



## Skin Elasticity as a Measure of Radiation Fibrosis: Is it Reproducible and Does it Correlate with Patient and Physician-reported Measures?

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Current means of measuring RT-induced fibrosis are subjective. We evaluated the DermaLab suction cup system to measure objectively skin deflection as a surrogate for fibrosis. Sixty-nine patients with E-STs were treated with limb-sparing surgery and 50-66 Grays (Gy) of RT. Using a "scleroderma" DermaLab Suction Cup, the skin stiffness was measured by two clinicians. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale, the Musculoskeletal Tumor Rating Scale (MSTS) and Toronto Extremity Salvage Score (TESS) questionnaires were completed for each patient. Levels of agreement between measurers were estimated using the Kappa ( $\kappa$ ) coefficient and the concordance correlation coefficient (CCC). All sixty-nine patients were included. The level of agreement between measurers for NCI-CTCAE grading was moderate (range  $\kappa = 0.41-0.59$ ). The CCC for the elasticity measurements were higher, with CCC = 0.82 for fibrotic skin and CCC = 0.84 for normal skin. The elasticity measurements were significantly higher when MSTS scores were <30 and or TESS scores were <90. Suction Cup measurement of skin elasticity is more reproducible than CTCAE grading and shows promise in generating reproducible measurements for radiation-induced skin fibrosis. Furthermore, it correlates well with the MSTS and TESS.

Key words: Radiation; Fibrosis; Sarcoma; Elasticity.

### Introduction

Current protocols for treatment of extremity soft tissue sarcomas (E-STs) include radiation (RT) and limb-sparing surgery (1, 2). Multiple trials have demonstrated the advantages of limb-sparing therapy compared to amputation or surgical resection of entire limb muscle compartments, including better function with comparable disease-free and overall survival (3-6). However, with the use of external beam RT (EBRT), up to 50% of patients develop clinically detectable fibrosis after receiving 60-65 Grays (Gy) delivered in 2-3 Gy fractions (7, 8), making it one of the most common late effects in this patient population.

This is comparable to many other sites treated with RT. As an example, in patients with head and neck cancers treated with curative doses of RT, up to 45% will

**Abbreviations:** NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; MSTS: Musculoskeletal Tumor Rating Scale; TESS: Toronto Extremity Salvage Score;  $\kappa$ : Kappa; CCC: Concordance Correlation Coefficient; E-STs: Extremity Soft Tissue Sarcomas; RT: Radiation; EBRT: External Beam Radiation; Gy: Grays; PCC: Pearson Correlation Coefficient; SCC: Spearman Correlation Coefficients; LE: Lower Extremity; UE: Upper Extremity; RTOG: Radiation Therapy Oncology Group; ICC: Intraclass Correlation Coefficient; TCM: Tissue Compliance Meter.

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experience trismus (9). This manifestation of fibrosis may have adverse effects on chewing, swallowing, maintenance of oral hygiene and pulmonary function. In a more common malignancy, women treated with breast-conserving surgery and a median dose of 55 Gy of RT had 43% risk of fibrosis, 77% of retraction or atrophy of the skin and 54% of pain (10).

Subcutaneous fibrosis (11, 12) is manifested by a loss of pliability and flexibility of the soft tissues down to the muscle layers. The underlying cellular processes of radiation-induced fibrosis are not well understood. However, it is known that normal tissues are replaced by mesenchymal cells and that these cells overproduce extracellular matrix. Transforming growth factor- $\beta$  has a role in the development of fibrosis via the induction and deposition of extracellular matrix, stimulation of fibroblast growth, collagen deposition, and angiogenic effects on vascular endothelial cells. Radiation has been reported to induce a premature differentiation of fibroblasts into mature collagen-forming fibrocytes.

Symptoms associated with fibrosis vary by anatomic site but may include pain, neuropathy, loss of joint range of motion, and distal lymphedema (13-16). These symptoms and impairments may, in turn, limit functionality and activity, including difficulty with activities of daily living, mobility and self-care (9, 10).

Current means of measuring and documenting radiation-induced fibrosis are subjective. A common scale is the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (17) for grading fibrosis in the deep connective tissue. Functional scales include the revised Musculoskeletal Tumor Society Rating Scale (MSTS 1993) (18, 19) and the Toronto Extremity Salvage Score (TESS) (20-22). Davis *et al.* (23) noted that existing fibrosis rating scales have limited inter-rater reliability and do not discriminate severity. Consequently, quantitative measures have been developed, using compression or impedance. Although more precise in measuring tissue fibrosis these devices require skilled technicians for application and interpretation of the data, thus limiting their implementation.

Skin elasticity, a surrogate for fibrosis, can be measured through vacuum suction devices. The DermaLab<sup>®</sup> skin elasticity module (Cortex Technology, Hadsund, Denmark) uses a suction chamber to measure objectively the visco-elastic properties of the skin. This study was designed to analyze the utility of this suction cup device as a means to evaluate radiation related fibrosis in E-STS. The results using the device were also compared to the NCI-CTCAE, MSTS and TESS scores for all patients.

### Materials and Methods

The prospective study was reviewed and approved by the local research ethics committee. The study was carried out in

the multidisciplinary sarcoma clinic. No funding or material support was provided by the manufacturer of the device.

Skin fibrosis in patients with E-STS undergoing limb-sparing therapy was measured with the suction cup device, the NCI-CTCAE, the MSTS and the TESS scores. Measurements from the suction cup device were compared to scoring using established subjective scales.

### Patients

Inclusion criteria were defined as:

1. Patients aged 18 years or older having been treated limb-sparing surgery with curative intent
2. Patients having received pre- or post-operative radiation therapy
3. Patients having received a dose  $\geq 50$  Gy, delivered in 2 Gy fractions, at least 90 days prior to registration into the study

Exclusion criteria were defined as:

1. Patients with active or previous chemotherapy/biotherapy within 30 days of recruitment
2. Prior brachytherapy
3. Connective tissue disease known to affect skin elasticity or unhealed wounds
4. Local tumor recurrence

### Recruitment

Patients diagnosed with E-STS between 1998 and 2008 were identified at our multidisciplinary clinic from 2008 to 2010. Patients provided written informed consent and relevant patient, tumour and treatment information were extracted from the medical chart.

### Fibrosis Measurements

Skin fibrosis was assessed during a single routine follow-up appointment for each patient, using four different methods: NCI-CTCAE, MSTS, TESS and the suction cup device. Suction cup measurements were performed using a scleroderma probe since this probe allows for use with less elastic tissues as the detectors are placed closer to the skin surface. Measurements were performed with the patients lying down for the lower extremity or sitting with the arm supported for the upper extremity. Two measurements were taken independently by two health care workers, to assess for reproducibility of the process. One measurement was taken on a cleaned area of the skin deemed by the observer to display the most fibrosis. The second measure was taken at a corresponding area on the untreated contralateral extremity. Each investigator also graded connective tissue toxicity along the CTCAE

**Table I**  
NCI-CTCAE v4.03 grading for radiation-induced fibrosis.

Fibrosis grade	Appearance
0	Normal skin
1	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)
2	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL (including preparing meals, shopping for groceries or clothes, using the telephone, etc.)
3	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
4	Generalized; associated with signs or symptoms of impaired breathing or feeding

scales. For each patient, MSTS and TESS questionnaires were also completed.

#### NCI-CTCAE

The NCI-CTCAE v4.03 is a descriptive terminology for adverse events reporting with a grading (severity) scale for each adverse events. The grading system for radiation-induced fibrosis is explained in Table I.

#### MSTS

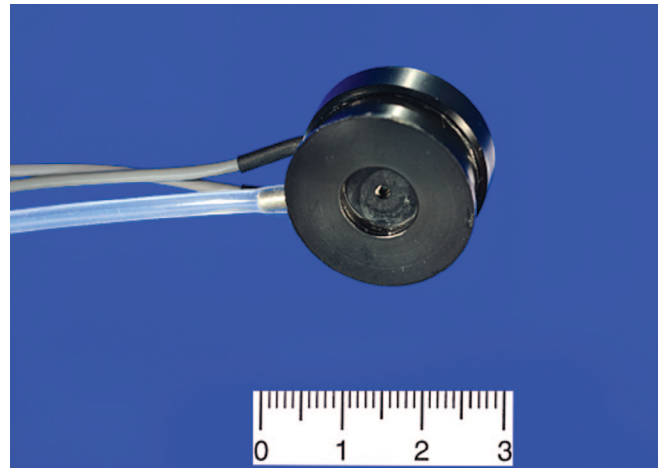
The MSTS is a clinician-rated scale that evaluates seven items including pain, joint range of motion, strength, joint stability, joint deformity, overall function, and general acceptance of the treatment. The score ranges from 0 to 35, with the lowest score indicating worse symptoms.

#### TESS

The TESS is a measure of physical disability developed specifically for patients with extremity sarcoma; the score ranges from 0 to 100. Patients rate the difficulty they experience performing routine daily activities. The lowest score indicates greater difficulty in performing these activities.

#### DermaLab Suction Cup (24)

The DermaLab elasticity module (Figure 1) consists of a light plastic probe that forms a closed chamber when attached to the skin surface using double-sided sticky tape. Within the probe chamber, two narrow beams of light run at different heights parallel to the skin surface that serve as elevation detectors. A computer-controlled vacuum pump is used to progressively increase the suction within the chamber over 30 to 60 seconds. The amount of suction in kilopascals (kPa) required to lift the skin is recorded electronically at the time



**Figure 1:** The DermaLab Suction Cup (Cortex, Hadsund, Denmark).

where each of the light beams is blocked and when the negative pressure within the chamber is maintained in equilibrium with the capacity of the pump. The software then calculates the mechanical properties of the skin based on Hooke's law, "the strain of any material is proportional to the load applied to it". With certain basic assumptions, the stiffness of the skin or its Young's modulus ( $E$ ) is expressed in mm/kPa and can be calculated from this stress-strain relationship as follows:

$$\Delta x = \Psi p \frac{r^4}{Es^3} = 0.3125 \frac{\Delta p}{\Delta x} \quad [1]$$

where  $p$  = pressure in kPa,  $x$  = distance in mm,  $\psi$  = elastic constant for a measured object estimated from civil engineering tables (0.5),  $r$  = radius of surface measured in mm (defined by the chamber geometry as 5 mm),  $s$  = thickness of the skin in mm (set to a standard of 1.0 mm by the manufacturer). The skin that is firm and taut will thus have a much higher stiffness index. The upper and lower elevation detectors of a normal probe are farther from the skin surface, when compared to a scleroderma probe. Many times, the stiff irradiated skin cannot be stretched enough to reach the level of its detectors. As a result, measurements were not registered consistently using a normal probe. Therefore, a scleroderma probe was used, as its upper and lower elevation detectors are closer to the skin surface, allowing measuring tight skin without excessive stretching.

#### Statistical Analysis

Levels of agreement between clinicians were estimated using the Kappa coefficient ( $\kappa$ ) for ordinal variables. The Pearson correlation coefficient (PCC) and concordance correlation coefficient (CCC) were used for continuous variables. The PCC estimates is a measure of association between the two variables whereas the CCC measures how close the two variables are to the line of unity. Association between ordinal

(i.e., NCI-CTCAE grade) and continuous outcomes were assessed using Spearman correlation coefficients (SCC).

All correlation coefficients are estimated values of association, which range from  $-1$  to  $1$ . A value of  $-1$  indicates perfect, negative association,  $+1$  indicates perfect, positive association and  $0$  indicates no association. Correlation coefficients between  $-0.3$  and  $0.3$  are considered to be weak or no association, between  $0.3$  and  $0.6$  or  $-0.3$  and  $-0.6$  are considered moderately associated, and values  $>0.6$  or  $<-0.6$  are considered strongly associated. Two-sided confidence intervals were constructed at the 95% level for selected outcomes.

## Results

### Patient Population

From 2008 to 2010, 69 patients with E-STS treated with limb-sparing surgery and RT met inclusion criteria and were included in the final analysis.

Patient and tumour characteristics are reported in Table II. Fifty-five patients (79.7%) had a tumour in the lower extremity (LE) and 14 (20.3%), in the upper extremity (UE). Thirty-seven (53.6%) participants were male with a mean age of 54.9 years (ranging from 23 to 85 years). The mean interval from radiation was 56.1 months, ranging from 13 to 130 months. All patients received a total radiation dose of 50-66 Gy at 2 Gy per fraction.

### Measurement Analysis

For the LE and UE groups, the mean MSTS total score was 31.2 (ranging from 5 to 35) and 32.9 (ranging from

Variable	No.
<i>n</i>	69
Age	
Mean, yrs	54.9
Range, yrs	23-85
Gender, no. (%)	
Female	32 (47.4)
Male	37 (53.6)
Anatomic site, no. (%)	
Upper extremity	14 (20.3)
Lower extremity	55 (79.7)
Interval from RT	
Mean, months	56.1
Range, months	13-130
Radiation dose, no. (%)	
50 Gy	28 (41.6)
66 Gy	41 (59.4)

**Table III**

Grading scale	No. (%)
NCI-CTCAE Edema	
Grade-A	
0	43 (62.3)
1	15 (21.7)
2	8 (11.6)
3	3 (4.4)
NCI-CTCAE Edema	
Grade-B	
0	34 (49.3)
1	20 (29.0)
2	9 (13.0)
3	6 (8.7)
NCI-CTCAE Fibrosis	
Grade-A	
0	7 (10.1)
1	26 (37.7)
2	23 (33.3)
3	13 (18.8)
NCI-CTCAE Fibrosis	
Grade-B	
0	6 (8.7)
1	35 (50.7)
2	11 (15.9)
3	17 (24.6)
MSTS Score (SD)	
Mean	31.2 (5.5)
N (%) $\geq 30$	51 (73.9)
TESS Score (SD)	
Mean	90.7 (12.2)
N (%) $\geq 90$	44 (63.8)

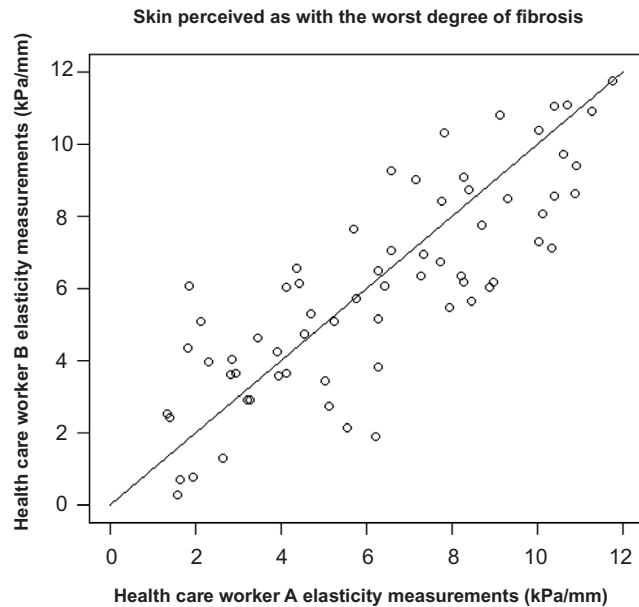
A: Measured by health care worker A.

B: Measured by health care worker B.

SD: Standard deviation.

21 to 35) respectively, while the mean score for TESS was 90.6 (ranging from 33 to 100) and 91.0 (ranging from 45 to 100) respectively. The health care workers had a tendency to score most patients as having RT-related toxicities (e.g., Grade 1 or higher) and almost 90% of patients having subcutaneous fibrosis and approximately 45% of patients having edema. These results are summarized in Table III.

The level of agreement between clinicians in terms of NCI-CTCAE grading was moderate and ranged from  $\kappa = 0.41$  for edema to  $\kappa = 0.59$  subcutaneous tissue-related late radiation morbidity. The concordance correlation coefficients (CCC) for the elasticity measurements were much higher, 0.82 for fibrotic skin and 0.84 for normal skin, suggesting a strong correlation between the two measurements. This relationship was illustrated in Figures 2 and 3. In addition, the mean difference in the measure of elasticity between clinician A and clinician B was 0.2 and  $-0.2$  for both the



**Figure 2:** Concordance correlation coefficient (CCC) for elasticity measurements on the treated limb. CCC = 0.82 (95% CI = 0.72-0.88). Each point represents a patient for which elasticity was measured by both observers.

treated and contralateral limb, indicating that the difference (noise) appears to be random.

Statistically significant associations between the elasticity measurements and the MSTs were found, with an elasticity of 7.9 kPa/mm vs. 5.7 kPa/mm for MSTs <30 and  $\geq 30$



**Figure 3:** Concordance correlation coefficient (CCC) for elasticity measurements on normal skin on the contralateral limb. CCC = 0.84 (95% CI = 0.75-0.90). Each point represents a patient for which elasticity was measured by both observers.

respectively ( $p = 0.002$ ). The elasticity also correlated with the TESS, with an elasticity of 6.9 kPa/mm and 5.9 kPa/mm for the TESS score of <90 and  $\geq 90$  respectively ( $p = 0.020$ ).

### Discussion

Our results suggest that the DermaLab suction cup device generates reproducible elasticity measurements that correlate well with subjective scores such as the MSTs and TESS scales.

It has been well established that fibrosis is associated with impaired extremity function (25). Therapeutic intervention with various agents such as pentoxifyllin and vitamin E (26, 27), copper/zinc superoxide dismutase (28, 29), Mn SOD (30-32), hyperbaric oxygen or even physiotherapy as done with head and neck patients, have been used in patients with measurable fibrosis. The efficacy of these sporadically used interventions has been difficult to measure.

Furthermore, it is pertinent to investigate new approaches to delivering radiation with reduced morbidity. The RTOG trial 0630 is a contemporary approach where the treated volume was reduced through the use of image-guided RT.

Evaluating these techniques and therapeutic interventions requires sensitive, reliable and valid measurements of fibrosis. Existing studies using clinician or patient-rated measurements of fibrosis suggest that these scales have poor reliability, and hence validity, that may limit their value as outcome measures (23). Objective measurements potentially offer greater accuracy and sensitivity in quantifying fibrosis. As well, a continuous rather than discrete scale may be more sensitive to change.

In this study, we utilized the DermaLab Suction Cup to evaluate the degree of fibrosis objectively. This device has been investigated in multiple clinical settings such as active burn scars (33), age-related connective tissue weakness (*e.g.*, cellulite) response following treatments (34), vaginal prolapse (35), and mapping of normal breast elasticity (36).

To assess the reproducibility of this apparatus, two independent clinicians measured skin elasticity. The mean difference in the measure of elasticity between clinician A and B appeared to be random. Furthermore, the DermaLab Suction Cup's elasticity measurement yielded a CCC suggesting a strong level of concordance between the two measurers, for both fibrotic and normal skin. These results thus suggest that the DermaLab generates reproducible results.

Other devices have previously been studied as an objective measurement of E-STs fibrosis with various limitations.



Leung *et al.* first reported using an ultrasound probe and computer algorithm in 2002 (37). The deformation of the soft tissue due to a measured applied force was measured. Huang *et al.* (38) tested the same system, using a minimized version of the tissue ultrasound palpation system used by Leung *et al.* (37). Thirty-eight patients who received RT to the neck for nasopharyngeal carcinoma were studied. The intraclass correlation coefficient (ICC) values for intra- and inter-rater measurement were generally larger than 0.80, which are comparable to the DermaLab Suction Cup results. It was noted however, that this device's use had some limitations. Stringent measurement site consistency was required to maintain inter- and inpatient consistency. It was also estimated that several hours of training were required for an ultrasonography technician to learn the technique. In contrast, the DermaLab Suction cup does not require precise delineation of the skin site and any healthcare worker may use the device with minimal training.

Other objective methods of measurement such as the tissue compliance meter (TCM) used by Marinus *et al.* (39) showed significantly superior inter-observer reliability compared to that of the palpation method. Most importantly, its ICC was slightly higher than the CCC in our study for the DermaLab Suction Cup (ICC 0.91 vs. CCC 0.82 for radiated skin). However, the use of the TCM also had restrictions. The plastic disc, with its diameter of 8 cm, was rather large, therewith limiting an even positioning of the device and thus accurate measurement of tissue compliance. For instance, areas such as the axilla, the skin folds and other areas with convex or concave surfaces were not assessable. The DermaLab Suction cup's 2 cm diameter, in contrast, allowed more versatility with less anatomical limitations. Therefore, implementation in clinical settings will be easier, especially for patients with E-STS where the limb surface is often smaller than 8 cm.

Davis *et al.* (40) studied the usefulness of the BTC-2000 in evaluating the biomechanical tissue parameters of laxity and energy absorption in 41 patients treated for E-STS by surgery alone and surgery with preoperative RT (50 Gy), and postoperative RT (66 Gy). This method of measuring post-radiation fibrosis was the most similar to the DermaLab Suction Cup, having a laser beam system measuring the skin deflection by subatmospheric pressure through a chamber aperture. Promising quantitative measures of soft-tissue fibrosis were generated; discriminating patients treated with surgery alone, pre-operative EBRT and post-operative EBRT. However, BTC-2000's reliability and validity was not evaluated.

The CCC of the DermaLab Suction Cup in this study was also compared to the kappa for the NCI-CTCAE edema and fibrosis score. Our results showed a stronger correlation between measurements from the DermaLab Suction Cup compared to

the NCI-CTCAE scale ( $\kappa = 0.41$  for edema to  $\kappa = 0.59$  subcutaneous tissue-related late radiation morbidity compared to CCC of 0.82 for fibrotic skin and 0.84 for normal skin). This is in concordance with all the aforementioned studies (23, 33, 34, 41), which also demonstrated that objective measurements have better reproducibility than clinical scales.

Skin and subcutaneous fibrosis is a known progressive process (42). Data from Jung *et al.* indicate an apparent lifelong risk of developing late complications, without a plateau, suggesting that different kinetic mechanisms are in play (43). Interestingly, it appears that after four to six years, more than 50% of patients who received similar treatment protocols to our population will have experienced RT-related fibrosis (44). Although our measurements were taken at different interval from RT, the mean interval from RT was of 56.1 months (13-130 months). Thus, we believe we would have measured the majority of patients who would have been affected by RT-related fibrosis.

Finally, correlating our results with the MSTS and the TESS showed statistically significant association between elasticity and the MSTS with a higher elasticity measurement for MSTS < 30 compared to  $\geq 30$ . The elasticity also correlated with the TESS with a higher elasticity with TESS score of <90 compared to  $\geq 90$ . This suggests that the higher the elasticity measurement value, the more the patient's daily activities are affected by radiation-induced fibrosis. This is consistent with many studies that have demonstrated that increased fibrosis results in greater impairment in functionality (14, 45-48). The measurements of the suction cup device thus correlate with both patient and physician-reported measures of functional outcome. This has not been demonstrated with other devices.

### Conclusion

Sensitive, reproducible and clinically relevant measurements of radiation-induced fibrosis are necessary if new radiation approaches are to be shown to reduce this common late effect. The same is required for the study of therapy for pre-existing fibrosis.

With its simplicity and ease of use, a suction cup measurement of skin elasticity shows promise in generating simple and reproducible measurements of radiation-induced skin fibrosis. It is more reliable than CTCAE grading and correlates well with validated patient and physician-reported scores — in the case of E-STS, MSTS and TESS questionnaires.

### Conflict of Interest

The authors state no conflict of interest.

## Acknowledgement

Nil.

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