Does Chemo-radiation increases Therapeutic Ratio ?

Prof. U P Shahi
Institute of Medical Sciences,
Banaras Hindu University
shahiuday@gmail.com

Indications of Concurrent Chemoradiation

1.Head and Neck Cancer - locally advanced –Primary or Adjuvant

- 2.Non small cell lung Ca -stage IIIB-non operable,non metastatic
- 3.SCLC –limited stage
- 4.Esophageal ca –locally advanced
- 5.Rectal Ca-neoadjuvant
- 6.Anal Ca-primary
- 7.Gastric Ca- adjuvant
- 8.Pancreas Ca-Adjuvant,unresectable,advanced
- 9.Cholangiocarcinoma –Adjuvant,unresectable

10. Ca Cervix-Primary

- 11.Ca Urinary Bladder-Primary
- 12.Glioblastoma-Adjuvant
- 13.Sarcoma-Neoadjuvant

Concurrent chemoradiation

Commonly used agents	Benefit
1.Cisplatin,5 FU,FHX,Cetuxi	1.Organ preserv,survival
2.Cisplat,carbo/pacli,cisplat/etop	2.Curative
3.Cisplat/etop	3.Curative
4.Cisplat/5-FU	4.survival,cure,organ preserv
5.5-FU	5.Sphincter preserve,less failure
6.5 FU,MMC	6.Organ preserve
7.Cisplat,5 FU	7.Survival ?
8.5- FU	8.Locoregional control,?survival
9.5-FU	9.Survival ?
10. cisplat,5 FU,HydroxyU	10.local,distal control,organ preserve
11.Cisplat	11.Local control
12.Temozolamide	12.Survival
13.Doxorubicin	13.downstaging,organ preserve

Rationale for CT-RT Combine

- No interaction
- Independent action
- =>
- RT:local control(in field)
- --->radiation toxicities
- CT:distal control(out of field)-->CT toxicities
- =>independent toxicities

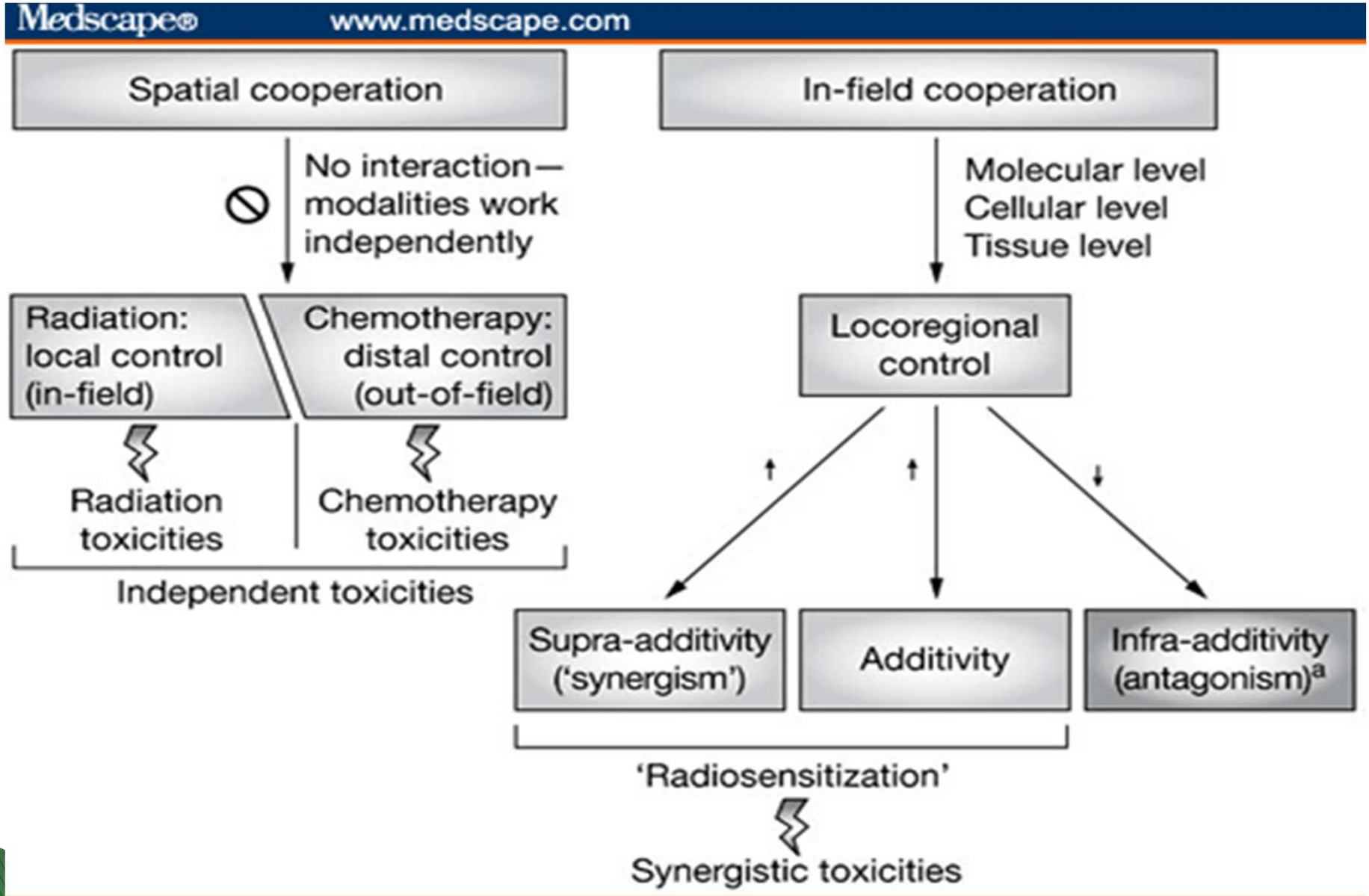
- Molecular/cellular/tissue level
- =>Locoregional control

- -->supra-additive(synergy)
- -->Additivity
- => Radiosensitization
- ->synergistic toxicities

- -->infra additive(antagonism)

Spatial co operation

In field co operation


Medscape®
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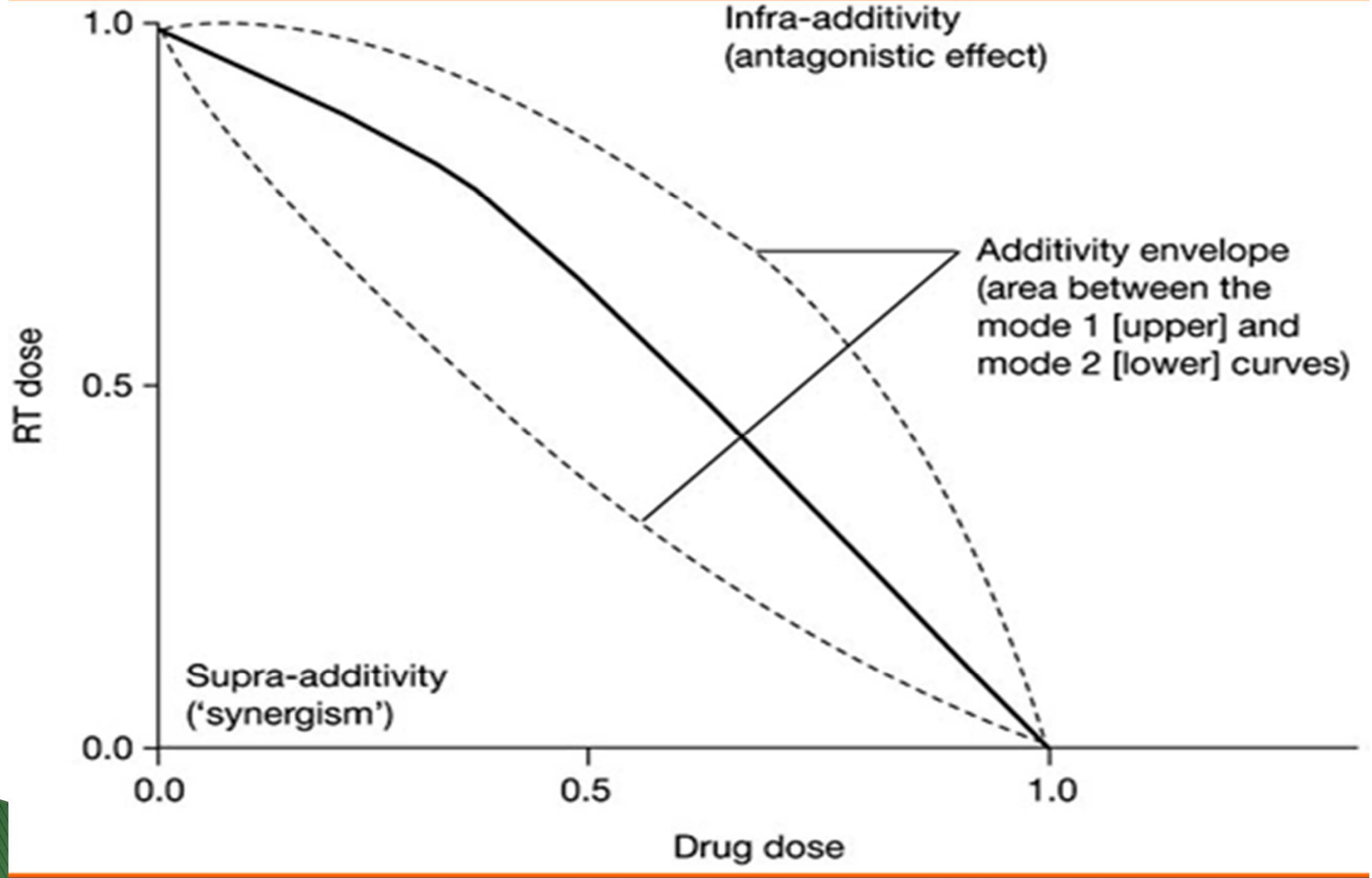
Spatial cooperation
No interaction—modalities work independently
Radiation: local control (in-field)
Chemotherapy: distal control (out-of-field)
Radiation toxicities
Chemotherapy toxicities
Independent toxicities
In-field cooperation
Molecular level
Cellular level
Tissue level
Locoregional control
Supra-additivity ('synergism')
Additivity
Infra-additivity (antagonism)[a]
'Radiosensitization'
Synergistic toxicities
Source: Nat Clin Pract Oncol © 2007 Nature Publishing Group

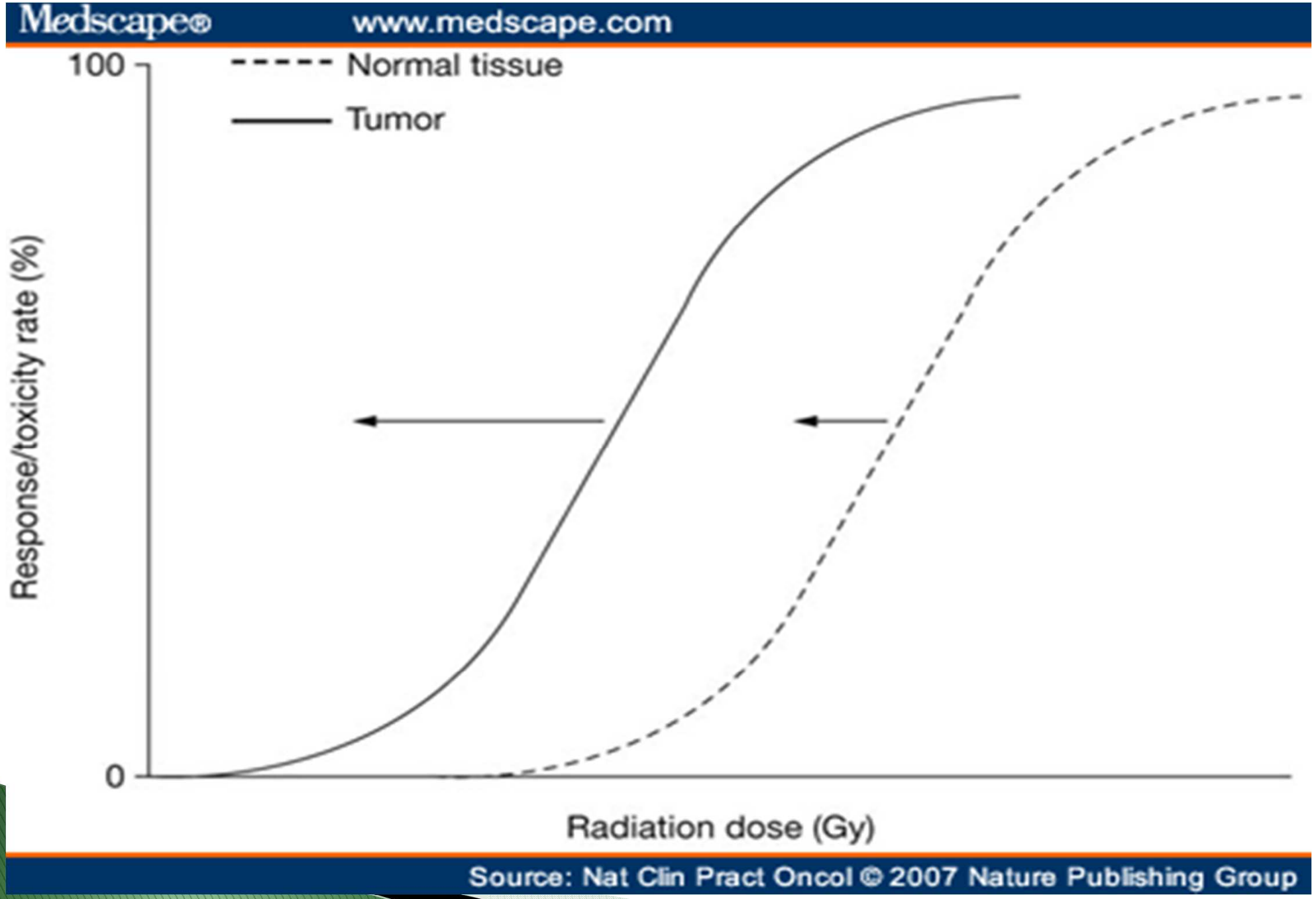
Isobologram for a combination of RT and CT agent

- Additivity Envelope
- Above Upper curve- infra additivity effect
- Below Lower curve-supra additivity effect



Dose response curve with RT

- CT–RT : leads to a shift of both curves for tumor response and normal tissue toxicity to the left,ideallywith a stronger shift of the tumor curve ,increasing Therapeutic Ratio.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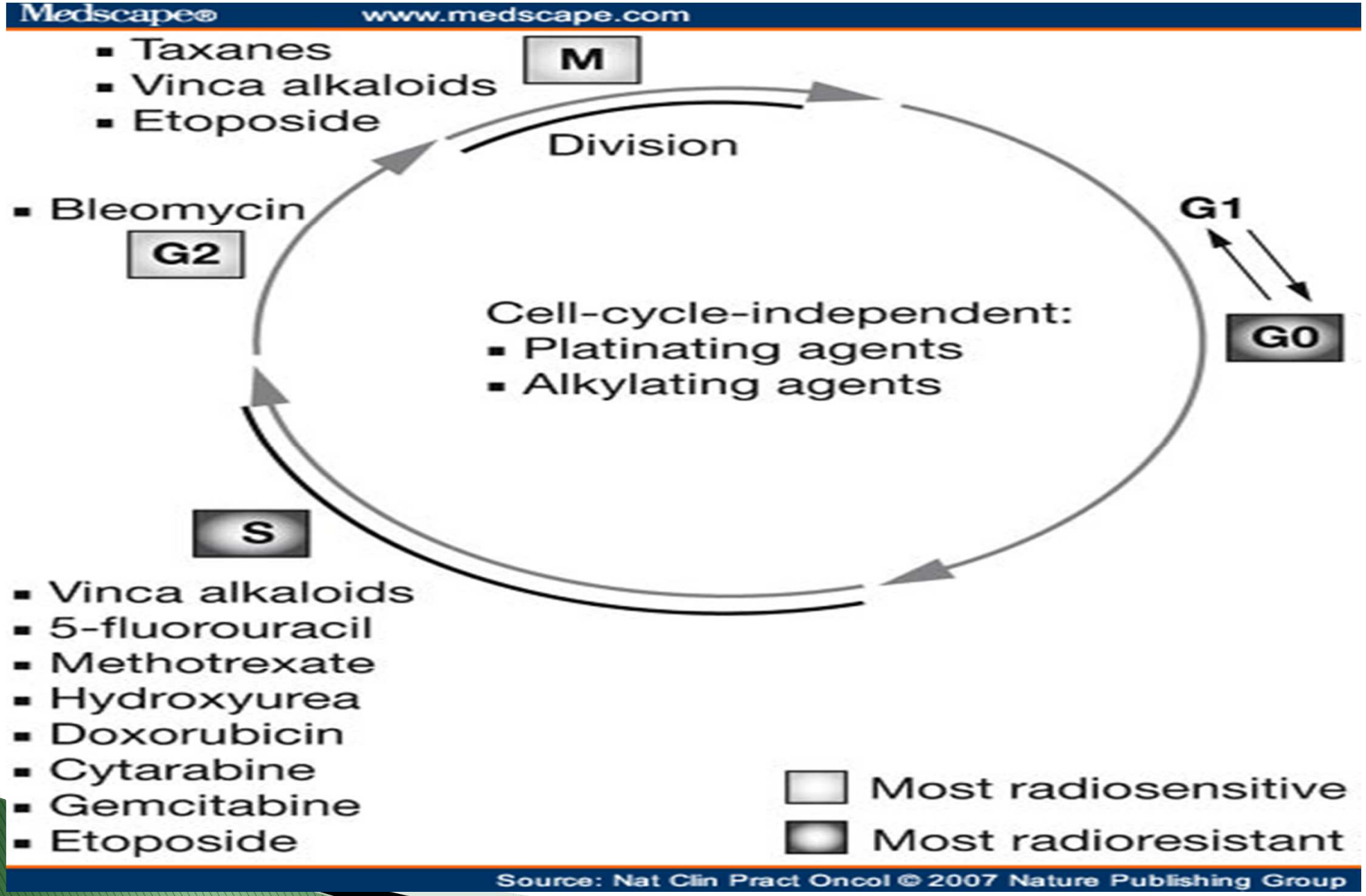
100
Normal tissue
Tumor
Response/toxicity rate (%)
0
Radiation dose (Gy)
Source: Nat Clin Pract Oncol © 2007 Nature Publishing Group


Medscape®
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Taxanes
Vinca alkaloids
Etoposide
M
Division
Bleomycin
G2
G1
G0
Cell-cycle-independent:
Platinating agents
Alkylating agents
S
Vinca alkaloids
5-fluorouracil
Methotrexate
Hydroxyurea
Doxorubicin
Cytarabine
Gemcitabine
Etoposide
Most radiosensitive
Most radioresistant
Source: Nat Clin Pract Oncol © 2007 Nature Publishing Group

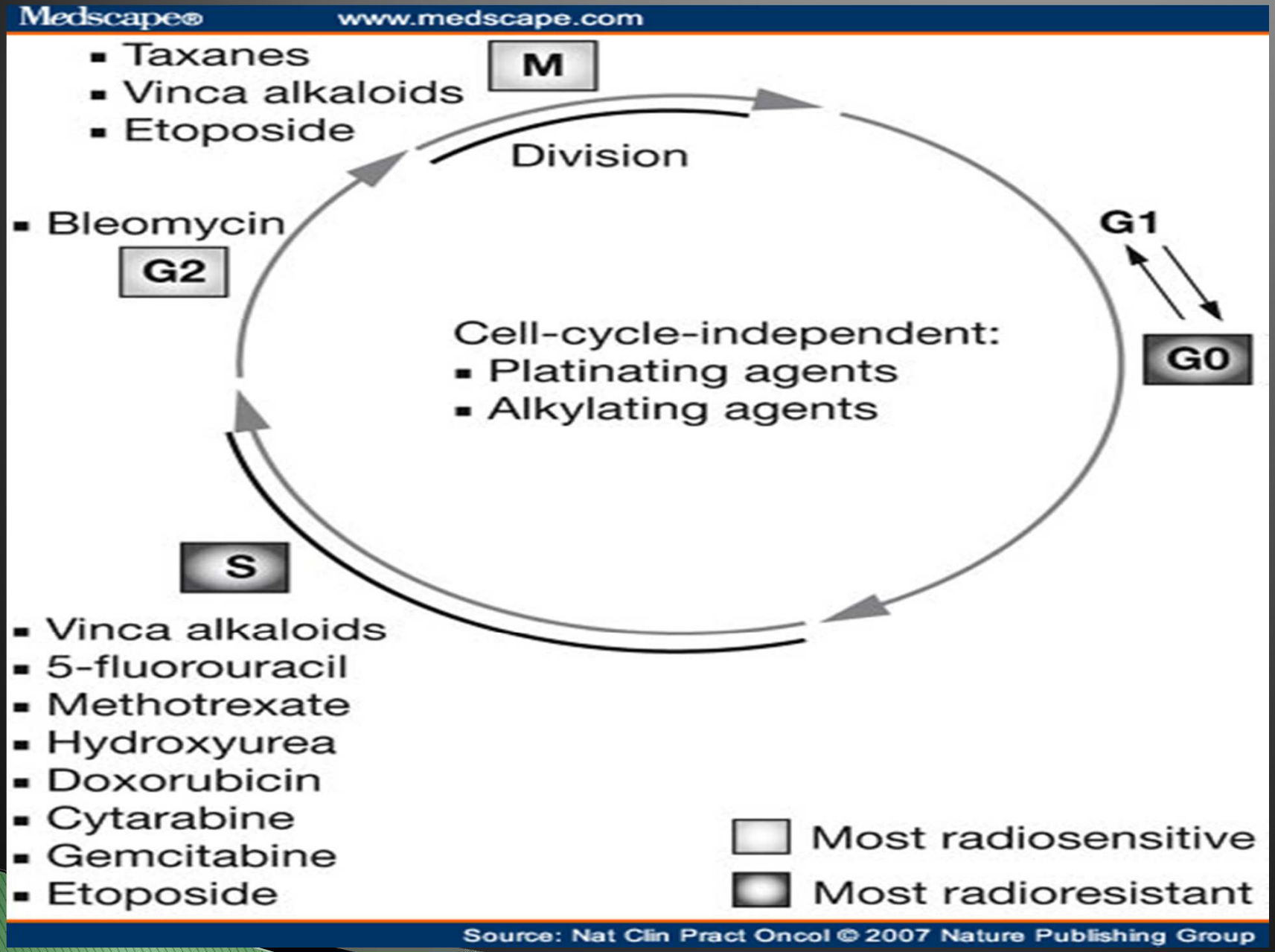
Radioresistance

- Large tumor cell burden
- Tumor cell micro environment/Hypoxia
- Inherent or acquired resistance : mutated p53,DNA repair gene amplification,increased scavanger,activation of EGFR,c-MET
- Repopulation

- Surgery to reduce tumor bulk or residual disease
- CT increase radiation effect:
  reoxygenation-tumor shrinkage with paclitax
  kill hypoxic cell-mmc
  hypoxic cell sensitizer

Avoid delay/interruptions in RT
Accelerated RT
Antimetabolites,active in S phase,5 FU
EGFR inhibitors block cell prolif

Process affected/mechanism	comments


Medscape®
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Taxanes
Vinca alkaloids
Etoposide
M
Division
Bleomycin
G2
G1
G0
Cell-cycle-independent:
Platinating agents
Alkylating agents
S
Vinca alkaloids
5-fluorouracil
Methotrexate
Hydroxyurea
Doxorubicin
Cytarabine
Gemcitabine
Etoposide
Most radiosensitive
Most radioresistant
Source: Nat Clin Pract Oncol © 2007 Nature Publishing Group

Mechanisms of CT-RT interaction

- Process affected
- 1.Increase radiation damage by incorporating drug into DNA/RNA
- 2.inhibit DNA repair(post RT)

- Drugs examples

1.1.5-FU->DNA

Cisplat:Xlink with DNA/RNA,both hypoxic/euoxic cells

2. Halogenated pyrimidine(5-FU,BdUR,IdUR);nucleoside analogue,gemcitabine Cisplatin,MTX,Doxorubicin,Etoposide,hydroxyurea,lomustine

CT-RT interaction

3.Cytokinetic co operation, synchronization

accumulate cells in G2,M ph

eliminate cells in resistant S phase

4. Action on hypoxic cells

Reoxygenation

CT eliminates hypoxic cells

- Process affected

3.Taxanes-cell cycle arrest

nucleoside analogs,gemcitabine,etoposide,MTX,hydroxyU

4. Most drugs

Taxanes

Tirapazamine,mmc

Hypoxic cell sensitizers

- Drug example

CT-RT interaction

5. Prevent repopulation

6.Inhibit prosurvival and poor prognosis markers

Targeted therapy,block signalling pathways

7.Hyper radiation sensitivity

- Process affected

5.Most drugs

Anti metabolite with S phase activity-inhibit repopulation

5-FU,HydroxyU

EGFR inhibitors –inhibit inter# proliferation

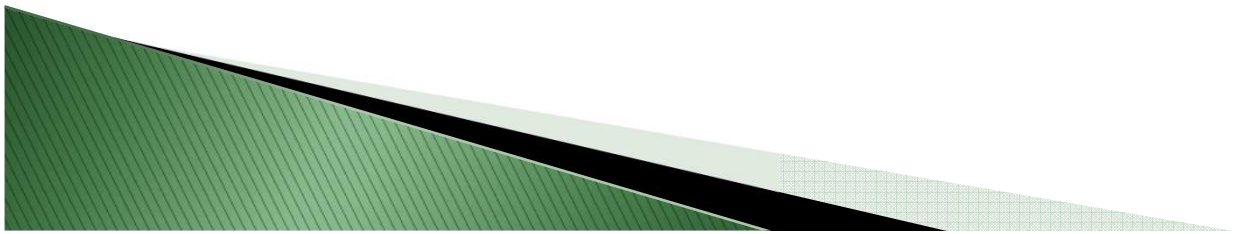
6.EGFR I,PKI-166,EGFR antisense

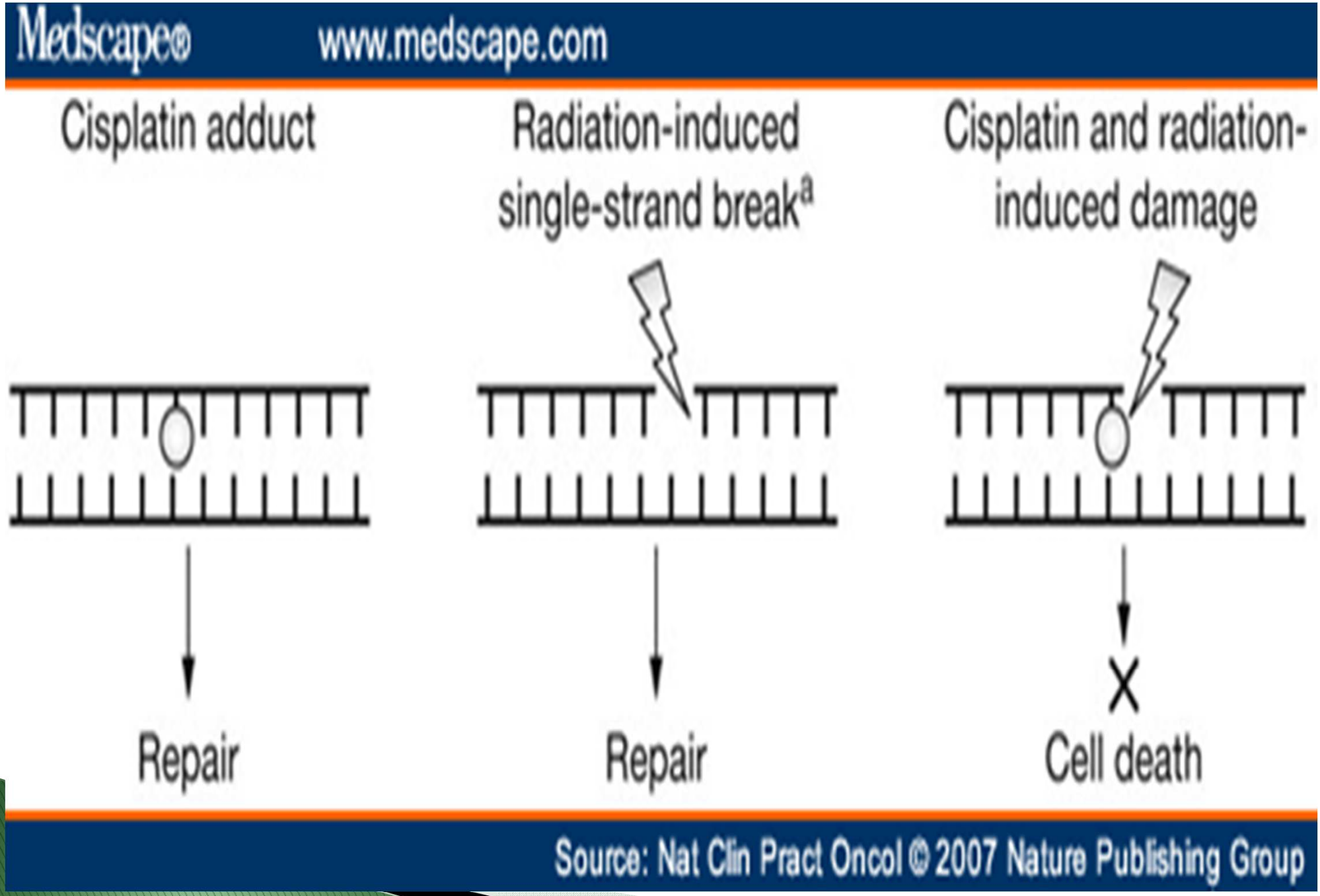
7.Taxane ,low fraction RT

- Drug example

CT-RT interaction and drugs with specific mechanisms

- Platinum Analogs
- X links,intrasrand/interstrand on DNA/RNA
- Blocks nucleotide replication en transcription
- Active in hypoxia en euoxic cells
- Inhibits DNA repair,fix the radiation damage
- Increase cell cycle arrest and apoptosis after RT




Medscape®
www.medscape.com
Cisplatin adduct
Radiation-induced single-strand break[a]
Cisplatin and radiation-induced damage
Repair
Repair
X
Cell death
Source: Nat Clin Pract Oncol © 2007 Nature Publishing Group

CT-RT interaction and drugs with specific mechanisms

- Antimetabolites
- 5-FU:
- Impedes nucleic acid synthesis thro inhibition of thymidylate synthetase
- Deplete nucleotide triphosphates -cell cycle changes DNA fragmentation-cell death
- Incorporated in DNA/RNA-inhibits DNA synthesis transcription, protein synthesis
- For radiosensitisation -continuous infusion during RT,kills cells in S phase progression from S phase to G2 phase impaired repair of radiation induced DSB

CT-RT interaction and drugs with specific mechanisms

- Antimetabolites

Capacitabine: oral prodrug->5-FU via thymidine Phosphorylase ; RT preferentially increase tumor TP level via induction of TNF;Trials underway

CT-RT interaction and drugs with specific mechanisms

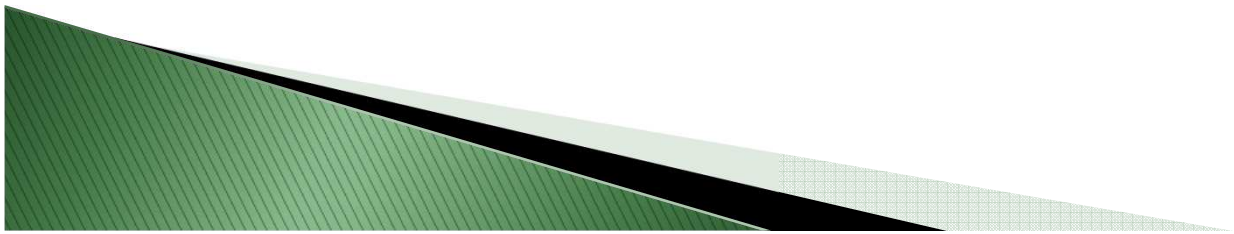
- Antimetabolites
- Gemcitabine : S-phase cell cycle specific pyrimidine analog,inhibits DNA synthesis and repair,throu depletion of deoxynucleoside triphosphate,dATP→required by DNA polymerase and nucleotide reductase
- Active alone or with platin.preclinical model-radiosensitization with low dose drug 24 hrs before RT,persisted upto 48 hrs—dATP depletion and S phase accumulation

CT-RT interaction and drugs with specific mechanisms

- Antimetabolites: Pemetrexed
- Multitargeted antifolate,inhibits thymidylate synthase,dihydrofolate reductase asnd glycinamide ribonucleotide formyl transferase—nucleotide synthesis
- => synergy with concurrent CRT+ interference with DNA synthesis
- Not cell cycle specific,equal efficacy in G1 en S
- Prolongation of S phase by RT increase the drug exposure

CT-RT interaction and drugs with specific mechanisms

- Hydroxyurea
- Radiosensitizer
- Used for HNC , Cervix, Gliomas , Pancreatic ca
- Inhibits ribonuclease reductase—prevents radiation induced DNA damage repair during nucleotide excision.
- Synchronize cancer cells at G1-S check points
- Selectively cytotoxic to cells in S- phase(radioresistant)



CT-RT interaction and drugs with specific mechanisms

- Taxanes
- Form high affinity bonds with microtubules,
- Promote tubulin polymerization en stabilization
- At high dose,block prophase-metaphase progression-disrupts the centrosome network-cell death
- Differing temporal interactions of pacli en doce with RT-due to excretion en cell cycle tropism
- Radiosensitization=>synchronization in G2-M phase
- Tumor shrinkage-reoxygenation

CT-RT interaction and drugs with specific mechanisms

- Mitomycin-C
- Inhibits DNA/RNA synthesis by interfering with DNA X-linking,at G-C pairs
- Induce cell cycle arrest at the G2-M transiton
- Hypoxic cell sensitizer
- Prevent repopulation

CT-RT interaction and drugs with specific mechanisms

- Tirapazamine

Hypoxic cell cytotoxic~ 100 fold increased potency under anoxia,via electron donation,causes formation of transient oxidizing radicals.->forms DNA radicals->cytotoxic DNA strand break.(in euoxic cells these radicals quickly bind with O2-nontoxic)

- Decrease topoisomerase II activity
- Systemic side effects observed

CT-RT interaction and drugs with specific mechanisms

- Temozolamide
- Oral alkylating agent, cross the BBB,CSF(30%)
- DNA damage by methylation of O6 guanine,activates p53 controlled DNA damage response pathway
- Tumors with methylation of MGMT,a p53 DNA damage repair enzyme are preferentially radiosensitized
- Inhibit signaling of radiation triggered cell migration en invasiveness
- Inhibit tumor cell repopulation

CT-RT interaction and drugs with specific mechanisms

- Temozolamide
- TZM +RT are additive in the GBM

- Attributable to radiation induction of MGMT (O-6-methylguanine DNA methyltransferase)

- Show additive and supra-additive activity

CT-RT interaction and drugs with specific mechanisms

- Advances in Radiotherapy
- Advances in Radiotherapy alongwith those in Imaging to achieve most precision RT decrease normal tissue toxicities

- And thus improve the therapeutic index of Chemoradiation.

CT-RT interaction and drugs with specific mechanisms

EGFR- targeted therapies

- EGFR activated upon binding of the ligand induce dimerization – phosphorylation of the intracellular EGFR tyrosine residue – mediate cellular response for tumor survival and growth – proliferation, invasion, angiogerms and metastasis and decreased apoptosis.

- EGFR (erb B1 and erb B2) are deregulated in HNC, Lung, Breast and Colo-rectal cancer. Causal link between EGFR expression and radio-resistence.

CT-RT interaction and drugs with specific mechanisms

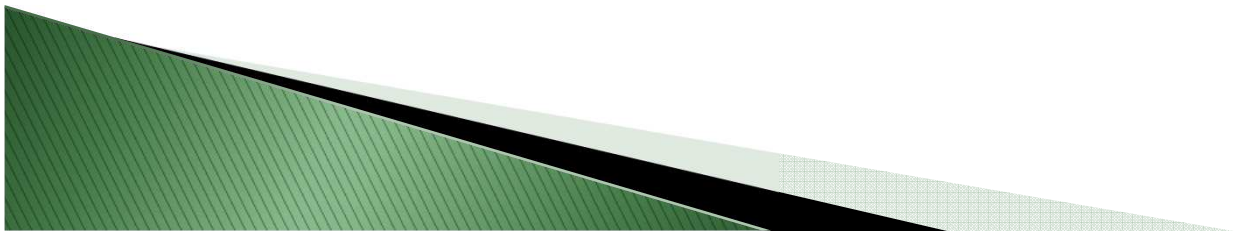
EGFR- targeted therapies

- EGFR Inhibitors: Cetuximab, Gefitinib, Erlotinib.
- Show enhanced radiosensitivity – supra addictive
- Mechanism: inhibit cell proliferation
  : impair DNA damage repair
  : alternate tumor angiogenesis
  : inhibit radiation induced EGFR nuclear import
  : promote apoptosis

CT-RT interaction and drugs with specific mechanisms

- Antiangiogenic and Anti VEGF Therapy
- Angiogenesis mediated by
- multiple pro anti angiogenic factor
- VEGF central role
- Anti VEGF agents

- Target VEGR ligand- bevecizumab
- Target receptor- PTK 787
- Others



CT-RT interaction and drugs with specific mechanisms

Conclusion

Core CT+RT

- Improved Cancer Care in multiple diseases.

  neoadjuvant/ Primary/ Adjuvant

- Radiosensitization.

  Additive/ Supra additive

- Mechanisms of Radiosensitization.
- Radioresistance

THANK YOU