RADIATION & ITS INDICATION

By
Prof S.N. Senapati
H.D.D., Division of Radiation Oncology
A.H. Regional cancer centre, Cuttack

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S.N. Senapati
H.O.D., Division of Radiation Oncology
A.H. Regional cancer centre, Cuttack
Chemotherapy
Surgery
Radiotherapy
TREATMENT OF CANCER
BASED ON MULTIDISCIPLINARY APPROACH

- SURGERY
- RADIATION
- CHEMOTHERAPY
- HORMONAL THERAPY
- IMMUNOTHERAPY
“There Is No ‘I’ In A Team”
PERIPHERAL FAILURE • RADIATION • CENTRAL FAILURE
INDICATION OF RADIATION

- Sequential
- Simultaneous
- Neoadjuvant
- Adjuvant
- Chemoradiation
- Palliative RT
- Prophylactic RT
- Reirradiation
Neoadjuvant Chemotherapy Prior to Radiation

**Pros**
- Tumor size reduction
- Effect on micrometastasis outside radiation field
- Theoretically less toxic concurrent Rx

**Cons**
- Delayed radiation as definite Rx
- Development of resistant clone --> Tumor regrowth
- Residual side effect from chemoRx --> delayed radiation
MODES OF ADMINISTRATION

CT + RT

CT  CT  CT

CT + RT

TUMOR

RT  RT+CT
SYSTEMIC MET

ADJUVANT

NEOADJUVANT

LR CONTROL

LR CONTROL

CONCURRENT

SEQUENTIAL

SIMULTANEOUS

CONCURRENT
ORGANS TO BE DISCUSSED

BRAIN

HEAD & NECK

CERVIX

BREAST
LOW GRADE GLIOMA

LOW DOSE VS HIGH DOSE

EORTC 22844
LOW DOSE Vs HIGH DOSE
EORTC 22844

n = 379 (343 evaluated)
Study period – 1985-91
27 institution 10 countries
Low grade Glioma, supratentorial

Arm A – 45Gy in 5 wks
Vs
Arm B – 59.4Gy in 6.6 wks

RESULT :- Median follow up -74 mo

<table>
<thead>
<tr>
<th></th>
<th>45 Gy</th>
<th>Vs</th>
<th>59.4Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 yrs O.S</td>
<td>59%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>DFS</td>
<td>50%</td>
<td>47%</td>
<td></td>
</tr>
</tbody>
</table>

No survival Advantages
**LOW VS HIGH DOSE**

**NCCTC**

**RTOG**

**ECOG**

<table>
<thead>
<tr>
<th>n = 211 (203 eligible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Study period (1986-94)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm A – 50.4 Gy in 28#</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 101)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm B – 64.8Gy in 36#</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 102)</td>
</tr>
</tbody>
</table>

**Result :-**

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over all 5 yr. survival</td>
<td>72%</td>
</tr>
<tr>
<td>Neuro toxicity ( Gr III to V)</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

No improvement in overall survival

[Numerous citations are mentioned, including Shaw E et al, JCO (2002)20: 2267-76.]
LOW GRADE GLIOMA
LOW Vs HIGH DOSE

• RTOG & EORTC HAVE ADOPTED 54Gy AS STANDARD DOSE FOR LOW GRADE GLIOMA.
Low grade gliomas : Role of RT

Main indications for adjuvant RT

• Subtotal surgical resection
• Substantial risk of residual disease
• Inoperable lesions
• Progressing lesions
• No feasibility of repeat surgical excision
• Follow up compliance : poor
Early post op RT /Deferred RT till Progression

EORTC - 22845

n = 311
Study period -1986-1996
24 institution across Europe

<table>
<thead>
<tr>
<th>Early radiation – 154 pts</th>
<th>Deferred radiation till progression = 157 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>vrs</td>
<td>RT Dose – 54Gy, 1.8Gy/#</td>
</tr>
<tr>
<td>RESULTS:</td>
<td>Median follow up- 7.8 yrs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median progression free survival</th>
<th>PORT</th>
<th>DIFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3 yrs</td>
<td>3.4 yrs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O.S</th>
<th>No difference</th>
</tr>
</thead>
</table>

| Median Survival                  | 7.4 yrs  | 7.2 yrs |

Improvement of progression free survival but No change in survival (Due to better effect of salvage RT)
### RT in Malignant Glioma

#### Study Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Post-operative Radiotherapy</th>
<th>No Post-operative</th>
<th>Risk Ratio for 1-year Mortality (Random Effects)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Total</td>
<td>Deaths</td>
<td>Total</td>
</tr>
<tr>
<td>Shapiro, 1976 (62)</td>
<td>12</td>
<td>17</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Andersen, 1978 (1)</td>
<td>44</td>
<td>51</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Walker, 1978* (78)</td>
<td>52</td>
<td>68</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Walker, 1980 (79)</td>
<td>74</td>
<td>118</td>
<td>82</td>
<td>111</td>
</tr>
<tr>
<td>Kristiansen, 1981 (36)</td>
<td>51</td>
<td>80</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Sandberg-Wollheim, 1991 (60)</td>
<td>34</td>
<td>84</td>
<td>50</td>
<td>87</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>267</td>
<td>418</td>
<td>264</td>
<td>340</td>
</tr>
</tbody>
</table>

* Only results for the evaluable patients were reported.

#### Graph

- **Study**:
  - 1 Shapiro 1976
  - 2 Andersen 1978
  - 3 Walker 1978
  - 4 Walker 1980
  - 5 Kristiansen 1981
  - 6 Sandberg 1991

- **Overall**:
  - 759

- **Risk Ratio**:
  - 0.81

- **95% CI**:
  - 0.74 to 0.88

- **Overall Risk Ratio**:
  - 0.81 (95% CI, 0.74 to 0.88; p<0.0001)

---

*Laperriere N
Radiother Oncol’02*
GBM: Stewart Meta-analysis
Chemotherapy yields a small survival benefit

Meta-analysis, n=3004
[Lancet, 2002] RT vs RT/CT:
1-yr survival = 40% vs 46%
Chemotherapy in Adult High-Grade Glioma: Meta-Analysis

  – Individual patient data
  – 3004 patients, 12 randomized controlled trials (RT + chemotherapy *versus* RT)
  – Hazard ratio: 0.85 (.78-.91, *p*<0.001)
    • 15% relative decrease in risk of death
    • 6% increase in 1-year survival (40% to 46%)
    • 5% increase in 2-year survival (15% to 20%)
    • 2 month increase in median survival
**Radiation Dose with Conventionally# RT**

**Stenning SP, Br J Cancer’91**
- 45 Gy, 20#
- 60 Gy, 30#
- 443 pts
- 3 mths increase in median surv in 60 Gy arm \[p < 0.007\]

**Nelson DF, RTOG 7401**
- 60 Gy WBRT
- 60 Gy WBRT + 10 Gy boost
- 60 Gy + BCNU
- 60 Gy + semustine + DTIC
- 626 pts
- No stat sig difference in surv in 4 arms
- Med.Surv = 9.3 mo in 60Gy Vs 8.2 in 70 Gy

**Lapaerriere N**
- Radiother Oncol’02:64,259-73
**RT Volume: RCTs**

*Shapiro et al., Arch Neurol’76*

571 Pts

- **RANDOMISE**
  - 60.2 Gy, WBRT
  - 43 Gy WBRT + 17.2 Gy boost (pre-RT enhanced Tm vol + 2 cm margin)

No stat sig difference in survival in both arms

*Kita et al., Gan No Rinsho’89*

- **RANDOMISE**
  - 40 Gy/20# WBRT f/b 18 Gy/9# boost = 23 pts
  - 56 Gy/28# Focal RT = 26 pts

No stat sig difference in survival rate

*Laperriere N Radiother Oncol’02:64,259-73*
Concomitant & Adjuvant \textit{TMZ}+RT : RCT

EORTC&NCIC Clinical Trials Groups

Stupp R 40\textsuperscript{th} ASCO Annual Meeting June’04

573 pts GBM

RT=60 Gy,30#,2 Gy/#

RT+TMZ

Concomitant-75mg/m2/d x 42 days

6# adj TMZ=150-200mg/m2/d x 5daysq28d

<table>
<thead>
<tr>
<th></th>
<th>RT (n=286)</th>
<th>RT/TMZ (n=287)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range) [years]</td>
<td>56.6 (23.1-70.8)</td>
<td>55.7 (19-70.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor resection</td>
<td>70%</td>
<td>68%</td>
<td>NS</td>
</tr>
<tr>
<td>WHO PS : 0 / 1 / 2</td>
<td>39% / 49% / 12%</td>
<td>39% / 48% / 13%</td>
<td>NS</td>
</tr>
<tr>
<td>Steroids at baseline</td>
<td>75%</td>
<td>67%</td>
<td>p=0.041</td>
</tr>
<tr>
<td>Progr.-free surv. (95% c.i.)</td>
<td>5.0 mo (4.2-5.5)</td>
<td>7.2 mo (5.8-8.3)</td>
<td>p&lt; .0001</td>
</tr>
<tr>
<td>Median survival (95% c.i.)</td>
<td>12 mo (11.2-13.2)</td>
<td>15 mo (13.6-16.8)</td>
<td>p&lt; .0001</td>
</tr>
<tr>
<td>2-year survival (95% c.i.)</td>
<td>8% (4-12%)</td>
<td>26% (20-32%)</td>
<td>p&lt;.0001</td>
</tr>
</tbody>
</table>
CT + RT TERMOZOLAMIDE (EORTC)

n = 573
G.B.M. 85 Institution median age -65

Arm A – RT (n = 286)
Arm B – RT + Canc Tm₂ + adj Tm₂ (n=287)
CT-
Canc Tm₂ - 75mg/m² (maxm – 49 days)
Adj Tm₂ - 200mg/m² 6 cycles (at 28 days int)
RESULT –
Median follow up 28 mo

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT+Tm²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median over all survival</td>
<td>12.1m0</td>
<td>14.6 mo</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2 yr O.S</td>
<td>10.4%</td>
<td>26.5%</td>
<td></td>
</tr>
<tr>
<td>Median time to progression</td>
<td>5.6 mo</td>
<td>6.9 mo</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug related toxicity</td>
<td>0%</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>

SURVIVAL BENEFIT
HIGH GRADE GLIOMA
ISSUES

• DOES POST OP RADIATION IMPROVES THE SURVIVAL: - **YES. STANDARD OF CARE**
• WHAT SHOULD BE THE DOSE OF RADIATION: - **60GY**
• WHETHER WHOLE BRAIN OR FOCAL RADIATION: - **NO WHOLE BRAIN RT**
• WITH DOSE ESCALATION SURVIVAL IMPROVES: - **NO**
• POST OP RADIATION + CHEMOTHERAPY DOES IT IMPROVES THE SURVIVAL: - **YES**
Head & Neck Cancer

Heterogeneous group of tumor.

Significance:

- Different anatomical site :-
  Different tumor kinetics, different biological behavior.
- Proliferation of cells not similar in all sites.
- Treatment outcome:- Differs.
General guidelines for selecting a treatment modality:

• Stage I / II disease - Single modality (Surgery or RT)

• Stage III & IV disease -- Combined modality
  Surgery + Radiotherapy (In most patients),
  Chemotherapy + radiotherapy (In selected patients)

When different modalities are available, the modality that gives *maximum chance of cure* should be used. When different modalities have similar results, a modality that gives *better quality of life, with organ / voice preservation, Functional and cosmetic results is preferred*.
**SURGERY VS RADIOThERAPY**

**Surgery is preferred over radiotherapy as a single modality in**
1. Young patients - due to high incidence of second primary
2. Sub mucous fibrosis
3. Lesions involving or close to bone - to prevent radionecrosis.
4. Sites where surgery is not morbid (cosmetically and functionally)

**RT is preferred over surgery as a single modality, where**
1. Severe impairment of function / cosmesis with surgery.
2. Surgery has high morbidity and poor results e.g. nasopharyngeal carcinoma.
3. Patient refuses surgery / high risk of surgery
Criteria of Unresectability:

Primary disease:
- Adequate surgical clearance is not achievable
- Extensive InfraT emporal Fossa involvement
- Extensive involvement of base skull
- Extensive soft tissue disease: skin oedema/ulceration.

Nodal Disease:
- Clinically fixed nodes
- Infiltration of Internal /Common carotid artery
- Extensive infiltration of prevertebral muscles, skull base.

Radiotherapy:
External beam radiotherapy and/or brachytherapy are used either as a single modality or as a part of multi-modality treatment. Radiotherapy is used in 3 different settings:

- Radical curative radiotherapy (Alone/combn.with C.T)
- Post-operative adjuvant radiotherapy
- Palliative radiotherapy
Indications for Brachytherapy (BRT):

- Accessible lesions
- Small (preferably < 3cm) tumours
- Lesions away from bone
- N0 nodal status
Tumour suitable for brachytherapy

- T1-2 N0: Radical BRT: 60-70Gy Low Dose Rate 192Iridium
  Or equivalent doses with fractionated high dose rate.

- T1-3 N0-1: External RT: 56-60Gy/28-30#/6 wks
  Boost BRT: Low dose rate 192Iridium: 15-20Gy or
  High Dose Rate: 14Gy in 4 fractions over 2 days (4-3-3-4 Gy)

Tumours not suitable for brachytherapy:

- T1-4 N0-2: Concomitant Chemoradiation: 66-70Gy/33-35#/6-7
  wks + concomitant weekly Cisplatinum, 30mg/m2 for 6-7 wks
  Or

- External RT: 66-70Gy/33-35#/6-7 wks (reducing fields)
Digital reconstructed radiograph (DRR) levels I–VI. CTV, clinical target volume.
MANAGEMENT OF NECK NODE

SURGERY

RADIATION

T1-4,NO

T-RT  N-ENRT

T1-4,N1

T-RT  N-RT  N-RT-S

TXN1

RT TO NPX, OROPHARYNX
PATIENT IN WHOM THE PRIMARY LESION TO BE TREATED BY RADIATION, WHO HAVE CLINICALLY-VE NODES AND WHOM THE RISK OF SUBCLINICAL DISEASE IS 20% OR GREATER, USUALLY RECEIVE ELECTIVE NECK RT OF 45-50 Gy

- OROPHARYNX, NASOPHARYNX, SUPRAGLOTTIC LARYNX AND HYOPHARYNX-LOWER NECK NODE WITH SINGLE ANT FIELD
IN +VE NECK NODE

- ADVANCED DISEASE HAS BETTER CHANCE OF CURE WITH ALTERED # CONCOMITANT RT

<table>
<thead>
<tr>
<th>NODE SIZE</th>
<th>DOSE OF RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 cm, MOBILE</td>
<td>50 GY</td>
</tr>
<tr>
<td>5-6 cm, FIXED</td>
<td>60 GY</td>
</tr>
<tr>
<td>7-8 CM</td>
<td>70-75 GY</td>
</tr>
</tbody>
</table>

TIME OF SURGERY: 4-6 WKS AFTER RT. INITIAL REGRESSION IS SLOW. MUCH REGRESSION AT 4-6 WKS
CERVICAL L.N METASTASIS WITH UNKNOWN PRIMARY

UPPER NECK NODE METASTASIS:-PROGNOSIS BETTER THAN LOWER NECK
ADENO CA.OF NECK NODE, PRIMARY:-BELOW THE CLAVICLE
IF UPPER NECK:-SALIVARY GLAND, PARATHYROID, THYROID
DIAGNOSIS:-CLINICAL EXAMINATION, DL BIOPSY, NEEDLE BIOPSY, CT, MRI, FDG PET

• TREAT INVOLVED AREA OF NECK
• RT TO NASOPHARYNX, OROPHARYNX, BOTH SIDE OF NECK
• ORAL CAVITY, LARYNX AND HYPOPHARYNX TO BE EXCLUDED
HEAD AND NECK CANCERS

Early
- Sx
- RT

Advanced
- Resectable
  - CT
  - Sx
  - RT
- Unresectable
  - CT
  - RT

CT

CISPLATIN

Sx
RT

CT

5FU
Bm
CDDP
Mtx
HU
Ifos
SURGERY Vs S+RT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Ipsilat neck failure (No –N₃b)</th>
<th>Contralat neck failure (No –N₃b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>51/199 (25.6%)</td>
<td>35/130 (27%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>54/292 (18.5%)</td>
<td>7/172 (4%)</td>
</tr>
<tr>
<td>Combined</td>
<td>8/105 (7.8%)</td>
<td>3/85 (3%)</td>
</tr>
</tbody>
</table>


(Post operative RT eliminated subclinical disease after surgery in both Ipsilat neck as well as Contralat neck)

But no comment on survival.
Resectable Head & Neck Cancer
Pre Vs Post op RT
RTOG 73 - 03

Estimated 4 yr Locoregional control percentage by Rx & Region

<table>
<thead>
<tr>
<th>Site</th>
<th>Pre op (%)</th>
<th>Post op (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>40</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>47</td>
<td>61</td>
<td>54</td>
</tr>
<tr>
<td>Supraglottic Larynx</td>
<td>53</td>
<td>77</td>
<td>64</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>50</td>
<td>61</td>
<td>55</td>
</tr>
<tr>
<td><strong>All Regions</strong></td>
<td><strong>48</strong></td>
<td><strong>65</strong></td>
<td><strong>57</strong></td>
</tr>
<tr>
<td>For 194 pts who</td>
<td>56</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>competed planned t/t</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Post of radiation is the standard of care*
Risk stratification in post op setting in H&N Cancer

**HIGH RISK FACTORS**: Extracapsular Extension Of Nodal Disease
≥2 of the following factors
- Oral cavity site
- Microscopically positive mucosal margins
- Nerve invasion
- ≥ 2 involved neck nodes
- > 1 positive nodal group
- Node size>3 cm

**INTERMEDIATE RISK FACTOR**: No ECE
One of the above risk factor

**LOW RISK FACTOR**: None of the above factor
Disease-Specific Survival
Vs Risk factors in Ca. Oral cavity

- T1: 94%, P<0.0001
  - T2: 76%
  - T3: 66%
  - T4: 58%

- N0: 84%
- N1: 58%
- N2, 3: 46%

- I: 94%
- II: 86%
- III: 66%
- IV: 58%

- Well diff.: 84%
- Mod. diff.: 72%
- Poor diff.: 67%

- Positive: 82%
- Negative: 57%

- <2mm: 80%
- 2.1-8mm: 96%
- >8mm: 64%

P<0.0001
**Depth of Invasion**

| DOI          | <2 mm  
n=60 | 2.1-8 mm 
n=190 | >8 mm  
n=187 |
<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Occult Metastasis</td>
<td>2%</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>Overall pN+</td>
<td>5%</td>
<td>27%</td>
<td>45%</td>
</tr>
</tbody>
</table>
**Fukano et al.** 34 pts,
For tumor thickness
- <5mm, 1/17 : 5.8%,
- >5mm, 11/17 : 64.7%,
- <3mm, no cervical LN, p=0.0003

**Shah et al:** depends on relation of the thickness of primary tumor with cervical nodal mets
- 2 mm or less : 13%
- 2-9 mm : 46%
- >9mm : 65%

**Bayers et al:** SCC of tongue, T1 to T4 with clinical node-ve
- <4mm depth : 31%
- 4-8mm : 47%
- >8mm : 76% p= 0.0001
FIGURE 30.1-3. Probability of having no local recurrence, accord-

Negative margins

Positive margins

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

Number at risk

0 2 4 6 8 10 12 13 24

Months

Probability of not having a local recurrence

1
- Early Disease (Stage I, II) - Monotherapy
  Surgery or Radio-therapy

NOOOOOOOOOOOOOOOOOOOO
Risk factor & Radiation Dose

• ECE the single most independent variable
• 2/more risk factors are associated with higher risk of recurrence
• No adverse surgical-pathologic features: No PORT .5yr LRC and survival 90% & 83% with surgery alone.
• One adverse feature & ECE – 57.6 Gy 5yr LRC-94%
• Highrisk (ECE, 2/more adv. Features) – 63 Gy 5yr LRC – 68%

## CONCURRENT CT RT IN HIGH RISK PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>#pt</th>
<th>F/U</th>
<th>LC</th>
<th>LRC (CTRT Vs RT)</th>
<th>DFS (CTRT Vs RT)</th>
<th>Survival (CTRT Vs RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9501 [31]</td>
<td>459</td>
<td>46 month median</td>
<td>Not reported</td>
<td>80% vs 68%</td>
<td>33% vs 25%</td>
<td>42% vs 36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$P = 0.003$</td>
<td>$p = 0.04$</td>
<td>$P = 0.19$</td>
</tr>
<tr>
<td>EORTC 22931 [30]</td>
<td>334</td>
<td>60 month median</td>
<td>Not reported</td>
<td>82% vs 69%</td>
<td>47% vs 36%</td>
<td>53% vs 40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$P = 0.007$</td>
<td>$p = 0.04$</td>
<td>$P = 0.02$</td>
</tr>
<tr>
<td>Bachaud (1996) [29]</td>
<td>83</td>
<td>5 year minimum</td>
<td>84% vs 59%</td>
<td>Not reported</td>
<td>68% vs 44%</td>
<td>72% vs 46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$P = 0.05$</td>
<td>$P &lt; 0.02$</td>
<td>$P &lt; 0.01$</td>
</tr>
</tbody>
</table>

CDDP-100MG/M2 AT 3 WEEKS INTERVAL
EBRT:-66Gy
• The survival benefit seen in CT & RT arm are due to Improved loco regional control

• 10% IMPROVEMENT IN 2YR LOCOREGIONAL CONTROL IS PREDICTED TO LEAD TO 6.7% 5YRS INCREASE IN OVERALL SURVIVAL (Wadsley et al, IJROBP-2004)

• Cisplatinum based concurrent chemo-radiation should be considered for high risk pts that are medically able to tolerate concurrent CT
Time factor in PORT setting.

- **Timing:** within 6wks of Post OP.
- **Duration of Rx Vs 5yrs acturial LRC**
  - $< 11$ wks – 5yrs LRC-76%
  - 11-13 WKS – 62%
  - $> 13$ WKS – 38%

Ang KK 51: 571-78, 2001
Treatment strategy in post op Head & Neck Cancer

- Low Risk → No adv. Factor − Obs
- Int Risk → One risk factor
  No ECI − RT
- High Risk → 2 risk factor
  & ECI − CT+RT. Alt#
NEOADJUVANT CT

- DECREASES THE TUMOR BURDEN
- CONTROL MICROSCOPIC SYSTEMIC DISEASES
- RESPONDER TO NEOADJUVANT CT RESPONDS TO SUBSEQUENT RADIATION
Recent Randomized Trials of Induction Chemotherapy followed by Locoregional Treatment versus Locoregional Treatment Alone

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Chemotherapy</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin (234)</td>
<td>1990</td>
<td>75</td>
<td>FP</td>
<td>No difference</td>
</tr>
<tr>
<td>Jortay (235)</td>
<td>1990</td>
<td>187</td>
<td>VBM</td>
<td>No difference</td>
</tr>
<tr>
<td>Richard (236)</td>
<td>1991</td>
<td>222</td>
<td>VB(IA)</td>
<td>Advantage:</td>
</tr>
<tr>
<td>Mazeron (237)</td>
<td>1991</td>
<td>131</td>
<td>FPBM</td>
<td>No difference</td>
</tr>
<tr>
<td>Jaulerry (238)</td>
<td>1992</td>
<td>100</td>
<td>PBVdMi</td>
<td>No difference</td>
</tr>
<tr>
<td>Jaulerry (238)</td>
<td>1992</td>
<td>108</td>
<td>FPVd</td>
<td>No difference</td>
</tr>
<tr>
<td>Tejedor (239)</td>
<td>1992</td>
<td>42</td>
<td>CpFt</td>
<td>No difference</td>
</tr>
<tr>
<td>Depondt (240)</td>
<td>1993</td>
<td>324</td>
<td>FCp</td>
<td>No difference</td>
</tr>
<tr>
<td>Di Blasio (241)</td>
<td>1994</td>
<td>69</td>
<td>FP</td>
<td>Advantage: standard</td>
</tr>
</tbody>
</table>
Tax 324: Response

<table>
<thead>
<tr>
<th>Chemotherapy and CRT</th>
<th>TPF (N=255)</th>
<th>PF (N=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall RR [95%CI]</td>
<td>77% [70.8 - 81.5]</td>
<td>72% [65.5 - 77.1]</td>
</tr>
<tr>
<td>Complete RR [95%CI]</td>
<td>35% [29.4 - 41.5]</td>
<td>28% [22.5 - 34.1]</td>
</tr>
</tbody>
</table>

Tax 324 Survival: ITT Population

<table>
<thead>
<tr>
<th></th>
<th>TPF - 255</th>
<th>PF - 246</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (Mo) 95% CI</td>
<td>70.6 ± 49 - NR</td>
<td>30.1 ± 20.9 - 51.5</td>
</tr>
<tr>
<td>Died *</td>
<td>41%</td>
<td>53%</td>
</tr>
<tr>
<td>KM Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - Year</td>
<td>80% [75.0 - 84.9]</td>
<td>69% [64.1 - 75.7]</td>
</tr>
<tr>
<td>2 - Year</td>
<td>67% [61.5 - 73.2]</td>
<td>54% [48.2 - 60.8]</td>
</tr>
<tr>
<td>3 - Year</td>
<td>62% [55.9 - 68.2]</td>
<td>48% [41.7 - 54.5]</td>
</tr>
</tbody>
</table>

| Hazard Ratio TPF:PF [95% CI] | 0.70 [0.54 - 0.90] |
| Log-Rank p Value             | 0.0058             |

*Cut-off: December 3, 2006; The Median Follow-Up is 42 Months
Current Data for Induction Chemotherapy

- Pignon, et al. Meta-analyses: 63 randomized trials
- Results:
  - Significant benefit to chemotherapy (10% reduction in hazard ratio of death, 4% absolute advantage in survival at 2 and 5 years)
  - CCR: clear benefit
  - ICT: no statistically significant benefit in survival and locoregional control (LRC)
    - Exception: patients receiving cisplatin and 5FU
    - Significantly different from other regimens

Conclusion: Induction Chemotherapy

- **CCRT** with platinum agents is standard of care
  - Meta-analysis favors either high dose cisplatin q 3 weeks or 2 agents in a weekly regimen.
- Sequential IC followed by CCRT vs. CCRT must be examined since a definitive survival advantage has not been demonstrated.
- If IC is used, TPF is better than PF; however, other regimens should be examined which may be less toxic, easier to administer and potentially more effective
Efficacy of radiation therapy and concurrent chemotherapy in Head & Neck cancer

<table>
<thead>
<tr>
<th></th>
<th>French Trial (n = 226)</th>
<th>P</th>
<th>German Trial (n = 270)</th>
<th>P</th>
<th>Nasopharynx Intergroup Trial (n = 193)</th>
<th>P</th>
<th>Duke University Trial (= 116)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local control rate %</td>
<td>66 v 42</td>
<td>--</td>
<td>35 v 17</td>
<td>&lt;.004</td>
<td>NR</td>
<td>--</td>
<td>70 v 44</td>
<td>.006</td>
</tr>
<tr>
<td>Disease-free survival rate, %</td>
<td>42 v 19</td>
<td>.002</td>
<td>NR</td>
<td>-</td>
<td>69 v 24</td>
<td>&lt;.001</td>
<td>60 v 40</td>
<td>.07</td>
</tr>
<tr>
<td>Survival rate %</td>
<td>51 v 31</td>
<td>.003</td>
<td>49 v 24</td>
<td>&lt;.0003</td>
<td>78 v 47</td>
<td>.005</td>
<td>42 v 28</td>
<td>.05</td>
</tr>
<tr>
<td>Mucositis rate %</td>
<td>67 v 36</td>
<td>-</td>
<td>38 v 16</td>
<td>&lt;.001</td>
<td>NR</td>
<td>-</td>
<td>77 v 75</td>
<td>-</td>
</tr>
</tbody>
</table>
### Randomized Trials of Concurrent Multiagent Chemotherapy and Radiotherapy versus Radiotherapy in Stage III and IV Disease

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>No. of Patients</th>
<th>Study Population</th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
<th>Local Regional Control (P)</th>
<th>Survival (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keane, 1993 (299)</td>
<td>212</td>
<td>Larynx and hypopharynx</td>
<td>MMC, 5-FU</td>
<td>50 Gy, split</td>
<td>40% vs. 40%</td>
<td>40% vs. 40%</td>
</tr>
<tr>
<td>Zakotnik, 1998 (300)</td>
<td>64</td>
<td>Unresectable</td>
<td>MMC, Bleo</td>
<td>66-70 Gy</td>
<td>75% vs. 29% (.007)</td>
<td>38% vs. 10% (.019)</td>
</tr>
<tr>
<td>Adelstein, 1999 (301,302)</td>
<td>100</td>
<td>Resectable</td>
<td>Cisplatin, 5-FU</td>
<td>60 Gy, split</td>
<td>7% vs. 45% (&lt;.001)</td>
<td>42% vs. 34% (.01)</td>
</tr>
<tr>
<td>Calais, 1999 (303)</td>
<td>226</td>
<td>Oropharynx</td>
<td>Carbo, 5-FU</td>
<td>70 Gy</td>
<td>66% vs. 42% (.03)</td>
<td>51% vs. 31% (.02) (3-y)</td>
</tr>
<tr>
<td>Merlano, 1996 (304)</td>
<td>157</td>
<td>Unresectable</td>
<td>Cisplatin, 5-FU</td>
<td>60-70 Gy</td>
<td>64% vs. 32% (.38)</td>
<td>24% vs. 10% (.01) (5-y)</td>
</tr>
<tr>
<td>(alternating)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adelstein, 2000 (305)</td>
<td>295</td>
<td>Unresectable</td>
<td>Cisplatin</td>
<td>70 Gy</td>
<td>57% vs. 20% (.016) (3-y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wendt, 1998 (306)</td>
<td>270</td>
<td>Unresectable</td>
<td>Cisplatin, 5-FU, L</td>
<td>70 Gy, b.i.d., split</td>
<td>36% vs. 17% (&lt;.004)</td>
<td>48% vs. 24% (&lt;.0003) (3-y)</td>
</tr>
<tr>
<td>Brizel, 1998 (307)</td>
<td>116</td>
<td>Resectable and unresectable</td>
<td>Cisplatin, 5-FU</td>
<td>70-75, Gy b.i.d.</td>
<td>70% vs. 44% (.01)</td>
<td>55% vs. 37% (.07) (3-y)</td>
</tr>
</tbody>
</table>
Status of Con. CT &RT

Metaanalysis

• Absolute Survival benefit at 5 yrs 8%
• CDDP alone is as good as Poly chemotherapy
• Effect of Chemotherapy decreases with Age
• Significant toxicity.
CONCLUSION - Concurrent CTRT

- RT+CT (concurrent) : LRC, DFS, OS
- MONOCHEMOTHERAPY using Cisplatinum seems give better overall result
- No consensus regarding optimal radiation - dose fractionation
- Acute toxicities with use of concurrent CT & RT is high, so can considered IMRT
- Recommended as standard of care in Locally advanced H&N cancer.
NEOADJUVANT CT

OUTCOME VERSUS TOXICITY (CONCURRENT CTRT)

DISTANT METASTASIS

TOXICITY
- LOCAL CONTROL

NO IMPROVEMENT OF OVERALL SURVIVAL

SURVIVAL
Meta-Analysis of Chemotherapy in H&N Cancer (MACH-NC)

- Analyzed 63 randomized trials, 1965 - 1993
- Locoregional Rx +/- chemotherapy
- Updated individual patient data
- Total of 10,741 patients

## Chemotherapy in Advanced Head & Neck Cancer—Overall Survival

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Absolute Risk Reduction</th>
<th>Benefit 5Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>1%</td>
<td>2+/-7%</td>
</tr>
<tr>
<td>Neo Adjuvant</td>
<td>2%</td>
<td>5+/-3%</td>
</tr>
<tr>
<td>Concomitant</td>
<td>8%</td>
<td>19+/-3%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4%</td>
<td>11+/-2%</td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGE

■ S+RT IS THE ACCEPTED MODALITIES OF TREATMENT IN ADVANCED HEAD & NECK CANCER

■ ORGAN PRESERVATION :- CT + RT CAN BE TRIED

■ CONCOMITTANT CT+ RT IS BETTER IN TERMS OF SURVIVAL THAN NEOADJUVANT CT.

■ MULTI AGENT CT CAN BE TRIED IN CONCOMITTANT SETTING

■ HIGH RISK POST OP SETTING CAN CONSIDER CT + RT FOR BETTER LOCOREGIONAL CONTROL

■ RECURRENT CA CAN TRY REIRRADIATION + CT
CARCINOMA CERVIX
FIGO Staging System (clinical)

- Stage I: confined to the cervix
  - IA  microscopic only (IA1 <3mm/IA2 <5mm)
  - IB  visible lesion or microscopic > IA
  - IB1  < 4cm diameter
  - IB2  >4cm diameter

- Stage II: beyond cervix but not to pelvic sidewall.
  - IIA  extension to upper 2/3 vagina (no parametrial involvement)
  - IIB  extension into parametria

- Stage III: IIIA lower 1/3 vagina
  - IIIB  extension to pelvic sidewall, hydronephrosis

- Stage IV: IVA  invades bladder or rectal mucosa
  - IVB  distant metastases

Lymph node involvement ↑ with Stage. Nodal involvement is not part of staging system.
STAGE Ib & Ila TREATMENT

Wertheim’s Hysterectomy
Or
Radical radiation therapy
(Ext + Brachy)

Choice of treatment determined by age, menopausal status, ovarian preservation, co-morbid conditions, patient’s wish & availability of expertise in surgery & RT

(NIH Guidelines 1997)
Risk Stratification (GOG Guidelines)

Deep stromal invasion
Large tumor diameter (>4 cm)
LVSI

Intermediate risk (Any two)

Positive nodes
Positive surgical margins
Positive parametria

High risk (Any one)
### Stage Ib/IIa Impact of Lymph node Metastases

<table>
<thead>
<tr>
<th></th>
<th>Survival(%)</th>
<th>Relapse(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.N -Ve</td>
<td>95.8 %</td>
<td></td>
</tr>
<tr>
<td>L.N +Ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>63.5%</td>
<td>32%</td>
</tr>
<tr>
<td>P.A</td>
<td>40.8%</td>
<td>57%</td>
</tr>
<tr>
<td>Pelvis+PA</td>
<td>18.4%</td>
<td>73.7%</td>
</tr>
</tbody>
</table>
## Early Stage Carcinoma Cervix
### Intermediate Risk: Role of Adjuvant Therapy

GOG 92: RCT (*Gynae Oncol* 73; 177-183: 1999)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Adj RT N = 140</th>
<th>Adj RT N = 137</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yr RFS</td>
<td>79%</td>
<td>88%</td>
<td>.008</td>
</tr>
<tr>
<td>2 yr OAS</td>
<td>79%</td>
<td>87%</td>
<td>.008</td>
</tr>
<tr>
<td>Pelvic rec</td>
<td>21%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Dist mets</td>
<td>7%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Risk of Recurrence reduced by 44% (RR 0.56, p=0.019). Mortality reduced by 36% (p=0.005). ADJUVANT PELVIC RT IS BENEFICIAL
# Early Stage Carcinoma Cervix

**High Risk: Role of Adjuvant Therapy**

**Intergroup 0107 RCT Trial (Gynae Oncol 73; 177-183: 1999)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PORT N = 116</th>
<th>POSTOPCT+RT N = 127</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4yr RFS</td>
<td>63%</td>
<td>80%</td>
<td>0.01</td>
</tr>
<tr>
<td>4yr OAS</td>
<td>71%</td>
<td>81%</td>
<td>0.01</td>
</tr>
<tr>
<td>Pelvic rec</td>
<td>17%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Distant mets</td>
<td>11%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Pelvic+ distant</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

**CHEMO-RADIATION SHOULD BE STANDARD OF CARE**

“**Grade A**”

**Defined a specific subgroup of patients with intermediate risk factors who are benefited from pelvic RT though at cost of increased toxicity**
A re-analysis of SWOG 8797
benefit of PO concurrent CRT

limited to those with

• Tumors > 2 cm,
• > 2 positive LN,
• Parametrial extension

STAGE Ib & IIa

WARTHIEMS HYSTERECTOMY

BULKY DISEASE :-RT/CT RT

LOW RISK
- OBSERVATION

INT. RISK
- RADIATION

HIGH RISK
- CHEMORADIATION
STAGE IIB, IIIIB

Concomitant
chemo radiation (weekly cisplatin)/Radical Radiation
Five major randomized phase III trials show that platinum based chemo when given concurrently with RT prolongs survival in women with locally advanced cervical cancer stages Ib2 - IVa as well as in women with stage I / IIa found to have metastatic pelvic lymph nodes, positive parametrial disease and positive surgical margins at the time of primary surgery.
Concurrent Chemoradiation
Results of Meta-analyses

Cochrane Collaborative Group (19 Trials) (4580 patients)

*Green JA et al Lancet 358;781 (Sept. 2001)*

- 19 RCTs between 1981 and 2000: 4580 randomized patients
- Increase in OAS by 12% & RFS by 16% (absolute benefit) (p=0.0001)
- Greater benefit in patients in stages IB2 and IIB
- Decrease in local and systemic recurrence (p=0.0001)

Update in July 2005: 21 trials and 4921 pts
- Similar findings (absolute benefit: 10%)
- Test for Heterogeneity: Positive
- No data on late toxicities

Green et al meta-analysis on concurrent chemoradiation: *update*

Review strongly suggests that concomitant chemoradiation improves OS and DFS whether or not platinum was used with absolute benefits of 10% and 13% respectively.

*Cochrane Database Syst Rev, 2005;Jul 20: (3)*
Chemoradiation in Advanced Carcinoma Cx
Results of Meta-analyses

Canadian Group (9 Trials) - 4 year survival data

*Lukka et al, Clinical Oncology 14;203(June 2002)*

❖ **Cisplatin based Concomitant Chemo-radiation**

❖ **Significant improvement in Overall Survival**
  - Advanced Stages (Only 30% tumors)
  - Bulky IB tumors (prior to surgery)
  - High risk early disease (post-surgery)

❖ **Toxicites** Acute Grade 3/4 Hematological and G.I
  significantly higher : all short lived

  2 deaths due to the toxicities

  No significant late toxicities seen

“Grade A”
CANADIAN STUDY

A CLINICAL Trial comparing Concurrent Cisplatinum & Radiation Vs Radiation alone for locally advanced Squamous Cell carcinoma of The cervix carried out by the National Cancer Institute of Canada Clinical trials Group


N=259

Stage III-Iva;32%

Cisplatinum

RT+CT Vs RT 0.90(0.63-1.29)

No benifit
Long term follow up of Potentiation of Radiotherapy by Cisplatinum in Advanced Cervical Cancer


N=64
Stage IIIA_IIB:30%
Cisplatinum
RT+CT Vs RT; -1.04 (0.58-1.87)
No benefit
TAKE HOME MESSAGE

Early stages
Post op RT - Intermediate risk group
Post op CT+RT :- High risk group
Concurrent chemoradiation - Bulky stage Ib/Iia
Neoadjuvant CT+ Surgery + RT- Still investigational
Locally Advanced
Concurrent chemoradiation
Radiation Therapy in Breast Cancer
TNM Grouping and Staging

**EBC**
- **Stage I**
  - T1*, N0, M0
- **Stage IIA**
  - T0, N1, M0
  - T1*, N1, M0
  - T2, N0, M0
- **Stage IIB**
  - T2, N1, M0
  - T3, N0, M0

**LABC**
- **Stage IIIA**
  - T0, N2, M0
  - T1*, N2, M0
  - T2, N2, M0
  - T3, N1, M0
  - T3, N2, M0
- **Stage IIIB**
  - T4, N0, M0
  - T4, N1, M0
  - T4, N2, M0
- **Stage IIIC**
  - Any T, N3, M0

**MBC**
- **Stage IV**
  - Any T, Any N, M1
INDICATIONS

• RADIATION TO INTACT BREAST- BCT

• POST MASTECTOMY

• PALLIATIVE RADIATION
Common Treatment Protocols

- Early breast cancer
  - (Stage & II):

- Locally advanced Breast cancer
  - (Stage IIIA & IIIB):

BCT

NON BCT

III A

III B

IV

Surgery
WBRT
Chemotherapy
Hormonal Th

Surgery
RT
Chemotherapy
Hormonal Th

Surgery
CT
LRRT
Hormonal Th

MRM
Chemotherapy
LRRT
Hormonal Th

MRM
CT
LRRT
Hormonal Th

Operable
Inoperable

CT
MRM
CT
LRRT
Hormonal Th

CT
RT
CT
Hormonal Th

PALLIATION

Early breast cancer
- (Stage & II):

Locally advanced Breast cancer
- (Stage IIIA & IIIB):
INDICATION OF RADIATION IN BREAST CANCER

- **Indications of Radiotherapy in EBC**
  - **BCT** - Radiotherapy forms an integral part of BCT
  - **Post Mastectomy Radiotherapy**
  - **Chest wall irradiation** - 1. Positive margins
    2. T3 tumors
    3. 4 or more + LN in axilla
    4. Unknown status
  - **Axillary irradiation** - 1. 4 or more + LN in axilla
    2. Extranodal disease
    3. Inadequate axillary dissection
    4. Unknown axillary status
PORT in High-Risk Premenopausal Women with Breast Cancer Who Receive Adjuvant Chemotherapy

1789 patients, 1982 – 1989, premenopausal, node + or Tumor > 5cm, M0
Total mastectomy, level I + II (partly) + CMF +/- 50Gy/25fx (electrons + photons)
Sx in 79 departments, RT in mainly 6 centres

Conclusions: The addition of postoperative irradiation to mastectomy and adjuvant chemotherapy reduces locoregional recurrences and prolongs survival in high-risk premenopausal women with breast cancer.
Adjuvant Radiotherapy and Chemotherapy in Node-Positive Premenopausal Women with Breast Cancer

**Conclusions:** Radiotherapy combined with chemotherapy after modified radical mastectomy decreases rates of locoregional and systemic relapse and reduces mortality from breast cancer.
Post Operative RT

- **Fletcher** showed the benefits of postoperative LRRT in reducing the nodal recurrence from 20% to <5%, and the chest wall recurrence from 30% to <10%.
Early Breast Cancer

All RCTs confirmed equivalence of BCT to Mastectomy

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Survival (Median FU)</th>
<th>Local Recurr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI Milan 1973-80</td>
<td>701 (13 yrs)</td>
<td>69%</td>
<td>4%</td>
</tr>
<tr>
<td>NSABP-06 1976-84</td>
<td>1444 (12 yrs)</td>
<td>62%</td>
<td>10%</td>
</tr>
<tr>
<td>EORTC 1980-86</td>
<td>903 (7 yrs)</td>
<td>75%</td>
<td>13%</td>
</tr>
<tr>
<td>Danish 1983-87</td>
<td>905 (6 yrs)</td>
<td>82%</td>
<td>3%</td>
</tr>
</tbody>
</table>
## Selected Randomized Trials of Breast-conserving Surgery with or without Radiation

<table>
<thead>
<tr>
<th>Study</th>
<th>T, N</th>
<th>No. of Patients</th>
<th>Follow-Up (yrs)</th>
<th>LR With RT(%)</th>
<th>LR Without RT (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al.</td>
<td>&lt;4 cm node positive/negative</td>
<td>930</td>
<td>10</td>
<td>12.4</td>
<td>40.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Liljegren et al.</td>
<td>&lt;2 cm node negative</td>
<td>381</td>
<td>10</td>
<td>8.5</td>
<td>24.0</td>
<td>.0001</td>
</tr>
<tr>
<td>Veronesi et al.</td>
<td>&lt;2.5 cm</td>
<td>579</td>
<td>10</td>
<td>5.8</td>
<td>23.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clark et al.</td>
<td>&lt;2 cm node negative</td>
<td>837</td>
<td>3</td>
<td>5.5</td>
<td>25.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fisher et al.</td>
<td>&lt;2 cm node negative</td>
<td>1,009</td>
<td>8</td>
<td>2.8</td>
<td>16.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Winzer et al.</td>
<td>&lt;2 cm node negative</td>
<td>347</td>
<td>5.9</td>
<td>3.2</td>
<td>27.8</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
## BCS Vs BCS+RT

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>LOCAL REC</th>
<th>LOCAL REC.</th>
<th>5 YRS.SURV</th>
<th>5YRS.SURV</th>
<th>FOLLOW UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILAN</td>
<td>S</td>
<td>S+RT</td>
<td>S</td>
<td>S+RT</td>
<td>18</td>
</tr>
<tr>
<td>NSABP</td>
<td>10</td>
<td>8</td>
<td>63</td>
<td>59</td>
<td>12</td>
</tr>
<tr>
<td>SWEDISH</td>
<td>18</td>
<td>2</td>
<td>90</td>
<td>91</td>
<td>08</td>
</tr>
<tr>
<td>ONTARIO</td>
<td>29</td>
<td>7</td>
<td>85</td>
<td>87</td>
<td>15</td>
</tr>
<tr>
<td>SCOTLAND</td>
<td>16</td>
<td>6</td>
<td>77</td>
<td>75</td>
<td>10</td>
</tr>
</tbody>
</table>
Tumor Bed Boost
EORTC data

- BCT for stage I and II breast cancer
- RT to whole breast 50Gy/25#/5wks

Randomized

(2657 pts) (2661 pts)
no boost additional 16Gy/8# boost

5 yr actuarial rates of local recurrence
7.3% 4.3%
p<0.001

Local recurrences in <40 yrs group
19.5% 10.2%
p=0.002

*NEJM 2001 vol 345, no 19, 1378-1387*
### Boost to the tumor bed
Comparison of electron vs implant

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrons</th>
<th>Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of pts</td>
<td>10 yr DFS</td>
</tr>
<tr>
<td>Fourquet et al</td>
<td>129</td>
<td>68%</td>
</tr>
<tr>
<td>Mansfield et al</td>
<td>416</td>
<td>78%</td>
</tr>
<tr>
<td>Perez et al</td>
<td>490</td>
<td>79%</td>
</tr>
<tr>
<td>Recht et al</td>
<td>79</td>
<td>-</td>
</tr>
<tr>
<td>Touboul et al</td>
<td>160</td>
<td>85%</td>
</tr>
</tbody>
</table>
Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

EBCTCG Lancet 2005; 366: 2087-2106
EBCTCG RESULTS

<table>
<thead>
<tr>
<th>Year started</th>
<th>Study name</th>
<th>RT sites</th>
<th>Events/woman-years</th>
<th>BCS + RT events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Logrank Variance BCS + RT : BCS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT sites</td>
<td>BCS + RT</td>
<td>BCS</td>
<td>O-E</td>
</tr>
<tr>
<td>1976</td>
<td>NSABP B-06</td>
<td>BW</td>
<td>125/6862</td>
<td>285/4991</td>
<td>-93.2</td>
</tr>
<tr>
<td>1981</td>
<td>Uppsala-Örebro</td>
<td>BW</td>
<td>10/1636</td>
<td>43/1511</td>
<td>-17.7</td>
</tr>
<tr>
<td>1982</td>
<td>St George's London</td>
<td>BW</td>
<td>12/1202</td>
<td>31/1047</td>
<td>-11.5</td>
</tr>
<tr>
<td>1984</td>
<td>Ontario COG</td>
<td>BW +5</td>
<td>19/2478</td>
<td>50/2005</td>
<td>-25.1</td>
</tr>
<tr>
<td>1987</td>
<td>INT Milan 3</td>
<td>BW +5</td>
<td>6/1810</td>
<td>40/1729</td>
<td>-17.3</td>
</tr>
<tr>
<td>1989</td>
<td>NSABP B 21</td>
<td>BW</td>
<td>33/3718</td>
<td>92/3429</td>
<td>-30.8</td>
</tr>
</tbody>
</table>

(a) Subtotal

5-year risk

(b) Radiotherapy to conserves breast and other sites

<table>
<thead>
<tr>
<th>Year started</th>
<th>Study name</th>
<th>RT sites</th>
<th>Events/woman-years</th>
<th>BCS + RT events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1982</td>
<td>St George's London</td>
<td>BW + AD</td>
<td>25/8/220</td>
<td>40/625</td>
<td>0.31 (SE 0.04), 2p&lt;0.00001</td>
</tr>
<tr>
<td>1985</td>
<td>Scottish</td>
<td>BW</td>
<td>3/112</td>
<td>4/288</td>
<td>0.32 (SE 0.06), 2p&lt;0.00001</td>
</tr>
<tr>
<td>1985</td>
<td>West Midlands, UK</td>
<td>BW</td>
<td>20/1000</td>
<td>23/1489</td>
<td>0.31 (SE 0.03), 2p&lt;0.00001</td>
</tr>
</tbody>
</table>

Addition of RT to BCS significantly reduces the risk of local recurrence by about 70% compared to BCS only.
**Breast cancer mortality (deaths/women)**

<table>
<thead>
<tr>
<th>Year started and study name</th>
<th>RT sites</th>
<th>Allocated BCS+RT</th>
<th>Allocated BCS</th>
<th>BCS+RT deaths</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Logrank 0-E</td>
<td>Variance of 0-E</td>
</tr>
<tr>
<td>(a) Radiotherapy only to conserved breast: 14% node positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976 NSABP B-06</td>
<td>BW*</td>
<td>267/731</td>
<td>305/719</td>
<td>-19.7</td>
<td>135.0</td>
</tr>
<tr>
<td>1981 Uppsala-Orebro</td>
<td>BW</td>
<td>37/184</td>
<td>34/197</td>
<td>2.3</td>
<td>16.8</td>
</tr>
<tr>
<td>1982 St George's London</td>
<td>BW*</td>
<td>24/128</td>
<td>25/122</td>
<td>-25</td>
<td>10.9</td>
</tr>
<tr>
<td>1984 Ontario COG</td>
<td>BW+S</td>
<td>91/416</td>
<td>123/421</td>
<td>-16.4</td>
<td>51.5</td>
</tr>
<tr>
<td>1987 INT Milan 3</td>
<td>BW+S*</td>
<td>40/294</td>
<td>51/273</td>
<td>-6.2</td>
<td>21.3</td>
</tr>
<tr>
<td>1989 NSABP B-21</td>
<td>BW</td>
<td>8/337</td>
<td>8/336</td>
<td>0.5</td>
<td>3.9</td>
</tr>
<tr>
<td>1991 Swedish BCCG</td>
<td>BW</td>
<td>32/593</td>
<td>41/594</td>
<td>-39</td>
<td>18.0</td>
</tr>
<tr>
<td><strong>(a) Subtotal</strong></td>
<td></td>
<td>499/77</td>
<td>587/7</td>
<td>-45.8</td>
<td>604.85</td>
</tr>
<tr>
<td>15-year risk</td>
<td></td>
<td>2683</td>
<td>2662</td>
<td>28.0%</td>
<td>33.2%</td>
</tr>
<tr>
<td>(b) Radiotherapy to conserved breast and other sites: 24% node positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1982 St George's London</td>
<td>BW+AF*</td>
<td>2/33</td>
<td>2/33</td>
<td>0.81</td>
<td>0.08</td>
</tr>
<tr>
<td>1985 Scottish</td>
<td>BW+S+(AF)+IBS</td>
<td>37/3</td>
<td>37/3</td>
<td>0.83</td>
<td>0.05</td>
</tr>
<tr>
<td>1985 West Midlands, UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1986 CRC, UK</td>
<td>Van</td>
<td>753/3</td>
<td>889/3</td>
<td>-72.7</td>
<td>382.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3673</td>
<td>3638</td>
<td>30.5%</td>
<td>35.9%</td>
</tr>
<tr>
<td><strong>(b) Subtotal</strong></td>
<td></td>
<td>796</td>
<td>-26.9</td>
<td>125.3</td>
<td></td>
</tr>
</tbody>
</table>

**Heckman test between 11 strata:** $\chi^2_{11}=3.8; p=0.96$

- **BCS Plus RT significantly reduces the risk of death as compared to BCS only.**
- **Addition of RT to BCS reduces the risk of mortality by about 17%.**
Accelerated Partial Breast Irradiation (APBI)

After Wide Excision of Lump & appropriate axillary surgery, irradiation of the tumour bed with 1-2 cm margins using a regime of accelerated RT (shortened course & with larger dose per fraction)
Why partial breast irradiation?

The vast majority of the recurrence (up to 90%) occurs in the index quadrant. Only 1% to 3% recurrence occurs in other quadrant.

-- U. Veronesi (Milan III)

Treatment is focused to area of highest risk of residual occult disease/recurrence.

---

T1 & T2 INVASIVE DUCTAL CARCINOMA SELECTED FOR BREAST CONSERVING SURGERY
N=217; Holland et al 1985

- Probability of Tumour Foci
- Distance from Index Cancer
## Patient Selection Criteria

<table>
<thead>
<tr>
<th></th>
<th>ABS (^1)</th>
<th>ASBS(^2)</th>
<th>William Beaumont Hospital (^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&gt;45</td>
<td>&gt;50</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Histology</td>
<td>Unifocal, IDC</td>
<td>IDC or DCIS</td>
<td>IDC</td>
</tr>
<tr>
<td>Tumor size</td>
<td>(\leq 3\text{cm})</td>
<td>(\leq 2\text{cm})</td>
<td>(\leq 2\text{cm})</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>Negative</td>
<td>Negative &gt; 2mm</td>
<td>Negative</td>
</tr>
<tr>
<td>Nodal status (Axillary/ sentinel)</td>
<td>N0</td>
<td>N0</td>
<td>N0</td>
</tr>
<tr>
<td>Cavity to skin distance</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;5 mm</td>
</tr>
</tbody>
</table>

Accelerate Dose

- The smaller tissue volume allows larger fraction sizes and thereby shorter overall treatment time
- Hypo-fractionation schedule decreases the time period
- Radiobiological modeling predicted safety of various dose fractionation schedules
  - 34Gy/10 fr/5 days BD equivalent to 50 Gy
  - 20Gy to 22 Gy Single fraction = 55Gy to 60 Gy
The Options for APBI

Interstitial Implant

MammoSite

TARGIT

Intra op electrons [ELIOT]

3DCRT / IMRT
INDICATION OF RADIATION

**BRAIN**
- Low grade: 54 Gy
- High grade: 60 Gy
- Focal RT
- RT+TMZ

**HEAD AND NECK**
- Low risk: OBS
- Intermediate risk: PORT
- High risk: CTRT
- Neoadjuvant CT: No survival adv.
- Conc CTRT: Survival adv.

**BREAST**
- BCS: S+EBRT+BOOST
- Post MRM

**CERVIX**
- Early stages
- Post op RT – Intermediate risk group
- Post op CT+RT: High risk group
- Concurrent chemoradiation – Bulky stage Ib/Iia
- Locally Advanced
- Concurrent chemoradiation

**TAKE HOME MESSAGE**
- Curative, palliative/prophylactic

- ...
THANK YOU
CONCURRENT CT WITH ALTERED FRACTION RADIATION
Table 40:5
INDICATIONS FOR POST-OP RADIOTHERAPY

Primary:
- Large primary - T4 or T3 with soft tissue infiltration
- Close or positive margins of excision
- Deep infiltrative tumour
- High grade tumour
- Lympho-vascular and perineural invasion

Lymph nodes:
- Bulky nodal disease N2 / N3
- Extra nodal extension
- Multiple level involvement

Post-operative radiotherapy:
- Primary and nodal disease: 50 - 60 Gy/25-30 fr/5-6 weeks, using reducing fields.
- Site of residual disease, positive cut margins: 4-10 Gy Boost
MAXILLARY ANTRUM

- Post-operative Radiation
- T4 tumors
- High grade T3 tumors
- Adenoid cystic carcinoma
- Microscopically positive margins
- Presence of perineural invasion
- Multiple positive nodes or extra- capsular spread
- Multiple levels of node involvement
Larynx

Postoperative Radiation (indication)
- close / +ve Margin
- soft tissue extrn of the primary to neck
- endothelial lined space invasion
- cartilage and perineural invasion
- multiple +ve nodes
- extranodal extension
- subclinical disease at opposite neck
TREATMENT STRATEGY NPX

- STAGE I,II:- RADIATION
- STAGE III,IVB:- CHEMORADIATION
## Concurrent Primary Chemoradiation

(Multi drug)

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Study</th>
<th>CT</th>
<th>Local % Control</th>
<th>Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zakotnik'98</td>
<td>64</td>
<td>unresectable</td>
<td>MMC, Bleo</td>
<td>75 vs 29</td>
<td>38 vs 10</td>
</tr>
<tr>
<td>Adelstein'99</td>
<td>100</td>
<td>resectable</td>
<td>Cisplat, 5FU</td>
<td>77 vs 45</td>
<td>42 vs 34</td>
</tr>
<tr>
<td>Calais'99</td>
<td>226</td>
<td>oropharynx</td>
<td>Carbo, 5FU</td>
<td>66 vs 42</td>
<td>51 vs 31</td>
</tr>
<tr>
<td>Merlano'96</td>
<td>157</td>
<td>unresectable</td>
<td>Cisplat, 5FU</td>
<td>64 vs 32</td>
<td>24 vs 10</td>
</tr>
<tr>
<td>Adelstein'00</td>
<td>295</td>
<td>unresectable</td>
<td>Cisplat, 5FU</td>
<td></td>
<td>29 vs 20</td>
</tr>
<tr>
<td>Wendt'98</td>
<td>270</td>
<td>unresectable</td>
<td>Cisplat, 5FU</td>
<td>36 vs 17</td>
<td>48 vs 24</td>
</tr>
<tr>
<td>Brizel'98</td>
<td>116</td>
<td>Resectable &amp;</td>
<td>Cisplat, 5FU</td>
<td>70 vs 44</td>
<td>55 vs 37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>unresectable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HEAD & NECK CANCER

MULTIDISCIPLINARY APPROACH
TREATMENT PROTOCOL IN HEAD & NECK CANCER
T1 / Selected T2 N0:
- Radiotherapy alone with or without Intraluminal Brachytherapy
- Bulky T2 & T3-4 N0 / Any T N+
- Neo Adjuvant CT 2 cycles + Concurrent CT + RT
- Close or positive margins
- Lymph node metastasis
- Adenoid cystic carcinoma
- High or intermediate grade tumours
- Deep lobe tumours
- Preop facial nerve paralysis
- Lymphatic or vascular invasion or perineural involvement
- Recurrent tumours
Margin directed boost..

- N =509; Stage I & II Ca breast.
- Post-lumpectomy, re-excision when margin< 2 mm.
- WBRT -50Gy, followed by e- boost.
- Median f/u – 121 mths.
- No boost when no residual on re-excision (LR-6%).

<table>
<thead>
<tr>
<th>Final margin status</th>
<th>+ve</th>
<th>0-2 mm</th>
<th>2-5 mm</th>
<th>&gt; 5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boost dose</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>14 Gy</td>
<td>10 Gy</td>
</tr>
<tr>
<td>LR (12 yrs)</td>
<td>17%</td>
<td>9%</td>
<td>5%</td>
<td>0</td>
</tr>
</tbody>
</table>