HYPOFRACTIONATION IN HEAD AND CANCERS: AN OVERVIEW

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Outcomes

- Stages I and II
  - 1/3 of patients
  - Curative results: 60% to 80%
  - SPTs: greater risk than recurrence
- Stages III and IV
  - 2/3 of patients
  - Multimodal treatment
  - 40% to 80% local recurrence
  - 10% to 30% distant disease

Treatment of **head and neck cancers** is influenced by

- fraction size,
- total dose
- overall treatment time

- The total radiation dose has demonstrated a direct impact to the tumor response as well as to the acute or late adverse events**.**
- For H&N cancer, most Authors suggest that repopulation begins only after a *T*k of about 3–5 weeks after the start of radiotherapy

Why Hypofractionation: Accelerated repopulation

- Occurs after 3-4 weeks for squamous carcinomas
- Up to 0.6 Gy of each daily dose would be “wasted” due to increased tumor cell load
- Withers et al. report that, a dose increment of approximately 0.6–0.7 Gy per day is required to counterbalance tumor repopulation and keep tumor control rates unchanged for OTTs times up to 55 days
- For each extra day, local control would decrease by 1% due to accelerated repopulation

Table 1. Examples of the regimens employed in studies of novel fractionation schedules in head and neck cancer

Regimen	Dose per fraction	*n* of fractions	Total dose (Gy)	Overall time (days)	Interfraction interval (hrs)	Interfraction interval (weeks)
						1 2 3 4 5 6 7
Hyperfractionation [2]	1.15	70	80.5	47	8	
Acceleration						
a) Pure [10]	2	24-27	48-54	9-11	4	
b) Pure [13]	2	33	66	38	24	
Acceleration with a split [18, 19]	1.6	40	64	40	4	
EORTC [3]	1.6	45	72	33	4	
Concomitant boost [22]	1.8 and 1.5	30 and 10	69	40	3-6	
CHART [23]	1.5	36	54	12	6	

HYPOFRACTIONATION

HYPOFRACTIONATION: RENEWED INTEREST

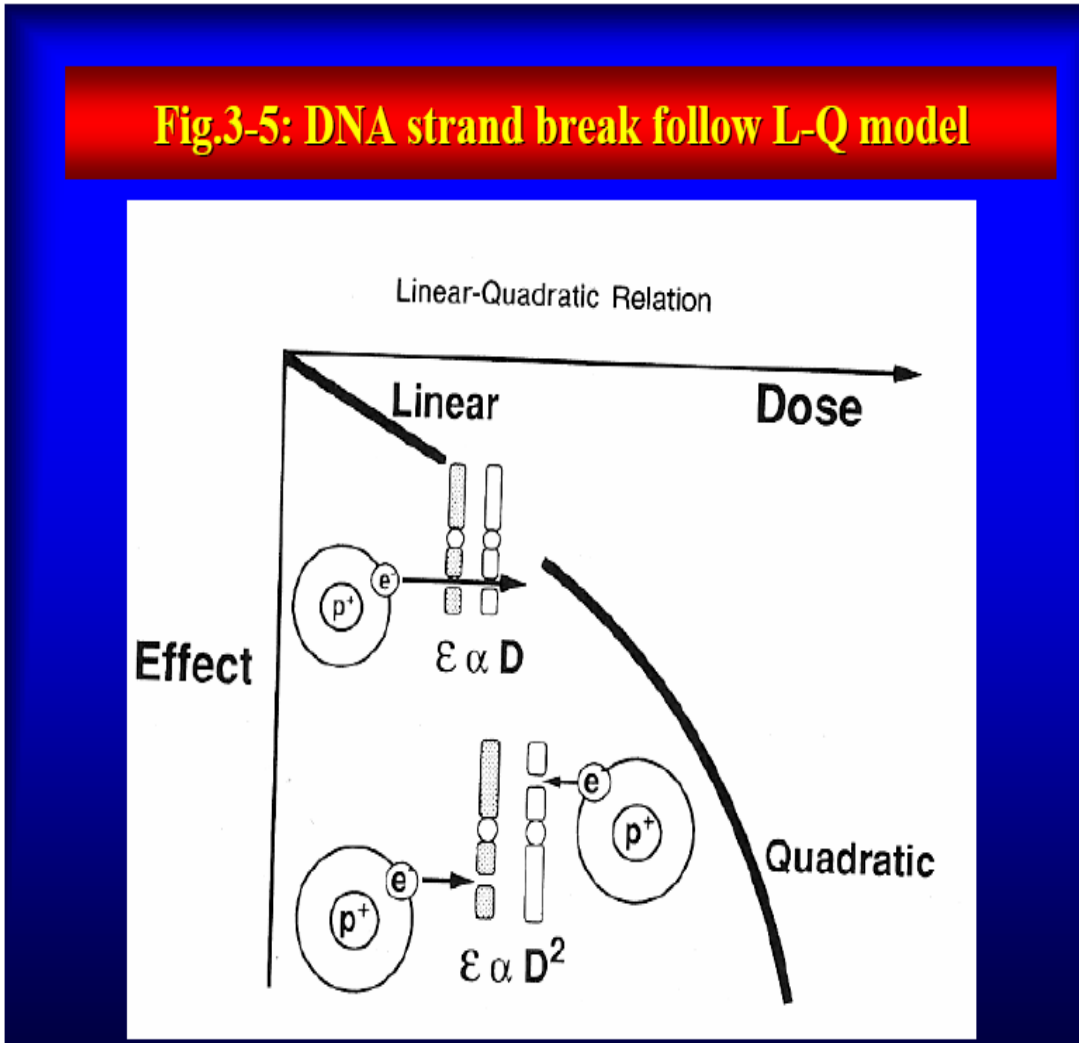
- 1) In tissues with α/β similar to ***late*** responding tissues e.g. prostate
- 2) Acceleration is better achieved by hypofractionation than hyperfractionation since ***late normal tissue repair*** is a limiting factor
- 3) ***IMRT***, tomotherapy & proton therapy result in improved dose distributions with minimal normal tissue receiving high dose
- 4) ***Carbon*** **ion beams** – better dose distribution/high LET
- Economical
- Late normal tissue damage

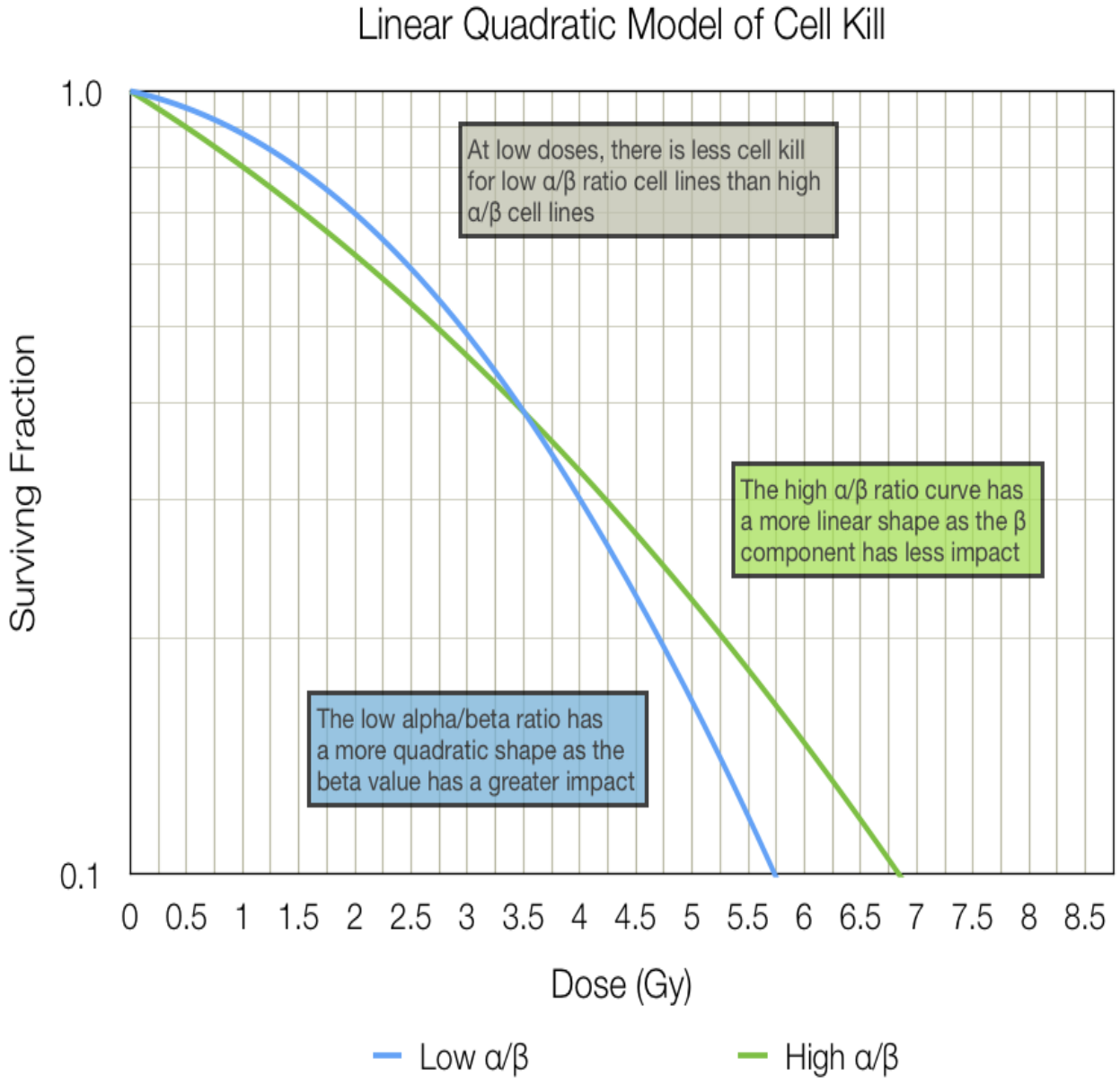
LINEAR QUaDRATIC MODEL

- A lethal event is supposed to be caused by one hit due to one particle track (the linear component αD)

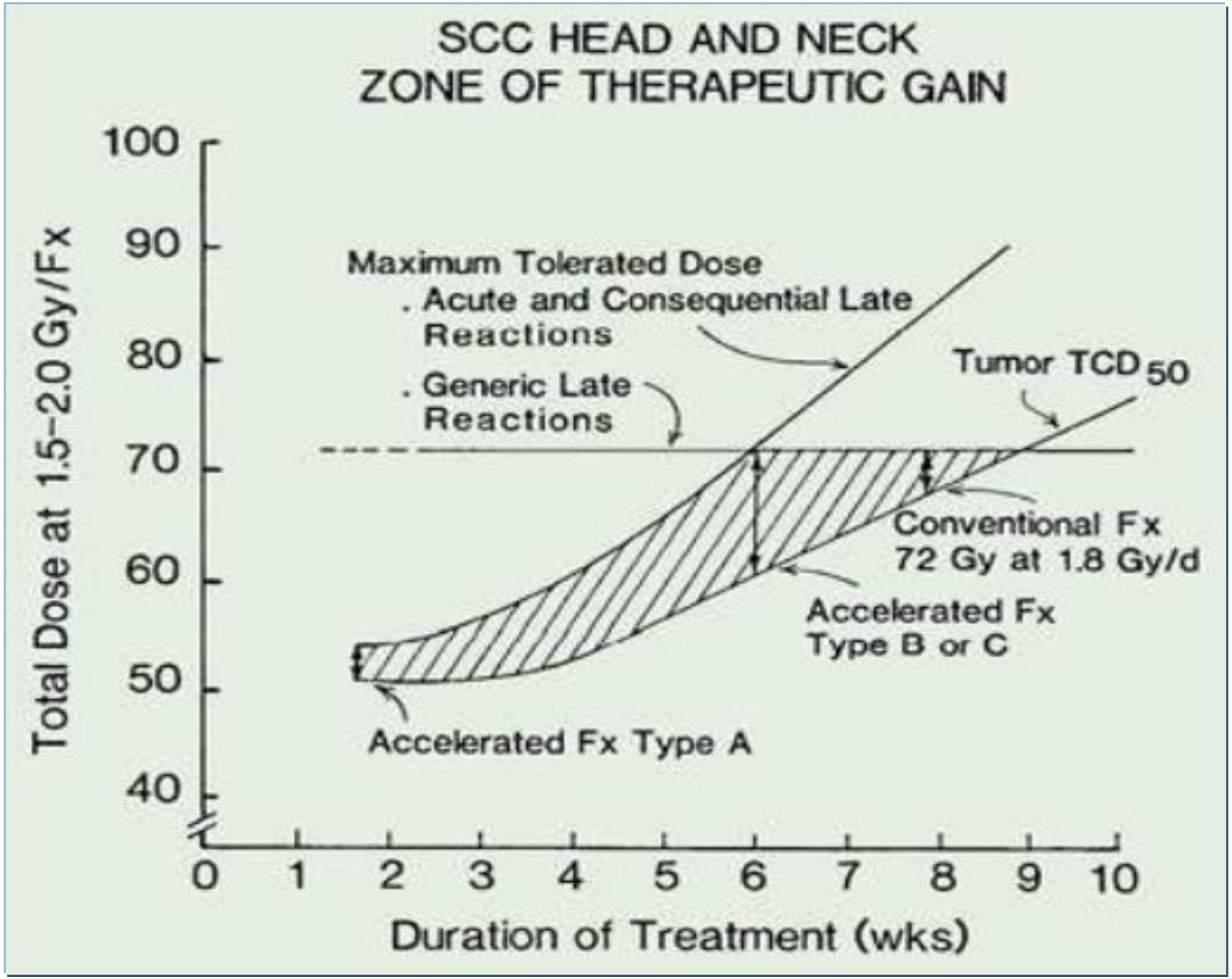
or

- Two particle tracks (the quadratic component βD2)
- Dual radiation action
- First component - cell killing is proportional to dose
- Second component - cell killing is proportional to dose squared





- Carcinomas of the head and neck and lung, it is higher
- Melanomas, sarcomas, prostate cancers etc it's low


SCC HEAD AND NECK
ZONE OF THERAPEUTIC GAIN
Total Dose at 1.5–2.0 Gy/Fx
100
90
80
70
60
50
40
Maximum Tolerated Dose
. Acute and Consequential Late Reactions
. Generic Late Reactions
Tumor TCD 50
Conventional Fx
72 Gy at 1.8 Gy/d
Accelerated Fx
Type B or C
Accelerated Fx Type A
0
1
2
3
4
5
6
7
8
9
10
Duration of Treatment (wks)

Why Hypofractionation: Intrinsic radiosensitivity

- Tumors can have variable degrees of radiosensitivity.
- Range from highly radioresistant (melanoma, renal cell carcinoma) to Highly radiosensitive (lymphomas)
- Based on the extent of sub-lethal damage repair

Hypofractionation

- Total dose delivered in a few high dose fractions with longer intervals between fractions
- Higher exposure increases tumour response
- Acute normal tissue reactions not increased
- Late normal tissue reactions increased

EUD

- ✖ Standard dose constraints assume that the **whole** organ is being **uniformly** irradiated at **1.8-2Gy/#.**
- ✖ In IMRT, aside from use of higher dose/# (in SIB), most OARs are only partially irradiated. There is also a steep dose gradient within a given OAR.
- ✖ Equivalent Uniform Dose (EUD) is that dose, which had the organ been wholly and uniformly irradiated, would have produced the same biological effect.
- ✖ Complex voxel-based calculation.

- Fowler's formula used to calculate equivalent doses from various hypofractionated regimens

- RE = (1 + d /a/β) where n is the fraction number; d the fraction dose and α and β coefficients describe the contribution to cell killing from linear and quadratic components, respectively

$$\mathrm{BED} = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\ln 2}{nd\alpha}\frac{T - T_k}{T_{pot}}$$

and

$$\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\ln 2}{nd\alpha}\frac{T - T_k}{T_{pot}} = \mathrm{RE}$$

$$\mathrm{NTD}_{2\,Gy} = \frac{\mathrm{BED}}{\mathrm{RE}_{2\,Gy}}$$

where RE_{2Gy} is the relative effectiveness of 2 Gy per fraction.

HYPOFRACTIONATION IN HNC: WHAT DO WE DISCUSS

- Hypo# in Palliative setting
- Hypo# in Definitive setting: accelerated regimes
- Hypo# in Definitive setting: SIB regimes
- Hypo# in Definitive setting: SBRT

Hypofractionation in Palliative setting

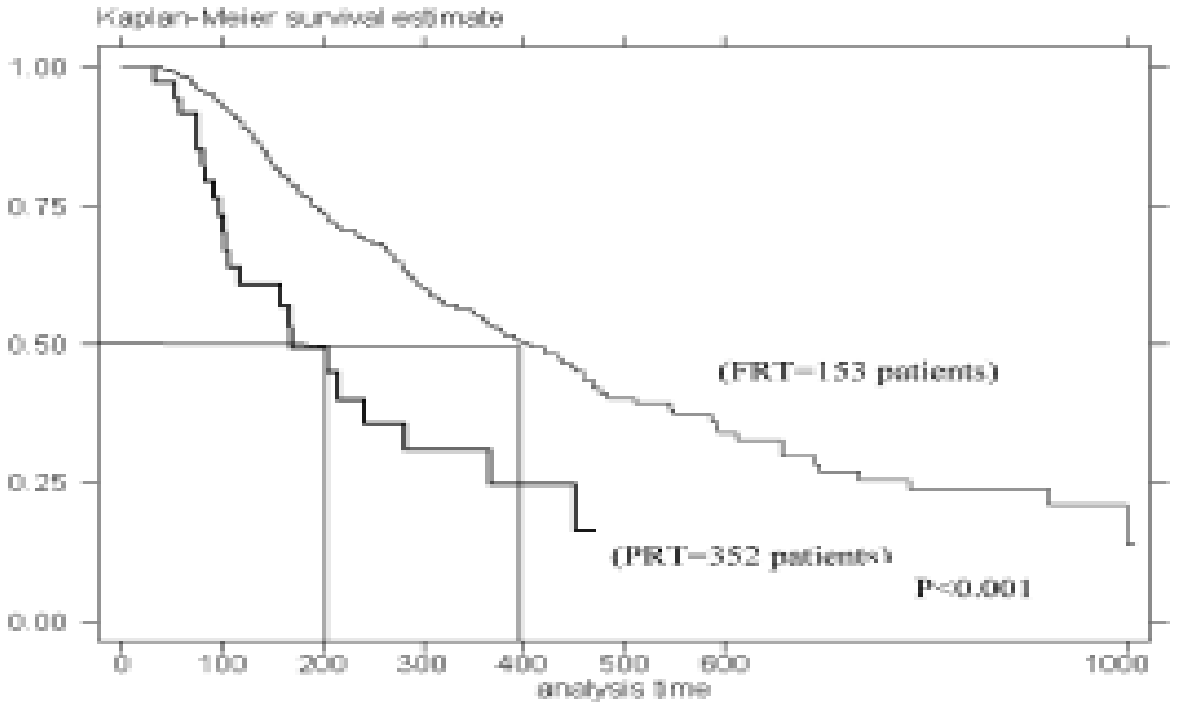
- phase II prospective study of 3.7 Gy BID times 4 over 2 days (the "**Quad Shot**") by Corry *et al.*

- This Quad Shot was then repeated at monthly intervals times 3, if patients did not progress or decline clinically.

- Median survival was 5.7 months. No grade 3 or more toxicity noted.

- The tumor RR was 53% and 44% of patients had QOL improvements.

Short course palliative radiotherapy of 20 Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study



Overall the RR for those receiving palliative radiation was 37% with 47-59% palliation of symptoms.

Outcomes of response adapted therapy

Radiotherapy and oncology, 2004

- Study by Das et al, CMC Vellore
- All patients had advanced head and neck cancers (27% IVA, 61% IVB, 9% IVC, TNM stage and 3% recurrent disease).
- Grade 3 mucositis and dermatitis and pain was 18%, 3%, and 24%, respectively.
- Reduction of pain was observed in 88% patients and 60% patients had improvement of performance status.
- Median overall survival of the cohort was 7 months.

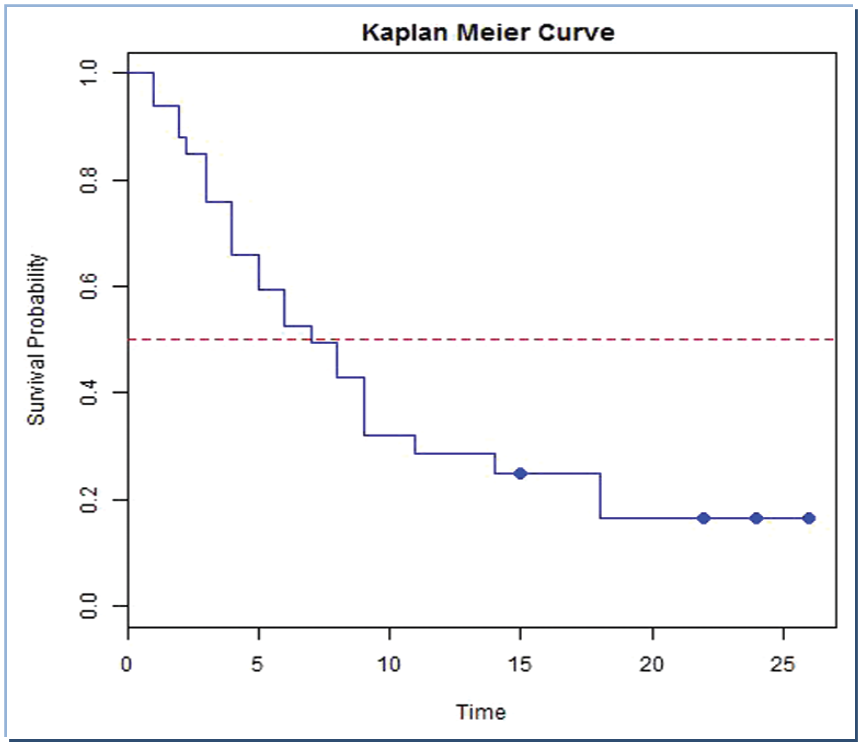


Table 3: Quality of life improvement

Scale	Before treatment mean±SD	After treatment (at completion) mean±SD	*P* value
PWB	15.1	17.0	0.095
SWB	17.4	20.01	0.036*
EWB	12.8	13.4	0.552
FWB	12.5	13.9	0.262
FACT G	59.2	64.5	0.092
FACT HN	25.1	25.0	0.938

PWB, Physical well-being; SWB, Social well-being; EWB, Emotional well-being; FWB, Functional well-being; FACT G, General score (summation of physical, social, emotional, and functional well-being); FACT HN, Head and neck-specific score

Table 3 Hypofractionated radiation therapy trials in head and neck cancer

Reference Trial design	# Patients	Dose/fx	# fx	Schedule	Efficacy	Toxicity
Chen (50) Retrospective review	83 77 67 86 60	3.7 BID 2 3 2.5 4	4 35 10 15 5	Repeated x3 at 2-3 weeks Daily Daily Daily Daily	No difference	9% RTOG Quad Shot regimen *vs.* 37%
Corry (51) Single arm	30	3.7 BID	4	Monthly x3	53% RR 44% improved QOL	No ≥ grade 3 toxicity
Paris (52) Single arm	37	3.7 BID	4	Monthly x3	77% RR	No late toxicity
Carrascosa (43) Single arm	7 HN*	3.7 BID	4	Monthly x3 with paclitaxel	95% RR 90% palliation	10% grade 3 acute No late toxicity
Monnier (53) Retrospective review	78	3 Gy	8	Day 1 & 3 Repeated weeks 1, 3, 5, 7 cisplatin	54% RR	31% needed break 4% acute grade 3-4 12% late grade 3-4
Das (54) Single arm	33	4	10	Twice/week	88% pain relief 60% improved PS	Grade 3 mucositis 18%, dermatitis 3%
Kancherla (55) Retrospective review	33	4	5	Repeated after 2 weeks	79% symptom relief 72% RR	18% grade 3 acute
Mohanti (56) Single arm	505	4	5	Addl RT for responders	37% RR 47-59% symptom relief	Not stated for palliative RT
Porceddu (57) Single arm	37	6	5-6	Twice weekly	80% RR 62% improved QOL 67% improved pain	Grade 3 mucositis 26% Grade 3 dysphagia 11%
Weissberg (58) Randomized	64	2 4	30-35 10-12	Daily Daily	No difference between arms	No difference between arms

*, this trial included 7 patients with head and neck primaries and 13 with pelvic malignancies; RR, response rate, including complete and partial response; fx, fractions; RTOG, Radiation Therapy Oncology Group; QOL, quality of life; HN, head & neck cancer patients; Addl, additional; PS, performance status; RT, radiotherapy; #, number of.

Bledsoe *et al*: SCAHRT in HNC for the Elderly or Infirm ANTICANCER RESEARCH *36*: 933-940 (2016)

- Patients received two courses of 30 Gy/10 fractions separated by 3-5 weeks to allow for toxicity recovery.
- 58 out of 65 patients (89%) completed both courses of treatment.
- Patients without metastatic or recurrent disease were evaluated for treatment response and survival (n=39).
- Among this group, total tumor response was 91%, and median locoregional failure-free survival and overall survival were 25.7 and 8.9 months, respectively.
- Study concluded that high risk patients unable to tolerate continuous-course definitive (chemo)radiation can safely be treated by SCAHRT to achieve durable locoregional disease

Early Glottic Ca : Stage I / II

(1975-89)

Group I	Group II	Group III
50Gy/ 15fr/ 3wks (3.3Gy/fr)	60-62.5Gy/24-25fr/5wks (2.5Gy/fr)	50-60Gy / 25-30Fr/ 5-6wks (2-2.5Gy/fr)

- *Acceptable local control*
- *Acceptable late complication*
- *No difference in either groups*

Less protracted schedules can be used

Dinshaw et al IJRO BP 48(3) 723-35, 2000

Hypofractionation for early glottic cancers

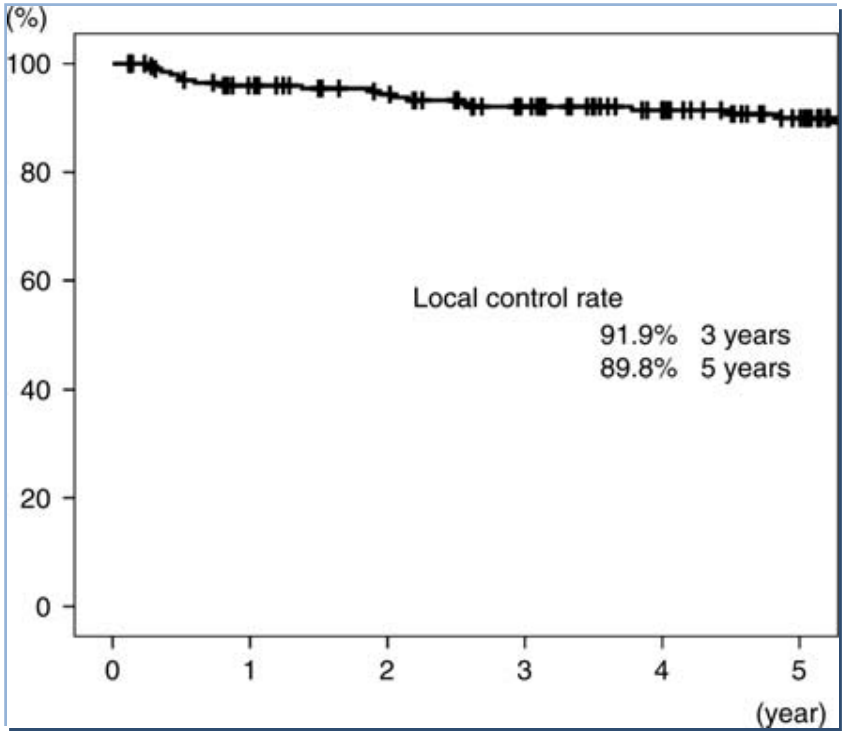
Yamazaki et al (2006)

- N=180
- T1N0M0
- 5-year LCR 77% (conv) vs
- 92% (hypo) (p=0.004)
- No significant difference in survival
- No significant difference in acute/ late toxicities.

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 77–82, 2006

- KROG-0201 (2013)
- N=156; T1-T2N0M0
- 5-year LFPS 77.8%(conv) vs
- 88.5%(hypo) (p=NS)
- 5-year LFPS for T1a 76.7% (conv) vs 93% (hypo) (p=0.056)
- No significant difference in survival
- No significant difference in acute/ late toxicity

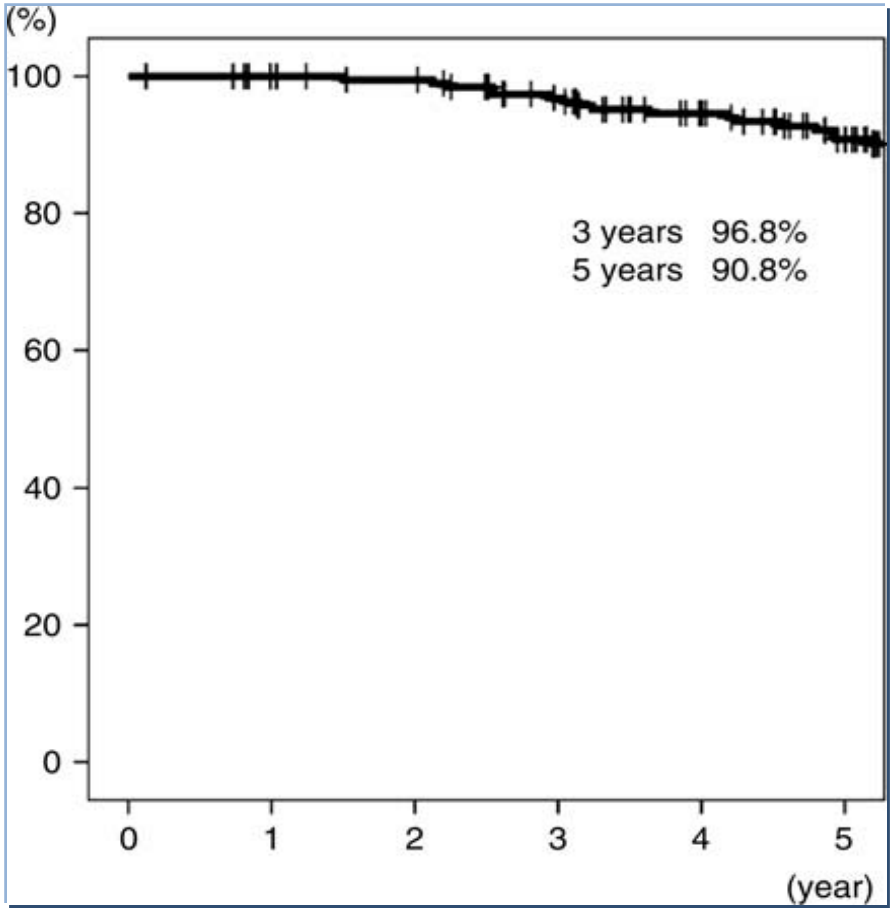
Moon et al. Radiotherapy & Oncology, 2013 (ahead of print)



The local control curve for all patients. The local control rate was 91.9% at 3 years and 89.8% at 5 years

Radiotherapy for Glottic T1N0 Carcinoma with Slight Hypofractionation and Standard Overall Treatment Time: Importance of Overall Treatment Time

Jpn J Clin Oncol 2011;41(1)103–109

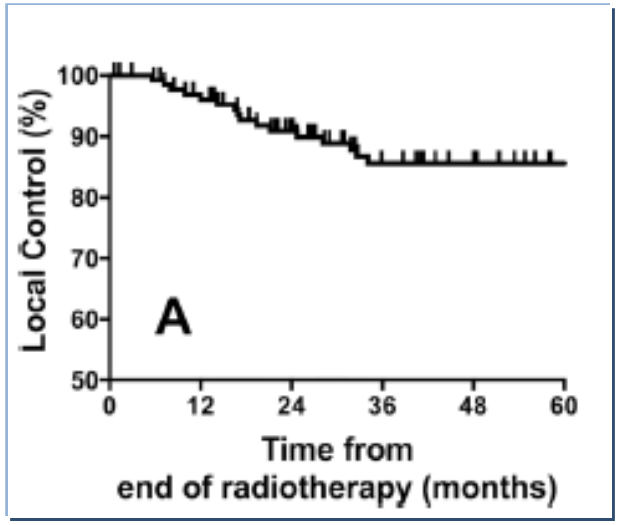


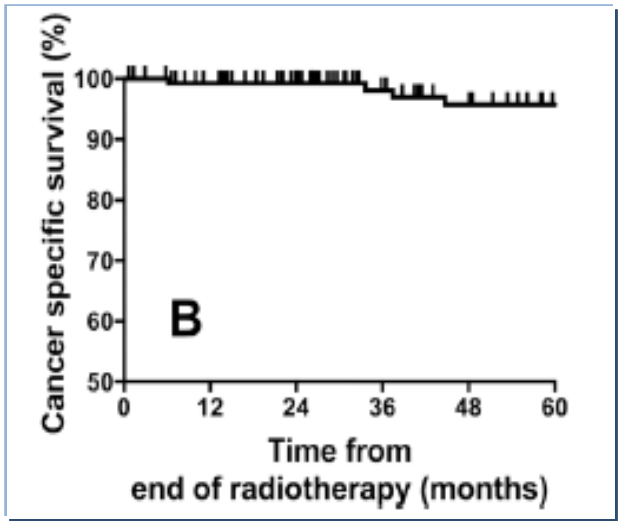
The overall survival rate (OAS) curve. The OAS was 96.8% at 3 years and 90.8% at 5 years.

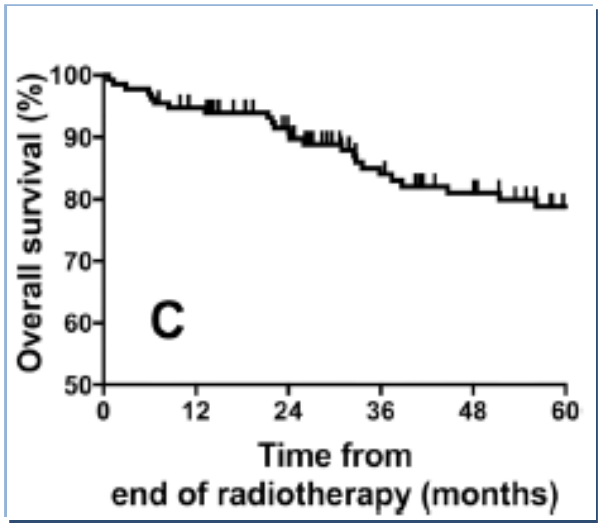
Table 2. Other studies of radiotherapy for T1N0 glottic cancer

Author	Total dose (Gy)	Number of fractionation	OTT (day)	BED_{10} (GY_{10})	BED_{10} (GY_{10})	Local control (%)
Fein et al. (4)	66	33	49	79.2	60.3	89
Spector et al. (14)	66.5	33	45	79.9	64.6	89
Reddy et al. (2)	66	33	45	79.2	63.9	86.1
Medini et al. (3)	70	39	56	82.6	57.4	92.3
van der Voet et al. (15)	60	25	35	74.4	68.1	91
Gowda et al. (9)	50	16	21	65.6	65.6	93
Yamazaki et al. (8)	56.25	25	35	68.9	62.6	92

OTT, overall treatment time; BED, biologically effective dose.







Ermiş et al. Radiation Oncology (2015) 10:203

Cheah et al. 2009 [11]	100 (T1 only)	50Gy in 16 fractions	3.125Gy	22	65.6	7	90 %	85 %	N/A
Short et al. 2006 [29]	145 (*n* = 102 T1)	60–66Gy in 30–33 (*n* = 51)	2	40–44	58.1–62.3	4.9	All T1 LRC 75 % conv		LRC 80 % (conv)
		52.5-55Gy in 20 (*n* = 94)	2.625–2.75	26	63.2–67.0		LRC 91 % hypo		LRC 81 % (hypo)
Yamazaki et al. 2006 [8]	180 (T1 only)	RCT: 60–66Gy in 30–33				Not stated	All T1		
		(66Gy if >2/3 of cord) (*n* = 89)	2Gy	40–44	58.1–62.3		LC 77 % conv		
		56.25Gy in 25 or 63Gy in 28 (>2/3cord) (*n* = 91)	2.25Gy	33–38	60.4–64.9		LC 92 % hypo		
Gowda 2008 [12]	200 (T1 only)	50–52.5Gy in 16	3.12–3.28Gy	22	65.6–68.7	5.8	93.1 %	89.1 %	

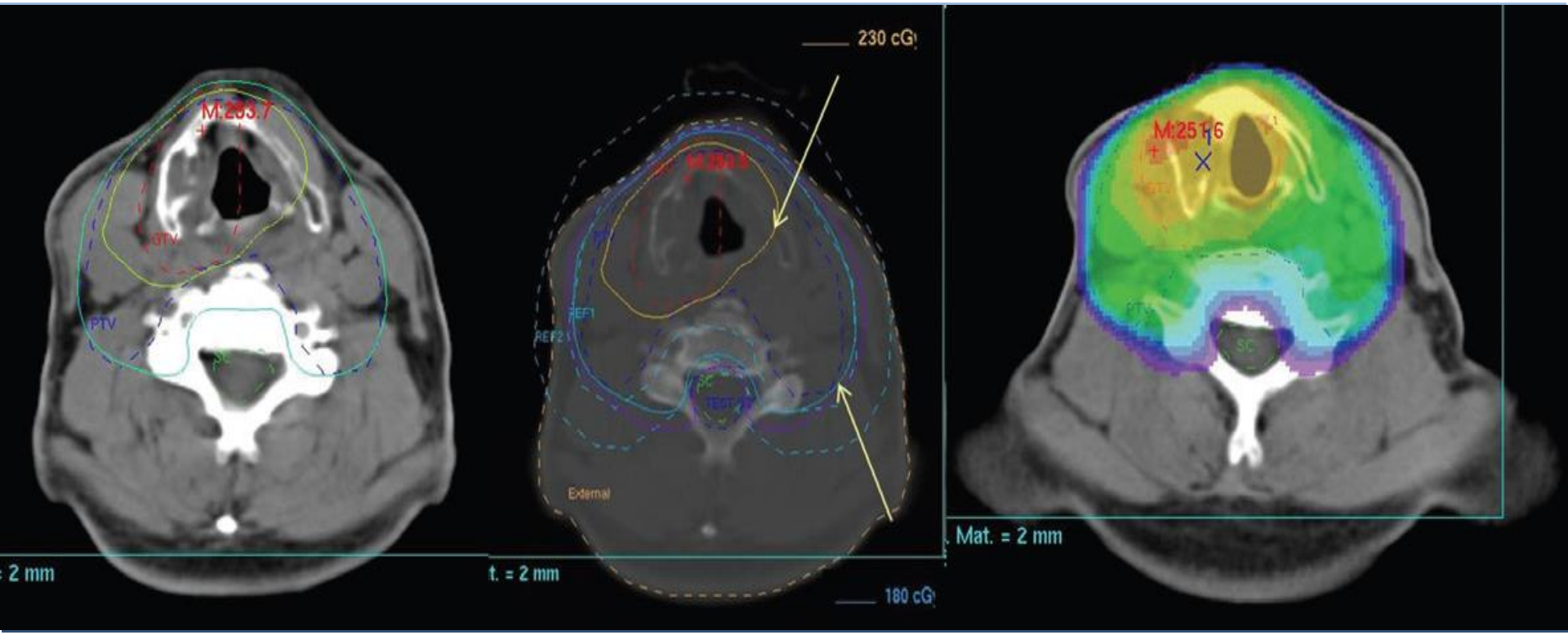
Accelerated Hypofractionation

Retrospective study from Birmingham UK

- N=81; Stage II-IV SCCHN
- EBRT 55Gy/20#/4 weeks with concurrent chemotherapy (MTX/ Carboplatin)
- Impressive disease outcomes:
  - 2yr LCR=75.4%; DFS rate=68.6%; OS rate=71.6%
- Acute toxicities were tolerable. No unexpected late toxicities at 24-month FU

Sanghera et al. Int J Radiat Oncol Biol Phys 2007 67;5:1342-51

SIMULTANEOUS BOOST INTEGRATED IMRT / VMAT



- RTOG H-0022 trial for oropharyngeal carcinomas SIB-IMRT in head and neck cancer, the use of 2.0, 2.11 or 2.2 Gy per session is highly effective and safe with respect to tumor response and tolerance.

- The overall radiation therapy treatment time plays an important role, since every single one day prolongation of treatment beyond 30 days leads to loss of tumor control

SIB-IMRT/SMART vs sequential IMRT

- Dosimetric advantage: Superior PTV conformality & superior parotid gland sparing. Dogan et al (2003)
- Logistical advantage : lesser number of treatment days required.
- Radiobiogical advantage: Due to higher dose/# (to the target) and lesser duration of treatment, the NTD (Normalised Total Dose=EQD2) is actually higher than the Nominal Dose.

		Prescribed			Actual	
Treatment Strategy	Anatomic structure	NTD (Gy)	Nominal dose in 30 fractions (Gy)	Nominal dose/fx (Gy) for 30 fractions	Nominal equivalent uniform dose in 30 fractions (Gy)	Equivalent uniform NTD (Gy)
SIB-IMRT1	GTV	70.0	65.9	2.20	67.3	73.5
	Elective	50.0	54.0	1.80	51.4	46.2

SIB vs SEQ-B

- Retrospective matched cohort analysis on patients with LAHNC treated with definitive chemoradiotherapy to 69.3 Gy in 33 fractions. Treatment was delivered via sequential boost (n = 68) or SIB (n = 141)
- At 4 years, the OS was 69.3% in the sequential boost cohort and 76.8% in the SIB cohort (p = 0.13). Disease-free survival was 63 and 69% respectively (p = 0.27).
- Rates of acute grade 3 or 4 dysphagia (82% vs 55%) and dermatitis (78% vs 58%) were significantly higher in the SIB group (p < 0.001 and p = 0.012 respectively).

Table 4 Overall performance of patients treated with sequential boost and integrated boost at 4 years

4 year follow up	Sequential boost	Integrated boost
Overall survival	69.3% (56.5–79)	76.8% (68.6–83.1)
Disease Free Survival	63% (50.4–73.3)	69% (60.4–76.1)
Local recurrence-free survival	88.2% (76.7–94.2)	85.9% (78.2–91)
Regional recurrence-free survival	92.1% (82.1–96.7)	91.6% (84.8–95.4)
Distant disease-free survival	89.9% (78.8–95.4)	88.9% (82–93.3)

Vlacich et al. Radiation Oncology (2017) 12:13

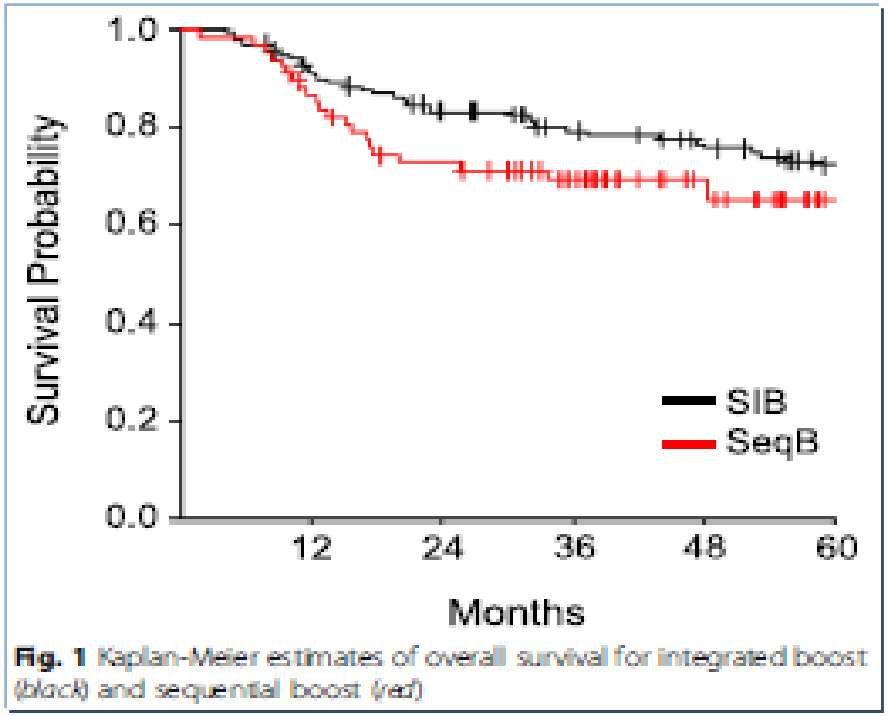


Fig. 1 Kaplan-Meier estimates of overall survival for integrated boost (*black*) and sequential boost (*red*)

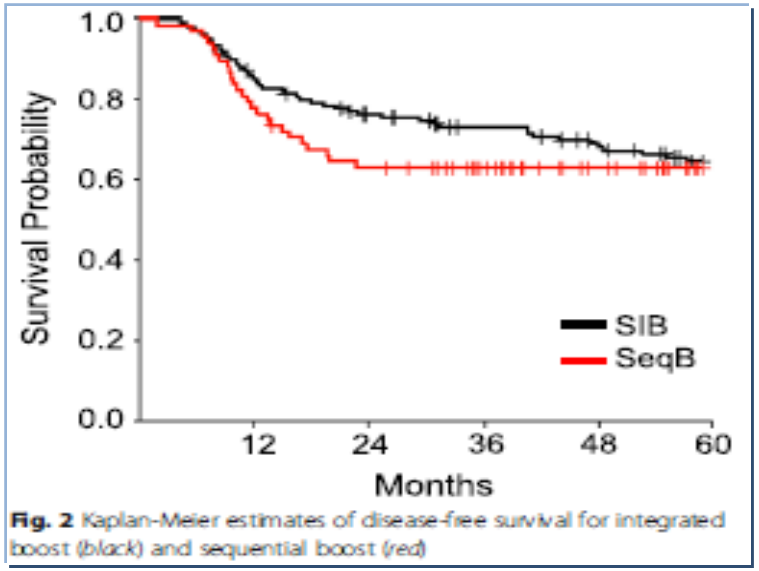


Fig. 2 Kaplan-Meier estimates of disease-free survival for integrated boost (*black*) and sequential boost (*red*)

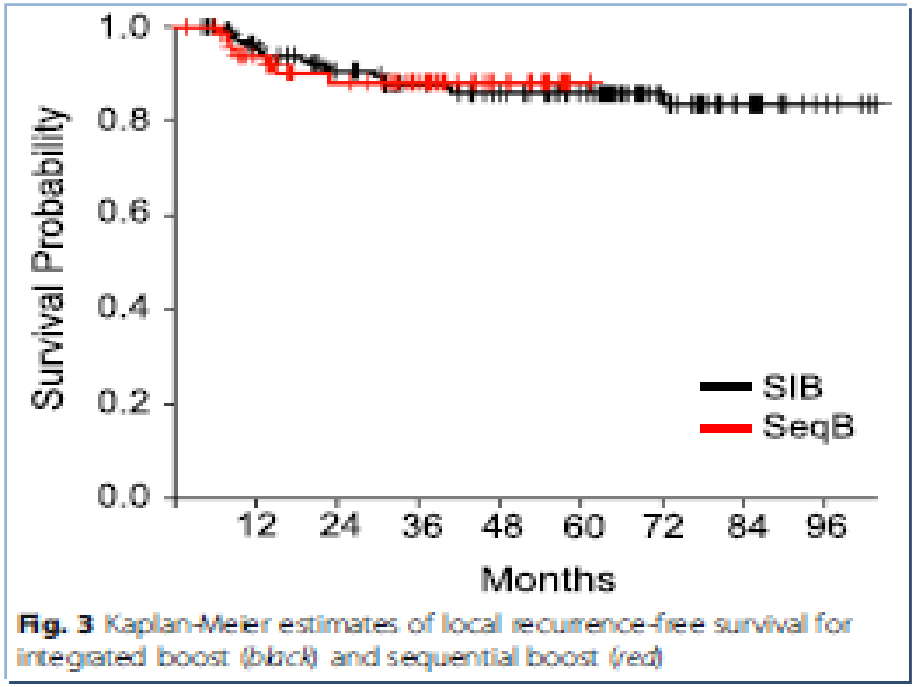


Fig. 3 Kaplan-Meier estimates of local recurrence-free survival for integrated boost (*black*) and sequential boost (*red*)

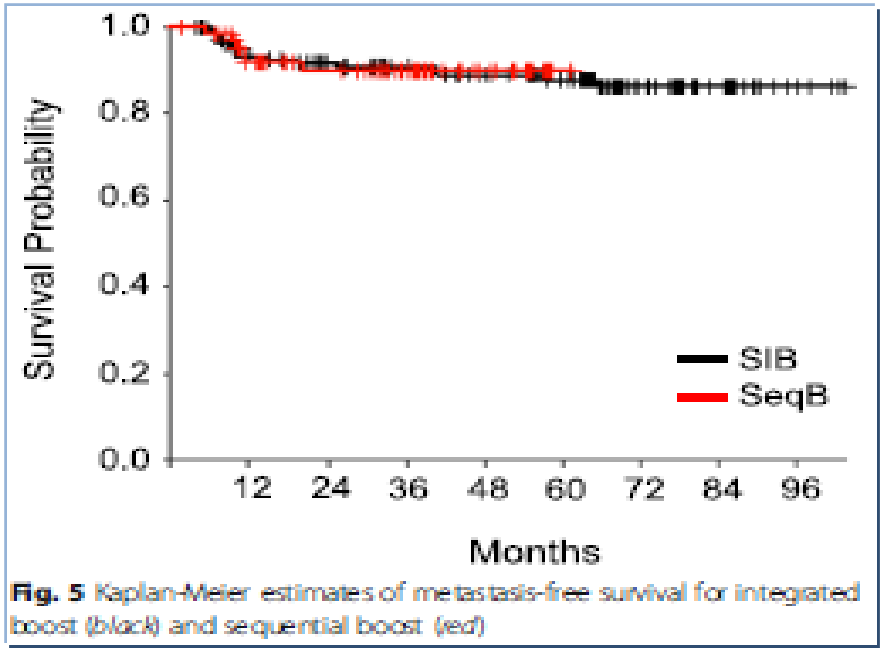


Fig. 5 Kaplan-Meier estimates of metastasis-free survival for integrated boost (*black*) and sequential boost (*red*)

SIB-IMRT vs Concomitant Boost RT (CBRT) (MSKCC, 2006)

- ✖ Study period Sep 1998- Jun 2004
- ✖ N=293
- ✖ All were patients of Ca oropharynx (112 were stage III/IV).
- ✖ 41 received SIB-IMRT with concurrent chemotherapy
- ✖ 71 received conventional 2DRT with late concomitant boost (CBRT) along with concurrent chemotherapy
- ✖ RT dose was 70 Gy. Parotid dose constraint for IMRT was mean dose <=26 Gy.
- ✖ Significant advantage in terms of **PEG-dependancy** & **severe xerostomia at 2 years**, in favour of IMRT.

Nancy Lee, et al

Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 4, pp. 966–974, 2006

Patients characteristics and regimens of SIB-IMRT in selected nasopharynx series.

Author	*N* of pts	Clinical stage (% pts III–IV)	Chemotherapy, *N* of pts	Prescribed dose and fractionation			OTT (weeks)
				Elective volume	Intermediate volume	Boost volume	
Lee et al. [74]	67	I–IV (70%)	50	50–60 Gy in 28–31 fr (1.8–2.0 Gy)	–	65 Gy in 31 fr (2.1 Gy) or 69.75 Gy in 31 fr (2.25 Gy)	6.2
Kam et al. [75]	63	I–IV (57%)	19	60 Gy in 33 fr (1.82 Gy)	–	66 Gy in 33 fr (2 Gy)[a]	6.6
Kwong et al. [76]	50	III–IV (100%)	34	70 Gy in 35 fr (2 Gy)	72 Gy in 35 fr (2.06)	76 Gy in 35 fr (2.17)	7
Wolden et al. [77]	74 (59 IMRT-CB; 15 SIB-IMRT)	I–IV (77%)	69	54 Gy in 30 fr (1.8 Gy)	–	70.2 Gy in 30 fr (2.34 Gy)	6 (for SIB)
Lee et al. [78]	20	III–IV (100%)	18	46 Gy in 23 fr (2 Gy)	60 Gy in 30 fr (2 Gy)	72 Gy in 30 fr (2.4 Gy)	6
Wu et al. [79]	75	I–IV (56%)		56 Gy in 28 fr (2 Gy)	–	70 Gy in 28 fr (2.5 Gy)[b]	5.6 (for SIB)
RTOG 0225 Trial [87]	–	I–IVb	Stage >T2b or N+	59.4 Gy in 33 fr (1.8 Gy)	–	70 Gy in 33 fr (2.12 Gy)	6.6

[a] T1–T2a: additional brachitherapy boost; 36% of T2b–T4 cases: additional 3DCRT boost.
[b] 47% of cases (T4 of poor responders): additional boost of 10 Gy.

Patients characteristics and regimens of SIB-IMRT in selected oropharynx series.

Author	Total N pts (definitive)	Clinical stage (% pts III–IV)	Chemotherapy, N of pts	Prescribed dose and fractionation			OTT (weeks)
				Elective volume	Intermediate volume	Boost volume	
Chao et al. [18]	74 (31)	I–IV (93%)	20	56 Gy in 35 fr (1.6 Gy)	–	70 Gy in 35 fr (2 Gy)	7
De Arruda et al. [80]	50 (48) 11 IMRT-CB, 39 SIB-IMRT	I–IV (6th ed.) (92.6%)	43	54 Gy in 33 fr (1.64 Gy)	59.4 Gy in 33 fr (1.8 Gy)	70 Gy in 33 fr (2.12 Gy)	6.6 (for SIB)
RTOG 0022 Trial [12]	–	T1-2 N0-1	No CT allowed	54 Gy in 30 fr (1.8 Gy)	60 Gy in 30 fr (2 Gy)	66 Gy in 30 fr (2.2 Gy)	6

Patients characteristics and regimens of SIB-IMRT in selected miscellaneous sites series.

Author	Total *N* pts (definitive)	Clinical stage (% pts III–IV)	Chemotherapy, *N* of pts	Prescribed dose and fractionation			OTT (weeks)
				Elective volume	Intermediate volume	Boost volume	
Butler et al. [17]	20 (20)	II–IV (4th ed.) (80%)	–	50 Gy in 25 fr (2 Gy)	–	60 Gy in 25 fr (2.4 Gy)	5
Lauve et al. [81]	20 (20)	II–IV (90%)	–	54 Gy in 30 fr (1.8 Gy)	60 Gy in 30 fr (2 Gy)	68.1 Gy in 30 fr (2.27 Gy) 70.8 Gy in 30 fr (2.36 Gy) 73.8 Gy in 30 fr (2.46 Gy)	6
Yao et al. [82]	151 (99) IMRT-SEQ; SIB-IMRT-SEQ	III–IV (85.4%)	68	54 Gy in 30 fr (1.8 Gy)	60 Gy in 30 fr (2 Gy)	IMRT SEQ boost 10–14 Gy	6 (for SIB)
Studer et al. [83]	115 (80)	62% T3–T4 or T1–2/N2c–N3	89	54 Gy in 30 fr (1.8 Gy) 54 Gy in 33 fr (1.64 Gy) 56 Gy in 35 fr (1.6 Gy)	–	66 Gy in 30 fr (2.2 Gy) 69 Gy in 33 fr (2.11 Gy) 70 Gy in 35 fr (2 Gy)	6 6.6 7
Schwartz et al. [84]	49 (49)	III–IV (100)	29	50 Gy in 25 fr (2 Gy)		60 Gy in 25 fr (2.4 Gy)	5
Guerrero Urbano et al. [85]	30 (30)	T1–4, N1–N3	30	51.8 Gy in 28 fr (1.85 Gy) 56 Gy in 28 fr (2 Gy)		63 Gy in 28 fr (2.25 Gy) 67.2 Gy in 28 fr (2.4 Gy)	5.6
Lee et al. [86]	31 (31) (4 IMRT-CB; 27 SIB-IMRT)	III–IV	31	54 Gy in 33 fr (1.64 Gy)	59.4 Gy in 33 fr (1.8 Gy)	70 Gy in 33 fr (2.12 Gy)	6.6

Abbreviations for Tables 1A–C: pts: patients; La: larynx, NP: nasopharynx; CT: chemotherapy; FS(Gy)/NF/PD(Gy): fraction size/number of fraction/prescribed dose (Gy); ICB: intracavitary brachiterapy; IMRT-CB: IMRT with accelerated fractionation with concomitant boost; SIB-IMRT: simultaneous integrated boost IMRT; IMRT-SEQ: sequential IMRT; MCT N pts: number of patients receiving chemotherapy; CT N patients definitive RT: number of patients receiving definitive IMRT and chemotherapy.

Comparing Sequential and SIB doses for EQD2, Early and Late tissue doses for nasopharyngeal cancers

Author	FS(Gy)/NF/PTD(Gy)	Tumor	
		BED (Gy)	NTD_{2Gy}(Gy)
Conventional	2/35/70	71.5	70
Lee et al. [74]	2.1/31/65.1	68.2	66.8
	2.25/31/69.75	74.2	72.7
Kwong et al. [76]	2.17/35/76	79.1	77.4
Wolden et al. [77]	2.34/30/70.2	76.5	74.9
Lee et al. [78]	2.4/30/72	78.9	77.3
RTOG [87]	2.12/33/69.96	72.9	71.4

Comparing Sequential and SIB doses for EQD2, Early and Late tissue doses for nasopharyngeal cancers

Author	FS(Gy)/NF/PTD(	Acute responding tissues BED (Gy)	Late reacting tissues BED (Gy)
Conventional	2/35/70	56.3	116.9
Lee et al. [74]	2.1/31/65.1	53.8	112.4
	2.25/31/69.75	60.5	122.9
Kwong et al. [76]	2.17/35/76	64.7	130.1
Wolden et al. [77]	2.34/30/70.2	63.7	126.0
Lee et al. [78]	2.4/30/72	66.4	130.6
RTOG [87]	2.12/33/69.96	58.4	120.4

Comparing Sequential and SIB doses for EQD2, Early and Late tissue doses for oropharyngeal cancers

Author	FS(Gy)/NF/PTD(Gy)	Tumor		Acute responding tissues	Late reacting tissues
		BED(Gy)	NTD2Gy(Gy)	BED(Gy)	BED(Gy)
Conventional	2/35/70	71.5	70	56.3	116.9
Concomitant boost					
RTOG 9003 [19]	1.8/30/54+1.5/12/18	76.9	73.9	61.5	113.4
Butler et al. [17]	2.4/25/60	68.2	66.8	56.4	108
Chao et al. [18]	2/35/70	71.5	70	56.3	116.9
Lauve et al. [81]	2.27/30/68.1	73.8	72.3	58.6	120.6
	2.36/30/70.8	77.3	75.7	64.6	127.5
	2.46/30/73.8	81.3	79.6	69.1	135.3
De Arruda et al. [80]	2.12/33/69.96	72.9	71.4	58.4	120.4
Studer et al. [83]	2/35/70	71.5	70	56.3	117.6
	2.11/33/69	72.5	71	58	119.6
	2.2/30/66	71.1	69.6	57.6	115.4
Schwartz et al. [84]	2.4/25/60	68.2	66.8	56.4	108
Guerrero Urbano et al. [85]	2.25/28/63	68.7	67.3	55.7	110.6
	2.4/28/67.2	74.3	72.7	61.8	121.3
Lee et al. [86]	2.12/33/69.96	72.9	71.4	58.4	120.4
RTOG 0022 [12]	2.2/30/66	71.1	69.6	57.6	115.4

Common SIB Dose schedules

- (1) 70 Gy/35# to PTV (GTV)
  63 Gy/35# to PTV (CTV1:high risk microscopic ds)
  54 Gy/35# to PTV (CTV2: low risk microscopic ds)

- (2) 66 Gy/30# to PTV (GTV)
  60 Gy/30# to PTV (CTV1:high risk microscopic ds)
  54 Gy/30# to PTV (CTV2: low risk microscopic ds)

Highest Early and Late toxicities for nasopharyngeal cancers

Author	Worst acute toxicity		Worst late toxicity	
	Type/grade (G)	Frequency (%)	Type/grade (G)	Frequency (%)
Lee et al. [74]	Mucositis G3	22.4	Soft tissues necrosis G3	1.5
	G4	1.5	Hearing loss G4	7.5
	Pharyngitis/dysphagia G3	22.4	Chronic dysfagia G4	1.5
	G4	1.5		
Kwong et al. [76]	Mucositis G3	78	Soft tissues fibrosis G2/G3	14
			Hearing loss G2/G3	42
			Pseudoaneurysm internal carotid artery in the skull base	4
			Asintomatic temporal lobe necrosis	4
Wolden et al. [77]	–		Hearing loss G3	15
Lee et al. [78]	Mucositis G3	25		
	Pharyngitis/dysphagia G3	45/55		

Highest Early and Late toxicities for oropharyngeal cancers

Author	Worst acute toxicity		Worst late toxicity	
	Type/grade (G)	Frequency (	Type/grade (G)	Frequency (%)
Butler et al. [17]	Mucositis G3	80		–
	Pharyngitis/dysphagia G3	50		
Chao et al. [18]	Mucositis G3	37.8		
	G4	5		
Lauve et al. [81]				
Dose level 1 (TD = 68.1 Gy)	Mucositis G3	83.3	Mucositis G4	33.3
	Dysphagia G3	16.7	Mucositis G4	16.7
Dose level 2 (TD = 70.8 Gy)	Mucositis G3	66.7	Dysphagia G3	8.3
	Dysphagia G3	41.7	Trismus G3/G4	8.4
	Dysphagia G4	8.3		
Dose level 3 (TD = 73.8 Gy)	Mucositis G3	100		
	Dysphagia G3	100		
De Arruda et al. [80]	Mucositis G3	38	Cervical esophageal stricture	6
	Pharyngitis/dysphagia G3	16		
Studer et al. [83]	Mucositis G3	15	Mucositis G3/G4	10.4
	Dysphagia G3	20	Dysphagia G3	1.7
			Dysphagia G4	0.9
			Mandible radionecrosis G3	0.9
			Laryngeal fibrosis G4	0.9
Schwartz et al. [84]	Mucositis G3	55	Dysphagia G3	4
	Dysphagia G3	20	Mandible radionecrosis G3	2
Guerrero Urbano et al. [85]				
Dose level 1 (TD = 63 Gy)	Mucositis G3	67		
	Dysphagia G3	67		
Dose level 2 (TD = 67.2 Gy)	Mucositis G3	40	Dysphagia G3	10
	Dysphagia G3	87	Esophageal stricture G3	10
Lee et al. [86]	Mucositis G3	22.6	Dysphagia G3	6 pts
	Pharyngitis G3	12.9	Percutaneous endoscopic gastrostomy-dependency due to pharyngoesophageal stricture	6pts
			Laryngeal oedema G4	2 pts

Treatment outcomes

Disease outcome following definitive SIB-IMRT in nasopharyngeal series.

Author	Median follow up (months)	Local control % of pts	Regional control % of pts	Loco-regional control % of pts	Overall survival % of pts	Time point (years)
Lee et al. [74]	31	97	–	98	88	4
Kwong et al. [76]	25	–	–	95.7	92.1	2
Wolden et al. [77]	35	91	93	–	83	3
Lee et al. [78]	27	–	–	88	–	2

Author	Median follow up (months)	Local control % of pts	Regional control % of pts	Loco-regional control % of pts	Overall survival % of pts	Time point (years)
Butler et al. [17]	15.2	–	–	95% CR[a] 5% PR[b]	–	–
Chao et al. [18]	33	–	–	77	–	4
Lauve et al. [81]	20	76.3	66.7	–	–	2
De Arruda et al. [80]	18	98	–	88	98	2
Studer et al. [83]	18 (mean)	74	–	–	–	2
Schwartz et al. [84]	25		–	83	80	2
Guerrero Urbano et al. [85]	87 weeks (dose level 1) 40 weeks (dose level 2)			83% CR[a] 17% PR[b]		
Lee et al. [86]	24	86	94	84	63	2

Chemo: BED

HOW MUCH RADIATION IS THE CHEMOTHERAPY WORTH IN ADVANCED HEAD AND NECK CANCER?

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Conclusions: Chemotherapy increases BED by approximately 10 Gy_{10} in standard and modified fractionated radiotherapy, equivalent to a dose escalation of 12 Gy in 2 Gy daily or 1.2 Gy twice daily. Such an escalation could not be safely achieved by increasing radiation dose alone. © 2007 Elsevier Inc.

Methods: The biologic equivalent dose (BED) of radiotherapy in nine trials of standard and five trials of modified fractionated radiotherapy with or without chemotherapy was calculated using the linear-quadratic formulation. Data from Radiation Therapy Oncology Group (RTOG) study 90-03 were used to calculate the relationship (S) between increase in locoregional control (LRC) and increase in BED with modified vs. standard fractionated radiotherapy. The increase in LRC with chemoradiotherapy vs. radiotherapy alone, the BED of the radiotherapy-alone arms, and the "S" value were used to calculate the BED contribution from chemotherapy and the total BED of chemoradiotherapy from each study.

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 5, pp. 1491–1495, 2007

RTOG 00-22 (2010)

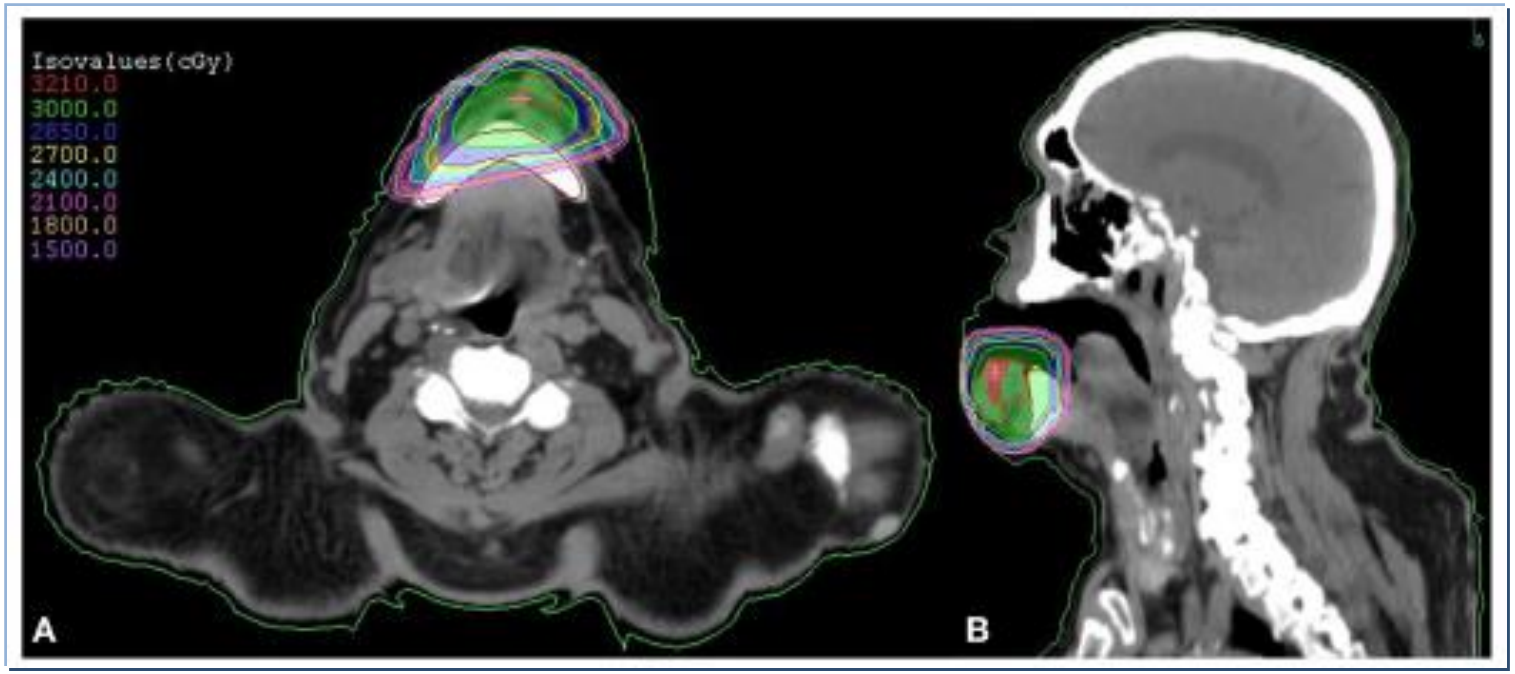
- N=69 (14 institutions)
- All patients of **Ca oropharynx**, stage T1-T2,N0-N1,M0
- No chemo was permitted
- RT dose was 66Gy/30# to PTV(gross disease) and 54-60Gy/30# to PTV (subclinical)
- Median FU=2.8 years
- 2-yr LRF was only **9%**.
- **Very low rate of severe (>grade 2) late toxicities**: skin (12%), mucosa(24%). Xerostomia (grade 2) was seen in 55% patients at 6 months but reduced to 16% at 2 years
- Moderately hypofractionated IMRT without chemotherapy in early oropharyngeal carcinomas, is safe & well-tolerated.

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1333–1338, 2010

- SIB-IMRT with conc chemotherapy is well-tolerated and effective for all common head-neck sites.
- Trials included mostly locally advanced cases.
- Locoregional failure rates are around 5-20%.
- Overall survival rates are around 60-85%.
- 2-yr severe xerostomia rates are around 0-30%.

EXTREME HYPOFRACTIONATION: SBRT

- Fractionated SBRT allows for delivery of highly conformal treatment of targets that are in close proximity to critical structures.



- Radiobiologically, the higher dose per fraction with SBRT- based treatments has been shown to provide improved local control over standard fractionation.
- According to QUANTEC guidelines, spinal SBRT partial cord irradiation max dose constraint is reported at 13 Gy for single fraction treatment and 20 Gy for three fractions treatment is thought to be associated with <1% risk for myelopathy.
- Typical re-irradiation dose constraints derived from the Pittsburgh and Georgetown series prescribe spinal max point ≤8Gy in one fraction and ≤ 12Gy in two fractions but these are based on re-irradiation SBRT.
- SBRT is effective for recurrent head and neck patients previously irradiated, but for patients with tumors encompassing the carotid artery, SBRT hypofractionation should be considered cautiously. IMRT or VMAT may be better options.

Single-fraction treatment				
Brain	5–10	12[a]		Necrosis {<20%}
Optic pathway	<0.2	8	10 12	Neuritis Neuritis {<10%}
Cochlea			12 ≤14[a]	Hearing loss Hearing loss {<25%}
Brainstem	<1	10	15 <12.5[a]	Cranial neuropathy Cranial neuropathy {<5%}
Spinal cord	<0.25 <1.2	10 7	14 13[a]	Myelitis Myelitis {<1%}

Three-fraction treatment				
Optic pathway	<0.2	15 (5 Gy/fx)	19.5 (6.5 Gy/fx)	Neuritis
Cochlea			20 (6.67 Gy/fx)	Hearing loss
Brainstem	<1	18 (6 Gy/fx)	23 (7.67 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25 <1.2	18 (6 Gy/fx) 11.1 (3.7 Gy/fx)	23 (7.67 Gy/fx)	Myelitis

Five-fraction treatment				
Optic pathway	<0.2	20 (4 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			27.5 (5.5 Gy/fx)	Hearing loss
Brainstem	<1	26 (5.2 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25 <1.2	22.5 (4.5 Gy/fx) 13.5 (2.7 Gy/fx)	30 (6 Gy/fx)	Myelitis

Emami Organ Tolerances 2017, Tolerances for SBRT

University of Pittsburgh Medical Center (UPMC) conducted a Phase I dose escalation study to determine the maximum tolerated dose (MTD) for SBRT in recurrent, unresectable SCCHN.

Doses of 15 – 44 Gy (median dose of 35 Gy) were delivered with fraction sizes of 4-18 Gy. The median follow up for all patients was six months (1.3 – 39 months).

1 and 2-year local control rates were 51.2% and 30.7%, respectively; and 1 and 2-year overall survival rates were 48.5% and 16.1 %, respectively.

Those patients who received SBRT < 35 Gy had significantly lower local control than those with ≥35 Gy at 6 months median follow-up time.

Benign Tumors		Malignant Tumors	
Dose (Gy)	# of fractions	Dose (Gy)	# of fractions
14-16	1	8-12	1
18-21	3	12-18	3
25-45	5	34-45	5

Table 2 | Review of SBRT for head and neck cancers.

Authors (reference)	Prospective/ retrospective study	Number of patients	First-line or recurrent therapy	Radiation course	Concurrent therapy	Median PFS	Median OS
Heron et al. (13)	Prospective	25	Recurrent	25–44 Gy total in 5 fractions over 2 weeks	N/a	4 mo	6 mo
Roh et al. (19)	Retrospective	36	Recurrent	18–40 Gy in 3–5 fractions	N/a	61% at 12 mo	16.2 mo
Siddiqui et al. (20)	Retrospective	44	Both	Range of single fraction 13–18 Gy or 36–48 Gy in 5–8 fractions	N/a	83.3% at 12 mo (primary), 60.6% at 12 mo (recurrent)	28.7 mo (primary), 6.7 mo (recurrent), 5.6 mo (metastatic)
Kawaguchi et al. (23)	Retrospective	14	1st line	35–42 Gy in 3 or 5 fractions	S-1 (an oral 5-fluorouracil)	71.4% at 36 mo	78.6% at 36 mo
Rwigema et al. (26)	Retrospective	85	Recurrent	Median dose 35 Gy in fraction sizes of 4–18Gy	N/a	5.5 mo	11.5 mo

TAKE HOME MESSAGE

- Hypofractionation has emerged as a viable alternative in breast, prostate & lung cancers

- It may be better tolerated & even more effective

- Aside from tumor DNA damage, the extra effectiveness of hypofractionation may be due to its anti-angiogenic effect on microenvironment vasculature

- IMRT allows parotid gland sparing and less xerostomia ? Better QoL
- IGRT allows margin reduction → less normal tissue irradiation? Better QoL
- Advanced imaging techniques and delineation protocols also mean more accurate targeting
- With these advances SIB-IMRT can improve upon treatment responses and OTT.
- SBRT can help especially in reirradiation or even primary irradiation of very small volumes.

Thank you