16TH SURGERY SYMPOSIUM

University of Pretoria

05-06 OCTOBER 2012

Management of advanced head and neck squamous cell carcinoma

Role of Radiotherapy

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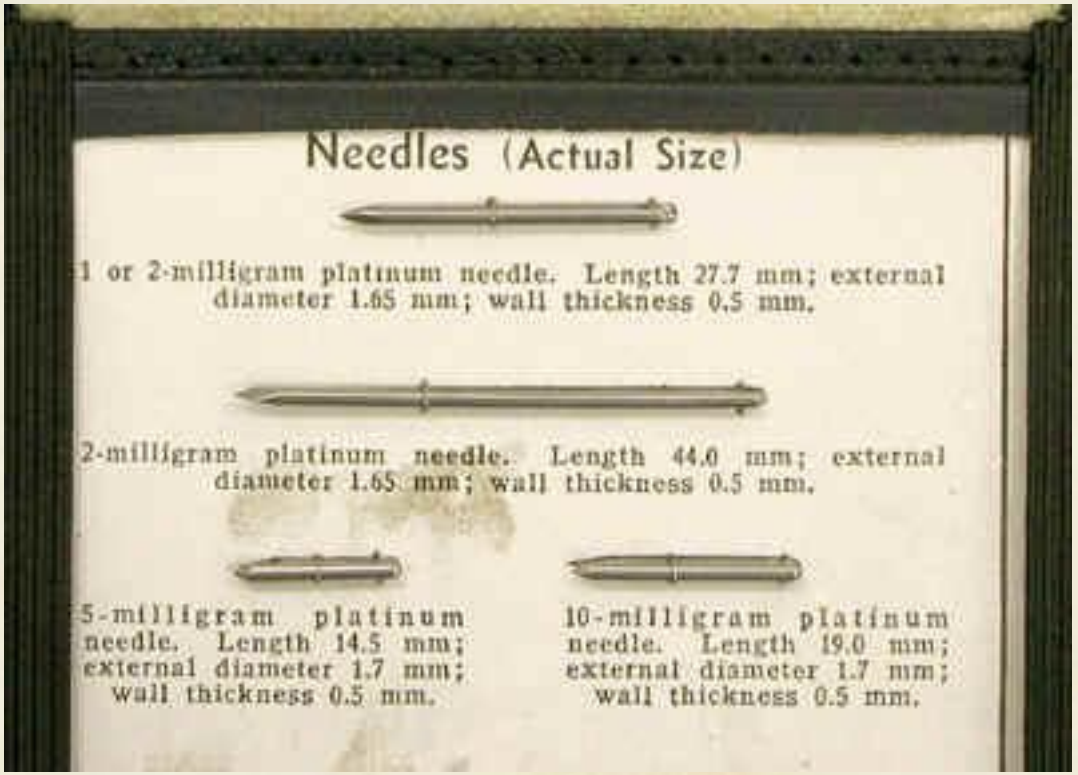
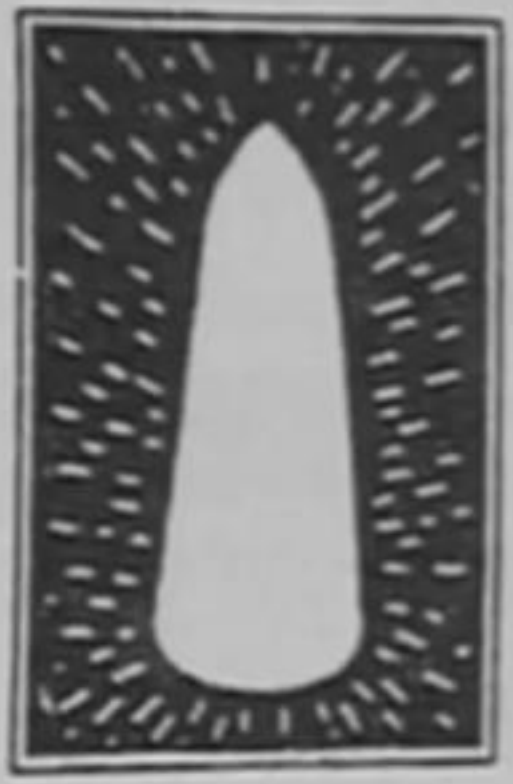
Steve Biko Hospital


Needles (Actual Size)
1 or 2-milligram platinum needle. Length 27.7 mm; external diameter 1.65 mm; wall thickness 0.5 mm.
2-milligram platinum needle. Length 44.0 mm; external diameter 1.65 mm; wall thickness 0.5 mm.
5-milligram platinum needle. Length 14.5 mm; external diameter 1.7 mm; wall thickness 0.5 mm.
10-milligram platinum needle. Length 19.0 mm; external diameter 1.7 mm; wall thickness 0.5 mm.

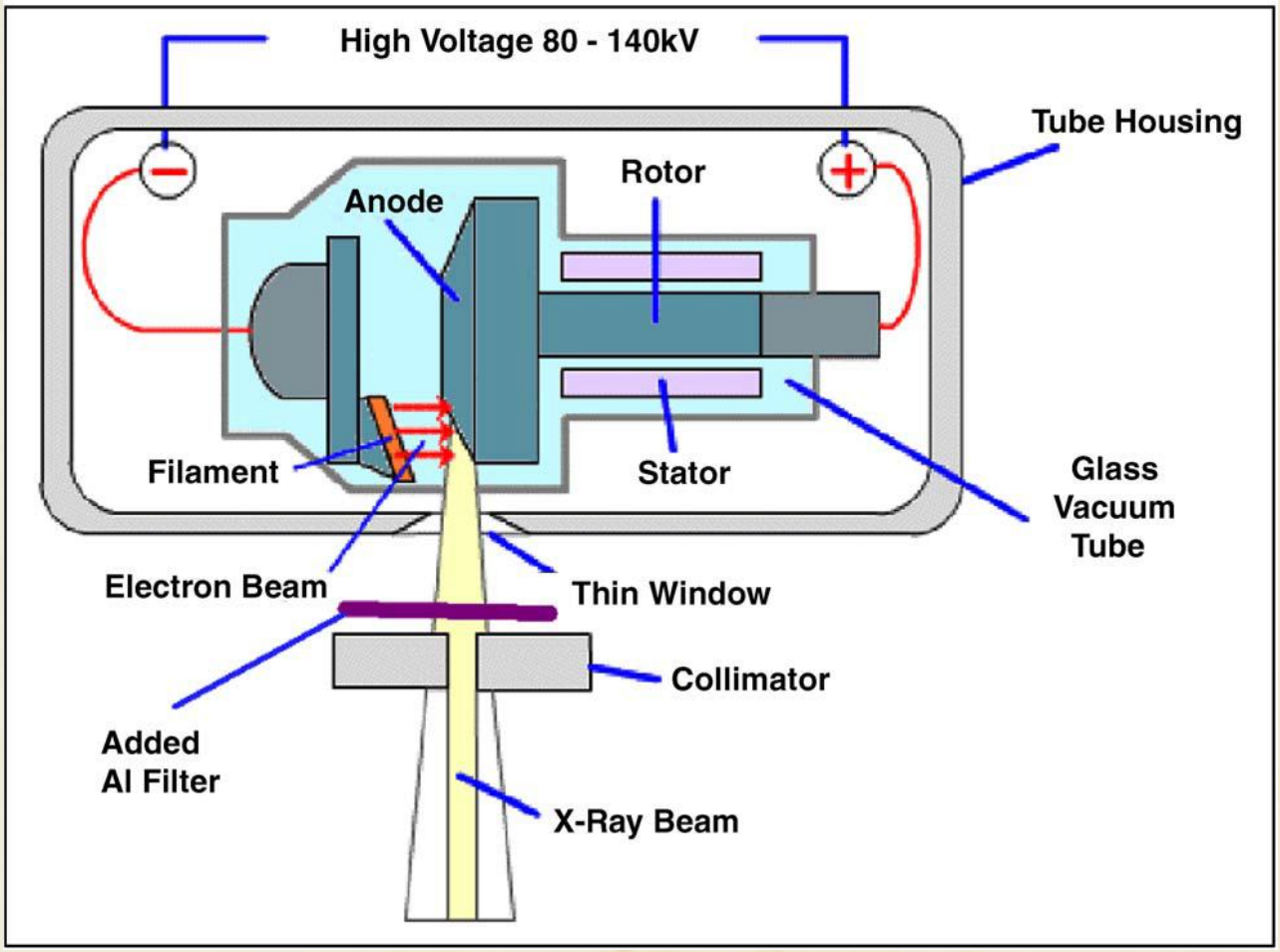
VITA RADIUM SUPPOSITORIES



Actual Size of Suppository

OUR VITA RADIUM SUPPOSITORIES (HIGH STRENGTH) are one of the outstanding triumphs of Radium Science. These Suppositories are guaranteed to contain REAL RADIUM—in the exact amount for most beneficial effect. They are inserted per rectum, one each night, this being one of the several practical and successful ways of introducing Radium into the system.

After insertion, the Suppository quickly dissolves and the Radium is absorbed by the walls of the colon; then, within a few minutes, it enters the blood stream and traverses the entire body. Every tissue, every organ of the body is bombarded by its health-giving electric atoms. Thus the use of these Suppositories has an effect on the human body like recharging has on an electric battery.


High Voltage 80 - 140kV
Tube Housing
Rotor
Anode
Filament
Stator
Glass
Vacuum
Tube
Electron Beam
Thin Window
Collimator
Added
Al Filter
X-Ray Beam

1920-1930's

- Radiation effective for treatment of Head & Neck tumours.
- Major H & N surgery was difficult, dangerous
- RT became main modality for treatment of these tumours, Larynx especially.
- No laryngectomies performed at Memorial Hospital between 1918 and 1933.

- Majority of patients who die, do so from local regional failure.
- Distant metastasis are an uncommon cause of treatment failure in Head and Neck cancer.

Mid 50's

- Salvage surgery following radiotherapy fraught with complications
- New interest in surgery ,RT adjunct to surgery either preoperatively or postoperatively.
- Initially: low dose RT (50 Gy) followed by surgery but many complications and no improvement in cure rate

1970's

- Postoperative RT after surgery became the standard of care.
- RT as effective as elective radical neck dissection for treatment of the clinical negative neck(Fletcher)

RTOG 73-03

- Phase III randomised prospective study

- Pre op RT : 50 Gy
- Post op RT: 60 Gy

- Supraglottic larynx
- Hypopharynx

RTOG 73-03

- 277 evaluable patients

LRC better for postoperative RT

Highly significant for supraglottic larynx

Postoperative Vs Preoperative RT

- **RTOG 73-03**

- Preop RT worse local control than postop RT but no difference in overall survival.
- LRC: preop 58% vs post op 70 %.
- Post op better for LRC especially in supraglottic larynx
- Why RT better post op?
- Concerns about operating in irradiated field
- Ability to use pathologic findings to adapt RT dose.

POSTOP RT

- T3/T4
- +ve or close margins
- 2 or more +ve LN
- Extracapsular nodal extension
- Perineural or lymphovascular invasion

1990’s

- Chemo alone: only symptomatic response
- Radiosensitiser and predictor of radiosensitivity.

- Chemotherapy added to RT: increases absolute survival by 6.5%.
- Largest gains obtained by using chemotherapy synchronously with radiotherapy.

Induction Chemotherapy plus Radiation Compared with Surgery plus Radiation in Patients with Advanced Laryngeal Cancer

The Department of Veterans Affairs

Laryngeal Cancer Study Group*

N Engl J Med 1991; 324:1685-169

- 332 pts with ca larynx-Stage III-IV randomised to:

1. 3 cycles 5-FU,Cisplatin followed up by RT
2. Surgery + PORT

RT : 50 Gy for N0

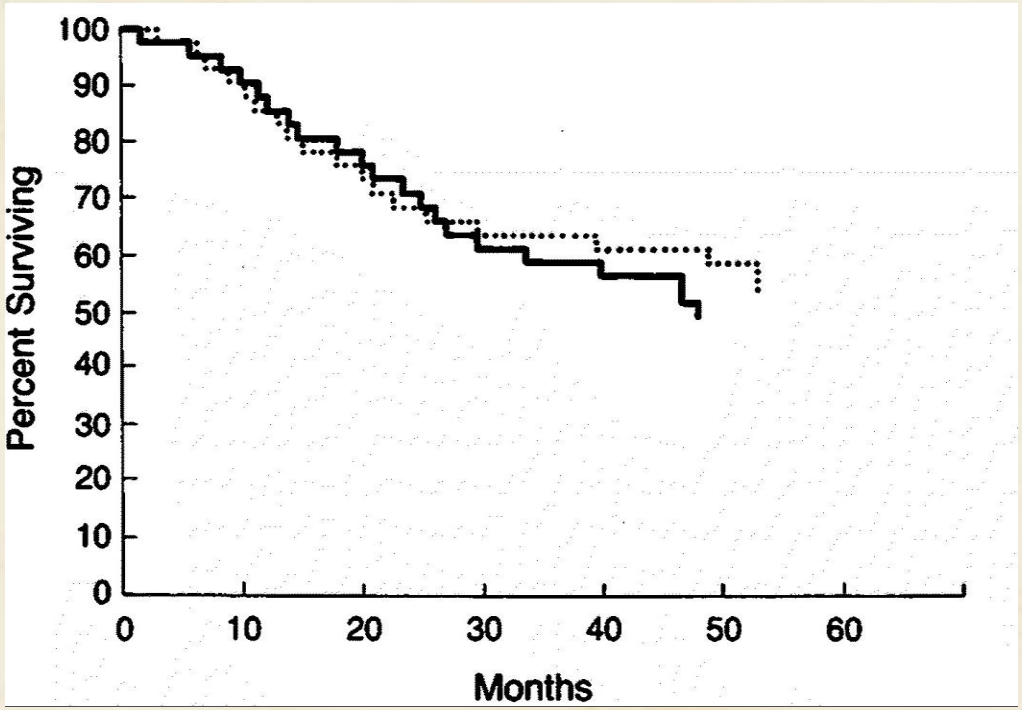
66Gy for Nodes < 2cm

70 Gy > 2 cm < 4 cm

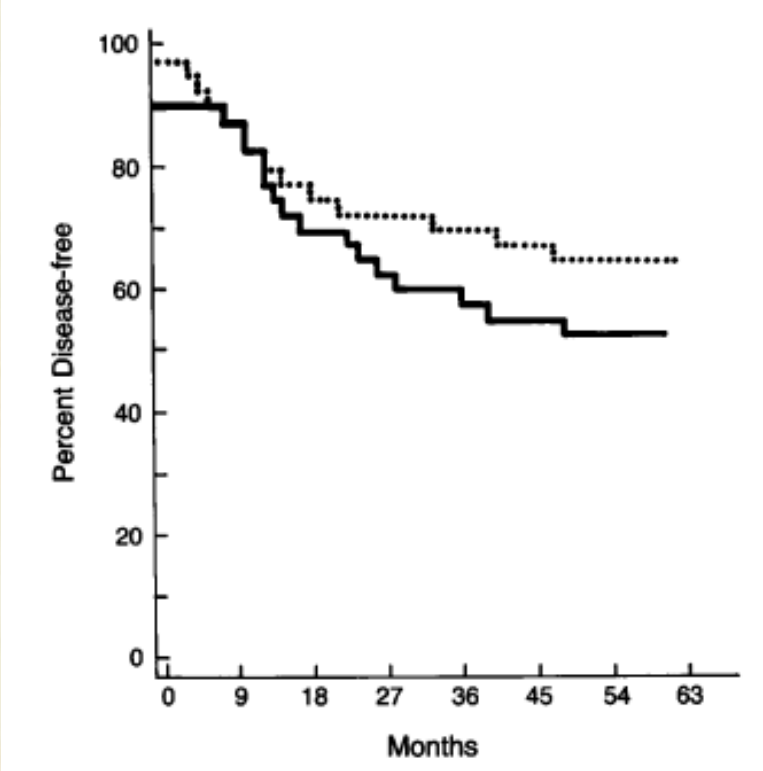
75 Gy > 4cm

- 64 % assigned to induction chemo had larynx preserved

- Patients assigned to chemotherapy : 66 % larynx preservation at 2 years.



Overall survival of 322 pts : 68 % for both groups at 2 years(p:0.9846)



_____: Chemo+RT

----------:PORT

Disease-free interval survival shorter in chemo group, but difference not statistically significant.(p=0.1195)

POST OP RT + CHEMO

EORTC 22931
RTOG 9501
NEJM 2004;350:1937-1952

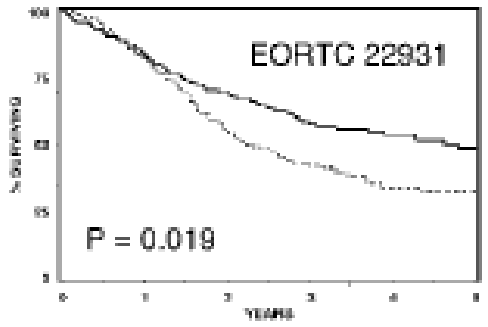
RTOG: 60 Gy
EORTC: 66Gy

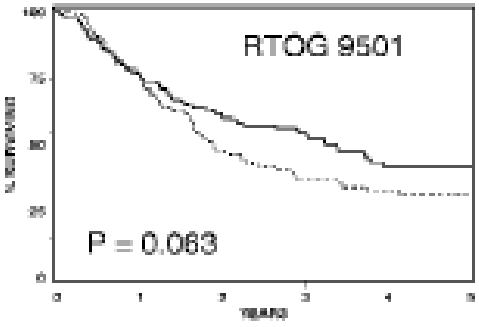
Chemo: Cisplatin

100mg/m2 D1,22,43

Overall Survival

Patients with positive margin and/or ECE





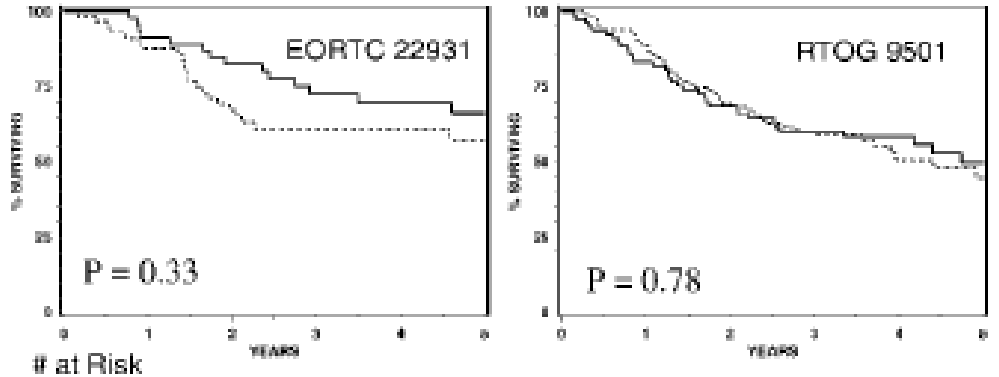
at Risk

Year		0	2	5	0	2	5
RCT	——	122	82	31	130	80	16
RT	---	111	59	16	116	55	11

A

Overall Survival

Patients without positive margin and/or ECE



at Risk

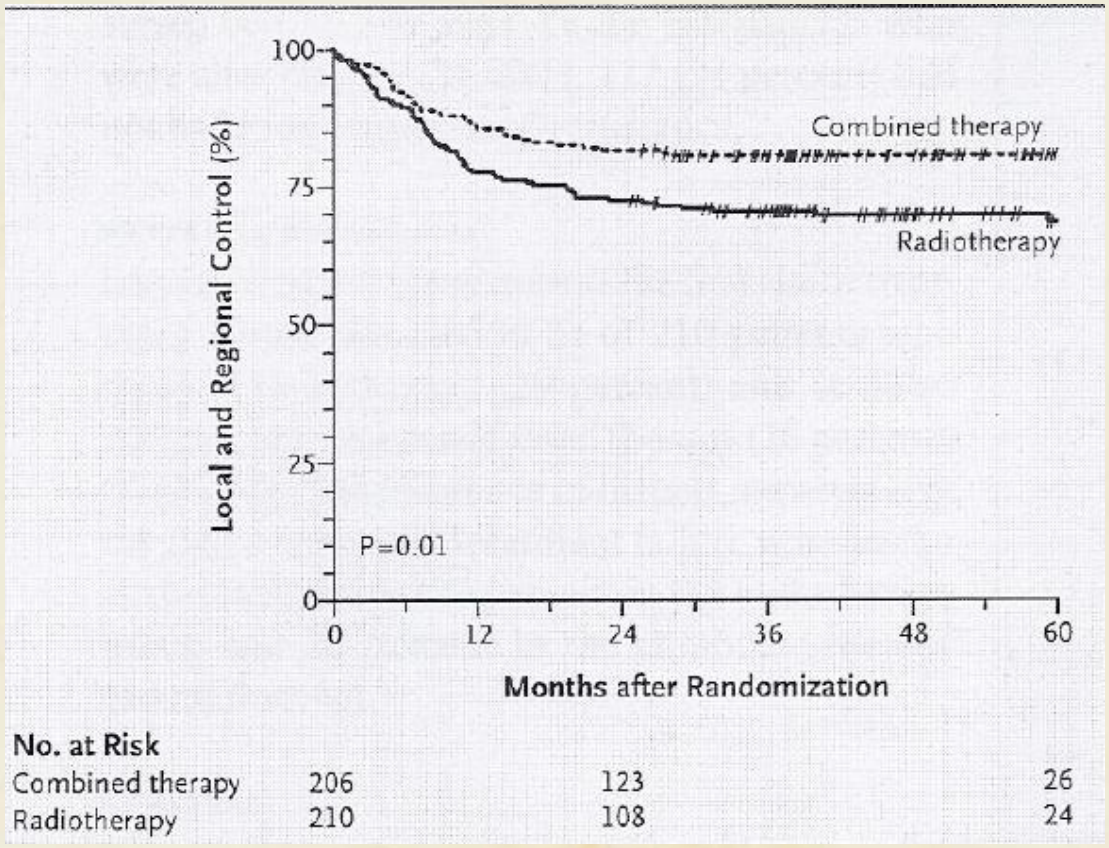
Year	0	2	5	0	2	5
RCT ——	45	36	16	76	52	11
RT ---	56	34	15	94	65	14

B

RTOG 9501
ECOG 9501 SWOG 9515

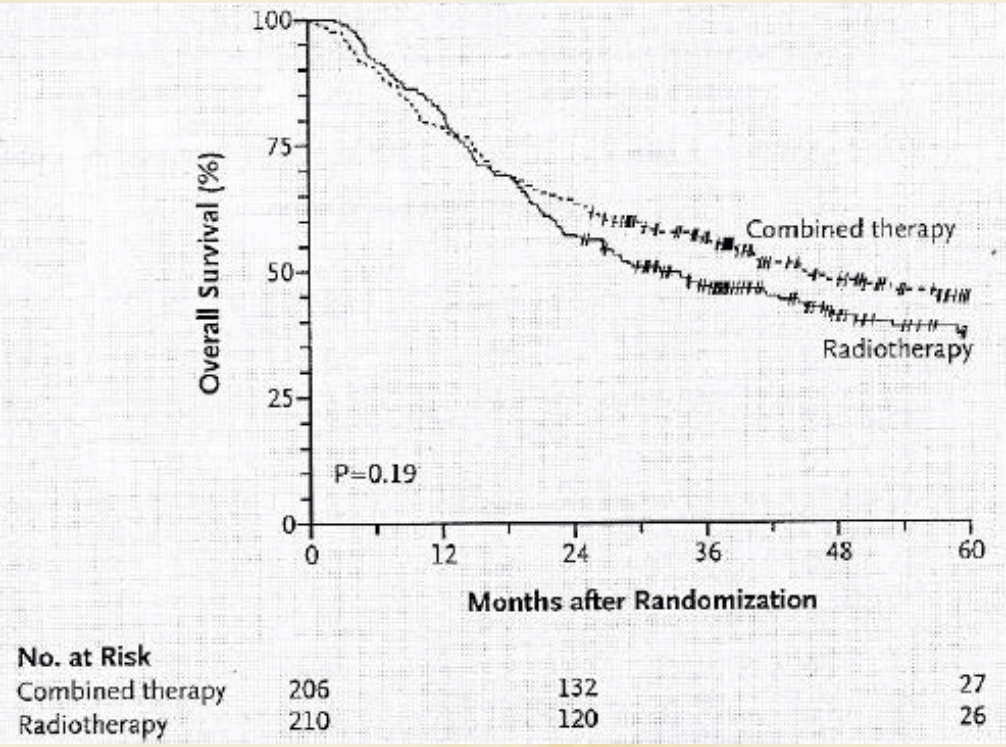
- RT : 60 Gy
- Cisplatin @ 100mg/m2 D1,D22,D43

RTOG 9501

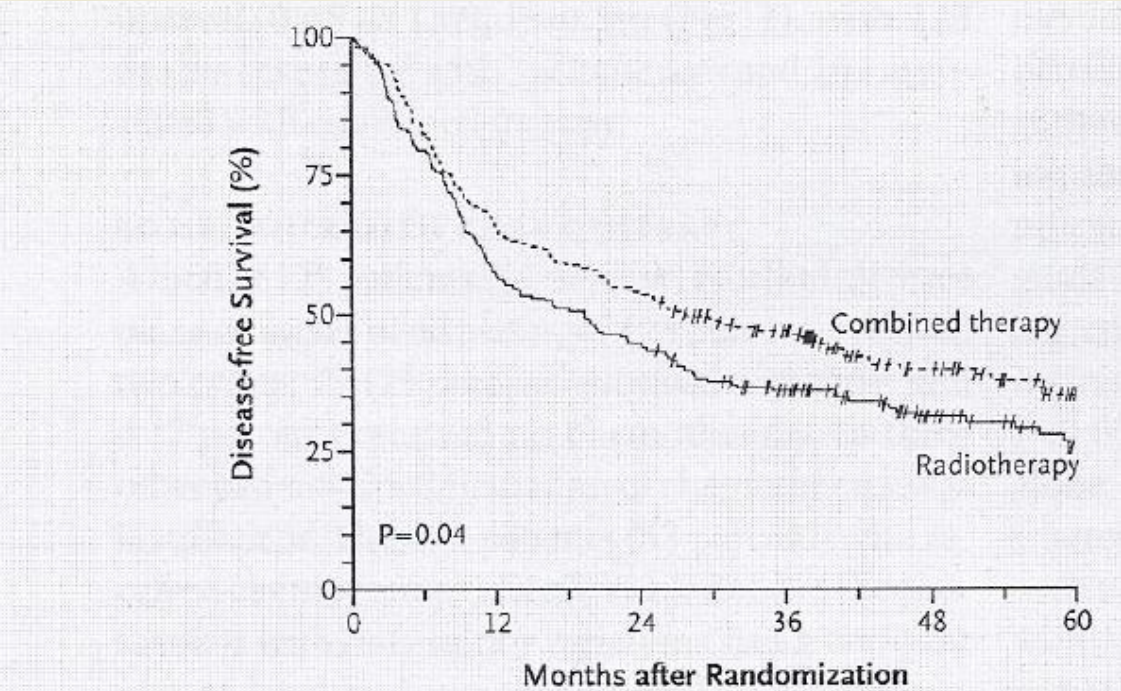


No. at Risk			
Combined therapy	206	123	26
Radiotherapy	210	108	24

RTOG

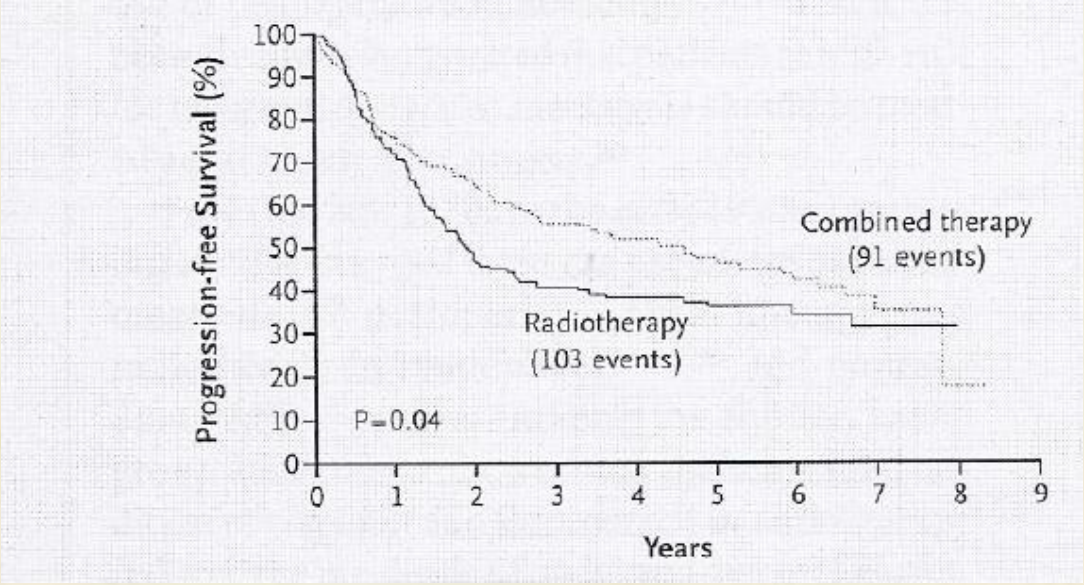

100
75
50
25
0
Overall Survival (%)
Combined therapy
Radiotherapy
P=0.19
0
12
24
36
48
60
Months after Randomization
No. at Risk
Combined therapy 206 132 27
Radiotherapy 210 120 26

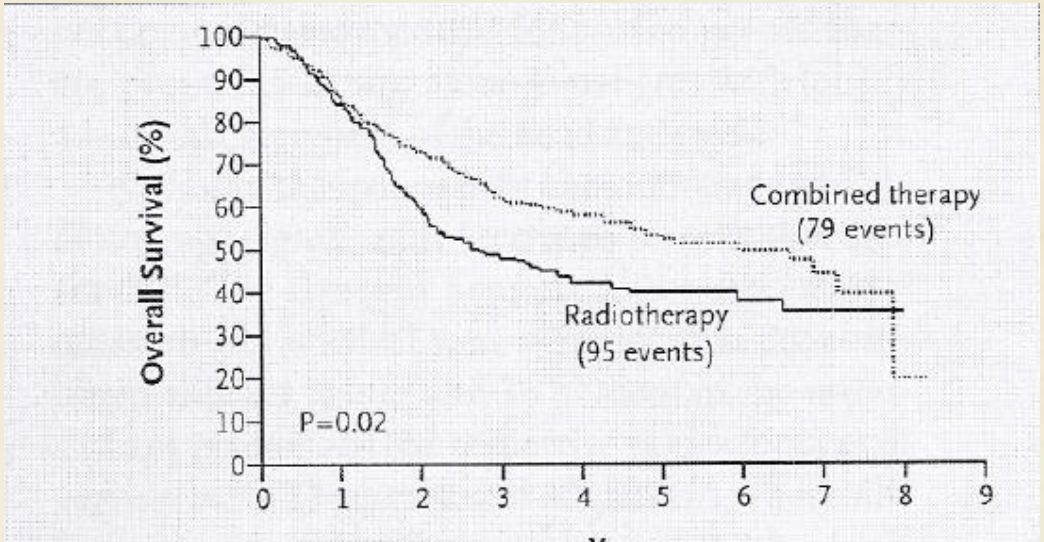
RTOG



No. at Risk			
Combined therapy	206	111	21
Radiotherapy	210	94	19

EORTC 22931


Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9
Years
Combined therapy
(91 events)
Radiotherapy
(103 events)
P=0.04


Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9
Combined therapy
(79 events)
Radiotherapy
(95 events)
P=0.02

ABSOLUTE INDICATIONS for PORT

1. Microscopically involved mucosal margins of resection
2. Extra capsular extension of nodal disease

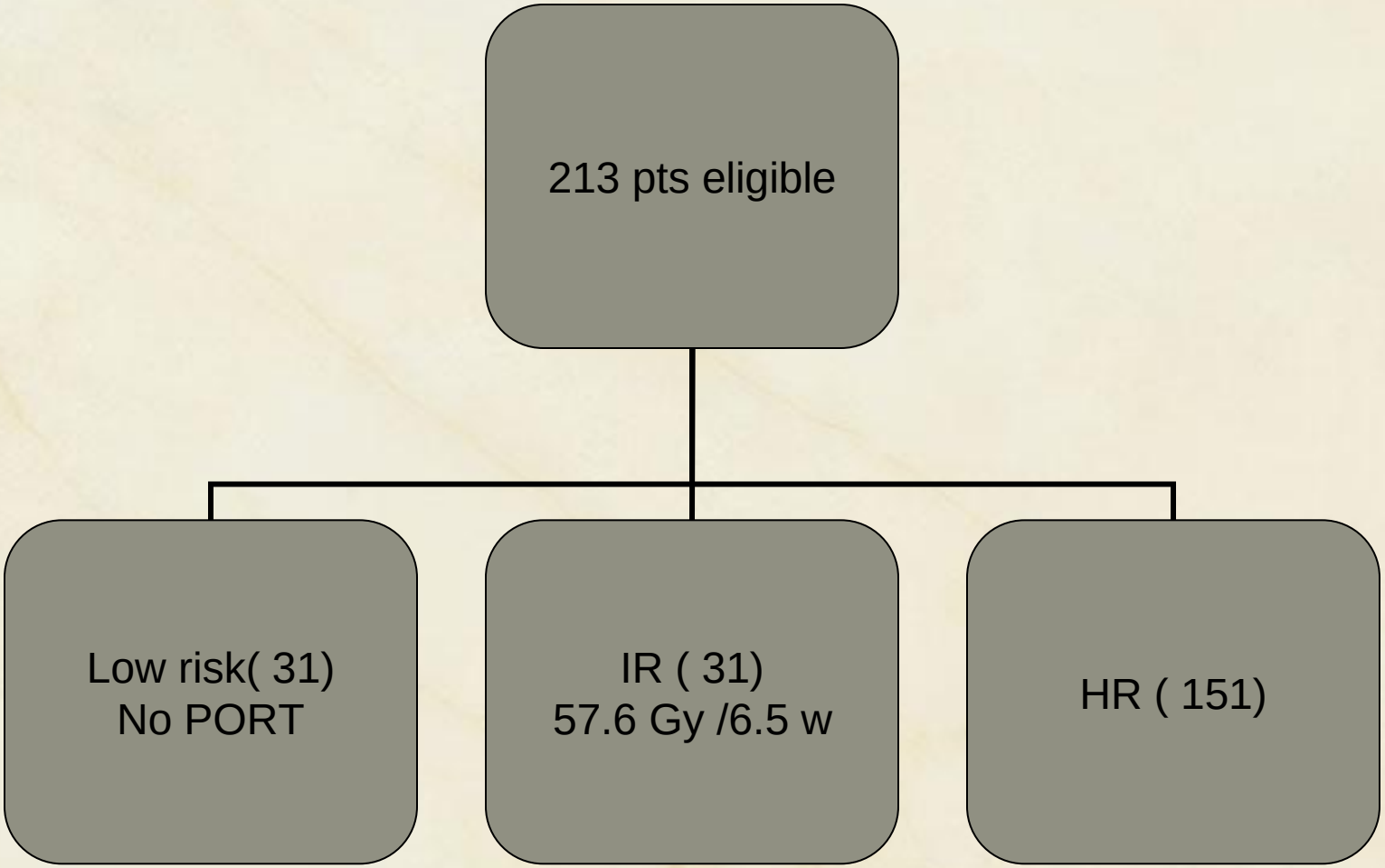
RELATIVE INDICATIONS

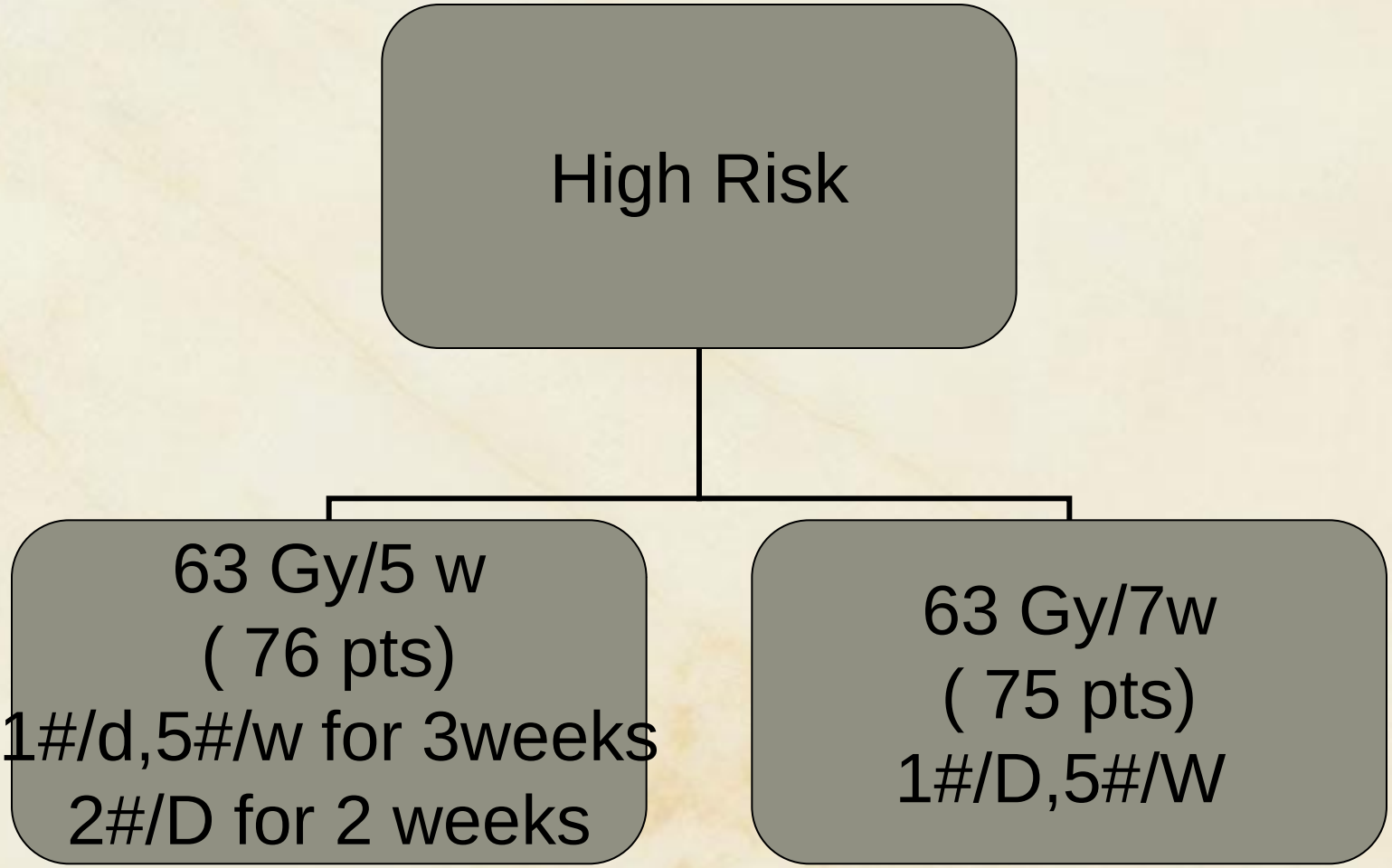
1. Close resection margins <5mm
2. Histological evidence of metastasis in 2 or more nodes
3. Perineural involvement or microvascular emboli

- PORT improves outcome of advanced H&N SCC but 5-year rate of disease-free survival is < 50%!
- Recurrent local and regional disease remains the most common form of treatment failure

Risk features and Time factors

- Prospective, randomised trial(1991-1997)
- 288 pts with locally advanced Head & Neck


213 pts eligible
Low risk(31)
No PORT
IR (31)
57.6 Gy /6.5 w
HR (151)


High Risk
63 Gy/5 w
(76 pts)
1#/d,5#/w for 3weeks
2#/D for 2 weeks
63 Gy/7w
(75 pts)
1#/D,5#/W

TIME

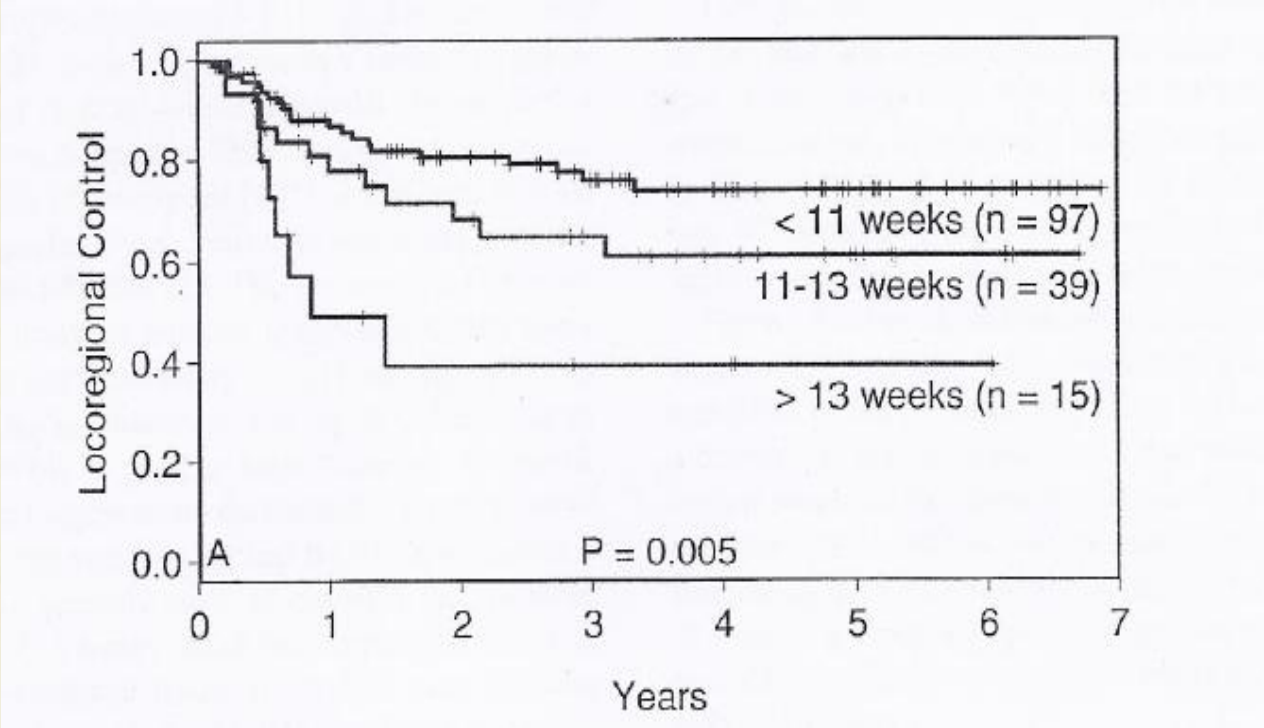
- Patients with high-risk features

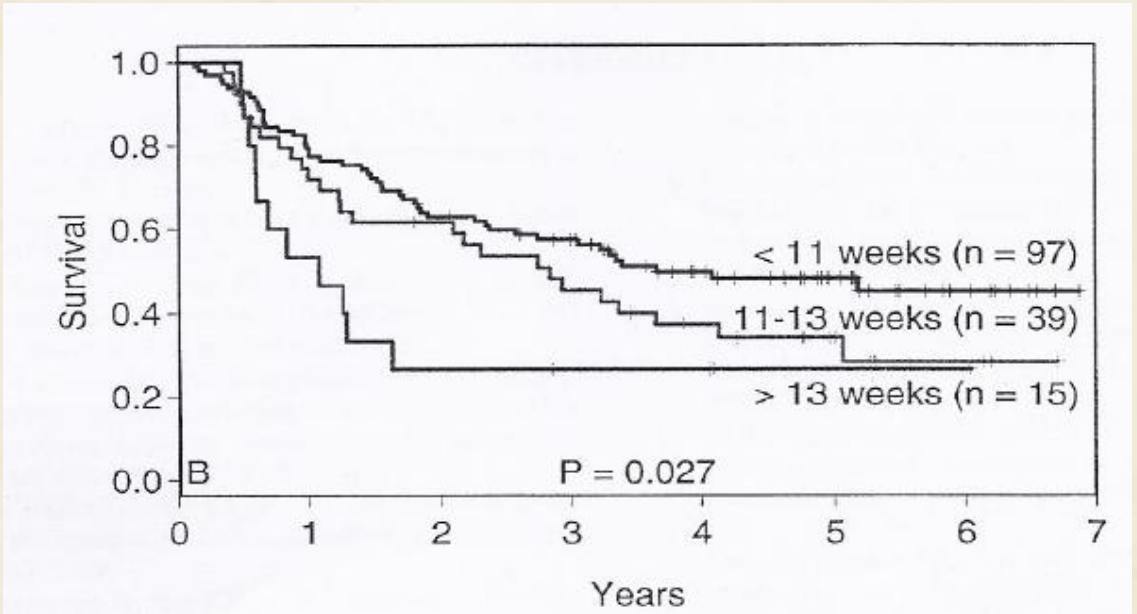
→ Trend worse LRC and survival rates if delay > 6 weeks.

-→ trend toward higher LRC and survival rates when PORT delivered in 5 weeks rather than 7 weeks

LRC

- Retrospective studies : trend towards association between > 6-weeks delay in starting postop RT and worse LRC and survival rates


1.0
0.8
0.6
0.4
0.2
0.0
Locoregional Control
A
P = 0.005
< 11 weeks (n = 97)
11-13 weeks (n = 39)
> 13 weeks (n = 15)
0
1
2
3
4
5
6
7
Years



High risk patients

EORTC 22851

SQUAMOUS CARCINOMA

T2 T3 T4
all head and neck sites
(except for hypopharynx)

WHO status 0, 1, 2

< 75 years old

R A N D O M I S A T I O N

Arm 1 :
Conventional regime
Single fraction per day :
1.8-2 Gy, 7-8 wks overall time
70 Gy / 35 fractions / 7 weeks

Arm 2 :
Accelerated fractionation regime
3 fract. per day : 1.6 Gy / fract.
- 1st course : 28.8 Gy / 18 fr. / 8 days
12 to 14 days split
- 2nd course : 43.2 Gy / 27 fr. / 17 days
72 Gy / 45 fractions / 5 weeks

EORTC 22851

- 5 weeks hyper fractionated and accelerated (AF)RT without reduction of total dose.
- AF arm : pts did better with regard to LRC over CF-→ 13 % gain in 5 years
- Larger magnitude improvement in patients with poorer prognosis (N2/3,T4)
- Acute and late toxicity increased in the AF arm

- Number of fractions
- Dose per fraction
- Total dose given
- Overall treatment duration

Probability of severity of acute and late toxicity after altered fractionation radiotherapy, association of radiation with radiosensitizer, chemotherapy or targeted therapy

Severe Toxicity	Accelerated RT	Hyperfractionated RT	Radiosensitizer* -RT	Concomitant CT–RT	Targeted therapy[a] -RT
Epidermitis	++	+	+	+	+
Mucositis	+++	++	++	+++	+
Hematological toxicity	–	–	–	+++	+
Systemic side-effects	–	–	+	+++	++
Acne form rashes	–	–	+	-	+++
Xerostomia 2-D technique	++	++	++	++	++
Xerostomia 3-D RT/ IMRT technique	+	+	+	+	+
Late mucosa atrophy	+	+	+	++	+
Fibrosis	+	+	+	+	+

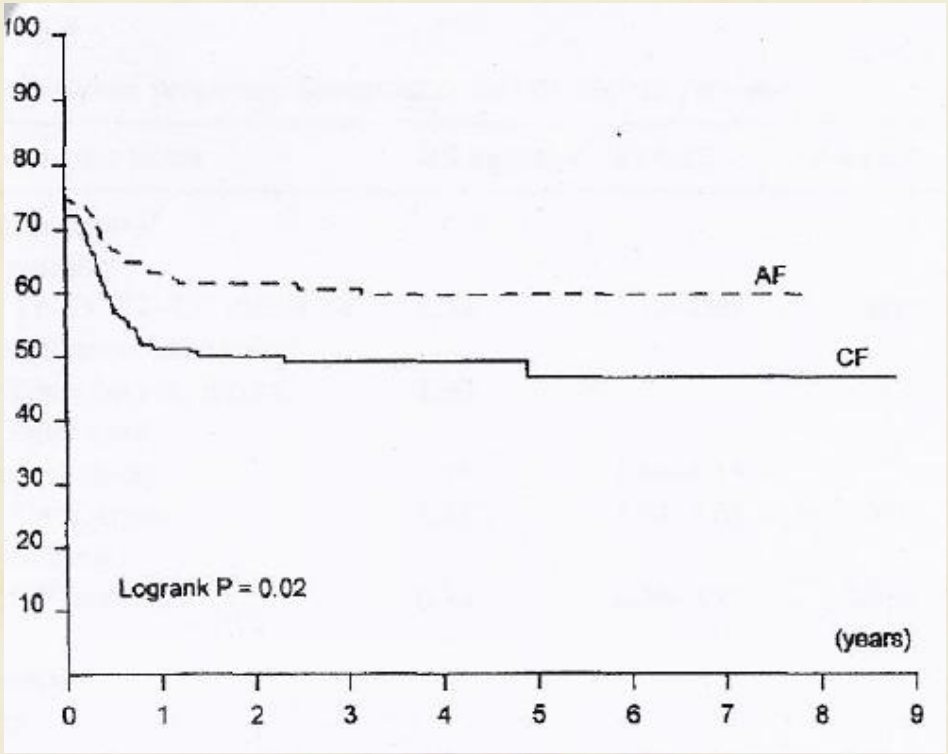
Symbols: +, ++, +++: low, increased and high probability of severe toxicity, respectively; incidence may vary according to radiotherapy technique, fractionation and total dose, primary site, chemotherapy regimen and timing.
RT, radiotherapy; CT, chemotherapy; IMRT, intensity-modulated radiotherapy; *nimorazole.
[a] Cetuximab.

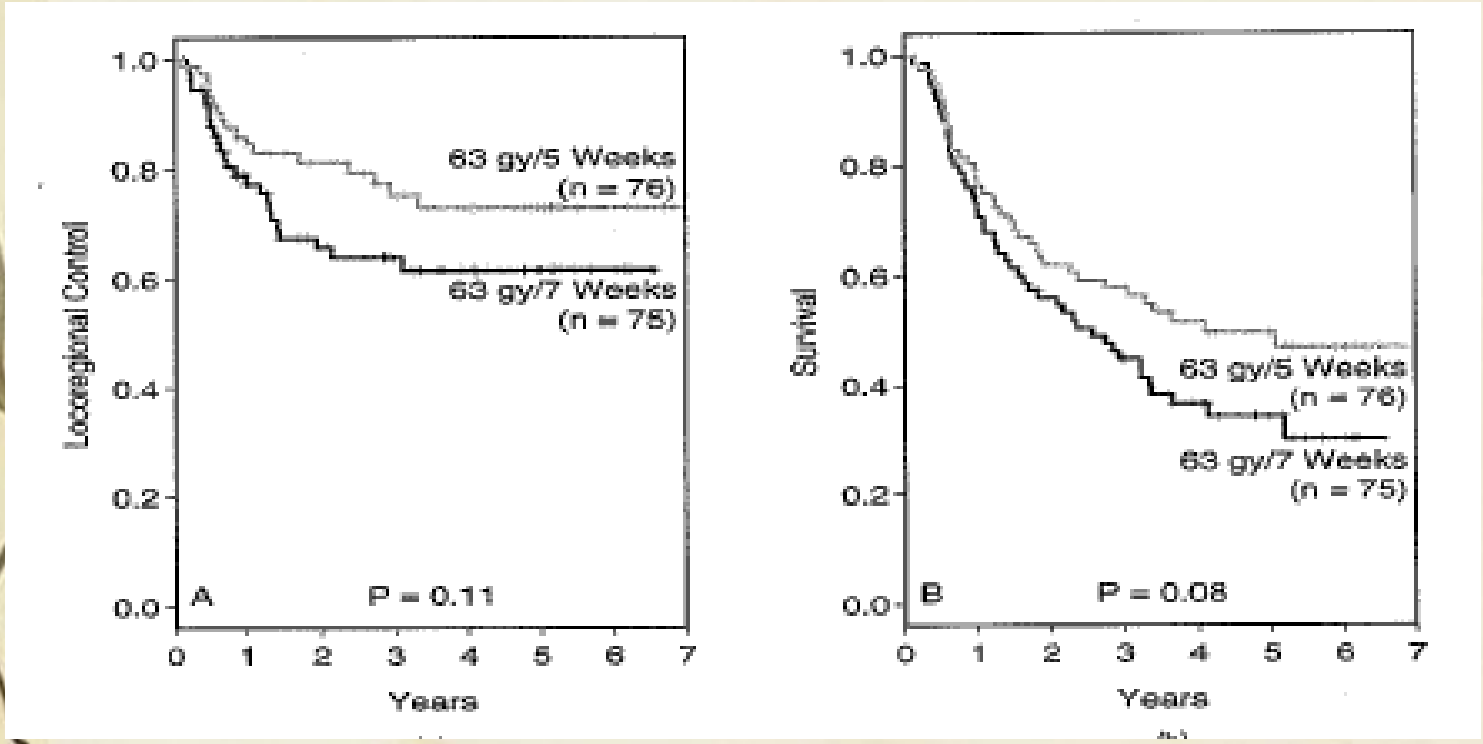
- Shorten overall duration of treatment and use small dose -→ more than one treatment must be given each day

- --→ improvement in local control
- 15 % higher tumour control rate

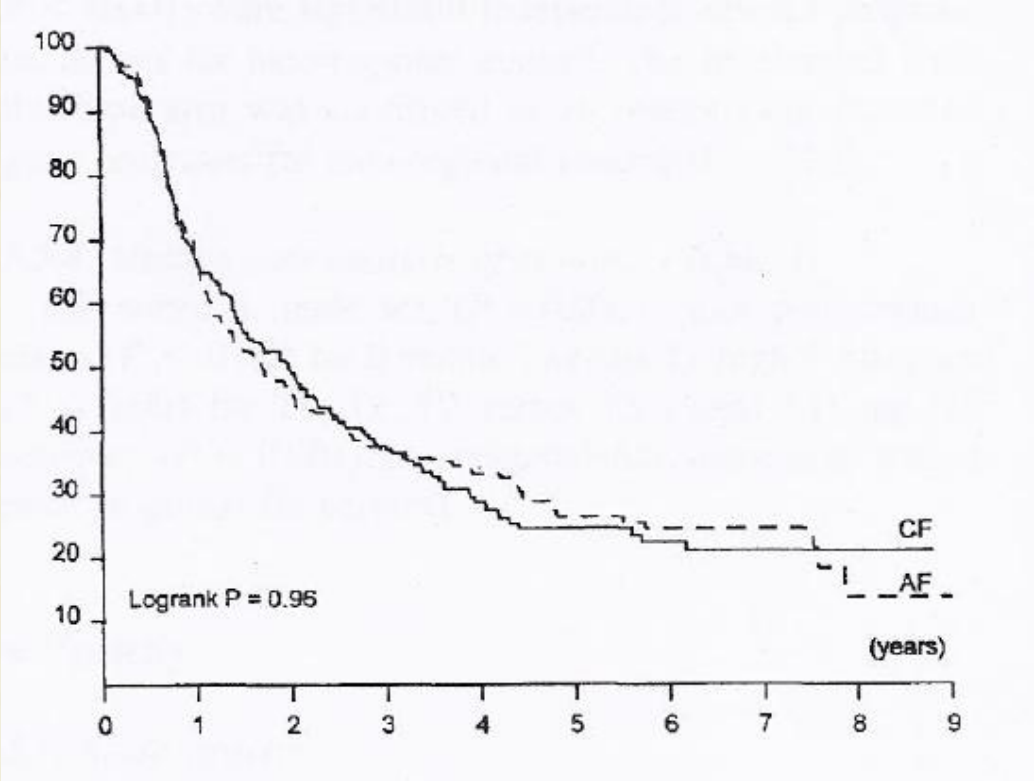
EORTC 22851

LRC



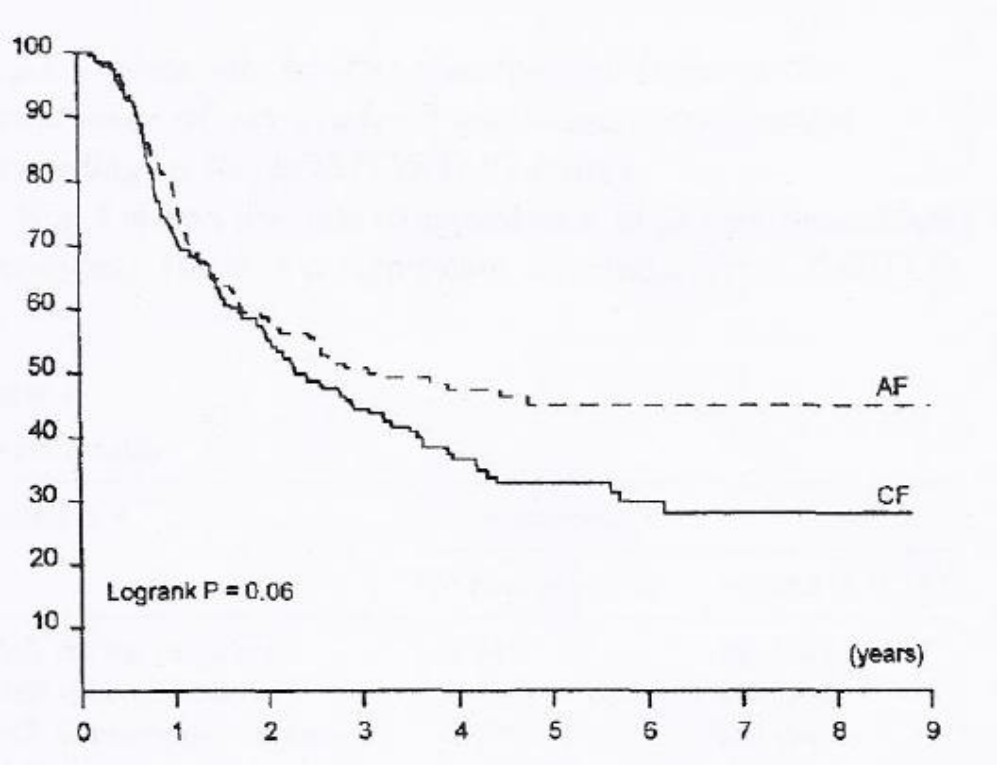

Locoregional Control
1.0
0.8
0.6
0.4
0.2
0.0
63 gy/5 Weeks
(n = 76)
63 gy/7 Weeks
(n = 75)
A
P = 0.11
0 1 2 3 4 5 6 7
Years
Survival
1.0
0.8
0.6
0.4
0.2
0.0
63 gy/5 Weeks
(n = 76)
63 gy/7 Weeks
(n = 75)
B
P = 0.08
0 1 2 3 4 5 6 7
Years

EORTC 22851



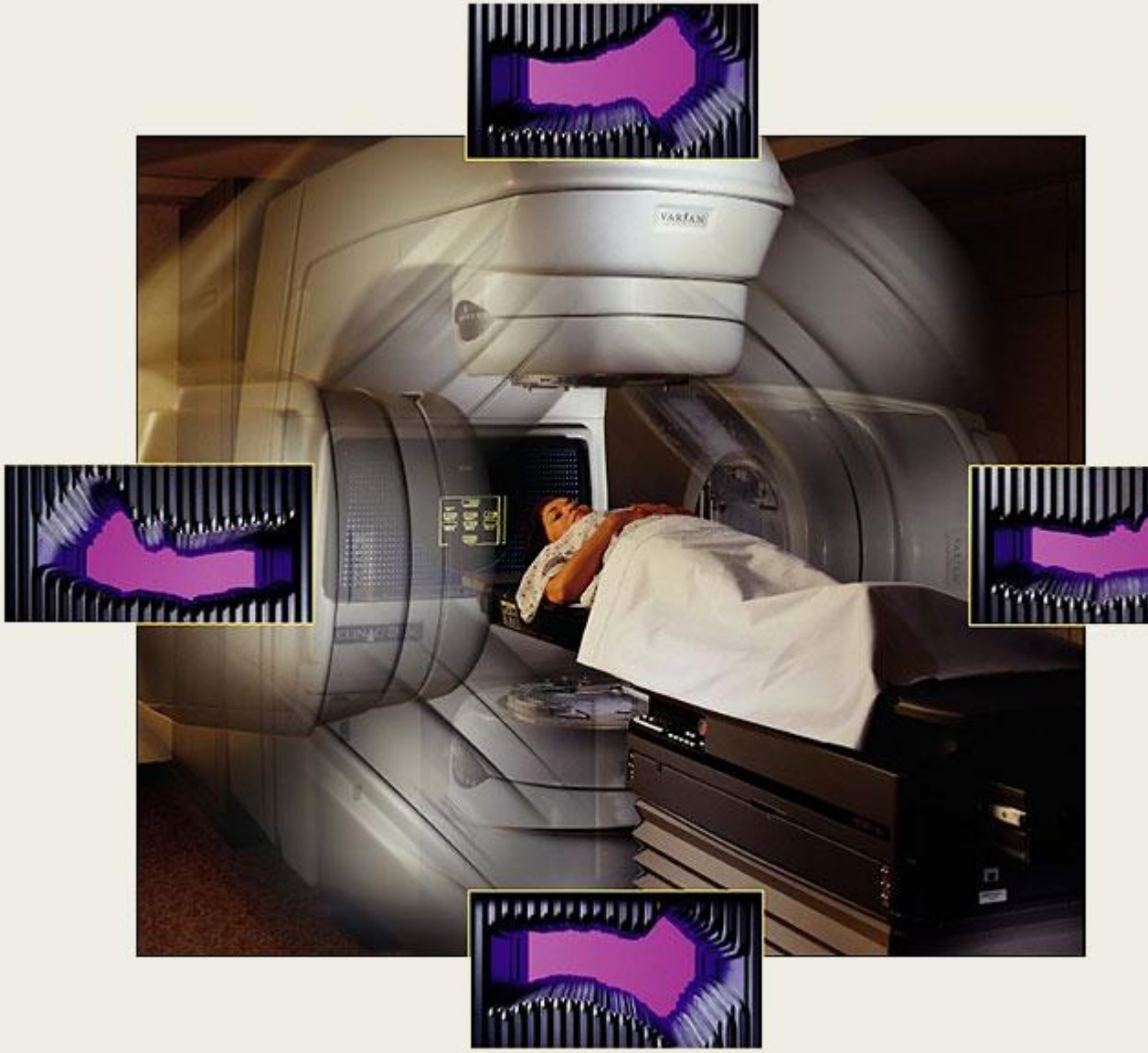
Overall survival

EORTC22851

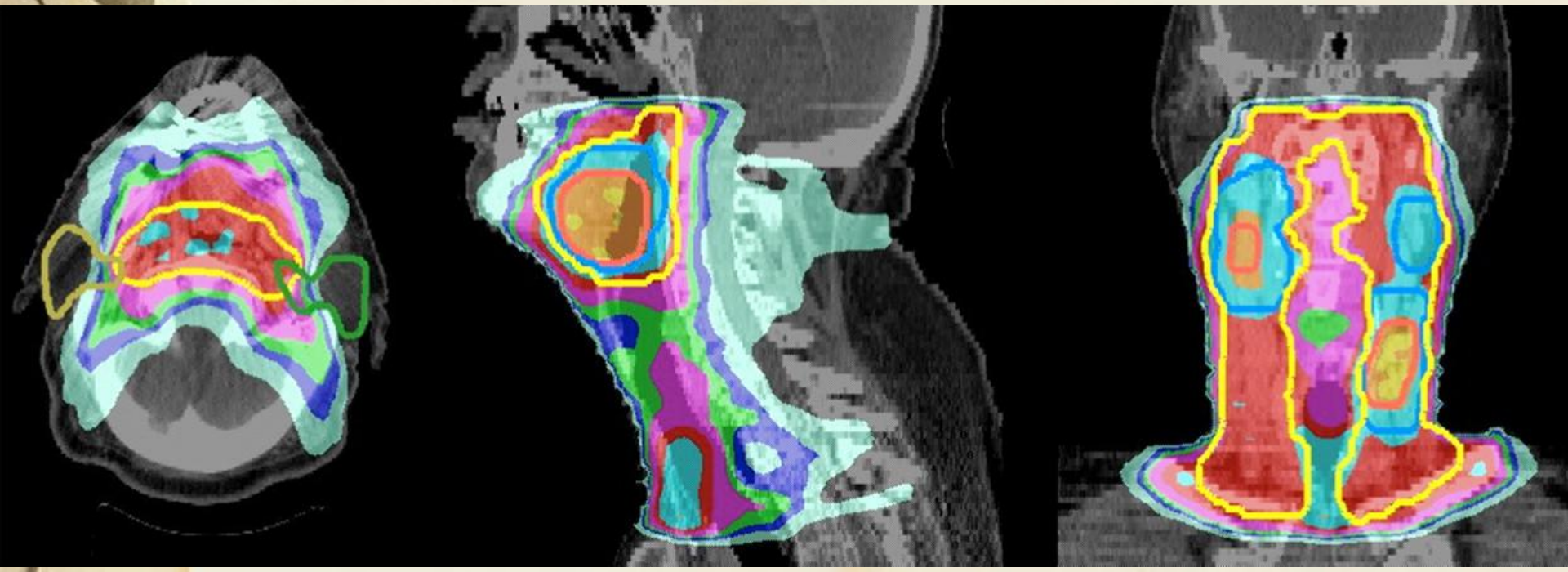


Specific survival

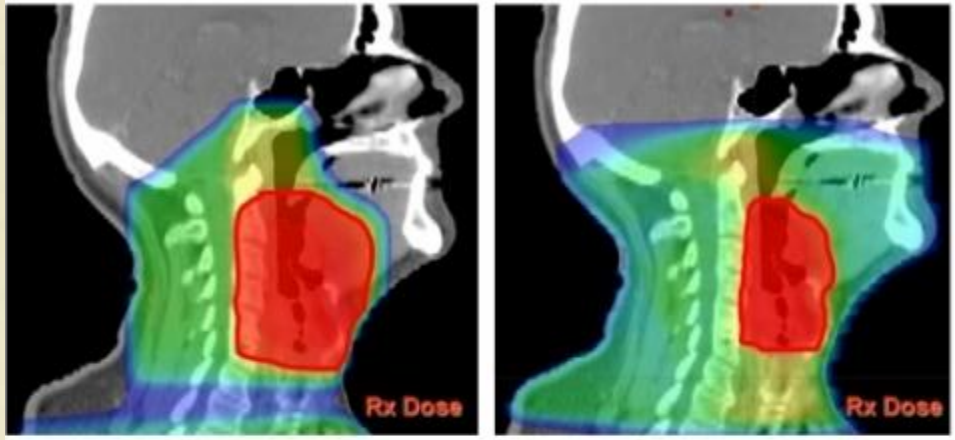

Final
Absolute


VARIAN

IMRT



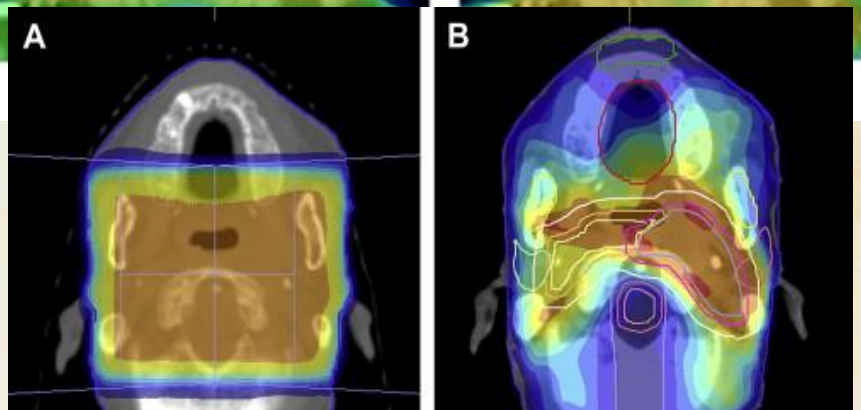
IMRT delivers less dose to normal tissue...



Conventional

IMRT

IMRT spares parotids to minimize dry mouth...



MULTIDISCIPLINARY

Multidisciplinary team :

- Pathologist
- Surgeons
- Radiation Oncologist
- Speech therapist
- Medical Oncologist
- Radiologist –MRI/CT scan
- Dietician
- Palliative care team

END