Pharmacology of Chemoradiation

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General Problems of chemoradiation

Two most challenging therapeutic agents in all of medicine

The oncologist must consider

- Risk of serious toxicities
- Narrow efficacy profiles
- Adjustment on a routine basis
- Heterogeneous patient populations
Clinical pharmacology is defined as the study of drugs in humans subdivided into two major disciplines:

- **Pharmacokinetics**
- **Pharmacodynamics**
Pharmacokinetics

- “What the body does to the drug.”

- absorption, distribution, metabolism, and excretion
Pharmacodynamics

“What the drug does to the body.”

clinical drug effects
  efficacy
toxicity
Paul Ehrlich coined the term chemotherapy in 1865. The anticancer effect of Potassium Arsenite was observed in the 1860s. The 1950s saw the introduction of Methotrexate and other agents. Carboplatin was developed in the 1990s. Paclitaxel and Docetaxel were also developed in the 1990s.
The discovery that certain toxic chemicals can cure certain cancers is one of the greatest in modern medicine.

The early revolution in cancer therapy was largely American, powered by American Government, which funded the NCI with the same "big-idea" philosophy as the Apollo Program.

In fact, it was only later that the pharmaceutical industry became heavily involved.
The cell cycle

- **G₀**: Cell cycle arrest.
- **G₁**: Cellular contents, excluding the chromosomes, are duplicated.
- **G₂**: The cell "double checks" the duplicated chromosomes for error, making any needed repairs.
- **S**: Each of the 46 chromosomes is duplicated by the cell.

**Mitosis**

**Cytokinesis**
Cell Cycle and Chemotherapy

Cell Cycle

Specific Agents

Non-Specific Agents

STAGES OF THE CELL CYCLE:

- $G_1$
- $S$
- $G_2$
- $M$
Rationale of Concomitant chemoradiotherapy

- Increased loco-regional control
- Organ preservation
- Decreased distant metastasis
- Better survival
Rationale of Concomitant chemoradiotherapy

- Drugs and radiation may act against differing subsets of tumor cells
- Increased recruitment of cells into radiation responsive phase of cell cycle
- Chemotherapy may inhibit repair of sublethal radiation damage
Cisplatin and Radiation Synergism

**Figure 5** Increased DNA damage by addition of cisplatin to radiation.

^a Radiation can also induce other DNA damage, of which double-strand breaks are considered lethal.
Why chemoradiation?

First, concomitant chemoradiotherapy can be used with organ-preserving intent, resulting in improved cosmesis and function compared with surgical resection.

Second, chemotherapy can act as a radio sensitizer, improving the probability of local control and survival, by aiding the destruction of radioresistant clones.

Third, chemotherapy given as part of concurrent chemoradiation may act systemically and potentially eradicate distant micro metastases.
<table>
<thead>
<tr>
<th>Process affected</th>
<th>Mechanism&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Drug examples</th>
</tr>
</thead>
</table>
| Increased radiation damage<sup>a</sup>               | Incorporation of chemotherapy drug into DNA/RNA                                         | 5-FU: incorporation into DNA, increasing susceptibility to RT damage  
Cisplatin: cross-links with DNA or RNA (intrasand and interstrand); works for both hypoxic and oxygenated cells<sup>51</sup> |
| Inhibition of DNA repair process<sup>a</sup>          | Interference with the DNA repair process after radiation                                | Halogenated pyrimidines (e.g. 5-FU, bromodeoxyuridine, iododeoxyuridine)  
Nucleoside analogs (e.g. gemcitabine, fludarabine)  
Cisplatin  
Methotrexate  
Camptothecins and doxorubicin  
Etoposide  
Hydroxyurea  
Carmustine, lomustine |
| Cell-cycle interference (cytokinetic cooperation and synchronization)<sup>a</sup> | Most cytotoxic chemotherapies as well as radiation are cell-cycle-specific, and proliferating cells are most susceptible  
Accumulation of cells in the G2 and M phases (the most radiosensitive phases)  
Elimination of radioresistant cells in the S phase | Taxanes lead to cell-cycle arrest via tubulin stabilization  
Nucleoside analogs (e.g. gemcitabine, fludarabine), etoposide, methotrexate, hydroxyurea |
| Enhanced activity against hypoxic cells<sup>a</sup>   | Reoxygenation second to tumor shrinkage. Hypoxic cells are 2.5–3.0 times less radiation-sensitive than normoxic cells<sup>18,44</sup>  
Chemotherapy can help to eliminate hypoxic cells | Most chemotherapeutic agents; described in particular for paclitaxel<sup>45</sup>  
Tirapazamine, mitomycin (selective killing of hypoxic cells); nitroimidazoles (resensitize hypoxic cells to radiation) |
| Radiotherapy enhancement by preventing repopulation<sup>a</sup> | Systemic therapy can slow or stop rapid proliferation, which could otherwise be the basis for repopulation phenomenon | Most chemotherapeutic agents, in particular: Antiemetinines with activity in the S phase inhibit repopulation (e.g. 5-FU, hydroxyurea)  
EGFR inhibitors, which impede cell proliferation between RT fractions<sup>100</sup> |
| Inhibition of prosurvival and ‘poor prognosis’ markers<sup>a</sup> | Targeted therapies (best demonstrated for EGFR inhibition) block signaling pathways that might be responsible for radioresistance and poor prognosis | EGFR inhibitors—shown for anti-EGFR antibody, PKI-166 (small-molecule TKI), and EGFR antisense, but on the basis of clinical experience likely to be a class effect<sup>109,132</sup> |
| Hypermethylation sensitivity<sup>a</sup>             | HNSCC cells resistant to standard-fraction CRT can be resensitized to CRT by using smaller fraction sizes (<1 Gy) more frequently | Effect demonstrated for taxane-based CRT including paclitaxel as well as docetaxel<sup>29,50</sup>  
Low-dose fraction radiation |

<sup>a</sup>Chemoradiotherapy potenation through drug addition.  
<sup>b</sup>Chemoradiotherapy potenation through alteration in radiation administration.  
Abbreviations: 5-FU, 5-fluorouracil; CRT, chemoradiotherapy; HNSCC, head and neck squamous cell carcinoma; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
**How chemotherapy prevents radioresistance**

<table>
<thead>
<tr>
<th>Process affected</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large tumor cell burden</td>
<td>Tumor size is inversely correlated with tumor response. Radiation-induced cell kill is a random event—the higher the number of cells, the higher the chance of cells escaping a lethal hit.</td>
<td>Upfront or completion surgery should be considered to reduce tumor bulk or residual disease.</td>
</tr>
<tr>
<td>Tumor cell microenvironment/hypoxia</td>
<td>Oxygen is needed to generate ROS and other radicals with radiation. ROS are thought to be essential to the cytotoxic effect from radiation (reviewed in Cook et al.123).</td>
<td>Hypoxic cells are 2.5–3.0 times less radiation-sensitive than normoxic cells.18,44 Both hypoxia and HIF1α are adverse prognostic factors.127 Chemotherapy can increase radiation effect:</td>
</tr>
<tr>
<td></td>
<td>Hypoxia is present for two reasons:</td>
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</tr>
<tr>
<td></td>
<td>1. increased interstitial pressure may cause hypoperfusion, hypoxia and acidosis;124–126</td>
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<tr>
<td></td>
<td>2. cancer-related anemia contributes to local hypoxia (HIF1α is a marker of tumor hypoxia).</td>
<td></td>
</tr>
<tr>
<td>Inherent or acquired tumor cell resistance</td>
<td>Multiple mechanisms are thought to contribute, including mutated p5329, DNA repair gene amplification, increased levels of ROS scavengers, activation of pro-survival/poor-prognosis oncogenes (EGFR,100,101 c-MET29).</td>
<td>Delays or interruptions in radiotherapy are known to lead to the development of radioresistance and allow such resistant cells to repopulate.</td>
</tr>
<tr>
<td>Repopulation</td>
<td>Regrowth of tumor cells between doses of radiotherapy or chemotherapy. Accelerated repopulation might lead to treatment failure and emergence of true radioresistance (see row above).22</td>
<td>Accelerated radiation schemes are intended to prevent repopulation.129 Antimetabolites with activity in the S phase of the cell cycle (5-FU, hydroxyurea) also inhibit repopulation. EGFR inhibitors can block cell proliferation between radiotherapy fractions.101</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; HIF1α, hypoxia-inducible factor 1-alpha; ROS, reactive oxygen species.
Chemoradiation principle in Sigmoid curve of radiation

Figure 3 Schematic dose–response curves for tumor and normal tissue damage with radiation. The offset between the two curves indicates the therapeutic range. Chemoradiotherapy leads to a shift of both curves to the left, ideally with a stronger shift of the tumor curve (as indicated by the longer arrow), increasing overall efficacy of treatment (radiation enhancement).
Pharmacology of Commonly used drugs for Chemoradiation
Cisplatin
Cis-diamminedichloroplatinum, CDDP

Mechanism of Action

- Cell cycle—nonspecific agent.
  Reacts with two different sites on DNA to produce cross-links
  (Covalently binds to DNA with preferential binding to the N-7 position of guanine and adenine)
- Inhibition of DNA synthesis and transcription.
  Binding to nuclear and cytoplasmic proteins may result in cytotoxic effects.
Cisplatin

Absorption
- Not absorbed orally.
- Systemic absorption is rapid and complete after intraperitoneal (IP) administration.

Distribution
- Widely distributed
- 1 hour after infusion < 10% remains

Metabolism
- Plasma concentrations decay rapidly
  - (half-life 20–30 minutes on bolus administration).
- After the first 2 hours → clearance delays
  - (covalent binding with serum proteins)
- 10%–40% of given dose excreted in the urine in 24 hours.
Cisplatin

Indications of concomitant chemoradiation
- Esophageal ca
- Head and neck ca
- NSCLC Lung
- Cervix ca

Doses
No Aluminium needles, protect from light
- Head and neck ca-100mg/m$^2$ 3 wkly, 40mg/m$^2$ wkly
- Cervix ca-100mg/m$^2$ 3 wkly, 40mg/m$^2$ wkly
- NSCLC-100mg/m$^2$ 100mg/m$^2$ 3 wkly,
- Esophageal ca- 75mg/m$^2$

Cisplatin for concurrent chemoradiation

Results

- Esophageal ca - 5yr OS – 26% vs 0% ¹
- Head and neck ca - OS - 78% vs 47% ²
- NSCLC - 5yr OS 16% vs 10% ⁴
- Cervix ca - 5yr OS – 69% vs 55% ³

Carboplatin

Mechanism of Action
- Cell cycle–nonspecific agent.
- Reacts with two different sites on DNA to produce cross-links (Covalently binds to DNA with preferential binding to the N-7 position of guanine and adenine)
- Inhibition of DNA synthesis and transcription.
- Binding to nuclear and cytoplasmic proteins may result in cytotoxic effects.

Absorption
- Not absorbed by the oral route.
**Carboplatin**

**Distribution**
- Widely distributed in body tissues.
- Crosses the blood-brain barrier and enters the CSF.

**Metabolism**
- Extensively cleared by the kidneys (60%–70% of drug excreted in urine /24 hours.)
- Half-life: 2–6 hours.

**Adverse Effects**
- Myelosuppression, nephrotoxicity
- Emetogenic, alopecia
Carboplatin

Indications:
- Head and neck ca
- Cervix ca

Dose:
- 300mg/m2

Result
- Head and neck ca  OS – 22% vs 16%
- Cervix ca No OS benefit

References:
Cetuximab

Trade Name: Erbitux

Mechanism of Action
- Recombinant chimeric IgG1 monoclonal antibody directed against the epidermal growth factor receptor (EGFR).

Metabolism
- Half-life: 5–7 days.
Cetuximab

- Binds with nearly 10-fold higher affinity to EGFR than normal ligands EGF and TGF-α

  Inhibition of EGFR.

- Prevents both homodimerization and heterodimerization of EGFR

  Inhibition of autophosphorylation and EGFR signaling.

- Inhibition of critical mitogenic and anti-apoptotic signals involved in proliferation, growth, invasion/metastasis, angiogenesis.
Concomitant Cetuximab in Head and Neck Cancer

Indications:
- Head and neck cancer concomitant with RT

Dose:
- 400mg/m² wk before RT f/b 250mg/m² wkly

Results:
- 5yr OS – 45% vs 36% ¹

5-Fluorouracil

Classification
- Antimetabolite

Mechanism of Action
- Fluoropyrimidine analog.
- Cell cycle–specific with activity in the S-phase.
- Activation to cytotoxic metabolite forms.
- Inhibition of the target enzyme thymidylate synthase by the 5-FU metabolite, FdUMP which then gets misincorporated into DNA in the form of dUTP → inhibition of DNA synthesis and function.
- Incorporation of the FUTP (5-FU metabolite) into RNA → alterations in RNA processing and/or translation.
5-Fluorouracil

Absorption
- Oral absorption is variable: 40% to 70%.

Distribution
- After IV administration, it is widely distributed to tissues.
- Penetrates into third-space fluid collections such as ascites and pleural effusions.
- Crosses the blood-brain barrier and distributes into CSF and brain tissue.
5-Fluorouracil

Metabolism

- Extensive enzymatic metabolism intracellularly to cytotoxic metabolites.
- Dihydropyrimidine dehydrogenase is the main enzyme responsible for 5-F catabolism, and it is highly expressed in liver and extrahepatic tissues such as GI mucosa, WBCs, and kidney.
- > 90% of drug is cleared in urine and lungs.
- Half-life is 10 to 20 min.
5-Fluorouracil for concurrent chemoradiation

Indications

- Anal ca
- Esophageal ca
- Gastric ca
- Rectal ca
- Head and neck ca
- Cervix ca
5-Fluorouracil for concomitant chemordiation

Doses
- Anal ca-1000mg/m2
- Esophageal ca-600mg/m2
- Gastric ca-600mg/m2
- Rectal ca-325mg/m2
- Head and neck ca-1200mg/m2
- Cervix ca-1000mg/m2

5-Fluorouracil

Results

- Anal ca - 3 yr OS – 65% vs 58% ¹
- Esophageal ca - 5yr OS – 26% vs 0% ²
- Gastric ca - 3yr OS – 50% vs 41% ³
- Rectal ca - OS: 63%, DFS: 53% ⁶
- Head and neck ca - OS – 63% vs 50% ⁴
- Cervix ca - 5yr OS – 69% vs 55% ⁵

Paclitaxel

**Classification:** Taxane, anti-microtubule agent

**Mechanism of Action**
- Isolated from the bark of the Pacific yew tree, *Taxus brevifolia*.
- Cell cycle–specific (mitosis (M) phase).
- High-affinity binding to microtubules enhances tubulin polymerization.
- Dynamic process of microtubule is inhibited → inhibition of mitosis and cell division.
Paclitaxel

Distribution

- Distributes widely to all body tissues, including third-space fluid collections such as ascites.
- Extensive binding (90%) to plasma and cellular proteins.

Metabolism

- Metabolized extensively by the hepatic P450 microsomal system.
- 70%–80% excreted via fecal elimination.
- Half-life ranges : 9 to 50 hours.
Paclitaxel

Indication
- Cervix ca
- Head and neck ca

Doses
- 50mg/m²

Results
- No survival advantage over cisplatin

Temozolomide

Mechanism of Action
Nonclassic alkylating agent
- Cell cycle–nonspecific agent.
- Metabolic activation to the reactive compound MTIC is required for antitumor activity.
- Methylates guanine residues in DNA and inhibits DNA, RNA, and protein synthesis.
Absorption

- Widely distributed in body tissues.
- Oral bioavailability: 100%.
- Maximum plasma concentrations are reached within 1 hour after administration.
- Food reduces the rate and extent of drug absorption.
Temozolomide

Distribution
- Is lipophilic and crosses the blood-brain barrier.
- Levels in brain and CSF are 30%–40% of those achieved in plasma.

Metabolism
- Metabolized primarily by non-enzymatic hydrolysis at physiologic pH.
- Undergoes conversion to the metabolite MTIC, which is further hydrolyzed to AIC, a known intermediate in purine de novo synthesis, and methylhydrazine, the presumed active alkylating species.
- The half-life is 2 hours.
- 40%–50% is excreted in urine within 6 hours of administration.
Temozolomide for concurrent chemoradiation in High Grade gliomas

Dose
- 75mg/m2

Results
- 2 yr OS – 27% vs 10% ³

**Vinorelbine**

**Mechanism of Action**

Vinca alkaloid, anti-microtubule agent

- Semisynthetic alkaloid derived from vinblastine.
- Cell cycle–specific with activity in mitosis (M) phase.
- Inhibits tubulin polymerization, disrupting formation of microtubule assembly during mitosis → arrest in cell division → leading to cell death.
- Relatively high specificity for mitotic microtubules with lower affinity for axonal microtubules.
Vinorelbine

Distribution
- Widely and rapidly distributed into most body tissues with a large apparent volume of distribution (.30 L/kg).
- Extensive binding to plasma proteins (about 80%).

Metabolism
- Metabolized in the liver by the cytochrome P450 microsomal system.
- Small quantities of at least one metabolite, desacetyl vinorelbine, have antitumor activity similar to that of parent drug.
- Mainly excreted in feces.
- Half-life: 27–43 hours.
Vinorelbine for concomitant chemoradiation in Head and Neck Carcinoma

Dose
- 10mg/m2 wkly

Result
- Supra-additive effect on HNSCC

Cancer Res Clin Oncol. 2007. Concurrent use of vinorelbine and gefitinib induces supra-additive effect in head and neck squamous cell carcinoma cell lines.
Mitomycin-C

**Mechanism of Action**

**Antitumor antibiotic**

- Isolated from the broth of *Streptomyces caespitosus species*.
- Alkylating agent to cross-link DNA $\rightarrow$ inhibition of DNA synthesis and function.
- Bioreductive activation by NADPH cytochrome P450 reductase, and DT-diaphorase to oxygen free radical forms $\rightarrow$ inhibit DNA synthesis and function.
- Preferential activation in hypoxic tumor cells.

**Absorption**

- Administered mainly by the IV
Mitomycin-C

Distribution
- Rapidly cleared from plasma after IV administration.
- Widely distributed to tissues.

Metabolism
- Metabolism in the liver (cytochrome P450 system and DT-diaphorase) with formation of both active and inactive metabolites.
- Excreted mainly through the hepatobiliary system into feces.
- Half-life: 50 minutes.
Mitomycin-C for concomitant chemoradiation

Indications
- Anal cancer
- Head and neck cancer

Doses
- Anal cancer - 12mg/m²
- Head and neck cancer - 8mg/m²

Mitomycin-C for concomitant chemoradiation

Results

- Anal cancer - 3 year OS 65% vs 58% 
- Head and neck ca - MS – 16.5 mth vs 13mth

**Etoposide**

**Mechanism of Action**

**Epipodophyllotoxin, topoisomerase II inhibitor**

- Cell cycle-specific agent with activity in **late S-** and **G2-phases**.
- Prodrug form must first be dephosphorylated for etoposide to be active.
- Stabilizes the topoisomerase II-DNA complex and prevents the unwinding of DNA.
Etoposide phosphate

**Distribution**
- Rapidly distributed into all body fluids and tissues.
- Large fraction of drug (90%–95%) is protein-bound, mainly to albumin. Therefore, decreased albumin levels result in a higher incidence of host toxicity.

**Metabolism**
- Etoposide phosphate is converted to etoposide in plasma, which is then metabolized primarily by the liver to hydroxyacid metabolites. These metabolites are less active than the parent compound.
- 15%–20% of the drug is excreted in urine
- Elimination half-life: 3 to 10 hours.
Etoposide for concomitant chemoradiation in lung cancer

**Indication**
- NSCLC

**Dose**
- 50 mg PO

**Result**
- 5yr OS – 13% vs 10%

**Gefitinib**

**Trade Names**
- Iressa, ZD1839

**Classification**
- Signal transduction inhibitor

**Mechanism of Action**
- Potent and selective small molecule inhibitor of the EGFR tyrosine kinase → inhibition of EGF autophosphorylation and EGFR signaling.

- Inhibition of critical mitogenic and anti-apoptotic signals involved in proliferation, growth, metastasis, angiogenesis, and response to chemotherapy and/or radiation therapy.
Gefitinib

Distribution
- Extensive binding (90%) to plasma proteins, including albumin and \( \alpha_1 \)-acid glycoprotein, and extensive tissue distribution.

Metabolism
- Metabolism in the liver primarily by CYP3A4 microsomal enzymes.
- Elimination is mainly hepatic with excretion in the feces.
- Terminal half-life: 48 hours.
Gefitinib for concurrent chemoradiation

**Indication**
- Head and neck ca

**Dose**
- 250mg PO

**Result**
- Supra-additive effect on HNSCC cell

Vinblastine

Mechanism of Action:
Vinca alkaloid, anti-microtubule agent

- Plant alkaloid extracted from periwinkle plant *Catharanthus roseus*.

  Inhibition of tubulin polymerization
  ↓
  Disrupts assembly of microtubules
  (important part of the cytoskeleton and the mitotic spindle).
  ↓
  mitotic arrest in metaphase
  ↓
  cell division stops
  ↓
  cell death.
Distribution
- Widely and rapidly distributed into most body tissues
- Poor penetration into the CSF.

Metabolism:
- By the liver P450 system
- Majority of the drug excreted in feces via biliary system.
- Dose modification required in liver dysfunction.
- Plasma terminal half-life of about 25 hours
Vinblastine for concomitant chemoradiation in Lung Cancer

**Indication**
- NSCLC

**Dose**
- 6mg/m2

**Result**
- 5yr OS 16% vs 10%

Methotrexate

Mechanism of Action

**Antimetabolite**

- Cell cycle–specific antifolate analog (S-phase).
- Enters cells through specific transport systems mediated by the reduced folate carrier and the folate receptor protein.
- Requires polyglutamation by the enzyme folylpolyglutamate synthase (FPGS) for its cytotoxic activity.
- Inhibition of dihydrofolate reductase (DHFR) resulting in depletion of critical reduced folates.
- Inhibition of de novo thymidylate synthesis and purine synthesis.
Methotrexate

Absorption

- Oral bioavailability is erratic.
- Completely absorbed from parenteral routes of administration, and peak serum concentrations are reached in 30–60 minutes after IM injection.
Methotrexate

Distribution
- Widely distributed throughout the body.
- High-dose yields therapeutic concentrations in the CSF.
- 50% bound to plasma proteins.

Metabolism
- In liver and in cells by FPGS to higher polyglutamate forms.
- Renal excretion is the main route of elimination.
- Terminal half-life of 8–10 hours.
Methotrexate for concomitant chemoradiation in Head and neck cancer

Indication
- Head and neck ca

Dose
- 30mg/m2

Result
- OS – 47% vs 37%

Oxaliplatin

Mechanism of Action

- Diaminocyclohexane platinum, Third-generation platinum compound.
- Cell cycle–nonspecific agent.
- Reacts with two different sites on DNA to produce cross-links (Covalently binds to DNA with preferential binding to the N-7 position of guanine and adenine)
  - Inhibition of DNA synthesis and transcription.
- Binding to nuclear and cytoplasmic proteins may result in cytotoxic effects.
Oxaliplatin

Distribution
- Widely distributed to all tissues with a 50-fold higher volume of distribution than cisplatin.
- Extensively binds to plasma proteins (98%)

Metabolism
- As observed with cisplatin, oxaliplatin undergoes aquation reaction in the presence of low concentrations of chloride.
- The major species are monochloro-DACH, dichloro-DACH, and mono-diaquo-DACH platinum.
- Mainly renal excretion
- Half-life: 240 hours.
Oxaliplatin

Indication
- Rectal ca

Dose
- 80mg/m2

Result
- OS-63%, DFS-53%

Docetaxel

**Mechanism of action**

Taxane, anti-microtubule agent

Semisynthetic taxane derived from European yew tree

- Cell cycle–specific agent (mitotic (M) phase)
  - high-affinity binding to microtubules
    - enhancement of tubulin polymerization
      - Mitotic spindle poison
        - Inhibits mitosis
**Distribution**
- Distributes widely to all body tissues.
- Extensive binding (>90%) to plasma and cellular proteins.

**Metabolism**
- By the hepatic P450 microsomal system.
- 75% of drug is excreted via fecal elimination.
- Terminal half-life: 11 hour
Docetaxel for concurrent chemoradiation

Indication

- Esophagus ca

Dose

- 20mg/m2

Result

- 2yr OS – 52% 1

Capecitabine (Xeloda)

Mechanism of Action

Antimetabolite
Fluoropyrimidine carbamate prodrug form of 5-fluorouracil (5-FU).
Capecitabine itself is inactive.

Activation involves 3 successive enzymatic steps.
1. In liver to 59-deoxy-5-fluorocytidine (59-DFCR) by the carboxylesterase enzyme
2. To 59-deoxy-5-fluorouridine (59-DFUR) by cytidine deaminase (found in liver and in tumor tissues).
3. Finally to 5-FU by the enzyme thymidine phosphorylase (higher levels in tumor versus normal tissue.)
Capecitabine

- Increased activity of DNA repair enzymes, uracil glycosylase and dUTPase.
- Decreased expression of mismatch repair enzymes (hMLH1, hMSH2).

Absorption
- Capecitabine is readily absorbed by the GI tract.
- Peak 5-FU levels are achieved at 2 hours after oral administration.
- The rate and extent of absorption are reduced by food.

Distribution
- Plasma protein binding (<60%)
Capecitabine

Metabolism
- Capecitabine undergoes extensive enzymatic metabolism to 5-FU.
- Catabolism accounts for >85% of drug metabolism. Dihydropyrimidine dehydrogenase is the main enzyme responsible for the catabolism of 5-FU (liver and extrahepatic tissues such as GI mucosa, WBCs, and the kidneys)
- Mainly renal excretion.
- The major metabolite excreted in urine is a-fluoro-b-alanine (FBAL). 
- Half-life: 45 minutes.
Capecitabine

Indication
Esophagus ca

Dose
1000mg/m2

Result
2yr OS - 52% 1

Bevacizumab (Avastin)

Mechanism of Action
- Recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF).
- Binds to all isoforms of VEGF-α (pro-angiogenic growth factor that is overexpressed in a wide range of solid human cancers, including colorectal cancer.)
- Inhibits formation of new blood vessels in primary tumor and metastatic tumors.
Bevacizumab for concurrent chemoradiation in head and neck cancer

**Indication**
- Head and neck ca *experimental with cisplatinum*

**Dose**
- 15mg/kg

**Result**
- 2yr OS – 88%, no increased toxicity

Mechanism of Action

- **Antimetabolite**
- Cell cycle-specific (S-phase)
- Antitumor activity of gemcitabine is determined by a balance between intracellular activation (deoxycytidine kinase) and degradation and the formation of cytotoxic triphosphate (dFdCTP) metabolites.
Gemcitabine

Indication
- Pancreatic ca
- NSCLC
- Head and neck ca
- Glioblastoma
- Cervical ca

Doses
- Pancreatic ca - 1000mg/m²
- NSCLC - 300mg/m²
- Head and neck ca - 300mg/m²
- Glioblastoma - 300mg/m²
- Cervical ca - 300mg/m²
Toxicity of Anticancer Agents

- Narrow Safety profile

- Toxicity because of two main reasons
  - Increased killing of normal cells
  - e.g. bone marrow suppression
  - Inherent cell kill by specific drugs

- Can Involvement any organ in body
Chemotherapy is administered on a dose-response relationship (the more drug given the more cancer cells killed).

It has a narrow therapeutic index – meaning there is a very small difference between the amount of drug that equals results and the amount of drug that equals harm.

\[
\frac{\text{Benefit}}{\text{Harm}} = \frac{\text{Relief of Cancer Symptoms}}{\text{Treatment-Related Toxicity}}
\]
Early Toxicity Comparison between Sequential and Concurrent CT/RT

% Gr 3/4 Esophagitis

23%

4%

WJLCG
GLOT
CZECH
LAMP
RTOG 9410
BROCAT
Side effects of chemotherapy

- Mucositis
- Nausea/vomiting
- Diarrhea
- Cystitis
- Sterility
- Myalgia
- Neuropathy
- Alopecia
- Pulmonary fibrosis
- Cardiotoxicity
- Local reaction
- Renal failure
- Myelosuppression
- Phlebitis
## Chemotherapy Drug Toxicity

<table>
<thead>
<tr>
<th>Chemotherapeutic drugs</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Nephrotoxicity, neurotoxicity, ototoxicity, myelosuppression. Emetogenic</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Myelosuppression, nephrotoxicity Emetogenic, alopecia</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Myelosuppression, neurotoxicity, Hypertension, alopecia, mucositis</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Myelosuppression, nephrotoxicity (ARF), mucositis</td>
</tr>
</tbody>
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# Chemotherapy Drug Toxicity

<table>
<thead>
<tr>
<th>Chemotherapeutic drugs</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>Myelosuppression, Hand-foot syndrome, mucositis, neurologic toxicity</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Myelosuppression, mucositis, alopecia,</td>
</tr>
<tr>
<td>Mitomycin-c</td>
<td>Myelosuppression, mucositis, hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>Myelosuppression, nausea &amp; vomiting, headache, photosensitivity</td>
</tr>
</tbody>
</table>
### Chemotherapy Drug Toxicity

<table>
<thead>
<tr>
<th>Chemotherapeutic drugs</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>Neurotoxicity, emetogenic, diarrhoea, myelosuppression, hepatotoxicity</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Myelosuppression, GI toxicity, nausea &amp; vomiting, neurotoxicity, alopecia</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Elevation in B.P, Skin rash, pruritis</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Diarrhoea, nausea &amp; vomiting, Hand-foot syndrome, ↑LFT, neurologic toxicity</td>
</tr>
<tr>
<td>Chemotherapeutic drugs</td>
<td>Toxicity</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Infusion related symptoms, skin rash, pruritis, pulmonary toxicity, hypomagnesemia</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Myelosuppression, hypersensitivity reaction, neurotoxicity, alopecia, transient asymptomatic sinus bradycardia, mucositis</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Myelosuppression, hypersensitivity reaction, fluid retention syndrome, skin rash, pruritis, alopecia</td>
</tr>
</tbody>
</table>
# Chemotherapy Drug Toxicity

<table>
<thead>
<tr>
<th>Chemotherapeutic drugs</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Gastrointestinal perforations and wound healing complications. Bleeding complications, Increased risk of arterial thromboembolic events, including MI, Hypertension</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Myelosuppression, nausea &amp; vomiting, flu like syndrome, transient hepatic dysfunction.</td>
</tr>
</tbody>
</table>
## Indications Dose and Results of chemoradiation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Esophageal ca</td>
<td>75mg/m²</td>
<td>5yr OS – 26% vs 0% ¹</td>
</tr>
<tr>
<td></td>
<td>Head and neck ca</td>
<td>100mg/m²</td>
<td>OS - 78% vs 47% ²</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td>100mg/m²</td>
<td>5yr OS 16% vs 10% ⁵</td>
</tr>
<tr>
<td></td>
<td>Cervix ca</td>
<td>75mg/m²</td>
<td>5yr OS – 69% vs 55% ³</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Head and neck ca</td>
<td>300mg/m²</td>
<td>OS – 22% vs 16% ²</td>
</tr>
<tr>
<td></td>
<td>Cervix ca</td>
<td></td>
<td>No OS benefit ⁴</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>NSCLC</td>
<td>6mg/m²</td>
<td>5yr OS 16% vs 10% ⁵</td>
</tr>
</tbody>
</table>


# Indications Dose and Results of chemoradiation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Head and neck ca</td>
<td>30mg/m²</td>
<td>OS – 47% vs 37% ¹</td>
</tr>
<tr>
<td>5-FU</td>
<td>Anal ca</td>
<td>1000mg/m²</td>
<td>3 yr OS – 65% vs 58% ²</td>
</tr>
<tr>
<td></td>
<td>Esophageal ca</td>
<td>600mg/m²</td>
<td>5yr OS – 26% vs 0% ³</td>
</tr>
<tr>
<td></td>
<td>Gastric ca</td>
<td>600mg/m²</td>
<td>3 yr OS – 50% vs 41% ⁴</td>
</tr>
<tr>
<td></td>
<td>Rectal ca</td>
<td>325mg/m²</td>
<td>OS-63%, DFS-53% ⁷</td>
</tr>
<tr>
<td></td>
<td>Head and neck ca</td>
<td>1200mg/m²</td>
<td>OS – 63% vs 50% ⁵</td>
</tr>
<tr>
<td></td>
<td>Cervix ca</td>
<td>1000mg/m²</td>
<td>5yr OS – 69% vs 55% ⁶</td>
</tr>
</tbody>
</table>


### Indications Dose and Results of chemoradiation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| Mitomycin-c         | Anal cancer Head and neck ca | 12mg/m² 8mg/m²² | 3 yr OS 65% vs 58% ¹  
MS – 16.5 mth vs 13mth ² |
| Temozolamide        | Brain tumor         | 75mg/m²²    | 2 yr OS – 27% vs 10% ³ |
| Oxaliplatin         | Rectal ca           | 80mg/m²²    | OS-63%, DFS-53% ⁴ |
| Etoposide           | NSCLC               | 50 mg PO    | 5yr OS – 13% vs 10% ⁵ |

## Indications Dose and Results of chemoradiation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomab [Bevacizumab]</td>
<td>Head and neck ca</td>
<td>15mg/kg</td>
<td>2yr OS – 88%, no increased toxicity &lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Head and neck ca</td>
<td>10mg/m²</td>
<td>CR = 90% vs 70% [Cis- as CCRT] &lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td>10mg/m²</td>
<td>RR = 80% &lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Head and neck ca</td>
<td>250mg PO</td>
<td>Supra-additive effect on HNSCC cell &lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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# Indications Dose and Results of chemoradiation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>Esophagus ca</td>
<td>1000mg/m²</td>
<td>2yr OS - 52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Head and neck ca</td>
<td>400mg/m² wk before RTf/b</td>
<td>5yr OS – 45% vs 36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250mg/m² wkly</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Pancreatic ca</td>
<td>1000mg/m²</td>
<td>Phase I/II trials</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td>300mg/m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Head and neck ca</td>
<td>300mg/m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glioblastoma</td>
<td>300mg/m²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cervical ca</td>
<td>300mg/m²</td>
<td></td>
</tr>
</tbody>
</table>

### Indications Dose and Results of chemoradiation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Cervix ca&lt;br&gt;Head and neck ca</td>
<td>50mg/m²</td>
<td>No survival advantage over cisplatin ¹</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Esophagus ca</td>
<td>20mg/m²</td>
<td>2yr OS – 52% ²</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>High grade glioma</td>
<td>10mg/m²</td>
<td>OS same as RT alone ³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>Indication and treatment</th>
<th>Commonly used agents</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper aerodigestive tract cancers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>Locally advanced HNC—primary or adjuvant treatment</td>
<td>Cisplatin, 5-FU, FHx, cetuximab</td>
<td>Improved organ preservation and survival compared with radiation alone</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>Stage IIIB, nonoperable nonmetastatic disease</td>
<td>Cisplatin, carboplatin/paclitaxel, cisplatin/etoposide</td>
<td>Curative approach in poor surgical candidates or IIIB disease</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>Limited stage disease</td>
<td>Cisplatin/etoposide</td>
<td>Curative in ~20% of patients</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Locally advanced disease</td>
<td>Cisplatin/5-FU</td>
<td>Survival benefit, increased cure rates, organ preservation</td>
</tr>
<tr>
<td><strong>Gastrointestinal malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>Neoadjuvant</td>
<td>5-FU</td>
<td>Improved sphincter preservation, decrease in local and distal failures</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>Mainstay of curative treatment</td>
<td>5-FU, MMC</td>
<td>Improved organ preservation</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Adjuvant</td>
<td>Cisplatin, 5-FU</td>
<td>Some data indicate a survival benefit</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Adjuvant, unresectable locoregionally advanced tumors</td>
<td>5-FU</td>
<td>Improved locoregional control, possibly a survival benefit</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Adjuvant, unresectable locoregionally advanced tumors</td>
<td>5-FU</td>
<td>Some data indicate a survival benefit</td>
</tr>
<tr>
<td><strong>Gynecological and genitourinary cancers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Primary modality</td>
<td>Cisplatin, 5-FU, hydroxyurea</td>
<td>Improved local and distal control, organ preservation</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Primary modality</td>
<td>Cisplatin</td>
<td>Improved local control</td>
</tr>
<tr>
<td><strong>Other cancers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Adjuvant</td>
<td>Temozolomide</td>
<td>Survival benefit</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Neoadjuvant</td>
<td>Doxorubicin</td>
<td>Downstaging, improved organ preservation</td>
</tr>
</tbody>
</table>

*This is a limited overview, and concurrent chemoradiotherapy is used in most solid tumors either as a standard treatment or investigationally. For further details please refer to the organ-specific literature. Abbreviations: 5-FU, 5-fluorouracil; FHx, 5-FU, hydroxyurea and radiation; HNC, head and neck cancer; MMC, mitomycin C.*
<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Arms (Radiation/Chemotherapy Dose)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 90-01</td>
<td>493, stage IIB–IVA (or IB/IIA &lt; 5 cm/biopsy-proven node)</td>
<td>• 45 Gy to pelvis &amp; lower para-aortics, 1–2 LDR implants&lt;br&gt;• 45 Gy to pelvis, 1–2 LDR implants with 5-FU 1,000 mg/m² x 96 h + cisplatin 75 mg/m² over 4 h on d1–5, 22–26, 2nd implant</td>
<td>52% 5-yr OS 72% 5-yr OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P &lt; .0001)</td>
</tr>
<tr>
<td>GOG 123</td>
<td>368, node-negative, bulky, stage IB</td>
<td>• 45 Gy to pelvis, 1–2 LDR implants followed by hysterectomy&lt;br&gt;• Same radiation with weekly cisplatin 40 mg/m² x 6</td>
<td>74% 3-yr OS 85% 3-yr OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P = .008)</td>
</tr>
<tr>
<td>SWOG 8797</td>
<td>268, post-radical hysterectomy (+ margins, pelvic nodes, parametrial involvement)</td>
<td>• 49.3 ± 45 Gy to para-aortic nodes&lt;br&gt;• Same radiation with 5-FU 1,000 mg/m² x 96 h + cisplatin 70 mg/m² over d1–5, 22–26 + 2 additional cycles afterwards</td>
<td>63% 4-yr OS 80% 4-yr OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P = .003)</td>
</tr>
<tr>
<td>GOG 85</td>
<td>388, stage IIB–IVA (node-negative)</td>
<td>• Radiation to pelvis (dose varied by stage), 1–2 LDR implants with 5-FU 1,000 mg/m² x 96 h + cisplatin 50 mg/m² on d1, 29&lt;br&gt;• Same radiation with hydroxyurea 80 mg/kg biweekly</td>
<td>55% 8.7-yr OS 43% 8.7-yr OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P = .018)</td>
</tr>
<tr>
<td>GOG 120</td>
<td>526, stage IIB–IVA</td>
<td>• Radiation to pelvis (dose varied by stage) + weekly cisplatin 40 mg/m² x 6 cycles&lt;br&gt;• Same radiation with cisplatin 50 mg/m² + 5-FU 1,000 mg/m²/d x 96 h on d1, 29 + hydroxyurea twice weekly x 6&lt;br&gt;• Same radiation with hydroxyurea 3 g/m² twice weekly x 6</td>
<td>65% 3-yr OS 47% 3-yr OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(P &lt; .004)</td>
</tr>
</tbody>
</table>

Data from references 10–14.

5-FU = fluorouracil; GOG = Gynecologic Oncology Group; LDR = low-dose-rate brachytherapy; OS = overall survival; PFS = progression-free survival; RTOG = Radiation Therapy Oncology Group; SWOG = Southwest Oncology Group.
Chemoradiation in Cervix cancer

Ademocarcinoma cervix.  Squamous cell Carcinoma Cervix

Anticancer Research, June 2010 vol. 30 no. 6 2341-2346
Chemoradiation in Cervical cancer reduces risk of death by 30-50%

Relative risk estimate of survival from five phase III, randomized, controlled clinical trials of chemoradiation in women with cervical cancer. A relative risk of 1 would indicate no difference in outcome between the treatment arms. A risk smaller than 1 indicates a benefit for the experimental treatment. A relative risk of 0.6, for example, would indicate that the treatment has reduced the risk of death by 40%. The relative risks of survival for all five trials, with 90% confidence intervals shown, range from 0.70 to 0.50, indicating that the concurrent chemoradiation decreased the risk of death by 30-50%.
Figure 2: Overall Survival—Patients receiving concurrent radiation therapy and chemotherapy (cisplatin plus gemcitabine, paclitaxel, or vinorelbine). Modified, with permission, from Vokes.[31]
## Advantage of Chemoradiation in Head and Neck Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Primary treatment</th>
<th>Adjuvant therapy</th>
<th>Grade 3 and 4 toxic effects</th>
<th>Increased local control rate</th>
<th>Difference in overall survival in favor of chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTCa 22931</td>
<td>167 with high-risk features on pathology</td>
<td>Surgery</td>
<td>CRT (P); RT alone</td>
<td>Acute: CRT 41%; RT 21%; Chronic: difference NS</td>
<td>Yes: CRT 82%; RT 69% (at 5 years)</td>
<td>Yes: CRT 53%; RT 40% (at 5 years)</td>
</tr>
<tr>
<td>RTOGa 9501</td>
<td>459 with high-risk features on pathology</td>
<td>Surgery</td>
<td>CRT (P); RT alone</td>
<td>Acute: CRT 77%; RT 34%; Chronic: difference NS</td>
<td>Yes: CRT 82%; RT 72% (at 2 years)</td>
<td>No: CRT ~65.0%; RT ~57.5% (at 2 years – but significant difference in DFS)</td>
</tr>
<tr>
<td>Bachaud et al. (1996)</td>
<td>83 with high-risk features on pathology 510 with laryngeal cancer</td>
<td>Surgery</td>
<td>CRT (P); RT alone</td>
<td>Acute: CRT 41%; RT 18%; Chronic: difference NS</td>
<td>Yes: CRT 77%; RT 59% (at 4 years)</td>
<td>Yes: CRT 72%; RT 46% (at 2 years)</td>
</tr>
<tr>
<td>Intergroup 91-11 Larynx (2003)</td>
<td></td>
<td>CRT (P); RT plus induction chemotherapy; RT alone</td>
<td>NA</td>
<td>Acute: CRT 77%; RT + I 51%; RT 47% Chronic: CRT 30%; RT + I 24%; RT 36% (difference NS)</td>
<td>Yes: CRT 80%; RT + I 64%; RT 58% (at 2 years)</td>
<td>No: CRT 76%; RT + I 74%; RT 75% (at 2 years) but increased larynx preservation (CRT 88%; RT + I 75%; RT 70%)</td>
</tr>
<tr>
<td>Al-Sarraf et al. (1998)</td>
<td>193 with NPC</td>
<td>CRT (P) plus consolidation with PF; RT alone</td>
<td>NA</td>
<td>Acute: CRT 75.6%; RT 50% Chronic: not reported</td>
<td>Yes: CRT 89.2%; RT 74.0%</td>
<td>Yes: CRT 76%; RT 46% (3-year OS)</td>
</tr>
<tr>
<td>Adelstein et al. (2003)</td>
<td>295 with unresectable tumors</td>
<td>RT alone; CRT (P); CRT (PF) split course</td>
<td>NA</td>
<td>Acute: RT 52%; CRT 85%; CRT\text{\textsuperscript{a}} 72% Chronic: not reported</td>
<td>Not reported but raised CR rate after therapy: RT 27%; CRT 41%; CRT\text{\textsuperscript{b}} 37%</td>
<td>Yes: RT 23%; CRT 37%; CRT\text{\textsuperscript{b}} 27% (3-year OS)</td>
</tr>
<tr>
<td>Jeremic et al. (2000)</td>
<td>130 with stage III or IV disease</td>
<td>HFX (RT); HFX (CRT and daily P)\text{\textsuperscript{f}}</td>
<td>NA</td>
<td>Acute: difference NS\text{\textsuperscript{d}} Chronic: difference NS</td>
<td>Yes: RT 27%; CRT 53%</td>
<td>Yes: RT 25%; CRT 46% (5-year OS)</td>
</tr>
</tbody>
</table>
Chemotherapy increases BED by approximately 10 Gy (10) in standard RT, equivalent to a dose escalation of 12 Gy in 2 Gy/F. Such an escalation could not be safely achieved by increasing radiation dose alone.

Conclusion

- Chemotherapy or targeted agents can increase the efficacy of radiation.
- The combined effect can be additive or synergistic because of multiple mechanisms e.g.
  - Increased radiation damage
  - Inhibition of DNA repair
  - Cell cycle synchronization
  - Increased cytotoxicity against hypoxic cells
  - Inhibition of prosurvival pathways
  - Abrogation of tumor cell repopulation
- Concurrent chemoradiation has improved cancer care in last three decades in many malignancies.