Clinical aspects and implications of Chemo-radiation

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**Radiation**: Major treatment modality for loco-regional disease control in cancer

**Rate of failure** is still high due to –

a) Large tumour size

b) Advanced stage of disease
Advances in Radiation Oncology

A. Technical innovations

Introduction of conformal radiation e.g. 3DCRT, IMRT, IGRT or SBRT can deliver higher doses of radiation to tumour and lower doses to the normal tissues thereby increasing therapeutic ratio but little effect on local control and survival however decrease in radiation morbidity

B. Modulation of biological response –

a) Altered fractionation regimens.

b) Chemo-radiation

i) Combined modality treatment by chemical and biological agents.

ii) Targeting molecular processes and signal pathways
Chemo - radiation

1. Chemo-radiation perhaps has strongest impact on cancer radiation therapy practice.

2. Chemo-radiation has become common treatment option in many clinical settings which is particularly true of concurrent chemo-radiation.

3. Chemo-radiation is superior to radiation alone for local control of disease and also for improving survival.
Biological basis of Chemo-radiation

1. Chemotherapy drugs reduces number of tumour cells by their cytotoxic activity.

2. Renders tumor cells more susceptible to radiation therapy – Radio sensitization effect.

3. By virtue of systemic activity of chemotherapy drugs, may act on distant metastasis.

Goals of Chemo-radiation

1. To improve survival by improving local control.
2. To decrease or eliminate distant metastasis.
3. To preserve organ & tissue integrity as well as function.
4. To have independent toxicity.
5. To enhance tumour radio response.
Combinations of Chemo-radiation

1. Sequential Chemo radiation
2. Concurrent Chemo radiation
3. Concurrent Chemo radiation and adjuvant chemotherapy
4. Induction or Neo-adjuvant chemotherapy and Concurrent Chemo-radiation
## Advantages and disadvantages of different combinations

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.Sequential Chemo-radiation</td>
<td>• Least toxic</td>
<td>• Increased treatment time</td>
</tr>
<tr>
<td></td>
<td>• Maximize systemic therapy</td>
<td>• Lack of local synergy</td>
</tr>
<tr>
<td></td>
<td>• Smaller radiation fields if induction shrinks tumour</td>
<td></td>
</tr>
<tr>
<td>2.Concurrent Chemo-radiation</td>
<td>• Shorter treatment time</td>
<td>• Compromise systemic therapy</td>
</tr>
<tr>
<td></td>
<td>• Radiation enhancement</td>
<td>• Increases toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No cytoreduction of tumour</td>
</tr>
<tr>
<td>3.Concurrent Chemo-radiation &amp; Adjuvant</td>
<td>• Maximize systemic therapy</td>
<td>• Increased toxicity</td>
</tr>
<tr>
<td>chemotherapy</td>
<td>• Radiation enhancement</td>
<td>• Increased treatment time</td>
</tr>
<tr>
<td></td>
<td>• Both local and distant therapy delivered upfront</td>
<td>• Difficulty to complete chemotherapy after chemo-radiation</td>
</tr>
<tr>
<td>4.Induction or Neo-adjuvant chemotherapy and</td>
<td>• Maximize systemic therapy</td>
<td>• Increased toxicity</td>
</tr>
<tr>
<td>concurrent chemo-radiation</td>
<td>• Radiation enhancement</td>
<td>• Increased treatment time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Difficult to complete chemo-radiation after induction chemotherapy</td>
</tr>
</tbody>
</table>
Indications for Chemo-radiation

1. Lung cancer-SCLC & NSCLC
2. Head & Neck cancer
3. Carcinoma Cervix
4. Carcinoma urinary bladder
5. Carcinoma Anal Canal
6. Carcinoma Oesophagus
7. Carcinoma Rectum
8. Glioblastoma Multiforme
Drugs for Chemo-radiation

1. Platinum based drugs:
   a) Cisplatin
   b) Carboplatin

2. Taxanes:
   a) Paclitaxel
   b) Docetaxel

3. Mitomycin C

4. Antimetabolites:
   a) 5-Flurouracil
   b) Methotrexate
   c) Gemcitabine

5. Topoisomerase:
   a) Irinotecan
   b) Topotecan
HEAD AND NECK
CHEMORADIATION IN CA NASOPHARYNX

• NPC is highly radiosensitive and chemosensitive tumour.

• High rate of local-regional failure and distant dissemination in advanced disease.

• 5-year survival rate $\sim 35\%$ for stage III-IV disease with radiation therapy alone.

• Main objective of using chemotherapy in locally advanced NPC is to potentially enhance the radiation therapy local control rate and reduce the incidence of distant failure in high-risk patients.
“Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized INTERGROUP STUDY

Concurrent chemo-Rt: Cisplatin (100mg/m²) on day 1, 22, 43{3 weekly} in + RT (70Gy/35#)

followed by

Adjuvant chemotherapy: Cisplatin (80mg/m²) and 5FU(1gm/m²) on days 71, 99 and 127{3 weekly}

3-year survival rate for patients randomized to radiotherapy was 46%, and for the chemo-Rt group was 76% (P < .001)
# Results of Chem-oradiation in Ca.Nasopharynx

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>RT</td>
<td>193</td>
<td>284</td>
<td>350</td>
<td>222</td>
<td>221</td>
<td>348</td>
</tr>
<tr>
<td>CT-Cisplatin</td>
<td>70 Gys</td>
<td>70-74 Gys</td>
<td>66 Gys</td>
<td>62-68 Gys</td>
<td>70 Gys</td>
<td>68 Gys</td>
</tr>
<tr>
<td>Adjuvant CT</td>
<td>100mg x3 3wks</td>
<td>80mg x2 4wks</td>
<td>40mg x6-8 weekly</td>
<td>Weekly 6-7</td>
<td>25mg d1-4 weekly</td>
<td>100mg x3 3wks</td>
</tr>
<tr>
<td>D.F.S. -%</td>
<td>58 vs 29</td>
<td>72 vs 53</td>
<td>60 VS 52</td>
<td>69 vs 58</td>
<td>72 vs 53</td>
<td>72 vs 53</td>
</tr>
<tr>
<td>O.S.-%</td>
<td>67 vs 37</td>
<td>72 vs 53</td>
<td>70 vs 59</td>
<td>87 vs 77</td>
<td>80 vs 65</td>
<td>78 vs 78</td>
</tr>
</tbody>
</table>

Local control-%

D.F.S. -%

O.S.-%
Meta analysis of chemotherapy with radiation in ca nasopharynx

<table>
<thead>
<tr>
<th>Timing of chemo/Trial</th>
<th>Deaths/Patients</th>
<th>Hazard Ratio (Chemo/Control)</th>
<th>Risk Redn. (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemo</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>(a) Induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWH – 88</td>
<td>15/37</td>
<td>13/40</td>
<td>1.8 6.9</td>
</tr>
<tr>
<td>AOCCOA</td>
<td>54/167</td>
<td>55/167</td>
<td>−0.3 27.2</td>
</tr>
<tr>
<td>VUMGA – 89</td>
<td>94/171</td>
<td>93/168</td>
<td>−0.2 46.7</td>
</tr>
<tr>
<td>Japan – 91</td>
<td>17/40</td>
<td>20/40</td>
<td>−2.5 9.2</td>
</tr>
<tr>
<td>■ subtotal (a)</td>
<td>180/415</td>
<td>161/415</td>
<td>−1.2 90.1</td>
</tr>
<tr>
<td>(b) Concurrent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INT 0095</td>
<td>42/97</td>
<td>66/96</td>
<td>−20.3 26.2</td>
</tr>
<tr>
<td>PWH-QEH – 94</td>
<td>60/174</td>
<td>73/178</td>
<td>−10.6 33.1</td>
</tr>
<tr>
<td>QMH – 95Conc</td>
<td>12/56</td>
<td>11/55</td>
<td>0.2 5.7</td>
</tr>
<tr>
<td>QMH – 95Conc+</td>
<td>9/57</td>
<td>17/54</td>
<td>−5.3 6.4</td>
</tr>
<tr>
<td>■ subtotal (b)</td>
<td>123/384</td>
<td>167/381</td>
<td>−36.1 71.4</td>
</tr>
<tr>
<td>(c) Adjuvant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCOG – 94</td>
<td>35/80</td>
<td>42/78</td>
<td>−2.4 19.2</td>
</tr>
<tr>
<td>QMH – 95Adj</td>
<td>17/54</td>
<td>11/55</td>
<td>3.5 7</td>
</tr>
<tr>
<td>QMH – 95Adj+</td>
<td>9/57</td>
<td>12/56</td>
<td>−2 5.2</td>
</tr>
<tr>
<td>■ subtotal (c)</td>
<td>61/181</td>
<td>65/189</td>
<td>−0.9 31.4</td>
</tr>
<tr>
<td>■ total (a ... c)</td>
<td>364/990</td>
<td>413/985</td>
<td>−38.1 192.9</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $X^2 = 19.9, \ P = 0.03$

Concurrent chemotherapy showed maximum benefit
Absolute survival benefit of 6% at 5 yrs.

Concomitant trials showed a better treatment effect than induction trials or adjuvant trials.

CONCLUSION:
“The addition of chemotherapy to standard RT provides a small, but significant, survival benefit in patients with ca nasopharynx and hence chemoradiation is the standard of care.”

- n=332

64% retain larynx

Equivalent survival for both groups
Concurrent chemoradiation showed maximum benefit 6.5% at 5 yrs

No major benefit from induction and adjuvant chemotherapy

MACH-NC (Pignon et al; updated in 2009)
Benefit of chemotherapy based on patient characteristics

Better P.S - Better results

Locally advanced cancers - Better results

Best results with Ca Oropharynx

Most significant factor was ‘Age’

Decreasing benefit of chemotherapy on survival with Increasing age.
Benefit of chemotherapy based on chemotherapeutic agent

PLATINUM BASED COMBINATIONS SHOWED MAXIMUM BENEFIT

CISPLATIN AS SINGLE AGENT SHOWED MAXIMUM BENEFIT

Test for heterogeneity: $\chi^2_1 = 1.69$, $p = 0.19$
Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D.,


- Cetuximab: initial dose of 400 mg/m² followed by 250mg/m² weekly with radiotherapy

![Graphs showing locoregional control and overall survival with Radiotherapy plus cetuximab compared to Radiotherapy alone.](graphs.png)

**LOCOREGIONAL CONTROL**

**OVERALL SURVIVAL**

HR=0.68  
HR=0.74
CANCER CERVIX
<table>
<thead>
<tr>
<th>Author</th>
<th>Trial</th>
<th>No.</th>
<th>Investigational Arm</th>
<th>Control Arm</th>
<th>Tumor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keys 1999</td>
<td>GOG 123</td>
<td>369</td>
<td>RT+ Cisplatin Surgery</td>
<td>RT alone Surgery</td>
<td>Stage IB (≥ 4cm)</td>
<td>Combined with Surgery</td>
</tr>
<tr>
<td>Peters 2000</td>
<td>SWOG 8797</td>
<td>243</td>
<td>Surgery RT+Cisplatin+5FU</td>
<td>Surgery RT alone</td>
<td>IA2, IB, IIA (with postop high risk)</td>
<td>Combined with Surgery</td>
</tr>
<tr>
<td>Morris &amp; Eifel 1999 &amp;.2004</td>
<td>RTOG 9001</td>
<td>388</td>
<td>RT+Cisplatin+5FU</td>
<td>Extended-field RT</td>
<td>IB or IIA (≥5cmorPLN+) IIB, III, IVA</td>
<td>Surgical staging for PALN</td>
</tr>
<tr>
<td>Whitney 1999</td>
<td>GOG 85</td>
<td>368</td>
<td>RT+Cisplatin+5FU</td>
<td>RT+ Hydroxyurea</td>
<td>IIB, III, IVA</td>
<td>Surgical staging for PALN</td>
</tr>
<tr>
<td>Rose 1999</td>
<td>GOG 120</td>
<td>526</td>
<td>RT+Cisplatin + 5FU + Hydroxyurea</td>
<td>RT+ Hydroxyurea</td>
<td>IIB, III, IVA</td>
<td>Surgical staging for PALN</td>
</tr>
<tr>
<td>Pearcey 2002</td>
<td>NCIC</td>
<td>253</td>
<td>RT+Cisplatin</td>
<td>RT alone</td>
<td>IB2, IIA(≥5cm), IIB, III, IVA</td>
<td>No surgical staging for PALN</td>
</tr>
</tbody>
</table>
Reduction in the risk of death from six chemoradiation clinical trials in cervix cancer
“based on significant improvement in both progression–free survival and overall survival when cisplatin–based chemotherapy was given concurrently with radiotherapy”

“. . . strong consideration should be given to the incorporation of concurrent cisplatin–based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer.”
META-ANALYSIS OF THE RANDOMISED TRIALS

Green JA, et al Lancet. 2001 Sep 8;358

TRIALS WITH PLATINUM
- Whitney^{10}
- Tseng^{20}
- Morris^{8}
- Peters^{13}
- Keys^{7}
- Rose^{9}
- Pearcey^{12}
- Leborgne^{†}

TRIALS WITHOUT PLATINUM
- Non-platinum
- Hernandez^{27}
- Wong (1999)^{11}
- Roberts^{14}

Subtotal

Total

Chemoradiation improves overall survival
(Hazard Ratio 0.71, p<0.0001)
Cisplatin-based concurrent chemoradiation showed improvement in terms of:

- Locally Advanced Disease
- Bulky Stage IB Disease
- Post-op High Risk in Early Stages
META-ANALYSIS OF THE RANDOMISE TRIALS

- Absolute **survival benefit of 12%**
- Absolute increase **in P.F.S by 13%**
- Significant impact **on both local and distant recurrences**
- **Greater benefit** in trials with **early stage** patients (IB2 and IIB)
- Most striking finding was **highly significant reduction of distant metastasis** in the chemo-radiation group.
In conclusion chemo-radiation is Standard of Care in all stages of Carcinoma Cervix at present
CARCINOMA
ANAL CANAL
Combined Therapy for Cancer of the Anal Canal: A Preliminary Report

Norman D. Nicro, M.D.,† V. K. Vaitkevicius, M.D.,‡ Basil Considine, Jr., M.D.§

From Wayne State University, School of Medicine, Detroit, Michigan

Report of Three Cases

Pre-op 30 Gy @ 1.8 Gy/# + 5 FU and mitomycin

The lesions in all three patients reported here disappeared following the preoperative therapy.
“complete histological remission led to a treatment strategy of **definitive radiochemotherapy**, reserving **surgery** as a **salvage** procedure for patients with persistent or relapsing tumors”
Three randomised trials showing benefit of chemo-RT

<table>
<thead>
<tr>
<th>EORTC</th>
<th>Radiotherapy</th>
<th>Radiotherapy + 5-FU + MMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible patients</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>T1-T2 N0</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>T1-T2 N+</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>T3-T4 N0</td>
<td>48%</td>
<td>45%</td>
</tr>
<tr>
<td>T3-T4 N+</td>
<td>32%</td>
<td>39%</td>
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</table>

<table>
<thead>
<tr>
<th>UKCCCR</th>
<th>Radiotherapy</th>
<th>Radiotherapy + 5-FU + MMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible patients</td>
<td>218</td>
<td>213</td>
</tr>
<tr>
<td>T1</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>T2</td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td>T3</td>
<td>40%</td>
<td>41%</td>
</tr>
<tr>
<td>T4</td>
<td>11%</td>
<td>15%</td>
</tr>
<tr>
<td>N+</td>
<td>17%</td>
<td>23%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RTOG/ECOG</th>
<th>Radiotherapy + 5-FU</th>
<th>Radiotherapy + 5-FU + MMC</th>
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</thead>
<tbody>
<tr>
<td>Eligible patients</td>
<td>145</td>
<td>146</td>
</tr>
<tr>
<td>T1</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>T2</td>
<td>35%</td>
<td>42%</td>
</tr>
<tr>
<td>T3</td>
<td>42%</td>
<td>33%</td>
</tr>
<tr>
<td>T4</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>N0</td>
<td>82%</td>
<td>83%</td>
</tr>
<tr>
<td>N+</td>
<td>17%</td>
<td>17%</td>
</tr>
</tbody>
</table>
EORTC TRIAL

Locoregional control
\( p = 0.02 \) (log rank test)

- 18% better local control at 5 yrs (\( p=0.02 \))

Colostomy-free interval
\( p = 0.002 \) (log rank test)

- 36% increased colostomy free survival at 5 yrs (\( p=0.002 \))
UKCCR TRIAL

DECREASED LOCAL FAILURE FROM 61% TO 39% IN CMT ARM.

NO DIFFERENCE IN OVERALL SURVIVAL 58% RT vs 65% CMT
RTOG STUDY

- Importance of mitomycin C within the chemotherapy regimen
- Difference in local control more pronounced for T3/T4 tumors
- Hematologic toxicity, ‘neutropenic sepsis’ deaths in mitomycin C arm.
U.S. GI Intergroup RTOG 9811

Evaluated the role of **cisplatin** in chemoradiation regime

Hence chemo-radiation is standard of care in Carcinoma Anal Canal
Carcinoma Oesophagus
## Treatment Options in Ca. Esophagus

<table>
<thead>
<tr>
<th>Modality</th>
<th>L. C.</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Surgery alone</td>
<td>-</td>
<td>26 – 40 % 2 Yrs.</td>
</tr>
<tr>
<td>2. Radiation alone</td>
<td>-</td>
<td>11 – 21 % 2 Yrs.</td>
</tr>
<tr>
<td>3. Post operative Radiation</td>
<td>Improved</td>
<td>Effect unclear</td>
</tr>
<tr>
<td>4. Pre-operative radiation plus Surgery</td>
<td>-</td>
<td>10 – 35 % 5 Yrs.</td>
</tr>
<tr>
<td>5. Pre-operative Chemotherapy plus Surgery</td>
<td>-</td>
<td>No benefit</td>
</tr>
<tr>
<td>6. Neo-adjuvant Chemotherapy plus Radiation</td>
<td>-</td>
<td>No benefit</td>
</tr>
<tr>
<td>7. Chemo-radiation alone</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>8. Chemo-radiation plus Surgery</td>
<td>Improved</td>
<td>Unclear but increased toxicity</td>
</tr>
</tbody>
</table>
Chemo-radiation in Ca. Esophagus

RTOG Phase III Trial in Locally Advanced Ca. Esophagus

Chemo-radiation vs Radiation alone

(Al-sarraf, M et al, 1997)

Regimen: RT – 50 Gys in 25 Fractions or 64 Gys in 32 Fractions

CT: 5-F.U. 1000mg/M2 in 96 hrs.

Inj Cisplatin: 75mg/m2 day 1

Chemo every 4 wks during RT and every 3 wks afterwards

RESULTS:

5 Years Overall Survival - 26% vs 0%

Local Failure - 45% vs 68%

Grade 4 toxicity - 20% in CRT arm including death

Standard of care for locally advanced carcinoma Esophagus
## Pre-operative Chemo-radiation vs Surgery alone in Ca. Esophagus

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Path CR</th>
<th>Median F.U. (Yrs.)</th>
<th>3 Yrs Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urb,2001</td>
<td>5-FU +CP +45GYS.</td>
<td>50</td>
<td>28%</td>
<td>8.2</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>-</td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>Bosset,1997</td>
<td>CP + 37 Gys.</td>
<td>143</td>
<td>20%</td>
<td>4.6</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>138</td>
<td>-</td>
<td></td>
<td>36%</td>
</tr>
<tr>
<td>Walsh.1996</td>
<td>5-F.U.+ CP+40 Gys.</td>
<td>58</td>
<td>22%</td>
<td>1.5</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>-</td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Burmeister, 2005</td>
<td>5-F.U.+ CP+35Gys.</td>
<td>128</td>
<td>16%</td>
<td>5.4</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>128</td>
<td>-</td>
<td></td>
<td>31%</td>
</tr>
<tr>
<td>Tepper,2006</td>
<td>5-F.U.+ CP+50 Gys.</td>
<td>30</td>
<td>40%</td>
<td>6.0</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>-</td>
<td></td>
<td>16%</td>
</tr>
</tbody>
</table>
Chemo-Radiation plus Surgery in Ca. Esophagus

French study by Bedenne.I et al., 2007

Total Patients
445 (Scc or Adeno)

Regimen: 5-F.U. + CP + RT 46 Gys in 4.5 wks or 30 Gys in 2 wks

259 patient with PR – Randomized to Surgery or further
Chemoradiation to a total dose of 66 Gys.

Results:
1. 2 years survival - 34% vs 40%
2. Death rate – 9% vs 1%
3. Patients with surgery had worst quality of life.

In conclusion addition of surgery does not enhances survival and complication rate is high.
Chemo-Radiation plus Surgery in Ca. Esophagus

German Study by Stahl M. et al., 2005

Total patients – 172

Induction CT - 5FU=Etoposide+CP x 3 cycles followed by Concurrent CP+Etoposide+ 40 Gys.

Randomized to either Surgery or further Chemoradiation up to total dose of 60-65 Gys.

Results:

1. Local control – 64% vs 41%
2. 2 years survival – 31% vs 24%
3. 3 years survival – 18% vs 9%
4. Hospital mortality -11% vs 0%
5. Over all Mortality – 13% vs 3.5%

Increased local control but no significant effect on survival
Neo-adjuvant Chemo-radiation in Resectable Carcinoma Esophagus

Limitations of Studies

1. All the studies were under powered
2. Used unconventional radiation regimens
3. Unbalanced treatment arms
4. Results were conflicting

Do not accept pre-operative chemo-radiation outside the clinical trials
Contra-indications for Chemo-radiation

1. Low general condition

2. Elderly person

3. Deranged renal functions

4. Affordability
CONCLUSIONS

1. Chemoradiation has become standard of care in many cancers more so if locally advanced with emphasis on concurrent chemoradiation.

2. Increased tumour control have been achieved in most of cancers so treated but survival has also increased in some with agents e.g. Cisplatin and 5 F.U.

3. Cure rates of majority of tumors still remain poor however addition of chemotherapy is frequently associated with significant normal tissue toxicity.

4. There is a considerable room for improvement however, selection of drugs or optimal treatment approach remains a significant challenge.
Future Directions

1. Use of drugs which interfere with one or more radioresistance mechanism e.g. Taxanes, nucleosides analogues and topomerases.

2. Those drugs that have high potential for increasing therapeutic effectiveness of radiation and need evaluation.

3. Studies of mechanism of chemotherapy-radiation interaction at the level of genetic-molecular, cellular and tumor or normal tissue microenvironmental levels need to be done for obtaining clear insight into the remodulating the potential of chemotherapeutic agents and their ability to increase radio-therapeutic effect.

4. Recent advances in molecular biology has exposed many potential targets e.g. EGFR, COX-2 angiogenic molecules and various components of signal transduction pathways that these molecules initiate.

4. It is possible to intervene in these molecular pathways to improve therapeutic ratio. And hence molecular targeting strategies can be introduced in chemo-radiation for better control of different cancers.
THANK YOU