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TOPIC HIGHLIGHT

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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 nitricoxide 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.

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.

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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 of the late complications of radiotherapy (Table 1). 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].

Table 1 Summary of key findings

With improved oncologic outcomes, RIS are increasingly seen in long-term survivors of head and neck cancers
There is no subsite predilection; They can arise in any irradiated tissue of mesenchymal origin
Common histologic subtypes parallel their de novo counterparts
Imaging features of RIS are not pathognomonic but large size, extensive local invasion with bony destruction, and marked enhancement within a prior radiotherapy field 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
Management is challenging, entailing surgery in irradiated tissue and limited scope for further radiotherapy and chemotherapy
RIS is associated with significantly poorer outcomes than stage-matched de novo sarcomas
Surgical resection with clear margins appears to offer the best chance for cure

RIS: Radiation-induced sarcomas.

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[3,4]. 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 radiated. 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 nitricoxide synthase, and fibrosarcoma. Other histologies encountered include rhabdomyosarcoma (particularly in children), angiosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors[1,2,9]. 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-

ciated 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[21]. 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[22,23]. Whether chemotherapy also potentiates the tumorogenic 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[24,25]. 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[26-28]. 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[29-34]. 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[35].

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[36,37]. 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 cradiocaudal extent
Relatively inexpensive	Less image degradation caused by artifacts arising from dental amalgam
Provides assessment of tissue composition (vascularity, lipid content *etc.*)	Does not involve ionizing radiation
Ideal at demonstrating cortical bone erosion	Contrast material is less likely to produce allergic reaction
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 (vascularity, 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[38]. 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[1,2,9,10].

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)[39].

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

Table 3 TNM staging for soft tissue sarcoma

Primary tumor (T)				
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1	Tumor 5 cm or less in greatest dimension			
T1a	Superficial tumor			
T1b	Deep tumor			
T2	Tumor more than 5 cm in greatest dimension			
T2a	Superficial tumor			
T2b	Deep tumor			
Regional lymph nodes (N)				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	Regional lymph node metastasis			
Distant metastasis (M)				
M0	No distant metastasis			
M1	Distant metastasis			
Histologic grade (G)Δ				
GX	Grade cannot be assessed			
G1	Grade 1			
G2	Grade 2			
G3	Grade 3			
Anatomic stage/prognostic groups				
Stage Ⅰ A	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage Ⅰ B	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage Ⅱ A	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage Ⅱ B	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage Ⅲ	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage Ⅳ	Any T	Any N	M1	Any G

show MYC amplification, a finding not seen in primary angiosarcomas[40]. Studies using microarray analysis have implicated mitochondrial genes and genes involved in antioxidant pathways in radiation-induced tumors, suggesting that mitochondrial dysfunction or chronic oxidative stress could play key roles in their pathogenesis[39,41].

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[3]. 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[5]. 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[42]. The poorer outcomes could be due to: (1) difficulties and hence delayed diagnosis in previously radiated tissue; (2) compromised resection margins, due to proximity of the tumor to critical structures; (3) limited of treatment options in a maximally radiated 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[5,13,42-44].

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 4 TNM staging for bone tumors other than lymphoma and myeloma

Primary tumor (T)				
TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumor			
T1	Tumor 8 cm or less in greatest dimension			
T2	Tumor more than 8 cm in greatest dimension			
T3	Discontinuous tumors in the primary bone site			
Regional lymph nodes (N)				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	Regional lymph node metastasis			
Distant metastasis (M)				
M0	No distant metastasis			
M1	Distant metastasis			
M1a	Lung			
M1b	Other distant sites			
Histologic grade (G)				
Grade is reported in registry systems by the grade value. A two-grade, three-grade, or four-grade system may be used. If a grading system is not specified, generally the following system is used:				
GX	Grade cannot be assessed			
G1	Well differentiated-low grade			
G2	Moderately differentiated-low grade			
G3	Poorly differentiated-high grade			
G4	Undifferentiated-high grade			
Anatomic stage/prognostic groups				
Stage Ⅰ A	T1	N0	M0	G1, 2 Low grade, GX
Stage Ⅰ B	T2	N0	M0	G1, 2 Low grade, GX
	T3	N0	M0	G1, 2 Low grade, GX
Stage Ⅱ A	T1	N0	M0	G3, 4 High grade
Stage Ⅱ B	T2	N0	M0	G3, 4 High grade
Stage Ⅲ	T3	N0	M0	G3, 4 High grade
Stage ⅣA	Any T	N0	M1a	Any G
Stage ⅣB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

outcomes regardless of whether they were radiation-induced or de novo sarcomas[10]. 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[45]. In this regard, tertiary centers with high-volumes of head and neck sarcoma patients and extensive experience in re-irradiation are best suited to plan therapy in patients with RIS[46].

The benefit of chemotherapy for head and neck soft tissue sarcomas after optimal local therapy is uncertain[47]. 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[48], 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 Head and neck Genitourinary Biliary tract	T1 or T2	a or b	Any N	M0
2	Bladder/prostate Extremity Cranial parameningeal OtherΔ	T1 or T2	a	N0 or NX	M0
3	Bladder/prostate Extremity Cranial parameningeal OtherΔ	T1 or T2	a b	N1 Any N	M0
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.

chemotherapy, chemotherapy alone, radiotherapy alone, and best supportive care. Overall survival was shortest in patients undergoing chemotherapy alone (median: 6 mo), and longest in those who underwent surgery alone (median: 42 mo). It was intermediate in patients who underwent surgery plus chemotherapy (median 28 mo). Interpretation of this data is limited by the retrospective nature of this study with small sample sizes and inherent selection biases, the heterogeneity of systemic agents used, as well as suboptimal chemotherapy administration often limited by performance status[49].

While the majority of trials have evaluated the role of adjuvant chemotherapy in the management of soft tissue sarcomas, neoadjuvant chemotherapy has also been used in this setting and has several theoretical advantages: (1) tumor cytoreduction in bulky disease both to facilitate curative surgical resection and to permit smaller, less morbid surgery; (2) early treatment of micrometastases; and (3) avoidance of delay in commencement of systemic therapy due to postoperative complications. Potential disadvantages include impaired wound healing and delayed time to definitive local treatment particularly in the event that chemotherapy is ineffective. The discussion and decisions regarding neoadjuvant and adjuvant chemotherapy should be individualized and take into account factors such as patient age, comorbidities, performance status, histopathologic subtype of the sarcoma, as well as wishes of the patient. Needless to say, any systemic therapy should preferably be undertaken in the context of a clinical trial where tumor outcomes and toxicities are closely monitored.

On the other hand, there are certain clinical scenarios where the use of chemotherapy is less controversial. For instance, radiation-associated bone sarcomas are generally treated with chemotherapy in addition to surgery[50]. Systemic therapy is also a routine component of treatment for several soft tissue sarcomas that occur predominantly 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 significant 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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