**Advances in Brief**

**Clinicopathologic Assessment of Postradiation Sarcomas: KIT as a Potential Treatment Target**

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**Abstract**

**Purpose:** Postradiation sarcoma, a sarcoma developing in a previously irradiated field, is a rare tumor. Surgery appears to be the only curative treatment option. In general the prognosis is poor, and new treatments options are needed. One study reported the expression of KIT receptor tyrosine kinase in two postradiation angiosarcomas. Success of inhibition of KIT in malignant gastrointestinal stromal tumors with imatinib mesylate seems mutation-dependent, with a favorable response in the presence of exon 11 mutations.

**Experimental Design:** We performed a clinical, immunohistochemical, and genetic assessment of postradiation sarcomas, including angiosarcomas. Archival tumor tissue was available from 16 patients diagnosed with a postradiation sarcoma between 1978 and 2001. Data on the first and secondary tumor, treatment, and follow-up was documented. KIT expression was assessed by immunohistochemistry. For comparison, 23 spontaneous soft tissue sarcomas of similar histological types were analyzed. Exon 11 of the c-kit gene was analyzed by direct DNA sequencing.

**Results:** Fifteen patients received initial irradiation for malignant disease and 1 patient for a benign condition. The median delivered dose was 50 Gy. The median latency period between irradiation and diagnosis of postradiation sarcomas was 222 months. Histological types included: angiosarcoma, fibrosarcoma, malignant fibrous histiocytoma, osteosarcoma, rhabdomyosarcoma, and unspecified sarcoma. In concordance with the literature, patients had a poor outcome. Only 3 of 16 patients were disease-free 43, 60, and 161 months after being diagnosed of postradiation sarcoma, all 3 having favorable tumor and treatment characteristics. Fourteen of 16 tumor samples were KIT-positive (88%). In 8 cases >80% of tumor cells stained positively. Five of 23 (22%) spontaneous soft tissue sarcomas of comparable histological types, including 2 angiosarcomas, were KIT-positive. Molecular genetic analysis of exon 11 of the c-kit gene was attainable for 13 of the 16 postradiation sarcomas. No mutations were found.

**Conclusions:** Postradiation sarcomas are aggressive malignancies, seldom amenable to curative treatment. A majority of the analyzed tumors showed extensive expression of the KIT protein, but no mutations in exon 11 of the c-kit gene were found. Still, without the availability of effective therapies, treatment with the KIT inhibitor imatinib mesylate might be considered for patients with postradiation sarcomas.

**Introduction**

Sarcomas developing in previously irradiated fields are rare. Nevertheless, these so-called postradiation sarcomas pose a major clinical problem. In general, surgery is the only curative treatment; still, even radical surgery does not prevent recurrence of the disease in a majority of cases. The role of additional radiation therapy is limited, because the maximum tolerated cumulative dose to the target region has often already been reached. Moreover, in case radiotherapy can be applied, postradiation sarcomas appear to be radioresistant. The role of chemotherapy in the treatment of postradiation sarcomas is also very limited (1).

The report of Miettinen et al. (2) including two postradiation angiosarcomas expressing KIT (c-kit protein) prompted us to study a larger series of postradiation sarcomas. The c-kit gene is the cellular homologue of the v-kit oncogene of the Hardy-Zuckerman 4 feline sarcoma virus (3) and is located on the long arm of chromosome 4. It encodes the KIT transmembrane receptor tyrosine kinase, which is involved in cell signal transduction. KIT is consistently expressed in malignant GISTs (4), the most common sarcomas of the gastrointestinal tract. KIT appears to play a major role in the oncogenesis of these tumors (5, 6). Mutations of the c-kit gene leading to ligand-independent activation of KIT tyrosine kinase are common in malignant GISTs (5, 7). Like postradiation sarcomas, GISTs are notoriously resistant to standard cytotoxic agents (8). However, imatinib mesylate (Glivec in Europe, Gleevec in the United States; Novartis Pharma) is able to induce apoptosis in GIST cells in vitro.

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2 The abbreviations used are: GIST, gastrointestinal stromal tumor; NOS, not otherwise specified; MFH, malignant fibrous histiocytoma; BCT, breast conservative treatment.
vitro by inhibiting KIT activity (9). In the clinical situation, imatinib mesylate has been reported to induce promising clinical and radiological tumor response rates in patients with metastasized GISTs (10, 11). Noticeable, it appears that tumors bearing an activating exon 11 mutation of the c-kit gene are the most responsive to imatinib mesylate (12).

Imatinib mesylate and other KIT-targeted agents may have therapeutic potential for malignancies other than GISTs, which are also subjected to a KIT-mediated oncogenic drive. Given the preliminary data on postradiation angiosarcomas, KIT expression was assessed on a series of 16 postradiation sarcomas with various histological diagnoses.

Materials and Methods

Using the computerized files of the department of Pathology at the University Hospital Groningen, data from 27 patients with a postradiation sarcoma were retrieved. Of these 27 patients, frozen and/or paraffin-embedded tumor material was available in 16 cases. These patients were diagnosed, treated, and/or referred for consultation between 1978 and 2001. The criteria for postradiation sarcoma included: (a) different histopathologic features between index lesion (i.e., indication for initial radiotherapy) and sarcoma; (b) sarcoma arising within the irradiated field; and (c) a latency period of at least 3 years (13, 14). Sarcomas were reviewed on H&E-stained sections with additional immunostains and classified according to Weiss and Goldblum (15).

Patient demographics, tumor characteristics (of both the index lesion and the postradiation sarcoma), treatment, and follow-up were documented. The latency period was calculated from the moment of initial radiotherapy until the diagnosis of the postradiation sarcoma.

Cytogenetics. Of four postradiation sarcomas, a karyotype was obtained. Fresh tumor material was cultured for 5–15 days in RPMI 1640 (Life Technologies, Inc.), supplemented with 13.5% FCS, l-glutamine, and penicillin/streptomycin. Cultures were harvested, and chromosome samples were made according to standard cytogenetic techniques. The metaphases were air dried and stained with Giemsa after G banding with either trypsin (Difco; Fisher Scientific, Hertogenbosch, the Netherlands) or pancreatin (Sigma, St. Louis, MO).

Immunohistochemistry. For detection of KIT the rabbit polyclonal antibody A-4502 (DAKO, Glostrup, Denmark) was used in a 1:100 dilution. First, samples were deparaffinized in xylene and rehydrated in alcohol. As described by others, heat-induced epitope retrieval was performed to facilitate epitope-antibody interaction (7, 16–18). Samples were heated in 0.1M Tris-hydrogen chloride (pH 9.0) for 8 min in a microwave (700 watt). Endogenous peroxidase was blocked with 0.3% hydrogen peroxide in PBS before proceeding to a 1-h incubation with the primary antibody. Next, a biotin-streptavidin immunoperoxidase method was applied, using biotinylated swine antirabbit IgG (1:100; DAKO) and streptavidin conjugated to horseradish peroxidase (1:300; DAKO). Bound peroxidase was developed with dianinobenzidine and hydrogen peroxide.

Normal small intestine tissue was used as a positive control, demonstrating KIT-positive interstitial cells of Cajal within in the muscular layers (19). As internal positive controls, melanocytes (for samples including epithelial layers) and mast cells were to be detected.

Samples were scored as negative when no immunoreactive tumor cells were observed. Positive samples were semiquantitatively categorized according to the percentage of immunoreactive tumor cells: <50%, 50–80%, and >80%. For comparison of the immunohistochemistry, 23 spontaneous soft tissue sarcomas were studied for KIT expression, using an identical immunohistochemical procedure. This control group included histological types similar to the postradiation group. Sarcoma types that are not or only seldom reported in association with prior irradiation (e.g., liposarcoma and synovial sarcoma) were omitted from this study.

Genetic Analysis of Exon 11 of c-KIT. DNA was isolated from frozen or paraffin-embedded material using standard methods (20). Sequence analysis of exon 11 of the c-KIT gene was performed on PCR products made with the following two M13 tailed primers: cKit-for 5’-CGACGGTGTGAAAGGAGGCCAGTTTGTCTCCTCACAGGT-3’ and the cKit-rev 5’-CAGGAAACAGCTATGACAGTCACTGTTATGTGTACCC-3’. Direct sequencing using M13 primers in both sense and antisense directions was performed using the BigDye terminator sequencing kit V-3.1(Applied Biosystems) and an ABI PRISM 377 DNA sequencer (PE Biosystems).

Results

Patient demographics, tumor data, and treatment schedules are summarized in Table 1. The study group consisted of 9 females and 7 males. The median patient age at time of initial irradiation was 29 (range, 2–72) years. Fifteen patients received radiation therapy for a malignant index lesion. As part of clinical routine of the sixties, 1 patient received 16 Gy before diagnostic biopsy of a suspected osteosarcoma. However, the definitive histopathological diagnosis in this case was an ossifying myositis, a nonmalignant condition.

Irradiation Dose and Additional Treatments. The total delivered irradiation dose was known in 12 cases, with a median of 50 Gy and range from 16 to 70 Gy. In 4 cases information on the irradiation dose was not retrievable, all involving a prolonged latency period after radiotherapy (≥32 years). Six patients had received systemic therapy for the index lesion as well; 5 were treated with cytotoxic agents, and 1 patient was treated with hormones.

Latency Period. The median latency period between radiotherapy for the index lesion and diagnosis of the postradiation sarcoma was 222 months. The shortest latency period was observed for a patient with a sarcoma NOS 40 months after irradiation with 60 Gy for a squamous cell carcinoma of the floor of the mouth. The longest latency period was seen for a patient who developed a sarcoma NOS 41 years after a squamous cell carcinoma of the vulva (irradiation dose unknown). The median age of patients at time of diagnosis of postradiation sarcoma was 53.3 (range, 22–83) years.

Histological Types of Postradiation Sarcomas. Five different histological types of postradiation sarcomas were diagnosed. Three patients had angiosarcomas, 2 had fibrosarcomas, 2 had osteosarcomas, 2 had MFH, and 1 had a rhabdomyo-
### Table 1  Patient, tumor, and treatment characteristics

| Patient | Sex | Age (yrs) | Type | Index lesion surgery | Chemotherapy | RT (Gy) (mo) | Latency (yrs) | Type | Surgery | Chemotherapy | RT (Gy) (mo) | OS (mo) | Follow-up | Site | Surgery | Chemotherapy | LF | DF | Status | KIT |
|---------|-----|-----------|------|----------------------|--------------|--------------|--------------|-------------|-------|---------|--------------|--------------|--------|-----------|------|---------|--------------|----|-----|--------|-----|
| 1       | F   | 47        | Breast ca. | BCT | No | 50 | 54 | 84 | ANGIO | Breast | Mastectomy | No | Yes | 13 | Yes | No | DOD | <50% |
| 2       | F   | 72        | Breast ca. | BCT | No | 70 | 79 | 84 | ANGIO | Breast | Mastectomy | No | No | 58 | Yes | Yes | AWD | >80% |
| 3       | F   | 63        | Breast ca. | BCT | Hormonal | 70 | 67 | 53 | ANGIO | Breast | Mastectomy | No | No | 22 | Yes | Yes | AWD | >80% |
| 4       | M   | 35        | Ossifying myositis | Incision | No | 16 | 51 | 204 | MHI | Thigh | Resection | VAC/DTIC | No | 161 | No | No | NED | >80% |
| 5       | F   | 43        | Adeno ca. | Hysterectomy | No | Dose unk | 83 | 480 | MHI | GROIN | Resection | No | No | 60 | No | No | NED | >80% |
| 6       | M   | 16        | Hodgkin | No | MOPP-ABV | 60 | 22 | 72 | FIBR | Pelvis | No | EC | 39 | 14 | Yes | Yes | DOD | 50–80% |
| 7       | F   | 28        | Hodgkin | No | MOPP-ABV | 40 | 34 | 65 | FIBR | Mediastinal | No | VI | No | 9 | Yes | No | DOD | 50–80% |
| 8       | F   | 22        | Hodgkin | No | Vinblastine/chlorambucil | 35 | 53 | 372 | OSTEO | Breast | Resection | No | 25 | Yes | Yes | DOD | <50% |
| 9       | M   | 12        | RMS | No | VAC | 55 | 33 | 252 | OSTEO | Maxilla | Resection | MTX/Cisplatin | No | 43 | No | No | NED | <50% |
| 10      | M   | 2         | Retinoblastoma | Enucleation | No | 45 | 22 | 258 | RMS | Nose | No | EVI | No | 5 | Yes | No | DOD | >80% |
| 11      | F   | 21        | Hodgkin | No | No | 40 | 39 | 240 | NOS | Sternotomlvular | Resection | EVI | 60 | 11 | Yes | No | DOD | Neg |
| 12      | F   | 18        | Hodgkin | Unk | Unk | Dose unk | 50 | 384 | NOS | Rib | Resection | Unk | Unk | Unk | Unk | Unk | Unk | 50–80% |
| 13      | M   | 25        | Osteosarcoma | Resection | No | Dose unk | 61 | 432 | NOS | Supra-orbital | No | No | 21 | Yes | No | AWD | >80% |
| 14      | M   | 68        | SCC | No | 60 | 71 | 40 | NOS | Mouth | No | No | 11 | Yes | No | DOD | Neg |
| 15      | F   | 30        | SCC | Resection | No | Dose unk | 71 | 492 | NOS | Vulva | No | No | 2 | Yes | Yes | AWD | >80% |
| 16      | M   | 47        | Adenocarcina | Resection | 5-FU/Levamisol | 50 | 55 | 102 | NOS | Pelvis | Resection | No | 2 | Yes | No | AWD | >80% |

RT, radiotherapy; SCC, squamous cell carcinoma; ANGIO, angiosarcoma; MHI, malignant fibrous histiocytoma; FIBR, fibrosarcoma; OSTEO, osteosarcoma; RMS, rhabdomyosarcoma; OS, overall survival; LF, local failure; DF, distant failure; DOD, dead of disease; AWD, alive with disease; NED, no evidence of disease; MOPP/ABV, mechlorethamine, vincristine, procarbazine, prednisone/adriamycin, bleomycin, vinblastine; VAC, vincristine, adriamycin, cyclophosphamide; 5-FU, 5-fluouracil; DTIC, dacarbazine; EC, epirubicin, cyclophosphamide; VI, vindesine, ifosfamide; EVI, epirubicin, vinodesine, ifosfamide; MTX, methotrexate; Unk, unknown.
osarcoma. All 3 of the angiosarcomas developed after BCT for breast cancer. The rhabdomyosarcoma had developed 21.5 years after treatment for hereditary retinoblastoma. Despite additional immunohistochemical staining, the histological type could not be specified in 6 cases, referred to as sarcoma NOS. In 4 cases a karyotype of the postradiation sarcoma was established (Table 2). This revealed complex karyotypes known to be characteristic for such tumors (21). In 1 case, 5 abnormal metaphases with clear chromosomal abnormalities were seen, but chromosomes were not individually analyzable.

**Follow-Up.** The median survival after diagnosis of the postradiation sarcoma was 17.5 months for 15 evaluable patients (range, 2–161 months). Twelve patients were either alive with disease or dead of disease, with a median overall survival of 13 months (range, 2–58 months) after being diagnosed with a postradiation sarcoma. Eleven patients with recurrent disease had local failure, whereas 4 also had distant metastases. One patient, diagnosed with a postradiation angiosarcoma, suffered from distant disease without a recurrence at the primary site. Three patients were disease-free at 43, 60, and 161 months after treatment for postradiation sarcoma. One patient was not evaluable for clinical follow-up because no clinical record was available anymore.

**KIT Expression in Postradiation Sarcomas.** The results on KIT scoring are given in Table 1. Fourteen of 16 tumor samples were positive for KIT (88% of cases). Eight specimens demonstrated >80% immunoreactive tumor cells (50% of cases). Three samples had 50–80% positive tumor cells (19% of cases). In 3 samples <50% of positive tumors cells were observed (19% of cases). Two samples revealed no KIT-positive tumor cells (13% of cases), yet immunoreactive mast cells were present.

**KIT Expression per Histological Type of Postradiation Sarcoma.** Two of 3 angiosarcomas revealed >80% positive tumor cells, whereas the third had few solitary positive tumor cells. Both MFH were strongly positive for KIT (>80% of the tumor cells). The 2 fibrosarcomas showed 50–80% positive tumor cells. The 1 postradiation rhabdomyosarcoma had >80% positive tumor cells. Both osteosarcomas revealed positive tumor cells, but in each specimen this totaled <50%. Of the 6 sarcomas NOS, 3 were strongly positive (>80%), 1 had 50–80% positive tumor cells, whereas 2 were negative.

**KIT Expression in Spontaneous Soft Tissue Sarcomas.**

<table>
<thead>
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<th>Patient</th>
<th>Histological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>MFH</td>
</tr>
<tr>
<td>6</td>
<td>Fibrosarcoma</td>
</tr>
</tbody>
</table>

Table 2. Cytogenetic analysis of postradiation sarcomas

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<table>
<thead>
<tr>
<th>Patient</th>
<th>Histological type</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>MFH</td>
</tr>
<tr>
<td>6</td>
<td>Fibrosarcoma</td>
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</tbody>
</table>

**Exon 11 of the c-kit Gene.** Direct sequencing of exon 11 of the c-kit gene could be performed in 13 cases; all of these tumor specimens were obtained in 1994 or later. In 3 cases the PCR to obtain an adequate DNA sample had failed; these specimens were paraffin-embedded and dated 1993 or before. None of the analyzed samples revealed a mutation in exon 11.
Discussion

Previous radiotherapy is a recognized risk factor for the development of sarcomas (22). Amendola et al. (23) estimated an incidence of 0.09–0.11% after all cases of radiation therapy. Recent reports suggest an increasing incidence, possibly because of the introduction of techniques such as BCT for breast carcinoma (24). Three patients of the current series underwent BCT; all 3 were diagnosed with an angiosarcoma. One patient, who had been treated at the 2 years of age with bulbar enucleation and subsequent irradiation for hereditary retinoblastoma, developed a rhabdomyosarcoma after almost 22 years. Hereditary retinoblastoma is a recognized additional risk factor for postradiation malignancies, both carcinomas and sarcomas. Nevertheless, the presentation of a postradiation rhabdomyosarcoma as observed in this case is rare (25).

Prognosis for patients diagnosed with a postradiation sarcoma is generally poor (26). Lagrange et al. (14) reported a median survival of 23 months in a series of 80 patients. Patients from the current study survived a median period of only 17.5 months. Radical resection results in a relatively favorable outcome with up to 39% 5-year survivors, but may not be feasible (14). Distal location of the postradiation sarcoma is a favorable factor, as it increases the possibility for radical surgery (27). In the current study, 3 of 15 evaluable patients were disease-free 43, 60, and 161 months after diagnosis. The latter 2 patients had distally located sarcomas (primary site: groin and upper leg), and both underwent radical surgery. Twelve patients had recurrent disease, which was accompanied by a median survival of only 13 months. Local recurrence was observed in 73% of the patients and appears to be a major cause of death. Distant disease was observed in 33% of the cases and was in all but 1 case accompanied by a local recurrence.

Mertens et al. (21) described the complex karyotypes found in 10 newly described postradiation sarcomas and 8 cases published previously. The complexity of the karyotypes was in concordance with our findings; the reported high frequency of rearrangements of chromosome 3 was also observed in 3 of 4 cases of the present series. However, no distinctive cytogenetic aberrations are known to be specific for (a subset of) postradiation sarcomas.

Five patients of the current study with postradiation soft tissue sarcoma were treated with anthracycline-based chemotherapy: 4 of them died of disease within 14 months after treatment. Only 1 patient who received adjuvant chemotherapy after radical surgery is alive after 161 months without evidence of disease. To date, no randomized studies have been performed to reveal the value of chemotherapy for postradiation sarcomas, which can be explained by the extreme rarity of the disease. Anecdotal reports mostly concern patients with disease in an advanced stage, a situation in which conventional chemotherapy appears to be ineffective (1, 28, 29). Favorable results have been reported for postradiation osteosarcomas after methotrexate-based treatment, comparable with the spontaneous osteosarcomas (30–32). In the current series, 2 patients had a postradiation osteosarcoma. One was treated with methotrexate plus cisplatin followed by surgical resection and is alive 43 months after diagnosis without overt disease.

KIT tyrosine kinase activity has been linked to the genesis of GIST. Rubin et al. (7) reported that GIST (benign, borderline, and malignant) all demonstrated elevated levels of KIT tyrosine kinase activity, whereas 92% harbored a mutant c-kit gene. Inhibition of KIT by the small-molecular agent imatinib mesylate renders considerable response rates in patients with metastasized malignant GIST (11). To date, it is unknown whether other cancer types are driven by KIT-mediated cell signaling and might therefore benefit from inhibition of KIT activity. In the current series of postradiation sarcomas, 14 of 16 cases were positive for KIT expression. Ten of these 14 positive samples revealed >50% immunoreactive tumor cells. Eight samples had even >80% positive tumor cells. KIT expression was not only evident in postradiation angiosarcomas, but also in other histological types. KIT expression was considerably more pronounced in postradiation sarcomas compared with a group of nonpostradiation, non-GIST sarcomas. Hornick and Fletcher (33) also found limited expression of KIT in spontaneous soft tissue sarcomas when using the same antibody. In the current group of 23 spontaneous sarcomas, 2 angiosarcomas and 1 sarcoma NOS revealed >50%, but not >80% positive tumor cells. Angiosarcomas, also when spontaneously arising, were reported to express KIT in a substantial amount of cases (2). Two spontaneous MFH revealed limited KIT expression, and 2 were negative, in contrast with the 2 postradiation MFH with strong and diffuse (>80%) positive tumor cells. Spontaneous rhabdomyosarcomas and fibrosarcomas were found to be KIT-negative, similar to the findings of Hornick and Fletcher (33). Four of the 5 spontaneous sarcomas NOS, high-grade tumors with insufficient characteristics for specific histological typing, were KIT-negative.

Whether postradiation sarcomas will respond to KIT inhibition remains to be established. In malignant GISTs, the responsiveness to imatinib mesylate depends on the presence of specific mutations in the c-kit gene. Heinrich et al. (12) found a far better response in malignant GISTs bearing an activating mutation in exon 11 of the c-kit gene. Their results prompted a

<table>
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<th>Histological type</th>
<th>Negative</th>
<th>&lt;50% positive tumor cells</th>
<th>50–80% positive tumor cells</th>
<th>&gt;80% positive tumor cells</th>
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<td>0</td>
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<td>6</td>
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<td>2</td>
<td>0</td>
<td>3</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Sarcoma NOS</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 3 KIT expression in spontaneous soft tissue sarcomas.
molecular analysis on this exon for the postradiation sarcomas. However, 0 of 13 analyzed samples revealed a mutation in exon 11. Our results on exon 11 status suggest that different roles of KIT function exist between postradiation sarcomas and malignant GIST. An anticancer effect of KIT inhibition may be expected when it actually mediates an oncogenic drive. This may still involve mutational activation of KIT, yet in that case it is more likely to occur in regions other than exon 11. Deregulated autocrine or paracrine loops between KIT and its ligand provide an alternative mechanism in which imatinib mesylate or other KIT inhibitors may interfere (34).

The presented results warrant additional study on KIT inhibition in patients diagnosed with primarily irresectable postradiation sarcomas. To date, it is unclear whether KIT inhibition will demonstrate activity against postradiation sarcomas. However, because of the rarity of such tumors, this report aims to raise the awareness to a potential treatment against these typically aggressive and resistant tumors.

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