Review Article

Wielding a double-edged sword in head and neck cancers—diagnosis, risk factors and mitigation strategies of radiation-induced head and neck sarcomas: a narrative review

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Objective: This review serves to present a summary of (I) the incidence, (II) diagnosis, (III) contributing risk factors, (IV) management options, (V) prognosis and lastly, (VI) mitigation strategies in managing patients with higher risks of radiation-induced head and neck sarcoma (RISHNN).

Background: Radiation induced sarcomas of the head and neck are perils that mark the victory of a successful initial treatment. Although a rare occurrence, with estimated risks of 0.1% to 0.3%, radiation induced sarcomas have a significantly worse prognosis than their *de-novo* counterparts. It remains unclear if the wide-spread use of intensity modulated radiotherapy (RT) techniques for head and neck cancer places patients at a higher risk of developing RISHNN. Diagnosis of RISHNN remains challenging. In addition patients with RISHNN often experience a delay in diagnosis because of the challenges in examining previously radiated tissue, lack of specific symptoms, long latency period and difficulties in obtaining histopathological confirmation. In view of the limited treatment options, it is paramount to institute mitigation strategies for patients deemed at higher risk of RISHNN.

Methods: Literature search was performed using the MEDLINE/PubMed database. MeSH headings was used to identify articles pertaining to RISHNN. The headings include "radiation – induced", "sarcomas", "head and neck sarcomas" and "radiation therapy". Articles published between years 1990 to 2021 were reviewed. Non-English language articles were excluded. Non radiation induced head and neck sarcomas were excluded.

Conclusions: Curative RT plays a cornerstone in the management of head and neck cancers—resulting in many patients overcoming the initial cancer—but living with the potential long-term risk of developing a radiation-induced secondary malignancy. Amongst this, RISHNN is a particularly challenging condition to manage. It is imperative for oncologists to counsel patients (who have higher probability of long-term survival) undergoing curative head and neck RT about this rare consequence. The preferred management for patients with localised RISHNN should be surgical resection, with or without reconstruction, with clear margins. However, we do acknowledge, given the location of the tumour, that this may be hard to achieve in some cases. In these cases, the patient may be better served with a palliative intent and maximising quality-of-life.

Keywords: Radiation induced; sarcoma; head and neck; cancer; treatment management

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Introduction

Radiotherapy (RT) is an essential arm in the contemporary multimodality management of head and neck cancers. The use of both definitive and adjuvant RT, in addition to improvements in surgery and systemic therapy, have led to an increase in survival of patients over time (1).

Delayed complications are the perils of our own success, which only occur in patients who have managed to overcome the first diagnosis. Hall, during his inaugural Frank-Ellis lecture said "*There can be few worse things for a patient than to survive the initial treatment, live with the long-term morbidity of treatment, only to find that they have developed a radiation-induced second cancer, which may have a worse prognosis than their original tumour*." (2).

Radiation-induced sarcoma (RIS) is a rare occurrence with estimated risks of 0.1% to 0.3% (3-5). Amongst all sarcomas, RIS accounts for only 3% to 6% of cases (6,7). It is undoubtedly challenging to differentiate RIS from *de novo* sarcoma. Cahan proposed a diagnostic criterion, which was later modified by Murray (8,9). These are as follows:

(I) Tumour arises in a field that has been previously irradiated.
(II) First tumour is histologically distinct from the subsequent one.
(III) No evidence of the new tumour at the time of the initial RT.
(IV) New tumour developed after a latency period from RT.

Radiation-induced head and neck sarcoma (RISHNN) represents merely 1% of all head and neck sarcomas. Although rare, RISHNN poses as a challenging entity to diagnose and manage. Patients have a poorer prognosis than *de novo* sarcomas, with the 5 year overall survival (OS) rate ranging between 24–38% (5,10-12). There is no specific area within the head and neck region which is predisposed to developing RISHNN. Studies from Asia seem to indicate that the para-nasal sinuses are most commonly affected (13,14). However, this may be related to the endemic nature of nasopharyngeal carcinoma within Asia. This condition is almost exclusively treated with chemo-RT, with the para-nasal sinuses being irradiated electively.

Patients with RISHNN often experience a delay in diagnosis because of the challenges in examining previously radiated tissue, lack of specific symptoms, long latency period and difficulties in obtaining histopathological confirmation. As the treatment options for RISHNN are limited, mitigation strategies should be considered upfront for patients considered to be at higher risk of RISHNN.

Therefore, this narrative review aims to present a summary of (I) the incidence, (II) diagnosis, (III) contributing risk factors, (IV) management options, (V) prognosis and lastly, (VI) mitigation strategies.

Methods

Literature search was performed using the MEDLINE/PubMed database. MeSH headings were used to identify articles pertaining to RISHNN. The headings include "radiation – induced", "sarcomas", "head and neck sarcomas" and "radiation therapy". Articles published between years 1990 to 2021 were reviewed. Non-English language articles were excluded. Non radiation induced head and neck sarcomas were excluded. *Figure 1* presents the PRISMA flow diagram summarizing the search strategy and the process of study selection. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/pcm-21-30).

Incidence

Multiple studies have reported the cumulative incidence of developing RIS to range between 0.03% to 0.3% (4,15,16). The length of follow-up is important to consider when interpreting this, as the median time to developing RIS is ~15 years (12). Yap *et al.* reported the cumulative incidence of sarcoma in breast cancer patients who received RT to be 0.32% at 15 years, compared to 0.23% in the patients who didn't receive RT (P=0.001) (17). Although the magnitude of the incremental risk is significant, the absolute risk is low.

As mentioned earlier, it does appear that the incidence of RIS is increasing over the years. This is exemplified by the cohort data from the Norway Cancer registry, spanning from years 1960–2007 (18). The mean incidence of secondary sarcoma (not exclusive to RIS) increased from 2.6% in 1960s to 14% from years 2000–2007. This incremental change trumps the increase of *de novo* sarcoma and cancers in general, with a larger average annual percent change seen in secondary sarcomas (6.2 *vs.* 2.5).

This increase could be attributed to several factors (19). Firstly, new surgical techniques, systemic therapies and other treatment options confer better survival outcomes for patients receiving RT (20). Secondly, the use of RT as part of cancer treatment regime has been steadily increasing.

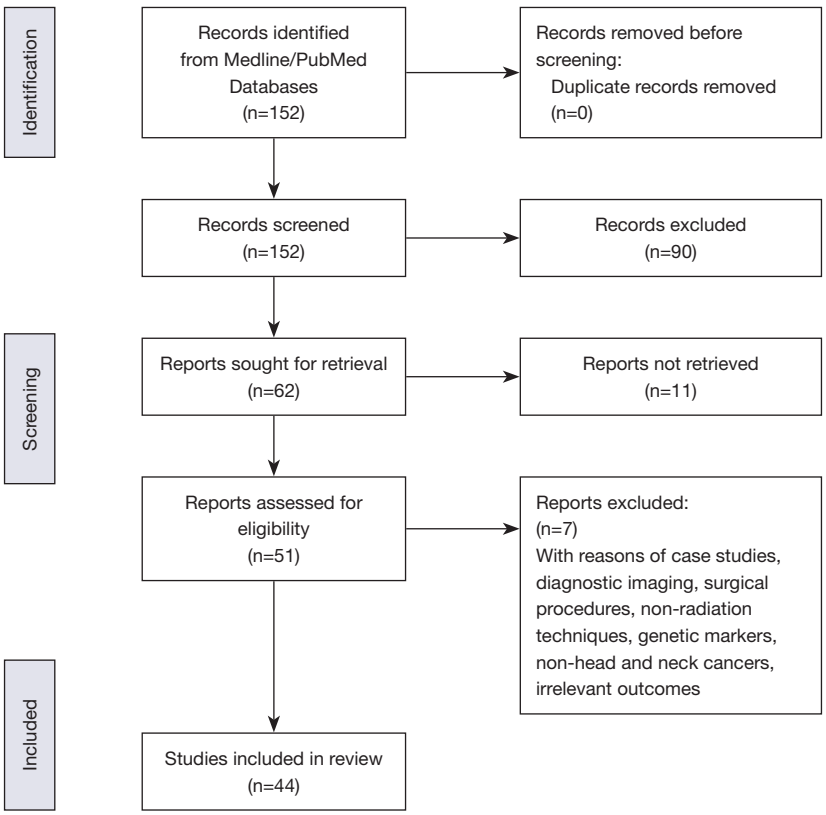

Figure 1 PRISMA flow diagram of studies reviewed.

Lastly, although modern RT techniques with intensity modulation allow for better normal tissue sparing, this is at the expense of larger volumes of normal tissues receiving low dose radiation. As even exposure to low dose radiation may result in genomic instability facilitating malignant change (21).

Within the context of RISHNN, Coca-Pelaz *et al.* performed a recent systematic review of the literature spanning from years 2000 to 2020 (22). The frequency of RISHNN was 0.15%, with the most common site of primary radiation being the nasopharynx. The mean latency between primary radiation and RISHNN was 11.1 years (range, 1.3–38 years). The most common site of RISHNN involves the sino-nasal region. The most common histological subtypes were osteosarcoma and fibrosarcoma.

Diagnosis

Imaging

Imaging plays an important role in the diagnosis and workup of RISHNN. Computed tomography (CT) and MRI play a complementary role, with MRI providing better soft tissue definition. They both provide multi-planar cross-sectional information on the locoregional tumour involvement, tissue composition and aid in planning biopsies for histopathological confirmation (10,23). In a study involving 63 patients, cross sectional imaging findings of bone sarcomas included soft tissue mass, cortical bone destruction, tumour mineralisation and periosteal reaction (24). In contrast, soft tissue sarcomas were commonly associated with findings of a destructive soft tissue mass in the absence of bone expansion and periosteal reaction.

Often, one is unable to distinguish RISHNN from *de novo* sarcomas based on imaging alone. However, MRI finding of normal marrow replacement with fat is suggestive of previous radiation (i.e., bright signal on T1-weighted imaging). This leans towards RISHNN (25).

In the workup for metastatic deposits, which typically involve the lung and/or liver, practice guidelines from

the National Comprehensive Cancer Network (NCCN) recommend a FDG-PET/CT scan (26,27).

Histopathological confirmation

Biopsy of the suspected primary lesion, or metastatic deposit, is crucial for diagnosis and treatment. Sole reliance on imaging is insufficient to ascertain between recurrence of the primary tumour, treatment-related changes or the development of a secondary malignancy. For both bone and soft tissue sarcomas, a core needle biopsy is minimally required (28). The placement and trajectory of the biopsy must be carefully planned, often in consultation with the sarcoma surgeon, in order not to compromise future surgical plans.

Histopathological findings

The histopathologic spectrum of RIS is broad and although all subtypes were observed in RIS, their frequency of occurrence varies from those of *de novo* sarcomas (29,30). In the review by Zhu *et al.* (n=323), the most common subtype was osteosarcoma (34.1%) followed by fibrosarcoma (19.2%) and unidentate pleomorphic sarcoma (15.8%) (31). Although the median size of RIS tumours are comparable to that of *de novo* sarcomas, RIS tend to have a higher proportion of high-grade tumors, with the presence of tumour necrosis (6,18,29,32). While there is still no pathogenomic features to discern between RIS and *de novo* sarcomas arising within previously irradiated fields, morphological changes of adjacent tissues may provide guidance if they demonstrate radiation-related changes such as atypical fibroblasts, dense cellular fibrosis, distortions in vascular structures (33).

Molecular signatures

Clearly, there are limitations in distinguishing RIS from *de novo* sarcoma based on clinical suspicion, imaging and histopathology alone. Therefore, the use of molecular and genetic signatures have been of interest in recent years (34).

Panse *et al.* found a complete loss of histone H3 lysine 27 trimethylation (H3K27me3) in 19% of patients with RIS in two tertiary care institutions (35). This was present in radiation-associated sarcomas of varying histological subtypes. In a study comparing MYC amplifications between RIS and *de novo* sarcomas, a significantly higher number of MYC amplifications were found in RIS than in *de novo* sarcomas (P<0.0001) (36). This has been found for leiomyosarcomas, undifferentiated pleomorphic sarcomas subtypes and is especially pronounced in angiosarcoma. However, Mito and colleagues cautioned that MYC expression is generally uncommon amongst RIS (save for angiosarcoma), and has a similar prevalence in *de novo* sarcomas. Therefore, it has limited diagnostic value in situations other than radiation-induced angiosarcomas (37). A study comparing the transcriptome of RI angiosarcoma with that of *de novo* angiosarcoma found 135 gene signatures, indicating mitochondrial dysfunction with chronic oxidative stress. This may aid in the diagnosis of RIS (38,39).

At present, molecular or genetic signatures influencing the diagnosis of RIS is still in its infancy. Although the presence of the above information may increase the probability of RIS (in addition to Cahan's criteria), there remains no gold standard within clinical practice (8,40).

Contributory risk factors

The four main factors that increase the risks of developing RISHNN cancers are: (I) age at first radiation exposure; (II) radiation-related factors; (III) previous cytotoxic chemotherapy; (IV) inherent genetic predisposition.

Age at first radiation exposure

The younger the age at first radiation exposure, the higher the risk for secondary sarcomas (41). Childhood Cancer Survivor Study found that the risk of secondary RIS was more than nine-fold higher amongst childhood cancer survivors compared to the general childhood population. Highest risk was observed in paediatric patients under four years old at the time of initial cancer diagnosis (41). Besides the long latent period, it is also likely that paediatric patients are more sensitive to radiation exposure. Possible explanations include a greater proportion of stem cells (exposed to radiation) in young patients predisposing them to be more prone to sarcoma-genesis. The development of childhood tumours could be related to underlying germline mutations, which predisposes them to RIS (41,42). An example would be retinoblastoma.

Radiation related factors

Dose

Carcinogenesis is a stochastic late effect of radiation

exposure, where there is no safety radiation threshold dose below which there is no risk of second malignancy (22,30). Two Japanese studies have reported RIS occurring at doses below 15 Gy with both describing increased risks of sarcogenesis with increasing radiation dose (43,44). The development of sarcoma exhibits a linear dose-response relationship, with soft tissue sarcoma having an excess relative risk of 1.01 per Gy (95% CI: 0.13 to 2.46 Gy; P=0.019) and osteosarcoma which having an excess relative risk of 7.5 per Gy (95% CI: 1.34 to 23.14 per Gy) after exceeding the dose threshold of 0.85 Gy (43,44). This correlation of increased sarcoma-genesis risks with increasing radiation dose is consistent with RIS studies on different body sites studied over the years (3,45-47). It is unclear if the linearity in the dose response can be extrapolated to higher doses. While there is no threshold dose at which RIS occurs, RIS is generally thought to occur at doses that catalyze sublethal damage at the cellular level that eventually results in sarcoma-genesis. Hence, it can be theorized that at extremely high radiation doses, where lethal damage predominates, the correlation between increased sarcoma-genesis risks with increasing radiation dose ceases. However, this theory has been contested by Berrington de Gonzalez *et al.* who demonstrated that there is little evidence that the dose-response curve plateaus at higher doses (such as >60 Gy) (40).

Despite the varying theories, the prevalence of RIS appearing in areas of intermediate dose areas within the primary radiation field supports the generally accepted theory that radiation dose delivered in the periphery areas surrounding the primary tumour is more important than the radiation dose delivered to the primary tumour (22,48). However, this is not concrete as there is scant published data.

Technique

It has been theorized that the use of newer RT techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), commonly used in head and neck cancer treatment in the modern era, has resulted in an increase in radiation induced secondary malignancies (30,49). They are an evolvement of three-dimensional conformal radiation therapy (3D CRT) and utilizes multiple modulating fields to create highly conformal doses specific to the tumour shape and volume. This has enabled curative doses delivered to the tumours while simultaneously reducing dose to healthy surrounding organs (50). While IMRT/VMAT is able to produce conformal RT plans for both high and intermediate dose regions (e.g., 80% and 50% respectively), the downside is a larger volume of low dose splash (e.g., 10–20%) (50,51).

Data to support or refute this comes mostly from modelling studies. There is no strong evidence from long term prospective cohort studies. For example, Serizawa and Hall, suggested a two-fold increase in secondary malignancies with the use of IMRT/VMAT, compared to 3DCRT. Similarly, Stathakis *et al.* showed a 40% increase in second malignancy risk when head and neck cancer patients were treated with IMRT compared to 3DCRT (52). In contrast, data from Gupta *et al.* did not show any increased risk of secondary malignancy with 3DCRT *vs.* IMRT. However, this trial only included 60 patients (i.e., likely underpowered for this outcome), with a median follow-up of 10 years (53).

Other factors to consider include beam energy (due to secondary neutron production) and monitor unit usage (resulting in radiation leakage through the machine) (54-57). It also remains unclear if the use of image-guided RT for head and neck cancers contributes to this risk. Performing daily IGRT (cone-beam CT scans) prior to each fraction, may allow a reduction in planning target volume margin. However, each cone-beam CT accounts for ~3–10 cGy to a large volume of tissue (58). Kim *et al.*, based on the linear no threshold model, estimated the lifetime attributable risk for secondary cancer to be ~4% if 30 CBCT scans were performed for pelvic tumours (59). This has to be interpreted cautiously as the risk depends on the chosen model. It is also unclear if it can be extrapolated to the head and neck region.

Previous cytotoxic chemotherapy

Particularly for childhood cancers, exposure to chemotherapy, in addition to RT, has been proven to increase the relative risk of RIS. Noticeably, the use of anthracyclines and alkylating agents have demonstrated strong associations with increased risks (41,42). Two cohort studies investigating the use of chemotherapy with RT for childhood cancers have found a 4 fold increase of RIS risk with cumulative drug exposure (41,42). However, it is still unclear whether these results can be extrapolated to adults.

Inherent genetic predisposition

Double strand breaks induced by primary radiation exposure can result in genomic instability which increases the potential of carcinogenesis and sarcoma-genesis (60). Certain rare familial genetic syndromes such as Li-Fraumei, Retinoblastoma, Neurofibromatosis 1, and Nijmnegen

breakage syndrome are associated with a higher risk of RIS. It is undeniable that the baseline risk of developing *de novo* malignancies is high in these individuals. Exposure to radiation may potentially increase the baseline risk of developing sarcoma. However, clinical data is scant as most of these patients would have been excluded from clinical trials. Also, the incidence of familial genetic syndromes is uncommon. In a large cohort study of retinoblastoma survivors, the use of RT increased the risk of secondary malignancies in both patients with hereditary and non-hereditary forms of retinoblastoma. Similarly, Hisada *et al.* (61) reported that RT contributed to the already elevated risk of second cancers in patients with familial Li Fraumeni syndrome.

Management options

RISHNN is a rare diagnosis, and as a result, there are no practice guidelines or randomized studies to follow. Moreover, RIS is a mixed bag of conditions involving varying histology subtypes, and affecting various anatomical sites (22,30,62). As such, management options are derived from *de novo* sarcomas, and from small institutional series of RIS patients. Surgical resection with wide negative margins is the preferred method for patients with non-metastatic RIS, and is the only chance of cure (30,62). In a multi-institutional retrospective study of 80 histologically confirmed sarcomas within previously irradiated fields, the OS rates at 2 years was 69% and 5 years was 39% for patients who had surgery as opposed to 10% and 0% at 2 years and 5 years respectively for those receiving chemotherapy alone (63). A recent systematic review including only patients with RISHNN found that approximately, only half of the patients with resectable tumors underwent surgery (22). In the context of head and neck region, we must acknowledge that this may not be possible due to complex neuro-vascular structures and adjacent vital organs, within the vicinity, which may compromise surgical resection. Moreover, previous radiation induced fibrotic changes in tissues with impaired circulation can lead to increased surgical complications, such as poor wound healing (64). This presents challenges in adhering to classical wide margin resections and limits the ability to be aggressive without unacceptable functional, physiological and aesthetic consequences (64,65).

The scope for definitive or adjuvant RT is limited as the RIS is located within previously irradiated tissue. As such, re-irradiation to a tumoricidal dose may lead to severe acute and late toxicities (such as osteoradionecrosis, soft tissue necrosis, radiation myelopathy and chronic non-healing ulcers) (62). Compromises in dose may mitigate these toxicities. However, this results in inadequate tumour control as sarcomas are inherently radio-resistant. The few studies reporting the use of re-irradiation, in conjunction with surgery, have predominantly been investigated in sites such as the thorax and extremities. Riad *et al.* reported improved local recurrence free interval with adjuvant RT (predominantly in extremities) of 7.7% *vs.* 34.5% (P=0.043) (66). About half of these patients, developed acute and/or late toxicity with re-RT. As such, re-RT must be used judiciously after having considered its risks and benefits. Factors to consider include previous irradiated volume, previous dose and fractionation regimen, dose received by critical organs and time elapsed since prior irradiation (30). Mitigation strategies for re-RT include using hyper fractionated RT regimes with smaller dose per fraction, highly conformal RT techniques such as intensity modulated proton therapy (IMPT), brachytherapy, using well-vascularised unirradiated tissue flaps during surgical resection and the use of concurrent chemotherapy allowing for a lower dose RT (67-71). These are elaborated further in the section below.

Despite aggressive resection, majority of the patients develop both local and distant relapses. Neuhaus *et al.* reported the outcome of 34 patients with RI soft tissue sarcoma who underwent curative resection. None of these patients received adjuvant RT, and 20% received neoadjuvant/adjuvant chemotherapy. In this cohort, the median survival was 54 months, with two-thirds of patients having local recurrence and 44% having distant relapse (20). In general, the use of chemotherapy, neo-adjuvant or adjuvant improves disease control. However, chemotherapy may not completely improve local control, as radiation induced fibrosis may impede chemotherapeutic agents from accumulating to adequate concentrations in the affected area (63). Unfortunately, the incremental survival benefit derived from chemotherapy is limited. It remains unclear if chemotherapy efficacy data can be extrapolated from *de novo* sarcomas. Experience from Italy, where 20 patients of radiation-induced osteosarcoma (involving the extremity) were treated with peri-operative multi-drug chemotherapy regimen (consisting of cisplatin, doxorubicin, methotrexate and ifosfamide) (72). Compared to patients with *de novo* osteosarcoma, the 5-year OS was inferior in the radiation induced osteosarcoma group (40 *vs.* 67%, P<0.01). In another series, 14 patients with RISHNN (of the

calvarium or skull base) underwent resection and adjuvant chemotherapy (73). Five patients had R0 resection, four had R1 resection and the remaining had subtotal resection (R2). Only one patient remained disease-free after ~4 years of follow-up.

Prognosis

The prognosis of RISHNN is generally worse than patients with *de novo* sarcomas. These reasons include delays in diagnosis, inherently aggressive tumour behaviour, higher rates of local recurrence owing to challenges with complete surgical resection within previously irradiated fields, inability to deliver full-dose re-RT and limitations in chemotherapy choices due to prior radiation exposure.

For RIS in general, Gladdy *et al.* reported patients having a higher risk of death (HR 1.7; range, 1.1–2.4) compared to a matched cohort with *de novo* sarcoma (74). Similarly, data from the Norwegian Cancer registry reported significantly inferior survival of patients with RIS compared to *de novo* sarcoma (5 year survival 32 *vs.* 51%) (18). The French Sarcoma Group reported slightly more encouraging outcomes for RIS patients who managed to achieve R0 resection, with a 5-year survival rate of ~50% (75).

Looking only at patients with RISHNN, Coca-Pelaz performed a systematic review and reported the median survival to be ~13 months (22). Data from National Cancer Centre Singapore, compared the outcomes of patients with RISHNN (n=28) to *de novo* head and neck sarcoma (n=60) (12). In general, the survival of patients of RISHNN was worse. However, if patients were able to be treated with a curative intent, there was no significant survival difference between the two groups. As such, despite the poor prognosis, localised RIS should still be managed aggressively as they are still potentially curable with well-planned R0 surgery.

Mitigation strategies

As RISHNN is known to be an aggressive condition with a dismal prognosis, the premise of mitigation would be prevention through optimal patient and treatment selection.

Patient selection

Patient factors such as age at time of radiation exposure, volume of treatment and expected survival after radiation should be considered during decision-making. Young patients can be considered for curative treatment, avoiding RT where possible. Although there is no universally agreed age group of young patients, one can consider the remaining life-expectancy of the patient taking into account their underlying malignancy and co-morbidities. For early-stage tumors, organ preservation can still be achieved with limited surgery followed by close surveillance. An example of this would be a patient with Stage 1 glottic cancer undergoing trans-oral laser surgery. For advanced tumors, this may be achieved through more radical surgery with clear resection margins. Neoadjuvant chemotherapy can be considered for tumour down-staging prior to surgical resection.

Selection of radiation therapy techniques

This can be achieved through minimizing exposure of normal tissues and organs to radiation. This strategy is two-pronged. In terms of treatment volumes, elective nodal irradiation should be avoided if the risk of isolated nodal relapse is low (e.g., below 10–15% risk), especially in young patients. Secondly, compared to conventional photon therapy, modalities such as charged particle therapy (e.g., proton/ion beam) or brachytherapy are able to reduce unintended radiation exposure of normal tissue. The finite range of charged particle therapy, exhibited by the Bragg Peak effect, confers an advantage in avoiding radiation exposure distal to the target. However, the proximal areas are still invariably radiated, and therefore it is critical to note that the use of proton therapy does not eliminate the risk of RIS. In support of this, data from Xiang *et al.*, using the National Cancer Database, does report a risk reduction of secondary malignancy with the use of proton beam therapy compared to IMRT (adjusted OR 0.31; 95% CI: 0.26–0.36, P<0.0001) (76). However, it is important to note that only 1.3% of this cohort were treated with proton beam therapy. This information has to be balanced with the fact that (I) the overall risk of secondary malignancies are generally low (~1.5 per 100 patient-years), (II) proton therapy is significantly more costly and (III) world-wide access and utility to proton therapy is currently limited.

Brachytherapy (as a monotherapy) has a limited role in head and neck cancers, being limited to early-stage oral cavity cancers (e.g., lip, mobile tongue) (77,78). As such, there is limited data to suggest if this can be used as a mitigating strategy. Extrapolating from uterine cancer where brachytherapy is commonly used, external beam therapy

has a 44% (95% CI: 19–75%) higher risk of secondary malignancies compared to brachytherapy alone (79). However, in the context of RISHNN, this should only be considered as hypothesis-generating data.

Conclusions

Curative RT is a cornerstone in the management of head and neck cancers—resulting in many patients overcoming the initial cancer—but living with potential long-term risk of developing radiation-induced secondary malignancies. Amongst this, RISHNN is a particularly challenging condition to manage. Although there are no pathognomonic features of RISHNN, compared to *de novo* head and neck sarcomas, exposure to previous therapeutic radiation gives rise to this clinical diagnosis. It is imperative for oncologists to counsel patients (who have high probability of long-term survival) undergoing curative head and neck RT about this rare consequence. To date, there are no specific genetic studies suggestive of a causative mechanism. The preferred management for patients with localised RISHNN should be surgical resection, with or without reconstruction, with clear margins. However, we are cognizant that given the anatomical complexities with head and neck cancers, resection with clear margins may be challenging to achieve. In this case, the patient may be better served with a palliative treatment regime that maximizes quality of life.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://dx.doi.org/10.21037/pcm-21-30

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