Head & Neck Cancers: SBRT

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SBRT in Head Neck Cancer

- 75% of HNSCC present in advanced stages: Hence, require locoregional treatment
- Even in early stage, high propensity for LN involvement, hence elective regional treatment

- Basic premise of SBRT: Small volumes, high dose per fraction, very small volumes of OARs irradiated: Precision RT

Role of SBRT in HNSCC:

Recurrent small volume tumors

& other situations in the HN like PGL, non-squamous histology, elderly: small volumes

Today: In combination with systemic therapy: SABR

SBRT in Recurrent Head & Neck Cancers

Need for Re-Treatment

- Cumulative estimated five year incidence of loco regional relapse is 29-31% in high risk patients.

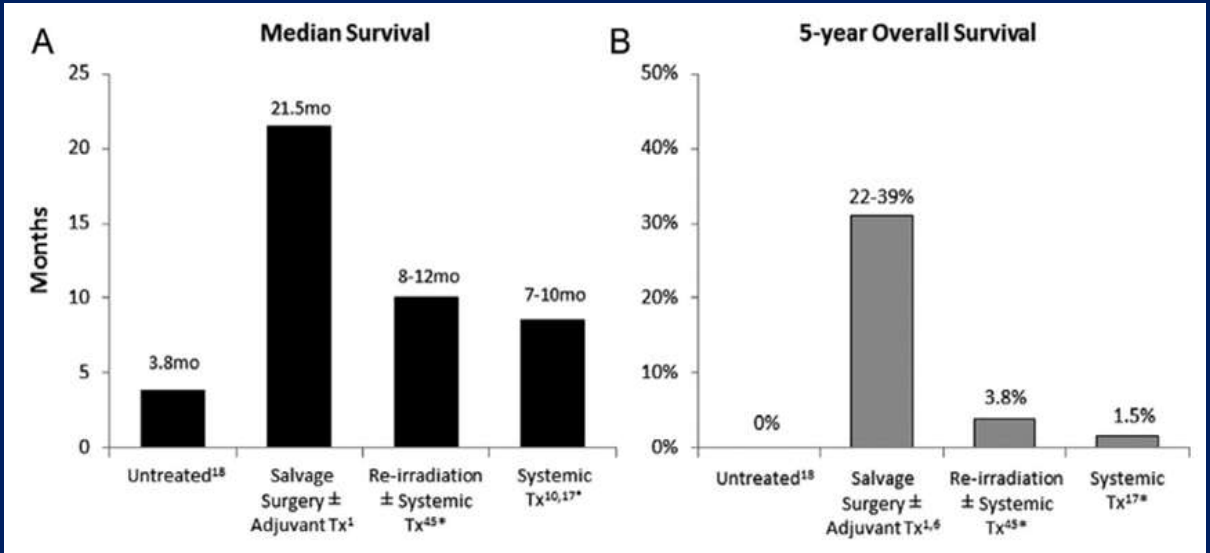
Bernier J, Cooper JS, Pajak TF et al.
Head Neck 2005;27:843-50.

- Risk of second cancers which is about 5% per year, the incidence being between 16-30%.

Haughey BH et al.
Ann Otol Rhinol Laryngol 1992;101:105-12.

- Longer survival: Probability of developing
  - Second Primary Tumors↑
  - Loco-regional recurrences ↑

Is Re-treatment Necessary ?



Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LGT.Head Neck 2014 Jan;36(1):144–51.

Factors affecting choice of treatment

Patient factors: Age
Co-morbidities
Functional status of the organ
Socio-economic issues
Compliance

Tumor factors: Stage & disease extent, volume
Subsite of disease
Involvement of adjacent structures
DFI, Sequelae of Prior Therapy

Treatment : Expertise available
Philosophy of the treating team

Salvage Modality: Surgery or RT

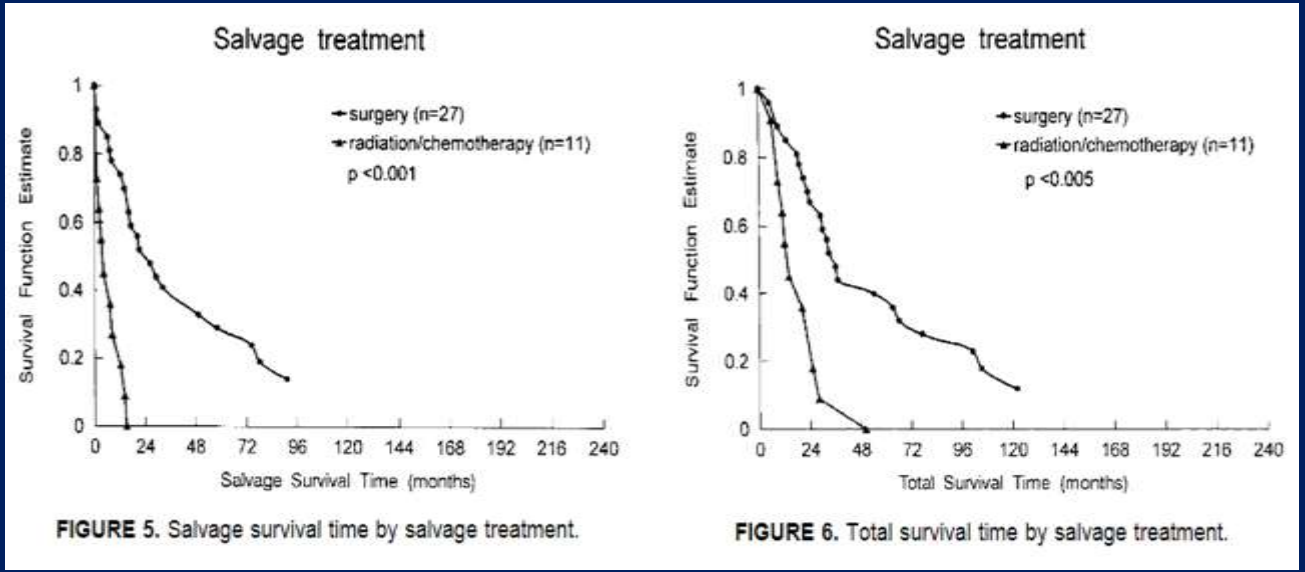


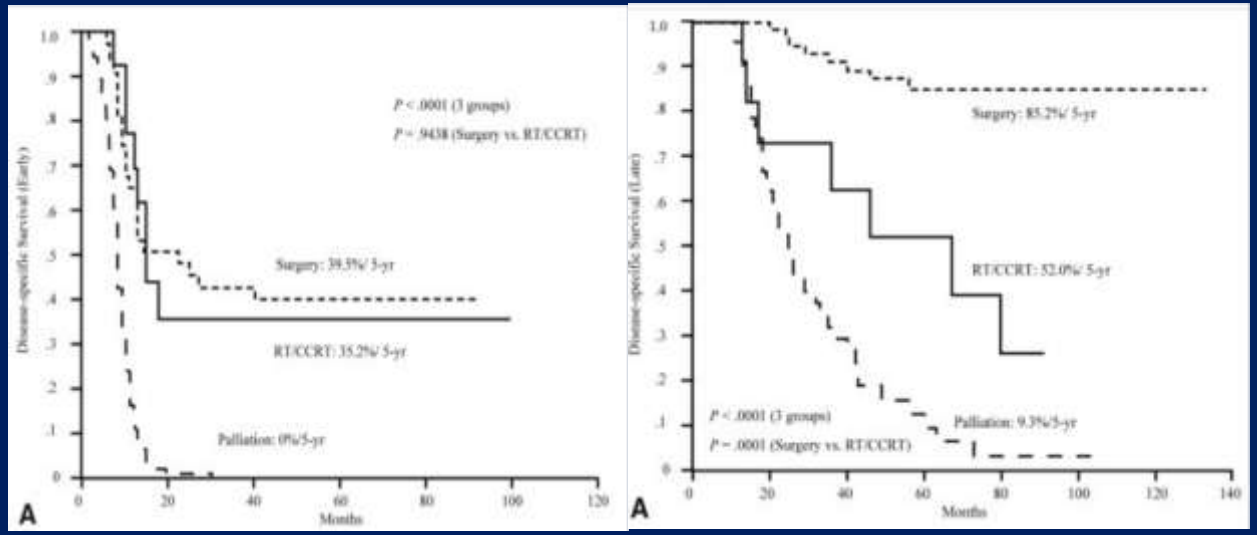
FIGURE 5. Salvage survival time by salvage treatment.

FIGURE 6. Total survival time by salvage treatment.

The “cure rate” for patients undergoing surgical salvage was 30% (8/27)

Schwartz GJ, Mehta RH, Wenig BL, Shaligram C, Portugal LG. Head and Neck 2000 Jan;22(1):34–41.

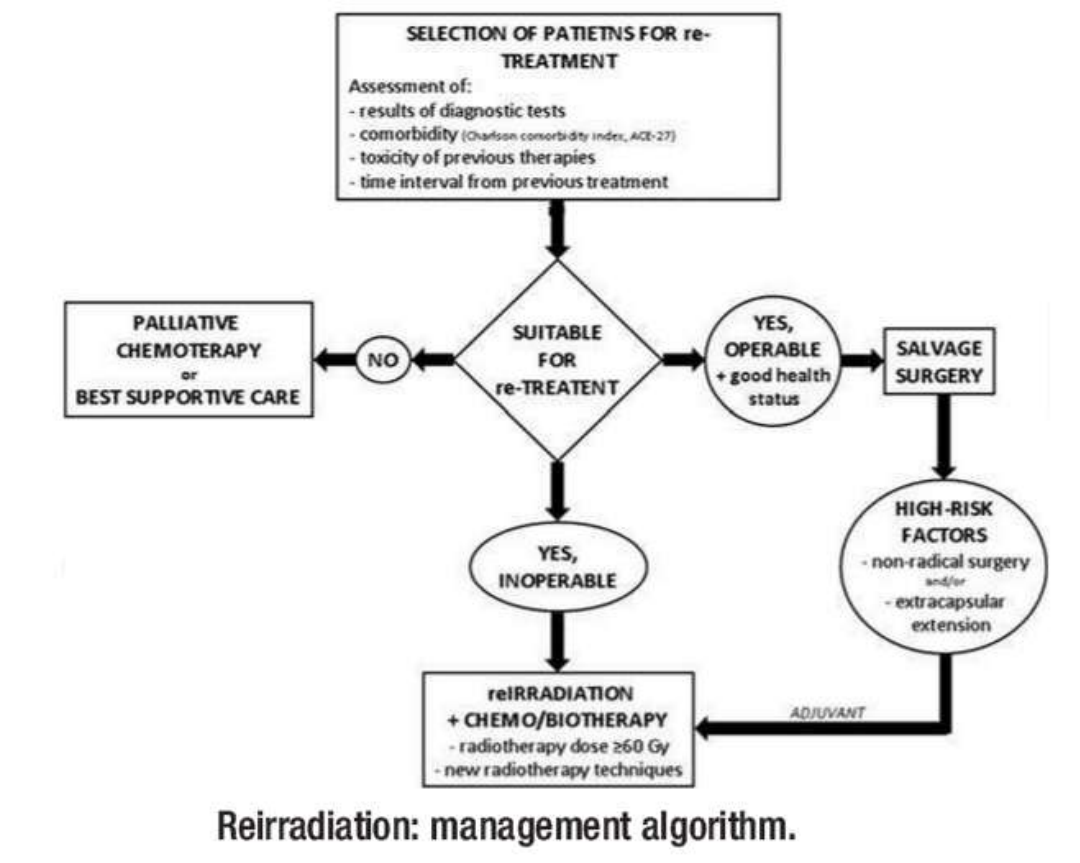
Salvage Modality: Surgery or RT



- Patients who had an early relapse (< 10 months) had equivalent outcomes with Surgery and CTRT
- However those with late relapses had better outcomes with surgery

Liao C-T, Chang JT-C, Wang H-M, Ng S-H, Hsueh C, Lee L-Y, et al. Cancer. 2008 Jan 1;112(1):94–103.

Salvage Algorithm



Reirradiation: management algorithm.

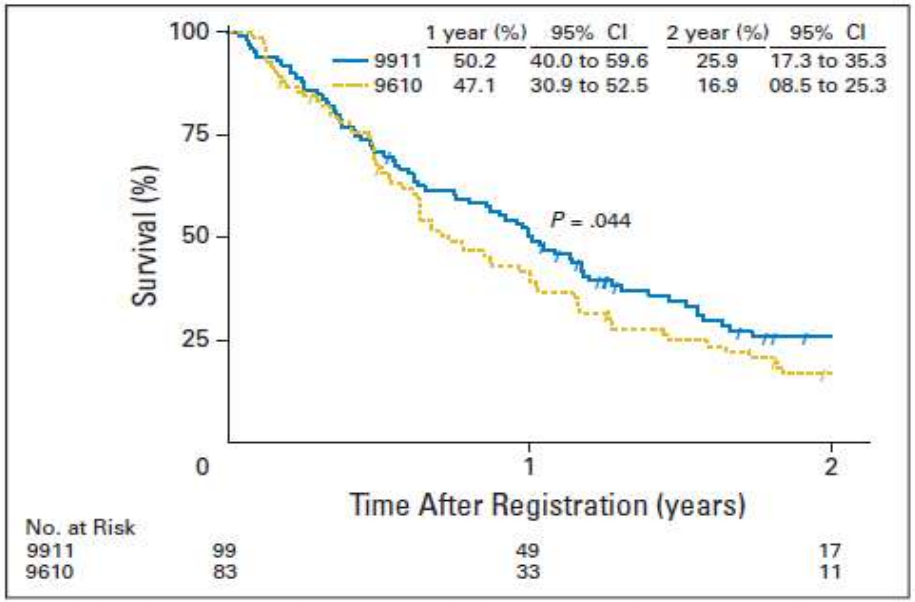
Strojan P et al , Head Neck. 2015 Jan;37(1):134-50.

Definitive Re-irradiation : Evidence

- More than 30 studies reported in the literature
- Mostly small (N = 30 - 50)
- 2 year OS ranges between 10 - 20%
- Serious late toxicity : 30 - 40%
- Toxicity related deaths : 0-10%

Definitive Reirradiation: Evidence

RTOG 96-10 & 99-11



Kaplan-Meier estimates of overall survival for Radiation Therapy Oncology Group protocols 9911 and 9610.

J Clin Oncol. 2007 Oct 20;25(30):4800-5.

Head Neck. 2008 Mar;30(3):281-8.

Definitive Reirradiation: Evidence

Radiother Oncol. 2011 Jul;100(1):70-5. doi: 10.1016/j.radonc.2011.06.025. Epub 2011 Jul 7.

Randomized phase III trial (GORTEC 98-03) comparing re-irradiation plus chemotherapy versus methotrexate in patients with recurrent or a second primary head and neck squamous cell carcinoma, treated with a palliative intent.

Tortochaux J[1], Tao Y, Tournay E, Lapeyre M, Lesaunier F, Bardet E, Janot F, Lusinchi A, Benhamou E, Bontemps P, Maingon P, Calais G, Daly-Schveitzer N, Verrelle P, Bourhis J.

Author information

Abstract

PURPOSE: This randomized phase III trial investigated the potential benefit of concurrent re-irradiation, fluorouracil and hydroxyurea versus methotrexate for patients treated with palliative intent for recurrent or second primary head and neck squamous cell carcinoma (HNSCC) in previously irradiated area.

PATIENTS AND METHODS: Patients with recurrent HNSCC or a second primary not amenable to curative-intent treatment were randomized to the R-RT arm (concurrent re-irradiation, fluorouracil and hydroxyurea) or to the Ch-T arm (methotrexate). The primary endpoint was overall survival (OS). Due to a very slow accrual, the trial was closed after inclusion of 57 patients.

RESULTS: Fifty-seven patients were included. All patients died in the two arms with a maximal follow-up of 5years. Although four complete responses were achieved in R-RT arm, (none in Ch-T arm) re-irradiation did not improve OS compared with methotrexate (23% versus 22% at 1year, NS). Sixteen patients experienced clinical grade ⩾3 late toxicities (>6months), 11 in R-RT arm and five in Ch-T arm.

CONCLUSIONS: Premature discontinuation of the trial did not allow us to draw firm conclusions. However, there was no suggestion that concurrent re-irradiation, fluorouracil and hydroxyurea improved OS compared to methotrexate alone in patients treated with palliative intent for a recurrent or second primary HNSCC.

When to Re-irradiate

Principles of Re-irradiation

- Goal of therapy should be curative
- Patient should have adequate life expectancy (> 12 months)
- Generally not considered before 1 year of the last course
- Dose should be high (> 50 Gy) whilst respecting normal tissue constraints
- Elective nodal irradiation is not recommended
- Patient related factors like extent of organ dysfunction / residual toxicity are important

Selecting Patients Who Benefit

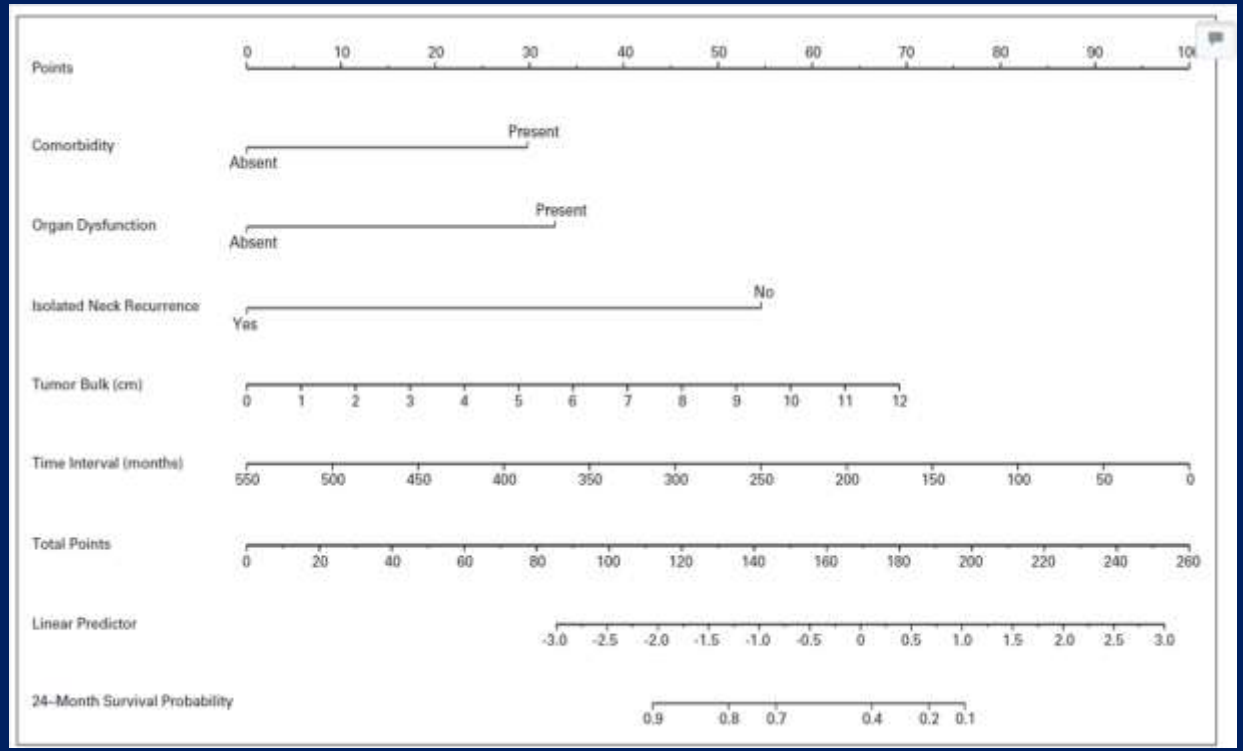
Significant prognostic factors:

- T & N Stage (disease volume)
- Oral Cavity site, Isolated neck recurrence
- Organ dysfunction: Pretreatment TT and Feeding Tube
- Disease free interval
- Comorbidity

Other prognostic factors identified in studies:

- Type of Re-irradiation technique
- Use of concurrent chemotherapy
- Re-irradiation dose > 50 Gy

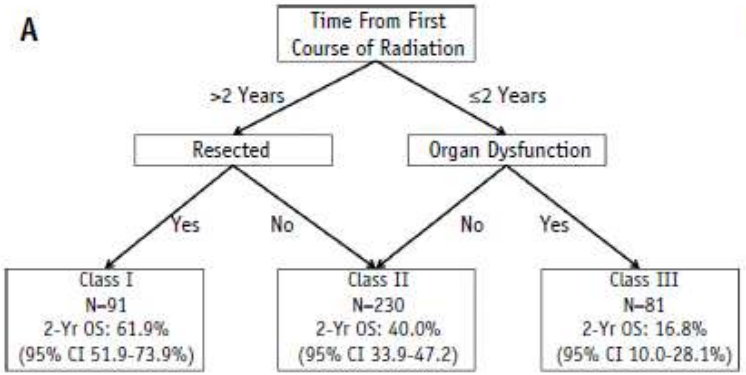
Nomograms !!



Tanvetyanon et al, J Clin Oncol, 2009 Apr 20;27(12):1983-91

A simpler way to determine ?

Refining Patient Selection for Reirradiation of Head and Neck Squamous Carcinoma in the IMRT Era: A Multi-institution Cohort Study by the MIRI Collaborative



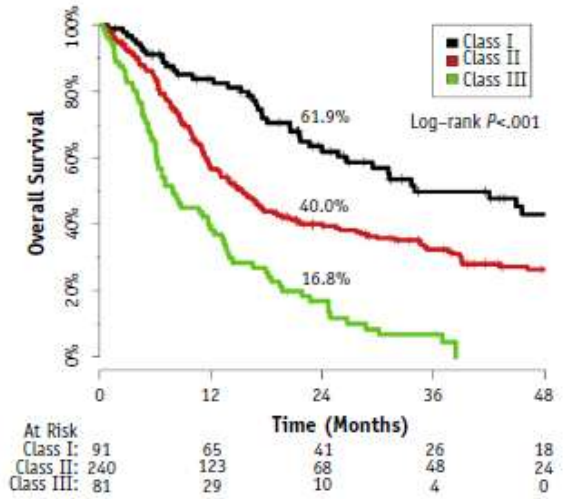


Fig. 3. (A) Recursive partitioning analysis (RPA) for overall survival. *Abbreviations:* OS = overall survival; CI = confidence interval. Organ dysfunction defined as pretreatment dependence on a feeding tube or tracheostomy. (B) Kaplan-Meier curves for overall survival separated by RPA class.

Int J Radiation Oncol Biol Phys, Vol. 100, No. 3, pp. 586–594, 2018

Reirradiation: How?

- Target Volume delineation
- Dose Fractionation
- Techniques & Modalities

Target Volumes

- Late radiation-induced morbidity ↑ with CTRT and will increase with larger volumes irradiated.

Langlois et al. 1985

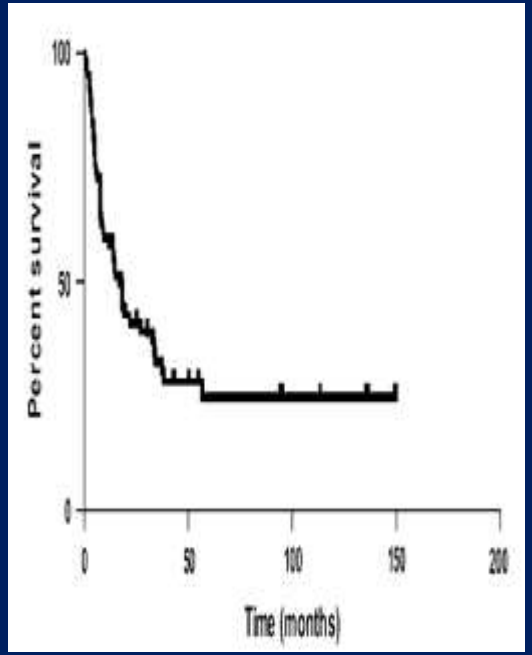
- Elective nodal irradiation:
  - Questionable in view of late sequelae
  - Primary in-field recurrences
  - Uncertainty with SPT
- Unpredictable pattern of recurrences with altered lymphatic pathways.

- Influence outcome of reRT: Disease control & morbidity

Target Volumes

- Retrospective Study
- N: 106
- Definitive Re-RT (3DCRT/IMRT) with/without CTRT
- Conv/HyperFr/Acc RT
- Target :
  - GTV with 0.5 cm margin
  - no prophylactic LN/Submucosal RT.
- Median Dose: 68 Gy
- 2 year Survival: 40%.LRC: 23%.
- All LRF within GTV except for 2 patients (4%)
- 29% ≥ Gr 3 Toxicities

Overall Survival



Popovtzer et al, Int J Radiat Oncol Biol Phys 2009;74:1342–1347.

Fractionation

Author	n	RT	Chemo	Results	Severe Toxicity
Dawso (2001) Michig	40	1.8-2.0Gy/fr (or 1.2Gy	33%	2 yr LRC 29%	Acute 10%
Lee (2 MSKC					
Sulma (2009) MDAC					
Popov (2009) Michig					
Dupre (2009) Ghent		Median 69Gy IMRT	Platinum based	5 yr LRC 40% 2yr OS 35% 5 yr OS 20%	Late: 13% Gr 3+ No deaths

Various fractionation regimens used:

- Split course
- Continuous
- Once daily vs hyperfractionation
- Hyperfractionation with breaks (RTOG studies)

Conventional and hyperfractionated schedules preferred

No definite advantage of one over the other.

Techniques

- In a Canadian Survey on Re-RT,
  - Most desirable for Re-RT: Brachytherapy
  - Highly conformal external irradiation techniques

Joseph et al, Int J Radiat Oncol Biol Phys. 2008 Dec 1;72(5):1523-9

- With the availability of advanced imaging like PET, MRI & option of image guided delivery of treatment, hypofractionation also a feasible modality.

Conformal RT Techniques

- Possible to deliver higher, clinically meaningful doses
- Superior OAR sparing
- Image guidance, reduce margins
- Acceptable toxicity
- Reasonable disease control
- Choice:
  - Patient and tumor characteristics
  - Expertise of the treating team
  - Infrastructure available

ReRT Technique

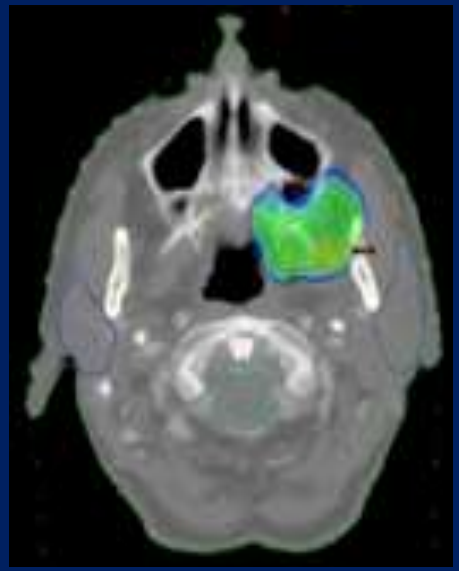
Author	RT Technique Re-RT dose Pre-RT dose	N FU duration	Results PFS/OS	Toxicities
Wang et al IJROBP 1987	Conventional 50 Gy	51 (rT1/T2)	LRC 50% @5years	NA
Nancy LEE et al IJROBP 2007	Conv:30% IMRT:70% 60Gy 70Gy	105	LRC 20% LRC 52% @ 2 years	23% G-3 12% G-4
Sulman et al IJROBP 2009	IMRT 60Gy	78	LRC 64%, OS 58%	20% G3/4
Kwang et al IJROBP 2008	FSRT, Cyberknife RS 30Gy/3-5fx/3-5days	N=36, Sites =44	80% LRC @ 17months	13/44 : acute G3/4 3/44:Late G3

SBRT

- Higher biological dose: Increased chances of tumor control
- Lower toxicity

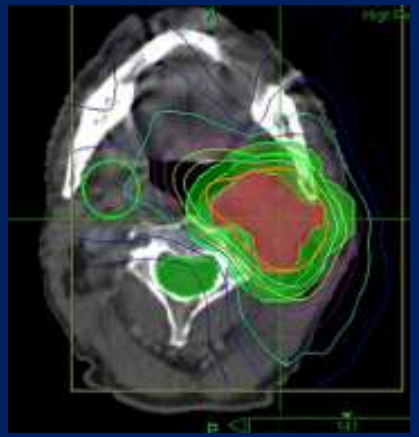
- May deliver lower dose to the critical structures

- Reproducible immobilization
- Precise target localization
- Steep dose gradient between target and critical structures

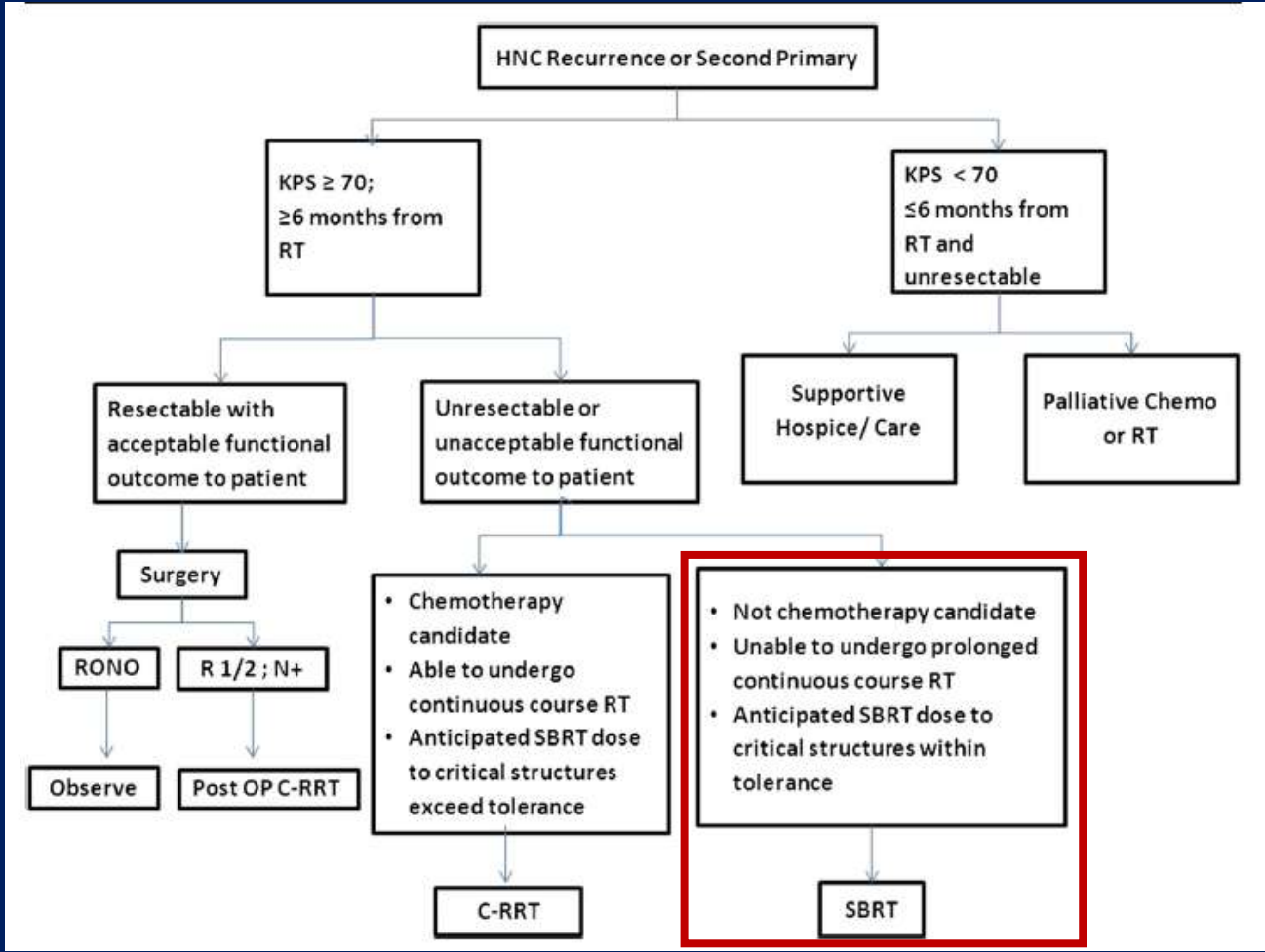


SBRT Head Neck: An attractive option

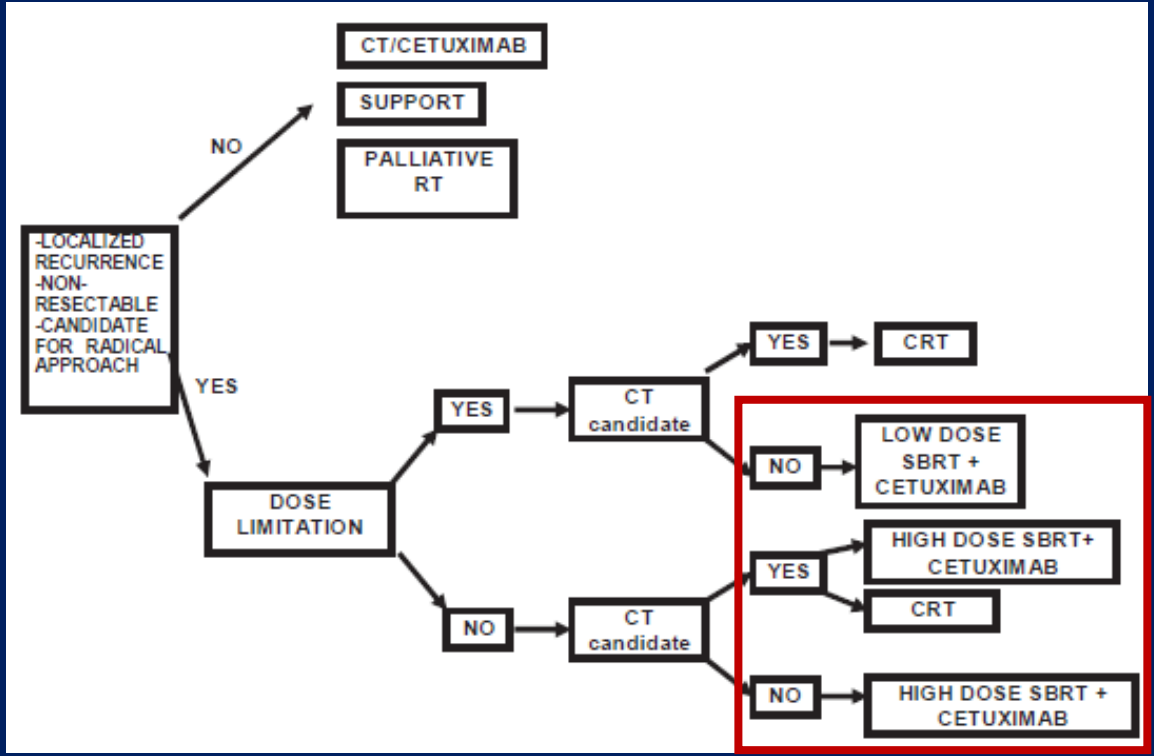
- Reliable, reproducible Immobilization
- Minimal movement
- Image guidance feasible
- Failures mainly at the gross site
- Precise target localisation with image fusion (CT, MRI, PET-CT)
- Hypoxic areas
- Predictive recurrence pattern



Cleveland Clinic Algorithm for Reirradiation



O. M. Mahmoud & S. A. Koyfman. J Radiat Oncol DOI 10.1007/s13566-015-0187-6



Relative Contraindications to SBRT:

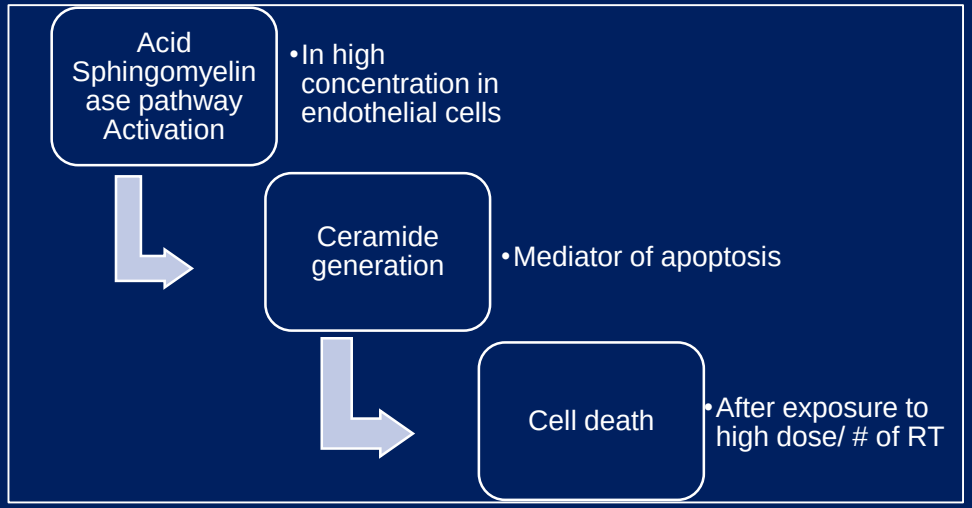
- Tumours located close to the fossa of Rosenmüller
- Very close to or in contact with the carotid artery
- Neurological structures in the vicinity of the tumour

Critical Reviews in Oncology / Hematology 122 (2018) 194–201

Mechanism of Action

- Complex interplay between the different modes of cell death, mitotic cell death, apoptosis, senescence, necrosis, necroptosis, immunogenic cell death

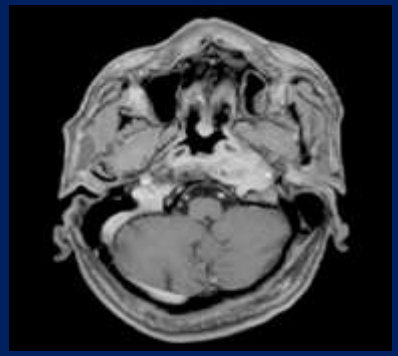
- Mediated by the apoptotic death of vascular endothelial cells (Fuks, Kolesnick, et al.)

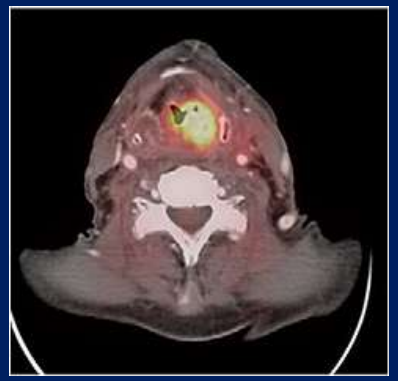


- Immunogenic: potential to release subcellular materials into the tumor microenvironment, liberating large quantities of tumor-associated antigens, eliciting a local inflammatory response, causing release of inflammatory cytokines that in turn could enhance antigen presentation and processing by dendritic cells and macrophages.

Target Volume Delineation

- Accurate target delineation: Most critical step
- Contrast enhanced CT scan with 1.25mm cuts
- RT planning MRI for target delineation
- PET based planning has been shown to improve the contouring accuracy
- **Volumes:** GTV +5 mm margins = PTV
- **Dose prescription:** 95% volume receiving 80% dose



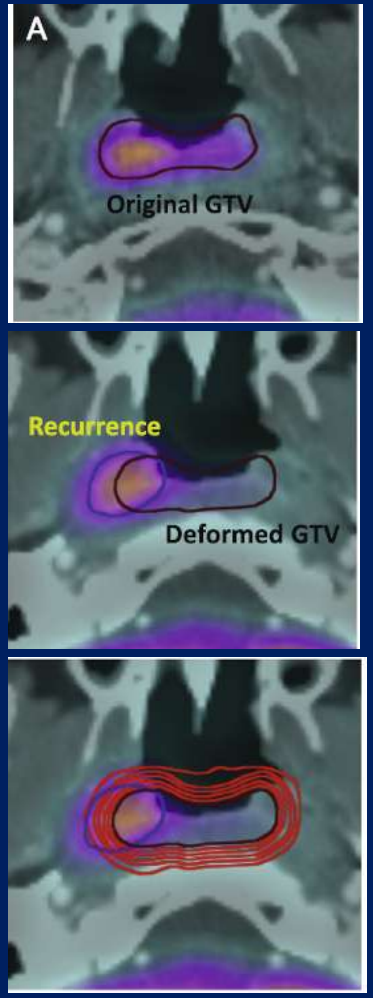


Margins

- N=89
- SBRT: GTV=CTV=PTV
- Recurrences studied
- Pretreatment planning scans were deformed to post treatment follow up scan

- With non-PET planning overlap increased from 11.7% to 48.2%

- PET based planning: 93.6% of the recurrences got covered with 5 mm margin



Wang K. Radiother Oncol 2013

Table 1. Target and organ at risk definition.

Parameters	Institutions														
	OCC	*UHSCC*	*MC*	*TCI*	*UCSF*	*HFHS*	*COL*	*GLCCC*	*HU*	*KU*	*SU*	*MDACC*	*UPCI*	*HKUCC*	*MSKCC*
Number of patients treated to date	80–100	50	200	30	30	60	>200	>700	200	50	30	60	400	145	50
Margin for microscopic disease (CTV)	No	Yes (3 mm)	Yes (0–10 mm)	No	Yes (3 mm)	Yes (2 mm)	Yes (3 mm)	Yes (non-uniform)	Yes (1–3 mm)	No	No	Yes (non-uniform)	No	Yes (1 mm)	No
PTV expansion	Yes (3 mm)	Yes (2 mm)	Yes (2–3 mm)	Yes (2.5–3 mm)	Yes (2 mm)	Yes (2 mm)	Yes (1 mm)	Yes (non-uniform)	No	Yes (1–2 mm)	Yes (1 mm)	Yes (2–3 mm)	Yes (2–5 mm)	Yes (2 mm)	Yes (3 mm)
Trim PTV to avoid overlap with OAR?	No	Yes (SC, BS, ON)	No	Yes (BS, eye, ON, SC, BP)	Yes (ON, carotid, esophagus, larynx, brain, ON, OC, BS, SC)	Yes (carotid, BS, ON, OC)	Yes (SC)	Yes (neurocritical)	Yes (carotid)	Yes (ON)	Yes (TL, ON, OC)	Yes (ON, OC, BS, SC)	Yes (brain, BS, ON, OC, skin)	Yes (BS, SC, ON, OC, BP)	Yes (BS, brain, SC, ON, OC)
Safety margins around OARs?	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No

BP: Brachial plexus; BS: Brainstem; COL: Center Oscar Lambret; CTV: Clinical target volume; GLCCC: Georgetown Lombardi Comprehensive Cancer Center; HFHS: Henry Ford Health System; HKUCC: The University of Hong Kong; HU: Hacettepe University; KU: Kyoto Prefectural University of Medicine; MC: Mayo Clinic; MDACC: MD Anderson Cancer Center; MSKCC: Memorial Sloan-Kettering Cancer Center; OAR: Organ at risk; OC: Optic chiasm; OCC: Odette Cancer Center; ON: Optic nerve; PTV: Planning target volume; SC: Spinal cord; SU: Stanford University; TCI: Taussig Cancer Institute – Cleveland Clinic; TL: Temporal lobe; UCSF: University of California; UHSCC: University Hospitals Seidman Cancer Center; UPCI: University of Pittsburgh Cancer Institute.

Table 3. List of dose/fractionation schedules and summarized dose constraints[†].

OAR constraint	Constraint for 1 fx		Constraint for 2 fxs		Constraint for 3 fxs		Constraint for 4 fxs		Constraint for 5 fxs	
	Primary disease	*ReRT*	*Primary disease*	*ReRT*	*Primary disease*	*ReRT*	*Primary disease*	*ReRT*	*Primary disease*	*ReRT*
Spinal cord	Dmax 10–16 Gy V10 <0.25 cc V14 <3 cc	Dmax 8–18 Gy V10 <0.25 cc	Dmax 18 Gy	Dmax 23 Gy	Dmax 22–23 Gy V18 <0.25 cc V22.5 <5 cc	Dmax 22–28 Gy V18 <0.25 cc	Dmax 28 Gy	Dmax 33 Gy	Dmax 20–30 Gy V22.5 <0.25 cc	Dmax 10–20 Gy
Brain	Dmax 15–20 Gy V10 <1 cc	Dmax 10 Gy	–	–	Dmax 23 Gy V18 <1 cc	–	–	–	Dmax 25–32 Gy	Dmax 10–25 Gy
Brachial plexus	Dmax 14 Gy V14 <10 cc	Dmax 10–16 Gy V14.4 <3 cc	–	–	Dmax 24 Gy	Dmax 23 Gy V 22.5 <3 cc	–	–	Dmax 30–40 Gy	Dmax 20–32 Gy V30 <3 cc
Brainstem	Dmax 15 Gy	Dmax 10–15 Gy V10 <1 cc	–	–	–	Dmax 23 Gy V18 <1 cc	–	–	Dmax 25–30 Gy	Dmax 9–15 Gy
Carotid artery	–	Dmax 10 Gy	–	–	–	–	–	–	Dmax 25–47 Gy	Dmax 15–34 Gy <50% gets PTV dose
Cochlea	Dmax 4–12 Gy	Dmax 12 Gy	–	–	Dmax 20 Gy	Dmax 24 Gy	–	–	Dmax 25–30 Gy	Dmax 20–27.5 Gy
Eustachian tube	–	–	–	–	–	–	–	–	Dmax 30 Gy	Dmax 20–25 Gy
Parotid	–	–	–	–	–	–	–	–		Dmax 20–25 Gy
Esophagus	Dmax 19 Gy	Dmax 10 Gy	–	–	–	–	–	–	Dmax 27–35 Gy	Dmax 20–25 Gy
Optic nerves	Dmax 12 Gy	Dmax 8–10 Gy V8 <2 cc	–	–	–	Dmax 19.5 Gy V15 <0.2 cc	–	–	Dmax 20–25 Gy	Dmax 10–12 Gy
Optic chiasm	Dmax 10–12 Gy V8 <0.2 cc	Dmax 8 Gy	–	–	Dmax 10.5 Gy, V15 <0.2 cc	–	–	–	Dmax 20–27 Gy V20 <0.2 cc	Dmax 10 Gy
Retina	Dmax 20 Gy	Dmax 10 Gy	–	–	–	–	–	–	Dmax 27 Gy	Dmax 10 Gy
Lens	–	–	–	–	–	–	–	–	ALARA	Dmax 6 Gy
Larynx	–	–	–	–	–	–	–	–	Dmax 20 Gy	Dmax 20 Gy
Skin	–	–	–	–	–	–	–	–	Dmax 30 Gy	–

[†]The selection of normal tissue constraints is dependent upon multiple factors including prior radiation dose exposure to various OARs. The constraints presented in **Table 3** represent a summary of practice patterns in individual treatment centers. Readers are advised to use discretion when interpreting the information as clinical situations may vary.
ALARA: As low as reasonably achievable; Dmax: Maximal dose; Fx: Fraction; OAR: Organ-at-risk; ReRT: Reirradiation.

Table 1.2 Illustrating the use of BEDs to compare and contrast conventional, hyperfractionated and hypofractionated treatment schedules for tissues with α/β ratios of 10 Gy versus 3 Gy

30 × 2 Gy = 60 Gy	BED of 72 Gy_{10} and 100 Gy_3	Conventional
35 × 1.8 Gy = 63 Gy	BED of 74.3 Gy_{10} and 100.8 Gy_3	
68 × 1.2 Gy = 81.6 Gy	BED of 91.4 Gy_{10} and 114 Gy_3	Hyperfractionated
70 × 1.15 Gy = 80.5 Gy	BED of 89.8 Gy_{10} and 111.4 Gy_3	
20 × 2.8 Gy = 56 Gy	BED of 71.7 Gy_{10} and 108 Gy_3	Hypofractionated
16 × 3.4 Gy = 54.4 Gy	BED of 73 Gy_{10} and 116.1 Gy_3	
3 × 15 Gy = 45 Gy	BED of 112.5 Gy_{10} and 270 Gy_3	

Commonly Utilised Fractionation Schedules

Dose/Fx	Number of fx	Total dose	Notes
9 Gy	2	18 Gy	Treat QOD [7]
11 Gy	3	33 Gy	Treat QOD [8]
12 Gy	4	48 Gy	Treat QOD [7]
6 Gy	5	30 Gy	Treat QOD [9]
6 Gy	8	48 Gy	Treat QOD [7]
8 Gy	6	48 Gy	Treat QOD [10]

A Multi-institutional Comparison of SBRT and IMRT for Definitive Reirradiation of Recurrent or Second Primary Head and Neck Cancer

Vargo et al.

Materials & Methods:

• Unresectable rSCCHN previously irradiated to > 40 Gy who underwent reirradiation with IMRT or SBRT were collected from 8 institutions.

• The prognostic value of MIRI proposed IMRT-based recursive partitioning analysis (RPA) separating those patients with unresectable tumors with an intertreatment interval >2 years or those with < 2 years and without feeding tube or tracheostomy dependence (class II) from other patients with unresected tumors (class III) was investigated among SBRT patients.

• Overall survival (OS) and locoregional failure were then compared between IMRT and SBRT by use of 2 methods to control for baseline differences: Cox regression weighted by the inverse probability of treatment and subset analysis by RPA classification.

Int J Radiation Oncol Biol Phys, Vol. 100, No. 3, pp. 595–605, 2018

Results:

- 414 patients with unresectable rSCCHN: 217 with IMRT & 197 with SBRT.

- Unadjusted 2-year OS rate was 35.4% for IMRT and 16.3% for SBRT (P<.01).

Conclusions:

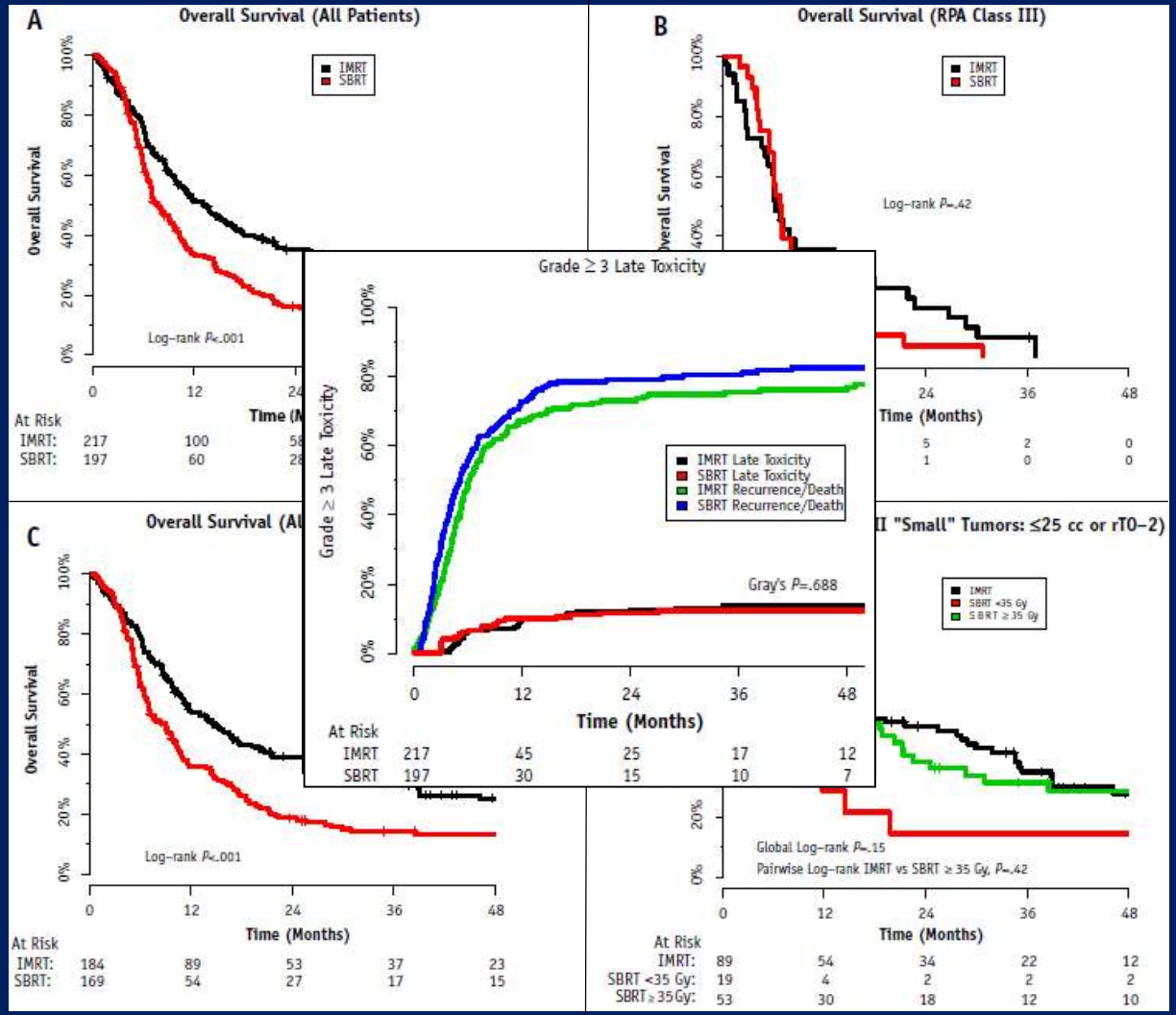
- Reirradiation both with SBRT and with IMRT appear relatively safe with favorable toxicity compared with historical studies.

- Outcomes vary by RPA class

- Survival is poor in class III patients, and alternative strategies are needed.

- **Further subset analysis demonstrated comparable OS when**

- 35 Gy was delivered with SBRT to small tumor volumes.
- Acute grade $\geq$ 4 toxicity was greater in the IMRT group than in the SBRT group (5.1% vs 0.5%, P<.01), with no significant difference in late toxicity.


A
Overall Survival (All Patients)
IMRT
SBRT
Overall Survival
100%
80%
60%
40%
20%
0%
Log-rank P<.001
0
12
At Risk
IMRT: 217 100
SBRT: 197 60
B
Overall Survival (RPA Class III)
IMRT
SBRT
Log-rank P=.42
24
36
48
Time (Months)
5 2 0
1 0 0
Grade ≥ 3 Late Toxicity
Grade ≥ 3 Late Toxicity
IMRT Late Toxicity
SBRT Late Toxicity
IMRT Recurrence/Death
SBRT Recurrence/Death
Gray's P=.688
0
12
24
36
48
Time (Months)
At Risk
IMRT 217 45 25 17 12
SBRT 197 30 15 10 7
C
Overall Survival (Al
Overall Survival
100%
80%
60%
40%
20%
0%
Log-rank P<.001
0
12
24
36
48
Time (Months)
At Risk
IMRT: 184 89 53 37 23
SBRT: 169 54 27 17 15
II "Small" Tumors: ≤25 cc or rT0–2)
IMRT
SBRT <35 Gy
SBRT ≥ 35 Gy
20%
0%
Global Log-rank P=.15
Pairwise Log-rank IMRT vs SBRT ≥ 35 Gy, P=.42
0
12
24
36
48
Time (Months)
At Risk
IMRT: 89 54 34 22 12
SBRT <35 Gy: 19 4 2 2 2
SBRT ≥ 35 Gy: 53 30 18 12 10

Supplemental Table 1: Cox Proportional Hazards Regression for Overall Survival, SBRT Patients Only

		Univariable			Multivariable (11 Deg of Freedom, 168 deaths)		
		HR	p	95% CI	HR	p	95% CI
Age		1.016	**0.025**	1.016-1.030	1.033	**<0.0001**	1.017-1.05
Gender	Male vs Female	0.803	0.207	0.578-1.133	0.757	0.12	0.534-1.073
Tumor Site	Nasopharynx/Base of Skull/Retropharyngeal Space	Ref	Ref	Ref			
	Skin/Salivary/Sinonasal	1.039	0.916	0.507-2.129			
	Larynx/Hypopharynx	1.223	0.467	0.705-2.143			
	Oropharynx	1.198	0.483	0.723-1.986			
	Neck Only	1.336	0.266	0.802-2.225			
	Oral Cavity	1.299	0.333	0.765-2.207			
Tumor Site (Simplified)	Nasopharynx/Base of Skull/Sinonasal/Other	Ref	Ref	Ref	Ref	Ref	Ref
	Oral Cavity/Oropharynx/Larynx/Hypopharynx/Neck	1.249	0.242	0.861-1.811	0.979	0.92	0.653-1.465
Recurrence or 2nd Primary	Recurrent vs 2nd Primary	2.423	**0.0009**	1.398-4.628	1.943	**0.034**	1.050-3.593
Organ Dysfunction	Yes vs No	1.440	0.073	0.966-2.088			
Time Between RT	*Continuous*	0.900	**<0.0001**	0.847-0.948			
	<6 Months	2.036	**0.0025**	1.293-3.159			
	6 Months-2 Years	1.581	**0.008**	1.124-2.245			
	>2 Years	Ref	Ref	Ref			
Previous Use of Systemic Therapy	Yes vs No	1.132	0.440	0.829-1.560	1.144	0.46	0.797-1.643
Systemic Therapy during Re-RT	Yes vs No	1.138	0.404	0.840-1.550	1.213	0.30	0.840-1.752
Previous Dose of RT	>70 Gy vs ≤70 Gy	1.192	0.276	0.867-1.624	1.243	0.22	0.881-1.753
GTV (6 missing)	*>25 cc vs ≤25 cc*	2.069	**<0.0001**	1.496-2.863	2.659	**<0.0001**	1.856-3.81
Dose	≥40 Gy vs <40 Gy	0.971	0.859	0.705-1.355			
	≥35 Gy vs <35 Gy	0.886	0.543	0.611-1.325	1.345	0.21	0.845-2.14
RPA Class	Class III vs Class II	1.659	**0.022**	1.078-2.464	1.707	**0.017**	1.099-2.653

- Localised small unresectable tumors
- GTV volume <25cc
- Ability to deliver doses >35Gy/5#

Definitive SBRT Reirradiation: Efficacy & Toxicity

Study	Number of patients	SBRT dose/#fractions	Median f/u (months)	Median survival/ 1y OS	Response rate (CR+PR)	Local-regional progression	Toxicity
Siddiqui, et al. (2009) [48]	29	36-48Gy 5-8fx	36	7 mths 38 %	69	4 %	14 % grade ≥3 (dysphagia, cataract, pain); 14 % grade 4 (fistula/ulceration)†
Roh, et al. (2009) [49]	44 (35 evaluable)	18-40Gy 3-5fx	17	16 mths 52 %	80 %	11 %	10 % grade ≥4 (soft tissue/bone necrosis/ death)
Unger, et al. (2010) [53]	38	21-35Gy 2-5fx	16	20 mths 40 %	80 %	32 %	12 % grade 4/5 (arterial bleed, death, fistula, soft tissue necrosis, dysphagia, trismus, cranial neuropathy)
Kodani, et al. (2011) [55]	21*	20-42Gy 3-8fx	28	16 mths 70 %	62 %	14 %	28 % late≥grade 3 (hemorrhage and death X 2, mucositis, skin necrosis, chronic ulcer)
Cengiz, et al. (2011) [47]	46 (37 evaluable)	18-35Gy 1-5fx	7	12 mths 46 %	57 %	13.5 %	13 % carotid blowout (7/8 died)‡ 13 % late≥grade 2 (Soft tissue/bone necrosis, dysphagia)
Comet, et al. (2012) [58]	40	36Gy 6fx	26	14 mths 58 %	79	23 %	10 % grade 3 (mucositis, dysphagia, fibrosis).
Vargo, et al. (2013) [59]	132	35-50Gy 5fx	6	7 mths 49 %	75 %**	44 %	7 % grade 3 (Dysphagia, Pain and Skin). No grade 4/5

O. M. Mahmoud & S. A. Koyfman. J Radiat Oncol DOI 10.1007/s13566-015-0187-6

Definitive SBRT Reirradiation: Efficacy & Toxicity

Author	Design	Patients	Treatment	Outcomes	Toxicity
Unger KR	Retrospective	65	30 Gy/5 Gy	2 y LCR 30% 2 y OS 51%	9% G4 late 29% G1-3 acute
Kress MA	Retrospective	85	30 Gy/5 Gy	Med OS 8.6 m 2 y OS 24%	5.9% G3
Rwigema JC	Retrospective	96	16–18 Gy/16–18 Gy, 20–50 Gy/4 Gy, 10 Gy, 15–24 Gy/2 to 4 fxs	3 y LRC of 15.9% vs 41.4% (15–36 Gy vs 40–50 Gy)	5.2% G3 acute 3.1% G3 late
Comet	Prospective	40	36 Gy/6 Gy	Med OS 13.6 m	10% G3
Cengiz M	Retrospective	46	30 Gy/6 Gy	Med OS 12 m	13.3% G2 17.3% CBO
Vargo JA	Retrospective	132	44 Gy/8.5 Gy	1 y OS 48%	7% G3
Heron DE	Phase I	31	25 Gy/5 Gy to 44 Gy/8.5 Gy	Median OS 6 m	No G3-G4 toxicity
Heron DE	Matched case-control	70	20 Gy/4 Gy, 32 Gy/5 Gy, 35 Gy/6.4 Gy, 35 Gy/7 Gy, 40 Gy/8 Gy, 44 Gy/8.8 Gy +/− CTX	OS 24.5 vs. 14.8 m	2.8% G3 acute SBRT 5.6% G3 acute SBRT + CTX
Lartigau EF	Phase II	60	36 Gy/6 Gy + CTX	Med OS 11.4 m 1 y OS 47.5%	30% G3
Vargo JA	Phase II	50	40–44 Gy/8–8.5 Gy	Med OS 10 m 1 y OS 40%	6% G3 acute 6% G3 late

Critical Reviews in Oncology / Hematology 122 (2018) 194–201

SBRT: Phase 1-Dose Escalation Study

Dose tier	Subjects (*n*)	Prior RT dose (mean Gy/no. of fx)	Prior spinal cord dose (mean Gy)	Dose/fx (Gy)	No. of fx	Total dose (Gy)	Mean volume of GTV receiving PD (%)
1	3	69.2/36	45.5	5	5	25	98.4
2	3	69.6/35	45.2	6.4	5	32	96.7
3	3	66/30	40.7	7.2	5	36	95
4	6	68.5/36	44.6	8.0	5	40	92
5	10	66.8/35	45.1	8.8	5	44	94

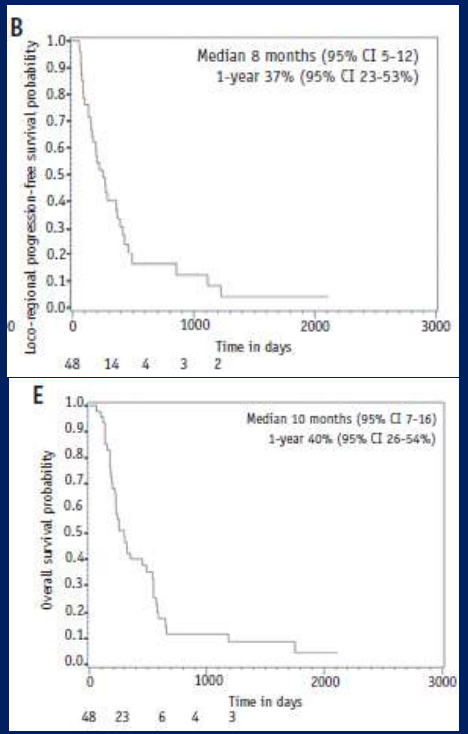
Abbreviations: RT = radiotherapy; fx = fraction; GTV = gross tumor volume; PD = prescription dose.

- 25 patients
- Dose escalation with SBRT
- No patient had grade 3-4 reactions
- Median time to progression 4 months
- Median overall survival 6 months

Heron DE. IJROBP 2009

SBRT with Cetuximab: Phase 2 trial

- July 2007-March 2013
- N=50
- Previously irradiated (Dose >60Gy) rec HN SCC
- SBRT: 40-44Gy/5# alternate days
- Cetuximab: 400mg/m2 on day -7, 250mg/m2 on day 0 and +8
- Toxicity: Acute and late toxicity: 6%



Vargo J et al. IJROBP 2015

Attempts at Intensification

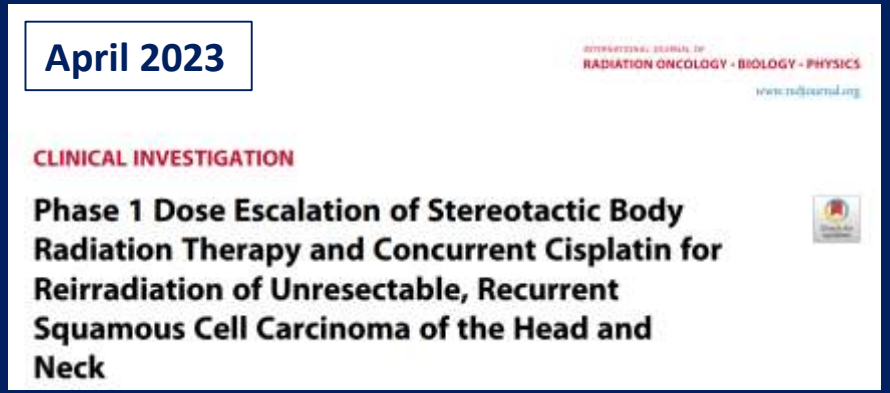
- 2 Phase I trials:

  SBRT + docetaxel 15 mg/m2 days 1, 8, 15 (NCT02110992)

  SBRT + Cisplatin 15 mg/2 days 1, 8, 15, (NCT02158234) starting dose of 25 Gy/5 Gy and 30 Gy/6 Gy, respectively

- Phase II trial (NCT02057107):

  SBRT (8.8 Gy–10 Gy per fraction to 44–50 Gy) + cetuximab (Day −7, 400 mg/m2; Days 0 and 8, 250 mg/m2; adjuvant cetuximab 250 mg weekly) +/docetaxel (25 mg/m2 weekly days 0 and 8; adjuvant 25 mg/m2 weekly) followed by adjuvant cetuximab +/− docetaxel.



- Aim: To establish a maximum tolerated dose of SBRT with concurrent cisplatin in previously irradiated locoregional SCCHN
- Inclusion: DFI of ≥6 months, ≥45 Gy received previously, presently non surgical/refused surgery, life expectancy > 6 months
- Planned for 5 # of SBRT on alternate days
- Starting dose level was 6 Gy x5 #, f/b 7 Gy x 5# and 8 Gy x 5#
- Concurrent Cisplatin 15 mg/m2 before each fraction of SBRT

Results

- 20 patients accrued from 2014 to 2019
- Monitored for DLT that occurred within 3 months of SBRT starting
- Median follow up of 9.5 months
- No DLTs observed
- Cumulative incidence of locoregional failure at 2 years was 61%, distant metastasis was 11% and overall survival was 22%
- Conclusion: Concurrent cisplatin and reirradiation with an SBRT dose of ≤40 Gy was safe and feasible in patients with locoregionally recurrent or second primary SCCHN

Sequelae of SBRT

- Osteoradionecrosis
- Soft tissue necrosis
- Fistula formation
- Cranial nerve palsies
- Brain necrosis
- Otitis media
- Carotid blow out
- Dysphagia
- Aspiration
- Myelopathy

Carotid Blow Out

- One of the most dreaded complications of ReRT
- Mortality rates as high as 60%
- Neurologic morbidity: 40%
- Reirradiation with standard fractionation: 2.6%
- Reirradiation with SBRT: 5.3%-18%

- Factors:
  - >180 degree carotid encasement
  - Carotid artery dose >100% prescription
  - Skin invasion
  - Presence of ulceration
  - Presence of infection, necrosis
  - Treatment of neck recurrences
  - Increased PTV size

MacDonald MW. IJROBP 2012
Gebhardt BJ. IJROBP 2018

Table 3. Observed cases of carotid blowout by treatment group

Variable	Any reRT	Fractionation Group 1	Fractionation Group 2	Fractionation Group 3	With chemotherapy	Without chemotherapy	With salvage surgery	Without salvage surgery
CB (*n*)	41	8	4	23	33	4	6	30
Patients (*n*)	1554	610	227	513	1010	271	294	917
% CB	2.6	1.3	1.8	4.5	3.3	1.5	2	3.3

Abbreviations as in Table 1.

Fractionation Group 1: continuous course with 1.8–2-Gy daily fractions or 1.2 Gy twice daily; Fractionation Group 2: split-course or alternating weeks with 1.8–2-Gy daily fractions; Fractionation Group 3: alternating week accelerated hyperfractionation, 1.5 Gy twice daily, or delayed accelerated hyperfractionation.

- RT schedule was important
- Not related to use of conc CT, surgery prior to RT
- Lower CBO in patients treated with CF and HF vs accelerated HF

MacDonald MW, et al. IJROBP, 2012: Vol.82(3), 1083 - 1089

A simple strategy to decrease fatal carotid blowout syndrome after stereotactic body reirradiaton for recurrent head and neck cancers

Abstract

Background: This study aimed to compare the therapeutic outcomes and fatal carotid blow out syndrome (CBOS) incidence rates between two different stereotactic body radiotherapy (SBRT) protocols.

Methods: The study included 75 patients with inoperable locally recurrent head and neck cancer treated with SBRT in our department between June 2007 and March 2011. The first 43 patients were treated sequentially (group I). Then our SBRT protocol was changed due to the high rate of CBOS, and the following 32 patients were treated every other day in a prospective institutional protocol (group II).

Results: Median overall survival in group I and group II was 11 months and 23 months, respectively (P = 0.006). We observed 11 cases of CBOS. Only 1 of 7 patients (14%) with CBOS survived in group I, whereas 2 of 4 patients (50%) in group II remain alive. CBOS free median overall survivals were 9 months, and 23 months in group I and group II respectively (P = 0.002). The median radiation dose received by the carotid artery in patients with CBOS was 36.5 Gy (range: 34–42.8 Gy), versus 34.7 Gy (range: 0–44 Gy) in the patients that didn't have CBOS (P = 0.15). CBOS did not occur in any of the patients with a maximum carotid artery radiation dose <34 Gy.

Conclusions: Every other day SBRT protocol for re-irradiation of recurrent head and neck cancer is promising in terms of decreasing the incidence of fatal CBOS.

Yazici *et al. Radiation Oncology* 2013, **8**:242

Table 4. Quoted risks for late toxicity by institution.

Late toxicity	Risk for primary disease head and neck cancer SBRT	Risk for recurrent head and neck cancer SBRT
Carotid blowout syndrome	1–20%	3–20%
Chronic ulceration	1–20%	5–25%
Mucosal hemorrhage	3–20%	1–20%
Fistula	5–20%	5–20%
Osteoradionecrosis	2–20%	2–50%
Soft tissue necrosis	2–20%	2–30%
Dysphagia	3–20%	1–50%
Death	1–5%	1–5%

SBRT: Stereotactic body radiotherapy.

Survey of current practices from the ISBRTC for head & neck cancers

Prognostic Factor for Overall Survival	Risk Factors for Adverse Reactions
• Debulking surgery prior to reirradiation • Anatomic site • Histology • Time interval since prior treatment • Second primary versus recurrent tumor • Dose–response relationship • Tumor size (T category)/volume of reirradiation • Treatment modality • Gender • Salvage treatment • Age	• Accumulated irradiated dose • Concurrent use of chemotherapy • Age • Mucosal involvement/ulceration • Treatment volume • Reirradiation schedule • Treatment modalities

Kim YS. Radiat Oncol J 2017;35(1):1-15. Optimal reirradiation strategy for head and neck cancer

For reRT.....

- Patient selection is the cornerstone to successful outcome:
- SBRT is a viable option in small, recurrent disease

- Ascertain details of previous RT
- Optimal treatment of localized recc: Maybe combined with C225/ Docetaxel

- Issues with ReRT:
  - Longer time intervals: Superior outcomes
  - Target volumes: Use of functional imaging
  - OAR doses: To be respected, as low as achievable
    - Restriction of doses possible
  - Volumes/ target localization: Volumes < 25 cc preferrable
    - Possible to deliver biologically higher/ equivalent doses
  - Treatment on alternate days, 35-45Gy/ 5 - 7#

- Attention to supportive care & QOL issues
- Diligent documentation & reporting

SBRT for Primary Unresectable Head Neck Cancers

SBRT for Primary Unresectable Head Neck Cancers

- Used seldom in patients unfit for chemotherapy and borderline Performance Status (ECOG 2/3)

- Lesser no of hospital visits/ shortened treatment time

- Criteria: (Usually) : Primary: 3-5 cm
  : Nodal: 4- 5 cm
  : Volume Primary: less than 30 cc
  : Volume Nodal: less than 50 cc

Ref: Survey of current practices from the International Stereotactic Body Radiotherapy Consortium (ISBRTC) for head and neck cancers, Future Oncology, 2016

Stereotactic Radiosurgery in Combination With Chemotherapy as Primary Treatment for Head and Neck Cancer

Koji Kawaguchi, DDS, PhD, Kengo Sato, MD,† Hiroyuki Yamada, DDS, PhD,‡ Akihisa Horie, DDS,§ Takayoshi Nomura, DDS, PhD,|| Susumu Ikehara, DDS, PhD,¶ Ikuyo Kanai, DDS, PhD,# Satoshi Suzuki, DDS, PhD,** Yasunori Nakatani, DDS,†† and Yoshiki Hamada, DDS, PhD‡‡*

- 14 patients from Sep 2006 to Nov 2007
- Median Age: 73 Years, All Sites
- T2 (5), T3 (3), T4 (6), N0 (13), and N1 (1).
- Median Fu: 36 months (14-40 months)
- Local control and overall survival rates were 71.4% (10/14) and 78.6% (11/14), respectively.

Table 2. TREATMENT DOSE LEVELS AND NUMBER OF FRACTIONS

	No. of Patients
Marginal dose (cGy)	
3,500 to 3,999	9
4,000 to 4,500	4
Fractions	
3	4
5	10

Table 3. TUMOR RESPONSE BASED ON FOLLOW-UP DURATION AND TREATED REGION (OVERALL MEDIAN FOLLOW-UP IS 36 MONTHS, RANGE 14 TO 40 MONTHS)

	No. of Patients
Assessment at 3 mo	
Complete response	5
Partial response	9
Local control rate	14/14 (100%)
Assessment at median 36 mo, range 14 to 40 mo	
Complete response	10
Partial response	0
Stable disease	0
Progressive disease	4
Not evaluable	0
Local control rate	10/14 (71.4%)
Overall response rate	11/14 (78.6%)
Overall survival by treated region	
Tongue	2/5 (40%)
Mandible	4/5 (80%)
Maxilla	1/1 (100%)
Maxillary sinus	2/2 (100%)
Soft palate	1/1 (100%)

Kawaguchi et al. Stereotactic Radiosurgery and Chemotherapy for Head and Neck Cancer. J Oral Maxillofac Surg 2012.

frontiers in ONCOLOGY

ORIGINAL RESEARCH ARTICLE

Survival outcomes of patients treated with hypofractionated stereotactic body radiation therapy for parotid gland tumors: a retrospective analysis

Sana D. Karam[1], James W. Snider[1], Hongkun Wang[2], Margaux Wooster[1], Christopher Lominska[3], John Deeken[4], Kenneth Newkirk[1], Bruce Davidson[5] and K. William Harter[1]*

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[2] Department of Biostatistics, Bioinformatics, and Biomathematics, Georgetown University Hospital, Washington, DC, USA
[3] Department of Radiation Oncology, The University of Kansas, Kansas City, KS, USA
[4] Department of Hematology/Oncology, Georgetown University Hospital, Washington, DC, USA
[5] Department of Otolaryngology, Georgetown University Hospital, Washington, DC, USA

Between 2003 and 2011, 13 patients diagnosed with parotid malignancies were treated with adjuvant or definitive SBRT to a median dose of 33 Gy (range 25–40 Gy)

Table 2 | Crude survival outcomes.

Median follow-up all patients (range)	14 months (0–59)
Median follow-up surviving patients (range)	24 months (3–59)
Median OS	20 months
Median LRC	Not reached
Median PFS	18 months
Local failure (%)	1/13 (7.7%)
Distant failure (%)	4/13 (30.8%)
Any progression (%)	5/13 (38.5%)
Cancer-specific mortality (%)	4/13 (30.8%)
Overall mortality (%)	7/13 (53.8%)
2-Year actuarial overall survival	0.46 (0.30–0.75)
2-Year actuarial locoregional control	0.84 (0.68–0.98)
2-Year actuarial progression-free survival	0.47 (0.47–0.81)

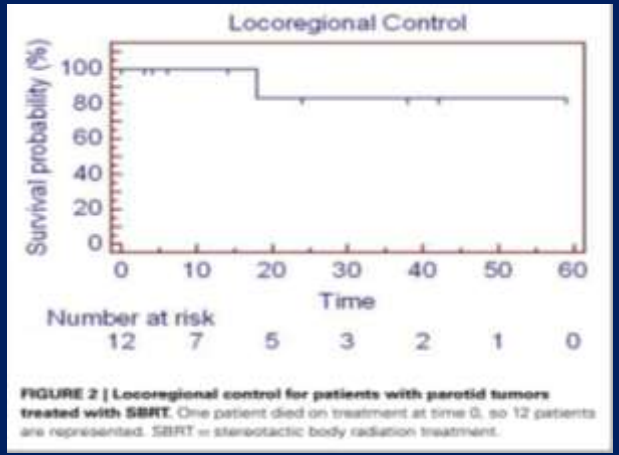


FIGURE 2 | Locoregional control for patients with parotid tumors treated with SBRT. One patient died on treatment at time 0, so 12 patients are represented. SBRT = stereotactic body radiation treatment.

Clinical Investigation

Stereotactic Radiation Therapy for De Novo Head and Neck Cancers: A Systematic Review and Meta-Analysis

November 2020

Nauman H. Malik, MD,[a] Michael S. Kim, MD,[b] Hanbo Chen, MD,[a] Ian Poon, MD,[a] Zain Husain, MD,[a] Antoine Eskander, MD,[c,d] Gabriel Boldt, MLIS,[e] Alexander V. Louie, MD, PhD,[a] and Irene Karam, MD[a,*]

Population	Patients with previously untreated head and neck cancers, including skin cancers and lymphadenopathy treated in the head and neck region and base of skull tumors.
Intervention	Stereotactic radiation therapy, defined as precise and accurate delivery of external beam radiation therapy at high doses per fraction with anatomic targeting accuracy and reproducibility.
Control	No control group, or a study with multiple arms where stereotactic radiation therapy was used
Outcomes	Primary outcome: local control at 1 and 2 y Secondary outcomes: overall survival at 1 and 2 y, progression free survival, late grade $\geq$3 toxicities
Study design	Included prospective or retrospective clinical studies, with greater than 5 patients in the study

9 studies, 157 patients

Table 2 Studies evaluating de novo stereotactic radiation therapy for head and neck primary cancers

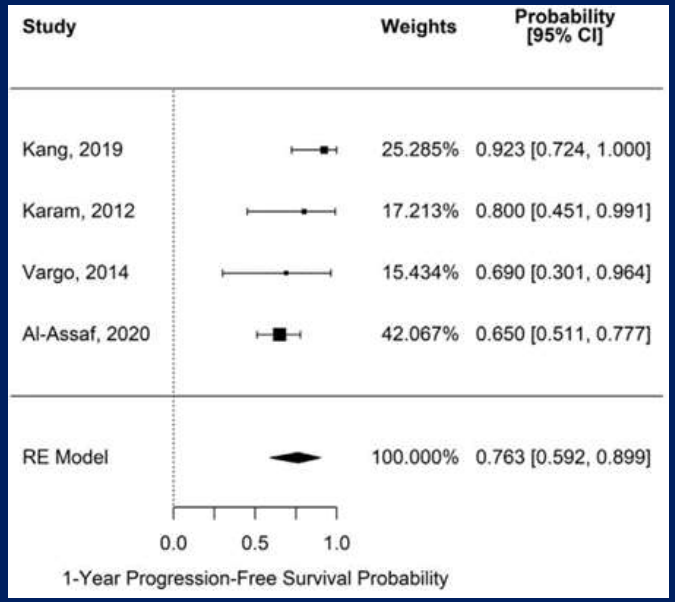
Study	Subsite	Study design	Sample size (n)	Median follow-up (mo)	Dose in Gy, median (range)	Fractions, median (range)	Median BED_{10}* ($\alpha/\beta = 10$)	Median BED_3† ($\alpha/\beta = 3$)	EQD2‡(Gy, $\alpha/\beta = 10$)
Kang[29]	Larynx	Prospective	13	26.6	59.5 (55-59.5)	17 (11-17)	80.3	128.9	66.9
Sher[25]	Larynx	Prospective	29	43.6	45 (42.5 − 50)	10 (5-15)	65.3	112.5	54.4
Karam[26]	Parotid	Retrospective	13	14	33 (25-40)	6 (5-7)	51.2	93.5	42.6
Kodani[27]	Mixed	Retrospective	13	16	30 (19.5-42)	5 (3-8)	48.0	90.0	40.0
Amini et al[10]	Mixed	Retrospective	2	6	25-30	5	42.6	77.9	35.5
Vargo[28]	Mixed	Retrospective	12	6	44 (20-44)	5 (1-6)	82.7	173.1	68.9
Khan et al[9]	Mixed	Retrospective	17	8	40 (35-48)	5 (5-6)	72.0	146.7	60.0
Siddiqui et al[15]	Mixed	Retrospective	10	32.7	36 (18-48)	6 (1-8)	57.6	108.0	48.0
Al-Assaf[30]	Mixed	Retrospective	48	10.5	41.6 (35.6 − 53.8)	5 (4-6)	76.2	157.0	63.5

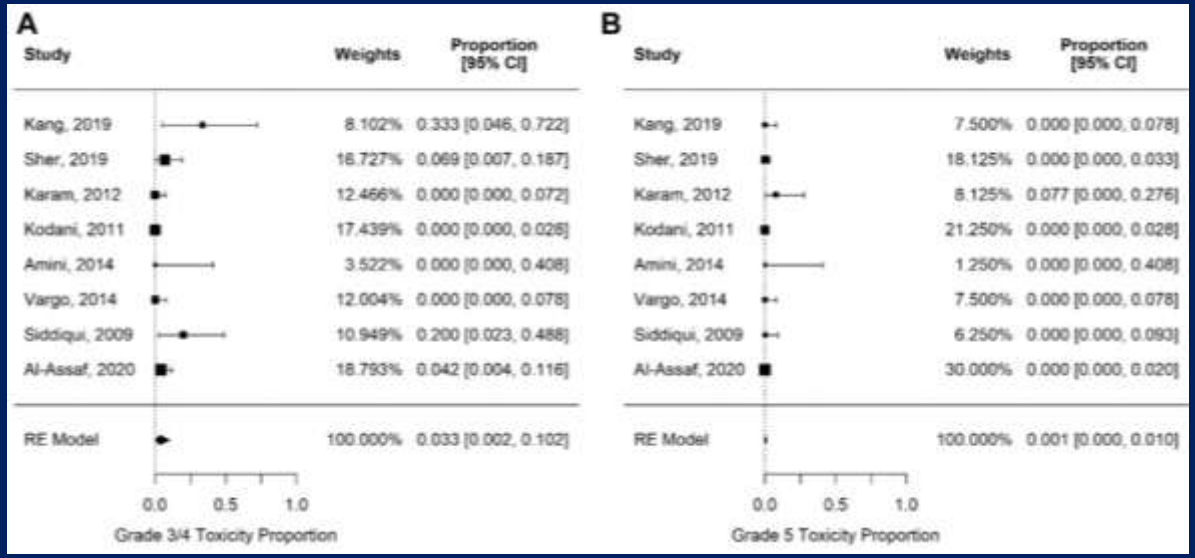
Abbreviation: BED = biologically effective dose.

* BED_{10} is biologically effective dose for tumor ($\alpha/\beta = 10$).

† BED_3 is biologically effective dose for tumor ($\alpha/\beta = 3$).

‡ EQD2 is the total equivalent dose in 2 Gy fractions.





- Local control rates at 1, 2, and 3 years were 90.7%, 81.8% and 73.5%
- Overall survival at 1, 2, and 3 years was 75.9%, 61.1% and 50.0%
- Late grade 3 to 4 toxicity rate was 3.3% and late grade 5 toxicity rate was 0.1%

Conclusions: SBRT for de novo HNC is safe and effective in providing locoregional control, with acceptable toxicities in most subsites. This finding warrants broader validation to guide its scope.

STUDY PROTOCOL Open Access

A phase 2 study of stereotactic body radiation therapy for squamous cell carcinoma of the head and neck (SHINE): a single arm clinical trial protocol

BMC Cancer

Justin Lee[1,2*], Nhu Tram Nguyen[1,2], James Wright[1,2], Ka-Kit David Yeung[1,2], Stephen Sagar[1,2], Do-Hoon Kim[1,2], Orest Ostapiak[1,2], Lilian Doerwald-Munoz[1,2] and Timothy Whelan[1,2]

April 2023

- Aim: To evaluate response rates to SBRT in older age patients with inoperable locally advanced HNSCC
- SBRT: 45 Gy/5 # in 3 to 4 days

TARGET POPULATION satisfying all of the following:

1) Age >= 60 years
2) Histologically confirmed diagnosis of squamous cell carcinoma of the head and neck region including primary skin SCC; (malignant cells with suspicious/likely SCC will be considered for study if repeat biopsy is not feasible)
3) Clinical stage ≥ T2, or any T-stage with N1-N3 disease, M0 or Mx
4) Measurable tumour present in the head and neck region on clinical examination and/or imaging at time of study enrollment
5) All patients will be assessed by a multi-disciplinary, head and neck oncology team with no systemic therapy being recommended at the time of enrollment
6) Primary surgery not recommended/performed due to any of the following:
   - Unresectable disease and/or borderline resectable
   - Medically inoperable / deemed high risk for post-operative morbidity/mortality by surgical team
   - Patient declined surgery
7) Deemed not to be a candidate for standard fractionation radiotherapy due to poor performance status and/or medical co-morbidities and/or advanced stage disease
8) Eastern Co-operative Oncology Group (ECOG) Performance Status ≤ 3

STUDY PROTOCOL Open Access

A multicenter prospective phase II study of postoperative hypofractionated stereotactic body radiotherapy (SBRT) in the treatment of early-stage oropharyngeal and oral cavity cancers with high risk margins: the STEREO POSTOP GORTEC 2017-03 trial

BMC Cancer

Julian Biau[1,2,3*], Emilie Thivat[2,3,4], Corinne Millardet[5], Nicolas Saroul[6], Nat[illegible][4], Bruno Pereira[8], Xavier Durando[2,3,4,9], Jean Bourhis[10] and Michel Lapeyre[1]

August 2020

- 1st prospective trial to evaluate head and neck cancer postoperative SBRT in the early oropharyngeal and oral cancers with high risk margins
- SBRT: 36 Gy/6 # over 2 weeks.
- Primary endpoint: Severe late toxicity defined as 2-year toxicity of grade ≥ 3 (CTCAE V4.03)
- Study accrual started from Jan 2018

Inclusion criteria

- Operated squamous cell carcinoma of the oral cavity (lips excepted) or oropharynx
- pT1 or pT2
- Indication of postoperative tumor site irradiation (confirmed by multidisciplinary tumor board) with at least one of the following criteria:
- positive R1 margin (re-resection not proposed)
- close margin < 5 mm (re-resection not proposed)
- margin estimated at risk, with uncertain pathological margin (re-resection not proposed)
- N0 after surgical treatment of the neck (neck dissection or sentinel lymph node biopsy) or pN1 without extracapsular extension (carcinological neck dissection)
- Age ≥ 18 years
- ECOG status ≤2
- Written signed informed consent before any specific procedure of the protocol
- Affiliation to a social security scheme or beneficiary of such a scheme

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Review

Stereotactic body radiotherapy (SBRT) for primary non-metastatic head and neck cancer: When less is enough

March 2021

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Department of Radiation Oncology, Tata Memorial Hospital (TMH), Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India

Primary Curative Setting

Patient factors

- Unresectable disease and/ or borderline resectable disease not amenable to cure with conventional protracted radiotherapy/ with or without concurrent chemotherapy
- Medically inoperable, elderly age with compromised performance status

Disease Factors

- T1-T3, small volume T4
- N1/N2, Small size and ipsilateral, not multiple levels, not involving the low neck

As Boost

Nasopharyngeal cancers with residual/ recurrent disease
As an alternative to brachytherapy boost in oropharynx cancer

SBRT for Metastatic Head Neck Cancers

853O

OMITting frontline chemotherapy in head and neck cancer (HNSCC) patients with 1-3 oligometastases using stereotactic ablative radiotherapy (SABR), the GORTEC 2014-04 "OMET" randomized phase II trial

J. Thariat[1], M. Bosset[2], A. Falcoz[3], D. Vernerey[4], Y. Pointreau[5], S. Racadot[6], J.C. Faivre[7], J. Castelli[8], S. Guihard[9], F. Huguet[10], S. Chapet[11], Y. Tao[12], J. Bourhis[13], X.S. Sun[14]

Background: Most trials in metastatic HNSCC compare systemic therapies; HNSCC were underrepresented in the few multihistology SABR trials; none has assessed SABR-alone vs chemo-SABR in often frail/heavily-pretreated HNSCC patients. The GORTEC 2014-04 phase IIR study assesses impact on survival without definitive quality of life (1yOS-QoL) deterioration of omitting frontline chemotherapy in oligo-metastatic HNSCC patients (pts) by using SABR alone.

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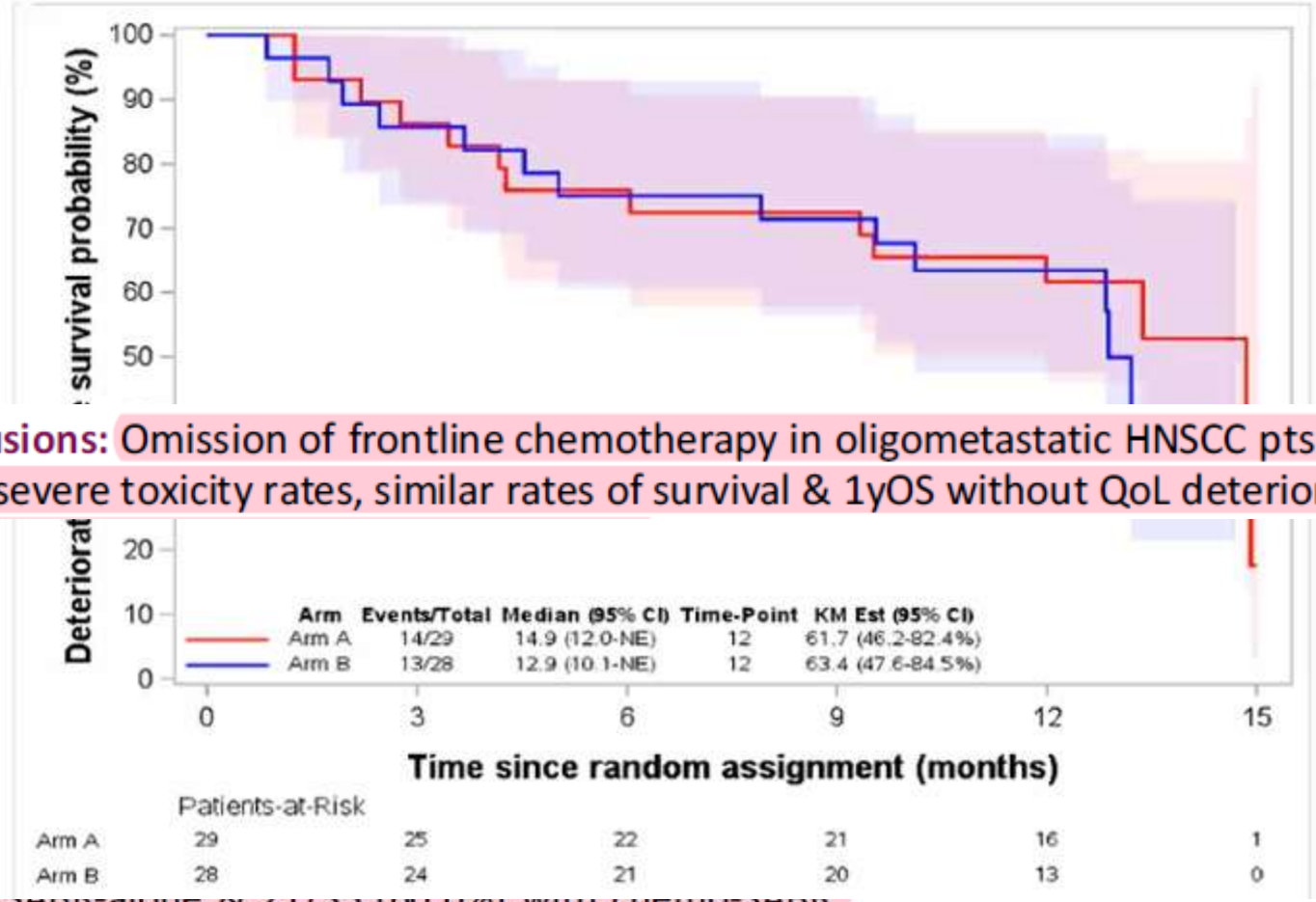
with SABR-alone & 21/33 (66.0%) with chemo-SABR.



Conclusions: Omission of frontline chemotherapy in oligometastatic HNSCC pts led to lower severe toxicity rates, similar rates of survival & 1yOS without QoL deterioration.

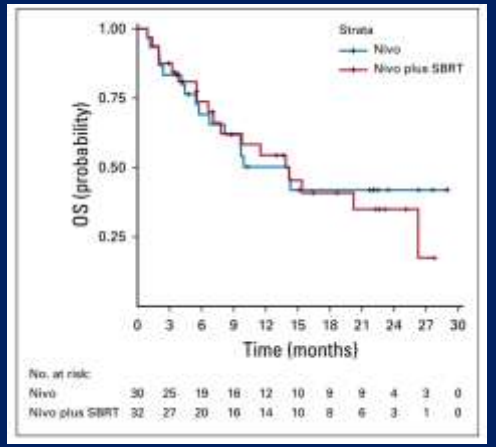
original reports

Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

July 2020

Sean McBride, MD, MPH[1]; Eric Sherman, MD[2,3]; C. Jillian Tsai, MD, PhD[1]; Shrujal Baxi, MD, MPH[2]; Jahan Aghalar, MD[1]; Juliana Eng, MD[1]; Wanqing Iris Zhi, MD, PhD[1]; Daniel McFarland, DO[1]; Loren Scott Michel, MD[1]; Robert Young, MD[4]; Robert Lefkowitz, MD[4]; Daniel Spielsinger, BS[1]; Zhigang Zhang, PhD[3]; Jessica Flynn, BS[5]; Lara Dunn, MD[2,3]; Alan Ho, MD, PhD[2,3]; Nadeem Riaz, MD, MSc[1]; David Pfister, MD[2,3]; and Nancy Lee, MD[1]

- 62 patients
- Patients had at least 2 metastatic lesions: one that could be safely irradiated and one measurable by RECIST version 1.1
- Arms: Nivolumab (3 mg/kg IV, 2 weekly) or Nivolumab+ SBRT (9 Gy x 3 #) to 1 lesion
- Primary end point: ORR in nonirradiated lesions



CONCLUSION We found no improvement in response and no evidence of an abscopal effect with the addition of SBRT to nivolumab in unselected patients with metastatic HNSCC.

HEAD AND NECK CANCER

Journal of Clinical Oncology

Phase I/II trial of durvalumab plus tremelimumab and stereotactic body radiotherapy for metastatic head and neck carcinoma: Final results.

Jan 2021

- SBRT sandwiched between cycles of D and T in oligometastatic HNSCC
- D (1500 mg) and T (75 mg) were given for 4 monthly cycles, followed by D for 8 monthly cycles.
- SBRT to 2-5 lesions was administered during cycle 2. Dose: 45 Gy/3-5 #
- Primary endpoint: Safety of TTC (Phase I) 6-month PFS (Phase II)
- 42% had Grade $\geq$ 3 AE attributable to D and T. One Grade $\geq$ 3 AE by SBRT
- 6 month PFS, was 69.7%, median OS was 25.1 months
- Conclusion: The addition of SBRT to dual-checkpoint inhibition led to 1 (3%) additional patient developing severe AE. Best response rates were encouraging. 6month PFS was attained and was higher than what was expected in this patient population

TABLE 2 Selected combination SBRT-immunotherapy clinical trials in head and neck cancer.

NCT ID	Title	Phase	Patients enrolled	HNSCC population	Number of SBRT fractions	Total SBRT dose	Sequence of treatments
NCT04576091	Testing the Addition of an Anti-cancer Drug, BAY 1895344, With RT to the Usual Pembrolizumab Treatment for Recurrent HN Cancer	1	37	Recurrent unresectable	3		IT on day 1 of 1st cycle, BAY1895344 starting day 7 of 1st cycle, SBRT starting day 2–8 of 2nd cycle
NCT03283605	IT and SBRT for Metastatic HN Carcinomas	1/2	45	Metastatic			SBRT after 2 cycles of IT
NCT03212469	A Trial of Durvalumab and Tremelimumab in Combination With SBRT in Patients With Metastatic Cancer	1/2	54	Metastatic			IT starting day 1, SBRT staring day 15
NCT04830267	The Efficacy of Camrelizumab Plus SBRT in R/M HNSCC	2	70	R/M	3	27 Gy	IT starting day 1, SBRT starting day 14
NCT02684253	Screening Trial of Nivolumab With Image Guided SBRT Versus Nivolumab Alone in Patients With Metastatic HNSCC	2	65	Metastatic	3	27 Gy	IT starting day 1, SBRT starting day 14
NCT03546582	SBRT ± Pembrolizumab in Patients With Local-Regionally Recurrent or Second Primary HN carcinoma	2	102	Recurrent or new second primary			SBRT for 2 weeks, followed by IT
NCT04862455	NBTXR3, Radiation Therapy, and Pembrolizumab for the Treatment of Recurrent or Metastatic HNSCC	2	60	R/M			Injection of NBTXR3 on day 1, SBRT with concurrent IT starting day 3–8
NCT05136768	Sintilimab Combined With Chemotherapy and SBRT in Limited Metastatic HNSCC	2	50	Limited metastatic			IT and chemotherapy starting day 1, SBRT starting after at least 2 cycles of IT and chemotherapy
NCT03313804	Priming Immunotherapy in Advanced Disease With Radiation	2	57	Metastatic		30 Gy	IT starting day 1, SBRT starting day 1–14
NCT03635164	RT With Durvalumab Prior to Surgical Resection for HPV Negative Squamous Cell Carcinoma	1	21	HPV negative resectable	2 (escalate to 3)	12 Gy (escalate to 18 Gy)	Neoadjuvant IT + SBRT, followed by surgery at 3–6 weeks after SBRT
NCT05053737	RT in Combination With Atezolizumab Prior to Surgical Resection for HPV Unrelated HNSCC	1/2	46	HPV negative	3	24 Gy	Neoadjuvant IT + SBRT, followed by surgery
NCT04938609	Neoadjuvant Immunoradiotherapy in HN Cancer (NIRT 2-HNC)	2	28	Stage III-IVa HPV negative	3	24 Gy	Neoadjuvant IT + SBRT, followed by surgery at week 7
NCT03618134	SBRT and Durvalumab With or Without Tremelimumab Before Surgery in Treating Participants With Human Papillomavirus Positive Oropharyngeal Squamous Cell Caner	1/2	82	HPV positive resectable oropharyngeal			Neoadjuvant IT + SBRT, followed by TORS and neck dissection between weeks 6–8

In Conclusion.....

cancers

October 2023

MDPI

Review

The Evolving Role of Stereotactic Body Radiation Therapy for Head and Neck Cancer: Where Do We Stand?

Issa Mohamad [1], Irene Karam [2], Ahmed El-Sehemy [3], Ibrahim Abu-Gheida [4,5], Akram Al-Ibraheem [6], Hossam AL-Assaf [7], Mohammed Aldehaim [8], Majed Alghamdi [9,10], Ibrahim Alotain [11], May Ashour [12], Ahmad Bushehri [13], Mostafa ElHaddad [14] and Ali Hosni [15,*]

Definitive SBRT for Primary HNC

Summary and Recommendation

There is limited evidence supporting the use of definitive SBRT for elderly or medically unfit HNC patients who cannot tolerate a standard long course of RT. A wide SBRT dose range was used (15 to 22 Gy in 1 fraction to 30 to 50 Gy in 5–6 fractions). Further studies are warranted to establish the optimal SBRT dose, fractionation, and criteria for selecting patients with primary HNC for definitive SBRT.

Definitive SBRT for Early-Stage Glottis Cancer

Summary and Recommendation

Two phase I trials evaluated SBRT for early glottis cancer and showed the development of pre-defined dose limiting toxicities. An ongoing phase II trial is evaluating the potential use of risk-adaptive SBRT dose selection in the setting of SBRT for early glottis cancer. SBRT twice a week for T1/T2 lesions is an interesting option, acknowledging the risk of severe late toxicity, including chondronecrosis, which may be dependent on pre-existing infiltration of the laryngeal framework.

Definitive SBRT as Boost after EBRT (Alternative to Brachytherapy Boost)

Summary and Recommendation

Despite an acceptable oncologic outcome of SBRT boost after EBRT for HNC, severe treatment-related toxicities have been reported. As such, the use of SBRT boost for HNC as an alternative to brachytherapy boost is recommended only in the investigational setting.

Neoadjuvant SBRT (with Immunotherapy) for HNC

Summary and Recommendation

Neoadjuvant SBRT with immunotherapy is a safe treatment for locoregionally advanced HNSCC, potentially resulting in relatively high rates of mPR with subsequent favorable outcomes. The commonly used SBRT regimen in the neoadjuvant setting is 24 Gy/3 fractions and 25–40 Gy in 5 fractions. Omitting elective nodal irradiation during neoadjuvant SBRT has a higher risk of regional nodal recurrence even in favorable HPV-related OPC despite the use of immunotherapy. Futures studies are warranted to further confirm the efficacy of this strategy [60–63].

Salvage SBRT for Recurrent Unresectable or Second Primary HNC

Summary and Recommendation

Salvage SBRT for recurrent (or 2nd primary) HNC in previously irradiated volume showed acceptable survival (Table 4) [17,64,65,71]. Rate of carotid blowout is relatively low with appropriate patient selection, target volume definition, and every-other-day treatment delivery. However, differences in patient selection criteria, tumor histology, and salvage SBRT doses make direct comparisons challenging. Therefore, a large, multi-institutional trial for re-irradiation using SBRT is warranted.

THANK YOU

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