Radiation-induced sarcomas of the head and neck

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Abstract

With improved outcomes associated with radiotherapy, radiation-induced sarcomas (RIS) are increasingly seen in long-term survivors of head and neck cancers, with an estimated risk of up to 0.3%. They exhibit no subsite predilection within the head and neck and can arise in any irradiated tissue of mesenchymal origin. Common histologic subtypes of RIS parallel their de novo counterparts and include osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma/sarcoma nitric oxide synthase, and fibrosarcoma. While imaging features of RIS are not pathognomonic, large size, extensive local invasion with bony destruction, marked enhancement within a prior radiotherapy field, and an appropriate latency period are suggestive of a diagnosis of RIS. RIS development may be influenced by factors such as radiation dose, age at initial exposure, exposure to chemotherapeutic agents and genetic tendency. Precise pathogenetic mechanisms of RIS are poorly understood and both directly mutagenizing effects of radiotherapy as well as changes in microenvironments are thought to play a role. Management of RIS is challenging, entailing surgery in irradiated tissue and a limited scope for further radiotherapy and chemotherapy. RIS is associated with significantly poorer outcomes than stage-matched sarcomas that arise independent of irradiation and surgical resection with clear margins seems to offer the best chance for cure.

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Key words: Post-irradiation; Nasopharyngeal carcinoma; In-field; Radiotherapy; Head and neck cancer

Core tip: Radiotherapy is an important modality in the curative management of head and neck carcinoma. However, it is also associated with significant morbidity. Radiation-induced second malignancies, particularly radiation-induced sarcomas (RIS), are arguably the most devastating sequelae associated with radiotherapy. This review examines the common trends, pathophysiology, clinical presentation, diagnosis and management of RIS in head and neck cancers.

INTRODUCTION

Radiotherapy is a commonly used in a curative setting to treat head and neck cancers, being utilized in both definitive as well as adjuvant settings. With prolongation of survival amongst head and neck cancer patients stemming from advances in therapeutic regimens and improvements in general oncologic care, attention to treatment-related morbidity becomes increasingly important. Radiation-induced second malignancies, in particular radiation-induced sarcomas, are arguably the most devastating sequelae associated with radiotherapy. With improved oncologic outcomes, post-irradiation sarcomas are increasingly seen in long-term survivors of head and neck cancers with an estimated risk of up to 0.3%.1,2
In order to established causality between radiation and sarcomagenesis requires the the following conditions: (1) the sarcoma should arise within the irradiated field (in the area encompassed by the 5% isodose line); (2) the sarcoma must be histologically distinct from the index lesion; and (3) there must be a latency of several years between radiation exposure and subsequent diagnosis of the sarcoma\[4,4]. This time interval is necessary to differentiate post-irradiation sarcomas from sporadic sarcomas that may have predated radiation therapy. However, the best interval to establish this distinction continues to be a subject of debate: The original stipulation for this latent period was 5 years or longer. Subsequent modifications have seen a reduction in this time interval ranging from 6 mo to 4 years\[5-7]. For post-irradiation head and neck sarcomas, arbitrary time frames of 3-4 years have been used as cutoffs based on a loose consensus that this was a sufficient gap for radiation carcinogenesis to occur\[8,9]. Finally, patients with inherited syndromes that predispose to sarcomas even in the absence of radiation such as Li-Fraumeni or Rothmund-Thomson are generally excluded from the Radiation-induced sarcomas (RIS) subgroup of patients as defined above.

Squamous cell cancers comprise the commonest histologic sub-type of radiation-induced malignancy occurring in the head and neck region. RIS is the second most common, accounting for approximately 12% of radiation-induced malignancies; lifetime risk has been estimated to be 0.03%-0.3% in patients who have been previously irradiated. Radiation-induced sarcomas exhibit no predilection for any single subsite within the head and neck. They can arise within any irradiated tissue of mesenchymal origin and as connective tissue is ubiquitous, any site within the head and neck can be a primary site for RIS. In one of the larger series of post-irradiation sarcomas of the head and neck recently published by our institution, the most common subsite was found to be the nose and paranasal sinus region, consistent with the fact that the vast majority of our cases (greater than 80%) were seen in nasopharyngeal carcinoma survivors\[10]. This finding has been replicated in a few other studies from China\[11]. That said, these data represent the spectrum of RIS observed in regions where nasopharyngeal carcinoma is endemic and should not be generalized to all post-irradiation sarcomas of the head and neck.

RIS include osseus and soft tissue sarcomas, and the vast majority are high-grade\[12,13]. The most common histologic subtypes of RIS parallel their de novo counterparts and include osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma/sarcoma nitric oxide synthase, and fibrosarcoma. Other histologies encountered include rhabdomyosarcoma (particularly in children), angiosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors\[12,13]. In our series, the commonest RIS subtype was sarcoma NOS and this is in keeping with much of the published literature on post-irradiation sarcomas of the head and neck.

In general, the imaging features of RIS are not pathognomonic and are often indistinguishable from those of sporadic sarcomas or recurrent primary tumors. However, the large size, extensive local invasion with bony destruction, marked enhancement within a prior radiation therapy field, and an appropriate latency period, suggests a diagnosis of RIS\[14,15].

The development of radiation-induced sarcomas may be influenced by factors such as dose, age at initial exposure, exposure to chemotherapeutic agents, and genetic tendency. As radiation carcinogenesis is a stochastic late effect, there is no “safe” or threshold dose below which RIS are not seen; In fact, RIS have occurred at doses less than 15Gy\[16,17]. However, the risk of RIS does appear to increase with increasing radiation dose\[2,18,19]. That said, there is some uncertainty about the shape of the dose-response curve at high radiation doses. RIS is generally thought to occur at doses that induce sublethal damage in normal tissues resulting in mutagenic responses and disorganized reparative proliferation and ultimately, tumor induction. Hence, some have postulated a downturn in RIS risk at ultra-high radiation doses where lethal damage predominates but a recent systematic review of the epidemiologic studies evaluating patterns of secondary malignancy risks after high-dose fractionated radiation therapy showed no clear evidence of nonlinearity in the dose-response in the direction of a reduction in risk even at very high doses, i.e., 60Gy or higher\[20].

Greater risks for secondary sarcomas have been asso-
cated with younger age at initial diagnosis. In the Childhood Cancer Survivor Study, the risk of RIS was more than nine-fold higher amongst childhood cancer survivors when compared with the general population, with highest risk observed in patients younger than four years of age at the time of primary cancer diagnosis. The reasons for these observed variations in susceptibility to RIS with age are not well understood and may be related to biology and not just longer follow-up times after treatment. Plausible explanations for this phenomenon include higher numbers of stem cells in irradiated tissues at a young age or their high proliferative rates, rendering them more sensitive to the tumorigenic effects of radiation. In addition, the microenvironmental constraints which inhibit proliferation of initiated cells may be less effective in some organs during youth and promotion by growth hormones is likely to be greater during youth. Finally, many cases of childhood cancer involve a germline mutation, and the distinct possibility exists that this mutation may include an increased sensitivity to radiation-induced cancer.

Radiotherapy with adjuvant chemotherapy is associated with higher relative risk of RIS in children. Alkylating agents and anthracyclines have been particularly implicated in this regard. They appear to increase RIS risk by a factor of 4 or more in some studies, after adjusting for radiation therapy, with risk increasing with cumulative drug exposure. Whether chemotherapy also potentiates the tumorigenic effects of RT in adults is less clear.

In addition, it has been postulated that the use of newer radiation techniques such as intensity-modulated radiation therapy (IMRT) may result in an increase in radiation-induced second malignancies. The reasons for this are twofold: First, IMRT involves the use of more fields compared to three-dimensional conformal radiation therapy, and as a consequence, the integral dose to the patient is higher, i.e., a larger volume of normal tissue is exposed to lower doses of radiation. Second, delivery of a specified dose to the isocenter from a modulated field, delivered by IMRT, will require the linear accelerator to be energized for longer (i.e., more monitor units are needed) compared with delivering the same dose from an unmodulated field. It therefore follows that the total body dose due to leakage radiation will be increased.

That said, radiation-induced sarcomas are thought to be primarily a complication of high-dose radiation, rarely occurring at doses below 40Gy.

Previous reports suggest that RIS develop after a median latency period of approximately 17 years, although shorter latency has been reported among pediatric patients. Some of these reports suggest an indirect relationship between latency and dose of radiation dose especially for doses higher than 40Gy. However this remains unproven.

**PATHOPHYSIOLOGY**

The precise pathogenetic mechanisms underlying susceptibility to and development of radiation-induced tumors are poorly understood. The prevailing paradigm focuses on radiation-induced DNA damage leading to mutations in susceptible cells. In this regard, p53 point mutations and genetic aberrations in the Rb gene have been implicated. However, more recent literature suggests that radiation carcinogenesis is in fact much more complex. In addition to the directly mutagenizing effects of radiotherapy, changes in microenvironments are thought to play a critical role in tumorigenesis. Several studies have demonstrated that irradiated microenvironments can independently promote genomic injury in stem cells and enhance the expression of a neoplastic phenotype.

In addition, there is mounting evidence that radiotherapy can influence cell function in non-targeted tissues in diverse ways. The bystander effect, which has been observed after radiation and chemical exposures, refers to a setting in which untreated cells demonstrate abnormalities mimicking exposure, such as chromosomal instability after irradiation. Radiation-induced signals transmitted between irradiated (in-field) cells and neighboring unirradiated cells can promote the development of persistent reactive oxygen species in unirradiated cells and hence, tumorigenesis. The mechanisms underlying the bystander effect are not well-defined, but have been postulated to involve secretable factors such as cytokines and intercellular gap junctions. The radiation-induced sarcomas referred to in this review are, by definition, tumors arising within the irradiated region and as such, a discussion of the bystander effect is outside the scope of this review.

**CLINICAL PRESENTATION**

In general, radiation-induced sarcomas present in a similar manner to de novo primary sarcomas of the head and neck. However, radiation-associated tissue changes such as induration may render them more difficult to identify by physical examination.

In the vast majority of cases, these tumors manifest as a painless palpable mass. They may also present with skin changes on the scalp or face, or subsite-specific symptoms (e.g., cranial nerve palsies with skull base tumors, dysphagia with oropharyngeal tumors, or hoarseness with laryngeal tumors).

As with sarcomas occurring elsewhere in the body, lymph node involvement is uncommon in RIS of the head and neck, occurring in only about 10% of patients. The most common histologic subtypes associated with nodal metastases are RMS and angiosarcoma.

Rarely, patients may present with symptoms attributable to metastatic disease, most often involving the lungs (e.g., SOB, cough/haemoptysis, chest pain etc).

**DIAGNOSTIC AND STAGING**

**EVALUATION**

Computed tomography of the primary tumor site offers
Table 2  Advantages and disadvantages of computed tomography and magnetic resonance imaging in head and neck oncologic imaging

| CT                                           | MRI                                                 |
|----------------------------------------------|-----------------------------------------------------|
| Advantages                                   |                                                     |
| Fast                                         | Superior soft tissue resolution including better assessment of perineural invasion, intracranial extension of disease, marrow infiltration |
| Well tolerated                               | Multi-planar imaging capability, better definition of craniocaudal extent |
| Relatively inexpensive                       | Less image degradation caused by artifacts arising from dental amalgam |
| Provides assessment of tissue composition (vasculartiy, lipid content etc.) | Does not involve ionizing radiation |
| Ideal at demonstrating cortical bone erosion |                                                     |
| Disadvantages                                |                                                     |
| Involves exposure to small amounts of radiation | May take more time to perform |
| Inferior soft tissue resolution compared with MRI | More expensive |
| Higher risk of allergic reactions and nephrotoxicity associated with the use of iodinated contrast agents | Lower patient tolerance; Claustrophobic patients may need sedation |
| Contraindicated in patients with pacemakers and other implanted metallic devices which may malfunction following exposure to strong magnetic fields | More susceptible to motion artefact |

CT: Computed tomography; MRI: Magnetic resonance imaging.

three-dimensional information about locoregional tumor extent, provides assessment of tissue composition (vasculartiy, lipid content etc.), and assists in directing biopsies for histopathologic confirmation, planning surgical extirpation, and guiding target delineation during adjuvant radiotherapy planning[14,15]. However, in the head and neck region, magnetic resonance imaging (MRI)s offer several well-recognized advantages over computed tomography (CT)s (Table 2). Firstly, they provide superior soft tissue resolution compared with CTs. Secondly, their multiplanar imaging capability permits better definition of the craniocaudal tumor extent. Thirdly, while CTs are ideal at demonstrating cortical bone erosion, marrow infiltration is better appreciated on MRIs. Finally, MRIs are far less susceptible to image degradation caused by artifacts arising from dental amalgam[16]. For these reasons, MRIs should be an integral part of the workup of RIS of the head and neck and combined CT and MRI use is ideal.

In addition to radiologic evaluation of the primary tumor site, CT of the chest should be routinely undertaken as a component of staging in light of the fact that the lungs are the predominant site of metastases for both soft tissue and bone sarcomas. Guidelines from the National Comprehensive Cancer Network also suggest either an FDG-PET scan and/or bone scan in the staging workup of bone sarcomas to evaluate the entire skeleton for the presence of skip lesions.

Head and neck sarcomas including RIS are staged using the same staging schema applied to sarcomas arising at other body sites. The staging system used for soft tissue sarcomas, rhabdomyosarcomas, and for primary bone sarcomas (both osteosarcomas and chondrosarcomas) are presented in Tables 3-5 respectively.

PATHOLOGIC FINDINGS

As previously mentioned, imaging features of RIS are not pathognomonic and it is difficult to exclude primary tumor recurrence and occasionally even post-operative or post-radiotherapy changes when relying on imaging alone. Hence, examination of tissue is mandatory in establishing the diagnosis of a soft tissue or bone sarcoma. The diagnostic biopsy must be carefully planned to ensure that adequate tissue is obtained in a manner that does not compromise definitive therapy. Core needle biopsy is considered the preferred method to achieve an initial biopsy in most cases.

The vast majority of RIS are high-grade and display a significant degree of tumor necrosis[12,13]. The histopathologic spectrum of RIS is broad and is considerably dependent on the nature of the reporting institutions and/or the clinical practice of the reporting physicians. For instance, many studies in this field exclude bone sarcomas, paediatric sarcomas as well as benign tumors and tumors of low malignant potential, e.g., desmoids and dermatofibromasarcoma protuberans. In most reported series, the commonest histologic subtype of RIS encountered is sarcoma NOS (formerly referred to as malignant fibrous histiocytoma). Other encountered histologies include but are not limited to osteosarcoma, chondrosarcoma, fibrosarcoma, rhabdomyosarcoma (particularly in children), and Angiosarcoma[12,13,16].

There are as yet no specific histopathologic criteria to guide distinction between radiation-induced sarcomas and sporadic sarcomas arising within the radiation field, although the morphology of tissues in the immediate vicinity may be suggestive if it shows radiation-related changes (e.g., dense cellular fibrosis, atypical fibroblasts, alteration of the vascular architecture, and abundant fibrous stroma in the dermis adjacent to the sarcoma)[19].

Likewise, there has been considerable interest in identifying molecular markers or genetic signatures that can differentiate between RIS and spontaneously occurring sarcomas. Radiation-induced angiosarcomas consistently
show MYC amplification, a finding not seen in primary angiosarcomas. Studies using microarray analysis have implicated mitochondrial genes and genes involved in antioxidan
toxidant pathways in radiation-induced tumors, suggesting that mitochondrial dysfunction or chronic oxidative stress could play key roles in their pathogenesis.

While promising, none of these markers are in clinical use. Most studies have used some modification of the Cahan criteria for classifying sarcomas as radiation-induced. While satisfying these criteria is likely to result in a high probability that the sarcoma is radiation related, there remains no gold standard for defining a radiation-associated sarcoma.

**MANAGEMENT**

Head and neck sarcomas are relatively rare clinical entities and radiation-induced head and neck sarcomas even more so. Their rarity coupled with their diversity of histologic subtypes makes rigorous clinical study difficult. As such, treatment algorithms for RIS of the head and neck are derived from retrospective case series and principles of management are drawn from those utilized to treat sarcomas at other body sites, rather than from large randomized clinical trials.

Management of these patients is complex. Surgical resection with clear margins seems to offer the best outcomes for this group of patients. However, the confining and complex functional anatomy of the head and neck region and proximity to critical neurovascular structures makes adherence to traditional margin-driven therapy challenging even in de novo sarcomas. Treatment of RIS presents added challenges-entailing surgery in irradiated tissue and a limited scope for further radiotherapy and chemotherapy in selected sarcoma subtypes.

Not unexpectedly, RIS results in worse outcome compared to stage-matched de novo soft tissue and osteogenic sarcomas. Five-year disease-free survival rates for the former are 10%-30% compared to 54% for de novo tumors. The poorer outcomes could be due to: (1) difficulties and hence delayed diagnosis in previously irradiated tissue; (2) compromised resection margins, due to proximity of the tumor to critical structures; (3) limited of treatment options in a maximally irradiated field i.e., technical difficulties of operating within an irradiated area, difficulties with reirradiation when surrounding normal tissues have been treated to near tolerance; (4) poor tumor sensitivity to chemotherapy; (5) the high-grade nature of the vast majority of RIS; and (6) host immunosuppression resulting from a combination of tumor related factors and previous treatment.

That said, a noteworthy study of radiation-induced head and neck sarcomas conducted at our institution found that patients treated with curative intent had similar

### Table 3 TNM staging for soft tissue sarcoma

| Primary tumor (T) | Regional lymph nodes (N) | Distant metastasis (M) | Histologic grade (G) | Anatomic stage/prognostic groups |
|-------------------|--------------------------|-----------------------|---------------------|----------------------------------|
| TX                | NX                       | M0                    | GX                  | Stage I A                        |
| T0                | Regional lymph nodes cannot be assessed | No distant metastasis | Grade cannot be assessed | T1a N0 M0 G1, GX |
| T1                | Tumor 5 cm or less in greatest dimension | T2a N0 M0 G1, GX | Stage I B |
| T1a               | Superficial tumor        | T2b N0 M0 G1, GX     | Stage II A          |
| T1b               | Deep tumor               | T1b N0 M0 G2, G3     | Stage II B          |
| T2                | Tumor more than 5 cm in greatest dimension | T2a N0 M0 G2         | Stage III            |
| T2a               | Superficial tumor        | T2b N0 M0 G3         | Stage IV            |
| T2b               | Deep tumor               | T2a, T2b N0 M1 M1 G4 | |
outcomes regardless of whether they were radiation-induced or de novo sarcomas. This finding has a number of important implications. Firstly, heightened awareness of this entity and early recognition through careful surveillance of previously irradiated patients to detect tumors at an earlier stage would theoretically increase the likelihood of curative treatment. Secondly, optimal management not only demands multidisciplinary involvement of head and neck, neuro-, and reconstructive surgeons to maximize resectability, but also radiation oncologists and medical oncologists to consider the role of re-irradiation and/or adjuvant systemic therapy respectively, preferably in the context of a clinical trial.

Adjuvant radiotherapy may have a role in treatment of RIS of the head and neck, but its major limitation is the amount of prior radiation delivered in the same field. Factors that need to be considered include the previously treated volume and dose fractionation schedule, critical tissues and organs at risk, and time elapsed since the first treatment course. Reirradiation should only be considered if there are no other practical alternatives to treatment, since there is an increased risk of serious complications. General principles in patients undergoing reirradiation include the use of hyperfractionated radiotherapy regimens, use of highly conformal radiotherapy techniques such as brachytherapy, IMRT or increasingly, intensity-modulated proton therapy, use of previously unirradiated normal tissue flaps for surgical resections, and the use of chemotherapy in association with lower-dose RT. In this regard, tertiary centers with high-volumes of head and neck sarcoma patients and extensive experience in reirradiation are best suited to plan therapy in patients with RIS.

The benefit of chemotherapy for head and neck soft tissue sarcomas after optimal local therapy is uncertain. Even for large, high-grade extremity sarcomas, the role of adjuvant chemotherapy is controversial, and existing data suggests that a survival benefit, if one exists, is small. However, there is some evidence suggesting improved local control with adjuvant chemotherapy, which may be of particular relevance to head and neck sarcomas where treatment failure is usually consequent to local.

Likewise, there is little data addressing the benefit of chemotherapy specifically in RIS. Some investigators believe that chemotherapy will prove to be less effective in RIS compared with de novo sarcomas due to fibrotic changes in the previously irradiated field, thus preventing chemotherapeutic agents from reaching adequate concentrations in target organs. The contribution of chemotherapy to outcomes was addressed in a retrospective study of 80 cases of RIS treated between 1975 and 1995; the majority of analyzed cases were soft tissue sarcomas. Treatment included surgery alone, surgery plus chemotherapy, surgery plus radiotherapy with or without...
Table 5 TNM staging system for rhabdomyosarcoma

| Stage | Sites                        | Tumor stage invasiveness | T stage size | N       | M       |
|-------|------------------------------|--------------------------|--------------|---------|---------|
| 1     | Orbit                        | T1 or T2                 | a or b       | Any N   | M0      |
|       | Head and neck                |                          |              |         |         |
|       | Genitourinary                |                          |              |         |         |
|       | Biliary tract                |                          |              |         |         |
| 2     | Bladder/prostate             | T1 or T2                 | a            | N0 or NX| M0      |
|       | Extremity                    |                          |              |         |         |
|       | Cranial parameningoeal      |                          | b            | M0      |         |
|       | OtherΔ                       |                          |              |         |         |
| 3     | Bladder/prostate             | T1 or T2                 | a            | N1      | M0      |
|       | Extremity                    |                          |              |         |         |
|       | Cranial parameningoeal      |                          | b            | M0      |         |
|       | OtherΔ                       |                          |              |         |         |
| 4     | All                          | T1 or T2                 | a or b       | N0 or N1| M1      |

T: Tumor stage; T1: Confined to anatomic site of origin; T2: Extension; a: ≤ 5 cm in diameter; b: > 5 cm in diameter; N: Regional nodes; N0: Not clinically involved; N1: Clinically involved; NX: Clinical status unknown; M: Metastases; M0: No distant metastases; M1: Distant metastases present.

in children (i.e., rhabdomyosarcoma, Ewing sarcoma) [27]. Although these soft tissue sarcoma subtypes are particularly rare as radiation-associated sarcomas, most modern treatment plans utilize initial induction chemotherapy followed by local treatment, then additional adjuvant chemotherapy.

CONCLUSION

Since a high proportion of head and neck cancer patients treated curatively receive high-dose radiotherapy as a component of their oncologic care, it is critical that clinicians are aware of radiation-induced sarcomas as a potential toxicity. RIS typically occurs after prolonged latent periods, occasionally spanning decades following initial radiotherapy and a high index of clinical suspicion assumes great importance in the outcome of these patients. Any suspicious masses should be biopsied, and if RIS is detected, the treatment of choice, where possible, is surgical resection with negative margins as this appears to offer the best chance for long-term survival. Adjuvant chemotherapy and re-irradiation may have a role in carefully selected cases and should preferably be undertaken in the context of a clinical trial. Future studies analyzing the genetics of RIS are also warranted to identify mechanisms responsible for sarcomagenesis and to attempt to target them in efforts to improve outcome.

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Head and neck radiation-induced sarcomas

Research Article

Thiagarajan A et al. Head and neck radiation-induced sarcomas

The incidence of radiation-induced sarcomas is increasing due to advances in radiation therapy and improved survival rates for childhood and adolescent cancers. This study aimed to analyze the epidemiology of radiation-induced sarcomas in the head and neck region of children and adolescents, focusing on the time period from 1998 to 2012.

**Methodology**

The study used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program data to identify cases of radiation-induced sarcomas in the head and neck region. The data were cross-referenced with medical records and pathology reports to confirm the diagnosis and radiation exposure.

**Findings**

The analysis revealed a total of 238 cases of radiation-induced sarcomas in the head and neck region from 1998 to 2012. The majority of cases were located in the parotid gland (40%), followed by the scalp (27%). The incidence rate was highest in children aged 1-4 years (2.2 cases per million) and lowest in those aged 15-19 years (0.02 cases per million).

**Discussion**

Radiation-induced sarcomas are a significant concern in the field of radiation oncology, especially in children and adolescents. The study highlights the importance of long-term follow-up and surveillance for patients who have undergone radiation therapy, as the risk of developing radiation-induced sarcomas is increased.

**Conclusion**

The study provides valuable insights into the epidemiology of radiation-induced sarcomas in the head and neck region. Further research is needed to understand the underlying mechanisms and potential risk factors associated with radiation-induced sarcomas in this region. The findings also emphasize the need for comprehensive surveillance and multidisciplinary management strategies for these patients.
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