Toxicity of ChemoRadiotherapy for Head and Neck Cancers

– A Practical Approach

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1st IAEA National Head and Neck IMRT Course
UKM
29 to 31 July 2016
Areas to be Discussed

- Skin
- Mucositis
- Xerostomia/Salivary Gland
- Taste Dysfunction
- Dysphagia, Swallowing Dysfunction
- Pain Management
- Teeth & ORN
- Trismus
Skin

- RTOG Grading
- 60-66Gy tolerated (conventional fractionation), albeit acute effects

<table>
<thead>
<tr>
<th>Grade</th>
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<tbody>
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<td></td>
<td>Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating</td>
<td>Tender or bright erythema, patchy moist desquamation / moderate edema</td>
<td>Confluent, moist desquamation other than skin folds, pitting edema</td>
<td>Ulceration, hemorrhage, necrosis</td>
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Skin Management

(1) careful cleansing of the skin

(2) moisturizing treated skin using a hydrophilic moisturizer
   (Aqueous cream, aloe vera gels)

(3) preventing mechanical or chemical irritation of treated
    skin (such as resulting from tight clothing or perfumes)

(4) in the cases of moist desquamation, extra precautions
    should be taken to minimize the possibility of skin infection
    and associated treatment delays

(5) pain management & nutritional support
Risk Factos

- Smoking
- Diabetes
- Poor nutrition
- Post-Op Neck
- Opposed fields, use non-opposed field arrangements
Topical Application
What if this side effect was seen in week 3 of concurrent chemo-radiotherapy?
Overdose

• 2001 to 2006 at the Jean Monnet Hospital in Epinal, France. They affected 450 prostate cancer patients and resulted in 12 deaths and numerous cases of urinary and digestive problems and sexual dysfunction.
Accidental Overexposure of Radiotherapy Patients in San José, Costa Rica
Skin Late Effects

- Fibrosis involving muscle, dermis, and/or the temporomandibular joint (TMJ) results in compromised oral function
- Lymphodema
- Increased risk of infection
Mucositis

• Oral mucositis results from radiation-induced mitotic death of the basal cells of the oral mucosal epithelium
Strategies

• Mouth bite – spare hard palate
• Nutritional status, Glutamine
• Regular, consistent oral hygiene
• Teat infections early
• Cover IA and (modified) IB only when necessary
Glutamine


• Oral glutamine was shown to be effective in 11 of the 15 studies included in the systematic review. It significantly reduced the incidence of grade 2, 3, or 4 mucositis and/or reduced weight loss as well as the duration, time of onset, and/or maximum grade of mucositis.

• 52 published papers (radiotherapy, chemotherapy, and hematopoietic stem cell transplant)

• Recommend using oral care protocols for preventing OM across all treatment modalities

• Do not using chlorhexidine mouthwash for head and neck cancer undergoing radiotherapy.

• Lack of evidence for dental care, normal saline, sodium bicarbonate, mixed medication mouthwash, chlorhexidine in patients receiving chemotherapy or hematopoietic stem cell transplant, or calcium phosphate.
Oral Hygiene

• Oral rinses – betadine mouthwash/oral 7, regular, after meals
• Gingival health – removal of plaques, soft tooth brushes, flossing
• Dental prostheses or orthodontic appliances have the risk of mucosal injury or infection
Mucositis
Xerostomia / Salivary Glands

- Salivary tissue changes include loss of acinar cells, alteration in duct epithelium, fibrosis, and fatty degeneration.
Oral Thrush
Parotid Sparing IMRT

Intensity-modulated radiation therapy: emerging cancer treatment technology.
Clinical experience with conventional irradiation of H&N tumor subsites has demonstrated a steep and rapid reduction in salivary flow rate (FR), ranging from 18% to 50% 1 week after initiation of RT.

**Mean parotid dose**
- <20Gy low risk
- 20-30Gy medium risk
- >40-50Gy high risk

- Largest study 222 patients
- TD50 of 40Gy and a complication probability of 17-26% with mean parotid doses in the range of 25–30 Gy (Michigan Utrect)
**Submandibular Gland** – also important (?thickness of saliva) <40Gy

**Uninvolved oral mucosa** - <10Gy/week

- Randomized trials have documented the benefits of amifostine, pilocarpine (PC) and, more recently, the pre-RT surgical transfer of submandibular glands to the submental space

Role of Dental Review

• Management of oral complications of cancer therapy includes identification of high risk populations, patient education, initiation of pretreatment interventions, and timely management of lesions.

• Examine the teeth, gingiva, periodontal area, tongue, cleanliness

• Extraction of irreversibly damaged teeth - minimize risk for poor wound healing and ORN

• Systemic complications (such as subacute bacterial endocarditis and associated complications)

• Oral hygiene – eg. scaling
Effects of RT on Teeth

• Loss of bone vitality, injury to osteocytes, osteoblasts, and osteoclasts

• Vascular disruption, relative hypoxia

• Soft tissue necrosis and ORN that result in bone exposure, secondary infection, and severe pain

• Life-long risks of tooth decay, infection, and ORN among others
ORN

- most frequently involving mandible versus maxilla.

- typically occurs within the first 3 years post-diagnosis, although it is thought that patients remain at indefinite risk

- diagnosis of ORN relies on the clinical examination of chronically exposed bone.

- Radiographic findings include decreased bone density and pathologic fractures.

- $\uparrow$Risk = Dose $>$60Gy
ORN Treatment

• Hyperbaric oxygen therapy (HBO) generally recommended

• Increases oxygenation of irradiated tissue, promotes angiogenesis, and enhances osteoblast repopulation and fibroblast function

• HBO is usually prescribed as 20–30 dives at 100% oxygen and 2–2.5 atm of pressure. If surgery is needed, 10 dives of postsurgical HBO are recommended

• Partial mandibulectomy may be necessary in severe cases of ORN.
Pain Management
Trismus

• Fibrosis of muscles of mastication and/or TMJ

• Jaw exercises including mandibular stretching exercises as well as use of prosthetic aids designed to reduce severity of fibrosis

• It is important that these approaches be instituted prior to the development of trismus.
“Dynamic Bite Opener”
SWOARs

“Try” and reduce mean dose to 40-50Gy V70<50%

- Base of tongue (BOT)
- Oesophageal inlet muscle (EIM)
- Superior/middle/inferior pharyngeal constrictor muscle (SPCM/MPCM/IPCM)
- Cricopharyngeal muscle (Crico)
- Cervical oesophagus (CEso),
- Supra-larynx and glottic larynx

Contouring guidelines Christianen et al 2011
Figure 1. Nomogram for tube feeding dependence to determine normal tissue complication probability (NTCP) values for each individual patient. Abbreviations: SF, conventional radiotherapy; ART, accelerated radiotherapy; CRT, chemoradiation.
doi:10.1371/journal.pone.0094879.g001
Temporal lobe necrosis

- Necrosis >60Gy
- Seizures
- MRI spectroscopy, DWI – tumour vs necrosis
- Resection
- Optic nerve / chiasm – 45-50Gy
Hearing

- Middle ear effusion – grommet
- Mean dose <40Gy (30% incidence)
- Baseline hearing tests
- Increase risk from Cisplatin
Addition of Chemotherapy

• Multiple prospective studies\(^1,2,3\) have demonstrated increased acute toxicities with the addition of chemotherapy to radiation particularly when administered concurrently

• However, the contribution of chemotherapy to the late toxicity profile post-RT is in need of further study

• Dose Constraint Recommendations does NOT take into account chemotherapy

Chemotherapy

- Cisplatin

- Chemotherapy side effects – renal, neutropenia, hyponatraemia/hypomagnesaemia
Summary

• Management of H&N patient requires multidisciplinary approach

• Aggressive, pre-emptive management of toxicities is recommended to ensure avoid RT delays

• Chemotherapy increases risk of side effects and the quantification of these effects are uncertain

• Respect dose constraints BUT the priority of disease cure or control may supercede this