Radiation therapy related down-regulation of PD-L1 on high-grade poorly differentiated sarcomas justify the combined radio-immunotherapy

Dongguang Wei[1], Robert J Canter[2], Hong Qiu[1], Arta M Monjazeb[3], Mingyi Chen[1]

1. Department of Pathology and Laboratory Medicine, University of California, Davis Medical Center, Sacramento, CA 95817
2. Division of Surgical Oncology, University of California at Davis Medical Center, Sacramento, CA 95817
3. Department of Radiation Oncology, University of California, Davis Medical Center, Sacramento, CA 95817

Background:

Successful multimodality management of adult, locally advanced soft tissue sarcomas (STS) remains a clinical challenge, and novel biomarkers of prognosis/treatment are needed. Although immune checkpoint blockade has shown great promise, only a minority of patients respond. Improved biomarkers could benefit both patient selection and treatment sequencing, especially since cytotoxic therapies like radiotherapy (RT) can alter the immune milieu. Since STS are known to harbor few tumor-infiltrating lymphocytes, the objective of this study was to characterize PD-L1 expression in locally advanced STS with or without preoperative RT.

Design:

17 cases of sarcoma include 5 liposarcoma, 4 myxofibrosarcoma, 4 pleomorphic sarcoma, 1 leiomyosarcoma, and 3 other were retrieved from the surgical pathology bank. Tissue microarrays (TMAs) were constructed using formalin-fixed, paraffin-embedded STS cases. 76% were high grade, and 47% received preoperative RT. A composite scoring system was applied to analyze/quantify the protein expression. TMA sections (4 µm) were immunostained using a commercially-available purified rabbit anti-human PD-L1 antibody (Sino Biological Inc, Clone ID: 015) with appropriate positive and negative controls. We used the avidin–biotin complex method (DAKO) with 3,3′-diaminobenzidine (DAB) for visualization. Stained slides were reviewed by a pathologist

A PD-L1 without radiation therapy

Six representative cases without radiation therapy show diffuse and strong PD-L1 staining

B PD-L1 with radiation therapy

Six representative cases with radiation therapy show weak/negative PD-L1 staining

C
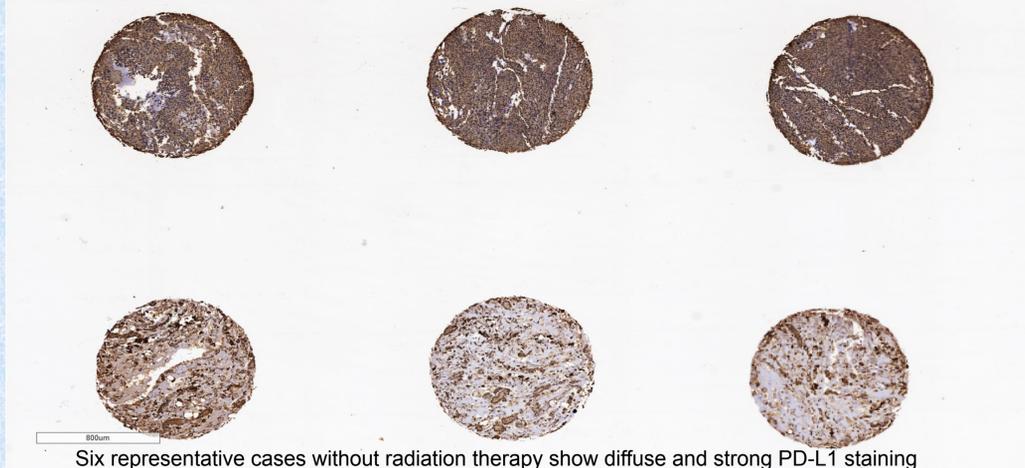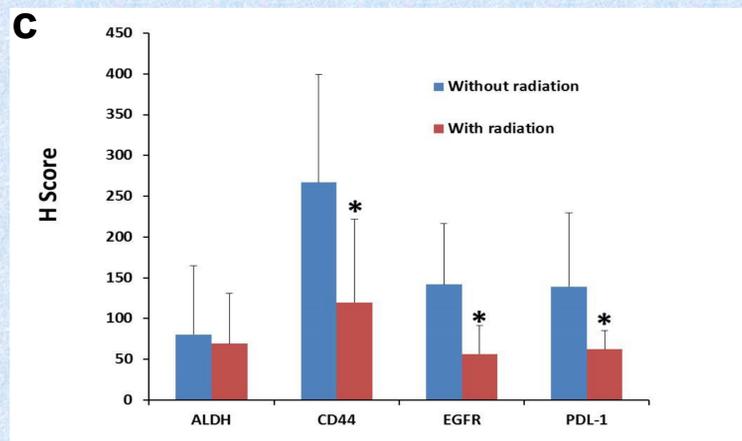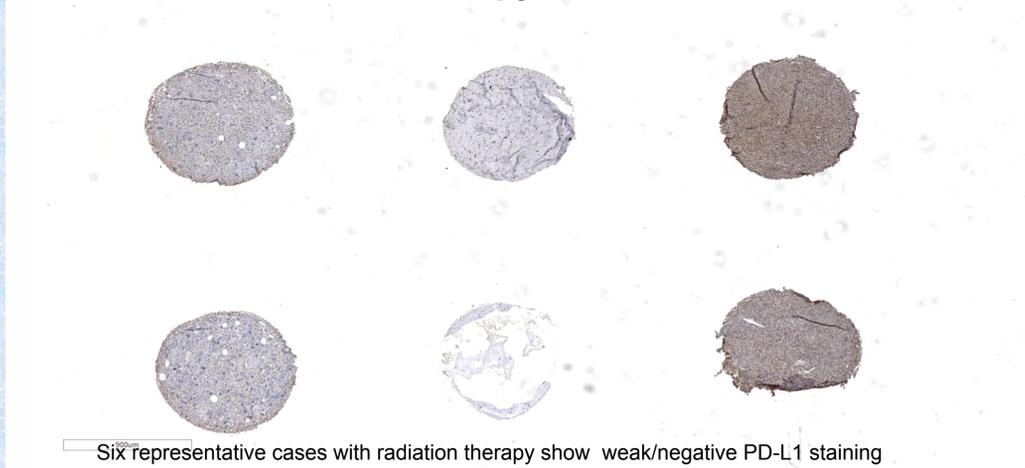
who was blinded to the clinical outcome and scored for percentage and intensity of PDL-1-positive cells. The product of the percentage of cells staining positive and the staining intensity was then calculated. Patients were categorized into PD-L1 high and low-expressing based on H-score above or below the median. Parametric and non-parametric statistics were used as appropriate.

Results:

Mean age was 55±21, 82% were female, and 53% of tumors were located on the extremity. Median tumor size was 15.5 cm (range 2.4-24.8 cm). We observed 9 recurrences, and 5 sarcoma deaths. Overall, PD-L1 expression was significantly lower (**Figures A-B**) among RT patients (H score 62.5±23.1 vs 139±90.5, p=0.04), and tumor stem cell markers EGFR/CD44 were also significantly lower (**Figure C**) among chemotherapy patients (p < 0.05). Distant recurrences were more common in PDL-1 high patients (5/8, 62%) than PDL-1 low patients (2/9, 22%), but this did not reach statistical significance (p=0.15).

Conclusions:

RT is associated with decreased PD-L1 expression in locally advanced STS, and lower PD-L1 expression is associated with improved long-term outcome. The modulation of PDL-1 expression by RT and the impact on prognosis in STS warrants further study.