factors as potential risk factors related to the patient.<sup>5,17,18</sup> As potential risk factors related to the procedure, we assessed the surgical specimen weight, the implant volume, and simultaneous [N]SSM/SDTI-IBR of the contralateral breast.<sup>17</sup>

### Outcome Measures

All complications, all unscheduled surgical reinterventions, and all implants losses during the first 16 postoperative weeks were noted for each reconstructed breast as the short-term outcome measures (►Table 2). This period was accepted because radiotherapy starts approximately 6 weeks postmastectomy and lasts 4 to 6 weeks. This way, all short-term complications that are potentially influenced by PMRT received by the interventional group could be assessed for this study. Furthermore, shorter periods of assessment may inadequately assess postoperative implant loss.<sup>8</sup>

We differentiated between minor complications that could be treated conservatively, and major complications that necessitated unscheduled surgery. For this study, we solely assessed the major complications because surgical reinterventions present an objective benchmark for clinically significant unfavorable results.<sup>5,19</sup> Of these major complications, implant loss is the primary outcome measure of implant-based reconstruction.<sup>5,17</sup>

### Statistical Analysis

The distribution of patient- and procedure-related characteristics in both groups was statistically compared to assess the level of similarity of both groups. Student's *t*-test was applied for continuous variables and the two-tailed chi-squared test, for dichotomous variables.<sup>20</sup>

**Table 2** Number (and prevalence in percentages) of major complications, unscheduled surgical reinterventions, and implant loss among our study groups

Short-term events	Interventional group (273 breasts)	Control group (739 breasts)	p-Value
Breasts requiring reintervention <sup>a</sup>	56 (20.5)	182 (24.6)	0.17
Ø Seroma	0 (0.0)	3 (0.4)	0.29
Ø Hematoma	14 (5.1)	27 (3.7)	0.29
Ø Infection	14 (5.1)	29 (3.9)	0.40
Ø Necrosis	28 (10.3)	123 (16.6)	<b>0.01</b>
Total number of reinterventions <sup>b</sup>	68 (24.9)	238 (32.2)	<b>0.00</b>
Ø 1 reintervention	46 (16.8)	134 (18.1)	0.64
Ø 2 reinterventions	8 (2.9)	40 (5.4)	0.10
Ø 3 reinterventions	2 (0.7)	8 (1.1)	0.62
Loss of implant <sup>c</sup>	16 (5.9)	45 (6.1)	0.89

Note: Statistically significant *p*-values are provided in bold.

<sup>a</sup>Number of breasts needing at least one extra, unscheduled surgical reintervention within 16 weeks after initial surgery.

<sup>b</sup>Total number of unscheduled reinterventions within 16 weeks as fraction of the number of operated breasts.

<sup>c</sup>Number of breasts in which the reinterventions comprised explantation of the implant.

The fractions of breasts requiring unscheduled surgical interventions, the fraction of total number of such reinterventions, and the fraction of loss of implant in both groups were statistically compared using the chi-squared test.<sup>20</sup>

Additionally, we differentiated between major complications, unscheduled surgical reinterventions, and implant loss presenting before the onset of radiotherapy and those presenting after, in the interventional group. Because radiotherapy started on average 6.2 weeks (SD 2.30) after combined [N]SSM/SDTI-IBR in the interventional group, we compared the differentiated fractions with those presenting in the control group prior to, respectively, after 6.2 weeks postoperatively.

*p*-Values of 0.05 or less were accepted as statistically significant.

## Results

### Comparability of Study Groups

While the distribution of procedure-related characteristics was similar among both study groups, the distribution of some patient-related characteristics significantly differed between the interventional group and the control group (► **Table 1**). As such, the interventional group featured a significantly higher prevalence of malignancy rather than premalignancy, whereas the control group was older, featured more tobacco abuse, and underwent a higher number of simultaneous contralateral breast surgery.

### Outcome of Combined [N]SSM/SDTI-IBR

Overall, we found 238 (23.5%) breasts to have undergone additional unscheduled surgical reinterventions after the total number of 1,012 combined procedures (► **Table 2**). These 238 breasts required a total of 306 reinterventions. In 61 (6.0%) breasts, the reinterventions comprised explantation of the implant.

The fraction of breasts needing such reinterventions (*p*=0.17) and the prevalence of the major complication resulting in implant loss (*p*=0.89) was lower in the interventional group than among the controls, but not significantly so (► **Table 2**). The total number of unscheduled reinterventions was, even, significantly lower in the interventional group (*p*=0.00).

### Pre- versus Postradiotherapy Complications

The fractions of breasts needing surgical reintervention, total number of reinterventions, and implant loss occurring after the onset of adjuvant radiotherapy in the interventional group did not differ statistically from those presenting after 6.2 weeks in the control group (► **Table 3**).

## Discussion

In this study, we found that PMRT following combined [N]SSM/SDTI-IBR does not result in a significantly higher risk of short-term postoperative complications leading to unscheduled surgical reinterventions, or loss of implant. Rather, the control group that was not irradiated during the first 16 postoperative weeks tended to do worse during those weeks than the interventional group, although mostly not significantly so.

Even though major complications, unscheduled reinterventions, and implant loss occurred less frequently in the interventional group, they occurred more often after the onset of PMRT than before when compared with those occurring after 6.2 weeks in the control group. However, this difference was not statistically significant.

Previous observations on the potential influence of PMRT on the outcome of breast reconstruction appear to be conflicting. Up to 2010, most authors found PMRT to compromise the outcome of implant-based breast reconstruction. More recent data suggest that surgical complications are not

**Table 3** Fraction (and percentages) of number of events that occurred after initiation of radiotherapy in the interventional group and after a comparable postoperative period of 6.2 weeks in the control group

Short-term event	Interventional group (273 breasts)	Control group (739 breasts)	<i>p</i> -Value
Breasts requiring reintervention <sup>a</sup>	9/56 (16.1)	17/182 (9.3)	0.16
Total number of reinterventions <sup>b</sup>	15/68 (22.1)	39/238 (16.0)	0.28
Loss of implant <sup>c</sup>	7/16 (43.8)	11/45 (24.4)	0.15

Note: Statistically significant *p*-values are provided in bold.

<sup>a</sup>Fraction of number of breasts needing at least one extra, unscheduled surgical reintervention.

<sup>b</sup>Fraction of total number of unscheduled reinterventions.

increased among women receiving PMRT using modern techniques.<sup>21</sup> In general, Jagsi et al concluded from a claim-based analysis that PMRT is not associated with contributing to an impaired wound healing or increased risk of infection within the first 6 months after treatment, regardless of type of reconstructive surgery.<sup>22</sup>

Since 2010, the potential influence of concurrent PMRT on the outcome of combined nipple- or skin-sparing mastectomy and (selective) ADM-assisted DTI-IBR is increasingly reported on. From a comparison of the outcome in two subgroups of women ADM-assisted DTI-IBR by Lin et al may be learned that the overall rate of complications in their PMRT group (17/149, or 11.4%) compared with that in the non-PMRT group (78/767, or 10.2%).<sup>23</sup> The authors furthermore reported 6/149 (4.0%) explantations and 17/149 (11.4%) reconstructive failures among the DTI-PMRT subgroup but, unfortunately, did not report on these rates in the non-PMRT subgroup. The authors concluded that, in the presence of PMRT, ADM-assisted DTI-IBR features a more favorable surgical outcome than two-staged IBR.<sup>23</sup>

Naoum et al observed comparable rates of 4.1% of skin necrosis in their subgroups of 171 mostly ADM-assisted DTI-IBR with PMRT and 462 DTI-IBR without PMRT.<sup>5</sup> Although the infection rates differed significantly with 11/171 (6.4%) in the PMRT subgroup and 12/462 (2.6%) in the non-PMRT subgroup, their rates of implant loss compared with 5/171 (2.9%) and 12/642 (2.6%) in the PMRT subgroup and the non-PMRT subgroup, respectively. This made the authors conclude that DTI-IBR may offer a valuable option for patients receiving PMRT.<sup>5</sup> Two more recent studies on ADM-assisted prepectoral DTI-IBR both reported PMRT not to significantly influence the rate of postoperative complications.<sup>24,25</sup> Still, we have been unable to trace an unambiguous recent report on the influence of PMRT on the short-term surgical outcome of non-ADM-assisted combined [N]SSM/SDTI-IBR.

We present an assessment of a single-institute, standardized surgical approach rather than a multicenter study. This implies that our observations may not be generalized. Still, a single group's extensive and long-term experience with uniformly performed [N]SSM/SDTI-IBR in both a concurrently irradiated and nonirradiated mammary region provides a unique opportunity to evaluate the potentially different outcomes in two otherwise uniformly treated populations.<sup>26</sup> The advantage of this approach is that the large confounding variable of (peri-)surgical treatment has been controlled for.<sup>5</sup>

Second, the oncologically implicit selection of women to undergo adjuvant radiotherapy may have influenced our observation. Subjects in the interventional group may potentially have been disadvantaged as more of them were treated for a malignancy rather than a premalignancy (DCIS). In general, it may be disputed whether, or not, a difference in malignancy grade or previous treatment is to be considered a relevant selection bias. The indication of radiotherapy implies less favorable oncological-associated characteristics that, therefore, are given facts. Even though these characteristics may be considered as potentially influential regarding the outcome of surgery, they should not prevent the assessment of an intervention. More specific, although some evidence exists that malignancies are associated with wound healing problems,<sup>8</sup> it has not been objectified to date whether invasive mammary carcinoma presents a higher risk of postoperative complications than DCIS does. Contrastingly, the higher prevalence of tobacco abuse among the controls is likely to have disadvantaged the outcome in that group.<sup>1,5,12,17</sup> In a previous study we found tobacco abuse to be correlated with increased risk of implant loss, but not of short-term complication, in our hands.<sup>17</sup> Even though the women of our interventional group were more burdened from an oncologic perspective, most of the remaining patient-related potential risk factors compared favorably to those of the control group in this study. This may, at least in part, explain their more favorable postoperative outcome.

Third, the oncologic surgeons and plastic surgeons were, implicitly, not blinded to the intervention. They may, knowingly or unknowingly, have tended to operate more conservatively in women whom they know to need to undergo PMRT. Still, if this had been true one may expect this to be reflected in a lower average weight of the surgical specimen (for the oncologic surgeon), or a lower average volume of the implant used (by the plastic surgeon). We found both this weight and the replacement volume not to differ significantly and the fraction of replaced-to-resected measures to be similar in the interventional group (433/499 mL/g, or 87%) and the control group (425/485 mL/g, or 88%).

Next, we did not assess possible long-term complications as these may be anticipated and do not result in unscheduled implant loss. Because long-term drawbacks may be predictably dealt with, we feel that these should no longer be considered as contraindications for [N]SSM/SDTI-IBR in cases where PMRT is indicated.<sup>3,13–15</sup>



Last, we did not assess concurrent chemotherapy as a possible risk factor for the short-term outcome of the combined surgical procedure in this study even though the information available on this topic may appear contradictory.<sup>5</sup> Neoadjuvant chemotherapy does not present an additional risk for complications of the combined surgical procedure,<sup>5</sup> provided surgery was performed at least 3 weeks after the completion of chemotherapy.<sup>27</sup> Furthermore, we previously showed that it does not negatively affect our surgical results.<sup>18</sup> Likewise, we recently showed that the application of adjuvant chemotherapy did not increase the rate or occurrence of major complications associated with breast surgery when the onset of chemotherapy was scheduled after the third postoperative week ( $p=0.60$ ).<sup>28</sup> Most important, adjuvant chemotherapy did not result in a significant increase of the most relevant outcome measure: loss of implant ( $p=0.86$ ).<sup>28</sup> Therefore, we accepted concurrent chemotherapy not to be a potential risk factor for short-term major complications after the combined procedure, in our hands.

Our observations suggest that it is justifiable to offer combined non-ADM-assisted [N]SSM/SDTI-IBR to women who might later need to undergo PMRT. The outcome we observed in this group compares to that in a control group in which such prevalence of short-term complications and loss of the implant is generally considered acceptable.<sup>3</sup> Because the short-term complications were not increased in the interventional group and because patient satisfaction rates in comparable groups have been reported to remain high at 80 to 100%,<sup>11</sup> the advantages of the combined procedure may indeed be considered to outweigh the risk of complications.<sup>13</sup> Its complication rates compare with those of ADM-based DTI-IBR but it is more cost effective.<sup>6</sup> For these reasons, we feel that women who might need to undergo PMRT should be offered the same reconstructive options as those who might not. The alleged short-term complications of adjuvant radiotherapy should not be considered valid arguments to advice against non-ADM-assisted combined [N]SSM/SDTI-IBR. Our comparable complication rates, furthermore, were obtained by using textured implants while smooth implant application appears to gain popularity. Because we feel that the aesthetic results of biodimensional implants are superior in oncological breast reconstructions, we continue using textured implants rather than smooth implants. Smooth implants have, so far, not been proven to lead to comparable results.

We differentiated between the major complications, unscheduled reinterventions, and implant loss occurring after the onset of adjuvant therapy and those occurring before such onset because those occurring prior to radiotherapy are not be considered to be induced, or even caused, by that therapy (–Table 3).<sup>29</sup> We found events to occur more often after the onset of PMRT when compared with those occurring after 6.2 weeks in the control group. Of these, the nonsignificantly higher fraction of breasts needing at least one unscheduled reintervention ( $p=0.16$ ) and of the total number of these interventions ( $p=0.28$ ) observed after the onset of PMRT may be explained by an increased number of reinterventions needed in case a major complication occurs in irradiated tissue. As such, PMRT still seems to have a negative effect on the healing of complications once they occur after combined (N)SSM/SDTI-IBR.

However, it may equally indicate that aggressive surgical treatment of major complications leads to lower numbers of loss of implants. We are inclined to liberally reintervene in case of inflammation or skin breakdown and found this inclination to be associated with a decrease of implant infection and loss (Kooijman, unpublished work). This may explain why complications tended to require multiple reinterventions more often once they occurred in the control group. Because implant loss is the most relevant outcome measure of implant-based breast reconstruction, we regard any decrease of implant loss as a valuable outcome.

In conclusion, our study shows that short-term major complications and implant loss equally appeared in women who underwent adjuvant radiotherapy within 16 weeks after combined [N]SSM/SDTI-IBR, and women who did not undergo such adjuvant treatment. Therefore, we conclude that women who might need to undergo adjuvant radiotherapy after mastectomy ought to be offered the same reconstructive options as those who likely need not. The alleged short-term complications of adjuvant radiotherapy should not be considered valid arguments to advice against or, even, refuse [N]SSM/SDTI-IBR.

#### Author Contributions

Conceptualization: M.M.L.K. and J.J.H. Data curation: M.M.L.K. and L.A.E.W. Formal analysis: M.M.L.K. and J.J.H. Methodology: M.M.L.K., J.J.H., and L.A.E.W. Project administration: J.J.H. Visualization: M.M.L.K. and J.J.H. Writing-original draft: M.M.L.K. and J.J.H. Writing-review and editing: M.M.L.K., J.J.H., A.N.S., M.-J.T.F.D.V.-P., and L.A.E.W. All authors read and approved the final manuscript.

#### Conflict of Interest

None declared.

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