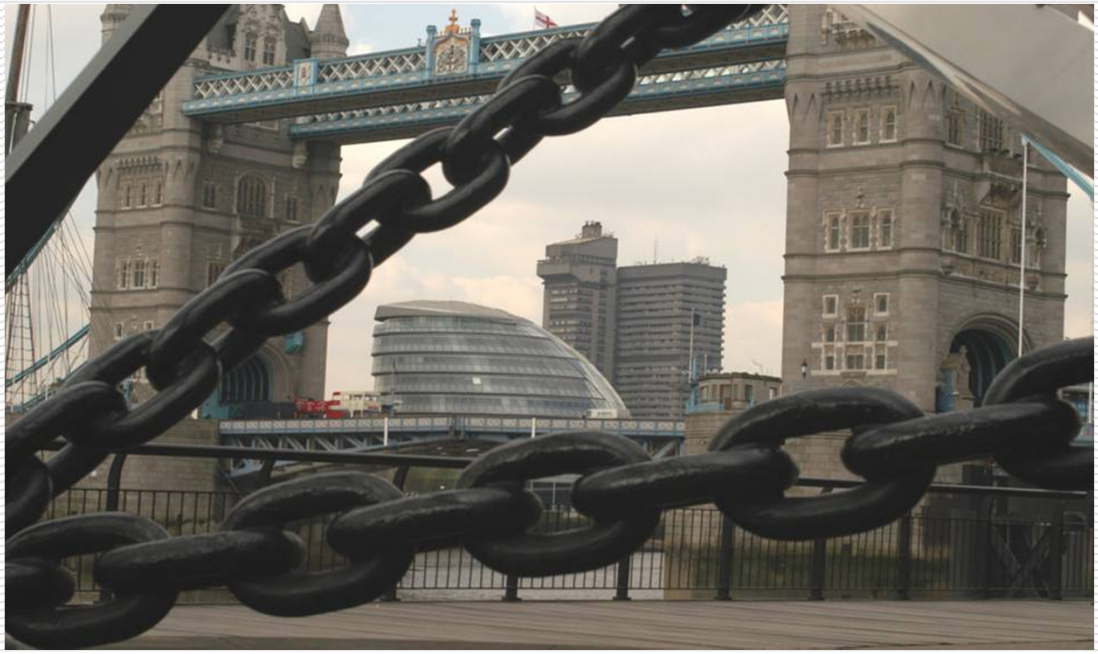
Radiation Fibrosis in the Head and Neck



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Guy's and St Thomas' NHS foundation Trust
OMICS Dubai 20th March

SYNOPSIS

- Overview of radiotherapy complications in the head and neck
- Dysphagia
- Trismus
- Osteoradionecrosis
- Fibroatrophic theory
- Genetic
- Solutions

What ‘s so special about the head and neck

- Speech
- Swallowing
- Mastication
- Aesthetics

All have great implications for survivorship!

SURGICAL SIDE EFFECTS

- Principally as a result of thousands of years of the study of anatomy surgical complications can be quite accurately
- defined



SIDE EFFECTS OF RADIOTHERAPY/CHEMOTHERAPY

- Much less defined but figures are out there.

Post radiotherapy/chemotherapy

Early Effects

- Dry Mouth 60-80%
- Stomatitis/soreness 60-75%

Post radiotherapy/chemotherapy

Late Effects

Speech pathology	10-53%
Swallowing difficulty	7-83%
Voice deterioration	5-40%
Trismus	5-30%
Osteoradionecrosis	2-25%
Carotid stenosis	?%

Post radiotherapy carotid stenosis

- The overall evolution showed that stenosis worsened in 24/32 (62%) patients in the radiotherapy group and 9/54 (17%) patients in the control groups ($P < 0.0001$).

QUALITY OF LIFE

- Speech, voice and swallowing have large determination on anxiety and depression scales

DYSPHAGIA

- Up to 83% 5 of patients receiving radiotherapy for head and neck cancer report some degree of dysphagia.

DYSPHAGIA

- When more objective measures are used up to around 32% suffer from laryngeal penetration, or severe dyspagia

DYSPHAGIA

- in a series of 18 patients requiring chemoradiotherapy 15 of them were still dependant on, feeding tubes at 6 months for nutrition.

DYSPHAGIA

- Increases with stage
- site, particularly the larynx and pharynx where the superior and middle constrictors are exposed, high radiotherapy doses causing increased thickness of constrictors
- increasing radiotherapy dose,
- the size of the area exposed to radiotherapy,
- **chemotherapy.**

DYSPHAGIA

- Chemo radiation dysphagia has been shown to be reduced using IMRT, but not in all studies

Trismus

- Consensus defines at 35mm inter incisorly
- Varies in severity
- Affects up to 50%
- post DXT



Trismus



- Fibrosis in muscles of mastication as visualized by MRI

Trismus

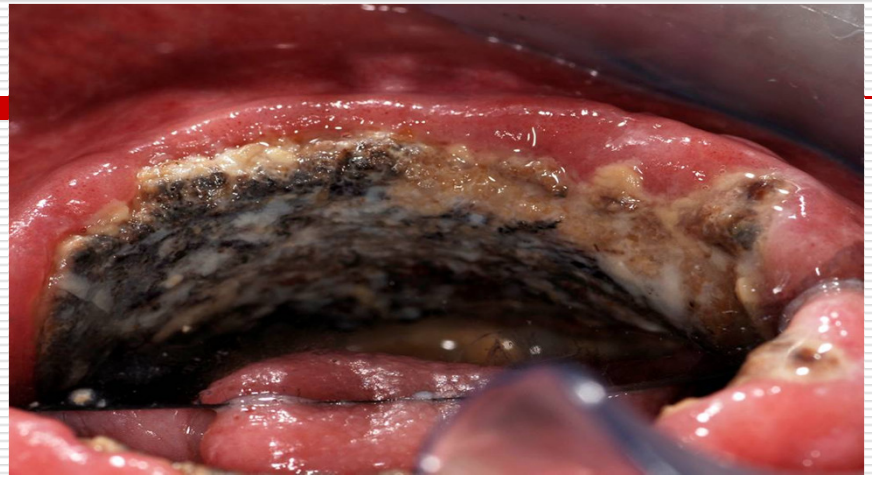
- Limits Speech
- Limits dietary intake
- Inhibits follow up

FIBROSIS

The cause of all muscle dependant complications in the head and neck!

- Dyspagia
- Trismus
- Speech

Osteoradionecrosis



Incidence 2-22%

Painful

May limit nutrition

Disfiguring

Definition of Osteoradionecrosis

A portion of bone exhibiting characteristic radiolucency that may cause breakdown of the overlying tissue

Fibroatrophic Theory

- Three distinct phases are seen:

1. prefibrotic phase in which changes in endothelial cells predominate,with the acute inflammatory response. (use glucocorticoids?)

Fibroatrophic Theory

2. constitutive organised phase in which abnormal fibroblastic activity predominates, and there is disorganisation of the extracellular matrix

Fibroatrophic Theory

3. late fibroatrophic phase, attempted tissue remodelling occurs with the formation of fragile healed tissues that carry a serious inherent risk of late reactivated inflammation in the event of local injury

Osteoradionecrosis Why Fact

Adjacent tissues especially muscles in osteoradionecrosis patients become fibrotic



Radiation damage is genetic?

Osteoradionecrosis in head-and-neck cancer has a distinct genotype-dependent cause.

Int J Radiat Oncol Biol Phys. 2012

FIBROSIS

Trismus following radiotherapy to the head and neck is likely to have distinct genotype dependent cause.

Lyons AJ, Crichton S, Pezier T.

Oral Oncol. 2013;49:932-6.

Osteoradionecrosis Why Fact

Post DXT/chemo complications in the head and neck are all in part probably transforming growth factor beta 1 dependant

FIBROATROPHY

In common with other fibro atrophic complications of radiotherapy and other forms of organ injury such as liver cirrhosis, can use:

pentoxifylline

vitamin E

clodronate

All drugs inhibit fibrosis, at least in vitro!

Osteoradionecrosis

- Classification

Stage 1

< 2cm length (damaged or exposed bone) asymptomatic

Medical treatment only.

(85% healing Pentoxifylline and vitamin E, Delanian 2005)

Spontaneous healing?

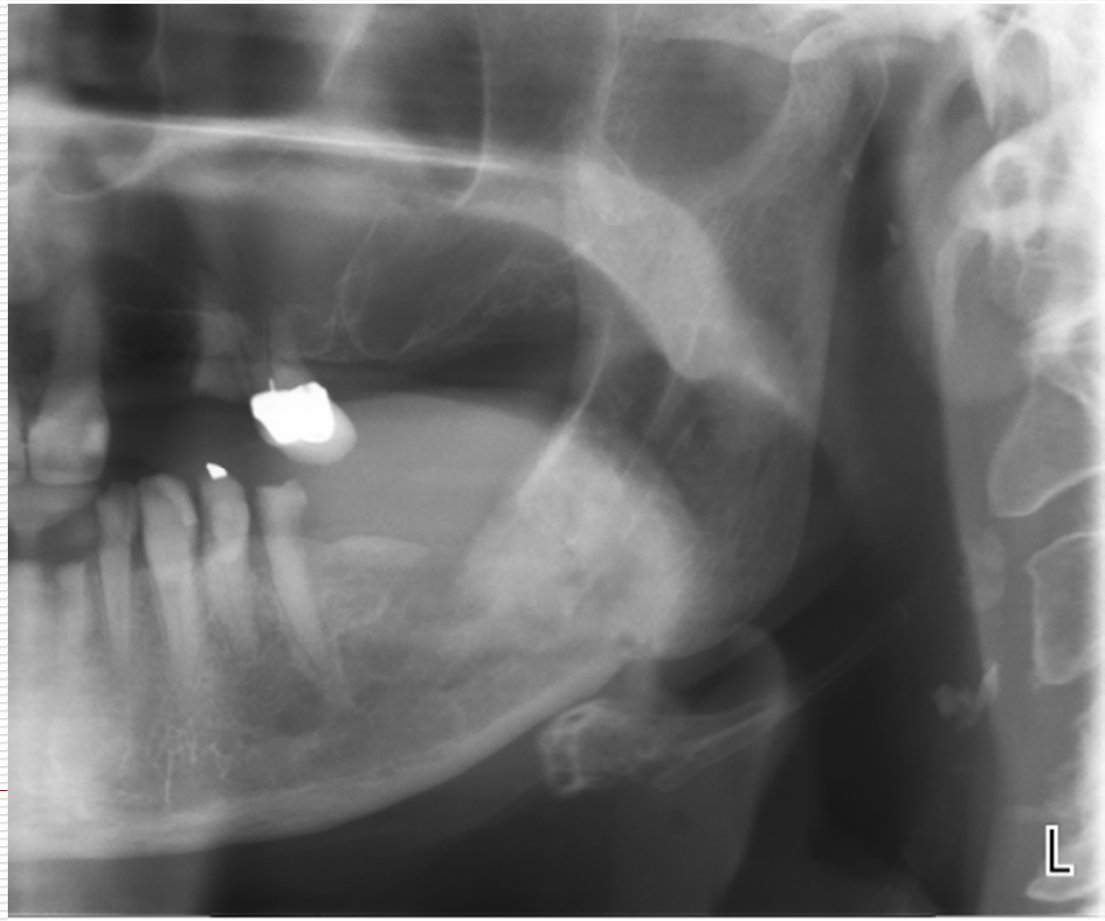




Stage 2

- 2cm length asymptomatic including pathological fracture and or ID nerve involvement
- Medical treatment only, unless dental sepsis or obviously loose necrotic bone

Stage 2



Stage 3

- 2cm length symptomatic but with no other features despite medical treatment
- Consider debridement of loose or necrotic bone and local pedicle flap



Class 4

- > 2cm length with pathological fracture and or ID nerve or orocutaneous fistula

  Symptomatic
- Reconstruct with composite flap



Why

- This classification is helpful for management
- Does not rely on hyperbaric oxygen
- This Classification is simple

Osteoradionecrosis

- Genetic cause of osteoradionecrosis is related to this classication
- The T allele at position 509 of TGF Beta 1

Osteoradionecrosis

- Higher grade classification is more associated with Trismus
  - Why
- The fibrotic process is more severe in theses cases (not entirely dependant on TGF genotype)

Osteoradionecrosis

- The C allele at position 509 of TGF Beta 1 is more prevelent in Class 1
  - WHY?
- The T allele is associated with progression to higher grades

Approaches to de-escalation

- Single modality?
- Omit cisplatin?
- Decrease total dose radiotherapy?
- Alter fractionation
- Omit induction chemotherapy?

- Trans-oral surgery + post-op radiotherapy?

ORIGINAL ARTICLE

Transoral Robotic Surgery for Advanced Oropharyngeal Carcinoma

Gregory S. Weinstein, MD; Bert W. O'Malley Jr, MD; Marc A. Cohen, MD; Harry Quon, MD

Objectives: To determine the oncologic and functional outcomes in patients undergoing primary transoral robotic surgery followed by adjuvant therapy as indicated with a minimum of 18-month followup for advanced oropharyngeal carcinoma.

Design: Prospective single-center cohort study.

Setting: Academic university health system and tertiary referral center.

Patients: Forty-seven adults with newly diagnosed and previously untreated advanced oropharyngeal carcinoma.

Intervention: Transoral robotic surgery with staged neck dissection and adjuvant therapy as indicated.

Main Outcome Measures: Margin status, recurrence, disease-specific and disease-free survival, gastrostomy tube dependence, and safety and efficacy end points.

Results: In the 47 patients enrolled with stages III and IV advanced oropharyngeal carcinoma, mean follow-up was 26.6 months. There was no intraoperative or postoperative mortality. Resection margins were positive in 1 patient (2%). At last follow-up, local recurrence was identified in 1 patient (2%), regional recurrence in 2 (4%), and distant recurrence in 4 (9%). Disease-specific survival was 98% (45 of 46 patients) at 1 year and 90% (27 of 30 patients) at 2 years. Based on pathologic risk stratification, 18 of 47 patients (38%) avoided chemotherapy, and 5 patients (11%) did not receive adjuvant radiotherapy and concurrent chemotherapy in their treatment regimen. At minimum follow-up of 1 year, only 1 patient required a gastrostomy tube.

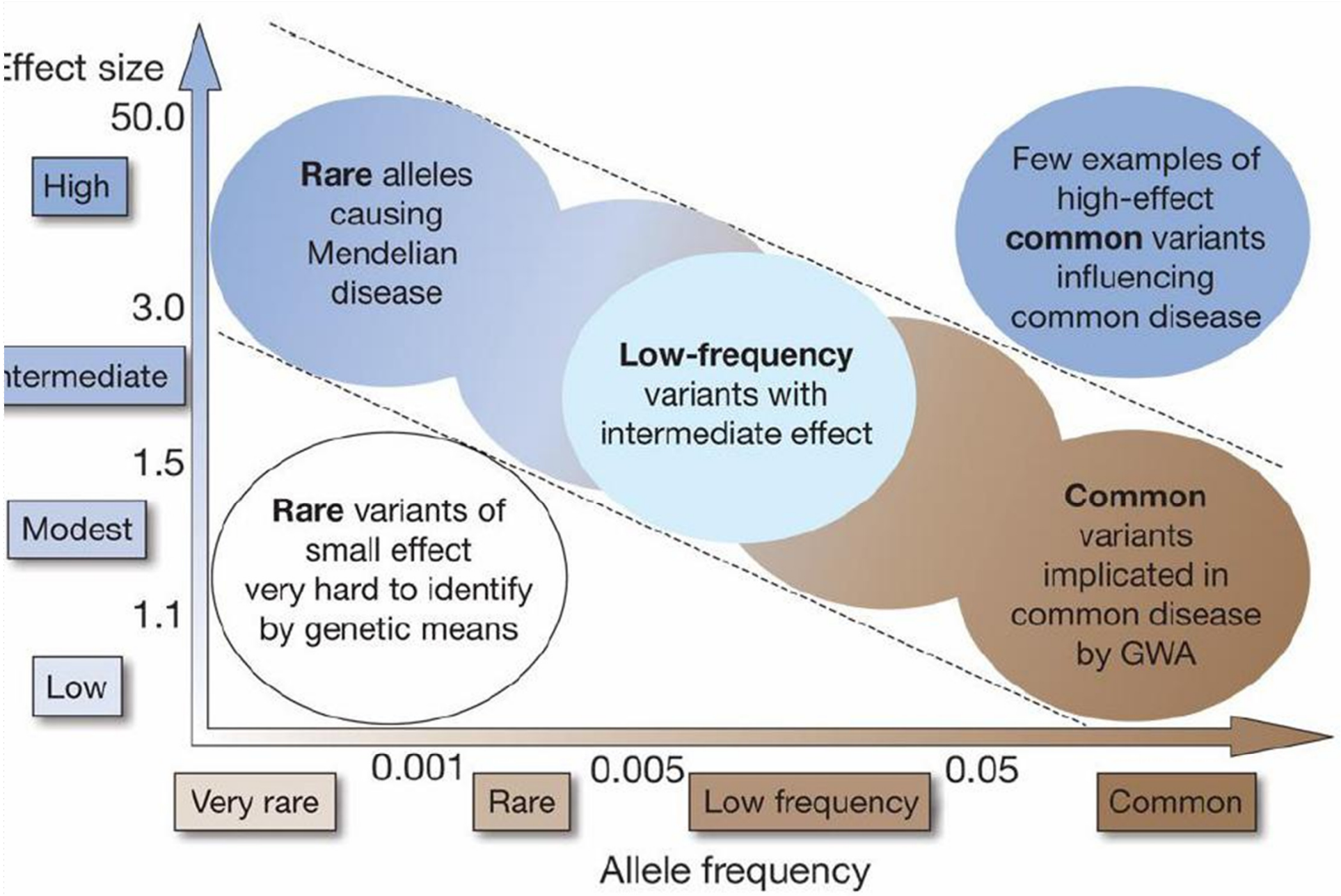
Conclusions: This novel transoral robotic surgery treatment regimen offers disease control, survival, and safety commensurate with standard treatments and an unexpected beneficial outcome of gastrostomy dependency rates that are markedly lower than those reported with standard nonsurgical therapies.

Arch Otolaryngol Head Neck Surg. 2010;136(11):1-7

2009 AHNS Beyer Award Recipient

Are there other genes out there?

- Swallowing commonest problem (30%)
- Find 100 pateints who have good swallowing and 100 patients who have bad swallowing
- Compare their genes



A et al. Finding the missing heritability of complex diseases. Nature. 2009 Oct 8;461(7265):747-53. d
ature08494

SOLUTIONS

Predict who will do badly with radiotherapy by genetic analysis

Surgery or less radiotherapy for those at risk

Antifibrotic drugs for those at risk

Conclusion

The life of the head and neck cancer survivor is going to improve!

