Protecting Salivary Gland Function During Radiotherapy

A/Prof Martin Borg
Adelaide Radiotherapy Centre
Tri-Society Head & Neck Oncology Meeting, Darwin 2014
Protecting Salivary Gland Function During Radiotherapy

- **Saliva**
  - Involved in
    1. mastication
    2. digestion
    3. swallowing
    4. speech
  - Function
    1. Lubrication of oral tissues
    2. Protection of oral tissues from bacterial infection
    3. Inhibition of enamel decalcification
    4. Provision of an excretory route for blood-bone urea, uric acid, ammonia + thiocyanate
Protecting Salivary Gland Function During Radiotherapy

- **Saliva**
- **Production**
  1. **Parotid Glands**
     - 60-65% of TSV; 20% at rest
  2. **Submandibular Glands**
     - 20-30% of TSV; 65% at rest
  3. **Sublingual/Minor SG**
     - 15% of TSV
- **Contributions vary across OC**
Protecting Salivary Gland Function During Radiotherapy

Radiotherapy Effects on SG
1. Reduced flow
2. Reduced pH
3. Reduced constituents
4. Increased viscosity
5. Xerostomia
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Xerostomia

*Affects quantity + quality*

- Dental caries and infections
- Alterations in speech and taste
- Difficulty with mastication/deglutition
- Inadequate nutrition
- Fissures and ulceration
- Osteoradionecrosis
- Oesophageal injury
- Sleep disruption
- Psychosocial/financial
Protecting Salivary Gland Function During Radiotherapy

- Xerostomia and Radiotherapy
  - Initial ($1^{st}$ wk) effect on serous (?acinar) cells (PG)
  - Subsequent effect on acinar cells (SG)
  - Effect ($p$-53 dependent apoptosis) varies with
    1. Total RT dose
    2. Volume of SG irradiated
  - Threshold PG/SG 26 Gy (26-39 Gy; ? none)
  - TD50 40 Gy: PGF = SGF
# Protecting Salivary Gland Function During Radiotherapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage</td>
<td>Surgery or RT, RT ± CT, RT ± CT ± Surgery</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>Surgery + RT ± CT, CT ± RT Surgery, Palliation</td>
</tr>
<tr>
<td>Recurrent and/or metastatic</td>
<td>RT ± CT ± Surgery, CT ± RT Surgery</td>
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<tr>
<td>Side Effect</td>
<td>RT (2-D)</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td>Xerostomia</td>
<td>&gt;66%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>35-68%</td>
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<tr>
<td>Sticky saliva</td>
<td>33%</td>
</tr>
<tr>
<td>Impaired taste</td>
<td>25-50%</td>
</tr>
<tr>
<td>Dental effects</td>
<td>33%</td>
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<tr>
<td>Pain</td>
<td>15-30%</td>
</tr>
<tr>
<td>Appearance</td>
<td>20-25%</td>
</tr>
</tbody>
</table>
Measures to Protect SGF
Protecting Salivary Gland Function During Radiotherapy

- Proper Patient + Treatment Selection
  1. MDT
  2. MDC (S, Rad/Med Onc, dentists, dieticians, nurses, SP, PE)
  3. Trials

- General
  1. Oral Care (prompt treatment of infections)
  2. Dental Care
  3. Nutrition

- Specific
  1. RT
  2. S (TORS + ↓ RT dose; transplant of SG)
  3. CT (Erbitux vs. Cisplatin: Bonner et al, NEJM 2006)
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- RT
  1. Modern techniques + delivery (IMRT, ?protons)
  2. Ipsilateral neck RT (early T stage; HPV SCC)
  3. ↓ field sizes + doses (with limited S: TORS)
  4. Immobilisation (daily cone beams)
  5. Radioprotectors (Amifostine)
  6. Stimulation of salivary flow (Acupuncture, HBOT, Pilocarpine: RTOG 97-09)
Multileaf Collimator

Leaf Movement in IMRT
IMRT

- Nutting C (RMH, ASCO/JCO 2009)
- PRCT (IMRT)
- OP/HP 94 pts (ST 3/4)
- IL parotid 59 Gy vs 45 Gy
- CL parotid 60 Gy vs 27 Gy
- ↓ SE: dysphagia, xerostomia (40%), skin rtc (not mucositis)
- ↑ SE: fatigue (↑ weight loss + hair loss, but P> 0.05)
IMRT

70 Gy + Cisplatin: day 35

70 Gy + Cisplatin: day 34
## NPC RMS

### RT doses

(Healy, Borg, Paediatric NP RMS, JMIRO 2010)

<table>
<thead>
<tr>
<th>NO</th>
<th>TL</th>
<th>BS</th>
<th>OC</th>
<th>PG</th>
<th>VC</th>
<th>PT</th>
<th>R</th>
<th>M/IE</th>
<th>SC</th>
<th>M</th>
<th>TG</th>
<th>L</th>
<th>O</th>
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<td>44/45</td>
<td>41</td>
<td>43</td>
<td>0</td>
<td>0/0</td>
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<tr>
<td>IMRT (2)</td>
<td>30</td>
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<td>17</td>
<td>1</td>
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<td>13/14</td>
<td>21</td>
<td>24</td>
<td>0</td>
<td>9/10</td>
<td>37</td>
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</tr>
</tbody>
</table>

TL: temporal lobe; BS: brainstem; OC: optic chiasm; PG: parotid gland; VC: vocal cords; Pituitary: PT; R: retina; M/IE: middle/inner ear; SC: spinal cord; M: mandible; TG: thyroid gland; L: lens; ON: optic nerve (mean of L+R)
Protecting Salivary Gland Function During Radiotherapy

- **IMRT**
- **Parotid Dose**
  1. 2-D : 70-80 Gy
  2. 3-D CRT: 50-60 Gy
  3. IMRT: 20-25 Gy
- **PG 26 Gy** (Eisbruch et al, WJS, 2003)
- **↓↓ RT doses to skin, VC, TG**
Flow rate of 2% citric acid-stimulated P/SM/SLG’s. Vissinik et al, IJROBP, 2010
Protecting Salivary Gland Function During Radiotherapy

- Sparing of Minor SG (SG/SL)
- Little et al (IJROBP, 2012)
- 78 pts, stage ¾ OP/NPC
- CT/RT (IMRT)
- Sparing parts of L+R PG, OC containing MSG + CL SG
- Objective + subjective
- OC < 40 Gy + CL SG < 50 Gy + time after RT ↓ xerostomia (P < 0.05)
- Standard practice for selected pts
Protecting Salivary Gland Function During Radiotherapy

- SGL Transfer Prior to RT (RTOG 0244)
- Naresh et al. IJROBP, 2012, 49 pts
- Ph II: SGL transfer to submental space
- No IMRT, Amifostine, or Pilocarpine; CT was allowed
- 2’ end-pt: ≤ 51% ≥ G2 acute xerostomia acceptable (1’: reproducibility of SGL transfer)
- Technique reproducible + 74% < G2 xerostomia
- Superior to Pilocarpine (Jha et al, Ph III RCT, Head and Neck 2009)

Literature: 81% ≤ G1; 19% ≥ G2 xerostomia (Jha et al, Seikaly et al, Pathak et al, Lui et al)
Protecting Salivary Gland Function During Radiotherapy

Summary

IMRT

↓ SE + ↑ outcomes (NP, OP): ↑ TG

1. G3/4 mucositis 61% vs. 90%
2. Chronic salivary dysfunction 22% vs. 38%
3. Xerostomia 25-40% vs. 75%

(Chao, IJROBP 2000; Mahadevan, ECCO12 2001, Verger, IJROBP 2009)

TROG/DOHA ANROTAT NPC Study (ARC)
Amifostine
Amifostine as a Radioprotector

- WR-2721, Ethyol (Schering-Plough)
- 40 years of clinical + lab experience
- Sulfhydryl compound (NH$_2$(CH$_2$)$_3$NHCH$_2$CH$_2$SPO$_3$H$_2$)
- Scavenger of oxygen free radicals
- Best radioprotector (Eric J Hall)
- DRF 2.0 for salivary glands
<table>
<thead>
<tr>
<th>Department</th>
<th>Name</th>
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<tbody>
<tr>
<td>Department of Rad Oncology</td>
<td>A/Prof Martin Borg (Chairman)</td>
</tr>
<tr>
<td>Dental Unit</td>
<td>Dr Elizabeth Coates</td>
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<tr>
<td>Ear, Nose and Throat Unit</td>
<td>A/Prof Suren Krishnan</td>
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<tr>
<td>Department of Pathology</td>
<td>A/Professor David Wilson</td>
</tr>
<tr>
<td>Clinical Dietetics</td>
<td>Mr David Cleghorn</td>
</tr>
<tr>
<td>Data Manager</td>
<td>Mrs Sonya Stevens</td>
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<tr>
<td>Department of Med Oncology</td>
<td>Professor Ian Olver</td>
</tr>
<tr>
<td>Oral and Maxillofacial Surgery</td>
<td>Professor Alistair Goss</td>
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<tr>
<td>Department of Nuclear Medicine</td>
<td>Dr Barry Chatterton</td>
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<tr>
<td>Diagnostic Service Laboratory</td>
<td>Dr David Nielsen</td>
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<tr>
<td>Adelaide Cancer Centre</td>
<td>Dr Brian Stein</td>
</tr>
<tr>
<td>Statistician</td>
<td>Dr Alvin Milner (PMCI)</td>
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</table>
Eligible patients
Definitive or adjuvant (postoperative) conventional RT for untreated SCC H&N
≥ 75% of each parotid gland included in planned treatment fields to ≥ 40 Gy (2-D technique)
WHO 0 - 2 and life expectancy ≥ 12 months
No distant metastasis
No primary parotid gland lesion or T1-2 N0 cancer of true VC
No concurrent chemotherapy likely to affect salivary glands

Stratify + Randomise
Treating staff and patients are blind to the randomised treatment

Amifostine (200 mg/m² IV) or placebo (normal saline)
Study drug (amifostine or placebo) as 3 minute IV infusion
No more than 30 minutes prior to each radiotherapy fraction
Radiation therapy 1.8 - 2.0 Gy/d for 30 - 35 fractions, 5 d/wk
Concurrent chemotherapy, if prescribed
<table>
<thead>
<tr>
<th>Late RT Toxicity (≥ G 2)</th>
<th>Amifostine (16)</th>
<th>Placebo (17)</th>
<th>p-value (HR/CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Time (mths)</td>
<td>Rate (%)</td>
<td>95% CI</td>
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<tr>
<td>Salivary Gland</td>
<td>6</td>
<td>51.9</td>
<td>28-75</td>
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<tr>
<td></td>
<td>12</td>
<td>65.6</td>
<td>40-84</td>
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<td>Subcut. Tissues</td>
<td>24</td>
<td>27.7</td>
<td>11-55</td>
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<td>16-66</td>
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<tr>
<td>Mucositis</td>
<td>24</td>
<td>54.3</td>
<td>30-77</td>
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<tr>
<td></td>
<td>36</td>
<td>63.4</td>
<td>36-84</td>
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</table>
Estimated % age with grade 2+ late salivary gland toxicity

<table>
<thead>
<tr>
<th>Months following commencement of radiotherapy</th>
<th>Placebo</th>
<th>Amifostine</th>
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<tbody>
<tr>
<td>0</td>
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<td>16</td>
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<td>35</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Number at risk

- Placebo: 17, 10, 3, 2, 1, 1, 0, 0, 0
- Amifostine: 16, 8, 5, 4, 4, 3, 1, 1, 0
<table>
<thead>
<tr>
<th>Phase III Trials</th>
<th>Borg et al (RT + CT)</th>
<th>Brizel et al (RT)</th>
<th>Antonadou et al (RT)</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>41</td>
<td>303</td>
<td>50</td>
</tr>
<tr>
<td>Amifostine</td>
<td>200mg/m² IV</td>
<td>200mg/m² IV</td>
<td>300mg/m² IV</td>
</tr>
<tr>
<td>Acute ≥ G 2 Xerostomia*</td>
<td>80% vs 76%</td>
<td>51% vs 78%</td>
<td>27% vs 74%</td>
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<tr>
<td>Late ≥ G 2 Xerostomia*</td>
<td>66% vs 82%</td>
<td>20% vs 36%</td>
<td>5% vs 30%</td>
</tr>
<tr>
<td>Mucositis*</td>
<td>63% vs 78%</td>
<td>39% vs 35%</td>
<td>9% vs 100%</td>
</tr>
</tbody>
</table>

* A vs RT alone +/- P
AMIFOSTINE

Summary

- ↑ acute toxicities
  - (skin reactions [Amifostine rash], mucositis, vomiting and fatigue)
- ↓ late toxicities
  - (salivary gland, subcutaneous tissue, mucositis)
- No significant difference in FFS or OS @ 4 yrs
  - (6% + 10% differences, respectively)
- IV delivery on a daily basis (equivalent subcut)
Estimated percentage surviving without failure

Number at risk

Placebo 21 14 14 7 3 1 0
Amifostine 20 12 11 6 3 0 0
Acupuncture
Protecting Salivary Gland Function During Radiotherapy

Acupuncture

- Simple and safe
- Placebo effect?
- ↑ evidence in peer review literature
- Utilised (classical needle technique) at ARC last 4-5 yrs: trained physiotherapists (x2)
- 2 courses
- Concurrent or ≥ 3-6/12, or both
- Ongoing RTOG trial
- Duration of benefit ≥ 3 years with 2 courses
- No evidence of deleterious effects but care/exclude if heart ds (valves, etc.), bleeding disorders, infection, needle phobias
Protecting Salivary Gland Function During Radiotherapy

⚠️ Acupuncture

Mechanisms of Action

Unclear - probably biological (↑ fMRI activity; Deng et al 2008, Fang et al 2004)

1. Altered cerebral activity - alter biochemistry - neurotransmitter + neurohormonal release - affect sensation, involuntary body functions (autonomic system): change in blood flow, body temperature, blood pressure

2. Autonomic stimulation of SG directly or through ↑ blood supply

- Differing acu-points

- Not yet mainstream (CAM)
Protecting Salivary Gland Function During Radiotherapy

- Adelaide Radiotherapy Centre
  - 2 treatments (≥ 6/12 after RT)
  - Physiotherapist (Sean Bushby) trained in Dry Needling + Western Acupuncture (part of APA Acupuncture course)
  - Limited (phone) review (8.8.14)
  - 18 pts (18/30)
  - 17.2.11- 5.1.14
  - 14 +ve subjective responses after 2^{nd} treatment
  - 4 maintained responses at mean 15/12 FU (5-48/12; only 7 respondents)
Protecting Salivary Gland Function During Radiotherapy

**Acupuncture Protocol** (Dr Richard Niemtzow, USA)

- 2 treatments, within 24 hrs. of each other
- Points
  1. Salivary gland 2(SG 2) - Ear
  2. Large Intestine 1 (LI 1) - Index finger
  3. Modified Point Zero - Ear
  4. Shen Men - Ear
  5. 1 inch proximal to LI 1 - Index Finger (utilised if saliva production is low)
- Order
  
  R SG 1, R LI 1, L SG 2, LI 2, L modified pt zero, L shen men then corresponding pts on RHS
Protecting Salivary Gland Function During Radiotherapy

- Acupuncture
- Menq et al, Cancer 2012
- NPC, RCT, 40 vs. 46 pts, subjective/objective measures, concurrent + adjuvant, RR 0.63 vs. 0.38
Protecting Salivary Gland Function During Radiotherapy

- **Acupuncture**
- Single institutional phase II trial, McMaster University (Canada)
- Non-invasive acupuncture-like transcutaneous nerve stimulation (ALTENS) on selected sets of acupuncture points based on traditional Chinese medicine principles
- ↑ whole salivary production + ↓ RT-induced xerostomia symptoms > 6-12/12
- ↑ improvement in tongue dryness, speech, swallowing, overall oral, consistency of saliva + oral mucous, *and taste*
- Effective in managing RT-induced xerostomia symptoms + overcomes
  1. pt reluctance to needle insertions
  2. the requirement of trained expertise for treatment delivery
- Wong RK et al, IJRBP 2003;57(2):472-480
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Acupuncture


- Wong et al. RTOG 0537. Phase 2/3. Multi-institutional. ALTENS vs. Pilocarpine. 3-24/12 post RT. 47 pts. 24 sessions. 94% compliance rate. 86% +ve treatment (QOL scores). 10% GI SE, 2% pain. Phase 3 RTOG study ongoing
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- **Acupuncture**
  - Simcock et al, Annals of Oncology 2013
  - >18/12 (?time frame for ‘spontaneous recovery) after RT, 145 pts
  - Comparative study of Ac vs. standard oral care (objective + subjective)
  - Puncture sites: both ears, index fingers, nasolabial grooves
  - Needles retained for 20 mins and rotated after 10 mins
  - No electric devises allowed
  - X8 weekly sessions
  - Controlled for social + emotional QoL, priming
  - ↓ in severity of dry mouth + sticky saliva, and need to drink water to swallow food + quench thirst at night (none were worse)
Protecting Salivary Gland Function During Radiotherapy

Acupuncture

- Overview
  

- Only 2 trials ‘acceptable’. Excluded the rest
- Low quality evidence that acupuncture results in a small ↑ in saliva production in patients with dry mouth following RT
- Insufficient participants + 'placebo' acupuncture
- Insufficient evidence to determine the effects of electrostimulation devices on dry mouth symptoms
- Dry mouth symptoms may be problematic even when saliva production is increased, yet only two of the trials reported dry mouth symptoms
- Reported adverse effects of acupuncture are mild + of short duration
- No reported adverse effects from electrostimulation (ALTENS)
HYPERBARIC OXYGEN THERAPY
Protecting Salivary Gland Function During Radiotherapy

► HBOT
  ► Transient effects
  1. ↑ Oxygen delivery
  2. ↓ Oedema
  3. Phagocytosis
  4. ↑ Mobilisation of stem cells from BM (NT recovery)

► Late effects
  1. Neovascularisation
  2. Osteoneogenesis
  3. Stimulation of collagen formation by fibroblasts (↑ fibrosis)
  4. Does NOT promote cancer growth
Protecting Salivary Gland Function During Radiotherapy

- HBOT
- Complex treatment
- 5-6 weeks
- Mon-Sat, 90 mins each dive
- Expensive
- SE: lung, ears, retina (restrict potential pts)
- Limited availability
- Difficult to accrue in trials + blind patients
- RAH trial, 1998 (blinded, multicentric)
Protecting Salivary Gland Function During Radiotherapy

- HBOT
  - Teguh et al. IJROBP, 2009 (Early HBOT, PIII RCT)
  - OP/NP (IMRT +/- BT/CBK boost; +/- CT)
  - +/- HBOT 30 sessions within 2 days after* RT
  - Slow accrual + poor funding
  - 19 pts only received HBOT
  - Sticky mouth + dry mouth: P < 0.05 (2/52 after RT, and ≥ 13/52; not acute SE*) (EORTC H&N35)
  - Also pain (VAS score) (≈ 0%), dysphagia
  - ? Placebo effect
## Protecting Salivary Gland Function During Radiotherapy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Outcomes</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amifostine</td>
<td>Phase III trials; concern re tumour protection (restrict to PORT?), few patients, few trials with placebo</td>
<td>II</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Cannot be recommended: varying results, transient effects, 1 RCPT showed benefit for mean PG doses &gt; 40 Gy*</td>
<td>II</td>
</tr>
<tr>
<td>IMRT</td>
<td>At least 3 RPCT (OP/NP) support its use</td>
<td>II</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Limited data but available</td>
<td>II</td>
</tr>
<tr>
<td>HBOT</td>
<td>Limited data</td>
<td>?II</td>
</tr>
</tbody>
</table>

Adapted from Vissinik et al, IJROBP 2010  
*Burlage et al, IJROBP 2008*
Protecting Salivary Gland Function During Radiotherapy

Conclusions

- HN SCC is lethal and disfiguring, thus justifying aggressive + toxic treatments aiming for LC + cure
- Standard therapies (S/ND, CT, RT) combine to potentiate SG dysfunction
- The advent of HPV+ SCC affecting the OP has seen a surge in younger patients with improved prognosis
- SG dysfunction is devastating to patients affecting QOL in many ways
- Improvements in S, RT + CT, patient selection + MDC have ↓ deleterious effects on SGF: more pts are able to lead a normal life
- Prevention is better than cure but plenty of room for improvement
- Current approaches should be used in combination and not in isolation
- Newer approaches: IGF 1, botulinum toxin, tempol, GT, SC therapies