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IS POST-OPERATIVE BREAST RADIOTHERAPY SAFE IN PATIENTS WITH SCLERODERMA?

Running title: Breast radiotherapy and scleroderma

Case presentation

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Case Presentation

Is post-operative whole breast radiotherapy safe in patients with scleroderma?

Connective vascular diseases (CVD), including scleroderma, are reported to represent a relative or absolute contraindication to radiotherapy. We would like to discuss here the indication, fractionation schedule and follow-up of one patient with scleroderma.

A 65-year-old female patient, with a history of limited cutaneous sclerosis as CREST syndrome as a result of calcinosis cutis, Raynaud syndrome, treated by cortisol and acetylsalicylic acid due to the vascular decomposition. Although Raynaud's phenomenon and arthrosclerosis were present in our case, there was no internal organ involvement.

Three years after the scleroderma diagnosis, mammography screening showed breast microcalcifications in the upper outer quadrant of the left breast. The physical examination at the first visit revealed a 3cm mass in the upper quadrant of the left breast without regional nodes. The pathological examination of the macrobiopsy specimen showed an intermediate grade intraductal carcinoma in situ (DCIS).

The patient underwent a large lumpectomy of the left breast. Final pathology report confirmed one lesion of 29 mm with two components of grade II and III DCIS with necrosis, negative margins (measured at 18mm), hormone receptors positive.

The decision of the multidisciplinary board meeting was to recommend adjuvant radiotherapy.

Questions:

- 1. Would you recommend to this patient total mastectomy to omit RT?**
- 2. In case of conservative surgery, do you think that adjuvant radiotherapy is safe for this patient?**
- 3. Do you consider hypofractionated RT schedule as an option in this case?**
- 4. Could accelerated partial breast irradiation (ABPI) be the best choice for this patient?**
- 5. Would you recommend particular follow-up for sclerodema patients after RT?**

Gray Zone Expert Opinion 1

Postoperative radiation therapy in DCIS for patients with scleroderma: “Between uncertainties and overtreatment”

The decision-making process between the medical team and the patient, which is quite typical but not exclusive to oncology, has to put all possible benefits and drawbacks of every single diagnostic, therapeutic, and other intervention into the right proportion for obtaining a balance that is individualized to patient- and tumor-related characteristics. Postoperative radiation therapy after lumpectomy for DCIS reduces the risk of recurrences by 50% and decreases the long-term rate of mastectomy. It should therefore be considered as standard treatment for most DCIS patients apart from those with very low risk features.

1. Would you recommend to this patient total mastectomy to omit RT?

In this specific case, the patient should be informed that there is a higher risk for radiation-related complications including radiation-induced fibrosis. However, performing a mastectomy does not improve survival and could be considered as an over-treatment because of the negative influence on the body image of the patient (1). Factors that support omitting radiotherapy or performing mastectomy include a high “activity” of the cutaneous sclerosis (extent of skin involvement, limited vs. extensive), pulmonary disease and visceral complications, for which collaboration with the rheumatologist is important.

2. In case of conservative surgery, do you think that adjuvant radiotherapy is safe for this patient?

Historically, connective tissue diseases have been associated with an increased risk for RT-related side-effects. However, literature reviews could confirm this only for scleroderma, and in lower frequencies than anticipated (2). This relative increased risk should be balanced

against the possible benefits of RT. Therefore, while we would advise patients to receive postoperative RT in the case of high-risk invasive disease, we would not do this in the specific case where the relative risk reduction, especially in terms of overall survival, can be considered as limited.

3. Do you consider hypofractionated RT schedule as an option in this case?

While explicit data about the influence of fraction size on the incidence and severity of radiation-related side-effects in patients with connective tissue diseases is lacking, we would not withhold the benefits of a shorter treatment time and a lower total dose in these cases. However, we would advise strict weekly follow-up during treatment with immediate interruption of radiotherapy course in the case of unexpected early side effects.

4. Could accelerated partial breast irradiation (ABPI) be the best choice for this patient?

Accelerated partial breast irradiation is not a recognized indication for pure DCIS cases with risk factors as in this patient (2.9 cm size, tumor grade 3) (3). However, theoretically the reduction of the treated volumes might reduce the risk and the severity of eventual side effects. Other approaches to decreasing the risk for side effects should be taken, similar as in every breast cancer patient: homogenous dose distribution, respiratory control, and risk-adapted dose reduction.

5. Would you recommend particular follow-up for sclerodema patients after RT?

There is no need to systematically recommend increasing the burden of follow-up for this patient as no validated treatment against radiation related side-effects exists (4). However, it is important that the patient will continue follow-up, including with her rheumatologist, to identify potential post-radiotherapy complications and to permit adequate-timely symptomatic intervention.

References

1. Stuart KE, Houssami N, Taylor R et al. Long-term outcomes of ductal carcinoma in situ of the breast: a systematic review, meta-analysis and meta-regression analysis. *BMC Cancer* 2015; 15: 890.
2. Wo J and Taghian A. Radiotherapy in setting of collagen vascular disease. *Int J Radiat Oncol Biol Phys* 2007; 69: 1347-1353.
3. Correa C, Harris EE, Leonardi MC, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol.* 2017;7:73-79.
4. Kaidar-Person O, Marks LB, Jones EL. Pentoxifylline and vitamin E for treatment or prevention of radiation-induced fibrosis in patients with breast cancer. *Breast J* 2018, *in press*.

Gray Zone Expert Opinion 2

Adjuvant radiotherapy in DCIS for patients with scleroderma: “only as an ultimate solution!”

1. Would you recommend to this patient total mastectomy to omit RT?

If mastectomy is not an issue for this patient, I would recommend mastectomy for many reasons:

- Since the pathology is DCIS, there will be no need for radiation after mastectomy.
- She is left sided so omitting radiotherapy will avoid any risk of cardiac toxicity.
- Cosmesis, one of the main target of lumpectomy; might be compromised in this case as the data showed that radiotherapy with scleroderma increases the rate of fibrosis which might affect the cosmetic outcome
- Finally, Morris and Powell data (1) showed that scleroderma itself increases the late toxicity with or without acute toxicity (more than any other Connective tissue disease). This was also described in Wo and Taghian review (2).
- Patient can have nipple sparing mastectomy with immediate reconstruction resulting in excellent cosmesis avoiding the hazard from radiation.

2. In case of conservative surgery, do you think that adjuvant radiotherapy is safe for this patient?

The effect of radiotherapy on patients with scleroderma is still not definitively well defined and the decision for conservative treatment should be taken case by case. Data published by Chen AM et al suggested that late complication from radiotherapy increased significantly in collagen vascular disease (CVD) which disappeared in subset analysis except in scleroderma

patients (3). Also, Morris and Powell (1) suggested that scleroderma and SLE patients were at increased risk of late toxicity. Finally, Phan and colleagues (4) again showed no difference in toxicity with CVD however the risk of complications increased with scleroderma patients. On the other hand, recent data published by Dhaval Shah et al (5) on scleroderma patients showed no significant difference in the exacerbation of the scleroderma symptoms.

In this context of conflicting data on radiation toxicity, lumpectomy alone without radiation should be discussed with the patient regarding the benefit/risk ratio even in small size DCIS. For example, in the ECOG-ACRIN E594 prospective single arm study, which included 561 patients with grade I-II and 104 with grade III DCIS (<1cm with minimum 3 mm negative margins) treated by lumpectomy alone without any breast radiation, the 12-y rates for developing ipsilateral tumor recurrence (IBTR) was 14.4% and 24.6% for grade I-II and III, respectively. The 12-y rates of developing an invasive IBTR were 7.5% and 13.4%, respectively. These risks are likely to increase over time since from the figures, it did not reach a plateau (6). It should be noted that our patient had a 2.9 cm grade III DCIS, which would likely result of a higher risk for IBTR as reported in the ECOG-ACRIN E594 trial. This information regarding the risk for invasive IBTR and the potential complications from radiation should be discussed with the patient (1), although the authors think that mastectomy would give a better outcome.

3. Do you consider hypofractionated RT schedule as an option in this case?

To our knowledge, there is no data available on the treatment of patients with scleroderma with hypofractionation, but to avoid the uncertainties of a high dose per fraction on patients with scleroderma, we would use a standard fractionation as being cautious.

4. Could accelerated partial breast irradiation (ABPI) be the best choice for this patient?

Again, to our knowledge, there is no available data on APBI with CVD. Furthermore, we do not use APBI in patients with grade III DCIS, we use it in grade I-II. Therefore, we do not recommend APBI in this case

5. Would you recommend particular follow-up for scleroderma patients after RT?

The patient should be followed up closely with multidisciplinary team to monitor the complications from the radiotherapy and even the possibility of the exacerbation of the scleroderma symptoms. For long term follow-up after the first 2 to 5 years, a yearly visit should be considered as a “minimal requirement” as patients’ survival is quite long in this disease. The survival rates of patients with systemic sclerosis is ranged between 85 to 90% at five years according to disease stage. Long-term prognosis is much better when no other organ than the skin is affected. In the literature, while earlier studies reported a 10-year survival rate as low as 50% (7), more recent studies including the EUSTAR registry reported 5-year and 10-year survival rates of 90% and 84% (8) to 88% (9), respectively. In addition, patients with scleroderma who received radiotherapy for breast cancer may have a long term outcome up to 12 years (1, 2).

References:

- 1- Morris M.M. and Powell S.N.: Irradiation in the setting of collagen vascular disease: Acute and late complications. J Clin Oncol 1997; 15: pp. 2728-2735

- 2- Wo J and Taghian A. Radiotherapy in setting of collagen vascular disease. *Int J Radiat Oncol Biol Phys* 2007; 69: 1347-1353.
- 3- Chen A.M., Obedian E., Haffty B., et al: Breast-conserving therapy in the setting of collagen vascular disease. *Cancer J* 2001; 7: pp. 480-491
- 4- Phan C., Mindrum M., Silverman C., et al: Matched-control retrospective study of the acute and late complications in patients with collagen vascular diseases treated with radiation therapy. *Cancer J* 2003; 9: pp. 461-466
- 5- Shah DJ, Hirpara R, Poelman CL, et al. Impact of Radiation Therapy on Scleroderma and Cancer Outcomes in Scleroderma Patients with Breast Cancer. *Arthritis Care Res (Hoboken)* 2018.
- 6- Solin LJ, Gray R, Hughes LL, Wood WC, Lowen MA, Badve SS, Baehner FL, Ingle JN, Perez EA, Recht A, Sparano JA, Davidson NE. Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study. *J Clin Oncol.* 2015 20;33(33):3938-44. doi: 10.1200/JCO.2015.60.8588.
- 7- Bennett R, Bluestone R, Holt PJ, Bywaters EG. Survival in scleroderma. *Ann Rheum Dis.* 1971; 30:581–588. doi: 10.1136/ard.30.6.581.
- 8- Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis.* 2010; 69:1809–1815. doi: 10.1136/ard.2009.114264.
- 9- Hu S, Hou Y, Wang Q, Li M, Xu D, Zeng X. Prognostic profile of systemic sclerosis: analysis of the clinical EUSTAR cohort in China. *Arthritis Res Ther.* 2018 22;20(1):235. doi: 10.1186/s13075-018-1735-4.

Adjuvant radiotherapy in DCIS for patients with scleroderma: “Shared decision making is The Gold Standard”!

1. Would you recommend to this patient total mastectomy to omit RT?

Performing mastectomy for RT avoidance after DCIS diagnosis is individualized. Breast conserving surgery (BCS) is selectively followed by RT to reduce the risk of local recurrence (both DCIS and invasive cancer), with no impact on survival (1). In a retrospective cohort study, RT-related survival benefits were approximated based on patient risks: this patient would have a non-significant score of 3 for breast-related mortality (2). Nomograms predicting the benefit of adjuvant treatments after conservative surgery for DCIS lesions can be a useful for decision-making (**Table 1**) (3). However, this could not be extrapolated to patients concerned about excessive risk of fibrosis. The shared decision in this context can allow the patient to opt either for mastectomy or conservative surgery followed by radiation therapy.

Table 1. Estimated local recurrence risk (LRR) by intervention based on MSKCC nomogram (3) for this patient.

Intervention	5-year LRR (%)	10-year LRR (%)
Lumpectomy only	9	14
Lumpectomy and RT	3	5
Lumpectomy and hormone therapy	4	7

2. In case of conservative surgery, do you think that adjuvant radiotherapy is safe for this patient?

As we have no strong rational to advocate total mastectomy to omit RT, conservative surgery should be followed theoretically by RT. In this case, the patient must be informed that data on the association of RT and calcinosis cutis/ scleroderma/ dermatomyositis are scarce, but collectively point towards an increased risk of skin fibrosis (4), possibly being less prominent than previously considered (5). The risk of any grade toxicity has been estimated at 64-71% at 1-5 years after RT, with toxicity > grade 3 of 17.5% (4). Other complications might include, as reported in some series, arm lymphedema, rib fracture or pulmonary fibrosis (mainly incidental finding on imaging) (4). In another series of irradiated patients with vascular disease, 79% of patients were free from late complications vs 56% at 10 years (unless they had rheumatoid arthritis, for which outcomes were improved) (6). Modern techniques might permit adjusting normal tissue constraints and increase dose distribution homogeneity in the breast (without “hot spots”) resulting in less toxicity (7). This information should guide the shared decision with patients.

3. Do you consider hypofractionated RT schedule as an option in this case?

Hypofractionation is currently an accepted option in patients undergoing local radiation and those who do not have large-size breasts; which was one of the exclusion criteria in the Canadian trial (8). Hypofractionated techniques using higher doses per fraction might be theoretically associated with an increased risk for late toxicity (9), although this has not been reported in hypofractionation studies (8, 10). Given that hypofractionation has not been studied in patients with connective tissue disease, hypofractionation should not be considered for this patient. Conversely, we would discuss the use of lower dose per fraction of 1.8Gy per fraction up to 45-50.4Gy without boost, in order to decrease the risk of late skin fibrosis.

4. Could accelerated partial breast irradiation (APBI) be the best choice for this patient?

The rationale to use of APBI is to reduce the irradiated volume, with however an increased dose per fraction twice daily. APBI using interstitial brachytherapy has been shown to be associated to lower late skin toxicities but only 6% of the included patients presented with DCIS in the relevant study (11). APBI has not been studied in the context of connective tissue disease. Therefore, it should not be considered as an option for this patient.

5. Would you recommend particular follow-up for sclerodema patients after RT?

The standard rhythm of follow-up in DCIS should be considered as the “minimal requirement” in this case. Close monitoring of skin toxicities and interdisciplinary follow-up would permit to identify excessive acute toxicities and prescribe appropriate interventions, as in all patients who present excessive radiation-toxicity. If fibrosis is noted a few years later, some available anti-fibrotic treatments have been reported in the literature (12).

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P, Taylor C, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr. 2010;2010(41):162-77.
2. Sagara Y, Freedman RA, Vaz-Luis I, et al. Patient Prognostic Score and Associations With Survival Improvement Offered by Radiotherapy After Breast-Conserving Surgery for Ductal Carcinoma In Situ: A Population-Based Longitudinal Cohort Study. J Clin Oncol. 2016;34(11):1190-6.
3. <http://nomograms.mskcc.org/Breast/DuctalCarcinomaInSituRecurrencePage.aspx>

4. Gold DG, Miller RC, Petersen IA, Osborn TG. Radiotherapy for malignancy in patients with scleroderma: The Mayo Clinic experience. *Int J Radiat Oncol Biol Phys.* 2007;67(2):559-67.
5. Giaj-Levra N, Sciascia S, Fiorentino A, et al. Radiotherapy in patients with connective tissue diseases. *Lancet Oncol.* 2016;17(3):e109-17.
6. Morris MM, Powell SN. Irradiation in the setting of collagen vascular disease: acute and late complications. *J Clin Oncol.* 1997;15(7):2728-35.
7. Diao K, Chen YH, Catalano PJ, et al. Radiation toxicity in patients with collagen vascular disease and intrathoracic malignancy treated with modern radiation techniques. *Radiother Oncol.* 2017;125(2):301-309.
8. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010 Feb 11;362(6):513-20.
9. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Int J Radiat Oncol Biol Phys.* 1982;8(11):1981-97.
10. Haviland JS, Owen JR, Dewar JA, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 2013;14(11):1086-94.
11. Polgár C, Ott OJ, Hildebrandt G, et al; Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2017 Feb;18(2):259-268.

12. Delanian S, Lefaix JL. Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. *Semin Radiat Oncol.* 2007;17(2):99-107.