Scientific Article

Effect of Favorable Pathologic Response After Neoadjuvant Radiation Therapy Alone in Soft-tissue Sarcoma

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Abstract

Purpose: Whether the therapeutic response of soft-tissue sarcoma to neoadjuvant treatment is predictive for clinical outcomes is unclear. Given the rarity of this disease and the confounding effects of chemotherapy, this study analyzes whether a favorable pathologic response (fPR) after neoadjuvant radiation therapy (RT) alone is associated with clinical benefits.

Methods and Materials: An institutional review board-approved retrospective review was conducted on a database of patients with primary soft-tissue sarcoma treated at our institution between 1987 and 2015 with neoadjuvant RT alone followed by surgical resection. Time-to-event outcomes estimated with a Kaplan−Meier analysis included overall survival, progression-free survival (PFS), locoregional control, and distant control (DC). Cox regression analyses were performed to determine prognostic variables associated with clinical outcomes.

Results: Of the overall cohort of 315 patients, 181 patients (57%) were included in the primary analysis with documented pathologic necrosis (PN) rates (mean: 59%) and a median follow up from diagnosis of 48 months (range, 4-170 months). The median neoadjuvant RT dose was 50 Gy (range, 40-60 Gy), and the majority of patients had negative surgical margins (79%). Only 35 patients (19%) achieved a fPR (PN ≥95%), which was associated with a higher R0 resection rate (94% vs. 75%; P = .013), a significant 5-year PFS benefit (74% vs. 43%; P = .014), and a nonsignificant 5-year DC benefit (76% vs. 62%; P = .12) compared with PN <95%. On multivariable analysis, fPR was an independent predictor for PFS (hazard ratio: 0.47; 95% confidence interval, 0.25-0.90; P = .022).

Conclusions: Achieving fPR with neoadjuvant RT alone is associated with a higher R0 resection rate and possible DC benefit, translating into a significant improvement in PFS. Further studies to improve pathologic response rates and prospectively validate this endpoint are warranted.

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Introduction

In soft-tissue sarcoma (STS), there is uncertainty regarding the clinical significance of pathologic necrosis (PN) after neoadjuvant therapy. Retrospective studies of patients treated with predominately neoadjuvant chemoradiation have demonstrated improvements in overall survival (OS) associated with increased PN,1-4 with another analysis showing improved freedom from distant...
metastases with PN ≥90%.6 Recently, a phase 2 trial of treatment escalation with NBTXR3 crystalline hafnium oxide demonstrated a statistically significant doubling in the primary endpoint of favorable pathologic response (fPR).6 In this study, fPR was defined as PN ≥95%, and associated with an improvement in the margin negative (R0) resection rate.6 Resection margins have, in turn, been associated with local control7 as well as distant recurrence and survival in large retrospective databases.8,9 Despite these findings, reports regarding tumor response to radiation therapy (RT) alone are limited, with a small retrospective analysis suggesting an improvement in 3-year distant recurrence-free survival. However, this result was not statistically significant.10

Nevertheless, the use of PN as a clinically meaningful surrogate is controversial, because other investigators have found no association between pathologic response and oncologic outcomes,11–15 even when stratified with the endpoints of PN ≥95%14–16 or ≥80%.17 However, these series were limited by smaller sample sizes and confounded by a number of patients receiving concurrent chemotherapy. A more recent retrospective study of 330 patients, with two-thirds of patients treated with neoadjuvant RT alone, demonstrated improvements in OS and disease-free survival associated with PN ≥95%.18 Treatment with neoadjuvant RT alone tends to be more easily tolerated than chemoradiation, and has been associated with a potential distant control (DC) benefit,10,19 suggesting a potential uncharacterized immunostimulatory quality that may affect oncologic outcomes. To this end, the aim of this single institution retrospective analysis was to assess the influence of fPR after neoadjuvant RT alone on R0 resection rates and patient outcomes.

Methods and Materials

Patients and treatment

After institutional review board approval, a retrospective institutional database of patients with a diagnosis of primary STS and treated with neoadjuvant RT, followed by surgical resection, between 1987 to 2015 was reviewed. Patients were staged according to the American Joint Committee on Cancer system, 8th edition. Neoadjuvant RT was recommended after multidisciplinary discussion with consideration of several factors, including risk of positive margin and anatomic location, tumor grade and size, and histopathologic subtype. The exclusion criteria included age <18 years, recurrent sarcoma, pathologically confirmed metastatic disease at the time of diagnosis, delivery of any neoadjuvant chemotherapy or concurrent chemoradiotherapy, uterine sarcoma, or any bone sarcomas derived from or involving the bone (eg, Ewing’s sarcoma, chondrosarcoma, or osteosarcoma). Thus, patients whose standard treatment required neoadjuvant chemotherapy were excluded.

From this cohort of 315 patients, a total of 181 patients had documented pathologic necrosis rates and were included in the final analysis with outcomes of surgical margin status, OS, progression-free survival (PFS), locoregional control (LRC), and DC. In addition, the entire cohort (n = 315) was analyzed to identify factors associated with outcomes that may be underpowered in the subset analyses. Although no patients in this study received neoadjuvant/concurrent chemotherapy before surgery, a subset analysis (n = 148) was performed excluding patients who also received chemotherapy after surgery (eg, adjuvant or postoperative chemotherapy) to account for potential confounding.

All patients underwent preoperative conventionally fractionated external beam RT alone, followed by wide local excision or limb-sparing resection, within 4 months of completing RT. Per institutional protocol, all sarcoma specimens were processed according to the standard practice of the College of American Pathologists20 with standardized grading between 3 specialty-trained sarcoma pathologists across the 30 years of the cohort. In brief, the treated tumor was sectioned by taking 1 full cross-sectional slab at its greatest cross-sectional area with tumor photograph documentation and mapping. Although PN is a component of grading, posttreatment necrosis cannot reliably be distinguished from pretreatment necrosis.21 Therefore, the term “pathologic necrosis” is commonly synonymous with “pathologic response” in this study, meant to depict the proportion of nonviable cancer cells, including necrosis, fibrotic/inflammatory changes, and hemorrhage by meticulous microscopic examination.

The pathologic necrosis/response was documented on the final pathologic report as the sum of all areas, excluding all viable cancer cells, divided by the total cross-sectional tumor. A fPR was defined as PN ≥95%.6,15,18 Only specimens that could be estimated accurately for overall pathologic response by our sarcoma pathologists were included in this cohort. Clinical data for this cohort included clinical tumor (T) stage, clinical nodal (N) stage, tumor grade, tumor location, histology, RT dose, patient age, and Karnofsky performance status (KPS) score.

Statistical analysis

OS, PFS, LRC, and DC were estimated using a Kaplan–Meier analysis, compared via a log-rank test. OS was calculated from the date of diagnosis to the date of last contact or death. PFS was calculated from the date of diagnosis to the first recurrence or death, censored at the date of the last follow up. LRC and DC were calculated from the date of treatment to the date of local or distant recurrence, respectively. Date of recurrence was recorded at the time of pathologic confirmation, if available.
However, a radiographic recurrence or progression was recorded if clinically documented.

The association between PN and surgical margin status was assessed with an independent-samples Kruskal–Wallis test, and the association of fPR with surgical margin status was assessed with a Pearson $^2$ test. Univariable and multivariable (Cox proportional hazards model) analyses were performed to determine prognostic variables in correlation with the clinical outcomes. The multivariable analysis included clinical T stage, grade, surgical margins, fPR, age (continuous), and KPS ($\geq 80$). For all analyses, the type I error was set at 0.05, and all tests were 2-sided. The statistical analysis was performed in SPSS, version 25.0 (IBM Corp.; Armonk, NY).

**Results**

A total of 315 patients were identified with stage I to III resected STS treated with definitive intent neoadjuvant RT, followed by surgery, and with a documented margin status (Table E1). In this cohort, R0 resection was associated with a significant 5-year LRC benefit (91% vs. 80%; $P = .018$).

A documented pathologic necrosis rate was identified in 181 patients (57%) with a median follow up of 48 months from diagnosis (Table 1). The median age was 64 years (range, 25-89 years), patients were predominantly male (63%), and had a KPS score of $\geq 80$ (94%; mean KPS: 93), tumor grade 2 to 3 (78%), and extremity tumor location (70%). The median clinical tumor size was 11 cm (range, 2-34 cm), and the preoperational median RT dose was 5000 cGy (range 4000-6000 cGy) with a median time from RT to surgery of 72 days (range: 38-129 days). The mean PN response for the cohort was 59% (range: 0%-100%), and fPR (PN $\geq 95$%) was achieved in 35 patients (19%). A fPR was associated with a higher R0 resection rate (94% vs. 75%; $P = .013$) and extremity site (97% vs. 64%; $P = .008$) compared with a PN $< 95%$. A lower stratification point of PN $> 90$% was explored, and there was no association with 5-year DC ($64\%$ vs. 65%; $P = .87$) or PFS ($53\%$ vs. 47%; $P = .80$) in our cohort. There was no significant association between fPR and histologic grade ($P = .4$), and no significant difference in mean pathologic necrosis ($P = .20$) or fPR ($P = .24$) across grade for GI/G2/G3/GX with 39%/50%/64%/48% and 0.8%/17.2%/12.8%/5.2%, respectively. There was no association between achieving a fPR and days to surgery from RT (72 vs. 73 days; $P = .55$).

A fPR was associated with a statistically significant 5-year PFS benefit (74% vs. 43%; $P = .014$; Fig. 1A) and non-statistically significant improvements in 5-year LRC (94% vs. 85%; $P = .24$; Fig. 1B), DC (76% vs. 62%; $P = .12$; Fig. 1C), and OS (76% vs. 61%; $P = .27$; Fig. 1D) compared with PN <95%. A negative surgical margin, defined as no tumor on ink, was achieved in 143 patients (79%), and associated with a higher PN rate compared with R1 resection (75% vs. 45%; $P < .001$). R0 resection demonstrated a trend toward association with improved 5-year LRC (89% vs. 79%; $P = .14$). On multivariable analysis, fPR (hazard ratio: 0.47; 95% confidence interval, 0.25-0.90; $P = .022$) and high KPS score independently predicted for PFS (Table 2).

Although no patients received chemotherapy before surgery, a subset analysis of patients (n = 148) who also did not receive chemotherapy after surgery (eg, adjuvant/postoperative) continued to show an association between fPR and improved 5-year PFS (77% vs. 47%; $P = .043$).

**Discussion**

Neoadjuvant RT is increasingly used in the treatment of STS$^{22}$ with advantages in tumor cytoreduction and capsule fibrosis,$^{23}$ translating into lower positive margin resection rates,$^{24,25}$ improved outcomes after marginal excisions,$^{26}$ and decreased late toxicity, compared with postoperative treatment.$^{27}$ We present the first data to show that achieving fPR with neoadjuvant RT alone is associated with a lower risk for positive margin resections, and demonstrated a 22% nonsignificant improvement in DC, translating into a significant 31% absolute PFS improvement. On multivariable analysis, fPR was the only variable associated with PFS (more than twice as likely to survive without disease recurrence), suggesting a significant mechanism independent of surgical margins, stage, or performance status.

The influence of tumor response after neoadjuvant RT alone has been unclear, because many studies that show an oncologic benefit of neoadjuvant treatment are confounded by systemic therapy, such as ifosfamide-based regimens, which are associated with improved PN and thought to drive the DC benefit.$^{1,5}$ However, the widespread adoption of neoadjuvant chemotherapy has been limited by significant toxicity burden.$^{28}$ and matched-pair analyses comparing neoadjuvant RT alone versus chemoradiation have demonstrated no difference in OS, local control, or DC with the addition of concurrent chemotherapy.$^{29,30}$ To account for any confounding effects of chemotherapy in our study, a subset analysis of patients who did not receive any chemotherapy (eg, neoadjuvant, concurrent, or adjuvant) showed that achieving a fPR from RT alone was associated with a 30% improvement in 5-year PFS, suggesting the distant DC seen with fPR may be from other unknown mechanisms.

Although chemotherapy frequently induces lymphopenia and an immunosuppressed state, RT has documented immunostimulatory qualities with resulting abscopal and bystander effects.$^{31-33}$ In our series, achieving fPR resulted in a 22% relative improvement in DC, which may be related to the immunomodulatory effects of RT, as previously described in sarcoma.$^{34,35}$ To this end, there has
|                          | Total | Non-fPR | fPR | P   |
|--------------------------|-------|---------|-----|-----|
| **N = 181**              |       |         |     |     |
| **Non-fPR** n = 146 %    |       |         |     |     |
| **fPR** n = 35 %         |       |         |     |     |
| **Age**                  |       |         |     |     |
| <50 y                    | 42    | 23.2    | 33  | 22.6|
| ≥50 y                    | 139   | 76.8    | 113 | 77.4|
| **Sex**                  |       |         |     |     |
| Female                   | 67    | 37.0    | 51  | 34.9|
| Male                     | 114   | 63.0    | 95  | 65.1|
| **Histologic grade**     |       |         |     |     |
| Grade 1                  | 13    | 7.2     | 12  | 8.2 |
| Grade 2-3                | 141   | 77.9    | 111 | 76.0|
| Grade unknown            | 27    | 14.9    | 23  | 15.8|
| **Tumor location**       |       |         |     |     |
| Extremity                | 127   | 70.2    | 93  | 63.7|
| Retroperitoneal          | 25    | 13.8    | 25  | 17.1|
| Pelvis                   | 11    | 6.1     | 10  | 6.8 |
| Thorax                   | 4     | 2.2     | 4   | 2.7 |
| Head/neck                | 2     | 1.1     | 2   | 1.4 |
| Abdomen                  | 12    | 6.6     | 12  | 8.2 |
| **Histology type**       |       |         |     |     |
| Chondrosarcoma, NOS      | 1     | 0.6     | 1   | 0.7 |
| Extraskeletal chondrosarcoma | 1    | 0.6   | 1   | 0.7 |
| Dedifferentiated chondrosarcoma | 3   | 1.6 | 3   | 2.1 |
| Myxoid chondrosarcoma    | 3     | 1.6     | 3   | 2.1 |
| Liposarcoma              |       |         |     |     |
| Dedifferentiated liposarcoma | 14  | 7.7 | 14  | 9.6 |
| Liposarcoma, NOS         | 3     | 1.6     | 3   | 2.1 |
| Mixed liposarcoma        | 3     | 1.6     | 0   | 0.0 |
| Myxoid liposarcoma       | 11    | 6.1     | 6   | 4.1 |
| Pleomorphic liposarcoma  | 5     | 2.8     | 4   | 2.7 |
| Well differentiated liposarcoma | 6   | 3.3 | 6   | 4.1 |
| **Other**                |       |         |     |     |
| Angiosarcoma             | 2     | 1.1     | 2   | 1.3 |
| Dermatofibrosarcoma, NOS | 1     | 0.6     | 1   | 0.7 |
| Ewing sarcoma (extraskeletal) | 2  | 1.1 | 1  | 0.7 |
| Fibrosarcoma, NOS        | 3     | 1.6     | 3   | 2.1 |
| Leiomyosarcoma, NOS      | 11    | 6.1     | 11  | 7.5 |
| Malignant hemangiopericytoma | 4    | 2.2 | 4   | 2.7 |
| Malignant peripheral nerve sheath tumor | 4 | 2.2 | 4 | 2.7 |
| Malignant solitary fibrous tumor | 2 | 1.1 | 2 | 1.4 |
| Myxofibrosarcoma         | 16    | 8.9     | 15  | 10.3|
| Osteosarcoma, NOS (extraskeletal) | 1 | 0.6 | 1 | 0.7 |
| Table 1 (Continued) | Total | Non-fPR | fPR | P |
|---------------------|-------|---------|-----|--|
|                     | N = 181 | n = 146 | n = 35 | |
| Rhabdomyosarcoma, NOS | 2 | 1.1 | 2 | 1.3 | 0 | 0.0 |
| Synovial sarcoma | 7 | 3.9 | 6 | 4.1 | 1 | 2.9 |
| Undifferentiated pleomorphic sarcoma/undifferentiated sarcoma | 46 | 25.4 | 33 | 22.6 | 13 | 37.2 |
| Unclassified | | | | | |
| Myxoid sarcoma, NOS | 2 | 1.1 | 1 | 0.7 | 1 | 2.9 |
| Sarcoma, NOS | 13 | 7.2 | 9 | 6.2 | 4 | 11.3 |
| Spindle cell sarcoma, NOS | 18 | 9.9 | 13 | 8.9 | 5 | 14.2 |
| Clinical T stage | | | | | |
| T1 | 12 | 6.6 | 10 | 6.8 | 2 | 5.7 | .3 |
| T2 | 63 | 34.8 | 46 | 31.3 | 17 | 48.6 |
| T3 | 58 | 32.0 | 47 | 32.0 | 11 | 31.4 |
| T4 | 40 | 22.1 | 36 | 24.5 | 4 | 11.4 |
| Unknown | 8 | 4.4 | 7 | 4.8 | 1 | 2.9 |
| Clinical N stage | | | | | |
| 0 | 178 | 98.3 | 143 | 97.3 | 35 | 100.0 | .39 |
| 1 | 3 | 1.7 | 3 | 2.0 | 0 | 0.0 |
| SM status | | | | | |
| SM negative | 143 | 79.0 | 110 | 74.8 | 33 | 94.3 | .01 |
| SM positive | 38 | 21.0 | 36 | 24.5 | 2 | 5.7 |
| Karnofsky performance status score | | | | | |
| <80 | 9 | 5.0 | 5 | 3.4 | 4 | 11.4 | .12 |
| ≥80 | 170 | 93.9 | 139 | 94.6 | 31 | 88.6 |
| Unknown | 2 | 1.1 | 2 | 1.4 | 0 | 0.0 |
| Time to surgery | | | | | |
| Days, median (range) | 72 | 38-129 | 73 | 38-129 | 72 | 58-105 | .55 |
| Radiation therapy dose | | | | | |
| Gy, median (range) | 50 | 40-60 | 50 | 40-60 | 50 | 45-60 | .46 |

fPR, favorable pathologic response (<95% pathologic necrosis); NOS, not otherwise specified; SM, surgical margin
been growing interest in integrating immunomodulatory agents with RT, with the hope of a synergistic immunogenic effect.\(^\text{36,37}\) Further understanding of the drivers behind the immunomodulatory effects of RT in sarcoma are required, appropriately selecting patients based on gene profiling\(^\text{38}\) and improved understanding of the influence of tumor-infiltrating lymphocytes.\(^\text{39}\)

Understanding the prognostic value of fPR in STS has been limited by the rarity of the disease, the PN stratification point used in previous experiences, and the heterogeneity in treatment regimens. Notably, PN $\geq 80\%$ has been shown to have no significant effect on oncologic outcomes in historical experiences with twice daily\(^\text{17}\) or daily\(^\text{40}\) neoadjuvant RT. Prior studies have shown that PN $\geq 90\%$ was associated with improved freedom from distant metastases,\(^\text{4}^\) but in our current study, achieving a 90% response had no association with 5-year DC (64% vs. 65%; $P = .87$) or PFS (53% vs. 47%; $P = .80$). In a small analysis of 25 patients, the use of a higher stratification point of PN $\geq 95\%$ after neoadjuvant RT alone showed an association with improved 3-year event-free survival at 100% versus 59%, but was underpowered to reach statistical significance.\(^\text{14}\)

Analogous to our results, another retrospective analysis of 30 patients after neoadjuvant RT alone showed a nonstatistically significant 37% improvement in 3-year distant recurrence-free survival with an fPR, as well as no differences if stratified at PN 80%.\(^\text{10}\) Although the statistical power in these experiences was limited by smaller numbers, a larger report of 113 patients treated with chemoradiation with a mesna, adriamycin, ifosfamide, and dacarbazine regimen and a split course RT to 4400 cGy achieved a median PN of 90%, but found no difference in oncologic outcomes at 5 years, likely driven by the excellent outcomes in the PN $< 95\%$ cohort (5-year LRC and OS $\geq 85\%$).\(^\text{15}\)

Local control in STS remains imperative, because recurrences have been associated with poor survival.\(^\text{41,42}\) Historically, surgical margin status in STS (reviewed by Harati and Lehnhardt\(^\text{43}\)) has been associated with improved locoregional control, survival,\(^\text{44,45}\) and metastasis-free survival.\(^\text{47}\) The effect of surgical margins in our comprehensive cohort ($n = 315$) was consistent with the results of these previous studies, showing that a margin-negative resection offers an 11% LRC benefit after preoperative RT alone. Our study is underpowered to show a significant LRC association with fPR, but a

Figure 1  Kaplan–Meier survival analyses comparing time to event for patients achieving favorable pathologic response ($\geq 95\%$ pathologic necrosis) versus those not achieving favorable pathologic response ($< 95\%$ pathologic necrosis), showing A, progression-free survival, B, locoregional control, C, distant control, and D, overall survival.
A profound improvement in R0 resection rates (19%) contributed to improved LRC and potentially DC.

Finally, significant heterogeneity exists in PN rates between histologic phenotypes. Myxoid liposarcoma has been shown to be particularly radiosensitive with increased rates of PN after neoadjuvant treatment.\(^{14,48}\) This is consistent with our findings, where fPR had a higher proportion of myxoid liposarcoma (14% vs. 4%) than PN <95%. Teasing out the biologic susceptibilities between histologies may be critical in future investigations, because there is now growing evidence of heterogenous radiation sensitivities\(^{49}\) and benefits (eg, STRASS trial)\(^{50}\) within STS.

The limitations of this study include its retrospective nature, and the relatively low incidence of fPR poses difficulty in achieving statistical significance, particularly for modest benefits in LRC and DC. Our institutional practice is for our sarcoma-specialized pathologist to evaluate the specimens for pathologic response, but unfortunately, this not always possible. As a retrospective study, accounting for biases that may have influenced the missing pathologic response data in this study (eg, inadequate processing or documentation) is difficult. Classically, the presence of tumor necrosis is a component of STS grading; however, the pretreatment overall necrosis is difficult to estimate based on biopsy testing alone, potentially confounding the final pathologic response. With a higher baseline necrosis/grade, we would expect a higher pathologic response, which we see from grade 1 versus 2 versus 3 (39% vs. 50% vs. 64%) in this cohort, but the ability to achieve a fPR >95% was lower for grade 3 versus 2 (12.8% vs. 17%). This suggests that higher initial necrosis in grade 3 tumors may affect their average pathologic response, but achieving a 95% response threshold is unlikely affected because the remaining viable tissue may be innately radioresistant/hypoxic.

**Conclusions**

Achieving an fPR (pathologic necrosis ≥95%) with neoadjuvant RT alone is associated with an improved R0

| Table 2 | Multivariable Cox proportional hazards analyses evaluating clinical and pathologic variables associated with overall survival and PFS |
|---------|---------------------------------------------------------------------------------------------------------------------------------|
| Variable | Overall survival | P-value | PFS | P-value |
| cT stage | | | | |
| 1 ref | ref | ref | ref | ref |
| 2 | 1.4 (0.4-4.7) | .6 | 1.0 (0.4-2.7) | 1 |
| 3 | 1.7 (0.5-5.9) | .4 | 1.7 (0.7-4.4) | .3 |
| 4 | 1.5 (0.5-5.4) | .5 | 1.0 (0.4-2.7) | 1 |
| X | 1.6 (0.3-8.0) | .6 | 1.0 (0.3-3.9) | 1 |
| Grade | | | | |
| 1 ref | ref | ref | ref | ref |
| 2 | 1.4 (0.3-8.1) | .7 | 1.3 (0.4-4.8) | .7 |
| 3 | 3.4 (0.8-14.5) | 1 | 2.6 (0.9-7.3) | .07 |
| Unknown | 1.9 (0.4-8.9) | .4 | 1.5 (0.5-4.6) | .5 |
| Surgical margin | | | | |
| Negative | ref | ref | ref | ref |
| Positive | 1.3 (0.7-2.3) | .4 | 1.4 (0.8-2.3) | .19 |
| FAVORABLE PATHOLOGIC RESPONSE | | | | |
| <95% | ref | ref | ref | ref |
| ≥95% | 0.7 (0.3-1.4) | .3 | 0.47 (0.3-0.9) | .022 |
| Patient age | 1.00 (0.99-1.02) | .8 | 1.0 (0.98-1.01) | .77 |
| Karnofsky performance status score | | | | |
| <80 | ref | ref | ref | ref |
| ≥80 | 0.4 (0.2-0.98) | .045 | 0.44 (0.2-1.0) | .046 |
| Unknown | 0.8 (0.1-7.4) | .8 | 0.41 (0.05-3.8) | .44 |

PFS, progression-free survival; ref, reference
resection rate, as well as a relative DC benefit, leading to a profound PFS benefit on multivariable analysis. Prospective studies are required to validate this endpoint, and determine the mechanisms responsible for the potential benefit in disease control.

**Supplementary materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ador.2022.101086.

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