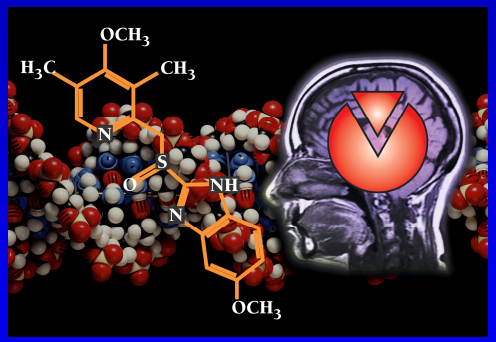
Pharmacology of Chemoradiation



Dr. Vivek Kaushal

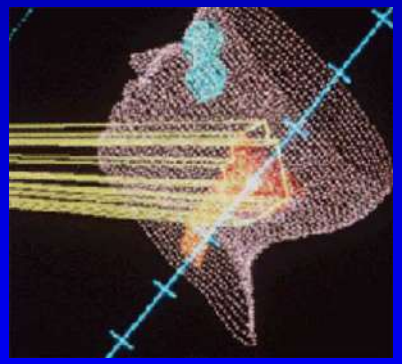
MD, DNB

Sr. Prof. and Head

Department of Radiotherapy,

Regional Cancer Centre

Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. Haryana.



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

Pharmaclogy of Drugs used in chemoradiation

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

Chemotherapy*

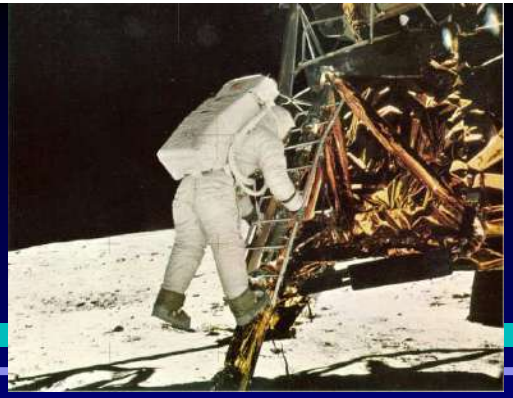
Paul Ehrlich coined the term chemotherapy

1865 The anticancer effect of Potassium Arsenite

1950's Methotrexate and other agents

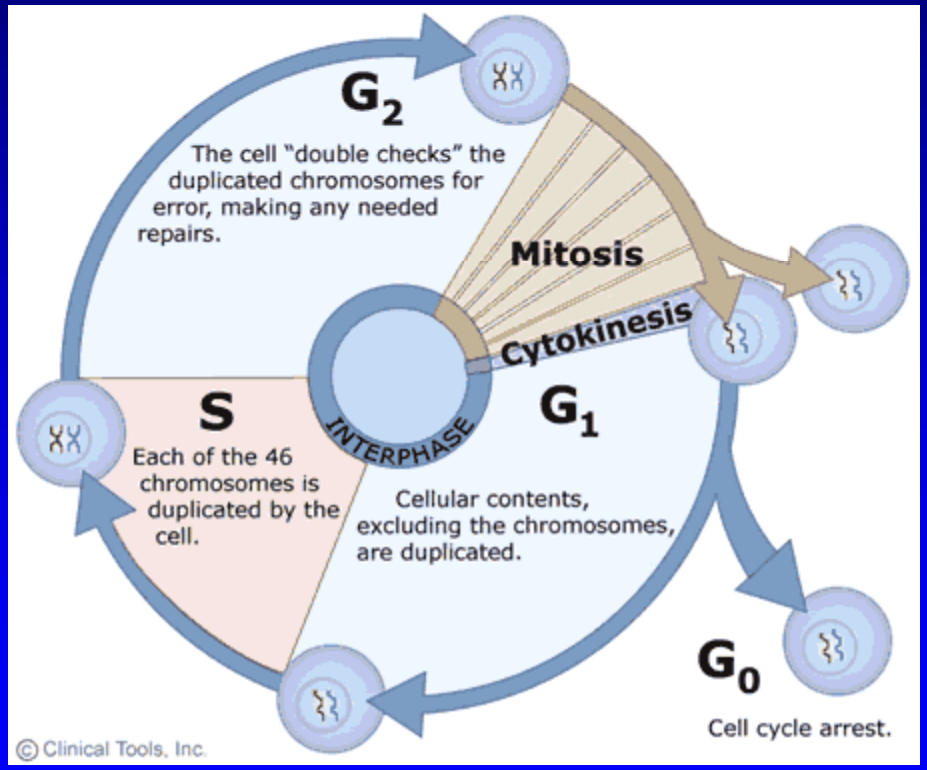
1990 Carboplatin

1990 + Paclitaxel Docetaxel etc

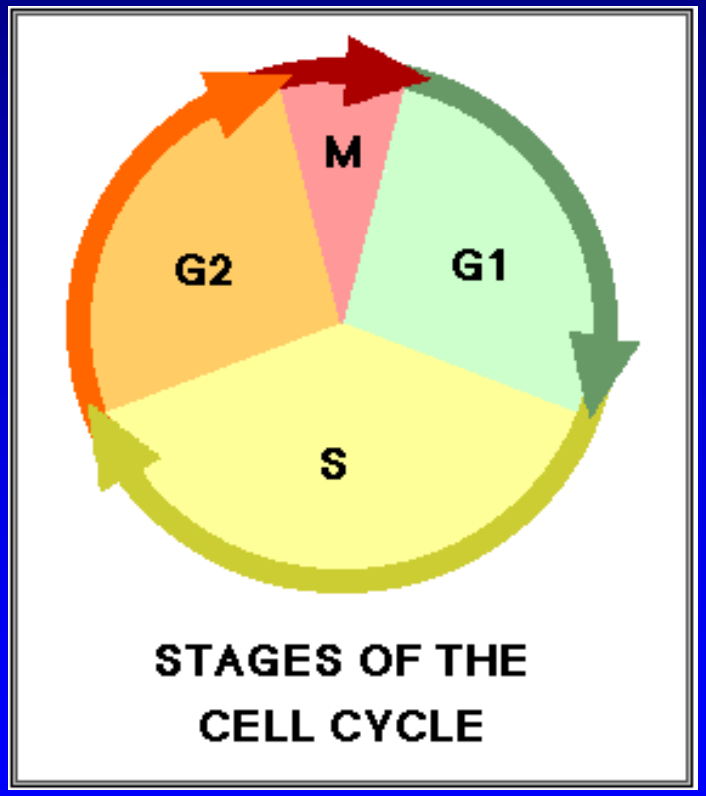


- The discovery that certain toxic chemicals can cure certain cancers is one of the greatest in modern medicine.
- The early revolution in cancer therapy was largely American, powered by American Government, which funded the NCI with the same "big-idea" philosophy as the Apollo Program.
- In fact, it was only later that the pharmaceutical industry became heavily involved.

The cell cycle



Cell Cycle and Chemotherapy

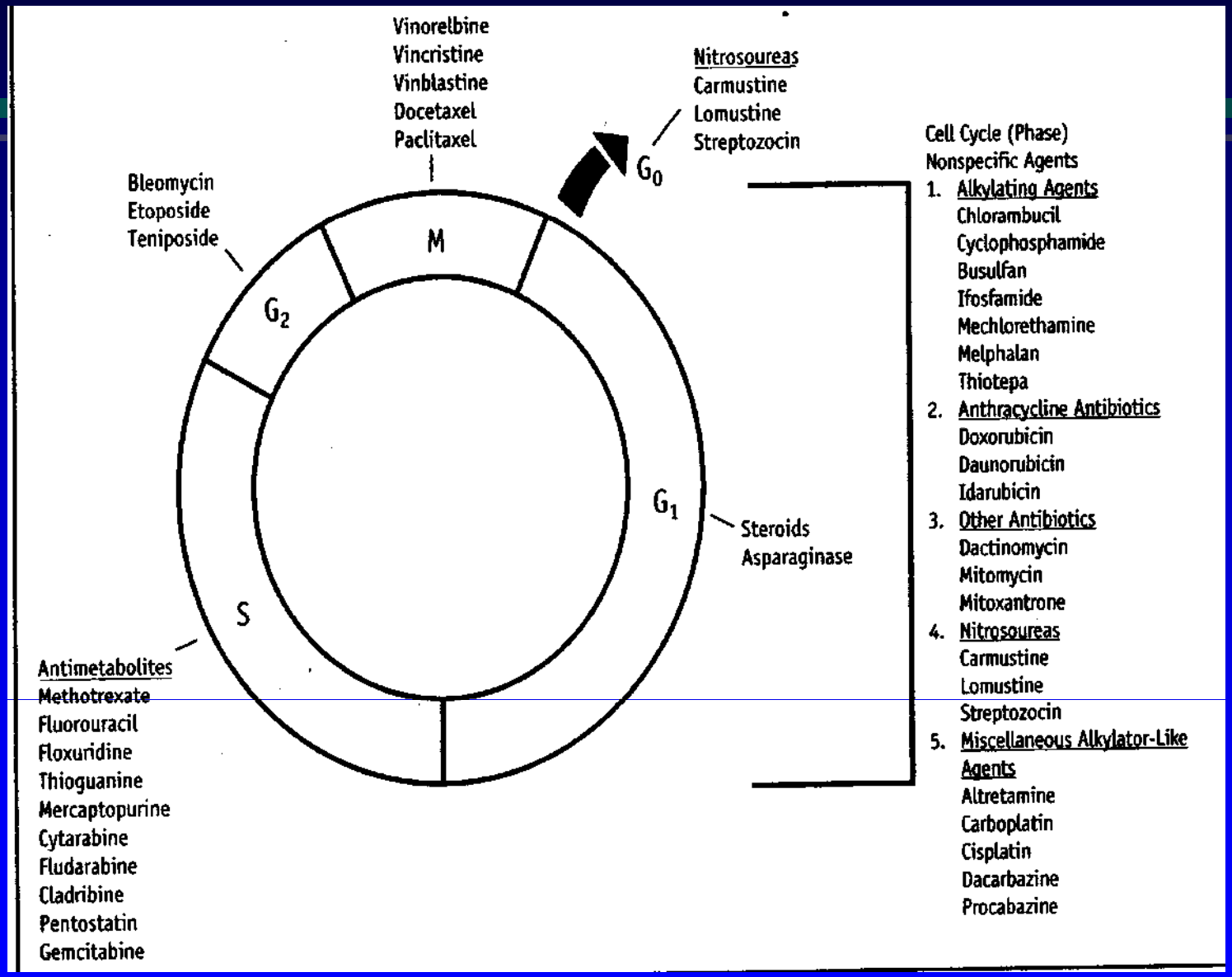


STAGES OF THE CELL CYCLE

Cell Cycle Specific Agents

Cell Cycle Non-Specific Agents

Cell Cycle Specificity of Anticancer Drugs



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

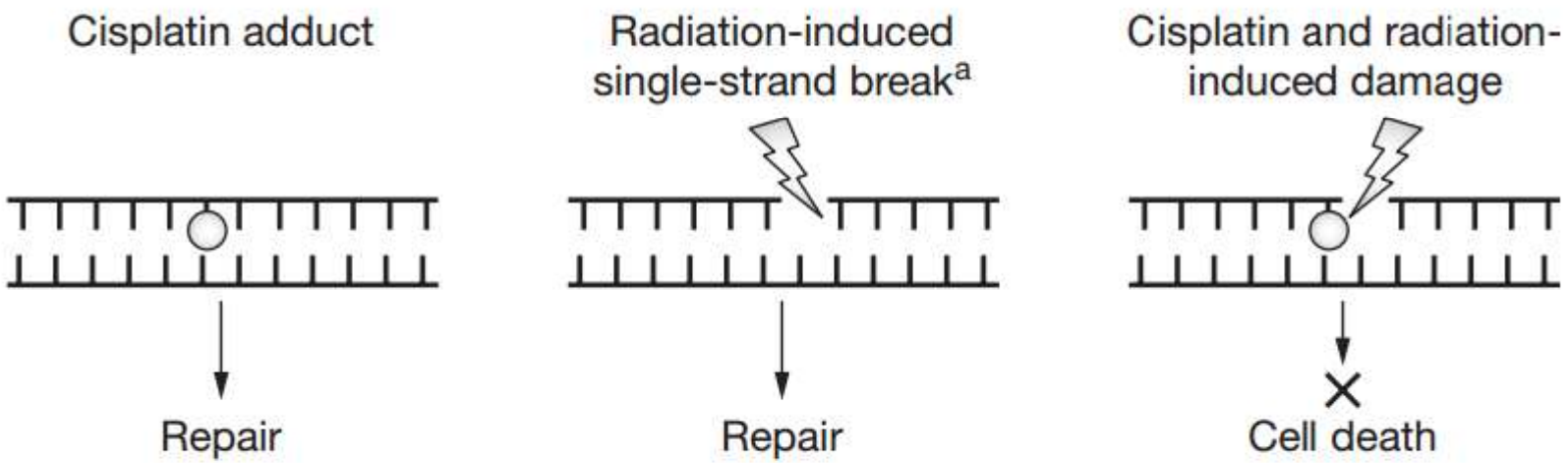


Figure 5 Increased DNA damage by addition of cisplatin to radiation.
[a]Radiation can also induce other DNA damage, of which double-strand breaks are considered lethal.

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 chemo radiation may act systemically and potentially eradicate distant micro metastases.

Table 3 Mechanisms of chemotherapy and radiotherapy interaction.

Process affected	Mechanism[a]	Drug examples
Increased radiation damage[a]	Incorporation of chemotherapy drug into DNA/RNA	5-FU: incorporation into DNA, increasing susceptibility to RT damage Cisplatin: cross-links with DNA or RNA (intrastrand and interstrand); works for both hypoxic and oxygenated cells[51]
Inhibition of DNA repair process[a]	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)[a]	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[a]	Reoxygenation second to tumor shrinkage. Hypoxic cells are 2.5–3.0 times less radiation-sensitive than normoxic cells[18,44] Chemotherapy can help to eliminate hypoxic cells	Most chemotherapeutic agents; described in particular for paclitaxel[45] Tirapazamine, mitomycin (selective killing of hypoxic cells); nitroimidazoles (resensitize hypoxic cells to radiation)
Radiotherapy enhancement by preventing repopulation[a]	Systemic therapy can slow or stop rapid proliferation, which could otherwise be the basis for repopulation phenomenon	Most chemotherapeutic agents, in particular: Antimetabolites with activity in the S phase inhibit repopulation (e.g. 5-FU, hydroxyurea) EGFR inhibitors, which impede cell proliferation between RT fractions[100]
Inhibition of prosurvival and 'poor prognosis' markers[a]	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,[129–131] but on the basis of clinical experience likely to be a class effect[49,132]
Hyperradiation sensitivity[b]	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[29,50] Low-dose fraction radiation

[a]Chemoradiotherapy potentiation through drug addition. [b]Chemoradiotherapy potentiation 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 2 Mechanisms of radioresistance.

Process affected	Mechanism	Comments
Large tumor cell burden	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.[121,122]	Upfront or completion surgery should be considered to reduce tumor bulk or residual disease.
Tumor cell microenvironment/ hypoxia	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]). Hypoxia is present for two reasons: 1. increased interstitial pressure may cause hypoperfusion, hypoxia and acidosis;[124–126] 2. cancer-related anemia contributes to local hypoxia (HIF1α is a marker of tumor hypoxia).	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: 1. through reoxygenation second to tumor shrinkage (e.g. with paclitaxel[46]); 2. by killing hypoxic cells selectively (e.g. with tirapazamine or mitomycin C); 3. through resensitization of hypoxic cells to radiation (nitroimidazoles—in development).
Inherent or acquired tumor cell resistance	Multiple mechanisms are thought to contribute, including mutated p53[29], DNA repair gene amplification, increased levels of ROS scavengers, activation of prosurvival/poor-prognosis oncogenes (EGFR,[100,101] c-MET[32]).	Delays or interruptions in radiotherapy are known to lead to the development of radioresistance and allow such resistant cells to repopulate.
Repopulation	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]	Accelerated radiation schemes are intended to prevent repopulation.[128] 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]

Abbreviations: 5-FU, 5-fluorouracil; HIF1α, hypoxia-inducible factor 1-alpha; ROS, reactive oxygen species.

Chemoradiation principle in Sigmoid curve of radiation

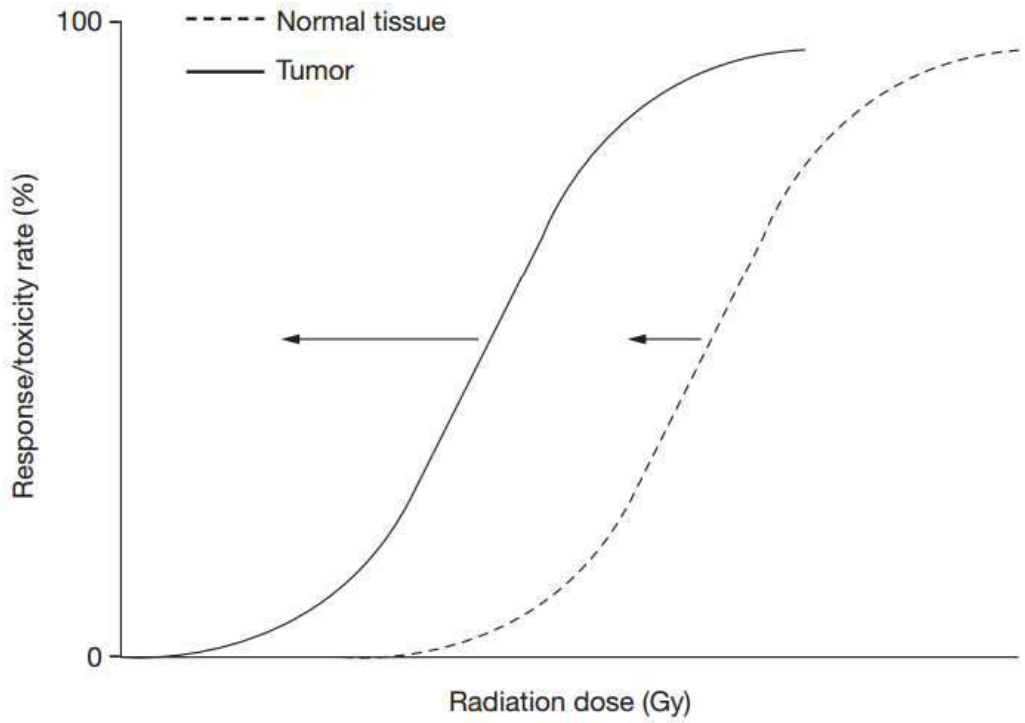


Figure 3 Schematic dose–response curves for tumor and normal tissue damage with radiation. The offset between the two curves indicates the therapeutic range. Chemoradiotherapy leads to a shift of both curves to the left, ideally with a stronger shift of the tumor curve (as indicated by the longer arrow), increasing overall efficacy of treatment (radiation enhancement).[120]

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

Pignon et al: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, *Radiother Oncol 92:4-14, 2009.*

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]

1 Cooper et al: Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group, *JAMA* 281:1623-1627, 1999.

2. Pignon, et al: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, *Radiother Oncol 92:4-14, 2009.*

3. Lukka et al Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer: a meta-analysis. Clin Oncol (R Coll Radiol) (2002) 14(3):203–212

4. J Natl Cancer Inst. 2011 Oct 5;103(19):1452-60. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410.

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**

- **1. Pignon JP: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, Radiother Oncol 92:4-14, 2009.**
- **2. J Med Imaging Radiat Oncol. 2013 Feb;57(1):97-104. Radiation with cisplatin or carboplatin for locally advanced cervix cancer: the experience of a tertiary cancer centre.**

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 ca concomitant with RT

Dose:

- 400mg/m^2 wk before RT f/b 250mg/m^2 wkly

Results:

- 5yr OS – 45% vs 36% [1]

1 Bonner JA, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck,
2 *N Engl J Med 354:567-578*,2006.

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 is10 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

1.UKCCCR Anal Canal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomized trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and mitomycin C. Lancet 1996;348:1049-1054

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]

1UKCCCR Anal Canal Cancer Trial Working Party Lancet 1996;348:1049-1054.

2. Cooper et al: Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group, *JAMA* 281:1623-1627, 1999.

3. Macdonald et al: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction, *N Engl J Med 345:725-730, 2001.*

4. Pignon: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, *Radiother Oncol 92:4-14, 2009.*

5. Lukka H et al (2002) Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer: a meta-analysis. Clin Oncol (R Coll Radiol) 14(3):203–212

6. Radiol Med. 2013 Jan 28. **Neoadjuvant oxaliplatin and 5-fluorouracil with concurrent radiotherapy in patients with locally advanced rectal cancer: a singleinstitution experience.**

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/m^2

Results

- No survival advantage over cisplatin [1]

1. Radiat Oncol. 2010 Sep 23;5:84. **A phase II randomized trial comparing radiotherapy with concurrent weekly cisplatin or weekly paclitaxel in patients with advanced cervical cancer.** Geara FB, Shamseddine A, Khalil A, Abboud M, Charafeddine M, Seoud M.
2. J Clin Oncol. 2010 May 1;28(13):2213-9. **Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine with concurrent radiation therapy in localized carcinoma of the esophagus or gastroesophageal junction.** Spigel DR, Greco FA, Meluch AA, Lane CM, Farley C, Gray JR, Clark BL, Burris HA , Hainsworth JD

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.

Temozolomide

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]

Stupp R et al Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005 352(10):987–996

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 → inhibition of DNA synthesis and function.
- Bioreductive activation by NADPH cytochrome P450 reductase, and DT-diaphorase to oxygen free radical forms → 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 ca

Doses

- Anal cancer - 12mg/m^2
- Head and neck ca - 8mg/m^2

Pignon JP, le Maitre A, Maillard E, et al: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, *Radiother Oncol 92:4-14, 2009*.

Mitomycin-C for concomitant chemoradiation

Results

- Anal cancer - 3 year OS 65% vs 58% [1]
- Head and neck ca - MS – 16.5 mth vs 13mth

UKCCCR Anal Canal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomized trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and mitomycin C. Lancet 1996; 348:1049-1054.

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%**

J Natl Cancer Inst. 2011 Oct 5;103(19):1452-60. **Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410.**

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 α1-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**

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

1. J

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.

Vinblastine

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%**

J Natl Cancer Inst. 2011 Oct 5;103(19):1452-60. **Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410.**

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%**

Anticancer Res. 2012 Feb;32(2):681-6. **Comparison of concurrent chemoradiotherapy versus induction chemotherapy followed by radiation in patients with nasopharyngeal cancer**

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%**

.

Radiation Med 2013 Jan 28. **Neoadjuvant oxaliplatin and 5-fluorouracil with concurrent radiotherapy in patients with locally advanced rectal cancer: a single institution experience.**

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

Docetaxel

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**

1. J Clin Oncol. 2010 May 1;28(13):2213-9. **Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine with concurrent radiation therapy in localized carcinoma of the esophagus or gastroesophageal junction.**

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

1. J Clin Oncol. 2010 May 1;28(13):2213-9. **Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine with concurrent radiation therapy in localized carcinoma of the esophagus or gastroesophageal junction.**

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**

Cancer. 2012 Oct 15;118(20):5008-14. **A phase 2 study of bevacizumab with cisplatin plus intensity-modulated radiation therapy for stage III/IVB head and neck squamous cell cancer.**

Gemcitabine

Mechanism of Action

- Antimetabolite
- Cell cycle-specific (S-phase)
- Antitumor activity of 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/m^2
- NSCLC - 300mg/m^2
- Head and neck ca - 300mg/m^2
- Glioblastoma - 300mg/m^2
- Cervical ca - 300mg/m^2

Toxicity of Anticancer Agents

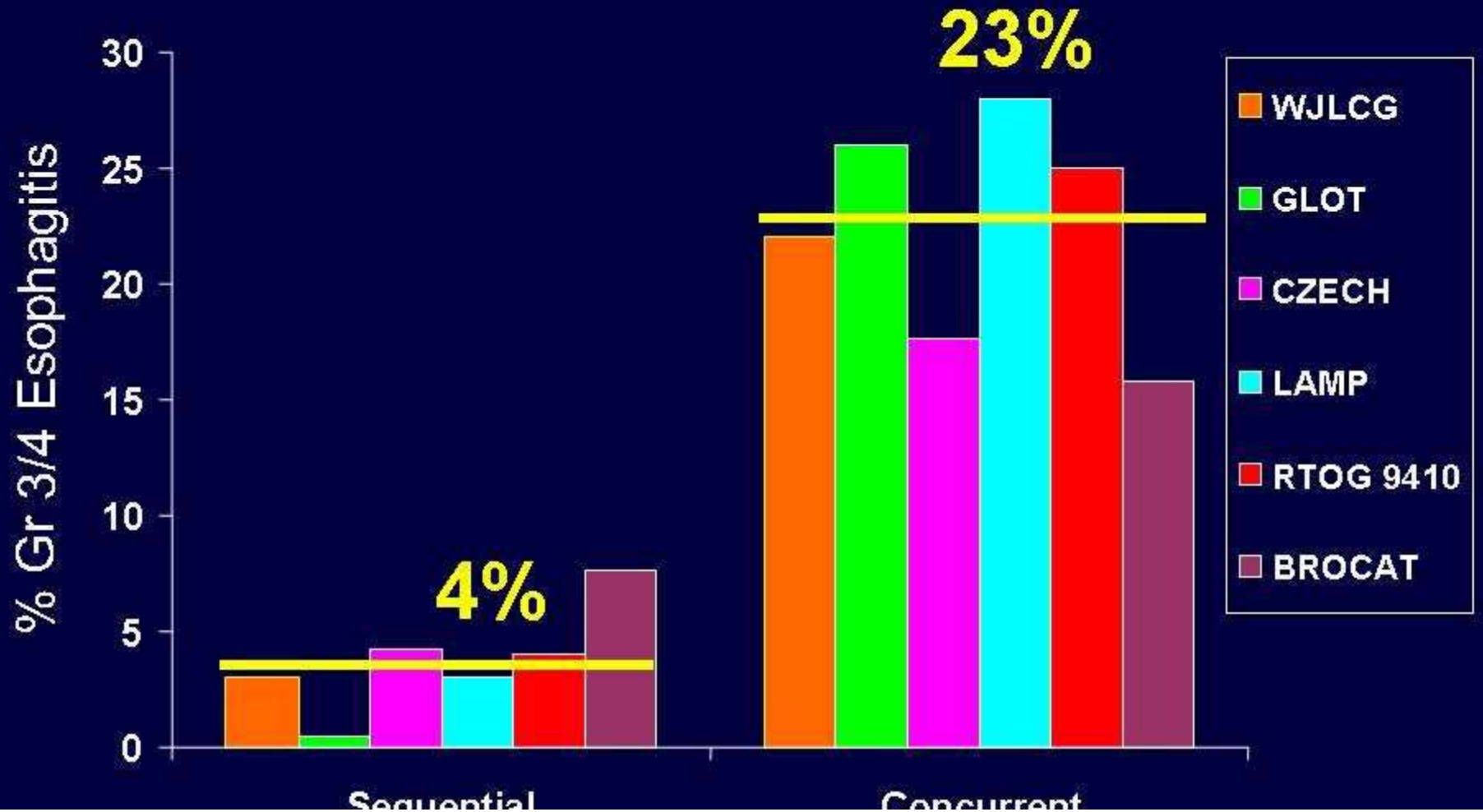
- Narrow Safety profile
- Toxiicty because of two main reasons
  - Increased killing of normal cells
    - e.g. bone marrow suppression
  - Inherent cell kill by specific drugs
- Can Involvement any organ in body

Chemotherapy Treatment

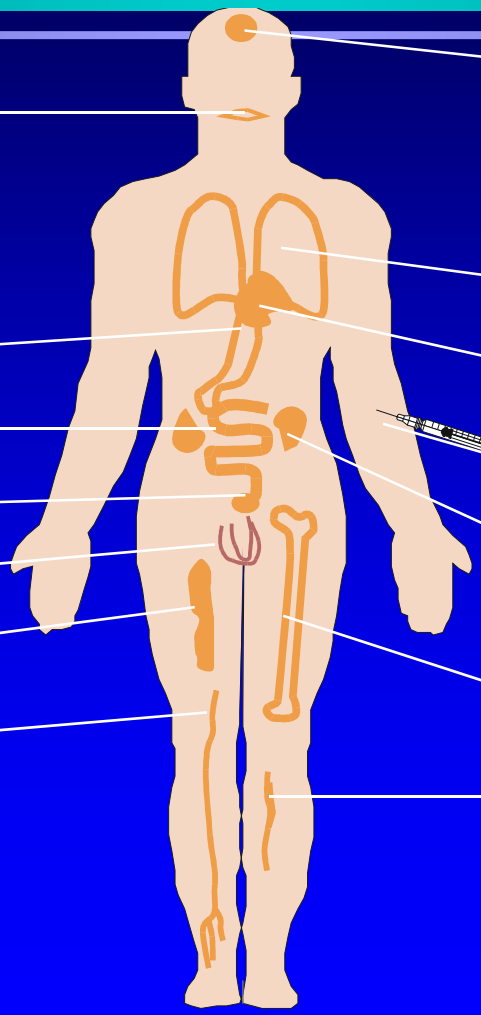
- Chemotherapy is administered on a dose-response relationship (the more drug given the more cancer cells killed)
- It has a narrow therapeutic index – meaning there is a very small difference between the amount of drug that equals results and the amount of drug that equals harm

$$\frac{\text{Benefit}}{\text{Harm}} = \frac{\text{Relief of Cancer Symptoms}}{\text{Treatment-Related Toxicity}}$$

Early Toxicity Comparison between Sequential and Concurrent CT/RT



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

Chemotherapeutic drugs	Toxicity
Cisplatin	Nephrotoxicity, neurotoxicity, ototoxicity, myelosuppression. Emetogenic
Carboplatin	Myelosuppression, nephrotoxicity Emetogenic, alopecia
Vinblastine	Myelosuppression, neurotoxicity, Hypertension, alopecia, mucositis
Methotrexate	Myelosuppression, nephrotoxicity (ARF), mucositis

Chemotherapy Drug Toxicity

Chemotherapeutic drugs	Toxicity
5-FU	Myelosuppression, Hand-foot syndrome, mucositis, neurologic toxicity
Etoposide	Myelosuppression, mucositis, alopecia,
Mitomycin-c	Myelosuppression, mucositis, hemolytic uremic syndrome
Temozolamide	Myelosuppression, nausea & vomiting, headache, photosensitivity

Chemotherapy Drug Toxicity

Chemotherapeutic drugs	Toxicity
Oxaliplatin	Neurotoxicity, emetogenic, diarrhoea, myelosuppression, hepatotoxicity
Vinorelbine	Myelosuppression, GI toxicity, nausea & vomiting, neurotoxicity,alopecia
Gefitinib	Elevation in B.P, Skin rash, pruritis
Capecitabine	Diarrhoea, nausea & vomiting, Hand-foot syndrome,↑LFT, neurologic toxicity

Chemotherapy Drug Toxicity

Chemotherapeutic drugs	Toxicity
Cetuximab	Infusion related symptoms, skin rash, pruritis, pulmonary toxicity, hypomagnesemia
Paclitaxel	Myelosuppression, hypersensitivity reaction, neurotoxicity, alopecia, transient asymptomatic sinus bradycardia, mucositis
Docetaxel	Myelosuppression, hypersensitivity reaction, fluid retention syndrome, skin rash, pruritis, alopecia

Chemotherapy Drug Toxicity

Chemotherapeutic drugs	Toxicity
Bevacizumab	Gastrointestinal perforations and wound healing complications. Bleeding complications, Increased risk of arterial thromboembolic events, including MI, Hypertension
Gemcitabine	Myelosuppression, nausea & vomiting, flu like syndrome, transient hepatic dysfunction.

Indications Dose and Results of chemoradiation

Drug	Indication	Dose	Remarks
Cisplatin	Esophageal ca Head and neck ca NSCLC Cervix ca	75mg/m^2 100mg/m^2 100mg/m^2 75mg/m^2	5yr OS – 26% vs 0% [1] OS - 78% vs 47% [2] 5yr OS 16% vs 10% [5] 5yr OS – 69% vs 55% [3]
Carboplatin	Head and neck ca Cervix ca	300mg/m^2	OS – 22% vs 16% [2] No OS benefit [4]
Vinblastine	NSCLC	6mg/m^2	5yr OS 16% vs 10% [5]

1. Cooper JS, Guo MD, Herskovic A, et al: Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group, *JAMA* 281:1623-1627, 1999.
2. Pignon JP, le Maitre A, Maillard E, et al: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, *Radiother Oncol 92:4-14, 2009.*
3. Lukka H et al (2002) Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer: a meta-analysis. Clin Oncol (R Coll Radiol) 14(3):203–212
4. J Med Imaging Radiat Oncol. 2013 Feb;57(1):97-104. **Radiation with cisplatin or carboplatin for locally advanced cervix cancer: the experience of a tertiary cancer centre.** Au-Yeung G, Mileshkin L, Bernshaw DM, Kondalsamy-Chennakesavan S, Rischin D, Narayan K
5 J Natl Cancer Inst. 2011 Oct 5;103(19):1452-60. **Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410.** Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, Movsas B, Wasserman T, Rosenthal SA, Gore E, Machtay M, Sause W, Cox JD

Indications Dose and Results of chemoradiation

Drug	Indication	Dose	Remarks
Methotrexate	Head and neck ca	30mg/m^2	OS – 47% vs 37% [1]
5-FU	Anal ca Esophageal ca Gastric ca Rectal ca Head and neck ca Cervix ca	1000mg/m^2 600mg/m^2 600mg/m^2 325mg/m^2 1200mg/m^2 1000mg/m^2	3 yr OS – 65%vs 58% [2] 5yr OS – 26% vs 0% [3] 3yr OS – 50% vs 41% [4] OS-63%, DFS-53% [7] OS – 63% vs 50% [5] 5yr OS – 69% vs 55% [6]

1. Anticancer Res. 2012 Feb;32(2):681-6. **Comparison of concurrent chemoradiotherapy versus induction chemotherapy followed by radiation in patients with nasopharyngeal carcinoma.** Komatsu M, Tsukuda M, Matsuda H, Horiuchi C, Taguch T, Takahashi M, Nishimura G, Mori M, Niho T, Ishitoya J, Sakuma Y, Hirama M, Shiono O

2. UKCCCR Anal Canal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomized trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and mitomycin C. Lancet 1996;348:1049-1054.
3. Cooper JS, Guo MD, Herskovic A, et al: Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group, *JAMA* 281:1623-1627, 1999.
4. Macdonald JS, Smalley SR, Benedetti J, et al: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction, *N Engl J Med 345:725-730, 2001.*
5. Pignon JP, le Maitre A, Maillard E, et al: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, *Radiother Oncol 92:4-14, 2009.*
6. Lukka H et al (2002) Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer: a meta-analysis. Clin Oncol (R Coll Radiol) 14(3):203–212
7. Radiol Med. 2013 Jan 28. **Neoadjuvant oxaliplatin and 5-fluorouracil with concurrent radiotherapy in patients with locally advanced rectal cancer: a singleinstitution experience.** Greto D, Paiar F, Saieva C, Galardi A, Mangoni M, Livi L, Agresti B, Franceschini D, Bonomo P, Scotti V, Detti B, Tonelli F, Valeri A, Messerini L, Biti G

Indications Dose and Results of chemoradiation

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

1. UKCCCR Anal Canal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomized trial of radiotherapy alone versus radiotherapy, 5-fluorouracil and mitomycin C. Lancet 1996;348:1049-1054.
2. Pignon JP, le Maitre A, Maillard E, et al: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC). An update on 93 randomised trials and 17,346 patients, *Radiother Oncol 92:4-14, 2009.*
3. *EORTC/NCI Canada 2005* , Stupp R et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(10):987–996
4. Radiol Med. 2013 Jan 28. **Neoadjuvant oxaliplatin and 5-fluorouracil with concurrent radiotherapy in patients with locally advanced rectal cancer: a singleinstitution experience.** Greto D, Paiar F, Saieva C, Galardi A, Mangoni M, Livi L, Agresti B, Franceschini D, Bonomo P, Scotti V, Detti B, Tonelli F, Valeri A, Messerini L, Biti G
5. 5 J Natl Cancer Inst. 2011 Oct 5;103(19):1452-60. **Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410.** Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, Movsas B, Wasserman T, Rosenthal SA, Gore E, Machtay M, Sause W, Cox JD

Indications Dose and Results of chemoradiation

Drug	Indication	Dose	Remarks
Biomab [Bevacizumab]	Head and neck ca	15mg/kg	2yr OS – 88%, no increased toxicity [5]
Vinorelbine	Head and neck ca NSCLC	10mg/m^2 10mg/m^2	CR = 90% vs 70% [Cis- as CCRT] [8] RR = 80% [7]
Gefitinib	Head and neck ca	250mg PO	Supra-additive effect on HNSCC cell [6]

5. Cancer. 2012 Oct 15;118(20):5008-14. **A phase 2 study of bevacizumab with cisplatin plus intensity-modulated radiation therapy for stage III/IVB headand neck squamous cell cancer.** Fury MG, Lee NY, Sherman E, Lisa D, Kelly K, Lipson B, Carlson D, Stambuk H, Haque S, Shen R, Kraus D, Shah J, Pfister DG.
6. J Cancer Res Clin Oncol. 2007. **Concurrent use of vinorelbine and gefitinib induces supra-additive effect in head and neck squamous cell carcinoma cell lines.** Erjala K, Raitanen M, Kulmala J, Grénman R.
7. Cancer Chemother Pharmacol. 2006 Sep;58(3):361-7. Epub 2005 Dec 6. **The combination of cisplatin and vinorelbine with concurrent thoracic radiation therapy for locally advanced stage IIIA or IIIB non-small-cell lung cancer.** Hirose T, Mizutani Y, Ohmori T, Ishida H, Hosaka T, Ando K, Shirai T, Okuda K, Ohnishi T, Horichi N, Kubota H, Adachi M.
8. Indian J Med Paediatr Oncol. 2010 Jan-Mar; 31(1): 4–7. **Comparison of vinorelbine with cisplatin in concomitant chemoradiotherapy in head and neck carcinoma** Devleena, Anup Majumdar, Soumita Poddar, and Anindya Chakraborty

Indications Dose and Results of chemoradiation

Drug	Indication	Dose	Remarks
Capecitabine	Esophagus ca	1000mg/m^2	2yr OS - 52% [1]
Cetuximab	Head and neck ca	400mg/m^2 wk before RTf/b 250mg/m^2 wkly	5yr OS – 45% vs 36% [2]
Gemcitabine	Pancreatic ca NSCLC Head and neck ca Glioblastoma Cervical ca	1000mg/m^2 300mg/m^2 300mg/m^2 300mg/m^2 300mg/m^2	Phase I/II trials [3]

1. J Clin Oncol. 2010 May 1;28(13):2213-9. **Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine with concurrent radiation therapy in localized carcinoma of the esophagus or gastroesophageal junction.** Spigel DR, Greco FA, Meluch AA, Lane CM, Farley C, Gray JR, Clark BL, Burris HA , Hainsworth JD
2. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck, *N Engl J Med 354:567-578*,2006.
3. BEA PAUWELS, ANNELIES E.C. KORST, FILIP LARDON, JAN B. VERMORKEN Combined Modality Therapy of Gemcitabine and Radiation. The Oncologist 2005;10:34-51.

Indications Dose and Results of chemoradiation

Drug	Indication	Dose	Remarks
Paclitaxel	Cervix ca Head and neck ca	50mg/m^2	No survival advantage over cisplatin [1]
Docetaxel	Esophagus ca	20mg/m^2	2yr OS – 52% [2]
Bleomycin	High grade glioma	10mg/m^2	OS same as RT alone [3]

1. Radiat Oncol. 2010 Sep 23;5:84. **A phase II randomized trial comparing radiotherapy with concurrent weekly cisplatin or weekly paclitaxel in patients with advanced cervical cancer.** Geara FB, Shamseddine A, Khalil A, Abboud M, Charafeddine M, Seoud M.

2. J Clin Oncol. 2010 May 1;28(13):2213-9. **Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine with concurrent radiation therapy in localized carcinoma of the esophagus or gastroesophageal junction.** Spigel DR, Greco FA, Meluch AA, Lane CM, Farley C, Gray JR, Clark BL, Burris HA , Hainsworth JD

3. Laperriere N (2002) Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. Radiother Oncol 64(3):259–273.

Table 1 Overview of disease entities and indications in which concurrent chemoradiotherapy is used.[a]

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

[a]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 2

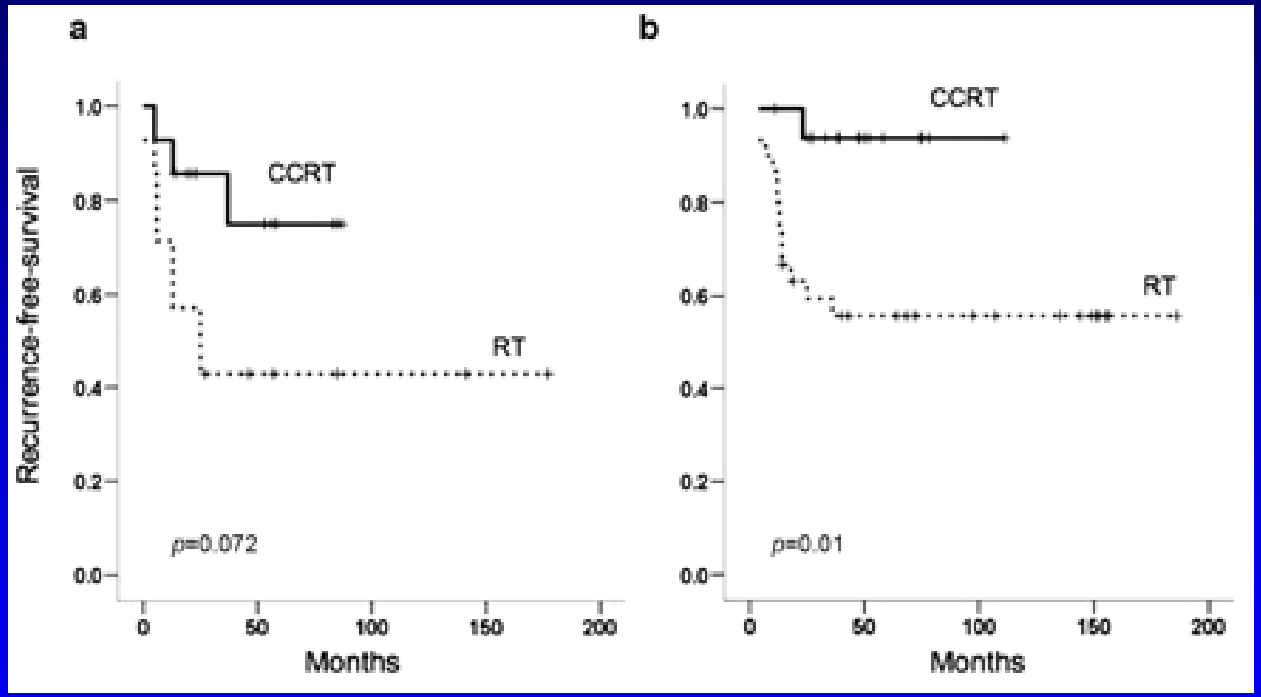
Randomized Trials of Chemoradiation in Cervical Cancer

Trial	Patients	Arms (Radiation/Chemotherapy Dose)	Outcome
RTOG 90-01	493, stage IIB–IVA (or IB/IIA < 5 cm/biopsy-proven node)	• 45 Gy to pelvis & lower para-aortics, 1–2 LDR implants • 45 Gy to pelvis, 1–2 LDR implants with 5-FU 1,000 mg/m² × 96 h + cisplatin 75 mg/m² over 4 h on d1–5, 22–26, 2nd implant	52% 5-yr OS 72% 5-yr OS (*P* < .0001)
GOG 123	368, node-negative, bulky, stage IB	• 45 Gy to pelvis, 1–2 LDR implants followed by hysterectomy • Same radiation with weekly cisplatin 40 mg/m² × 6	74% 3-yr OS 85% 3-yr OS (*P* = .008)
SWOG 8797	268, post–radical hysterectomy (+ margins, pelvic nodes, parametrial involvement)	• 49.3 ± 45 Gy to para-aortic nodes • Same radiation with 5-FU 1,000 mg/m² × 96 h + cisplatin 70 mg/m² over d1–5, 22–26 + 2 additional cycles afterwards	63% 4-yr OS 80% 4-yr OS (*P* = .003)
GOG 85	388, stage IIB–IVA (node-negative)	• Radiation to pelvis (dose varied by stage), 1–2 LDR implants with 5-FU 1,000 mg/m² × 96 h + cisplatin 50 mg/m² on d1, 29 • Same radiation with hydroxyurea 80 mg/kg biweekly	55% 8.7-yr OS 43% 8.7-yr OS (*P* = .018)
GOG 120	526, stage IIB–IVA	• Radiation to pelvis (dose varied by stage) + weekly cisplatin 40 mg/m² × 6 cycles • Same radiation with cisplatin 50 mg/m² + 5-FU 1,000 mg/m²/d × 96 h on d1, 29 + hydroxyurea twice weekly × 6 • Same radiation with hydroxyurea 3 g/m² twice weekly × 6	65% 3-yr OS (both cisplatin arms) 47% 3-yr OS (*P* < .004)

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

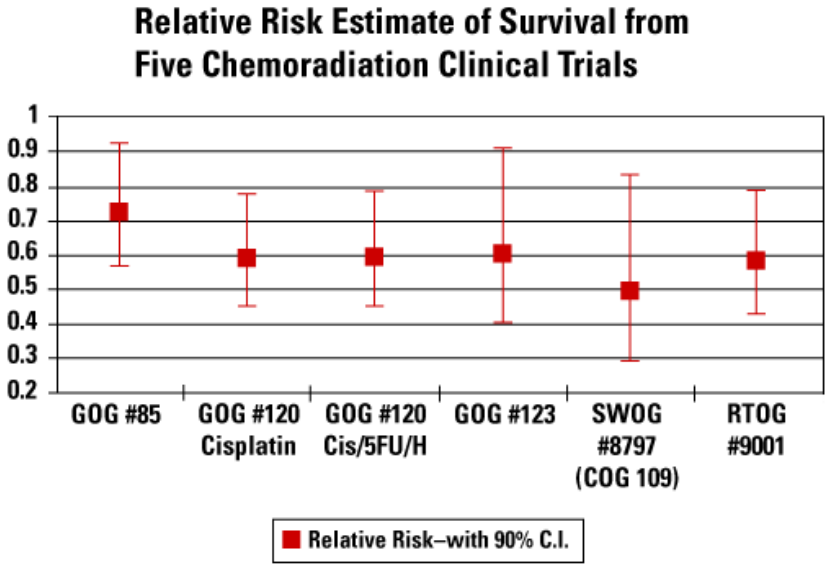


Ademocarcinoma cervix.

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%.

Chemoradiation in Lung Cancer

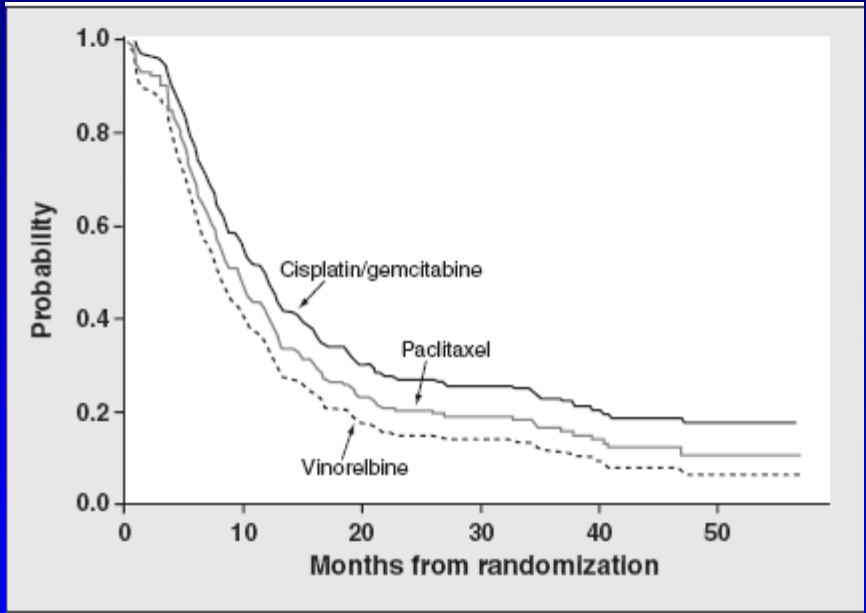


Figure 2: Overall Survival—Patients receiving concurrent radiation therapy and chemotherapy (cisplatin plus gemcitabine, paclitaxel, or vinorelbine). Modified, with permission, from Vokes.[31]

ONCOLOGY. Vol. 18 No. 8 5 **July 1, 2004**

Advantage of Chemoradiation in Head and Neck Cancer

Trial	Patients	Primary treatment	Adjuvant therapy	Grade 3 and 4 toxic effects	Increased local control rate	Difference in overall survival in favor of chemoradiotherapy
EORTC[a] 22931 (2004)[13]	167 with high-risk features on pathology	Surgery	CRT (P); RT alone[c]	Acute: CRT 41%; RT 21% Chronic: difference NS	Yes: CRT 82%; RT 69% (at 5 years)	Yes: CRT 53%; RT 40% (at 5 years)
RTOG[a] 9501 (2004)[14]	459 with high-risk features on pathology	Surgery	CRT (P); RT alone[c]	Acute: CRT 77%; RT 34% Chronic: difference NS	Yes: CRT 82%; RT 72% (at 2 years)	No: CRT ~65.0%; RT ~57.5% (at 2 years – but significant difference in DFS)
Bachaud *et al.* (1996)[17]	83 with high-risk features on pathology	Surgery	CRT (P); RT alone	Acute: CRT 41%; RT 18% Chronic: difference NS	Yes: CRT 77%; RT 59% (at 4 years)	Yes: CRT 72%; RT 46% (at 2 years)
Intergroup 91-11 Larynx (2003)[15]	510 with laryngeal cancer	CRT (P); RT plus induction chemotherapy; RT alone	NA	Acute: CRT 77%; RT + I 51%; RT 47%[a] Chronic: CRT 30%; RT + I 24%; RT 36% (difference NS)	Yes: CRT 80%; RT + I 64%; RT 58% (at 2 years)	No: CRT 76%; RT + I 74%; RT 75% (at 2 years) but increased larynx preservation (CRT 88%; RT + I 75%; RT 70%)
Al-Sarraf *et al.* (1998)[25]	193 with NPC	CRT (P) plus consolidation with PF; RT alone	NA	Acute: CRT 75.6%; RT 50% Chronic: not reported	Yes: CRT 89.2%; RT 74.0%	Yes: CRT 76%; RT 46% (3-year OS)
Adelstein *et al.* (2003)[24]	295 with unresectable tumors	RT alone; CRT (P); CRT (PF) split course[b]	NA	Acute: RT 52%; CRT 85%[a]; CRT[b] 72% Chronic: not reported	Not reported but raised CR rate after therapy: RT 27%; CRT 41%; CRT[b] 37%	Yes: RT 23%; CRT 37%[a]; CRT[b] 27% (3-year OS)
Jeremic *et al.* (2000)[37]	130 with stage III or IV disease	HFX (RT); HFX (CRT and daily P)[f]	NA	Acute: difference NS[d] Chronic: difference NS	Yes: RT 27%; CRT 53%	Yes: RT 25%; CRT 46% (5-year OS)

How much radiation is the chemotherapy worth in advanced head and neck cancer?

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.

Int J Radiat Oncol Biol Phys. 2007 Aug 1;68(5):1491-5.

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