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Sarcoma (SH Okuno, Section Editor)

Molecular Predictors of Radiotherapy Response in Sarcoma

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Opinion statement

Soft-tissue sarcoma is one of the few clinical cancer models in which pre-operative radiotherapy is commonly utilized and in which tumor response to radiotherapy could be assessed. However, clinical and histopathological features of soft-tissue sarcomas are not useful in predicting tumor radiotherapy response. Exploration of predictive markers of sarcoma response to radiotherapy is further confounded by discordance between radiological tumor size reduction, pathological changes, and clinical local recurrence rates. The diversity of disease histology and anatomical origin further influences which type of radiotherapy response (volumetric vs. cytotoxic) would best relate to patient outcome. Advances in molecular biology and understanding of sarcoma biology have recently resulted in the identification of several molecular and imaging predictive markers of radiotherapy response. As the underlying mechanism of radiation-induced cell killing involves the production of DNA damage through the production of oxygen radicals, the most promising biomarkers and imaging markers are related to DNA damage repair genes, hypoxia, and tumor vasculature. As bone and cartilaginous sarcomas are less often treated with radiotherapy, biomarkers of response in these diseases are less examined.

Introduction

Sarcomas are cancers of diverse histologic subtypes and origins. They are generally first subclassified into bone and soft-tissue sarcomas. The management of bone and cartilaginous sarcomas often involves surgery with adjunctive chemotherapy given before and/or after surgery. Radiotherapy is seldom used in the management of bone sarcomas unless surgery is precluded or if the surgical margins are positive. On the other hand,

multiple randomized controlled trials demonstrated the efficacy of adjuvant radiotherapy in reducing the need of extensive and morbid surgeries in the treatment of soft-tissue sarcomas [1–4]. Subsequent studies demonstrated that pre-operative radiotherapy induced less long-term irreversible radiation toxicities than post-operative radiotherapy, with similar rates of local control [1, 5–9]. Therefore, pre-operative radiotherapy is commonly offered to patients in the multidisciplinary management of their soft-tissue sarcomas. With recent technical advances in image-guided radiotherapy (IGRT), the volumetric changes occurring to the sarcoma during weeks of pre-operative radiotherapy can be monitored [7, 10•]. Subsequent radiological and biological responses of the tumor to pre-operative radiotherapy can then be assessed using images and surgical specimen obtained after radiotherapy.

Radiotherapy response

The definition of radiotherapy response is in itself not straightforward as it depends on the goal of radiotherapy in the multidisciplinary management of sarcomas. Radiotherapy mainly induces cellular toxicities through the production of free radicals that subsequently cause DNA single-strand and double-strand breaks. Although radiotherapy-induced DNA damages may result in rapid cell deaths through apoptosis in certain cancers such as lymphomas, radiotherapy commonly induces the activation of a wide range of cellular pathways that take time to resolve. At the conclusion of these intracellular molecular interactions, the same radiotherapy dose may be as cytotoxic to two different cancers but one tumor may show more rapid volumetric response than the other one in which more cells undergo mitotic cell deaths and senescence. Therefore, a lack of radiological response from radiotherapy does not necessarily mean that the treatment is inactive as cells could remain metabolically active, be senescent, and lose their capacity to form clones (Fig. 1) [11–14].

In sarcoma, the predominant fate of cell death following radiotherapy is unclear. However, the presence of a dose-dependent efficacy from radiotherapy in improving local control [15, 16] and limited volumetric change after radiotherapy suggest that sarcomas generally do not undergo rapid apoptotic cell deaths [10•, 12, 14]. Measuring radiation response based on sarcoma local control is complicated by the role of radiotherapy as an adjunctive modality to surgery. In the post-operative setting or in body areas where wide resection margins can be achieved, the aim of radiotherapy is to maximize the cytotoxicity to sarcoma cells in order to sterilize the peri-tumoral area and improve local control irrespective of the type of cell death or volumetric response. Conversely, in the treatment of sarcomas located close to critical organs and structures, volumetric response to neoadjuvant radiotherapy could influence the ability to obtain a negative resection margin. In this situation, local control may be improved by a reduction in tumor volume independent of the number of cells killed by radiotherapy. Therefore, markers of radiation response could be developed to predict for volumetric changes or sarcoma cytotoxicity secondary to radiotherapy.

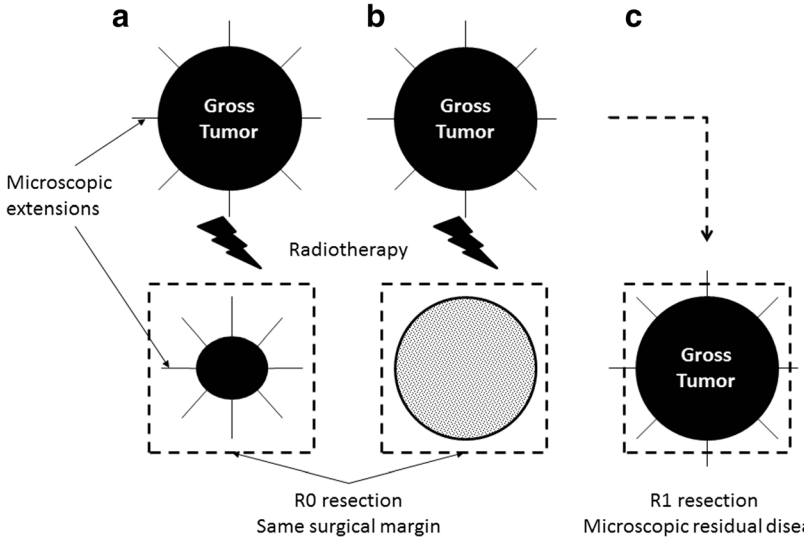

Fig. 1. Representations of the aim of pre-operative radiotherapy and sarcoma response to the treatment. Perceivable or measurable radiologic response to radiotherapy is from changes in the gross tumor. Radiotherapy may induce sizable volumetric response (*a)*) but may not change the outcome of patients in comparison to a tumor that did not respond as rapidly radiologically to radiotherapy, but with similar cancer toxicity (*b)*). Following the same surgery, both patients would have equivalent clinical outcome from their surgeries in comparison to an un-irradiated tumor undergoing the same surgery (*c)*) in which microscopic residual disease remains. A sizeable tumor response in tumors located close to vital organs may however render a marginally unresectable tumor resectable. Yet, the majority of radiotherapy response in soft-tissue sarcoma resembles *b)*, in which little radiological response is observed despite radiotherapy being efficacious in inducing clonogenic death of cancer cells.

Radiological and pathological response to radiotherapy in soft-tissue sarcomas

Soft-tissue sarcomas (STS) are often considered poorly responsive to radiotherapy. However, radiological volumetric response does not correlate well with pathological response [17•]. In a study reported by Roberge et al., 50 patients with STS (45 extremities and 5 trunks; 38 high-grade and 16 low-grade sarcomas) underwent pre-operative radiation therapy; each patient received a course of 50 Gy in 25 fractions over a median of 35 days. By comparing pre- and post-treatment MRI, median tumor volume changes were 0.5 % (range −85 to +285 %) and 36 % (range −89 to +42 %) for high-grade and low-grade STS, respectively. Myxoid liposarcoma was particularly responsive to radiation treatment with a median of 86 % decrease in tumor volume. Although there was minimal (median reduction in tumor volume <1 %) radiological response in high-grade STS, a median treatment-induced necrosis was observed in 50 % of the pathological samples. On the other hand, there was a median volumetric reduction of 13.8 % in low-grade non-myxoid STS but the median treatment-induced necrosis was observed in only 10 % of these tumors. Similarly, Canter et al. showed a median tumor necrosis of 30 % in 25 STS (18 extremity and 7

retroperitoneal) treated with neoadjuvant radiation therapy. None of the cases with over 80 % tumor necrosis had radiological responses [18•]. These studies are examples of the discordance between histopathological findings and radiological responses, with neither endpoints irrevocably associated with patient prognosis [19•, 20•]. However, based on different studies using tumor necrosis as a marker of response, the response rate of radiation therapy varies between 20 and 78 % depending on the radiation regimens used, histological subtypes included, and addition of concurrent chemotherapeutic or biological agents [21–23, 24•, 25, 26•]. In the ongoing PAZNTIS/ARST1321 study "A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib," the primary endpoints of the phase II study component is >90 % pathologic necrosis in the resected STS after neoadjuvant treatment (clinicaltrials.gov NCT02180867).

Although tumor necrosis can be used as a marker of response, previous reports suggest that tumor size, tumor grade, and histological subtype could have an impact on this measurement of radiation response. In particular, myxoid liposarcomas are more sensitive to radiation compared to other STS [17•, 27, 28]. Larger tumors tend to be more resistant to radiotherapy [29]. High-grade tumors could be more responsive than low-grade tumors except for myxoid liposarcomas [17•]. As histopathological tumor characteristics are insufficient to reliably predict for tumor response to radiotherapy, molecular markers were evaluated to determine their prognostic and predictive values.

Molecular and imaging predictive markers

Gene signature

To address the lack of molecular predictors, Yoon et al. attempted to identify a genetic signature that may predict radiation response of STS [26•]. In their study, 20 patients with STS (14 extremity and 6 retroperitoneal sarcomas) underwent pre-operative external beam radiation (50.0 to 66.4 Gy) along with concurrent bevacizumab (monoclonal VEGF-A antibody). Global gene expression profiles were obtained in pre-treatment biopsies using gene expression microarrays. With a cutoff value of 80 % post-treatment tumor necrosis being a marker of radiation response, 8 cases were classified as good responders and 8 cases as poor responders. While some histological subtypes, such as pleomorphic fibrosarcomas and liposarcomas, were clustered together, other sarcoma subtypes did not, suggesting histological subtype may not predict radiotherapy response. From this data set, the authors constructed a 24-gene signature predicting radiotherapy response. As the treatment consisted of concurrent radiotherapy and bevacizumab, it remains to be seen if this signature is generalizable to STS treated with radiation alone or along with other biological agents. Furthermore, a subsequent analysis of the same study suggested 20 genes associated with tumor response, which consisted of genes different from the ones described in the aforementioned signature [30••].

DNA damage response (DDR) regulators

As we had previously described, the principal method by which radiotherapy induces cell deaths is through the induction of DNA damage. Therefore, Ernst et al. irradiated a panel of six sarcoma cell lines (HT-1080, TE-671, SW-872, SW-

982, HS-729, and A-673), profiled the expression of DNA damage response regulators in these cell lines, and associated the expressions of these genes to the clonogenic survival of the cells following in vitro irradiation. Their results suggested that the expression levels of ataxia telangiectasia and RAD3 related (ATR), ataxia telangiectasia mutated (ATM), nijmegen breakage syndrome 1 (NBS1), and heat shock protein HSP90AB1 were correlated with radioresistance [31•]. The authors then used NW457 to inhibit the chaperone function of HSP90, which targets ATR, ATM, and NBS1, and showed that NW457 radiosensitized the sarcoma cell lines and delayed their clearance of γ-H2AX foci, which is a marker of DNA double-strand breaks [31•]. The inherent STS expression level of these DNA damage response regulators might therefore be predictive of radiotherapy response. In fact, overexpression of NBS1, also known as nibrin (NBN), was shown to confer radioresistance in prostate cancer cells and was correlated with a shorter relapse-free survival in 139 patients who received image-guided radiotherapy [32]. In a clinical study conducted in Spain where 87 patients received chemoradiotherapy for head and neck cancers, although biopsy samples overexpressing HSP90AA had a higher local relapse rate, it did not reach statistical significance [33].

Hypoxia-related markers

Most tumors regardless of their origin contain hypoxic regions [34•]. Hypoxia induces a myriad of events that promote cellular aggressiveness such as increased genomic instability, migration and invasive capacity, and resistance to radiotherapy. Brizel et al. had previously observed that lower tumor oxygenation in high-grade STS was prognostic of the development of metastasis [35]. Correspondingly, two studies have previously described prognostic molecular signatures composed of three hypoxia-related messenger RNA (mRNA) (HIF-1α, HB-EGF, and VEGF-C) expressions and a 177-mRNA gene signature [36, 37]. Recent pre-clinical work by Zhang et al. further suggested that the deletion of HIF-1α from primary murine sarcomas increases the sensitivity of the tumors to radiation in vivo [38]. A similar observation was reported in mouse hepatoma cell lines [39]. In addition, HIF-1α expression in esophageal squamous cell carcinomas was negatively correlated to response to chemoradiation, with a 44 % complete response rate when pre-treatment HIF-1α expression was negative [40]. Similarly, a strong HIF-1α expression prior to definitive radiotherapy for cervical cancer is associated with a lower complete response rate (72 vs. 91 % with no/weak expression) and a shorter progression-free survival [41].

Hypoxia also reduces microRNA (miRNA) genesis through the repression of DICER and DROSHA. In a murine undifferentiated pleomorphic sarcoma (UPS) model, Mito et al. observed that the deletion of one allele of DICER resulted in an increased rate of lung metastasis [42]. In our cohort of 42 human pre-treatment UPS fresh frozen samples, we also observed through global miRNA profiling that 166 (43.9 %) of the 378 quantified miRNAs were significantly underexpressed in UPS primaries compared to normal tissues ($p<0.0001$); no miRNAs were significantly overexpressed in UPS. Nevertheless, compared to non-metastatic primary tumor samples, metastatic primary samples and their corresponding metastases had higher expressions of certain miRNAs (miR-138 and miR-143) [43].

Lewin et al. recently reported results from their phase Ib/II study in which the influence of hypoxia in STS was investigated using PET hypoxia tracer [^{18}F]FAZA [44••]. Consistent with prior results by Brizel et al., 13 of the 23 evaluated STS were hypoxic (tumor-to-background ratio of 1.2 or greater). Hypoxic tumors demonstrated less radiologic volume response to pre-operative radiotherapy (p= 0.012) with no association with tumor necrosis in the final surgical specimen. This study further documented the discordance between the presence of tumor necrosis and clinical outcome as FAZA-PET hypoxic tumors were associated with a higher risk of local recurrence (HR 10.2, p=0.02) and shorter PFS (HR 8.37, p= 0.02) and OS (HR 41.42, p<0.04). In the second cohort of this study, the authors administered sunitinib concomitantly with radiotherapy to normalize tumor vasculature and reduce tumor hypoxia. Counterintuitively, these patients who received sunitinib developed high rates of grade 3+ hepatotoxicity and local failures (HR 8.1, p=0.004) in comparison to patients who were treated with pre-operative radiotherapy only [44••]. In their biomarker study, the authors did not observe a measurable difference in VEGF levels between hypoxic and non-hypoxic tumors but found that VEGF-A blood levels increased (p<0.001) during the radiotherapy of hypoxic tumors. The addition of sunitinib also significantly (p=0.06 and p=0.004, respectively) increased VEGF-A and VEGF-D blood levels.

Two recent publications were derived from the phase II clinical trial previously described in which 20 patients were treated with bevacizumab concomitantly with pre-operative radiotherapy. The trial included perfusion CT to characterize the tumor vasculature over the course of the treatments and observed significant reduction in mean positive pixels [45], blood flow, blood volume, mean transit time, and permeability [30]. While Tian et al. observed a correlation between mean positive pixels and the presence of tumor necrosis, there was no correlation between the presence of histopathological necrosis with other CT perfusion parameters [30]. There was no association between clinical outcomes with any of the parameters from perfusion CT. Of note, Kambadakone et al. paid special effort to analyze a large number of biomarkers (serum VEGF, PDGF, sVEGFR-1, sVEGFR-2, sVEGFR-3, bFGF, IL-6, IL-8, TNF-α, SDF-1a, and cKIT), pathological markers (tissue CD31 staining for assessing microvascular density, proliferation cell nuclear antigen staining for determining cellular proliferation, terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling for documenting apoptosis), and genetic expression profiles. Of these explorative analyses, only the microvascular density was associated with blood flow measured by perfusion CT (p=0.04 without Bonferroni correction). Finally, as alluded to previously, the authors proposed a set of 20 genes that were differentially expressed in high- and low-baseline perfusion tumors, suggesting that genes associated with radiological response may differ from those associated with the presence of tumor necrosis at the completion of radiotherapy and bevacizumab [26].

Other potential markers of response

Osteopontin is a secreted phosphoprotein involved in cell growth, cell migration, invasion, and metastasis [46]. Elevated expression of osteopontin is associated with poor prognosis in patients with STS [47]. In a study conducted by Hahnel et al., tissue expressions of three different splice variants of osteopontin were determined in 52 STS patients treated with radiotherapy [48]. A

high expression level of two splice variants (OPN-b and OPN-c) was significantly ($p<0.01$ for both variants) associated with a poor prognosis in the multivariate Cox regression analysis and a 10- to 11-fold increased risk of sarcoma-related death [48]. In rectal cancer patients who underwent pre-operative chemoradiation, a lower osteopontin level was associated with pathological complete response [49]. Although direct evidence is still lacking, the expression level of osteopontin could be a potential predictive marker of radiotherapy response in STS, as in rectal cancer.

Apart from perfusion CT as a potential image method to trace radiotherapy response, tumor perfusion and blood flow could also be evaluated using dynamic contrast-enhanced (DCE)-MRI techniques, which use gadolinium chelates as contrast agents to image and characterize tissue vascularity. Shapeero et al. described the use of DCE-MRI [50] as an imaging modality that could distinguish the response (≤10 % viable tumor) of STS to chemotherapy in 32 patients. The absence of a rapid enhancement within 3–10 s after arterial enhancement was interpreted as voxels with no viable tumor. Using this interpretation of DCE-MRI data, the authors identified all 11 responders, but no clinical outcomes from these patients were described. Additionally, this method could potentially distinguish tumor recurrence from post-radiotherapy inflammatory changes surrounding the surgical cavity. Meyer et al. reported their experience in the use of DCE-MRI to monitor the effects of pre-operative chemoradiation plus sorafenib in STS [22]. Eight patients from this phase I trial underwent at least two of the three planned DCE-MRIs. Pathological tumor necrosis (≥95 %) was observed in 44 % (n) of the post-treatment STS specimen. The authors introduced a new DCE-MRI measure ΔK^{trans}, which is a composite measure of vascular permeability (K^{trans}) calculated using two pharmacokinetic models (the standard (Toft) model and the shutter-speed model). The percent change in tumor DCE-MRI ΔK^{trans} after 2 weeks of sorafenib was inversely correlated with the amount of tumor necrosis ($R^2=0.67$, $p=0.012$) at the time of surgery. Volumetric change (RECIST) of the tumors at 2 weeks did not predict for histopathological response ($R^2=0.019$, $p=0.747$). After completion of all pre-operative treatments, multiple DCE-MRI parameters were capable of differentiating optimal from suboptimal responders, including RECIST, median values of K^{trans}(standard model), K^{trans}(shutter-speed model), and ΔK^{trans}. Recently, Spratt et al. investigated the use of DCE-MRI in 9 patients treated for spinal STS metastasis using stereotactic body radiotherapy (24 Gy in one fraction (50 %), 27/3 in 33 % and 30/3 in the last patient) [51]. There was one local failure (at 10.2 months post-treatment). At the 2-month post-treatment DCE-MRI, an increase in the maximum K^{trans} was observed in the sole lesion that subsequently recurred. The authors concluded that DCE-MRI could be used as a non-invasive method for early detection of radiotherapy outcome.

Bone and cartilaginous sarcomas

There are little advances in the molecular and imaging markers of radiotherapy response for bone and cartilaginous sarcomas as radiotherapy is seldom used in these sarcomas. The efficacy of radiotherapy in osteosarcomas and chondrosarcomas is controversial and largely untested prospectively. On the other hand, the treatment of Ewing's sarcomas sometimes involves radiotherapy

either as the sole modality for local treatment or in adjunct to surgery. Although the degree of tumor necrosis (<90 vs. ≥90 %) following chemotherapy is associated with Ewing's sarcoma patient prognosis, there had not been similar studies to examine the validity of this histopathological marker as a radiotherapy response marker as patients seldom undergo surgery following radiotherapy. In 1921, James Ewing first described the sensitivity of the disease to radiation through radiological observation of disease radiation response [52]. Nevertheless, the joint analysis of three prospective trials (INT-0091, INT-0154, and AEWS0031) observed that 40 % of patients treated with definitive radiotherapy recurred locally, suggesting that even though this disease often shows rapid volumetric response, it is not an indicator that radiotherapy is necessarily more efficacious in Ewing's sarcoma than in other diseases [53]. This analysis also showed that 30 % of patients treated with definitive surgery recurred locally, and on multivariate analysis, the local control treatment modality did not influence event-free survival, distant metastasis, or overall survival, highlighting the need to improve both local and systemic control in this disease.

Conclusion

Proven predictive molecular markers of radiotherapy response in sarcoma are currently lacking. Nevertheless, different potential molecular and imaging markers are on the horizon. With the concurrent improvement in biological high-throughput technologies and radiological imaging capabilities, it is hoped that combined studies would yield successful bio-imaging markers that could be validated clinically. Sarcomas represent one of the few clinical cancer models in which neoadjuvant radiotherapy is commonly used, and tumor specimen could be retrieved post-radiotherapy to measure treatment response. As such, despite their relative rarity in incidence, sarcoma is a good clinical model for the discovery of radiation response bio-imaging markers. Findings originating from sarcoma studies could then be translated to other cancers by adapting to different cancers' inherent biology and clinical needs from radiotherapy.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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