Radiotherapy in Head and Neck

Topic in depth

E F Post

05 Aug 2005

Radiotherapy

- How it works
- Radical vs palliative vs Adjuvant
- Types
- Indications
- Techniques / duration
- Side effects
- New thoughts

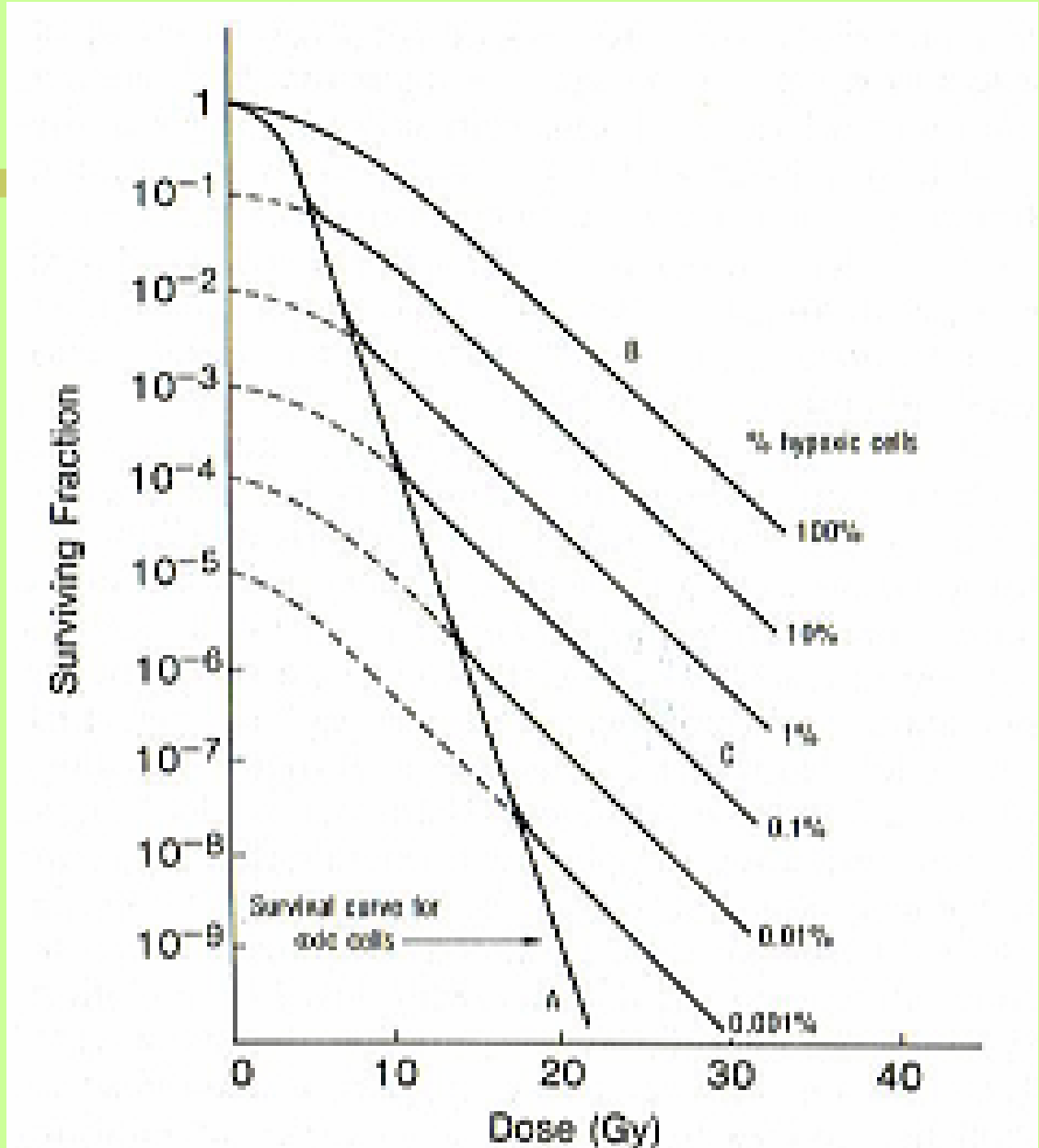
How it works

- Damage DNA direct + indirectly (interact with H20 → toxic free radicals)
- Breaks DNA double strand (all cells)
- Apoptosis at next mitosis if no repair
- Ca: ~ shorter cell cycle
  ~ lower repair capacity
  ~ divide more frequently

Rx response: influencing factors

- Oxygenation
  - hypoxia→ resistance (use fractioning)
- Repair
  - Normal cells can repair DNA
- Repopulation
  - Initially cells lost + ↑ division
  - Break in Rx → repopulate + resistance

Hypoxia


Surviving Fraction
1
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
10^{-7}
10^{-8}
10^{-9}
Survival curve for oxic cells
A
B
C
% hypoxic cells
100%
10%
1%
0.1%
0.01%
0.001%
0
10
20
30
40
Dose (Gy)

Rx response: influencing factors

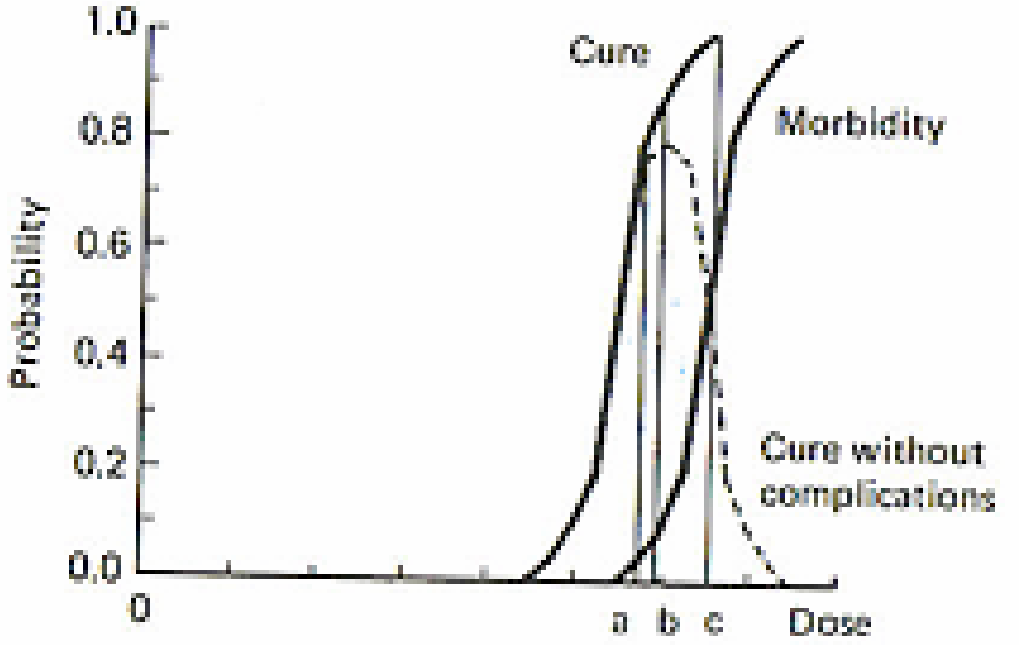
- Radiosensitivity
  - Cell cycle
    - Cells killed at mitosis
    - Max = active DNA synthesis (late G1/ S)
    - Least = early G1 phase
  - Types of cell
    - CNS: ↓repair, sensitive, irreversible damage
    - Eye lens: cataract
    - Lung: fibrosis

Cure vs complications

- Normal cells also damaged
- Aim: max dose to kill tumor, min complications

- SCCa <Ro sensitive: high dose
- Poorly diff more sensitive
  - (fast replicaiton and growth)

- SCCa (H+N)= <u>LOW therapeutic ratio</u>
  - Need ↑ dose to kill Ca→ ↑complications



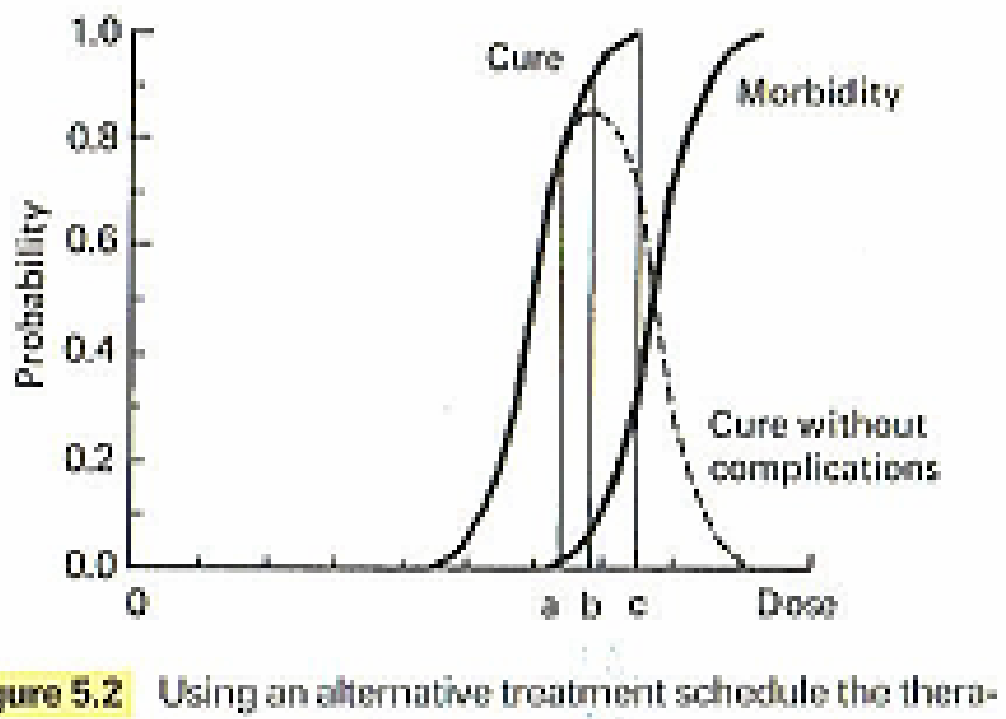


Figure 5.2 Using an alternative treatment schedule the thera-

Cure vs Complication

- Steep central part:
  - small ↑ dose: ↑ cure, ↑ complication
  - small ↓ dose: ↓ complication, ↓ cure
- Modify Rx to ↑ therapeutic ratio
  - Fractioning
  - ChemoTx 1st

Side Effects

- Early / Acute
  - during Rx, week 2 – 3
  - Non specific: ↓ Energy (+ depression, meds, travel)
  - Outside radiation field = no acute toxicity
  - Self limit till course finish = temporary loss of cell division in epithelial layer
  - Break reduces SE but cure falls 0.5% per day (2 weeks reduce cure by 5-7%)

Early SE

Site	Effect	Rx
Skin	Erythema→ desquamation Tan (dark skin)	Avoid irritants + trauma, Aqueos/ hydrocortisone cream
Mouth/ pharynx larynx	Mucosistis Candida Xerostomia Odynophagia Hoarse/ UAO	Rx candidiasis, Chlorhexidine, Analgesia ? NG feeds Trache prn
Scalp	Hair loss	Regrow after palliative Radical >50Gy→ order wig <50 Gy – OK > 3/12

Late SE

- Not temporary, not irreversible, progressive
- Months to years after radical course
- Loss of stem cell recovery potential
- Endarteritis obliterans (occlude small vessels because of damage)
- Risk: 2nd malignancy – rare
  - ↑ with LOW DOSE RoRx
  - ↑ with chemotherapy
  - Lymphoma / leukemia 3 – 10 yrs
  - Solid tumors 10 – 30 yrs

Late SE

Skin	Fibrosis, telangiectasis, necrosis, poor healing/ breakdown
Hypothyroidism	Up to 25%
Bone/ Dental	Xerostomia/ caries/ osteoradionecrosis (infx,trauma
CNS	Myelitis/ myelopathy 0.5%→ paraplegia/ L'Hermitte's S. Dry eye / optic chiasma/ cataract (6Gy)
Lung	Fibrosis

Radiation protection

- Room: lead for low energy beams + thick dense walls for high energy beams
- Dosemeter - monitor eyes
- Shield scattered radiation
  - Produce defined beam
- Implants: separate pt
- Monitor: Staff
  - Film badge - process ?exposed
  - Strict regulations – no evidence staff ↑ risk for Ca

Management options for cancer

- Surgery / Radiotherapy /(Chemotherapy)
- Combination
- Decide:
  - Rx or no Rx (TLC/ supportive)
  - Cure vs palliation
  - NO prophylactic palliation

Clinical use

- 1.Radical RoRx:
  - Full course
  - Justify SE if cure expected
  - ↑ survival
  - Alone or combination (surgery/CTx)
  - Vs Surgery: preserve function (voice)
    time/ travel

Clinical Use

- 2. Adjuvant RoRx:
  - Aim: ↓ chances of recurrence (occult mets)
  - Same dose as radical
  - Indicated after surgery if:
    - tumor > 5cm or
    - oropharynx/FOM > 2cm (N0 neck)
  - Not RoRx of residual disease (= combine/ radical)

Clinical Use

- 3. Palliative RoRx:
  - Reduce symptoms
    - eg pain/ hemorrhage/ obstruction
  - ↑ QOL
  - Eg 5x 5Gy
  - Not radical Rx if distant metastases or failed

RoRx use to cure (I)

- 1. Alone as principal RX
- 2. In conjunction with surgery
  - Pre / postoperative
- 3. Pathology guided postoperative
- 4. Salvage for recurrence after surgery

- Surgery: remove bulk, leave microscopic Ca
- RoRx: cure small volumes, not bulk
- Surgery option after failed RoRx

Postoperative RoRx

- Currently seldom preoperative because
  - Better staging guides RoRx
  - Free flap allow earlier RoRx
  - Intraop. tumor dissemination theoretical
  - Smaller volume left to irradiate

Postoperative RoRx

- Pathology guided
  - Malignant cells to margin
  - Nodes:
    - Multiple nodes Ca (2 or more)
    - ECS
  - Perivascular invasion
  - Perineural invasion

Types

- 1. Teletherapy / External beam
  - Beam of ionizing radiation from machine:

  i) High energy, electromagentic = Photon

  ii) Particulate radiation = e-,n,p+

- 2. Interstitial
- 3. Unsealed

i). Photon external beam

A) <u>Xrays</u>

1. Superficial: 100KV (50-150)

   ↓ penetrance, 1 cm, skin

2. Orthovoltage – not used

   3cm, skin damage, bone absorp (osteoradionecrosis/ laryngeal cartilage necrosis)

3. Megavoltage: 6MV (4-20)

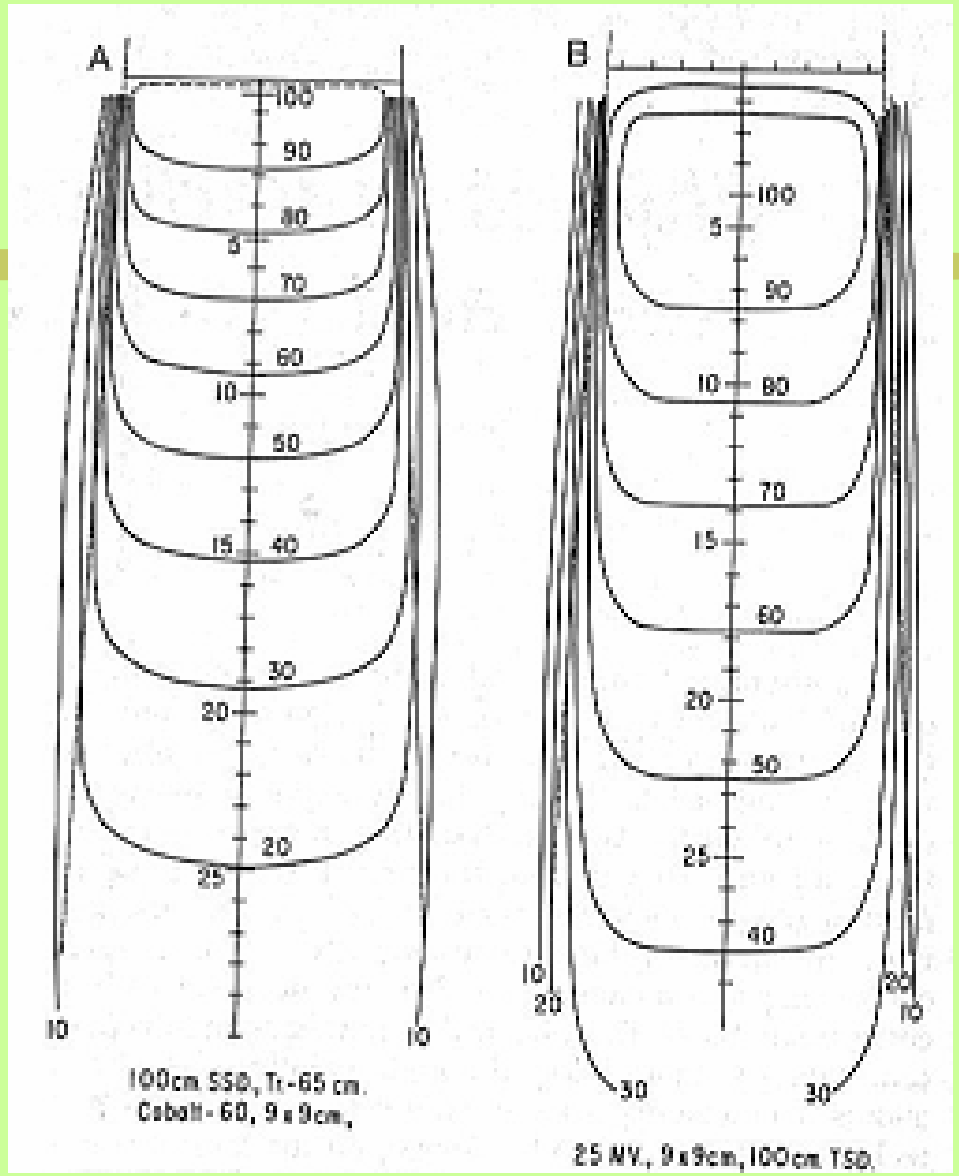
   Linear accelerators: ↑ penetration. No “build up”

   Adv: i) ↑ depth

   ii) skin sparing (max dose 1cm, rapid fall off)

   iii) ↑ precision (edges defined / penumbra)

   iv) ↓ bone absorption


A
100
90
80
5
70
60
10
50
15
40
30
20
20
25
10
10
100cm SSD, Tr-65 cm.
Cobalt-60, 9x9cm,
B
100
5
90
10
80
70
15
60
20
50
25
40
10
20
30
20
10
30
25 MV., 9x9cm, 100cm TSD.

i).Photon external beam

B) **<u>γ rays</u>**

Cobalt decays to Ni60 + release γ rays (2MV)

vs Linear accelerator:

(+) cheaper, less maintenance, older

(-) risk to staff, large penumbra, ↓ penetration

ii). Particle beam irradiation

- A) Electron
  - Uniform dose to specific depth
  - Rapid fall off
  - (+) tumor overlying spinal cord
    some skin sparing
    pinna / nose
- B) Neutron no benefit to e-
- C) Proton for clivus chordoma / ocular melanoma

2. Interstitial / Brachytherapy

- Radioactive isotopes in Ca / cavity
- (+) high dose to limited volume
- Very rapid fall off
- Afterloading ↓ risk: applicator, manual/ remote activation, isolated room
- Eg Irridium (radium old): 1/52 in situ (long t1/2)
  Gold: remain(short t1/2)

H+N: Post RoRx recurrent nodes → RND + applicator under flap

3. Unsealed sources

- Oral/ IV radioactive isotopes
- Eg. Thyroid follicular Ca: radioactive iodine

Measure

- **Gray** =
  - SI unit of radiation dose
  - Absorbed energy
  - 1 Gy = 1 Joule/ kg
  - 1 Gy = 100 rad (old unit)

- **Other factors**:
  - Volume Rx
  - Fractions (number, interval between, size)
  - Overall time
  - Beam energy / Photon vs neutron

Volume to Rx: concepts

- Microscopic infiltration around Ca
- Shrinking field technique
  - Moderate dose to large Ca, then high dose to reduced volume / brachyTx
  - (+) ↓ high dose to large area
- Prophylactic N0 neck (occult mets)
  - ↓ rate of salvage, but no change survival
  - Weigh up:
    - initial cure + SE
    - watch + wait / possible salvage

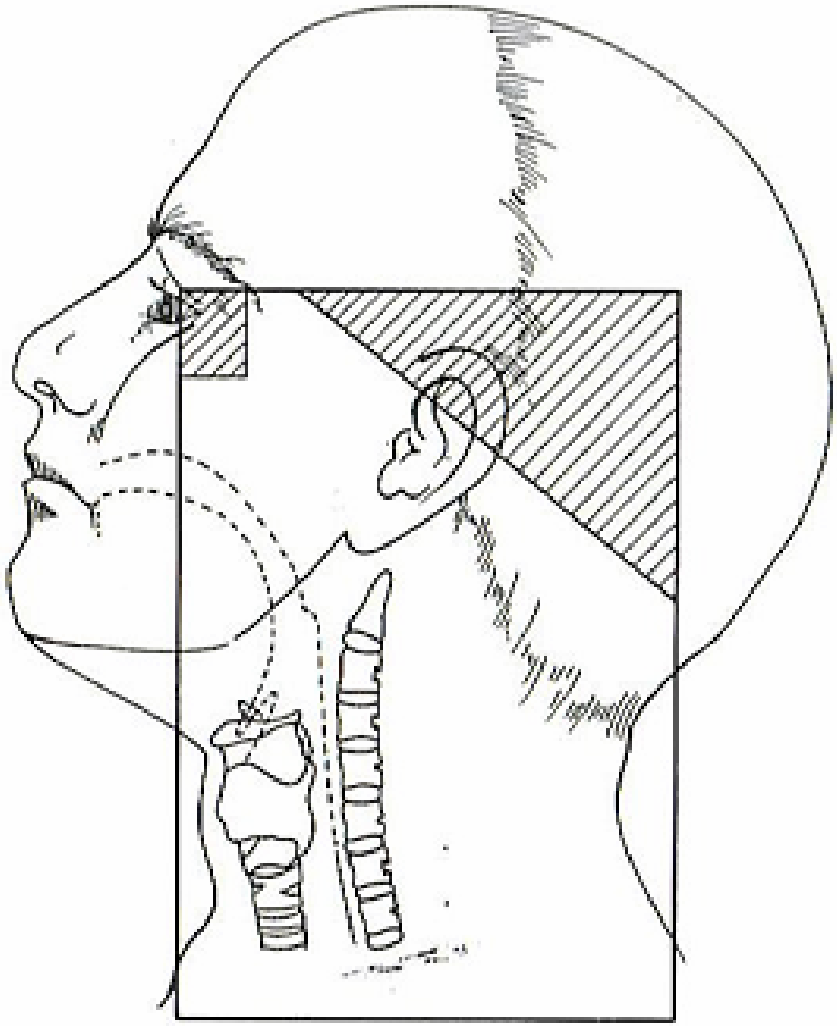
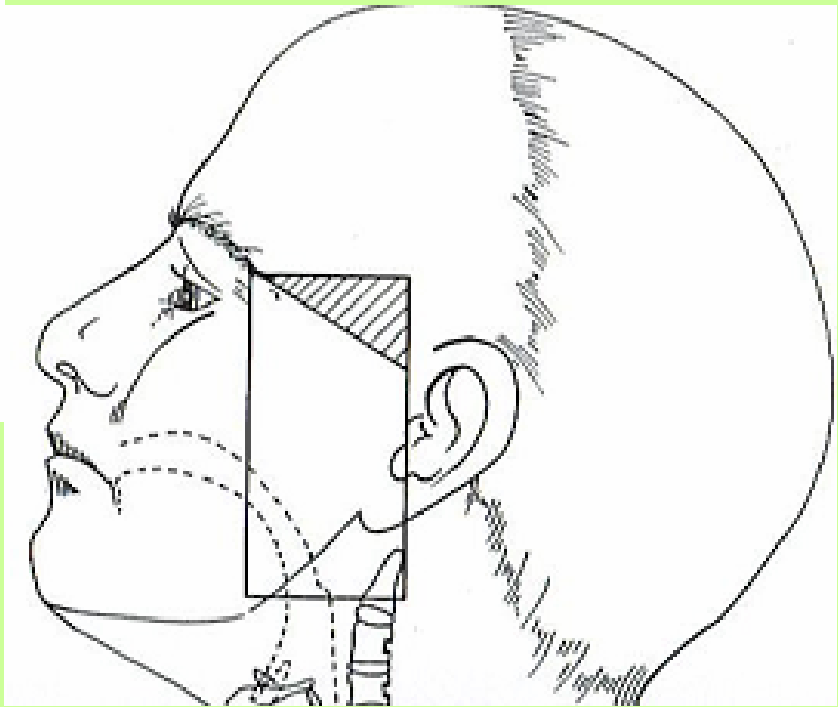


Figure 20.1 Radiotherapy field for the first phase of treatment of nasopharyngeal carcinoma.



Fractionation

- Tissue tolerance limits radiation in single dose
- Fractions of total dose:
  - ↑ total dose tolerated (+ ↑cure)
- Conventional: 60 – 65 Gy in 30-32 fractions over 6 – 6.5 weeks

Fractionation, alternatives

- Hyperfractionation
  - > number of fractions, each < 2Gy
  - Not longer period; 2 per day
  - Reduce Ca DNA repair / repopulation
  - Less SE
  - Minimum Interfraction time = 6 hr
    - Allow N cells to repair
  - Ideal but labour intensive

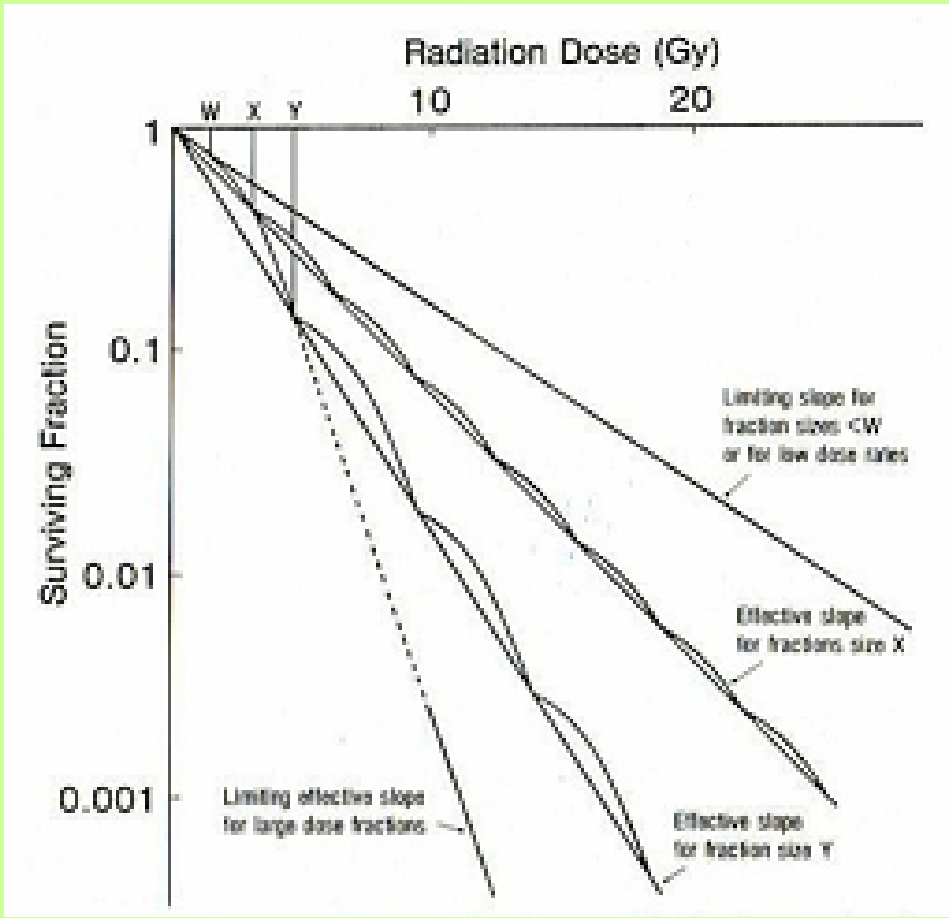
Fractionation, alternative

- Acceleration
  - **CHART**
  - Less time 12 days (3x per day)
    - Less repopulation
    - Less dose per fracion thus less late tissue damage

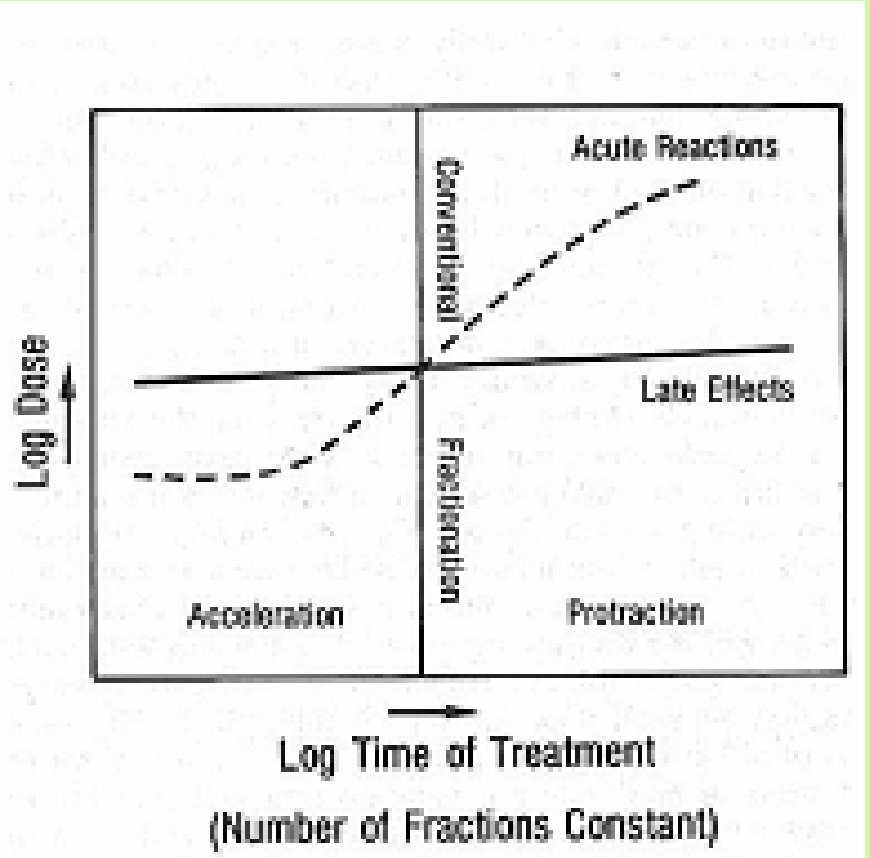
Fractionation, alternatives (-) not used

- Hypofractionation
  - Smaller number of fractions, each > 2Gy
  - Quicker: 3/52 (50Gy)
  - No change in cure,but >SE (mucosa reaction is dose dependant)
- Split courses
  - Rx then 2 week break then Rx
  - After 1st Rx get ↓ cure because: repopulation, ↑ DNA replication, radioresistance
  - If happen: same time but ↑ number of f per day

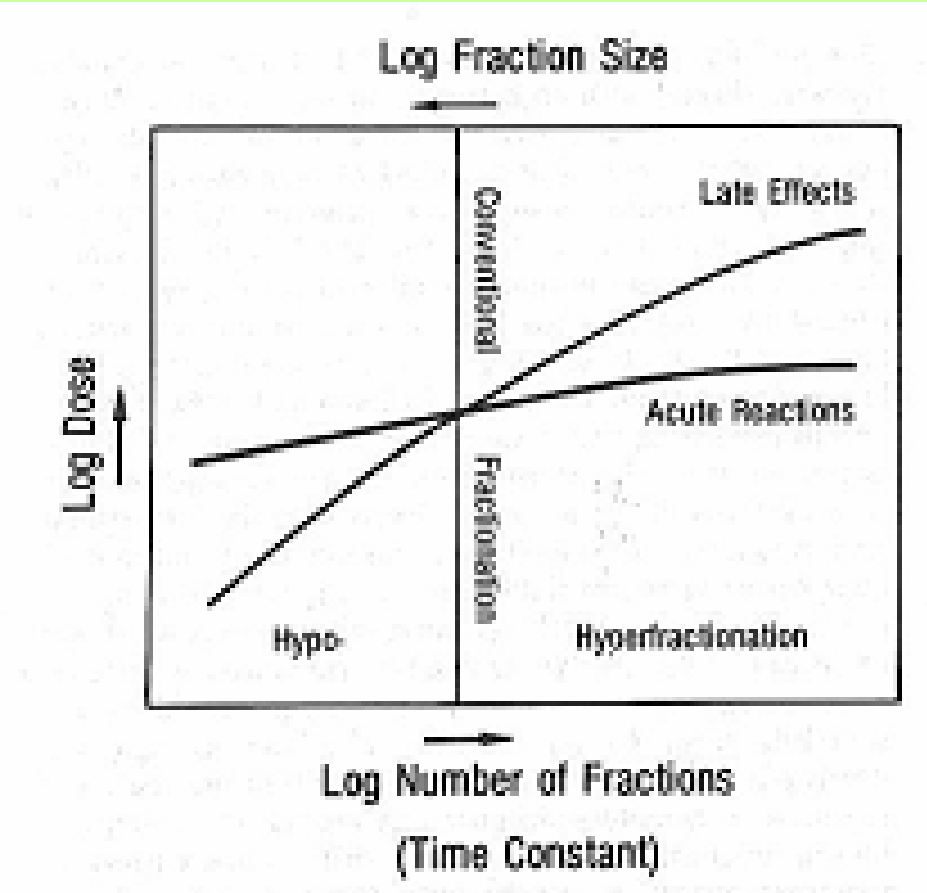
Effect of fractioning



Fractioning + Side effects



Fractioning + Side effects



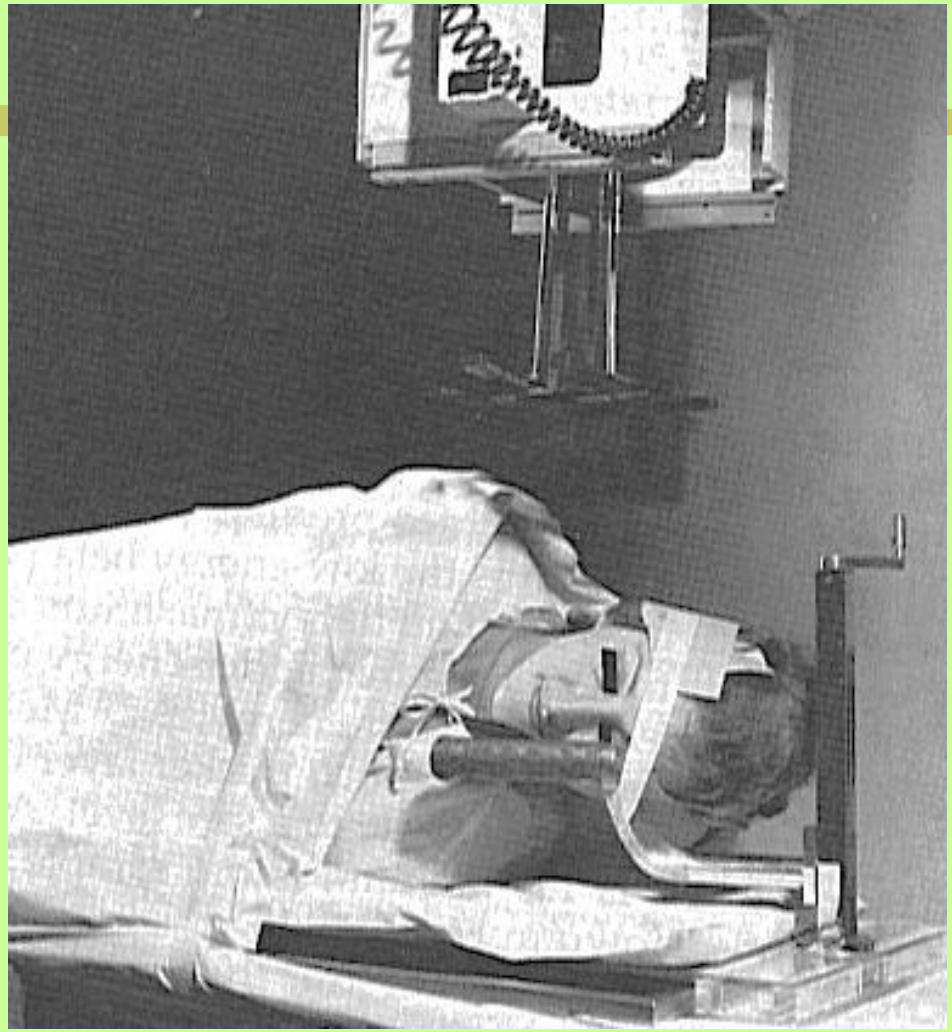
Rx duration

- Palliative Rx
  - Short schedules with few side effects
  - E.g. 25 Gy in 5 fractions – 5x 5Gy
  - Ideal single dose e.g 10Gy stat

Planning/ quality control

- Select volume: image or clinical, tumor type, spread expected, vital structures
- Immobilise pt – mask (POP mould, cast, plastic. Fit snugly: reduce “geographical miss”
- Treatment simulator (Dx Xray/ image intensifier) – record area to be Rx
- Beam shaping: blocks to protect
  multileaf collimators

Immobilise



Planning/ quality control

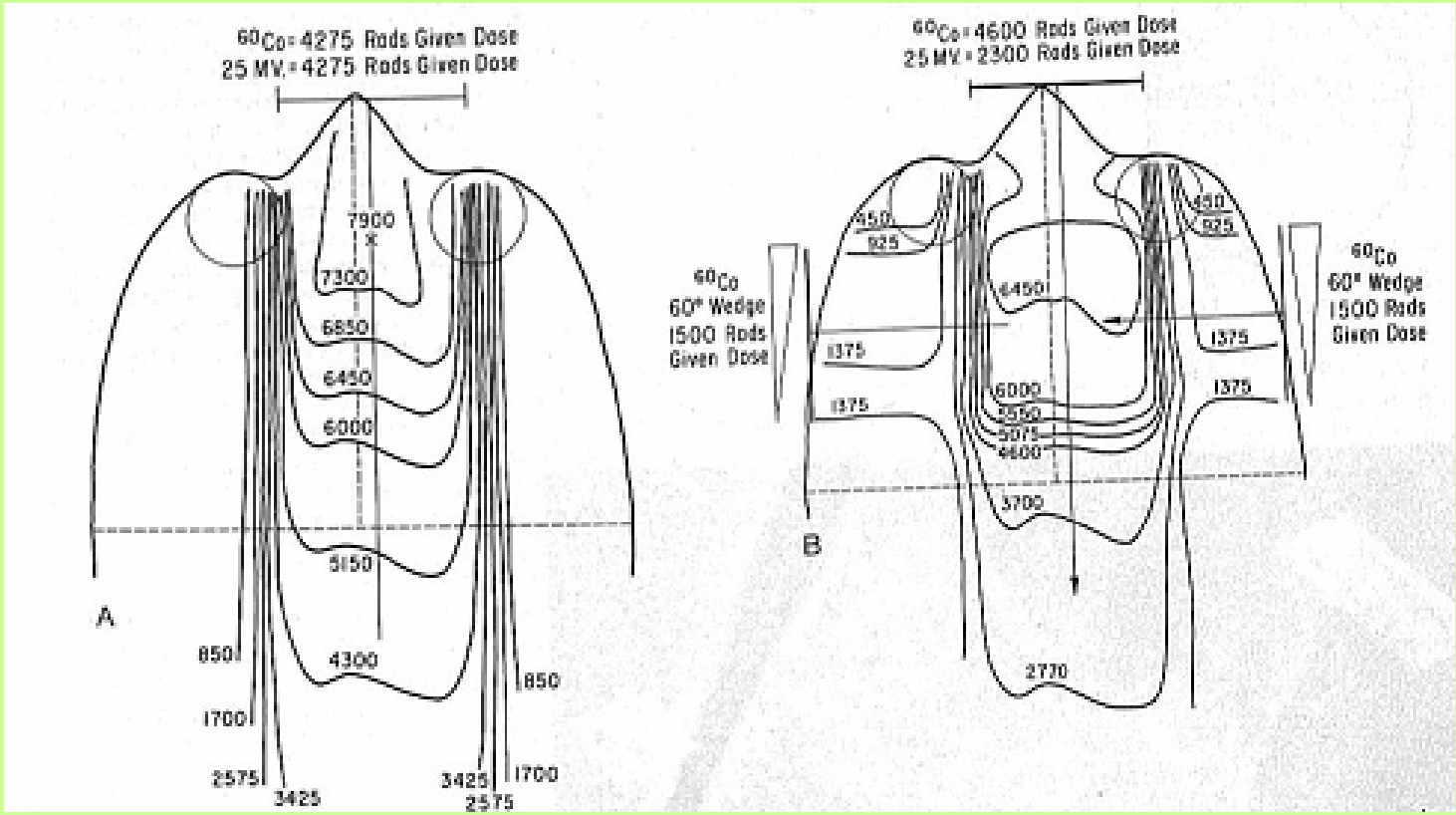
- Isodose planning

  CT (+MRI image fusion / 3D) shows map of radiation dose. Join lines (contours) of areas with same dose = isodose lines. Check Ca uniform high dose and vital organs not exceed limit.

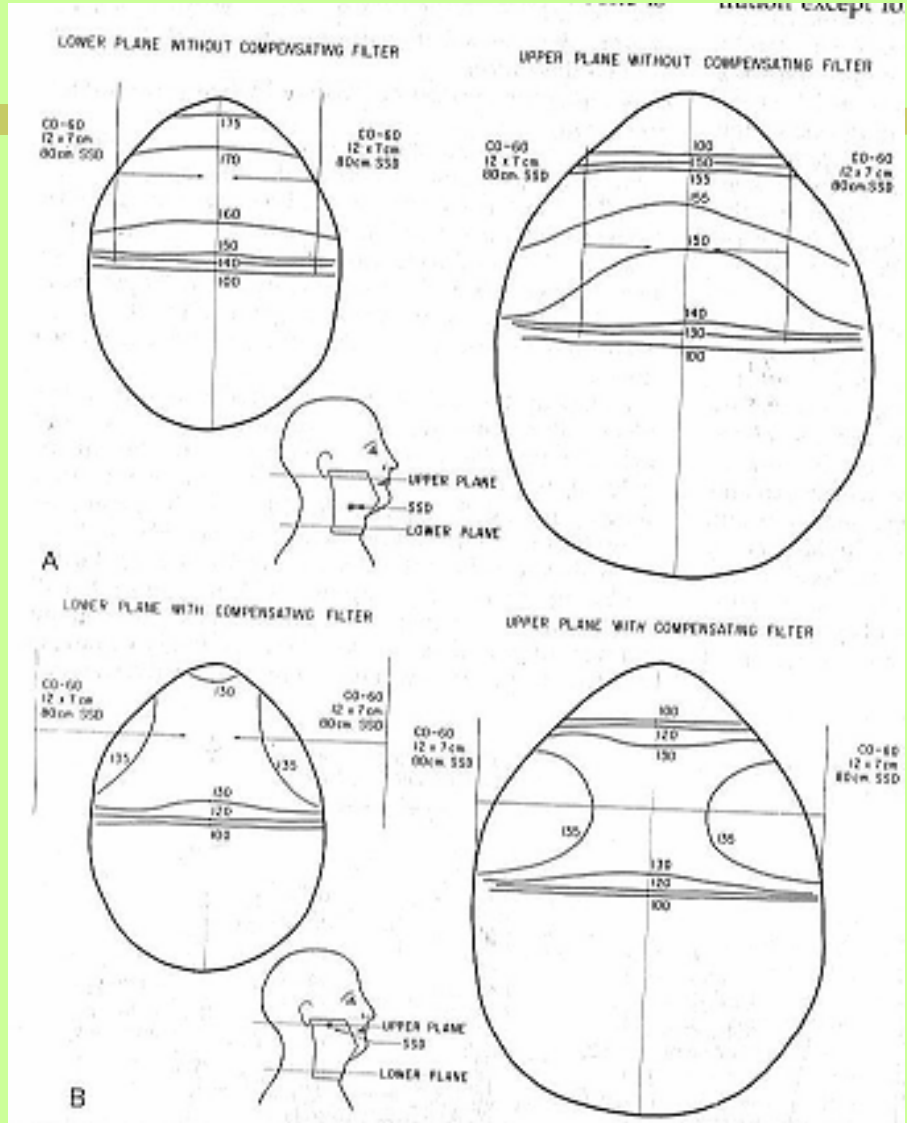
- Wedges + compensators

  Aim:Ca only receive high uniform dose. Beam loses penetration in tissue. 2/> beams used: intersect in Ca. Wedge at head of beam to concentrate beam to point. Compensators achieve dose homogeneity

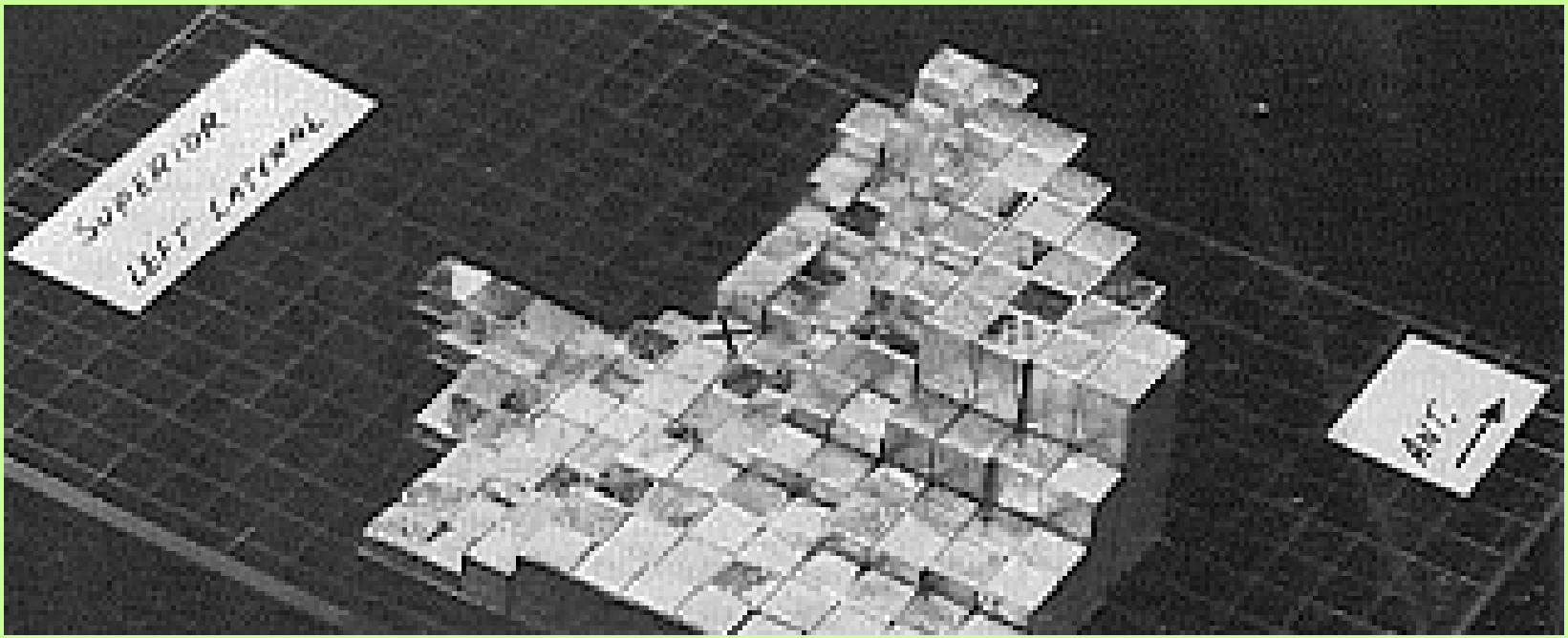
Isodose lines / wedges



Compensators



Compensators



Planning/ quality control

- Treatment verification

  Daily, during Rx check map/ plan and beams accuracy.New linear accelerators have on-line portals

NEW: Radiogenic Therapy

- Gene therapy as adjuvant/ improve effectiveness of RoRx: preferential Ca cells killed and spare N
- Transgenes with radiosensitizing properties
  - Gene correction therapy (genes responsible for radiation-induced apoptosis)
  - Enzymes that synergise radiation effect
  - Oncolytic adenovirus that synergise effect
  - Membrane transport proteins

When can I use RoRx only in H+N?

- Glottic (all sites): T1 – T2 (all sites)
- Oropharynx T1, No only
- Hypopharynx (all) T1-2, N0
- Oral cavity T1,N0 = brachyTx
- Nasopharynx all – shrink 1st

Table 14.7 Curative treatment of squamous cell carcinoma of the larynx

Glottis	N_0	N_1	N_2	N_3
T_1	Radiotherapy, ?endolaryngeal surgery (cordectomy for recurrence)	NA or surgery	NA or surgery	NA or surgery
T_2	Radiotherapy, ?hemilaryngectomy or TL + ?RT	TL + ?RT	NA or surgery	NA or surgery
T_3	? Radiotherapy, ?surgery (STL or TL + ?RT)	TL + ?RT	TL +RT	TL +RT
T_4	TL + RT	TL + RT	TL +RT	TL + RT
Supraglottis	N_0	N_1	N_2	N_3
T_1	Radiotherapy or endolaryngeal surgery	SGL + ?RT	SGL + RT	NA
T_2	Radiotherapy or surgery (SGL or TL) + ?RT	SGL or TL + ?RT	SGL or TL + RT	TL + RT
T_3	?Radiotherapy or surgery (SGL or TL) +?RT	SGL or TL + ?RT	SGL or TL + RT	TL + RT
T_4	Surgery + RT	TL + RT	TL + RT	TL +RT
Subglottis	N_0	N_1	N_2	N_3
T_1	Radiotherapy	TL + ?RT	TL + RT	TL + RT
T_2	Radiotherapy or surgery (TL)	TL + ?RT	TL + RT	TL + RT
T_3	Surgery (TL) + ?RT	TL + ?RT	TL + RT	TL + RT
T_4	Surgery (TL) + RT	TL + RT	TL + RT	TL + RT

NA: not usually applicable; SGL: supraglottic laryngectomy; TL: total laryngectomy; STL: subtotal laryngectomy; + RT: with elective postoperative radiotherapy; + ?RT: with postoperative radiotherapy in selected patients.

Prognostic variables related to a favourable outcome with radiotherapy

- Low tumour volume (tumours <3 cm^3 do better)
- Mobile cord
- No involvement of the ventricle
- No deep ulceration
- No fixation of anterior vocal cord
- Lack of spread to subglottis or anterior subglottic wedge
- Only one site involved
- Cessation of smoking

Table 15.4 Curative treatment of oral cancer

	N_0	N_{1-3}
T_1	Surgery or implant brachytherapy	Surgery with postoperative radiotherapy
T_2	Surgery, (with or without postoperative radiotherapy) or implant brachytherapy (low volume $T_2 \leq$ 2.5 cm)	Surgery and postoperative radiotherapy
T_3	Surgery and postoperative radiotherapy	Surgery and postoperative radiotherapy (if indicated)
T_4	Surgery and postoperative radiotherapy	Surgery and postoperative radiotherapy (if indicated)

Table 15.5 Curative treatment for oral cancer: approximate 5 year survival rates (ultimate local control)

Stage	5 year survival (%)
I	75–95%
II	65–85%
III	45–65%*
IV	10–35%*

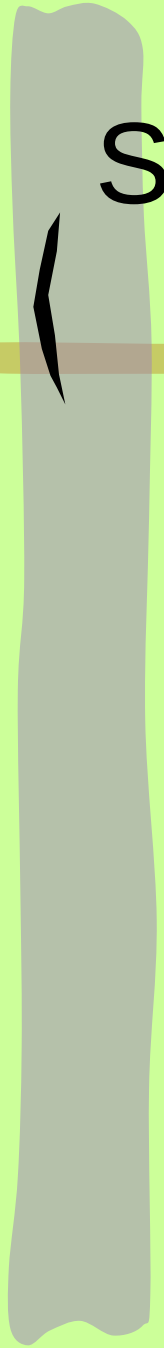
Shah (1996).
*Combination treatment which includes surgery and radiotherapy.

Radiotherapy technique for nasopharyngeal carcinoma

Target volume covers primary tumour and neck nodes bilaterally

- Phase I — *En bloc* treatment of nasopharynx and upper neck with parallel opposed lateral fields. Lower neck and supraclavicular fossae treated with anterior field
- Phase II — Reduced fields using electrons over posterior neck to keep spinal cord dose within tolerance

Sinus



Advantages of preoperative radiotherapy

- By shrinking the tumour, inoperable cancers may be rendered operable
- The magnitude of operation necessary may be reduced
- Reduces the chance that surgical manipulation may cause distant metastasis or local seeding, and is likely to be more effective without the hypoxia which may be caused by tissue disruption during surgery
- Avoids any treatment delay in therapy if wound healing is slow

Disadvantages of preoperative radiotherapy

- Surgical complications may be increased, either directly or through malnutrition
- Patient with a good initial response or unacceptable morbidity may then refuse surgery
- Tumour extent less well defined
- Wound healing may be impaired

Table 17.5 Curative treatment of hypopharyngeal tumours

	Piriform sinus	Posterior pharyngeal wall	Postcricoid
Stage I (T_1, N_0)	Primary radiotherapy or surgery (PP or PPPL)	Primary radiotherapy or surgery (PP)	Primary radiotherapy or surgery (TLP)
Stage II (T_2, N_0)	Primary radiotherapy or surgery (PPPL or TLP)	Primary radiotherapy or surgery (PP or TLP)	?Primary Radiotherapy or surgery (TLP) and postoperative radiotherapy
Stage III (T_{1-2}, N_+: T_3, N_0; N_+)	Surgery (TLPP or TLP) and postoperative radiotherapy	Surgery (PP or TLP) and postoperative radiotherapy	Surgery (TLP or TLPO) and postoperative radiotherapy
Stage IV (T_4; N_0,N_+)	Surgery and (TLPP or TLP) and postoperative radiotherapy	Surgery (TLP) and postoperative radiotherapy	Surgery (TLPO) and postoperative and radiotherapy

LR: local resection; PP: partial pharyngectomy; PPPL: partial pharyngectomy and partial laryngectomy; TLPP: total laryngectomy and partial pharyngectomy; TLP: total laryngopharyngectomy; TLPO: total laryngopharyngoesophagectomy.

Inclusion criteria for primary radical radiotherapy

- Vertical length of the tumour should not exceed 5 cm
- The vocal cords must be mobile
- N_0 neck

Table 16.3 Curative treatment of squamous carcinoma of the oropharynx

	N_0	N_1	$N_{2a/2b}$	N_{2c}	N_3
T_1	Conservation surgery and postoperative radiotherapy (or radiotherapy alone)	Conservation surgery and postoperative radiotherapy or primary radiotherapy for low-volume disease (one node less than 1 cm)	Surgery and postoperative radiotherapy	Surgery and postoperative radiotherapy	?Surgery, ?radiotherapy,
T_2	?Conservation surgery and postoperative radiotherapy or ? radiotherapy alone	?Conservation surgery and postoperative radiotherapy	Surgery and postoperative radiotherapy	Surgery and postoperative radiotherapy, or ?radiotherapy alone	?Surgery, ?radiotherapy
T_3	Surgery and postoperative radiotherapy	Surgery and postoperative radiotherapy	Surgery and postoperative radiotherapy	?Radiotherapy, or consider chemoradiation (see text)	?Surgery, ?radiotherapy. Consider chemoradiation (see text)
T_4	Surgery and postoperative radiotherapy, ?radiotherapy alone. If unfit for surgery, ?consider chemoradiation	?Surgery and postoperative radiotherapy, ?radiotherapy alone or consider chemoradiation	?Surgery and postoperative radiotherapy, ?radiotherapy alone or consider chemoradiation	?Radiotherapy, or consider chemoradiation	?Radiotherapy, ?chemoradiation (see text)

Table 16.4 Best achievable cure rates* for the treatment of oropharyngeal tumours (includes postoperative radiotherapy)

Stage	Pharyngeal wall	Tongue base	Tonsil	Soft palate
I	65	75	90	58
II	54	75	80	56
III	45	60	53	30
IV	8	55	45	20

Shah, 1996.
*Overall 5 year survival (%).