Strahlentherapie
und Onkologie

Original Article

Fibrotic Changes after Postmastectomy Radiotherapy and Reconstructive Surgery in Breast Cancer

A Retrospective Analysis in 109 Patients

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Purpose: The purpose of this study was to analyze the probability and time course of fibrotic changes in breast reconstruction before or after postmastectomy radiotherapy (PMRT).

Materials and Methods: Between 1995 and 2004, 109 patients were treated with PMRT at Tübingen University and underwent heterologous (HL) or autologous (AL) breast reconstruction prior or subsequent to radiation therapy. Fibrosis of the reconstructed breast after radiotherapy was assessed using the Baker score for HL reconstructions and the Common Terminology Criteria for Adverse Events (CTCAE) for all patients. Actuarial rates of fibrosis were calculated for the maximum degree acquired during follow-up and at the last follow-up visit documented.

Results: Median time to follow-up was 34 months (3–227 months). Radiotherapy was applied with a median total dose of 50.4 Gy. A total of 44 patients (40.4%) received a boost treatment with a median dose of 10 Gy. Breast reconstruction was performed with AL, HL, or combined techniques in 20, 82, and 7 patients, respectively. The 3-year incidence of $\geq$ grade III maximum fibrosis was 20% and 43% for Baker and CTCAE scores, respectively. The corresponding figures for fibrosis at last follow-up visit were 18% and 2%. The 3-year rate of surgical correction of the contralateral breast was 30%. Initially unplanned surgery of the reconstructed breast was performed in 39 patients (35.8%). Boost treatment and type of cosmetic surgery (HL vs. AL) were not significantly associated with the incidence of fibrosis.

Conclusions: We found severe fibrosis to be a frequent complication after PMRT radiotherapy and breast reconstruction. However, surgical intervention can ameliorate the majority of high grade fibrotic events leading to acceptable long-term results. No treatment parameters associated with the rate of fibrosis could be identified.

Key Words: Postmastectomy radiotherapy · Fibrotic changes · Breast reconstruction · Breast cancer · Treatment

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Fibrose nach Thoraxwandbestrahlung und Brustrekonstruktion: Eine retrospektive Analyse bei 109 Patientinnen

Zielsetzung: Ziel der Arbeit war es, die Frequenz und den zeitlichen Verlauf fibrotischer Veränderungen nach Thoraxwandbestrahlung und plastischer Rekonstruktion der Mamma zu analysieren.

Material und Methoden: Zwischen 1995 und 2004 wurde bei 109 Patientinnen in der Klinik für Radioonkologie des Universitätsklinikums Tübingen eine Thoraxwandbestrahlung nach Mastektomie durchgeführt. Vor oder nach der Bestrahlung erfolgte eine autologe (AL) oder heterologe (HL) Brustrekonstruktion. Fibrotische Veränderungen der rekonstruierten Brust wurden retrospektiv anhand des Baker-Scores (AL) bzw. der Definition der *Common Terminology Criteria for Adverse Events* (CTCAE) erhoben. Es wurden aktuarische Raten der stärksten beobachteten Ausprägung der Fibrose bzw. des Fibrosegrades zum letzten Beobachtungszeitpunkt für beide Scores erhoben.

Ergebnisse: Die mediane Nachbeobachtungszeit betrug 34 Monate (3–227). Die Strahlentherapie wurde mit einer medianen Gesamtdosis von 50.4 Gy appliziert. 44 Patientinnen (40.4%) erhielten eine Boostbestrahlung mit einer medianen Gesamtdosis von 10 Gy. Die Brustrekonstruktion erfolgte in AL- bzw. HL- oder kombinierter Technik bei 20, 82, bzw. 7 Patientinnen. Die 3-Jahresinzidenz der maximal beobachteten Fibrose $\geq$ Grad III betrug 20% nach der Baker-Klassifikation bzw. 43% nach CTCAE-Score.

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Die entsprechenden Fibroseraten für den letzten Beobachtungszeitpunkt betrugen 18% bzw. 2%. Die 3-Jahresrate operativer Korrekturen der kontralateralen Brust betrug 30%. Bei 39 Patientinnen (35.8%) wurden initial ungeplante operative Zweiteingriffe an der rekonstruierten Brust durchgeführt. Die Boostbestrahlung und die Rekonstruktionstechnik (AL bzw. HL) hatten keinen signifikanten Einfluss auf die Fibroserate.

Schlussfolgerung: Höhergradige Fibrosen stellen eine regelmäßige Komplikation nach Thoraxwandbestrahlung und plastischer Brustrekonstruktion dar. Offenbar kann der überwiegende Teil der fibrotischen Komplikationen operativ korrigiert werden. Wir konnten keine Risikofaktoren für die Entwicklung höhergradiger Fibrosen identifizieren.

Schlüsselwörter: Radiotherapie nach Mastektomie · Fibrotische Veränderungen · Brustrekonstruktion · Brustkrebs · Behandlung

Introduction

Breast cancer is the most frequent malignancy in women in western countries with approximately 60,000 new cases in Germany every year [12]. Surgery is the mainstay of local treatment, and breast-conserving surgery is performed in the majority of patients. However, mastectomy is still considered an acceptable approach particularly in locally advanced or multicentric disease [12].

Radiotherapy has been used as adjuvant local treatment for decades after mastectomy particularly in patients with locally advanced disease considered at high risk of local relapse. According to current guidelines, chest wall irradiation is indicated in patients with T3 or T4 tumors, node-positive disease, or in patients with marginal or incomplete resection [12, 20]. The benefits of chest wall irradiation have been illustrated in many prospective trials and several metaanalyses [8, 19, 25, 26]. It has, thus, been demonstrated that adjuvant radiotherapy reduces the risk of local relapse by approximately two-thirds ultimately improving long-term survival of the patients [7, 19, 23, 2].

Breast reconstruction can be offered to patients after mastectomy in order to reduce the psychological trauma of ablative surgery and to restore the physical integrity as far as possible. However, there is an abundance of literature indicating that clinical results of reconstructive surgery are impaired in those patients who undergo adjuvant radiotherapy before or after breast reconstruction as compared to patients without adjuvant radiotherapy [4, 13, 17, 28]. Radiation-induced fibrosis of skin and subcutaneous soft tissues is considered one of the main reasons for these observations. Yet, in patients requiring adjuvant radiotherapy a more detailed analysis of potential factors associated with fibrotic changes and clinical outcome of breast reconstruction, including timing and technique of reconstructive surgery or parameters of radiotherapy, is warranted. Therefore, we performed a retrospective analysis of our patients treated at the Department of Radiation Oncology at Tübingen University. Here, the results of the study with particular emphasis on fibrotic changes of the reconstructed breast after adjuvant radiotherapy are presented.

Material and Methods

Patients treated at the Department of Radiation Oncology at Tübingen University between 1995 and 2004 were eligible for the analysis. Inclusion criteria were uni- or bilateral breast cancer treated with mastectomy and surgical breast reconstruction preceded or followed by adjuvant radiotherapy. Patients who were submitted to mastectomy after initial breast-conserving surgery and radiotherapy to the residual breast or patients with breast reconstruction after partial mastectomy were not eligible for analysis. Patients were identified by searching the electronically stored treatment reports of the patients at the Department of Radiation Oncology, by searching the database of Tübingen Cancer Center, and by screening the operating logs of the two main referral centers of gynecological oncology (Tübingen University and Reutlingen Hospital). Follow-up information was acquired from the patient files of the Departments of Radiation Oncology and Gynecology. Furthermore, a questionnaire was mailed to general practitioners and gynecologists involved in the follow-up management of the patients identified for this analysis. The response rate to the questionnaire was 62.4% ($n=68$). In 13 cases, no questionnaire was mailed because the patients had already died, or complete follow-up information was available from the hospital charts.

The primary end-point of the analysis presented here is the rate of chronic fibrosis assessed by Common Terminol-

Table 1. Classification of fibrosis according to Common Terminology Criteria for Adverse Events v3.0 (**a**) and Baker (**b**). ADL: activity of daily life.

Tabelle 1. Klassifikation der Fibrose nach Definition der Common Terminology Criteria for Adverse Events v3.0 (CTCAE) Kriterien (**a**) und der Baker-Klassifikation (**b**). ADL: activity of daily life.

a	
Grade 1	Increased density, "spongy" feeling
Grade 2	Increased density with firmness or tethering
Grade 3	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL
Grade 4	Life-threatening; disabling; loss of limb; interfering with vital organ function
Grade 5	Death
b	
Grade 1	Breast with implant as soft as contralateral unaffected breast
Grade 2	Minimal – breast with implant with reduced softness, implant palpable but not visible
Grade 3	Moderate – breast with implant harder than contralateral breast, implant palpable and visible
Grade 4	Severe – breast with implant hard, tensious, painful, distortion is frequent

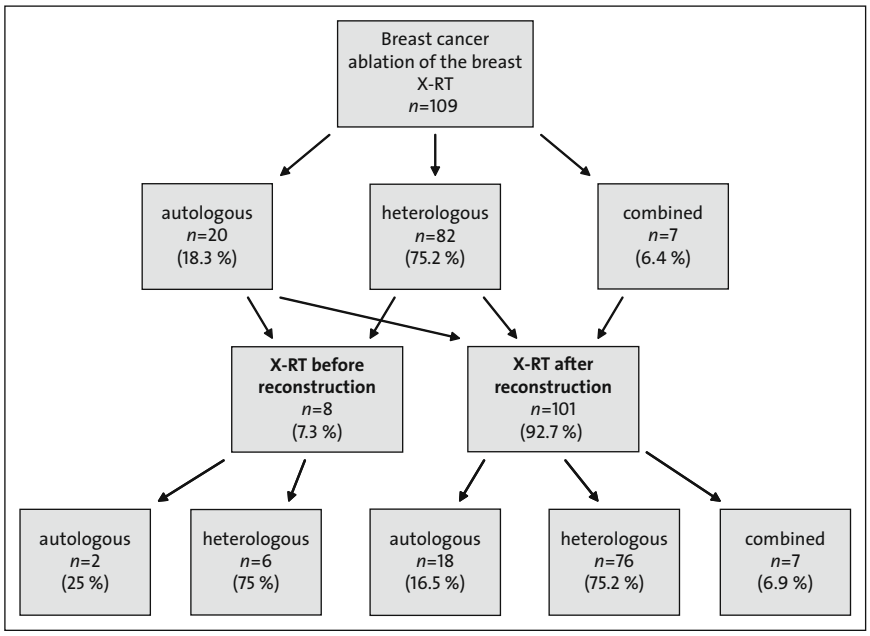

Figure 1. Type of breast reconstruction at the time of radiotherapy.

Abbildung 1. Art der Brustrekonstruktion zum Zeitpunkt der Strahlentherapie.

Table 2. Reasons for unplanned surgical interventions following breast reconstruction.

Tabelle 2. Gründe für initial nicht geplante Operationen nach Brustrekonstruktion.

Reason for surgery	Patients affected (n)
Flap loss	1
Loss of volume after radiotherapy	1
Dog ear resection	1
Organized hematoma	1
Unsatisfying cosmetic results	1
Protrusion of implant	2
Chronic infection	2
Complication with expander	3
Dislocation of expander	3
Distension of suture	6
Correction of the scar	10
Unplanned removal of expander or implant	12
Change of reconstruction technique	14
Nipple reconstruction	17
New implant/expander	18
Capsular fibrosis	20

ogy Criteria for Adverse Events v3.0 (CTCAE) (Table 1a). Furthermore, the Baker score was applied to all patients for evaluation of fibrosis after breast reconstruction with expander or implants (Table 1b) [16]. Both classifications were assessed for the maximum score acquired during the follow-up period and for the degree of fibrosis at the last date of follow-up available. Follow-up times were calculated from the last day of radiotherapy.

All data were tabulated in Excel® spreadsheets and were further processed using Statistica® for Windows. Time-dependent variables were analyzed using the Kaplan-Meier method and the log-rank test. A value of $p<0.05$ was considered statistically significant.

Results

Patients

A total of 109 patients were identified for this retrospective analysis. Median age was 47 years (range 31–74 years). Median time to follow-up was 34 months (range 3–227 months). The primary gynecological referral center where breast reconstruction was performed was Tübingen University in 54 patients, Reutlingen Hospital in 29 patients, and 9 additional departments in the remaining 26 patients. Adjuvant radiotherapy was performed at Tübingen University Hospital in all patients.

Radiotherapy

Three-dimensional treatment planning was performed in all patients. Radiotherapy with 6 MV photons was applied to the chest wall/the reconstructed breast in all 109 patients. The ipsilateral supraclavicular or internal mammary lymph nodes were irradiated in 64 and 39 patients, respectively. Median total dose to the chest wall and the lymph nodes was 50.4 Gy at a median fraction dose of 1.8 Gy. A boost treatment of the chest wall/reconstructed breast was given in 44 patients (40.4%) with a median total dose of 10 Gy. Boost radiation was performed with photons, electrons, or mixed-beam technique in 26, 15, and 3 patients, respectively. A bolus material was used in 2 patients (1.8%).

Systemic Treatment

Systemic treatment was applied in 101 patients (92.7%) with either endocrine treatment ($n=19$), chemotherapy ($n=18$), or chemotherapy followed by endocrine treatment ($n=64$). The preferred regimen for chemotherapy and endocrine treatment were anthracyclines with ($n=21$) or without ($n=45$) taxanes, and tamoxifen with ($n=10$) or without ($n=57$) LH-RH agonists. There were only 8 patients who did not receive adjuvant systemic treatment.

Breast Reconstruction

Breast reconstruction was accomplished with autologous ($n=5$: transverse rectus abdominis myocutaneous flap (TRAM);

$n = 15$: latissimus dorsi flap (LD)), heterologous ($n = 59$: expander followed by implants; $n = 23$: permanent implants) or combined techniques ($n = 7$). At the time of radiotherapy, 101 patients had been submitted to breast reconstruction, and 8 patients received reconstruction after irradiation (Figure 1). Due to the small number of patients with plastic surgery subsequent to radiotherapy, the timing of breast reconstruction and radiotherapy was not considered further in our analyses.

Complete breast reconstruction was achieved in 95 patients (87.2%); in 4 patients with implantation of expanders information was missing as to whether these were later removed and exchanged with implants. In 10 patients (9.2%), reconstruction of the breast was not completed due to interfering complications.

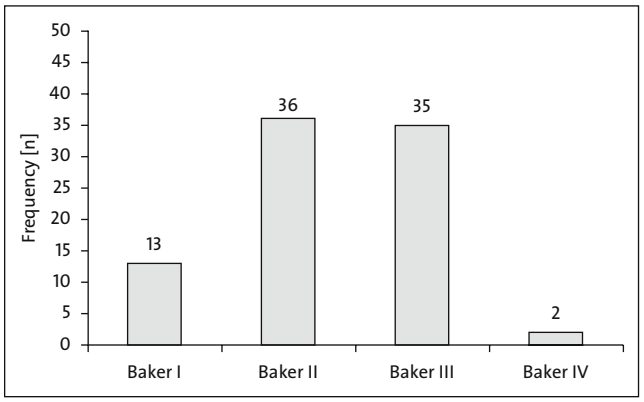

Figure 2. Fibrosis according to the Baker classification. Distribution of the highest score observed during the follow-up period.

Abbildung 2. Fibrose erhoben nach der Baker-Klassifikation. Dargestellt ist die Verteilung des höchsten Fibrosegrades während der Nachbeobachtungszeit.

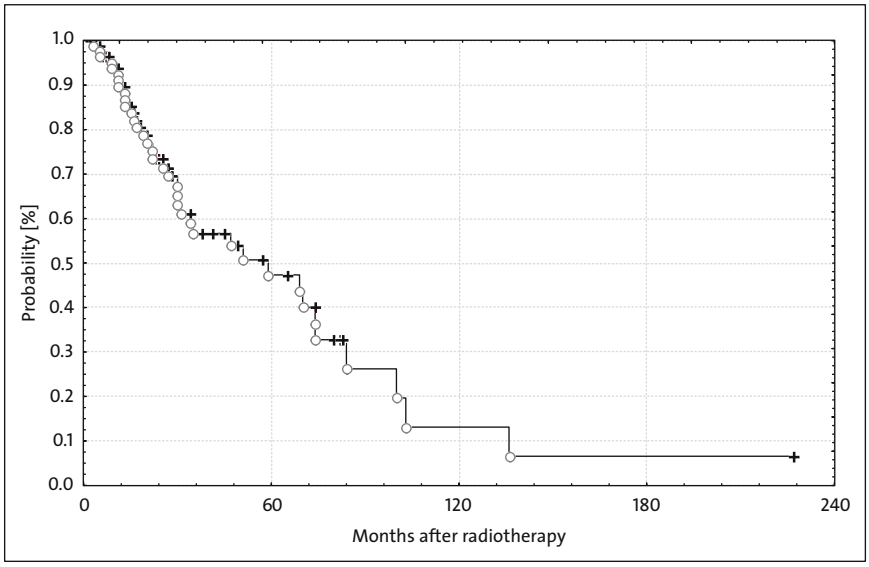

Figure 3. Fibrosis according to the Baker classification. Kaplan-Meier estimates for the probability of staying unaffected by ≥ grade III maximum scores during follow-up.

Abbildung 3. Fibrose erhoben nach der Baker-Klassifikation. Kaplan-Meier-Schätzung für die Wahrscheinlichkeit, keine Nebenwirkung ≥ Grad III als maximale Ausprägung während der Nachbeobachtungszeit zu entwickeln.

Unplanned Surgical Interventions Following Breast Reconstruction

Initially unplanned surgical interventions subsequent to breast reconstruction except those for local or regional relapse of breast cancer were necessary in 39 patients (35.8%). The most frequent reasons included capsular fibrosis and removal or exchange of the expander/implant (Table 2). The average of secondary surgical interventions was 0.8 per completed breast reconstruction.

Fibrosis According to the Baker Classification

Information on capsular fibrosis in patients reconstructed with the use of expander/implants was available in 86 patients including 2 cases of primary breast reconstruction with autologous material and secondary implantation of permanent implants (Figure 2). The actuarial incidence of a maximum ≥ grade III Baker fibrosis 3 years after radiotherapy was 43% (95% confidence interval: 30–65%) (Figure 3). Fifteen patients with and 22 patients without a radiation boost developed a maximum fibrosis ≥ grade III. There was neither a statistically significant difference between patients treated with or without an additional boost (log-rank; $p = 0.25$) nor between patients treated with autologuous or heterologuous reconstruction techniques (log-rank; $p = 0.34$).

When rating Baker fibrosis ≥ grade III at the last follow-up visit, a 3-year rate of 18% (95% confidence interval 8–29 %) was observed. Again, reconstruction technique and boost treatment had no significant influence (log-rank; $p > 0.05$).

Fibrosis According to the CTCAE Classification

Data on fibrosis according to the CTCAE classification were available in 103 patients (Figure 4); 18 patients developed fibrosis ≥ grade III. The actuarial incidence of the maximum grade CTCAE fibrosis ≥ grade III 3 years after radiotherapy was 20% (95% confidence interval 10–30%). Seven patients with a boost treatment and 11 patients without developed ≥ grade III fibrosis without a significant difference between both groups (log-rank; $p = 0.73$). The technique of breast reconstruction had no significant influence on the incidence of fibrosis according to the CTCAE classification (log-rank; $p = 0.46$)(Figure 5).

When considering fibrosis at the last follow-up visit, 5 patients suffered from ≥ grade III fibrosis corresponding to a

3-year rate of 2% (95% confidence interval 0–5%). The type of breast reconstruction (heterologous vs. autologous) and the application of a boost treatment had no influence on the incidence of ≥ grade III fibrosis at last follow-up visit (log-rank; $p > 0.05$).

Plastic Surgery for the Contralateral Breast

In 43 women, the contralateral breast was surgically corrected to gain symmetry with the reconstructed breast. In 11 patients this correction took place before radiotherapy. Excluding these cases, the Kaplan-Meier estimate for contralateral breast correction 3 years after the end of radiotherapy was 30% (95% confidence interval 21–40%). The type of primary breast reconstruction or the use of a boost treatment did not significantly influence the rate of contralateral surgery (log-rank; $p > 0.05$).

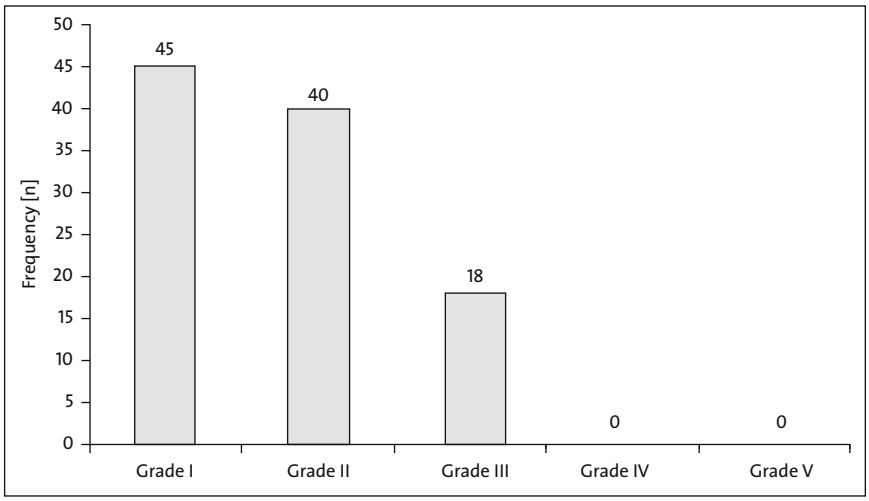

Figure 4. Fibrosis according to CTCAE score. Distribution of the highest score observed during the follow-up period.

Abbildung 4. Fibrose erhoben nach der CTCAE-Klassifikation. Dargestellt ist die Verteilung des höchsten Fibrosegrades während der Nachbeobachtungszeit.

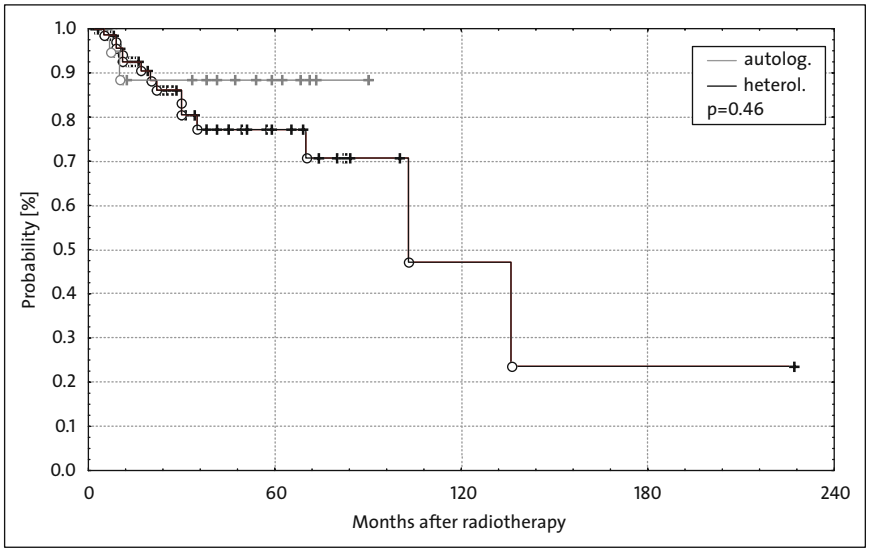

Figure 5. Fibrosis according to CTCAE score. Kaplan-Meier estimates for the probability of staying unaffected by ≥ grade III maximum scores during follow-up for patients with autologous and heterologous breast reconstruction.

Abbildung 5. Fibrose erhoben nach der CTCAE-Klassifikation. Kaplan-Meier-Schätzung für die Wahrscheinlichkeit, keine Nebenwirkung ≥ Grad III als maximale Ausprägung während der Nachbeobachtungszeit zu entwickeln.

Discussion

There are numerous reports assessing the interaction of breast reconstruction and local radiotherapy [4, 11, 13, 21, 22] in a variety of clinical settings. Comparison of the reported clinical outcomes is hampered by the complex matter of available surgical techniques of breast reconstruction, aspects of timing between radiotherapy and plastic surgery, inconsistent definition of endoints reported, and a small sample size in the majority of studies. Many authors report "complication rates". However, definitions of complications subsequent to surgery and radiotherapy vary greatly.

Fibrotic changes of the reconstructed breast induced by surgery and radiotherapy represent a frequent and consistently reported clinical challenge forming the basis for many secondary events ultimately summarized as "complication" in numerous reports [3, 5, 21]. We, therefore, focused our retrospective analysis on the incidence and time trends of fibrotic sequelae secondary to plastic surgery and radiotherapy.

When assessing the maximum degree of fibrosis observed during the follow-up period, a considerable rate of severe (≥ grade III) fibrosis with 20% and 43% at 3 years according to the CTCAE and Baker classification, respectively, was found. The substantial difference in fibrosis rate between the two scoring systems may in part be attributed to the retrospective nature of our report. It is of note, however, that those patients evaluated by the Baker classification, which is only valid for heterologous reconstructions, represent a subset of our entire population which was assessed with the CTCAE score.

As a consequence, our data suggest that fibrotic changes are more pronounced in women submitted to plastic surgery using heterologous material. This view is supported by the observation that heterologous reconstruction was complicated with an increased rate of fibrosis in patients assessed by the CTCAE scale as compared to patients with autologous reconstruction even though the difference was statistically not significant (Figure 5). Our data are, thus, in line with recommendations of a recent literature review [13] emphasizing the role of delayed autologous reconstruction in patients after mastectomy and adjuvant radiotherapy.

Our results are consistent with reported rates of fibrosis by other groups. Jhaveri et al. [11] found a 33.3% incidence of grade III capsular contracture following reconstruction with expander/implants and radiotherapy. Cordeiro et al. [6] observed contracture rates of 68% for patients treated with heterologous reconstruction and radiotherapy. In addition, this report outlines the fact that heterologous reconstruction bears a considerable risk of fibrosis even without radiotherapy: a 40% rate of capsular contraction was reported after heterologous reconstruction alone. Considering the timeline of fibrosis subsequent to radiotherapy as well as the rate of fibrotic events after heterologous reconstruction, it remains speculative as to whether a delay of breast reconstruction by 2–3 years after radiotherapy might reduce the substantial rate of unplanned secondary surgical events observed in our patient cohort.

Approximately one-third of our patients underwent cosmetic correction of the contralateral breast 3 years after the end of radiotherapy. The different reasons for contralateral surgical correction were not evaluated. However, volume loss and fibrotic shrinkage of the reconstructed breast after adjuvant radiotherapy can be expected with a high frequency [22], thus, subsequently requiring adoption of the contralateral breast. The 30% rate of contralateral surgical correction in our cohort is thus an indicator of – among other reasons – fibrotic changes in the reconstructed breast. We, therefore, assume that the actuarial rates of fibrosis calculated for our patients represent in fact a fair estimate of the "true" fibrosis rate for the treatment received.

In addition to the maximum degree of fibrosis observed in an individual patient, the status at last follow-up visit was evaluated. This method was chosen to gain insight into the final treatment outcome from the patients' perspective and to analyze variations of fibrosis with time. In fact, with a 3-year rate of 18% and 2% for $\geq$ grade III fibrosis according to Baker and CTCAE scores, respectively, a substantial decline in the fibrosis rate as compared to the maximum scoring method was observed. This finding is surprising at first glance, since the rate of radiation-induced fibrosis can be expected to increase rather than decrease with time [18, 28]. Again, the retrospective character of our study may account for some part of this observation. Yet, it is important to note that approximately 36% of our patients underwent initially unplanned surgical corrections of the reconstructed breast, and resection of capsular fibrosis or removal/replacement of expanders/implants were the most frequent reasons for doing so (Table 2). This rate is comparable to findings reported by other investigators [13] and indicates that fibrosis may to some extent successfully be surgically corrected resulting in an ultimately comparatively low rate of high grade fibrosis. To our knowledge, this is the first report providing a detailed analysis of time trends for fibrotic sequelae after breast reconstruction and radiotherapy using actuarial methods. Whitfield et al. [28] published 1–6 year data reporting rates of severe capsular contraction requiring surgical resection. Expectedly, they observed an increase of resection rate with time. Their 4-year rate of 21% is in the range of the maximum rate of high grade fibrosis observed in our patients. However, due to their primary endpoint, which was surgical intervention, no data on final fibrosis rate are available.

Treatment-related factors which may possibly interfere with long-term outcome of breast reconstruction and radiotherapy were also analyzed. Our series represents a large population of women who received radiotherapy prior to breast reconstruction, and only 8 patients underwent radiotherapy after plastic surgery. Therefore, the role of timing on treatment outcome could not be assessed. This factor has repeatedly been attributed a major role with different effects in heterologous and autologous reconstructions [5, 13, 22], while others did not observe any effect [4, 21]. Likewise, we were not able to analyze the effect of bolus materials used for radiotherapy, since these were used in only two of our patients. Bolus materials have previously been associated with impairment of cosmetic outcome after breast reconstruction and radiotherapy by some authors [15, 24]. In accordance with others [14], the application of a radiation boost dose was not associated with a significant influence on the endpoints of our study.

Systemic treatment was used in approximately 93% of our patients; thus, the influence of chemotherapy and endocrine treatment on the induction of fibrosis could not be evaluated. It should, however, be noted that tamoxifen has been associated with an increased rate of fibrosis of the lung and subcutaneous and breast tissue in conjunction with radiotherapy [1, 2, 9, 10]. Therefore, systemic treatment may have a considerable impact on fibrosis in breast reconstruction.

The technique of reconstruction (heterologous vs. autologous) did not apparently influence treatment outcome in our patients. Chawla et al. [4] analyzed 48 patients with either implants or TRAM flap reconstruction. The rate of complications and secondary surgery to the reconstructed breast was significantly higher with the use of heterologous materials. Spear et al. [21] reported treatment outcome in 79 patients receiving radiotherapy before or after reconstruction with different techniques. They concluded that satisfying results could be obtained regardless of the reconstruction method. However, more than 30% of their patients received radiotherapy as part of breast-conserving surgery, and plastic surgery was performed only

after local relapse and secondary mastectomy. Our study was exclusively confined to patients receiving postmastectomy radiotherapy, and autologous reconstruction was performed in 20 of our patients. We, therefore, can not rule out that our analysis did not have sufficient power to detect a possible influence of surgical techniques on the incidence of fibrosis.

Our study is limited by its retrospective nature with an inherent inaccuracy of evaluating and classifying endpoints of the analysis. Furthermore, we did not assess cosmetic outcome or quality-of-life issues which play an important role when restoration of the physical appearance is one of the primary goals of treatment in order to cope with the trauma of cancer-related loss of the breast.

Conclusion

This study has demonstrated that postmastectomy radiotherapy and cosmetic surgery of the breast is complicated with a considerable rate of high grade fibrosis of the reconstructed breast. However, due to the potential of surgical correction of fibrosis and secondary complications thereof, long-term rates of high grade induration are moderate. Treatment-related factors that significantly correlated with fibrosis of the reconstructed breast in association with adjuvant radiotherapy could not be identified.

References

1. Azria D, Gourgou S, Sozzi WJ, et al. Concomitant use of tamoxifen with radiotherapy enhances subcutaneous breast fibrosis in hypersensitive patients. Br J Cancer 2004;91:1251–60.
2. Bentzen SM, Skoczylas JZ, Overgaard M, Overgaard J. Radiotherapy-related lung fibrosis enhanced by tamoxifen. J Natl Cancer Inst 1996;88:918–22.
3. Chang DW, Barnea Y, Robb GL. Effects of an autologous flap combined with an implant for breast reconstruction: An evaluation of 1000 consecutive reconstructions of previously irradiated breasts. Plast Reconstr Surg 2008;122:356–62.
4. Chawla AK, Kachnic LA, Taghian AG, et al. Radiotherapy and breast reconstruction: complications and cosmesis with TRAM versus tissue expander/implant. Int J Radiat Oncol Biol Phys 2002;54:520–6.
5. Contant CM, van Geel AN, van der Holt B, et al. Morbidity of immediate breast reconstruction (IBR) after mastectomy by a subpectorally placed silicone prosthesis: the adverse effect of radiotherapy. Eur J Surg Oncol 2000;26:344–50.
6. Cordeiro PG, Pusic AL, Disa JJ, et al. Irradiation after immediate tissue expander/implant breast reconstruction: Outcomes, complications, aesthetic results, and satisfaction among 156 patients. Plast Reconstr Surgery 2004;113:877–81.
7. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 2000;355:1757–70.
8. Hammer J, Track C, Seewald DH, et al. Local relapse after breast-conserving surgery and radiotherapy: effects on survival parameters. Strahlenther Onkol 2009;185:431–7.
9. Hoeller U, Borgmann K, Feyer P, Souchon R. On the interactions of adjuvant radiotherapy and tamoxifen treatment for breast cancer. Strahlenther Onkol 2007;183:535–44.
10. Hoeller U, Grzyska B, Lorenzen J, et al. Is grading of breast fibrosis with mammography feasible? Strahlenther Onkol 2005;181:307–12.
11. Jhaveri JD, Rush SC, Kostroff K, et al. Clinical outcomes of postmastectomy radiation therapy after immediate breast reconstruction. Int J Rad Oncol Biol Phys 2008;72:859–65.
12. Kreienberg R, Kopp I, Albert U, et al. Interdisciplinary S3-guidelines for diagnosis, treatment and follow-up of breast cancer. Zuckschwerdt, Germering bei München: 2008.
13. Kronowitz SJ, Robb GL, Radiation therapy and breast reconstruction: a critical review of the literature. Plast Recostr Surg 2009;124:395–408 .
14. Krueger EA, Wilkins EG, Strawderman M, et al. Complications and patient satisfaction following expander/implantat breast reconstruction with and without radiotherapy. Int J Radiat Oncol Biol Phys 2001;49:713–21.
15. Kuske RR, Schuster R, Klein E, et al. Radiotherapy and breast reconstruction: clinical results and dosimetry. Int J Radiat Oncol Biol Phys 1991;21: 339–46.
16. Little G, Baker JL. Results of closed compression capsulotomy for treatment of contracted breast implant capsules. Plast Reconstr Surg 1980;65: 30–3.
17. Piroth MD, Piroth DM, Pinkawa M, et al. Immediate reconstruction with an expander/implant following ablatio mammae because of breast cancer: side effects and cosmetic results after adjuvant chest wall radiotherapy. Strahlenther Onkol 2009;185:669–74.
18. Poortmans PM, Collette L, Horiot JC, et al. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. Radiother Oncol 2009;90:80–5.
19. Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. Radiother Oncol 2009;91: 23–32.
20. Sauer R, Schulz KD, Hellriegel KP. Strahlentherapie nach Mastektomie – Interdisziplinärer Konsensus beendet Kontroverse. Strahlenther Onkol 2001;177:1–9.
21. Spear SL, Newman MK, Bedford MS, et al. A Retrospective analysis of outcomes using three common methods for immediate breast reconstruction. Plast Reconstr Surg 2008;122:340–7.
22. Tran NV, Chang DW, Gupta A, et al. Comparison of immediate and delayed free TRAM flap breast reconstruction in patients receiving postmastectomy radiation therapy. Plast Reconstr Surg 2001;108:78–82.
23. Van de Steene J, Soete G, Storme G. Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link. Radiother Oncol 2000;55:263–72.
24. Victor SJ, Brown DM, Horwitz EM, et al. Treatment outcome with radiation therapy after breast augmentation or reconstruction in patients with primary breast carcinoma. Cancer 1998;82:1303–9.
25. Vinh-Hung V, Truong PT, Janni W, et al. The effect of adjuvant radiotherapy on mortality differs according to primary tumor location in women with node-positive breast cancer. Strahlenther Onkol 2009;185:161–8.
26. Voordeckers M, Vinh-Hung V, Lamote J, et al. Survival benefit with radiation therapy in node-positive breast carcinoma patients. Strahlenther Onkol 2009;185:656–62.
27. Whelan TJ, Julian J, Wright J, et al. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 2000;18: 1220–9.
28. Whitfield GA, Horan G, Irwin MS, et al. Incidence of severe capsular contracture following implant-based immediate breast reconstruction with or without postoperative chest wall radiotherapy using 40 Gray in 15 fractions. Radiother Oncol 2009;90:141–7.

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