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Cervical osteoradionecrosis following accelerated fractionation radiation therapy for laryngeal cancer

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Introduction

Osteoradionecrosis is a serious complication that may occur following radiation therapy, particularly head and neck-directed radiation therapy. A very limited number of cases of cervical-spine osteoradionecrosis have been reported^{1–6} and only 2 involve altered fractionation radiation therapy.⁶ We present a patient with extensive osteoradionecrosis 9 years after receiving accelerated fractionation radiation therapy with concurrent chemotherapy.

Case report

A 51-year-old male presented with several months of odynophagia and dysphonia in 2005. Triple endoscopy revealed T4bN0M0 squamous cell carcinoma of the supraglottic larynx involving the left base of the tongue. The patient was enrolled on Radiation Therapy Oncology Group (RTOG) 0129 and treated with a course of accelerated fractionation radiation therapy with concurrent cisplatin chemotherapy.⁷ Per protocol, the patient received 18 fractions of 1.8 Gy daily followed by 12 days of twice-daily radiation therapy consisting of 1.8 Gy in the morning and a second daily fraction of 1.5 Gy for a total of 72 Gy delivered over the course of 6 weeks (Fig 1).

The patient had no evidence of recurrent disease until he developed neck pain; a computed tomography scan in October 2014 showed possible local recurrence versus abscess formation for which he was treated with antibiotics. A follow-up computed tomography and magnetic resonance imaging scan revealed a persistent large pocket of air in the right lateral retropharyngeal space and anterior wedge-shaped compression fracture deformities consistent with osteoradionecrosis (Fig 2).

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Conflicts of interest: None.

Discussion

The majority of reports of cervical osteoradionecrosis involve standard fractionation of 1.8 Gy once a day (Table 1). Despite the development of osteoradionecrosis, all of these patients recovered following surgical and/or antibiotic treatment with the exception of 1 patient treated with 2.2 Gy/fx who remained wheelchair-bound and a second³ who died before treatment.

There has been resurgent interest in the role of altered fractionation radiation therapy and concurrent chemotherapy for improved local control and decreased tumor repopulation in head and neck cancers. Radiation treatment de-escalation is currently being explored for human papilloma positive head and neck cancer through RTOG 1016,⁸ in which altered fractionation radiation therapy with concurrent cetuximab is the experimental arm. Major differences, however, between RTOG 1016 and RTOG 0129 include 6 once-weekly twice-daily treatments versus 12 sequential twice-daily treatments decreasing the likelihood of late effects as a result of incomplete repair on this more recent RTOG protocol. Although the incidence of mandibular osteonecrosis has been reported to increase with accelerated fractionation,⁹ incidences of cervical osteonecrosis after accelerated fractionation radiation therapy have only been reported once.⁶ Kosako et al⁶ describes 3 cases of cervical osteonecrosis (Table 2), 2 of whom were treated with accelerated fractionation and received antibiotic treatment for osteonecrosis but died from respiratory failure. Studies investigating accelerated versus standard fractionation radiation therapy for head and neck cancer have reported no difference in osteonecrosis rates^{10–13}; however, follow-up was only 5 years except for the MRC CHART Trial, which did not use concurrent chemotherapy. Although the time to development of mandibular osteoradionecrosis appears to be around 27 months (range, 3–129 months),¹⁴ the time to development of cervical osteoradionecrosis is not well recognized in the literature. From the cases reviewed,^{1–6} the median time to cervical osteoradionecrosis was approximately 34 months after radiation; though the range appears to be a quite wide (0–300 months), suggesting that the risk for cervical osteoradionecrosis may potentially persist longer. Our patient, having developed osteoradionecrosis at 9 years, is in line with the previously published reports.

It has been well documented¹⁵ that late complications from radiation therapy can be associated with slow recovery between fractions. This implies that, with 2 fractions per day and intervals of 6 hours, as used here, may be inadequate to allow complete recovery. The result of this is that the biologically effective dose for the whole schedule may be considerably larger than planned, thus increasing the possibility of late side effects. Further, this could be exacerbated by an extended schedule of 2 doses per day. The extended incomplete repair formulation described by Guttenberger et al¹⁶ was used to estimate the equivalent dose in 1.8 Gy fractions (EQD1.8) for the schedule as delivered with and without this incomplete repair assumption, using example parameters of $\alpha/\beta=0.85$ Gy for osteonecrosis¹⁷ and likely repair half-time ($T_{1/2}$) = 4 hours.¹⁵ Without incomplete repair, EQD1.8 = 70 Gy. Accounting for incomplete repair because of a 6-hour interfraction interval and repair $T_{1/2}$ of 4 hours, EQD1.8 = an estimated 80 Gy. Had standard fractionation been used, approximately 24 hours between fractions, or 6 repair $T_{1/2}$ periods would have occurred, thus there exists the possibility that using this hyperfractionated

course, biologically effective doses to the affected areas could have been as high as 10%–15% greater than planned, which could explain the osteoradionecrosis seen in this case. This supports the view that 2 fractions per day in head and neck cancer should be given with caution, always maximizing the interfraction interval.

Conclusion

This patient had no signs of osteoradionecrosis until 9 years after radiation therapy. It is conceivable that radiobiologic differences attributable to accelerated fractionation radiation therapy concurrent with chemotherapy contributed to his development of osteoradionecrosis. There has been increased interest in the role of altered fractionation radiation therapy with RTOG 1016 currently exploring radiation treatment de-escalation. If this trial demonstrates a survival benefit and accelerated fractionation with chemotherapy becomes standard of care, then knowledge of the late side effects of such therapy, including osteoradionecrosis, becomes crucial.

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Figure 1. Radiation treatment plan. A portion of the radiation treatment plan is shown. The 100% isodose line can be seen covering the anterior vertebral bodies.

Figure 2.
Computed tomography scan of cervical spine reveals anterior wedge-shaped compression fracture deformities consistent with osteoradionecrosis in the C5 and C6 vertebral bodies.

Table 1

Published osteoradionecrosis case studies

Author	Cancer histology/primary	Radiation dose (Gy/fx)	Chemotherapy	ORN treatment	Time to ORN
Donovan et al ¹	SCC/unknown	80/-	-	Surgery, antibiotics, and O ₂	25 y
	SCC/supraglottic larynx	59.4/1.8	-	Surgery, antibiotics, and O ₂	10 mo
	Undifferentiated/nasopharyngeal	82.2 (43.2)	-	Antibiotics and O ₂	10 y
Ng et al ²	SCC/posterior pharyngeal wall	45/1.8	-	Surgery and antibiotics	During RT (45 Gy in 25 treatments)
Lim et al ³	SCC/unknown	55.8/1.8	-	-	9 y
Van Wyk et al ⁴	SCC/right vocal cord	66/2.2	-	Surgery	20 y
Smith et al ⁵	SCC/tonsils	70/-	Concurrent/ Cisplatin-based	Surgery and antibiotics	15 mo

O₂, oxygen; ORN, osteoradionecrosis; SCC, squamous cell carcinoma.

Table 2

Case studies by Kosako et al⁶

Author	Cancer histology/primary	Radiation dose (Gyfx)	Chemotherapy	ORN treatment	Time to ORN
Kosako et al ⁶	SCC/hypopharynx	76.8/1.2 BID	Neoadjuvant and concurrent/cisplatin and 5FU	Surgery and antibiotics	2.5 y
	SCC/oropharynx	76.8/1.6 BID	Neoadjuvant and concurrent/cisplatin, carboplatin, and 5-FU	Antibiotics	2.3 y
	SCC/esophagus and hypopharynx	50/2 + additional 40	Concurrent/cisplatin and 5-FU	-	3.1 y

5-FU, 5-fluorouracil; ORN, osteoradionecrosis; SCC, squamous cell carcinoma.