Manipulating Radiation Response – Protectors and Physical Modalities

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Recovery curves of the type first described by Elkind and Sutton

A two-component survival curve for mammalian cells
Illustration of the concept of a Therapeutic ratio in turn of dose response relationships for tumour control and normal tissue damage.
Dose response relationships for normal tissue and tumour.

Modification of the response of tumour by radiosensitizers and normal tissue by radioprotectors is also shown.
Radiobiological Principals of Radiation Therapy Design
Radiobiological Principals of Radiation Therapy Design
Radiobiological Principals of Radiation Therapy Design
Interaction between DNA damage and repair process
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Defects</th>
<th>Tumor Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li-Fraumeni (AD: p53 heterozygote)</td>
<td>Cell cycle regulation, apoptosis</td>
<td>Breast, sarcoma, others</td>
</tr>
<tr>
<td>Lynch/HNPCC (AD: 1 D MLH1/MSH2) and others</td>
<td>Mismatch repair</td>
<td>Colorectal, uterine,</td>
</tr>
<tr>
<td>BRCA1, BRCA2 (AD: gene heterozygote)</td>
<td>HR and other DNA repair pathways</td>
<td>Breast, ovary</td>
</tr>
<tr>
<td>Ataxia telangiectasia (AR: AT-mutated [atm])</td>
<td>DSB repair; cell cycle</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td></td>
<td>Regulation</td>
<td>lymphomas</td>
</tr>
<tr>
<td>Xeroderma pigmentosum (AR: XP variants or complementation groups)</td>
<td>NER</td>
<td>Skin cancers</td>
</tr>
<tr>
<td>Fanconi’s anemia (AR: complementation variants)</td>
<td>Cross-link repair</td>
<td>Acute myeloid leukemia</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; DSB, double-strand breaks; HNPCC, hereditary nonpolyposis colorectal cancer; HR, homologous recombination; NER, nucleotide excision repair; XP, xeroderma pigmentosum.
Table 2. DNA Repair Pathways Involved in the DDR to Chemotherapy and Ionizing Radiation

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-homologous end joining (NHEJ)</td>
<td>Mediates repair of DNA DSBs without the need for sequence homology.</td>
</tr>
<tr>
<td>Homologous recombination (HR)</td>
<td>Mediates DNA strand breaks and replication lesions by copying a DNA sequence from intact DNA (often a newly synthesized sister chromatid)</td>
</tr>
<tr>
<td>Base excision repair (BER)</td>
<td>A repair process that replaces missing or modified DNA bases resulting from oxidative stress or cancer treatments (IR, alkylating drugs)</td>
</tr>
<tr>
<td>Direct (enzymatic repair (DR)</td>
<td>A repair process of alkylated base damage (e.g., TMZ treatment via O6-methylguanine-DNA methyltransferase (MGMT))</td>
</tr>
<tr>
<td>Nucleotide excision repair (NER)</td>
<td>A repair process that removes large DNA adducts or large base modifications causing DNA helix distortions using the opposite strand as a template for repair</td>
</tr>
<tr>
<td>Mismatch repair (MMR)</td>
<td>A repair process that functions during DNA replication (S-phase) To correct base-pairing errors made by DNA polymerase (slippage) or exogenously produced by IR and/or CT.</td>
</tr>
</tbody>
</table>
FIGURE 10-2. Sites of action of the commonly used anticancer drugs.
The 4 R’s of Radiation Therapy

- Restitution
- Repopulation
- Redistribution
- Reoxygenation
The 4 R’s of Radiation Therapy

• Reassortment (Redistribution)
  – Following a $D_0$ level radiation event cells die
    • Cells in $G_2$ and $M$ are most sensitive and more likely to be killed.
    • Cells in $S$ are more resistant and likely to survive
    • A radiation induce mitotic arrest is likely present
  – Cell growth kinetics tend to determine what percentage of the population will be in each phase of the cell cycle
The 4 R’s of Radiation Therapy

• Reassortment (cont.)
  – Following irradiation the percentage of cycling cells in each phase will be reestablished within 1-2 cell cycle times.
  – Reirradiation will then again selectively kill cells in the radiation sensitive portions of the cell cycle
  – Thus reassortment improves chances of cells being irradiated in a sensitive part of the cycle
The 4 R’s of Radiation Therapy

• Reassortment cont.
  – Tumor cells on average have shorter cell cycle times than normal tissues
  – This is especially true for late responding tissue
  – Reassortment then occurs more quickly in tumors.
  – Reassortment favors survival of normal late responding tissues
The 4 R’s of Radiation Therapy

• Repair – Following a D₀ level dose there is repair of radiation injury in surviving cells
  – Cells with long cell cycle times generally have a wider repair shoulder on the survival curve
  – Cells with short cell cycle time generally have a narrow repair shoulder.
  – Tumor cells are considered to have short cell cycle times
The 4 R’s of Radiation Therapy

• Repair – cont.
  – Fractionation will broaden the survival shoulder more for late responding tissue than early responding tissues.
  – At high doses the cell survival curve actually indicates lower survival for late responding cells
The 4 R’s of Radiation Therapy

• Regeneration
  – Following irradiation some cell populations will exhibit increased cell division
    • Usually follows a period of mitotic arrest
  – Repopulation tends to begin more quickly in normal early responding tissues than in tumors
  – Repopulation then favors survival of normal early responding tissues over tumors
  – Opposite is true of late responding tissues
The 4 R’s of Radiation Therapy

• Reoxygenation
  – Hypoxia in many tumors blunts radiation injury
    • 2-3 times as much dose required to kill hypoxic cells
  – Normal tissues are not hypoxic as a rule
  – This markedly favors survival of tumor cells for doses in the $D_0$ range.
  – However, of the well oxygenated cells in a tumor there is usually a high percentage of cycling cells.
The 4 R’s of Radiation Therapy

• Reoxygenation cont.
  – Large numbers of cycling tumor cells are killed
  – Cells previously of marginal oxygenation survive and move into the oxygenated zone
  – These newly oxygenated cells then start to cycle and are then susceptible to the next dose due to being oxygenated and cycling
  – Theoretically all tumor cells can be reoxygenated this way if enough fractions used
The 4 R’s of Radiation Therapy

• Recruitment
  – Recruitment is the “5th” of the “4 r’s”
  – Cells not previously part of the cycling pool are “recruited” to enter the cycling pool by one of the mechanisms of the 4 r’s
    • Leads to regeneration
    • Can be direct result of reoxygenation
    • Contributes cells to the reassortment process
    • Repair of injury allows cells to enter cycling pool.
Factors Affecting Tumor Growth

• Cell cycle time
  – Cell cycle times vary widely within a given tumor.
  – Some tumor cells may be very slowly cycling
  – Tumors of the same type may have different average cell cycle times
    • Slow is generally equated with benign tumors
    • Fast is generally equated with malignancy
Factors Affecting Tumor Growth

• Growth fraction (fraction of cells in population which are actually cycling)
  – Even in tumors most cells are not cycling
  – Cycling cells are well oxygenated and fed
  – Growth fractions of greater than 10% are unusual.
  – Growth fraction may be less than 1%
  – Large growth fraction will usually result in rapid tumor growth.
Factors Affecting Tumor Growth

• Cell loss fraction
  – Cells are lost from the tumor population in several ways.
  – Nonviable replication of deranged cells will result in loss of those cells
    • DNA is too altered for a functional cell to exist
  – Anoxia, cell death from poor blood supply
  – Attack of antigentic cells by immune system
  – Metastasis to blood stream > vast majority die
Factors Affecting Tumor Growth

• Tumor oxygenation
  – Poor tumor oxygenation = slow growth
  – Poor tumor oxygenation = increased cell death
  – Tumor oxygenation decreases as size increases
  – Both chronic and transient hypoxia may have effect.
Tumour Hypoxia is One of the Determinant of Poor Outcome Following Radiation
Outcome of Interactions

• Additive
• Supra additive – Sensitization
• Sub additive - Protection
Biological Basis

- Temperature above 41°C is differential to mammalian cells
- Sensitizes cells to ionising radiation
- Can activate 0 and S phase cells
- Preferentially kills hypoxic cells due to pH dependency
- Cell membrane may be the primary target
- Can inhibit DNA repair
Biological Basis for Hyperthermia

• Microenvironment is hostile in tumour to heat, and heat in turn perpetuates the state

• Better thermal washouts in normal tissue reduces the cytotoxic effects.

• A therapeutic window is created
Vascularity - Hypoxia - pH

Hyperthermia can totally occlude tortuous Neo-vascularization with concomitant alterations in oxygenation metabolism. Leading to hypoxia and low pH
<table>
<thead>
<tr>
<th>EFFECTS OF HEAT ALONE</th>
<th>INTERACTIONS WITH XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>46°C</td>
<td>Vascular destruction in highly perfused tissues</td>
</tr>
<tr>
<td>45°C</td>
<td>Vascular destruction in poorly perfused tissues</td>
</tr>
<tr>
<td>44°C</td>
<td>Cellular cytotoxicity enhanced at low pH and in S-phase</td>
</tr>
<tr>
<td>43°C</td>
<td>Increased perfusion in all tissue types</td>
</tr>
<tr>
<td>42°C</td>
<td>Normothermia</td>
</tr>
<tr>
<td>41°C</td>
<td></td>
</tr>
<tr>
<td>40°C</td>
<td></td>
</tr>
<tr>
<td>39°C</td>
<td></td>
</tr>
<tr>
<td>38°C</td>
<td></td>
</tr>
<tr>
<td>37°C</td>
<td></td>
</tr>
<tr>
<td>36°C</td>
<td></td>
</tr>
</tbody>
</table>
Tissue Oxygenation

Low flow $\longrightarrow$ Further decline

High Flow $\longrightarrow$ Perfusion may go up

Decline in pO2 may last for 24 hours
Targets for Hyperthermia

- Plasma Membrane
- Cytoskeleton
- Nucleus
Changes in Tissue pH

- Accumulation of lactic acids
- Changes equilibrium of intra and extra cellular buffer state
- Increase in ATP hydrolysis
- Increase in pCO$_2$ level
- Inhibition of the Na$^+$/H$^+$ ion pump
Variable to Affect the Outcome

- Heat dose i.e. temperature over a time period
- Thermal gradients
- Sequence and interval between two modalities
- Tumour volume
- Intrinsic sensitivity for heat
- Heating mechanism
Characteristics of Heat Susceptible Tumour

- Nutrient deprived tissue
- Poor perfusion
- Anerobic metabolism
- Lower pH
- Low on energy
Thermal Sensitizers

- Hyperglycemia
- Amiloride
- Hydralazine
- Nitroprusside
- Arsenic Trioxide
# Specification of the RF Heating System

<table>
<thead>
<tr>
<th>Power Source</th>
<th>Single phase, 200V, 50~60Hz, 30A</th>
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</thead>
<tbody>
<tr>
<td>Max. Input</td>
<td>4KVA</td>
</tr>
<tr>
<td>RF Output</td>
<td>8MHz</td>
</tr>
<tr>
<td>Electrode</td>
<td>Twin plate electrodes, 10cm, 14cm, 25cm</td>
</tr>
<tr>
<td>Temp. Measurement</td>
<td>Micro thermocouple sensor (0.64mm diameter)</td>
</tr>
<tr>
<td>Temperature Control</td>
<td>On-Off control</td>
</tr>
<tr>
<td>Heating Method</td>
<td>RF Capacitive coupling heating</td>
</tr>
</tbody>
</table>
HEATING TECHNIQUE

• THERMOMETRY – AT LEAST ONCE, WITH INVASIVE THERMISTOR PROBES

• PRIMARY – HEAD & NECK NOT DONE

• APPROPRIATE ANTENNAE ARE ARRANGED IN PARALLEL WITH ACTIVE SIDE TOWARDS THE LESION

• POWER : - 400 – 900 W

• RF – 8 MHz – THERMATRON – CAPCITATIVE HEATING
Relationship between time of heating temperature to produce a given effect in a range of normal tissues and tumours in situ. At temperatures above the break point 1°C is equivalent to a factor of two in heating time; below the break 1°C is equivalent to a factor of six.
ICMR – Hyperthermia Trial

Randomized

RT
64 – 70 Gy / 6 – 7 wks
200 cGy / day

N = 14

RT
64 – 70 Gy / 6 – 7 wks
200 cGy / day
+ Weekly Hyperthermia.

N = 14
Exclusion Criteria

Karnofsky’s Index <80

Histology other than sq.cell.ca

Early Head & Neck Cancer

Bilateral nodes

Emotionally incompetent

Short Neck
Inclusion Criteria

Squamous cell- carcinoma –confirmed histologically /FNAC

Karnofsky’s Index > 70

Loco-regionally advanced H&N cancer T3- 4/ No – N3
Only ipsilateral nodes

Emotionally capable of giving informed consent
Radiation Therapy

- Total dose of 66-70 Gy was given by appropriate portals with daily 200cGy per fraction.

- 6 1/2 – 7 weeks of treatment

- 4-6 MV energy rays used for treatment.
### Demographic data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RT-Group</th>
<th>RT + HT-Group</th>
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</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>26</td>
<td>28</td>
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<tr>
<td>@Age (yrs)</td>
<td>58.42</td>
<td>57.71</td>
</tr>
<tr>
<td>Mean</td>
<td>11.39</td>
<td>12.93</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>40-76 yrs</td>
<td>31-78 yrs</td>
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<tr>
<td>#Sex (%)</td>
<td>24(92.3)</td>
<td>22(78.6)</td>
</tr>
<tr>
<td>Male</td>
<td>22(78.6)</td>
<td>22(78.6)</td>
</tr>
<tr>
<td>Female</td>
<td>02(07.7)</td>
<td>06(21.4)</td>
</tr>
</tbody>
</table>

*By Student’s t’ Test P > 0.05 Not Significant*

*By Chi-square Test*
### TNM staging classification

<table>
<thead>
<tr>
<th>Response</th>
<th>RT-Group (N=26)</th>
<th>RT + HT-Group (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>T2N0</td>
<td>01</td>
<td>03.8</td>
</tr>
<tr>
<td>T2N1</td>
<td>01</td>
<td>03.8</td>
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<tr>
<td>T2N3</td>
<td>02</td>
<td>07.7</td>
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<tr>
<td>T3N1</td>
<td>02</td>
<td>07.7</td>
</tr>
<tr>
<td>T3N2</td>
<td>04</td>
<td>15.4</td>
</tr>
<tr>
<td>T3N3</td>
<td>06</td>
<td>23.1</td>
</tr>
<tr>
<td>T3NO</td>
<td>04</td>
<td>15.4</td>
</tr>
<tr>
<td>T4N0</td>
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<td>-</td>
</tr>
<tr>
<td>T4N1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T4N2</td>
<td>02</td>
<td>07.7</td>
</tr>
<tr>
<td>T4N3</td>
<td>04</td>
<td>15.4</td>
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</tbody>
</table>
## SITES OF DISEASE

<table>
<thead>
<tr>
<th>Site</th>
<th>RT-Group (N=26)</th>
<th>RT + HT-Group (N=28)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>17</td>
<td>65.4</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>05</td>
<td>19.2</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>04</td>
<td>15.4</td>
</tr>
</tbody>
</table>
# RADIATION DOSE IN BOTH GROUPS

<table>
<thead>
<tr>
<th>Response</th>
<th>RT-Group (N=26)</th>
<th></th>
<th>RT + HT-Group (N=28)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>&lt;=50GY</td>
<td>04</td>
<td>15.4</td>
<td>04</td>
<td>14.3</td>
</tr>
<tr>
<td>&gt;70GY</td>
<td>01</td>
<td>03.8</td>
<td>01</td>
<td>03.6</td>
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<tr>
<td>50-60GY</td>
<td>-</td>
<td>-</td>
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<td>03.6</td>
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<tr>
<td>60-70GY</td>
<td>21</td>
<td>80.8</td>
<td>22</td>
<td>78.5</td>
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</table>
## FOLLOW-UP PERIOD

<table>
<thead>
<tr>
<th>Durations</th>
<th>RT-Group (N=26)</th>
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<tbody>
<tr>
<td></td>
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<td>%</td>
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<tr>
<td>&lt; 6 months</td>
<td>16</td>
<td>61.5</td>
</tr>
<tr>
<td>6-12 months</td>
<td>08</td>
<td>30.8</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>02</td>
<td>07.7</td>
</tr>
</tbody>
</table>
## Compliance to Hyperthermia Treatment

<table>
<thead>
<tr>
<th>No. of hyperthermia treatments</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>03</td>
</tr>
<tr>
<td>2-4</td>
<td>02</td>
</tr>
<tr>
<td>5-7</td>
<td>23</td>
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</table>
## COMPARISON OF RESPONSE BETWEEN TWO TREATMENT GROUPS

<table>
<thead>
<tr>
<th>Response</th>
<th>RT-Group (N=26)</th>
<th>RT + HT-Group (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>11</td>
<td>42.4</td>
</tr>
<tr>
<td>Partial Response</td>
<td>13</td>
<td>50.0</td>
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<tr>
<td>No Response</td>
<td>01</td>
<td>03.8</td>
</tr>
<tr>
<td>PD</td>
<td>01</td>
<td>03.8</td>
</tr>
</tbody>
</table>
Kaplan-Meier Survival plot

Survival Plot (PL estimates)
Mechanisms of Thermal Enhancement

1. Increase in intracellular drug concentration
2. Stimulation of drug binding to DNA
3. Change in the spectrum of adducts formed
4. Reduction in DNA repair
5. Increase in perfusion
Chemotherapy

- Concurrent once a week chemotherapy given
- Cisplatin- 30mg/m² i/v
- Paclitaxel- 30mg/m² i/v
Chemoradiation with hyperthermia in the treatment of head and neck cancer

Nagraj G. Huilgol, Sapna Gupta, Rajesh Dixit
*Int.J. Hyperthermia, February 2010; 26(1): 21-25*

38 patients evaluated at the end of study

**Complete response**- 29/38 patients

**Partial response**- 09/38 patients

Mortality- 01/40

Incomplete treatment- 01/40
BASIS OF CHEMORADIATION

Increase patient survival

- improving loco-regional tumor control
- decreasing or eliminating distant metastases

SITE OF ACTION

Locoregional
Systemic
Steel and Peckham- strategies of combined modality

- spatial cooperation
- independent toxicity
- enhancement of tumor response
- protection of normal tissues.
Drug-Radiation Interactions

- Increasing Initial Radiation Damage
- Inhibition of Cellular Repair
- Cell Cycle Redistribution
- Counteracting Hypoxia-Associated Tumor Radio-resistance
- Inhibition of Tumor Cell Repopulation
Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon a,*, Aurélie le Maître a, Emilie Maillard a, Jean Bourhis b, on behalf of the MACH-NC Collaborative Group

Radiotherapy and Oncology 92 (2009) 4–14

Hazard ratio of different end-points

Overall Survival Curves
EVIDENCE SO FAR ……..!

- Chemoradiotherapy shows equal results of survival with the possibility of laryngeal preservation. It is higher with chemoradiation in laryngopharyngeal malignancies.

- CT+RT should be considered standard of care for small volume stage III/stage IV laryngeal and hypopharyngeal cancers (TMH – EBM)
## RESULTS OF TREATMENT OF ADVANCED CARCINOMA OF THE LARYNX UTILIZING CHEMOTHERAPY AND RADIATION THERAPY

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No.</th>
<th>Type of Therapy</th>
<th>Stage III/IV (%)</th>
<th>2 Year Survival (%)</th>
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</thead>
<tbody>
<tr>
<td>Veterans Affairs</td>
<td>1987</td>
<td>30</td>
<td>C/RT</td>
<td>100</td>
<td>52</td>
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<tr>
<td>Larynx Group</td>
<td>1991</td>
<td>166</td>
<td>S/RT</td>
<td>100</td>
<td>68</td>
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<tr>
<td>Pfister</td>
<td>1991</td>
<td>13</td>
<td>C/RT</td>
<td>98</td>
<td>77</td>
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<td>Karp</td>
<td>1991</td>
<td>14</td>
<td>C/RT</td>
<td>92</td>
<td>50</td>
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<td>Urpa</td>
<td>1994</td>
<td>8</td>
<td>C/RT</td>
<td>93</td>
<td>75</td>
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<td>Author</td>
<td>Total No. of Patients</td>
<td>CT/RT Schedule</td>
<td>CT Regimen</td>
<td>RT Fraction</td>
<td>Overall Survival Benefit (p&lt;0.05)</td>
</tr>
<tr>
<td>---------</td>
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<td>--------------</td>
<td>------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>GORTEC</td>
<td>226</td>
<td>Concurrent</td>
<td>CBDCA/5-FU</td>
<td>Standard</td>
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<tr>
<td>Adelsin</td>
<td>100</td>
<td>Concurrent</td>
<td>CDDP/5-FU</td>
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<td>Wendt</td>
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<td>Concurrent</td>
<td>CDDP/5-FU</td>
<td>Hyper-fractionated</td>
<td>Yes</td>
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<tr>
<td>Keane</td>
<td>212</td>
<td>Concurrent</td>
<td>MMC/5-FU</td>
<td>Standard</td>
<td>No</td>
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<td>Brizel</td>
<td>122</td>
<td>Concurrent</td>
<td>CDDP/5-FU</td>
<td>Hyper-fractionated</td>
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<td>Merlano</td>
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<td>Alternating</td>
<td>CDDP/5-FU</td>
<td>Standard</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Carbon Ion Accelerator
When the ratios of peak to plateau (a/b) are compared while considering biological effect, the carbon beam has the largest value.
IDEAL RADIATION PROTECTOR

- Pre-empt injury
- Promote repair
- High DRF
- Should protect all organ systems
- Should spare tumours
- Least toxic – unlike amifostine
- Compatible with other drugs
Protectors

- Methylene Blue
- Phenobarbitone
- Mannitol
- Antioxidants
- Diethyldithiocarbonate (DDTC)
- Disulfran (dimer of DDTC)
- Sodium thiosulfate
- Mercaptoetahnosulfonate
- (MESNA)
Clinical evidence of Pre-irradiation Latent injury | Morbidity

Clinical radioprotection

Prophylaxis, short term

Prophylaxis, continuous

Prevention, short term

Prevention, continuous

Treatment, short term

Treatment, continuous

amifostine

Cap, Ace blocker (kidney)

Cap, (lung) ; DEX (kidney) ASA (lung, kidney)

Cap, (kidney)

Cap, (kidney)

Cap, Ace blocker (kidney)

PTX (soft tissue)
Damage

• Scavangable damage - OH•
• Non Scavangable damage
  – Direct ionisation of DNA
    Reaction with H₂O⁺
    or non scavangable OH•
  Scavangable : 63
  Non Scavangable  : 35
Conversion of Amifostine

Amifostine (prodrug)

\[
\text{NH}_2-(\text{CH}_2)_3-\text{NH}-(\text{CH}_2)_2-S-\text{PO}_3\text{H}_2
\]

\[
\text{Membrane bound alkaline phosphatase}
\]

\[
\text{NH}_2-(\text{CH}_2)_3-\text{NH}-(\text{CH}_2)_2-\text{SH}
\]

WR-1065 (Active form)

\[
\text{Oxidation}
\]

\[
\text{NH}_2-(\text{CH}_2)_3-\text{NH}-(\text{CH}_2)_2-S
\]

\[
\text{HH}_2-(\text{CH}_2)_3-\text{NH}-(\text{CH}_2)_2-S
\]

WR-33278
Amifostine – WR2721
“Organic Thiophosphate”
- A Pro Drug

\[ \text{NH}_2-(\text{CH}_2)_3-\text{NH}(\text{CH}_2)_2-\text{S-P-OH} \]
Concentration of Dephosphorylated Amifostine

- High concentration of alkaline phosphates
- Facilitated uptake into normal cell
- High vascularity
- Normal pH
• Low concentration of alkaline phosphatase
• Passive uptake into cell
• Low vascularity
• Acidic pH
Comparison of Ethylol and Cyclophosphamide (CTX) concentration in the spleen and tumour
Examples of Protection Factors Achieved by Amifostine in
Different Normal Tissues and Tumours

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Protection Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary gland</td>
<td>2.3-3.3</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>1.8-3.0</td>
</tr>
<tr>
<td>Jejunum</td>
<td>1.5-2.1</td>
</tr>
<tr>
<td>Skin</td>
<td>1.4-2.1</td>
</tr>
<tr>
<td>Testis</td>
<td>1.5-164</td>
</tr>
<tr>
<td>Lung</td>
<td>1.2-1.4</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.3-1.5</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.3-1.5</td>
</tr>
<tr>
<td>Tumours</td>
<td>1.0-2.8</td>
</tr>
</tbody>
</table>
Onset of Xerostomia Significantly Delayed With Amifostine
Radiation Toxicity

Effects of Xerostomia

• Health
  - Loss of teeth
  - Osteoradionecrosis
  - Oral infections

• Quality of life
  - Eating
  - Sleeping

• Function
  - Speaking
Summary of Pivotal Phase III Study of Amifostine as a Radioprotector

• Amifostine significantly reduced the incidence of ≥ grade 2 xerostomia
  – Acute xerostomia was reduced from 78% to 51% (p < 0.0001)
  – Late xerostomia 57% to 34% (p < 0.002)

• Improved clinical benefit as assessed by PBQ
  – Mouth dryness (p < 0.001)
  – Mean summary score (p < 0.008)
Conclusion

Amifostine offers patients with head and neck cancer a new option to protect against long-term complications of xerostomia without affecting efficacy or survival.
Structure of various Vitamin E derivatives and their physical properties

Solubility in water (g/100g)

- Vitamin E: ~0
- Trolox: 0.02
- TMG: 100

Lipophilicity (n-Octanol/H₂O Partition Coefficient)
Illustration of the concept of a Therapeutic ratio in turn of dose response relationships for tumour control and normal tissue damage
Calmodulin regulated enzymes and cellular processes

- Myosin light chain kinase
- Phosphorylase Kinase
- Adenylate Cyclase
- Phosphodiesterase
- Gaunalate Cyclase
- Calmodulin
- \(Ca^{2+}\) ATPase
- Microtubule assembling
- Membrane phosphorylation
- Others
Inclusion Criteria in Ca. Cervix

- FIGO – STAGE III
- HISTOLOGICAL PROOF OF SQUAMOUS CELL CARCINOMA
- NORMAL RENAL PARAMETERS
- KL – 70 % & ABOVE
- AGE UP TO 70 AND AP/PA > 18 CMS
Biphasic Effects of CPZ

Cation radical of CPZ has marked non-specific inhibitory effects on various enzymatic processes in cells.

CPZ $10^{-6} -- 10^{-5}$ → Protective
$10^{-4} -- 10^{-2}$ → Toxic

Abe. et al
CANCER OF CERVIX

• FIGO – STAGE III
• HISTOLOGICAL PROOF OF SQUAMOUS CELL CARCINOMA
• NORMAL RENAL PARAMETERS
• KL – 70 % & ABOVE
• AGE UP TO 70 AND AP/PA > 18 CMS
Diagramatic Illustration of Cancer of Cervix

Bladder

Lateral Disease

Central Disease

Rectum
Proctitis

<table>
<thead>
<tr>
<th>Treatment Group Proctitis</th>
<th>Control No. of Pts. (%) n=15</th>
<th>CPZ No. of Pts (%) n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr. 0</td>
<td>0(0)</td>
<td>8(47.0)</td>
</tr>
<tr>
<td>Gr. I</td>
<td>1(6.66)</td>
<td>2(11.76)</td>
</tr>
<tr>
<td>Gr. 2</td>
<td>3(20)</td>
<td>4(23.52)</td>
</tr>
<tr>
<td>Gr. 3</td>
<td>10(66.66)</td>
<td>4(23.52)</td>
</tr>
<tr>
<td>Gr. 4</td>
<td>1(6.6)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>
Sanazole (AK-2123)

\[
\begin{align*}
\text{CH}_2\text{CONHCH}_2\text{CH}_2\text{OCH}_2
\end{align*}
\]
<table>
<thead>
<tr>
<th>Groups</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Stage</th>
<th>Initial response</th>
<th>Disease-free-survival</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>70</td>
<td>Ca. larynx</td>
<td>T4 N0 M0 T3 N3 M0</td>
<td>PR</td>
<td>Lost to FU with disease 7 months</td>
</tr>
<tr>
<td>Control</td>
<td>65</td>
<td>Ca. pyriform</td>
<td></td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>67</td>
<td>Ca. base tongue</td>
<td>T4 N3 M0 T3 N1 M0 T4 N3 M0</td>
<td>PR</td>
<td>Lost to FU with disease 18 months died 6 months lost to FU with disease</td>
</tr>
<tr>
<td>Control</td>
<td>70</td>
<td>Ca. base tongue</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>61</td>
<td>Ca. base tongue</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>25</td>
<td>Ca. tonsil</td>
<td>T4 N3 M0 T3 N0 M0 T4 N0 M0</td>
<td>CR</td>
<td>Lost to FU 2 years 2 years: rec.c. after 1 months</td>
</tr>
<tr>
<td>Control</td>
<td>50</td>
<td>Ca. pyriform</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>39</td>
<td>Ca. or pharynx</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>42</td>
<td>Ca. tonsil</td>
<td>T4 N3 M0</td>
<td>PR</td>
<td>2 months died with disease</td>
</tr>
<tr>
<td>AK-2123 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>880 mg x 9</td>
<td>60</td>
<td>Ca. pyriform</td>
<td>T3 N0 M0 T3 N0 M0 T3 N2 M0</td>
<td>CR</td>
<td>2 year 21 months 1 year, died without disease</td>
</tr>
<tr>
<td>880 mg x 9</td>
<td>25</td>
<td>Ca. floor of the mouth</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>880 mg x 9</td>
<td>60</td>
<td>Ca. base tongue</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>880 mg x 9</td>
<td>45</td>
<td>Ca. pyriform</td>
<td>T3 N3 M0</td>
<td>CR</td>
<td>6 months, rec. Lost to FU</td>
</tr>
<tr>
<td>990 mg x 9</td>
<td>70</td>
<td>Ca. pyriform</td>
<td>T3 N1 M0 T3 N3 M0 T3 N0 M0</td>
<td>CR</td>
<td>21 months 10 months 5 months: 2nd neoplasm in esophagus 1 year developed Striders</td>
</tr>
<tr>
<td>990 mg x 9</td>
<td>50</td>
<td>Ca. base tongue</td>
<td>T3 N0 M0</td>
<td>CR</td>
<td>1 year</td>
</tr>
<tr>
<td>990 mg x 9</td>
<td>55</td>
<td>Ca. pyriform</td>
<td></td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>990 mg x 9</td>
<td>48</td>
<td>Ca. base tongue</td>
<td></td>
<td>CR</td>
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</tr>
<tr>
<td>990 mg x 9</td>
<td>50</td>
<td>Ca. base tongue</td>
<td>T3 N0 M0</td>
<td>CR</td>
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</tbody>
</table>
Randomized clinical trials with hypoxic modification of radiotherapy in HNSCC.

<table>
<thead>
<tr>
<th>References</th>
<th>Trial acronym</th>
<th>Year</th>
<th>No. pts</th>
<th>fx</th>
<th>RT schedule</th>
<th>Hyposic modification</th>
<th>Endpoint</th>
<th>Obs. time</th>
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</thead>
<tbody>
<tr>
<td>[21] van den Brenk</td>
<td>HH</td>
<td>1968</td>
<td>30</td>
<td>7.75 Gy x 4 vs 7.25 Gy x 4 with HBO</td>
<td>HBO 4 atm</td>
<td>L D S</td>
<td>2 + years</td>
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<tr>
<td>[22] Evans 1</td>
<td>LL</td>
<td>1970</td>
<td>40</td>
<td>60 Gy/30 fx</td>
<td>Normobaric 02</td>
<td>L D S</td>
<td>2 + years</td>
<td></td>
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<tr>
<td>[23] Tobin</td>
<td>LL</td>
<td>1971</td>
<td>17</td>
<td>60 Gy/30 fx</td>
<td>HBO 3 atm</td>
<td>L D S</td>
<td>2 + years</td>
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<tr>
<td>[24] Chang</td>
<td>HHL</td>
<td>1973</td>
<td>31</td>
<td>6 Gy x 6+ HBO vs 6 Gy x 7 or 60 Gy/30 fx</td>
<td>HBO 3 atm</td>
<td>L D S M C</td>
<td>5 years</td>
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<tr>
<td>[25] Shigamats u</td>
<td>HL</td>
<td>1973</td>
<td>31</td>
<td>60-79 Gy/10 fx vs. 40-50 Gy/8-10 fx + HBO</td>
<td>HBO</td>
<td>L D S</td>
<td>2 + years</td>
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<tr>
<td>[26] Evans 2</td>
<td>LL</td>
<td>1975</td>
<td>44</td>
<td>60 Gy/30 fx</td>
<td>Normobaric 02</td>
<td>L D S M C</td>
<td>2 + years</td>
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<tr>
<td>[27] MRC 1 trial</td>
<td>HH</td>
<td>1977</td>
<td>276</td>
<td>45-55 Gy x 10</td>
<td>HBO</td>
<td>L D S</td>
<td>4 years</td>
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<tr>
<td>[28] MRC 3, trial</td>
<td>HL</td>
<td>1979</td>
<td>24</td>
<td>45-50/15 el 48.5-55/20 air vs. 40-45/10 HBO</td>
<td>HBO</td>
<td>L D S</td>
<td>c 5 years</td>
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<tr>
<td>[29] RTOG 70-02</td>
<td>LL</td>
<td>1979</td>
<td>254</td>
<td>60-70 Gy/30 fx</td>
<td>Carbogen</td>
<td>L D S M</td>
<td>2 + years</td>
<td></td>
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<tr>
<td>[30] Sause</td>
<td>HL</td>
<td>1979</td>
<td>44</td>
<td>48 Gy/12 fx + HBO vs. 62 Gy/25 fx</td>
<td>HBO 3 aim</td>
<td>L D S</td>
<td>2 + years</td>
<td></td>
</tr>
<tr>
<td>[31] Giau x</td>
<td>HII</td>
<td>1962</td>
<td>56</td>
<td>50 Gy/16 fx</td>
<td>MISO</td>
<td>L D S</td>
<td>34 months</td>
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<tr>
<td>[32] Sealy 1</td>
<td>HH</td>
<td>1962</td>
<td>97</td>
<td>56 Gy/6 fx/17 days</td>
<td>MISO</td>
<td>L D S</td>
<td>c 3 years</td>
<td></td>
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<tr>
<td>[33] B run in</td>
<td>HL</td>
<td>1963</td>
<td>101</td>
<td>72 Gy/36 fx</td>
<td>MISO</td>
<td>L D S</td>
<td>2 years</td>
<td></td>
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<tr>
<td>[34] MRC 10 fx</td>
<td>HH</td>
<td>1964</td>
<td>162</td>
<td>40-45 Gy/10 fx</td>
<td>MISO</td>
<td>L D S</td>
<td>c 3 years</td>
<td></td>
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<tr>
<td>[35] MRC 20 fx</td>
<td>LL</td>
<td>1964</td>
<td>89</td>
<td>50-57 Gy/20 fx</td>
<td>MISO</td>
<td>L D S</td>
<td>c 3 years</td>
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</tr>
<tr>
<td>[36] Panis</td>
<td>MM</td>
<td>1964</td>
<td>52</td>
<td>Split-course 1.1 Gy x 6 daily/ 5 days – 4 weeks split-repeat</td>
<td>MISO</td>
<td>L D S</td>
<td>c 2 years</td>
<td></td>
</tr>
<tr>
<td>[37] EORTC 22S11</td>
<td>MM</td>
<td>1966</td>
<td>330</td>
<td>1.6 Gy x 3/10 days – 3 weeks split + same to total of 67-72 Gy</td>
<td>MISO</td>
<td>L D S</td>
<td>c 5 years</td>
<td></td>
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<tr>
<td>[38] MRC 2, trial</td>
<td>HL</td>
<td>1966</td>
<td>103</td>
<td>64 Gy/30 fx vs. 41-44 Gy/10 fx + HBO</td>
<td>HBO 3 aim</td>
<td>L D S M C</td>
<td>4 years</td>
<td></td>
</tr>
<tr>
<td>[39] Sealy 2</td>
<td>HL</td>
<td>1966</td>
<td>124</td>
<td>63 Gy/30 fx (air); 36 Gy/6 fx (HBO)</td>
<td>HBO/MISO</td>
<td>L D S M C</td>
<td>1-2 years</td>
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<tr>
<td>[40] IAEA study</td>
<td>LL</td>
<td>1967</td>
<td>36</td>
<td>70 Gy/35 fx</td>
<td>On ids zo e</td>
<td>L D S</td>
<td>c 2 years</td>
<td></td>
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<tr>
<td>[42] Galacski</td>
<td>LL</td>
<td>1969</td>
<td>35</td>
<td>70 Gy/35 fx vs. 66 Gy/30 fx vs. 80.5 Gy x 70 fx</td>
<td>Metronidazole</td>
<td>L D S</td>
<td>c 3 years</td>
<td></td>
</tr>
<tr>
<td>[43] Dahanca 2</td>
<td>HL</td>
<td>1969</td>
<td>622</td>
<td>68-72/3-6:36 fx eller 61/22/9.5 weeks</td>
<td>MISO</td>
<td>L D S M</td>
<td>c 5 years</td>
<td></td>
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<tr>
<td>[44] RTOG 79-04</td>
<td>HH</td>
<td>1969</td>
<td>40</td>
<td>4 Gy/11-13 fx</td>
<td>MISO</td>
<td>L D S</td>
<td>c 5 years</td>
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<tr>
<td>[45] RTOG 85-27</td>
<td>HH</td>
<td>1995</td>
<td>504</td>
<td>66-74 Gy/33-37 fx</td>
<td>Etaizazole</td>
<td>L D S</td>
<td>c 5 years</td>
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<tr>
<td>[46] Hugol</td>
<td>LL</td>
<td>1996</td>
<td>18</td>
<td>54 Gy/45 fx/22 days</td>
<td>AK-2123</td>
<td>L D S</td>
<td>c 5 years</td>
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<td>[47] European trial</td>
<td>LL</td>
<td>1997</td>
<td>374</td>
<td>66-74 Gy/33-37 fx</td>
<td>Etaizazole</td>
<td>L D S</td>
<td>c 5 years</td>
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<tr>
<td>[49] Hafty</td>
<td>HH</td>
<td>1999</td>
<td>48</td>
<td>12.65 Gy x 2 vs. 11.50 Gy x 2 + HBO</td>
<td>HBO4 atm</td>
<td>L D S M</td>
<td>c 5 years</td>
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<td>[50] Mendenhall</td>
<td>MM</td>
<td>2005</td>
<td>101</td>
<td>76 Gy/12 Gy fx BIG</td>
<td>02 Carbogen</td>
<td>L D S s M</td>
<td>5 years</td>
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<tr>
<td>[51] Mullal</td>
<td>LL</td>
<td>2006</td>
<td>46</td>
<td>60 Gy/30 fx</td>
<td>AK-2123</td>
<td>L</td>
<td>c 3 months</td>
<td></td>
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<tr>
<td>[52] ARCON</td>
<td>LL</td>
<td>2010</td>
<td>345</td>
<td>64-68 Gy/32-34 fx accelerated fx</td>
<td>Nicotinamide</td>
<td>L D s</td>
<td>2 years</td>
<td></td>
</tr>
</tbody>
</table>

a H: Hypofract; L: conventional tract; M: hyperfract (multiple fx/day).

b L: Loco-regional failure; D: disease specific death; S: overall death; M: distant metastasis; C: complications.
Head and neck cancer - meta analysis - summary

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Events / Total</th>
<th>Odds ratio and 95% CI</th>
<th>Odds ratio</th>
<th>Risk Reduction</th>
<th>NNT**</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Hypoxic</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Loco-regional control</td>
<td>1203 / 2406</td>
<td>1383 / 2399</td>
<td>0.71 (0.63-0.80)*</td>
<td>8% (5-10%)*</td>
<td>13</td>
</tr>
<tr>
<td>Disease specific survival</td>
<td>1175 / 2335</td>
<td>1347 / 2329</td>
<td>0.73 (0.64-0.82)</td>
<td>7% (5-10%)</td>
<td>14</td>
</tr>
<tr>
<td>Overall survival</td>
<td>1450 / 2312</td>
<td>1519 / 2305</td>
<td>0.87 (0.77-0.98)</td>
<td>3% (0-6%)</td>
<td>31</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>159 / 1427</td>
<td>179 / 1391</td>
<td>0.87 (0.69-1.09)</td>
<td>2% (-1-4%)</td>
<td>57</td>
</tr>
<tr>
<td>Radiotherapy complications</td>
<td>307 / 1864</td>
<td>297 / 1822</td>
<td>1.00 (0.82-1.23)</td>
<td>0% (-3-2%)</td>
<td>&gt;&gt;</td>
</tr>
</tbody>
</table>

Hypoxia modification better   | Control better

Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

* 95% CI.
** Numbers of patients Needed to Treat to achieve benefit in one patients.

Hypoxia modification of radiotherapy.......Overgaard Jens, 100 (2011); 22-32, Radiotherapy and Oncology
### Endpoint: Loco-regional failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Modification</th>
<th>Events / Total</th>
<th>Odds ratio and 95% CI</th>
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<tr>
<td></td>
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<td>Hypoxic modification</td>
<td>Control</td>
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<tr>
<td><strong>Normobaric oxygen</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1970 Evans 1</td>
<td>O2</td>
<td>7 / 15</td>
<td>11 / 25</td>
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<tr>
<td>1975 Evans 2</td>
<td>O2</td>
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<td>19 / 24</td>
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<td>63 / 133</td>
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<td>9 / 51</td>
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<td>1968 van den Brenk HBO</td>
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<td>5 / 17</td>
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<td>1971 Tobin 1971</td>
<td>HBO</td>
<td>5 / 9</td>
<td>6 / 8</td>
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<td>1973 Chang 1973</td>
<td>HBO</td>
<td>8 / 26</td>
<td>13 / 25</td>
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<td>1973 Shigematsu</td>
<td>HBO</td>
<td>9 / 15</td>
<td>11 / 10</td>
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<td>29 / 50</td>
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<td>11 / 50</td>
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<td>MISO</td>
<td>15 / 51</td>
<td>18 / 80</td>
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<td>MISO</td>
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<td>53 / 80</td>
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<td>MISO</td>
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<td>30 / 46</td>
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<td>MISO</td>
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<td>16 / 26</td>
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<td>HBO/MISO</td>
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<td>46 / 84</td>
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<td>1986 EORTC 22/11</td>
<td>MISO</td>
<td>103 / 167</td>
<td>114 / 163</td>
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<td>1987 European trial ETA</td>
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<td>92 / 187</td>
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<td>1987 IAEA study</td>
<td>Ornidazole</td>
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<td>14 / 18</td>
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<td>1987 RTOG 79-15</td>
<td>MISO</td>
<td>113 / 147</td>
<td>104 / 150</td>
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<td>1989 Dahanca 2</td>
<td>MISO</td>
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<td>157 / 294</td>
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<td>1989 RTOG 79-04</td>
<td>MISO</td>
<td>16 / 21</td>
<td>17 / 19</td>
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<td>1989 Galecki</td>
<td>Metro</td>
<td>3 / 18</td>
<td>5 / 17</td>
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<td>1992 Gioux</td>
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<td>23 / 26</td>
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<td>1995 RTOG 85-27 ETA</td>
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<td>AK-2123</td>
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<td>7 / 9</td>
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<td>1998 Dahanca 5</td>
<td>NIM</td>
<td>104 / 219</td>
<td>125 / 195</td>
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<td>2006 Ulall</td>
<td>AK-2123</td>
<td>8 / 23</td>
<td>18 / 23</td>
</tr>
<tr>
<td><strong>Subtotal (Hypoxic sensitizer)</strong></td>
<td></td>
<td>970 / 1731</td>
<td>1039 / 1666</td>
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</tbody>
</table>

**All trials with hypoxic modification** | 1203 / 2406 | 1383 / 2399 <br>**Test for heterogeneity:** p = 0.12

**Meta Analysis - Hypoxic modification of radiotherapy in HNSCC**

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_Hypoxia modification of radiotherapy...... Overgaard Jens, 100 (2011); 22-32, Radiotherapy and Oncology_
Hypoxia modification of radiotherapy......Overgaard Jens, 100 (2011); 22-32, Radiotherapy and Oncology

Meta Analysis - Hypoxic modification of radiotherapy in HNSCC
Figure 1: Hazard ratio of death with altered fractionated radiotherapy versus conventional radiotherapy

The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of deaths in each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA=British Columbia Cancer Agency. CAIR=Continuous Accelerated Irradiation. CHART=Continuous Hyperfractionated Accelerated Radiation Therapy. DAHANCA=Danish Head and Neck Cancer Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GORTEC=Groupe d’ Oncologie Radiotherapie Tete et Cou. KBN=Korniet Badan Naszkowy (Committee for Scientific Research). O-E=observed minus expected. PMH-Toronto=Princess Margaret Hospital, Toronto. RT=radiotherapy. RT0G=Radiation Therapy Oncology Group. TROG=Trans-Tansman Radiation Oncology Group.

Hypwerfractionated or accelerated radiotherapy…… Bourhis J, Overgaard J. et., Vol. 368: 843-854; Sep 2, 2006, Lancet
Hypwerfractionated or accelerated radiotherapy...... Bourhis J, Overgaard J. et.,
Vol. 368: 843-854; Sep 2, 2006, Lancet
Figure 2: Survival curves by treatment arm for all trials and for the three groups of trials according to the type of altered fractionated radiotherapy.
(A) Hyperfractionation. (B) Accelerated fractionation without total dose reduction. (C) Accelerated fractionation with total dose reduction. (D) All three groups together. The slopes of the broken lines from year 6 to year 27 are based on the overall death rates in the seventh and subsequent years. RT = radiotherapy.

Figure 3: Hazard ratio of death with locoregional treatment plus chemotherapy compared with locoregional treatment by types of chemotherapy

Platin (cisplatin or carboplatin) + fluorouracil (FU), combination CT with platin (Poly CT + P), combination CT without platin (Poly CT w/o P), single-agent CT (mono CT) including platin. Test for heterogeneity between types of chemotherapy, p=0.02.

Hypferfractionated or accelerated radiotherapy...... Bourhis J, Overgaard J. et., Vol. 368: 843-854; Sep 2, 2006, Lancet
Figure 2

Hypwerfractionated or accelerated radiotherapy…… Bourhis J, Overgaard J. et.,
Vol. 368: 843-854; Sep 2, 2006, Lancet
Table 1: Randomised Trials in Recurrent/Metastatic Squamous Cell Cancer of the Head and Neck

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Regimen</th>
<th>Population</th>
<th>RR(%)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTREME</td>
<td>442</td>
<td>Carbo/CisE vs Carbo/Cis</td>
<td>1st-line</td>
<td>36 vs 20*</td>
<td>10.1 vs 7.4*</td>
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<tr>
<td>ECOG 5397</td>
<td>117</td>
<td>CisE vs Cis</td>
<td>1st-line</td>
<td>26 vs 10*</td>
<td>9.2 vs 8.0**</td>
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<tr>
<td>IMEX</td>
<td>486</td>
<td>Gefitinib 250mg vs gefitinib 500mg vs methotrexate</td>
<td>2nd-line</td>
<td>2.7** vs 7.6 vs 3.9</td>
<td>5.6** vs 6.0 vs 6.7</td>
</tr>
<tr>
<td>ECOG 1302</td>
<td>270</td>
<td>D + Gefitinib vs D</td>
<td>Any line</td>
<td>14** vs 6</td>
<td>6.8** vs 6.0</td>
</tr>
</tbody>
</table>

Carbo/Cis = carboplatin or cisplatin; Cis = cisplatin; D = docetaxel; E = cetuximab; OS = overall survival; RR = response rate.

*p<0.05; **Not statistically significant.