Histologic Markers Predictive Of Wound Healing Complications In Soft Tissue Sarcoma Treated With Preoperative Radiation

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Background

- Soft tissue sarcoma (STS) is a rare cancer frequently requiring resection. Postoperative wound healing complication (WHC) incidence is high due to surgical morbidity. Resection often follows preoperative radiation (Pre-XRT). This sterilizes resection margins to reduce recurrence, but WHC incidence increases to one third of patients. Radiation is implicated in WHC, but its true mechanism remains unknown.

Objective

- We investigated if clinical or histological factors in skin specimens of STS patients predict WHC as it may add to current knowledge and generate new interventions. Factors were compared in patients with and without Pre-XRT, plus WHC were assessed in Pre-XRT patients. We also evaluated dermal fibroblast nuclear expression of transcriptional coactivator with PDZ-binding motif (TAZ), a transcriptional regulator in the Hippo pathway.

Methods

- This retrospective study of 55 adult patients following STS resection with primary closure evaluated clinical features including age, sex, tumor factors, and treatment including Pre-XRT or neoadjuvant chemotherapy. A pathologist with dermatopathology expertise evaluated histopathology and was blind to clinical outcomes. Hematoxylin and eosin sections of STS resected skin were assessed for inflammation (location, cells/high-power field [HPF], cell type), dermal thickness, and vessel density (vessel cross sections/HPF). Elastichrome stains assessed elastin organization. TAZ immunohistochemistry was measured in dermal fibroblasts. The sum of primary and secondary H-scores (intensity * % of cells staining at that intensity) represented total H-score. Case-control analysis compared patients for development of WHC within 4 months of surgery. Chi-square, Fisher's Exact, and Wilcoxon Sum Rank were used for variable comparison.

Results

- First, comparing skin treated with and without Pre-XRT (Table 1), mean TAZ H-scores were higher following Pre-XRT (276.5 vs 253.9; p=0.017). Similarly, plasma cells were more often present in radiated skin (p=0.0006). Compared to non-radiated skin, radiated skin demonstrated a greater absence of hair follicles (p=0.0198) and sebaceous glands (p=0.0159) plus a decrease in vascularity (p=0.0323). The presence or absence of Pre-XRT did not show significant differences in patient clinical characteristics. Next, comparing the development or avoidance of WHC in the Pre-XRT cohort (Table 2), those without WHC had greater mean TAZ H-scores than patients with WHC (282.5 vs 260; p=0.0402). This group also trended toward more organized elastin, more frequent presence of neutrophils and hair follicles, and <100 inflammatory cells/HPF in those with WHC.

Table 1. Comparison of histologic characteristics between patients receiving and not receiving preoperative radiation (Pre-XRT). Significance p < 0.05.

Characteristic	Pre-XRT n = 31	No Pre-XR n = 24	p-value
Elastin Organization			
0-1	23	15	0.2573
2-3	7	9	
Neutrophils			
Yes	7	1	0.1191
No	24	23	
Plasma Cells			
Yes	12	0	p = 0.0006, OR = 31.4 (1.75-564.4)
No	19	24	
Inflammatory Cells			
> 100/HPF	13	8	0.5149
≤ 100/HPF	18	16	
Hair Follicles			
Yes	15	19	p = 0.0198, OR = 4.05 (1.21-13.61)
No	16	5	
Eccrine Glands			
Yes	31	23	0.4364
No	0	1	
Sebaceous Glands			
Yes	1	7	p = 0.0159, OR = 12.35 (1.4-109.1)
No	30	17	
Dermal Thickness (cm)			
≥ 4	6	7	0.3956
< 4	25	17	
Vessels/HPF			
> 30	2	7	P = 0.0323, OR = 5.97 (1.11-32.09)
≤ 30	29	17	
Total H-score			
Mean ± SD	276.5 ± 38.8	253.9 ± 48.5	0.017

Table 2. Comparison of histologic features in patients treated with preoperative radiation with and without wound healing complications (WHC) n = 31. Significance p <0.05.

Characteristic	WHC n = 9	No WHC n = 22	p-value
Elastin Organization			
0-1	8	15	0.1434
2-3	0	7	
Neutrophils			
Yes	4	3	0.1504
No	5	19	
Plasma Cells			
Yes	4	8	0.7039
No	5	14	
Inflammatory Cells			
> 100/HPF	2	11	0.2374
≤ 100/HPF	7	11	
Hair Follicles			
Yes	6	9	0.2524
No	3	13	
Eccrine Glands			
Yes	9	22	NA
No	0	0	
Sebaceous Glands			
Yes	1	0	0.2903
No	8	22	
Dermal Thickness (cm)			
≥ 4	2	4	1
< 4	7	18	
Vessels/HPF			
> 30	1	1	0.5032
≤ 30	8	21	
Total H-score			
Mean ± SD	260±57.32	282.5 ± 29.02	0.0402

Discussion and Conclusions

- Our most novel findings center on TAZ. Normally, Hippo inactivation allows YAP/TAZ complex localization to the nucleus where it functions as a transcriptional co-activator for genes involved in angiogenesis and tissue remodeling. This is an important step in a complex pathway that is not fully understood. Prior studies in animal models and human cell cultures demonstrate increased TAZ expression in early cutaneous wound healing and loss of TAZ in impaired wound closure. Thus, higher TAZ in our radiated versus non-radiated patients may reflect a response to injury while TAZ decreases might contribute to WHC following Pre-XRT. To our knowledge, plasma cells have not been described in cutaneous infiltrates following radiation. The significance of this finding is unclear. Neutrophils aid in early wound healing, but their persistence may contribute to chronic non-healing wounds. The trend toward greater frequency of neutrophils in skin with WHC raises the possibility they contribute to WHC. Decreased hair follicles, sebaceous glands, and vessel density concur with prior descriptions of radiated skin. Although TAZ expression differences in this cohort are not discriminative enough to be a stand-alone predictor of WHC, TAZ may help predict WHC when used with other histologic factors, and ultimately may suggest a contributory pathway and therapeutic target.