Onodera's Prognostic Nutritional Index in soft tissue sarcoma patients as a predictor of wound complications

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Background The ability to predict a wound complication after radiation therapy and surgery for soft tissue sarcomas remains difficult. Preoperative nutritional status, as determined by Onodera's Prognostic Nutritional Index (OPNI), has been a predictor of complications in patients undergoing gastrointestinal surgery. However, the role OPNI has in predicting wound complications for soft tissue sarcoma remains unknown.
Objective To evaluate the role OPNI has in predicting wound complication in patients treated with radiation and surgery for soft tissue sarcomas.
Methods OPNI was calculated based on the published formula OPNI = (10*albumin level [g/dL]) + (0.005*total lymphocyte count). The albumin level and total lymphocyte counts closest to the index operation were chosen. Major and minor wound complications were identified. A receiver operating curve was calculated to identify a cut-off point value for OPNI and for age based on the best combination of sensitivity and specificity.
Results 44 patients were included in the study. Patients with an OPNI of <45.4 had a 7.5-times increased risk of a wound complication (*P* = .005; 95% confidence interval [CI], 1.8-31.0). An OPNI of <45.4 had a sensitivity of 62% and specificity of 82% of predicting a wound complication. Being older than 73 years was associated with a 6.8-times increased risk of wound complications (*P* = .01; 95% CI, 1.6-28.7).
Limitations Small sample size for patients with a rare condition
Conclusion An OPNI of <45.4 and being older than 73 years are strong predictors of which patients will have a wound complication after radiation therapy for soft tissue sarcomas. Preoperative nutritional status could be an important modifiable factor to help decrease wound complications.

Wound complications after pre- or postoperative radiation for soft tissue sarcomas are well established.[1] The ability to predict who will have a wound complication remains difficult. Some studies have looked at risk factors such as smoking, and the preoperative nutritional status of patients has been identified as a risk factor for wound complication in patients with elective orthopedic surgical procedures.[2] One validated method of measuring preoperative nutritional status in patients with gastrointestinal malignant tumors has been with Onodera's Prognostic Nutritional Index (OPNI). It uses the patient's preoperative albumin (g/dL) and absolute lymphocyte values (per mm^3). The prognostic value of the OPNI has been demonstrated in patients with colorectal, esophageal, and gastric cancers, and has been shown to be prognostic for postoperative wound healing and overall prognosis.[3-5] In this study, we investigate the significance of preoperative nutritional status, measured by OPNI, as a predictor of wound complications in patients treated with pre- or postoperative radiation for soft tissue sarcoma.

Methods

After receiving Institutional Review Board approval for the study, we conducted a retrospective review of consecutive patients treated during July 2012-April 2016 for a soft tissue sarcoma by the orthopedic oncology division at Cooper University Hospital in Camden, New Jersey. Inclusion criteria were patients with biopsy-proven soft tissue sarcoma, who were older than 18 years, had received pre- or postoperative radiation, and who had a recorded preoperative albumin and total lymphocyte count. A minimum follow-up of 3 months was required to

Accepted for publication June 6, 2017. Correspondence: Tae Won B Kim, MD; kim-taewon@cooperhealth.edu. Disclosures: The authors report no disclosures or conflicts of interest. JCSO 2017;15(4):e204-e207. doi: https://doi.org/10.12788/jcso.0353

assess for postoperative wound complications. Exclusion criteria included patients who had a bone sarcoma, had not received radiation therapy, or had a missing preoperative albumin or total lymphocyte count.

All of the surgeries were performed by 2 fellowship-trained orthopedic oncologists. Patients received either pre- or postoperative radiation therapy by multiple radiation oncologists.

The OPNI was calculated based on the published formula OPNI = (10*albumin level [g/dL]) + (0.005*total lymphocyte count [per mm^3]). The albumin level and total lymphocyte counts closest to the index operation were chosen.

Demographic information including gender, age at diagnosis, height, and weight were recorded. Data related to the patients' pathologic diagnosis, stage at presentation, radiation therapy, and surgical resection were collected. A minor wound complication was defined as a wound problem that did not require operative intervention. Major wound complication was defined as a complication requiring operative intervention with or without flap reconstruction. Wound complications occurring within the 3-month postoperative period were considered.

Univariate and multiple variable analysis was performed. A *P* value <.05 was considered significant. A receiver operating curve as well as recursive partitioning was performed for OPNI and age to determine the best cut-off point to use in the analysis. The Sobel test was used to evaluate mediation. All statistical analysis was performed using SAS v9.4 and JMP10. (SAS Institute, Cary, NC).

Results

In all, 44 patients (28 men, 16 women) were included in the study. Their mean age was 61.2 years (range, 19-94). The average size of the tumors was 8.5 cm in greatest dimension (range, 1.2-27.4 cm), and all of the patients had nonmetastatic disease at the time of surgical resection; 37 patients had R0 resections, and 7 patients had a positive margin from an outside hospital, but obtained R0 resections on a subsequent resection (Table 1 and Table 2). In all, 30 patients received preoperative radiation, 14 patients received postoperative radiation, 32 patients received external beam radiation, 8 received Cyberknife treatment, and information for 4 patients was not unavailable. Mean preoperative external beam radiation and Cyberknife dose was 4,931 Gy and 3,750 Gy, respectively. Mean postoperative external beam and Cyberknife radiation dose was 6,077 Gy and 4,000 Gy, respectively. When evaluating radiation dose delivered between those who had wound complications and those who did not, there was no significant difference (Table 3).

Of the total, 13 patients had a wound complication (30%). Ten patients had preoperative radiation, and 3 had postoperative radiation. Ten patients had major wound complications requiring a combined 27 surgeries. Three patients had minor wound complications, which resolved with conservative management. One patient had a major wound complication in the group that had an initial R1 resection.

TABLE 1 Anatomic locations of soft tissue sarcomas (N = 44)

Location	No. of patients
Proximal thigh	14
Upper extremity	13
Distal thigh/knee	6
Axial	6
Leg	5

TABLE 2 Pathologic diagnoses of soft tissue sarcomas (N = 44)

Diagnosis	No. of patients
Undifferentiated pleomorphic sarcoma	11
Myxofibrosarcoma	8
Synovial sarcoma	4
Leiomyosarcoma	4
Myxoid liposarcoma	2
Angiosarcoma	2
Liposarcoma	2
High-grade soft tissue sarcoma	2
Spindle cell sarcoma	2
Solitary fibrous tumor	1
Mensenchymal chondrosarcoma	1
Low-grade soft tissue sarcoma	1
Dedifferentiated liposarcoma	1
Neurofibrosarcoma	1
Extraskeletal osteosarcoma	1
Pleomorphic rhabdomyosarcoma	1

TABLE 3 Average radiation doses among patients with and without wound complications (N = 44)

	Wound complication, dosage in Gy (n)		
Type of radiation	Without	With	*P*-value
EBRT and IMRT	5,480 (24)	4,989 (9)	*P* = .16
Cyberknife	3,812 (8)	3,750 (4)	*P* = .85

EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy

The OPNI was calculated based on the aforementioned formula. When the univariate analysis was performed, only age and OPNI were statistically significant. Patients older than 72.6 years had a 6.8 times higher risk of a wound complication (P = .01; 95% confidence interval [CI], 1.6-28.7). When the OPNI value of 45.4 was used as the threshold, a patient with a preoperative OPNI value of <45.4 had a 7.5 times increased risk of developing a wound complication (P = .005; 95% CI, 1.8-31.0).

When the receiver operating curve and recursive partitioning was performed, an OPNI value of 45.4 showed a sensitivity of 62% and specificity of 82% in predicting wound complications (Figure 1).

When a multiple variable analysis was performed, OPNI and age were not statistically significant (P = .06 and P = .11, respectively). A test for mediation was performed, and the OPNI seemed to mediate the effect age has on wound complications, accounting for 36% of the total effect (Sobel test statistic, 1.79; P = .07).

Discussion

Wound complications after pre- and postoperative radiation for soft tissue sarcomas are well known. The best study to date to demonstrate that relationship was a randomized controlled trial performed in Canada, which showed that preoperative radiation resulted in 37% wound complications, compared with 17% for postoperative radiation.[6] In that study, of the wound complications in both radiation types, more than 50%-60% required a secondary surgical procedure, designating it as a major wound complication. Other variables that have been shown to contribute to wound complications include being older than 40 years and/or having large tumors, diabetes, peripheral vascular disease, and begin a smoker.[7-10]

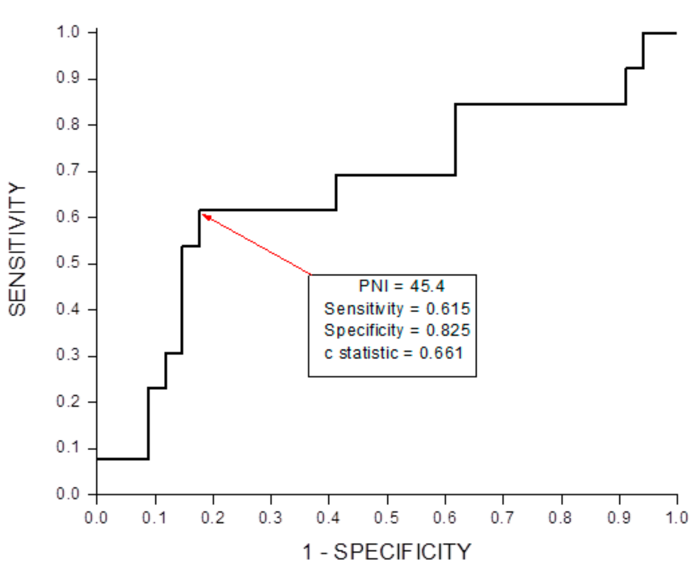

FIGURE The receiver operating curve for Onodera's Prognostic Nutritional Index in patients treated with radiation and surgery for soft tissue sarcoma. An OPNI threshold value of 45.4 had the highest sensitivity and specificity in predicting a wound complication.

In our study, we applied OPNI to orthopedic oncology and showed that the patient's age and preoperative nutritional status were significant predictors of developing a wound complication. An OPNI of <45.4 increased the chance of a wound complication by 7.5 times. Being older than 73 years increased the risk of a wound complication by 6.8 times. Most of these wound complications were major and required surgical intervention.

In general surgical oncology, the evaluation of nutritional status has had a significant impact on the care of patients, especially for those patients undergoing gastrointestinal surgery. The OPNI was initially designed to assess the nutritional and immunological statuses of patients undergoing gastrointestinal surgery.[11] Preoperative OPNI has been shown to be a good predictor of postoperative complications and survival in patients with colorectal cancer, malignant mesothelioma, hepatocellular carcinoma and in patients who undergo total gastrectomy.[12-15] Chen and colleagues evaluated the significance of OPNI in patients with colorectal cancer. They found an optimal cut-off value of 45. An OPNI value <45 has a sensitivity and specificity of 85% and 69%, respectively, in predicting 5-year overall survival.[16] Hong and colleagues noted that an OPNI cut-off value of 52.6 as a predictor of overall survival.[17]

Poor preoperative nutritional status has been shown to have a negative impact on wound healing. In patients who underwent emergency laparotomy, a low OPNI had significantly higher rates of wound dehiscence and infection.[18] This happens because protein deficiency leads to decreased wound tensile strength, decreased T-cell function, decreased phagocytic activity, which ultimately diminish the patient's ability to heal and defend against wound infections.[19-21]

In soft tissue sarcoma patients, poor preoperative nutritional status is further compromised by radiation therapy to the wound. Gu and colleagues showed that radiation to wounds in mice showed early inhibition of the inflammatory phase, injury and inhibition of fibroblasts, and collagen formation, and then prolonged re-epithelialization.[22] This "double hit" with radiation onto host tissue that is already nutritionally compromised could be an important cause of why wound complications occur at such high rates in our soft tissue sarcoma patients.

There are several limitations to this study. First, the study has a small sample size, which was a direct result of the number of patients who were excluded because an OPNI value could not be calculated for them. Second, we could not determine if the OPNI was more valuable in patients who underwent pre- or postoperative radiation. This study did not look at other nutritional indices such as prealbumin and vitamin levels. Third, the radiation was provided by different providers, so technique was variable, but the patients received nearly equivalent doses and variability in technique is likely limited. Fourth, we were not able to meaningfully analyze the role of chemotherapy in this patient population because there was a significant heterogeneity of patients receiving pre- and postoperative chemotherapy.

Our findings strongly suggest that a preoperative OPNI of <45.4 and being older than 73 years are strong predictors of patients who will experience a wound complication after radiation therapy for soft tissue sarcomas. This study has led us to start measuring preoperative albumin levels and assess complete metabolic panels. Our goal is to identify patients who are at high risk of wound complication and perform interventions to improve nutrition, then to study whether the interventions help lower the rates of wound complications.

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