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
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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 & Hypocellular tissue
  - Tissue breakdown
  - Chronic non-healing wound
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:
  o Pain, halitosis, dysgeusia, paresthesias, trismus, difficulty chewing, swallowing, dysarthria

• Severity:
  o 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.

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

- 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

- 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.

<table>
<thead>
<tr>
<th>PSS</th>
<th>ORN</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Follow up &lt;1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normalcy of diet</td>
<td>Yes</td>
<td>9</td>
<td>59</td>
<td>40</td>
<td>0.297</td>
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<tr>
<td>No</td>
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<td>9</td>
<td>78</td>
<td>24</td>
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<tr>
<td>Eating in public</td>
<td>Yes</td>
<td>9</td>
<td>64</td>
<td>44</td>
<td>0.605</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>9</td>
<td>81</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Understandability of speech</td>
<td>Yes</td>
<td>9</td>
<td>97</td>
<td>8</td>
<td>0.730</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>9</td>
<td>100</td>
<td>0</td>
<td></td>
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</tbody>
</table>

| Follow up 1–3 years|     |    |      |     |         |
| Normalcy of diet   | Yes | 11 | 46   | 40  | 0.016   |
| No                 | No  | 11 | 89   | 19  |         |
| Eating in public   | Yes | 11 | 55   | 38  | 0.005   |
| No                 | No  | 11 | 98   | 31  |         |
| Understandability of speech | Yes | 11 | 91   | 13  | 0.300   |
| No                 | No  | 11 | 98   | 8   |         |

| Follow up >3 years |     |    |      |     |         |
| Normalcy of diet   | Yes | 11 | 49   | 37  | 0.116   |
| No                 | No  | 11 | 73   | 22  |         |
| Eating in public   | Yes | 11 | 55   | 42  | 0.088   |
| No                 | No  | 11 | 84   | 27  |         |
| Understandability of speech | Yes | 11 | 90   | 18  | 0.705   |
| No                 | No  | 11 | 91   | 23  |         |

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

<table>
<thead>
<tr>
<th>PSS</th>
<th>ORN</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up &lt;1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EAT</td>
<td>Yes</td>
<td>7</td>
<td>24.43</td>
<td>9.36</td>
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<td>No</td>
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<td>7.56</td>
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<td>SHI</td>
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<td>7</td>
<td>30.00</td>
<td>15.75</td>
<td>0.142</td>
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<td>No</td>
<td>No</td>
<td>9</td>
<td>20.89</td>
<td>28.93</td>
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</table>

| Follow up 1–3 years|     |    |      |     |         |
| EAT       | Yes | 7  | 24.00| 13.04|0.004    |
| No        | No  | 8  | 5.13 | 7.49 |         |
| SHI       | Yes | 7  | 38.86| 25.61|0.072    |
| No        | No  | 8  | 15.62| 15.83|         |

| Follow up >3 years |     |    |      |     |         |
| EAT       | Yes | 4  | 15.00| 18.24|0.686    |
| No        | No  | 4  | 7.00 | 10.80|         |
| SHI       | Yes | 3  | 38.67| 56.89|1.000    |
| No        | No  | 3  | 7.33 | 6.81 |         |

18 patients
Eating Assessment Tool
Speech Handicap Index
(lower better)
Clinical Impact – QOL – Rogers, 2015

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

<table>
<thead>
<tr>
<th></th>
<th>Grade I/II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Surgery</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td>Surgery</td>
<td>10</td>
<td>18</td>
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</tbody>
</table>

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

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

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Longitudinal evaluation of health-related quality of life after osteoradionecrosis of the mandible.

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)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Surgery</td>
<td>32</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>32</td>
</tr>
<tr>
<td>Surgery + RT and ORN</td>
<td>32</td>
</tr>
</tbody>
</table>
Clinical Impact – QOL - Summary

• Since 2008, very few reports, and limited by:
  o Small cohorts
  o 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

<table>
<thead>
<tr>
<th>Author</th>
<th># Patients</th>
<th>Subgroups</th>
<th>Surgery?</th>
<th>Statistical Difference?</th>
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<tbody>
<tr>
<td>Jacobson</td>
<td>30 (phone)</td>
<td>18 (survey)</td>
<td>Yes</td>
<td>Mixed</td>
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<tr>
<td>Rogers</td>
<td>71</td>
<td>9-34 (by year)</td>
<td>Stratified</td>
<td>Mixed</td>
</tr>
<tr>
<td>Mucke</td>
<td>96</td>
<td>3 x 32</td>
<td>Yes</td>
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</tr>
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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:
  - Multivariate Analysis significant:
    - Smoking
    - Cardiovascular comorbidities
    - T-stage
    - Bisphosphonates
    - 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

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<th>1 Year</th>
<th>3 Years</th>
<th>5 years</th>
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<tr>
<td></td>
<td>3%</td>
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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...
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
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)
Osteoradionecrosis - Summary

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

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