BC CANCER

Provincial Health Services Authority

Osteoradionecrosis of the Jaw: Past, Present, Clinical and Economic Impact in Oncology

ISOO Session 01: Bone Necrosis

Jonn Wu
Radiation Oncologist, Vancouver Canada
Chair, Provincial H&N Tumour Group
June 30, 2018

Presenter Disclosure

Disclosure: Jonn Wu

Relationships with Commercial Interests: Nil, related to the topic.

Outline

Introduction – What is Osteoradionecrosis (ORN)

Clinical Impact – Economic Impact, Quality of Life (QOL)

Past, Present - Risk Factors and Radiation Dose

What is Osteoradionecrosis (ORN)

- Exposed, irradiated bone in the absence of recurrent or residual tumor.
- Marx, 1983:
  - All cases exposed to high doses of radiation
  - 9/26 cases no history of trauma
  - Microorganisms: inconsistent, surface contaminants
  - Histologic review
- Proposed Pathophysiology
  - Radiation
  - 3 H's → Hypoxic Hypovascular & Hypocelluar tissue
  - Tissue breakdown
  - Chronic non-healing wound

Osteoradionecrosis: a new concept of its pathophysiology
RE Marx Journal of Oral and Maxillofacial Surgery and 1983 | Elsevier , 1983 vol. 41 (5) pp. 283-288

Outline

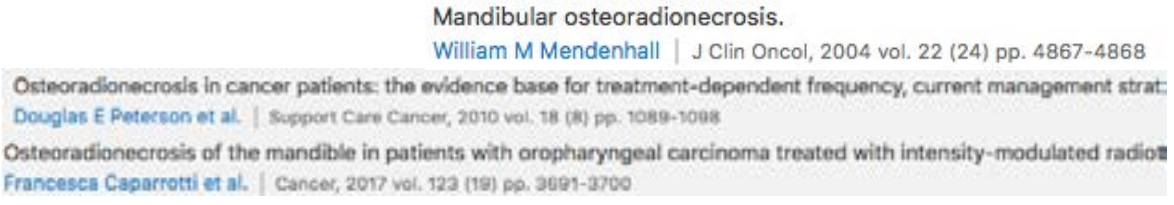
Introduction – What is Osteoradionecrosis (ORN)

Clinical Impact – Economic Impact, Quality of Life (QOL)

Past, Present - Risk Factors and Radiation Dose

Clinical Impact

- Incidence: 3-7%
- Symptoms, Signs:
  - Pain, halitosis, dysgeusia, paresthesias, trismus, difficulty chewing, swallowing, dysarthria
- Severity:
  - Asymptomatic exposure to progressive fistula, fracture, infection
- Management:



Clinical Impact – Quality of Life (QOL), Economic

Osteoradionecrosis in cancer patients: the evidence base for treatment-dependent frequency, current management strategies, and future studies

Douglas E. Peterson · Wolfgang Doerr · Allan Hovan · Andres Pinto · Debbie Saunders · Linda S. Elting · Fred K. L. Spijkervet · Michael T. Brennan

Abstract
Purpose The purpose of this study is to review the evidence base from 1990 to 2008 to (1) clarify the impact of cancer therapies on prevalence of osteoradionecrosis (ORN) in head and neck cancer patients, and to (2) evaluate management strategies and their consequences on quality of life and cost of care.

~~There were no studies evaluating the economic impact of ORN.~~

There were no studies evaluating the quality of life impact of ORN.

Since 2008, QOL:

- Most were severe ORN, post surgical, equivocal results
- 3 articles: ORN vs non-ORN in radiotherapy patients
- Limitations: Small cohorts, retrospective, non-standard grading systems

Osteoradionecrosis in cancer patients: the evidence base for treatment-dependent frequency, current management strat
Douglas E Peterson et al. | Support Care Cancer, 2010 vol. 18 (8) pp. 1089-1098

Clinical Impact – QOL – Jacobson, 2013

- 42 patients, retrospective chart review, Beth Israel Hospital, New York
- Severe ORN, all had segmental mandibulectomy + free flap
  - 30: telephone interview (Performance Status Scale)
  - 18: QOL questionnaires (Speech Handicap Index, EORTC H&N35, Eating Assessment Tool)
  - Mean 23.4 months post-surgery
- Pair wise match versus non-ORN HNC patients

Quality of life after management of advanced osteoradionecrosis of the mandible.
A S Jacobson et al. | International Journal of Oral & Maxillofacial Surgery, 2013 vol. 42 (9) pp. 1121-1128

Clinical Impact – QOL – Jacobson, 2013

- Pair wise match versus non-ORN HNC patients
  - Matching: No specifics, RT or Surgery?
  - Very small numbers – further subdivided by years

Table 4. Mann–Whitney test comparing PSS measures between ORN patients and other age matched head and neck cancer patients.

PSS	ORN	*n*	Mean	SD	*p* value
Follow up < 1 year					
Normalcy of diet	Yes	9	59	40	0.297
	No	9	78	24	
Eating in public	Yes	9	64	44	0.605
	No	9	81	24	
Understandability of speech	Yes	9	97	8	0.730
	No	9	100	0	
Follow up 1–3 years					
Normalcy of diet	Yes	11	46	40	0.016
	No	11	89	19	
Eating in public	Yes	11	55	38	0.005
	No	11	98	8	
Understandability of speech	Yes	11	91	13	0.300
	No	11	98	8	
Follow up >3 years					
Normalcy of diet	Yes	11	49	37	0.116
	No	11	73	22	
Eating in public	Yes	11	55	42	0.088
	No	11	84	27	
Understandability of speech	Yes	11	90	18	0.705
	No	11	91	23	

30 patients

Telephone interview + Performance Status Scale (higher better)

Table 5. Mann–Whitney test comparing QOL measures between ORN patients and other age matched head and neck cancer patients.

PSS	ORN	*n*	Mean	SD	*p* value
Follow up < 1 year					
EAT	Yes	7	24.43	9.36	0.002
	No	9	7.56	7.01	
SHI	Yes	7	30.00	15.75	0.142
	No	9	20.89	28.93	
Follow up 1–3 years					
EAT	Yes	7	24.00	13.04	0.004
	No	8	5.13	7.49	
SHI	Yes	7	38.86	25.61	0.072
	No	8	15.62	15.83	
Follow up > 3 years					
EAT	Yes	4	15.00	18.24	0.686
	No	4	7.00	10.80	
SHI	Yes	3	38.67	56.89	1.000
	No	3	7.33	6.81	

18 patients

Eating Assessment Tool

Speech Handicap Index

(lower better)

Quality of life after management of advanced osteoradionecrosis of the mandible.
A S Jacobson et al. | International Journal of Oral & Maxillofacial Surgery, 2013 vol. 42 (9) pp. 1121-1128

Clinical Impact – QOL – Rogers, 2015

- 71 patients, 1993 to 2011, University Hospital Aintree (UK), UWQoL-4
- 4 Groups: Grade (Notani) versus Treatment

	Grade I/II	Grade III
No Surgery	34	9
Surgery	10	18

- Treatments:
  - No Surgery: HBO, medical (tocopherol and pentoxyphylline)
  - Surgery: Segmental mandibulectomy + Free Flap

- Each Group compared to non-ORN patients
  - Primary radiotherapy
  - No radiotherapy

Longitudinal evaluation of health-related quality of life after osteoradionecrosis of the mandible.
Simon N Rogers et al. | British Journal of Oral & Maxillofacial Surgery, 2015 vol. 53 (9) pp. 854-857

Clinical Impact – QOL – Rogers, 2015

- Patients with ORN reported more severe problems with:
  - Pain, appearance, activity, recreation, swallowing, and chewing.
  - Statistical significance only compared to non-radiotherapy patients
- Worst scores with grade III ORN and after mandibular resection and reconstruction

Table 3. University of Washington quality of life (UWQoL) data closest to 5 years after diagnosis[a] of osteoradionecrosis (ORN) by clinical group. Data are number (%) unless otherwise stated.

	Notani grade I / II		Notani grade III		Total
	(A) No free flap (n = 14)	(B) With free flap (n = 5)	(C) No free flap (n = 3)	(D) With free flap (n = 8)	(n = 30)
Median (range) months from ORN to UWQoL	55 (37-90)	59 (70-112)	51 (46-153)	62 (46-129)	60 (37-153), IQR 50-70
Median (range) months from primary diagnosis to UWQoL	75 (54-171)	95 (81-229)	121 (58-158)	86 (63-150)	86 (54-229), IQR 66-126
Serious problem on UWQoL algorithm[b,c]:					
Pain	3	3	0	3	9 (30)
Appearance	4	1	1	1	7 (23)
Activity	2	1	0	2	5 (17)
Recreation	2	0	1	1	4 (13)
Swallowing	3	1	0	3	7 (23)
Chewing	3/13	2	0	2	7/29 (24)
Speech	1	1	0	1	3 (10)
Shoulder	3/13	0	0	1	4/29 (14)
Taste	0/13	0	0	0/7	0/28
Saliva	1/13	1	0	3	5/29 (17)
Mood	3	0	1	1	5 (17)
Anxiety	0	0	1	1	2 (7)
Median(range) physical subscale score	67 (30-86)	69 (31-88)	88 (63-91)	53 (27-100)	65 (27-100), IQR (49-82)
Physical subscale score <50	3	1	0	3	7 (23)
Median (range) social-emotional subscale score	67 (45-100)	75 (57-100)	80 (70-100)	78 (27-100)	75 (27-100), IQR (64-80)
Social-emotional subscale score <50	1	0	0	1	2 (7)
Overall QoL less than good (very poor/poor/fair)	7	1	1	4	13 (43)
Overall QoL good	2	2	1	2	7 (23)
Overall QoL very good/outstanding	5	2	1	2	10 (33)

[a]After 36 months of diagnosis of ORN, if a patient did several questionnaires then the one closest to 60 months was used.

[b]Serious problem trigger criteria: [c] pain, appearance, activity, recreation, mood: (scores of 0, 25, or 50 & important); swallowing, speech, anxiety (scores of 0 or 50); shoulder, taste, saliva: (scores of 0 or 50 & important); chewing: (score of 0)

Table 4. Comparison of patients with osteoradionecrosis (ORN) with other patients at the unit: University of Washington quality of life (UWQoL). Data are number (%) unless otherwise stated.

	Total No. of patients with ORN[a] (n = 71)	Total No. of patients without ORN who had radiotherapy in primary treatment (n = 961)	p-value	Specific subgroups of patients without ORN who had radiotherapy (RT) in primary treatment[b]			Total No. of patients who did not have ORN or radiotherapy[c,d] (n = 857)	p-value patients with ORN compared with those who did not have ORN or radiotherapy	Reference data from routine attenders at GDP practices (n = 349)[e]
				Oral (clinical stage 0-1) (n = 124)	Oral (clinical stage 3-4) (n = 339)	Pharyngeal (n = 265)			
No. with UWQoL data	30	301	-	89	107	103	356	-	349[e]
Percentage response adjusting for 36-month survival	60	54	-	63	59	56	61	-	-
Median (IQR) months from ORN to UWQoL	60 (50-70)	-	-	-	-	-	-	-	-
Median (IQR) months from primary diagnosis to UWQoL	86 (66-126)	62 (47-82)	-	59 (44-86)	66 (50-95)	58 (46-86)	69 (53-86)	-	-
Serious problem on UWQoL algorithm[b,c]:									
Pain	9 (30)	45/294 (15)	0.07	2/34 (6)	14/82 (17)	21/101 (21)	55/347 (16)	0.03	13%
Appearance	7 (23)	36/293 (12)	0.16	5/37 (14)	20/81 (25)	6/102 (6)	36/346 (9)	0.02	4%
Activity	5 (17)	37/294 (13)	0.57	1/35 (3)	9/82 (11)	11/102 (11)	48/345 (12)	0.57	8%
Recreation	4 (13)	36/295 (12)	0.77	1/34 (3)	11/83 (13)	13/102 (13)	31/341 (8)	0.30	5%
Swallowing	7 (23)	65/301 (21)	0.82	3/39 (8)	26/85 (31)	17/103 (16)	24/352 (6)	0.004	1%
Chewing	7/29 (24)	47/293 (16)	0.30	6/37 (16)	23/81 (28)	13/101 (13)	21/341 (5)	0.002	1%
Speech	3 (10)	35/293 (12)	0.99	3/38 (8)	11/83 (13)	13/99 (13)	28/344 (7)	0.48	2%
Shoulder	4/29 (14)	36/293 (12)	0.78	5/35 (14)	7/79 (9)	14/103 (14)	34/343 (9)	0.33	4%
Taste	0/28	46/286 (15)	0.02	3/35 (9)	17/75 (23)	18/101 (19)	24/341 (6)	0.39	0%
Saliva	5/29 (17)	47/294 (15)	0.39	9/34 (26)	16/75 (21)	14/102 (13)	45/373 (12)	0.39	1%
Mood	5 (17)	50/288 (17)	0.99	6/34 (17)	13/75 (17)	18/102 (18)	48/340 (13)	0.17	9%
Anxiety	2 (7)	45/299 (15)	0.28	6/39 (15)	14/83 (17)	16/101 (16)	47/353 (12)	0.16	10%
Median (IQR) physical subscale score	65 (49-82)	88 (53-93)	0.39	69 (56-83)	83 (44-75)	63 (51-78)	82 (68-96)	<0.001	100 (95-100)
Physical subscale score <50	7 (23)	81/299 (20)	0.64	5/38 (10)	26/83 (31)	24/103 (23)	27/341 (7)	0.006	1%
Median (IQR) social-emotional subscale score	75 (66-83)	78 (63-91)	0.17	74 (62-91)	75 (58-90)	78 (63-91)	82 (67-92)	0.08	91 (79-100)
Social-emotional subscale score <50	2 (7)	46/298 (16)	0.28	4/37 (11)	16/83 (19)	16/103 (16)	26/341 (7)	0.99	5%
Overall QoL less than good (very poor/poor/fair)	13 (43)	101/287 (35)		11/34 (31)	32/75 (43)	35/101 (35)	101/344 (29)		13%
Overall QoL good	7 (23)	78/287 (27)	0.68	8/34 (22)	23/75 (31)	26/101 (26)	122/344 (33)	0.19	34%
Overall QoL very good/outstanding	10 (33)	108/287 (38)		17/34 (47)	20/75 (27)	40/101 (40)	141/344 (39)		53%

[a]After 36 months of diagnosis of ORN, if a patient had several questionnaires then the one closest to 60 months was used.

[b]After 36 months of primary diagnosis, if a patient had several questionnaires then the one closest to 84 months was used.

[c]Serious problem trigger criteria: [d] pain, appearance, activity, recreation, mood: (scores of 0 or 25 or 50 & important); swallowing, speech, anxiety: (scores of 0 or 50); shoulder, taste, saliva: (scores or 0 or 50 & important); chewing: (score of 0)

[e]78 of these 83 had free flaps; [f] [g] values: Fisher's exact test apart from chi square test for overall QoL and Mann-Whitney test for subscale scores.

Longitudinal evaluation of health-related quality of life after osteoradionecrosis of the mandible.
Simon N Rogers et al. | British Journal of Oral & Maxillofacial Surgery, 2015 vol. 53 (9) pp. 854-857

Clinical Impact – QOL – Mucke, 2015

- University of Munchen, Germany
- 3 groups of patients:
- UWQoL-4
  - 24 months after treatment
  - Surgery + RT groups
    - 24 months after RT
    - Two copies, one for surgery, one for RT
- Surgery vs Surgery + RT
  - Reduced QOL after radiation therapy, much worse than surgery
- **No significant difference between Sx/RT vs Sx/RT/ORN**
  - Small numbers
  - Recall bias – questionnaires after RT
  - Patients might be focused on Sx vs RT rather ORN
  - Surgery as a confounder (primary composite resection and free flap reconstruction)
- **Ideal cohort = RT vs RT (ORN)**

Treatment	Patients
Surgery	32
Surgery + RT	32
Surgery + RT and ORN	32

Quality of life after different oncologic interventions in head and neck cancer patients.
Thomas Mücke et al. | J Craniomaxillofac Surg, 2015 vol. 43 (9) pp. 1895-1898

Clinical Impact – QOL - Summary

- Since 2008, very few reports, and limited by:
  - Small cohorts
  - Retrospective or prospective with potential biases or confounding factors
    - Treatment regimen
    - ORN management (+/- surgery)
    - Non standard ORN grading
    - Multiple QOL tools
    - Severe cases of ORN

Author	# Patients	Subgroups	Surgery?	Statistical Difference?
Jacobson	30 (phone)	18 (survey)	Yes	Mixed
Rogers	71	9-34 (by year)	Stratified	Mixed
Mucke	96	3 x 32	Yes	No

Outline

Introduction − What is Osteoradionecrosis (ORN)

Clinical Impact − Economic Impact, Quality of Life (QOL)

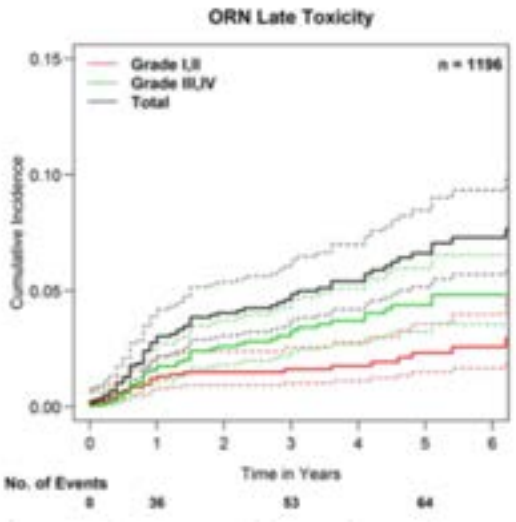
Past, Present - Risk Factors and Radiation Dose

ORN – Risk Factors – Caparrotti - 2017

- Retrospective series, 1196 patients SCC oropharynx, 2005 – 2014
- Curative intent IMRT +/- chemo
- Matched cohort: ORN vs non-ORN
- Incidence:

1 Year	3 Years	5 years
3%	5%	7%

- Multivariate Analysis significant:
  - Smoking
  - Cardiovascular comorbidities
  - T-stage
  - Bisphosphanates
  - Pre-RT extractions (poor hygiene? Less post-RT extractions)
- Volume of mandible receiving 50 Gy, and 60 Gy
  - Must compete with tumour and salivary glands

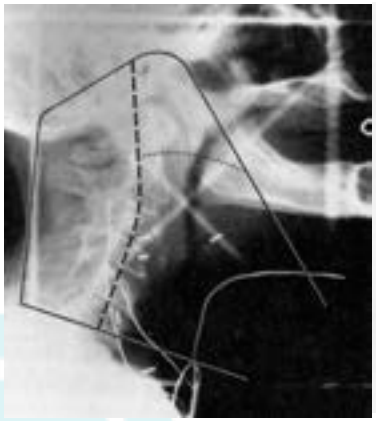


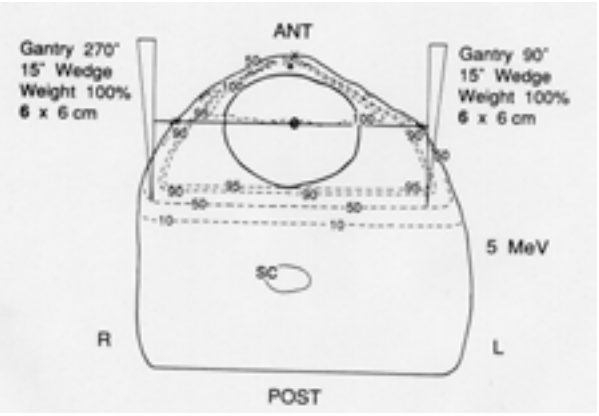
Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy.
Francesca Caparrotti et al. | Cancer, 2017 vol. 123 (19) pp. 3691-3700

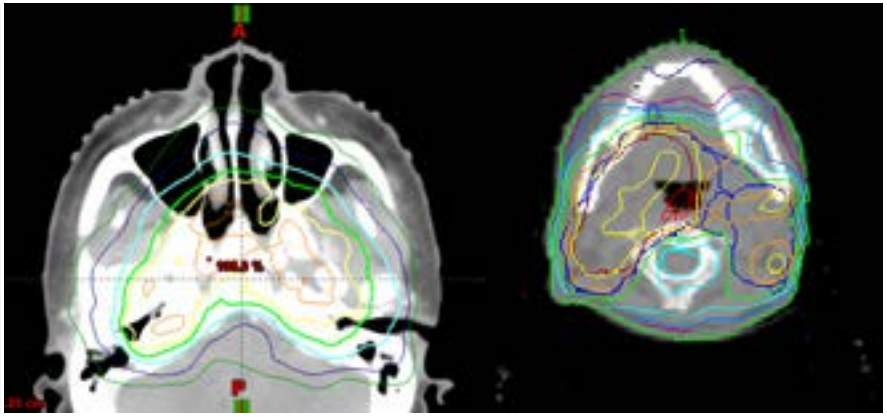
ORN – What about RT dose?

- Caparrotti, 2017: Volume of mandible receiving 50 Gy and 60 Gy
- Tsai, 2013: Volume of mandible receiving 50 Gy and 60 Gy
- Nabil, 2011: Extraction + Doses > 60 Gy

- If we know about dose…
- And radiation technique has evolved…







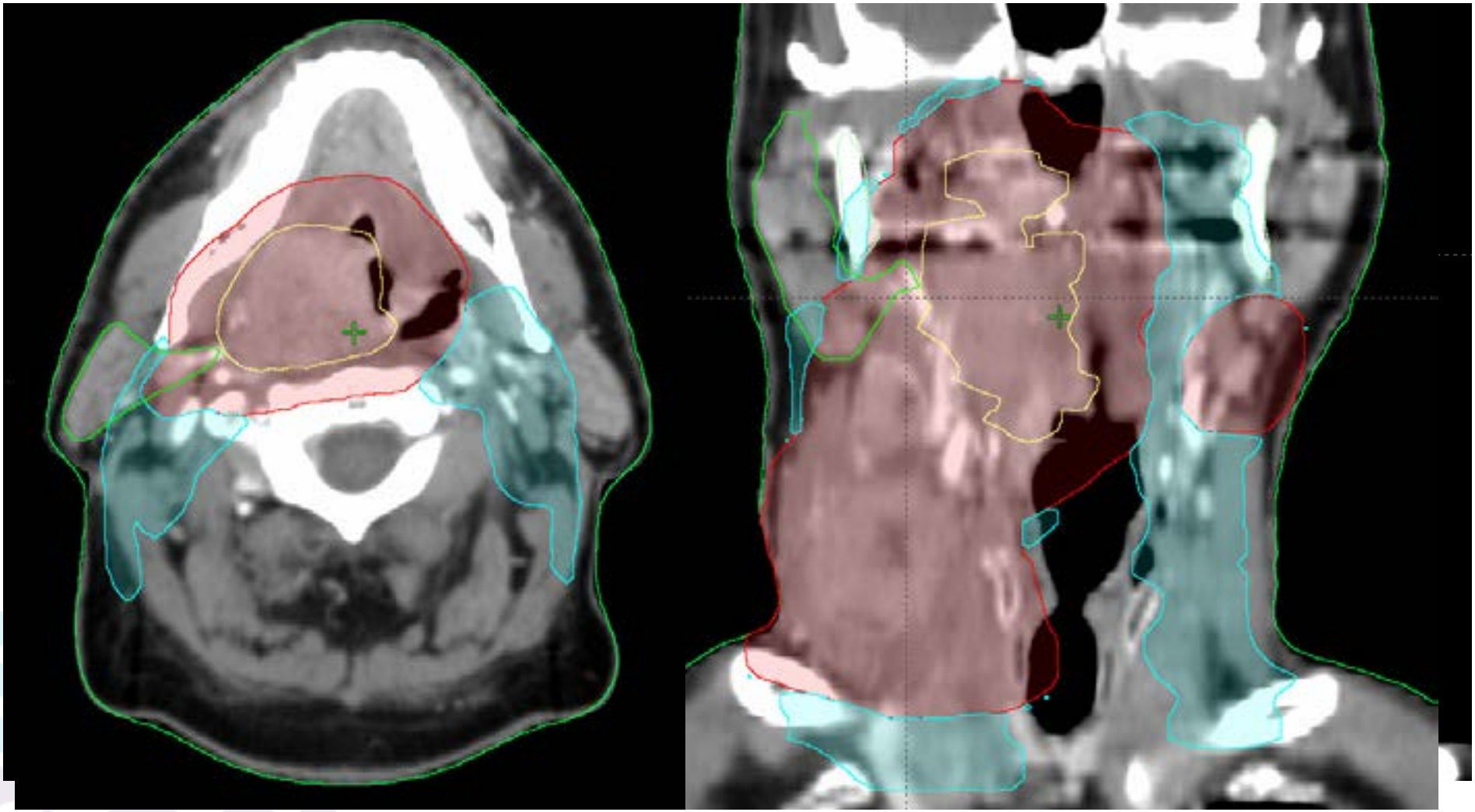
Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review.
S Nabil and N Samman | International Journal of Oral & Maxillofacial Surgery, 2011 vol. 40 (3) pp. 229-243

Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer.
Chiaojung Jillian Tsai et al. | Int J Radiat Oncol Biol Phys, 2013 vol. 86 (2) pp. 416-420

Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy.
Francesca Caparrotti et al. | Cancer, 2017 vol. 123 (19) pp. 3691-3700

ORN – What about RT dose?

…why can't we spare the mandible?



ORN – But it might be possible…!

- Review of all H&N IMRT on trials from 1996-2005 @ Ann Arbor
- 176 patients, minimal FU 6 months
  - Extractions: 17% pre, 7% post RT
  - 75% and 50% >= 65 and 70 Gy to >= 1% mandible
  - Average parotid dose: 22 Gy (contralateral), 53 Gy (ipsilateral)
- **Median FU 34 months: no ORN**

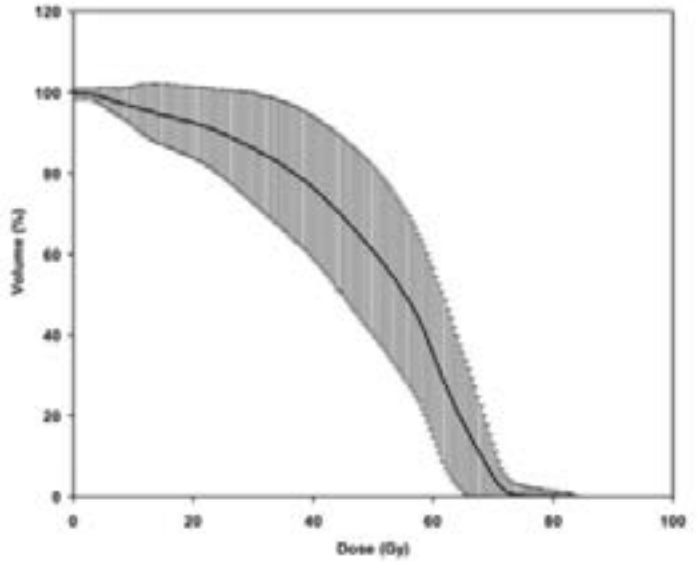
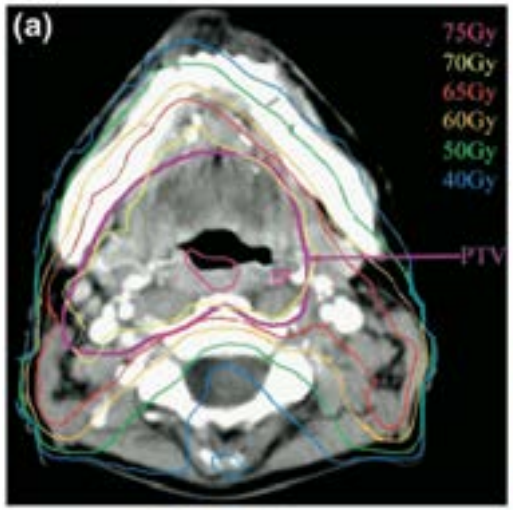
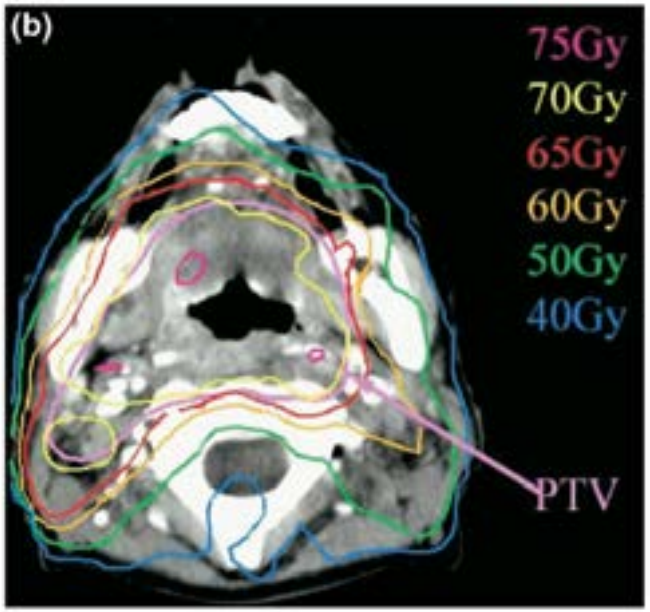


Fig. 2. Combined cumulative dose–volume histograms of mandible for all patients. Thick line represents mean dose volume, and vertical lines represent standard deviation values.

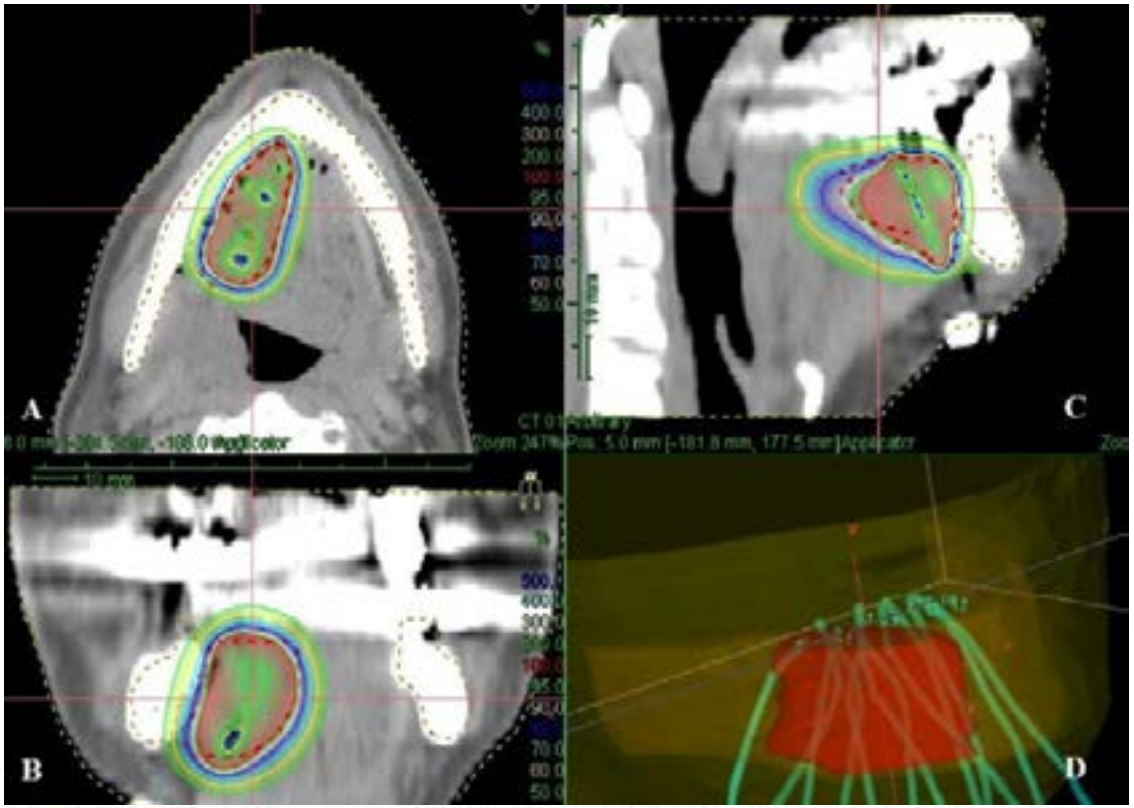




Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer
Merav A Ben-David et al. | Radiation Oncology Biology, 2007 vol. 68 (2) pp. 396-402

ORN – Brachytherapy – Extreme Past to Present

- Norwegian Radium Hospital, Oslo, Norway
- Ir-192 brachytherapy − oral cavity
- 1978 to 1994: calculation system underestimated (overdosed) by 20-25%
- 84 patients still alive
  - Clinical examination
  - EORTC QLQ-C30 & HN35
  - mean over dosage: 19.3%
  - No association dose vs QOL
- **** ORN = 45% !!!**
  - **Location: lateral tongue**
  - **Total activity (dose)**
  - **Dose rate (intensity)**



Reirradiation for patients with recurrence head and neck squamous cell carcinoma: a single-institution comparative study.
Viktoras Rudžianskas et al. | Medicina (Kaunas), 2014 vol. 50 (2) pp. 92-99

Side effects and quality of life after inadvertent radiation overdosage in brachytherapy of head-and-neck cancer.
Jan F Evensen et al. | Radiation Oncology Biology, 2002 vol. 52 (4) pp. 944-952

Osteoradionecrosis - Summary

1 Year	3 Years	5 years
3%	5%	7%

- Rare but potentially catastrophic for our patients
- May occur years after therapy

Author	# Patients	Subgroups	Surgery?	Difference?
Jacobson	30 (phone)	18 EORTC	Yes	Yes
Rogers	71	9-34	Stratified	Yes
Mucke	96	3 x 32	Yes	No

- Risk factors: Smoking, Oral Hygiene, Cardiovascular Disease
- Minimize radiation dose – compete with treating tumour and sparing organs
- ? Economic and QOL Impact