Constraints and toxicity in non-conventional fractionations

Head and Neck cancer: innovation and compliance

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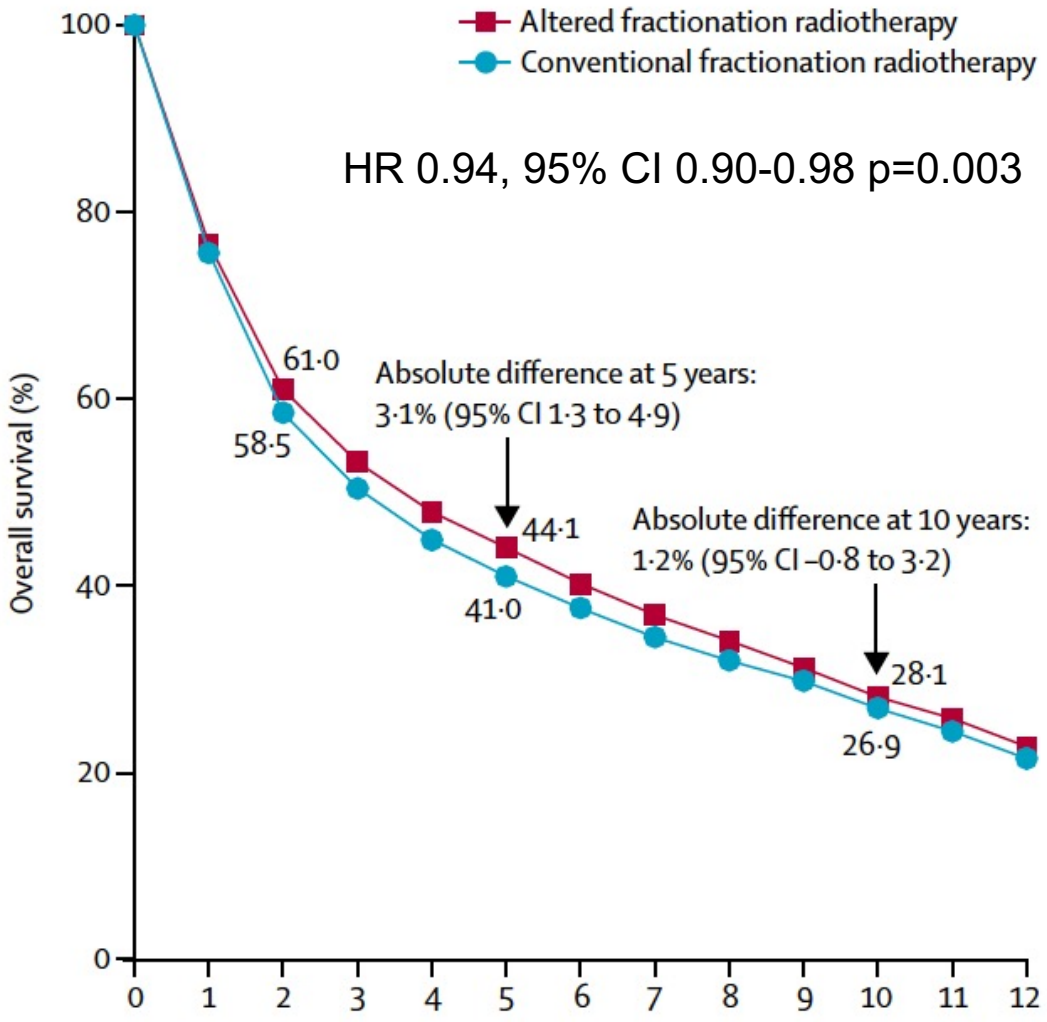
Disclosures

- Merck Serono
- Merck Sharp & Dhome
- Bristol-Myers Squibb
- Angelini Pharma

The ground truth: MARCH & MACH-NC meta-analyses



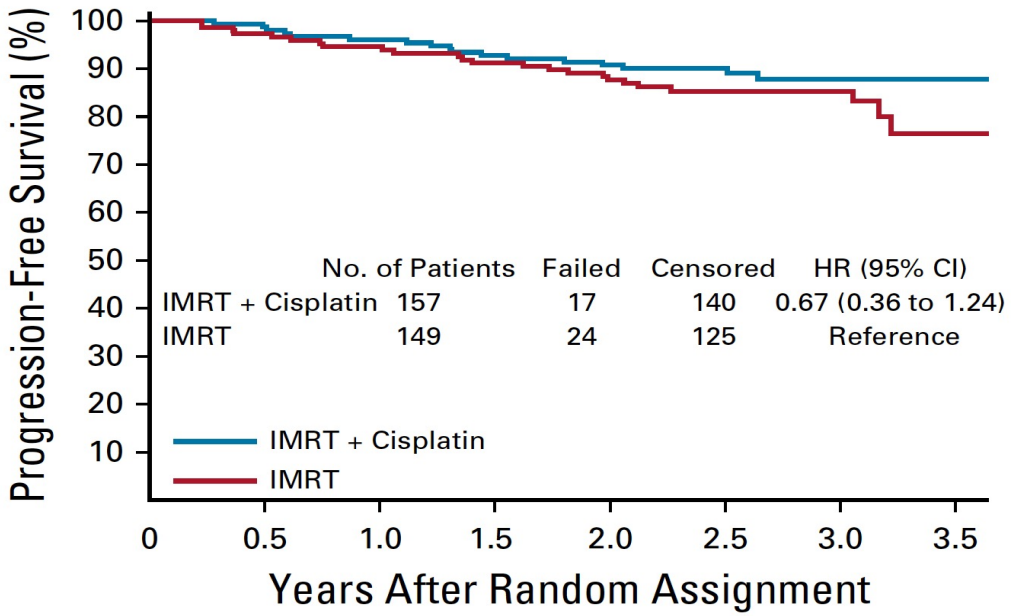
	Overall survival
Randomised controlled trials	115
Comparisons	154
Patients	28 978
Events	19 253
Gobal p value	0·074
p value for heterogeneity	0·013
p value for inconsistency	0·91
Hazard ratio (95% CI); P score (%)	
Locoregional therapy	1 (ref); 21%
HFCRT	0·63 (0·51–0·77)
IC_{TaxPF}-LRT	0·69 (0·56–0·85)
ACRT	0·75 (0·66–0·85)

- 33 trials; 11423 patients (>2.5 Gy/fx not included)
- Hyperfractionated RT + concomitant CT (**HFCRT**): ranked as best treatment

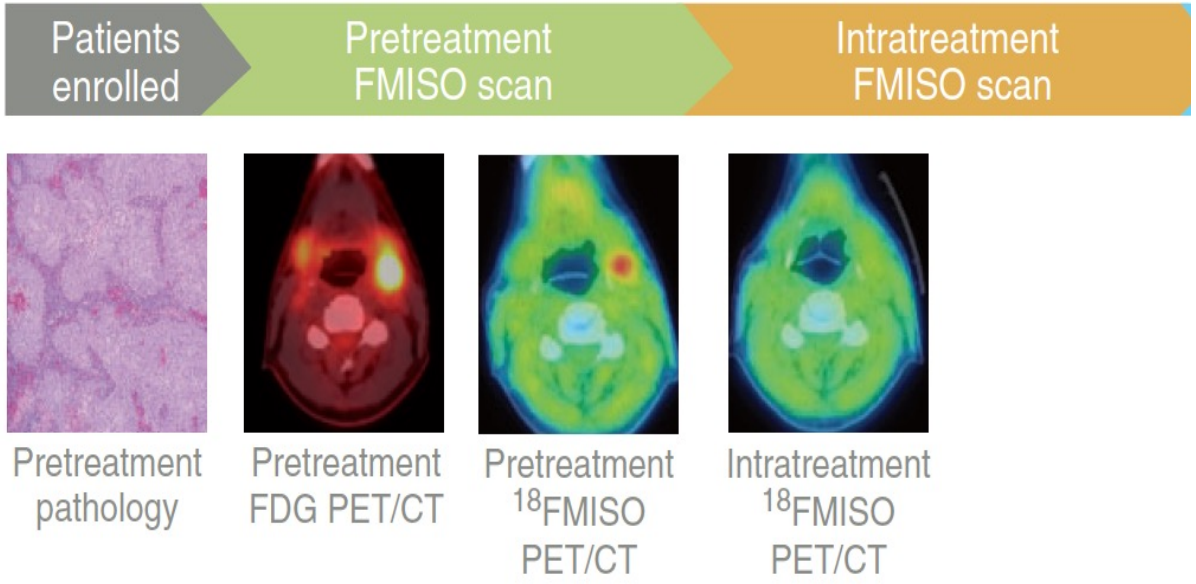
Lacas B, Lancet Oncol 2017
Petit C, Lancet Oncol 2021

Innovation in HNC: playing with total dose, rather than fractionation!

NRG HN002 rdm phase 2 trial



30 ROC pilot trial



- 60 Gy + C: 2-y PFS, 90.5%; 1-y mean MDADI CS, 85.3
- 60 Gy alone: 2-y PFS, 87.6%; 1-y mean MDADI CS, 81.7

Som Y, J Clin Oncol 2021

- 30 Gy + C: 2-year PFS, 92.9%
- No G3 toxicity

Riaz N, J Natl Cancer Inst 2020

Widespread adoption of evidence-based hypofractionation

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Long-Term Results of a Phase II, Randomized

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

JAMA Oncology | Original

Safety ted With Ablative Stereotactic igometastatic Cancer lysis

What about head and neck cancer?

Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study

FRACTIONATION AND CHANGES IN PATIENT CARE

Breast, Prostate, and Rectal Cancer: Should 5-5-5 Be a New Standard of Care?

Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial

Ost P, J Clin Oncol 2018; Gomez DR, J Clin Oncol 2019; Palma DA, Lancet 2019; Lehrer EJ, Jama Oncol 2020; Ling DC, Int J Radiat Oncol Biol Phys 2020; Chalkidou A, Lancet Oncol 2021; Tang C, Lancet Oncol 2021

Non-conventional fractionations in HNSCC

- Are there any opportunities for clinical use?
- Are there any constraints for clinical use?
- Future perspectives

Hypofractionation in HNSCC

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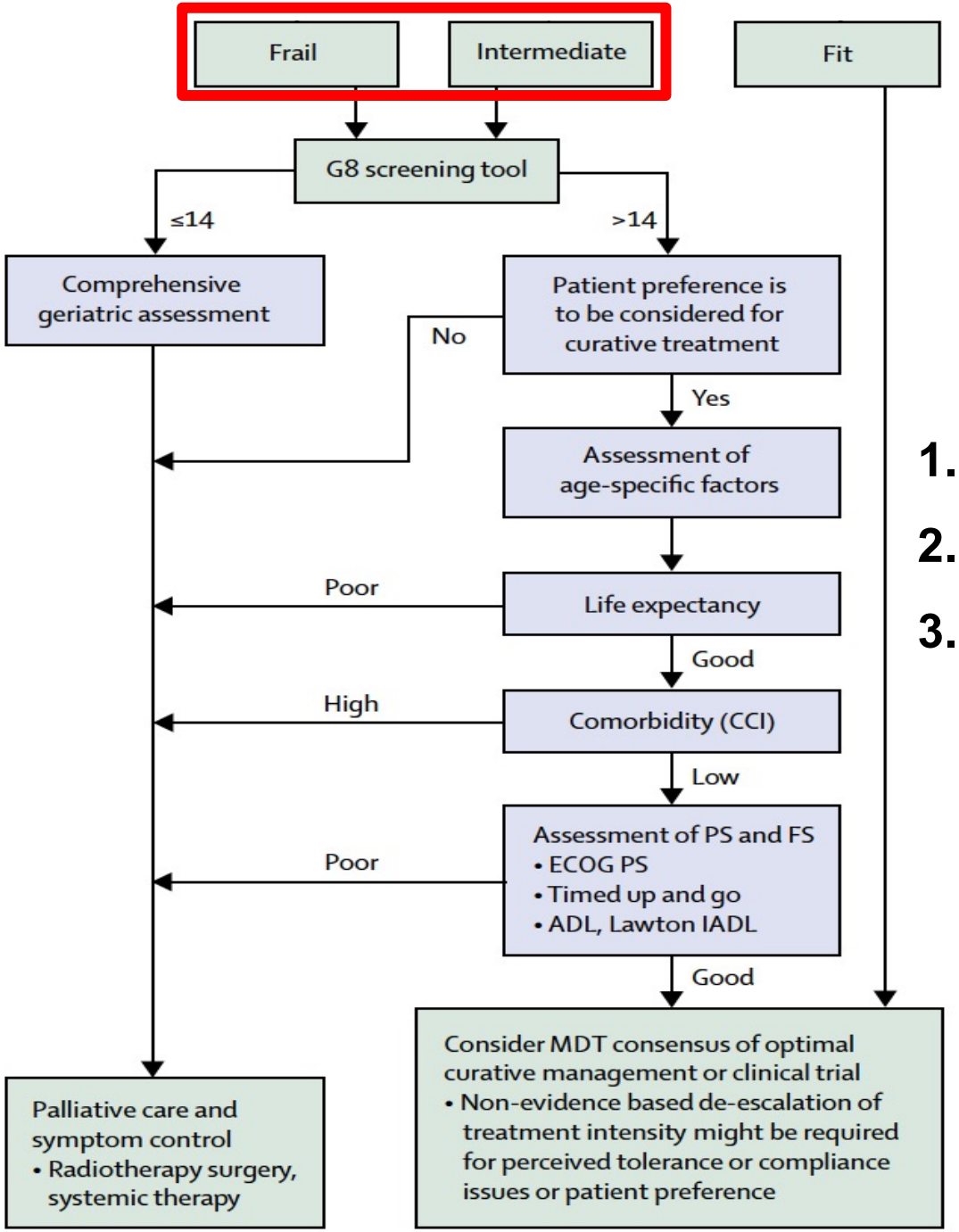
Are we ignoring the elephant in the room?

- HNSCC: predominantly, a disease of the elderly
  - peak incidence in the sixth decade of life[1]
  - HPV epidemic: shift in the burden to ≥65-year old patients[2]
- Less to gain from treatment intensification
  - decreasing benefit of altered fx and concomitant cht with increasing age[3]
- 70 Gy is our immutable paradigm: what about other options?
  - scarce evidence on SBRT as primary treatment[4]
  - large heterogeneity in hypofractionated regimens and patient selection[5,6]

[1]Pullte D, Oncologist 2010; [2]Tota JE, J Clin Oncol 2019; [3]Porceddu SV, Lancet Oncol 2017; [4]Iqbal MS, Br J Radiol 2021; [5]Iqbal MS, Radiother Oncol 2018; [6]Desideri I, Oral Oncol 2021



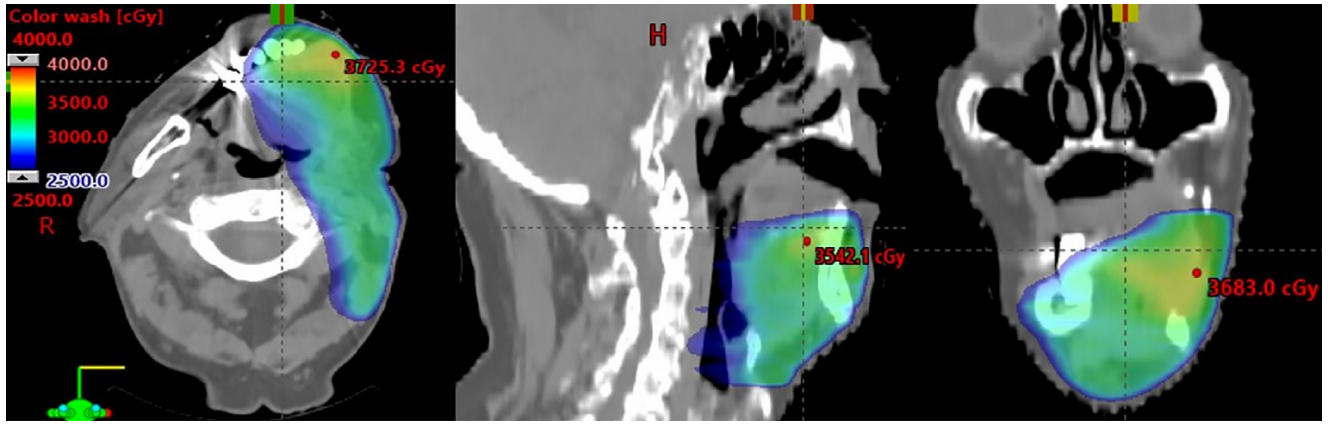
Wishlist

1. **to distinguish the frail from the vulnerable**
2. **to distinguish palliation from prolonged local control**
3. **to define standardized regimens for the unfit elderly**

Porceddu SV, Lancet Oncol 2017

SBRT as a tool for de-intensification in the vulnerable?

- n=66 deemed unfit for definitive tx
- median age, 70 years; median KPS, 70
- median G8 score: 10 (“vulnerable”)
- SBRT in 5 fractions
  - 35-40 Gy to GTV
  - 30 Gy to CTV



OAR	Constraint
PTV	*D* 95% = 98-100%
Larynx	Mean dose < 15 Gy
Mandible	Max dose[a] < 20 Gy
Cochlea	Mean dose < 15 Gy
Retina	Mean dose < 15 Gy
Lens	Max dose[a] < 5 Gy
Carotid artery	Max dose[a] < 32.5 Gy
Optic nerve/chiasm	Max dose[a] < 25 Gy
Temporal tips	Mean dose < 5 Gy
Skin	*D* (10 cc) < 39.5 Gy
Thyroid lamina	Max dose[a] < 30 Gy

- 1-year local control: 73%
- median time to local failure: 28.3 months
- ≥G3 toxicity: 3% (2/66 patients)

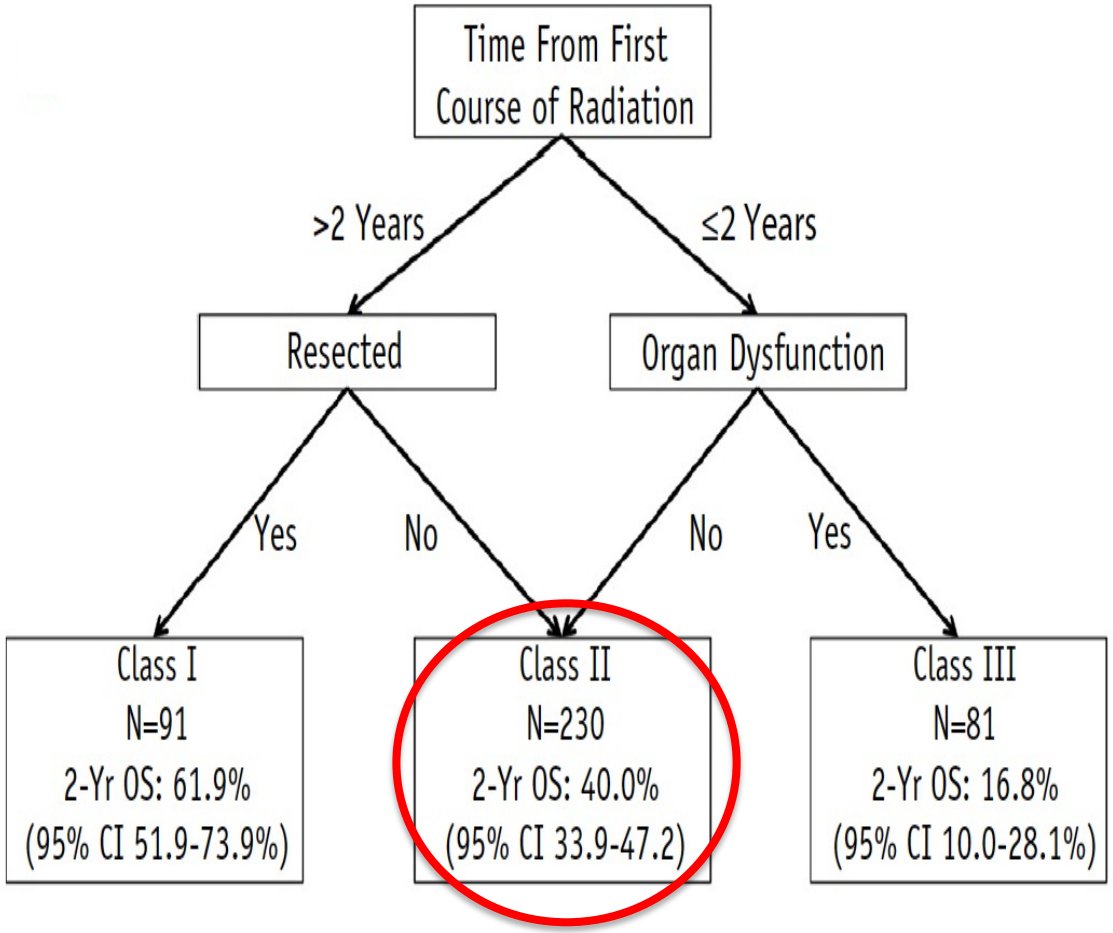
Gogineni E, Head Neck 2020

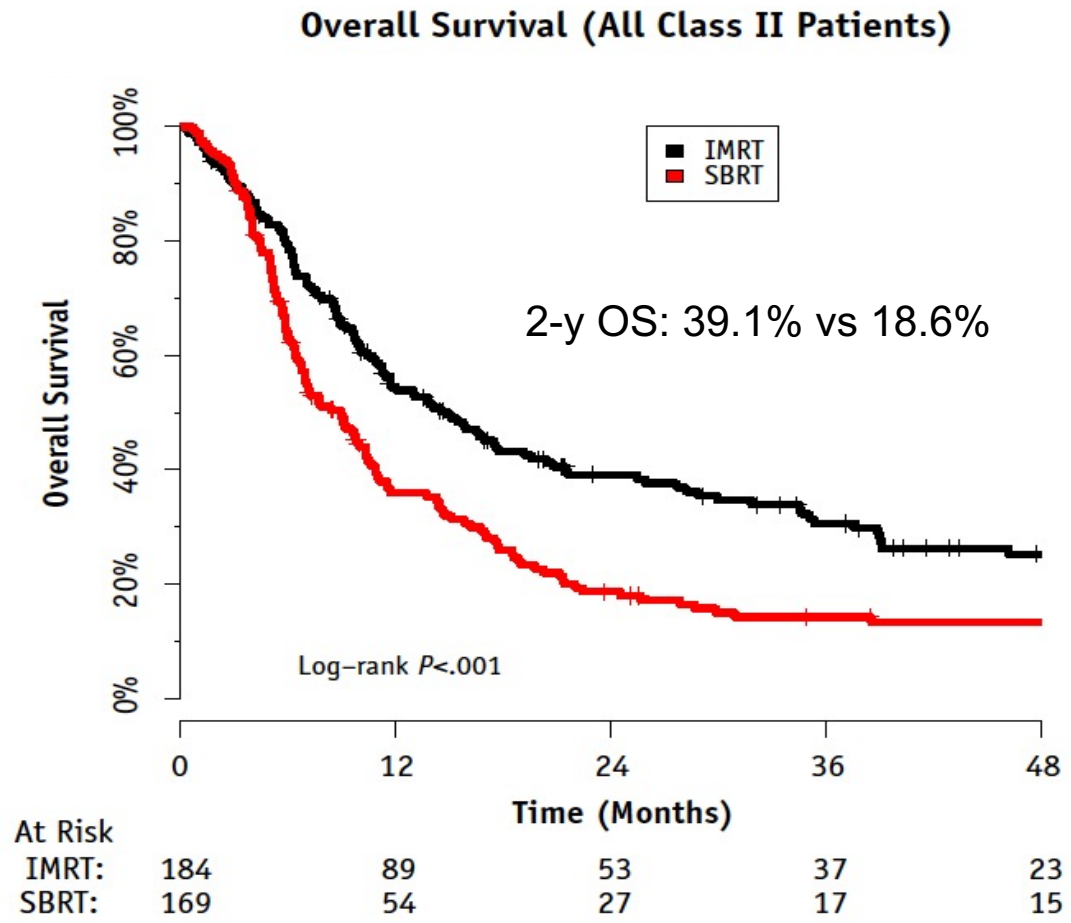
The burden of unresectable recurrence

- Uncontrolled loco-regional tumor growth
  - cause of death and major QoL impairment for many patients
- Salvage surgery: feasible in ≤ 1/3 of recurrent patients[1,2]
  - high rate of complications (≥25%), high rate of 2nd relapse (≈50%)
- Re-irradiation: only other treatment with curative potential
  - lack of evidence to guide decision-making, extensive counseling mandatory[3]
  - Multi-Institution Reirradiation (MIRI) collaborative: largest modern series [4]
  - after re-RT, the risk of PD or death is 4 times the risk of ≥G3 late toxicity[5]

[1]Goodwin WJ, Laryngoscope 2000; [2]Mehanna H, J Laryngol Otol 2016; [3]Foster CC, Semin Radiat Oncol 2020; [4]Margalit DN, Int J Radiat Oncol Biol Phys 2018; [5]Ward MC, Oral Oncol 2019

Patient selection and re-irradiation modality

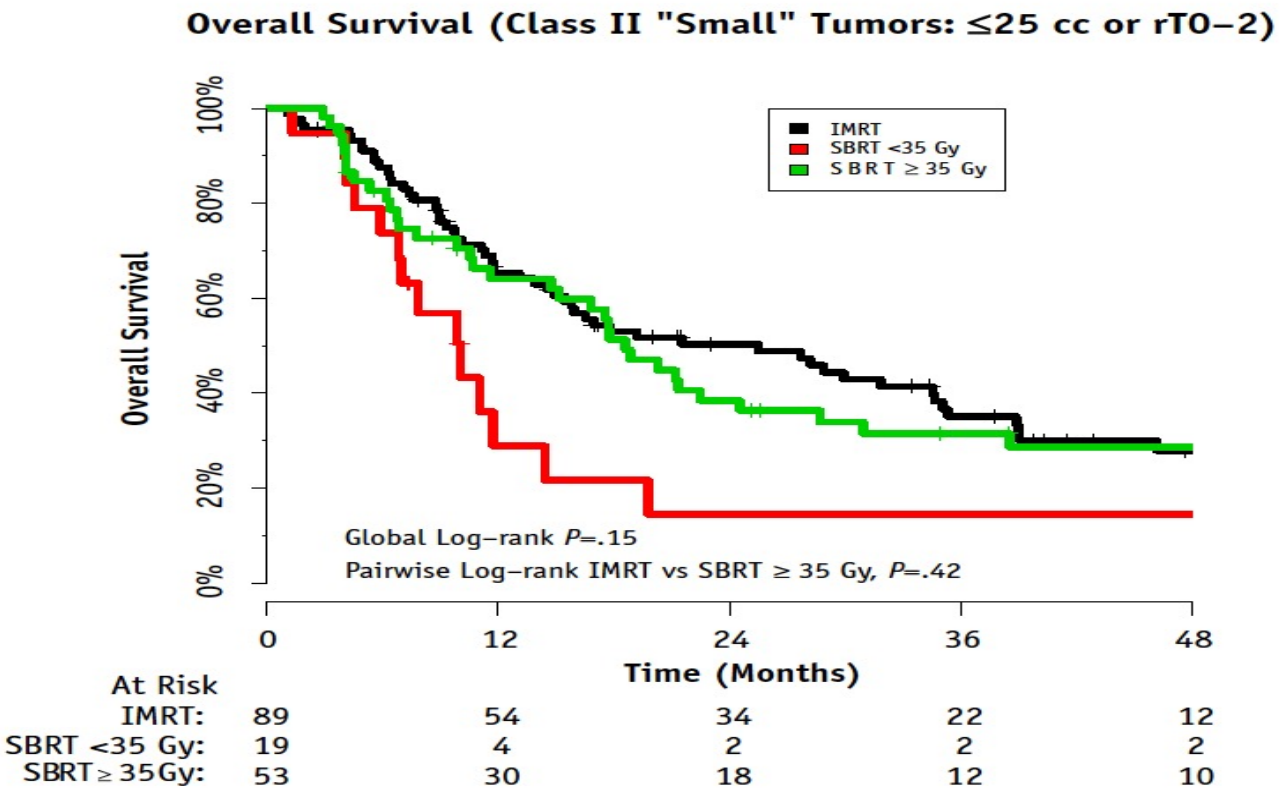


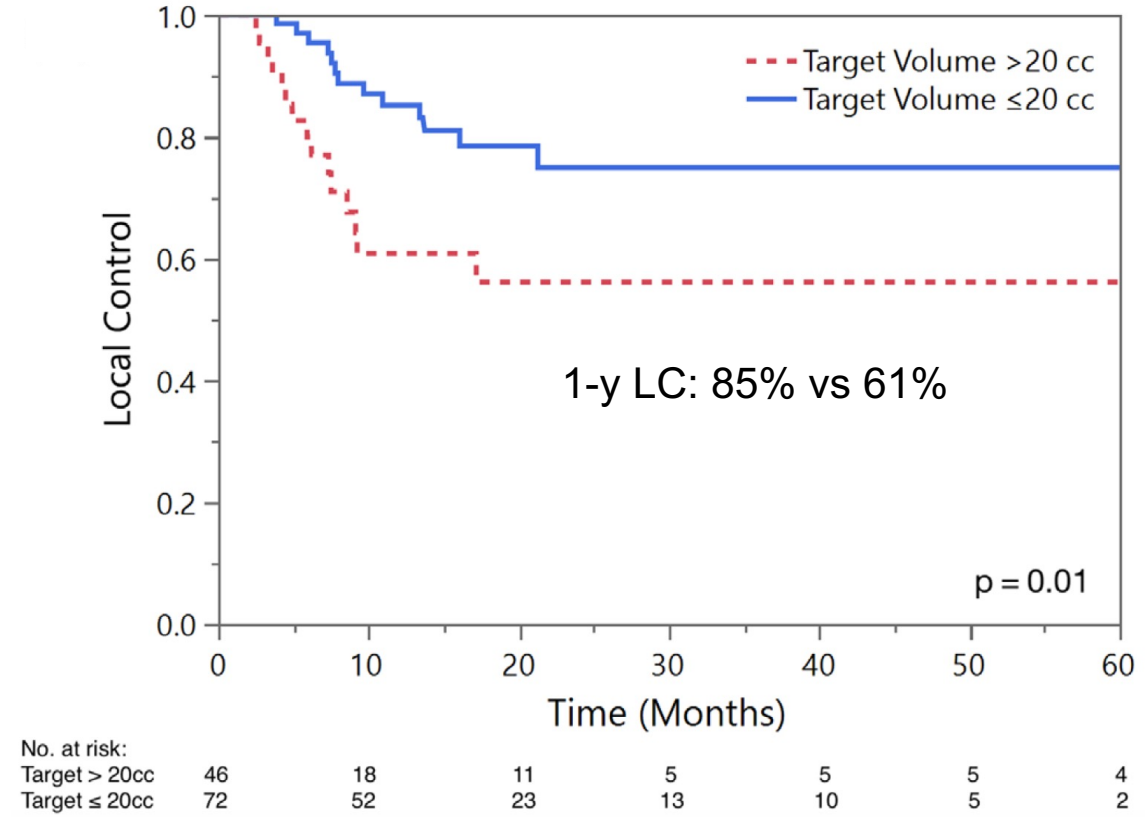


- Relapse/second primary tumor in ≥40 Gy field
- Median time interval from 1st radiation: 2.4 years

Ward MC, Int J Radiat Oncol Biol Phys 2018
Vargo JA, Int J Radiat Oncol Biol Phys 2018

SBRT as a tool for re-irradiation of low-volume disease?





- 2-year OS, IMRT vs SBRT ≥35 Gy: 50.3% vs 38.5% p=.42
- 2-year ≥G3 late toxicity: 12.4% vs 11.6% p=.69
- Treatment-related death: 1.8% vs 0.5% p=.42

- MDACC: n=137; median SBRT dose: 45 Gy

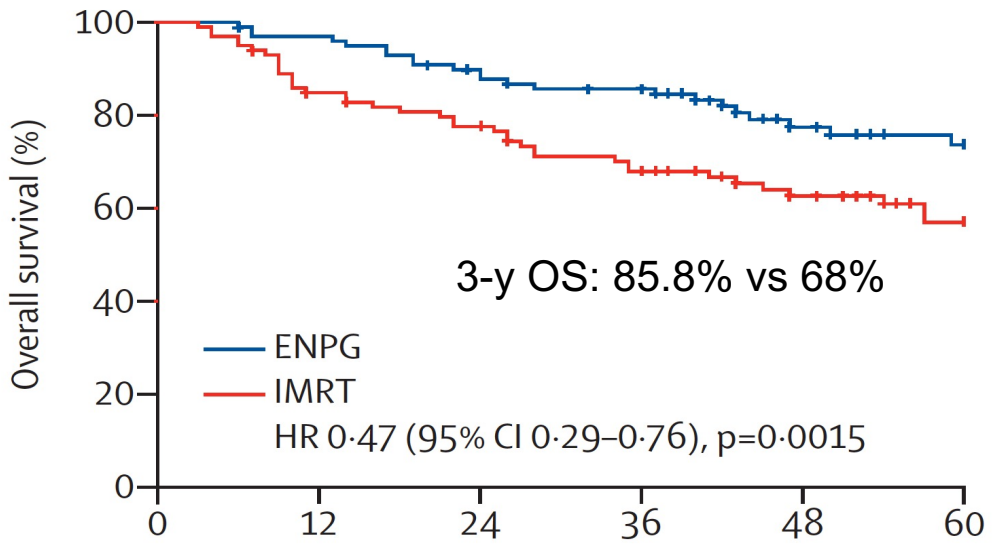
Vargo JA , Int J Radiat Oncol Biol Phys 2018
Diao K, Head Neck 2021

Locally recurrent nasopharyngeal cancer: randomized phase 3 trial

- n= 200 (recruitment: 09/11-06/17)

- Resectable local recurrence (TNM^{6th} ed.)
  - rT1 (nasopharynx cavity)
  - rT2a (post-naris/nasal septum)
  - rT2b (superficial PPS)
  - rT3 (base wall of sphenoid sinus)
  - ≥ 12-month disease-free interval

- 1:1 randomized to
  - endoscopic nasopharyngectomy (ENPG)
    or
  - IMRT re-irradiation
    (60-70 Gy in 27-35 fx, 2-2.36 Gy/fx)



- ≥G3 toxicity: 13% ENPG vs 37% IMRT
- Treatment-related death: 5% ENPG vs 20% IMRT

Liu YP, Lancet Oncol 2021

Hypofractionation in HNSCC

- Are there any opportunities for clinical use?
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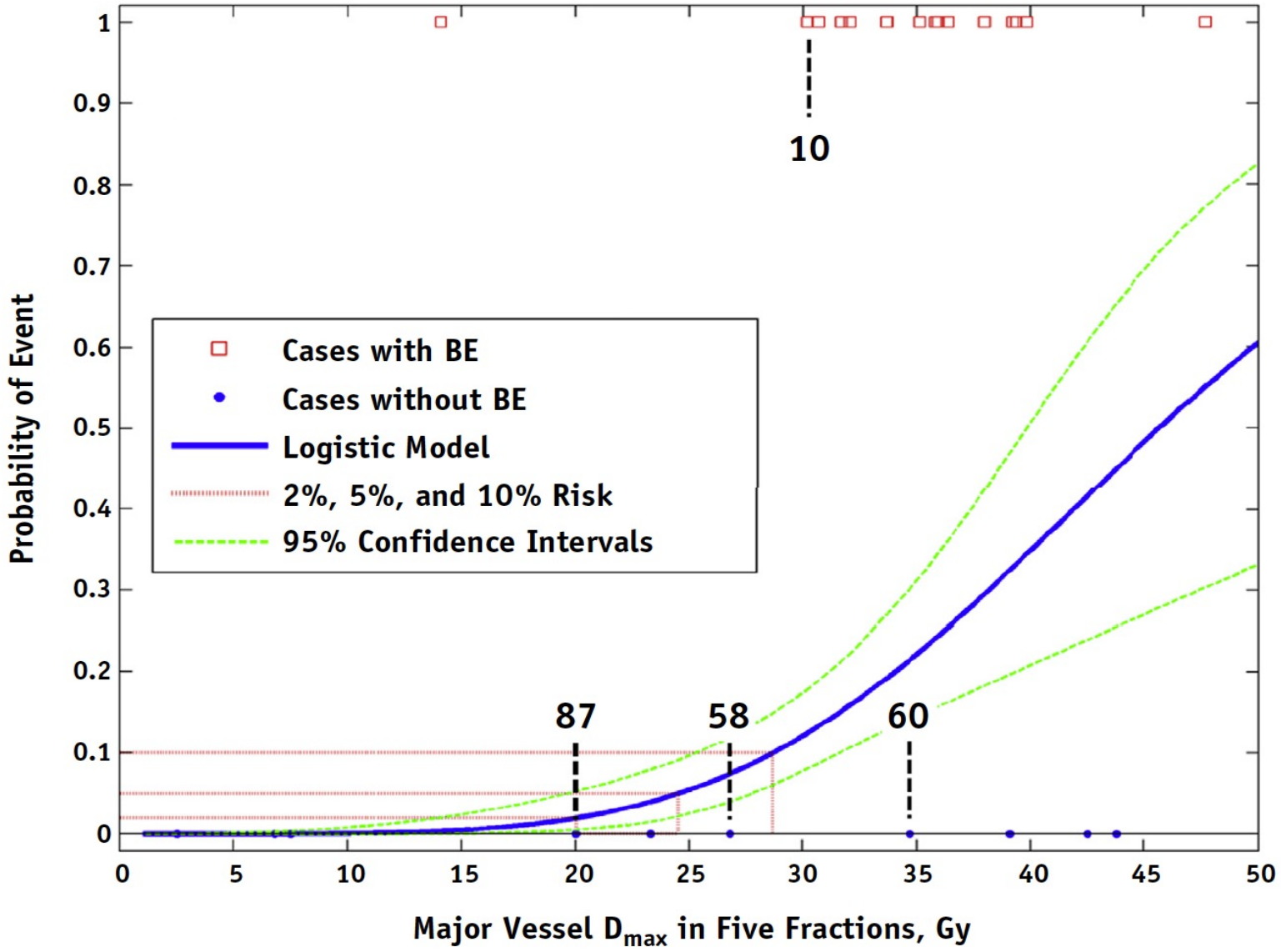
Dose tolerance of major vessels

- Carotid artery generally thought to have high tolerance to radiation
  - CTCAE ≥G3 bleeding event (BE): 1.3%-4.5% range in sys. review
  - RT-induced BE confounded by bleeding due to persistent/recurrent tumor
- Factors likely associated with lower risk of BE
  - extent of carotid encasement, no surgical manipulation before/after SBRT
  - no infection/necrosis at SBRT site, >6 month interval from prior RT
- HyTEC data pooling effort: no strong conclusions are possible
  - 238 major vessel maximum point doses from 6 articles

Grimm J, Int J Radiat Oncol Biol Phys 2021



- **Major vessels: keep D_{max} between 20 and 30 Gy**
- **Carotid artery $D_{0.5cc}$ < 20 Gy**

Grimm J, Int J Radiat Oncol Biol Phys 2021

Suggested constraints for 5-fraction stereotactic reRT

Table 3. Maximum cumulative BED and EQD_2 values (using an α/β ratio of 3Gy). These calculations are based on 65 Gy in 30daily fractions as a primary treatment and 35-40 Gy in 5 fractions as SBRTreirradiation.

			Primary treatment		Reirradiation			
Organ at Risk	DVH Parameter	α/β	Prescription dose (Gy)	Fractions	Constraint dose [Gy]	Fractions	Constraint BED [Gy3]	Constraint EQD2 [Gy3]
Carotid artery	Maximum dose	3	65.0	30	32.5	5	214.9	128.9
Lens	Maximum dose	3	10.0	30	5	5	17.8	10.7
Mandible	Maximum dose	3	65.0	30	20	5	158.6	95.2
Optic chiasm	Maximum dose	3	50.0	30	25	5	144.4	86.7
Optic nerves	Maximum dose	3	50.0	30	25	5	144.4	86.7
Larynx	Mean Dose	3	54.0	30	15	5	116.4	69.8
Cochlea	Mean Dose	3	45.0	30	15	5	97.5	58.5
Retina	Mean Dose	3	45.0	30	15	5	97.5	58.5
Temporal tips	Mean Dose	3	54.0	30	5	5	93.1	55.8
Skin	D10cc	3	65.0	30	39.5	5	255.5	153.3
Thyroid lamina	Maximum dose	3	65.0	30	30	5	201.9	121.2
Spinal cord								54.0
Brainstem								54.0

- Risk of ≥G3 laryngeal toxicity: 11.4% if D_{5cc} of 20 Gy

Iqbal MS, Br J Radiol 2021
Ling CD, J Radiosurg SBRT 2020

Suggested constraints for IMRT reRT in NPC

Table 2 Consensus recommendation on dose prioritization and acceptance criteria for radical reirradiation by IMRT/VMAT for recurrent nasopharyngeal cancer

Critical OAR	Priority			Reference tolerance dose for 1 course	Acceptance criteria (Cumulative dose of both primary and 2nd courses)*			
		Agree	Disagree		Desirable		Acceptable	
Organ	Priority	n/N (%)†	Alternative priority n (%)†		Cumulative dose (EQD2)	n/N (%)†	Cumulative dose (EQD2)	n/N (%)†
Brain stem	1	19/21 (90%)	2: 1 (5%) 3: 1 (5%)	D0.03 cc 54 Gy	≤70.2 Gy‡	24/24 (100%)	81 Gy‡	23/24 (96%)
Spinal cord	1	20/21 (95%)	3: 1 (5%)	D0.03 cc 45 Gy	≤58.5 Gy‡	24/24 (100%)	67.5 Gy‡	23/24 (96%)
Optic chiasma	1	23/24 (96%)	3: 1 (4%)	D0.03 cc 54 Gy	≤70.2 Gy‡	18/24 (75%)	81 Gy‡	18/24 (75%)
Optic nerve	Unilateral: 2 Bilateral: 1	11/19 (58%) 17/19 (89%)	1: 1 (5%) 3: 7 (37%) 2: 2 (11%)	D0.03 cc 54 Gy	≤70.2 Gy‡	24/24 (100%)	Unilateral: No dose constraint if patient accepts Bilateral: 81 Gy‡	19/20 (95%) 19/23 (83%)
Temporal lobes	2	13/17 (76%)	3: 4 (24%)	D0.03 cc 70 Gy	≤91 Gy‡	23/23 (100%)	105 Gy‡	23/23 (100%)
Carotid artery	3	15/19 (79%)	4: 2 (11%) Not specified: 1 (5%) No constraint: 1 (5%)	D0.03 cc 70 Gy	≤125 Gy§	16/24 (67%)	No constraint	15/23 (65%)

Ng WT, Int J Radiat Oncol Biol Phys 2021

Hypofractionation in HNSCC

- Are there any opportunities for clinical use?
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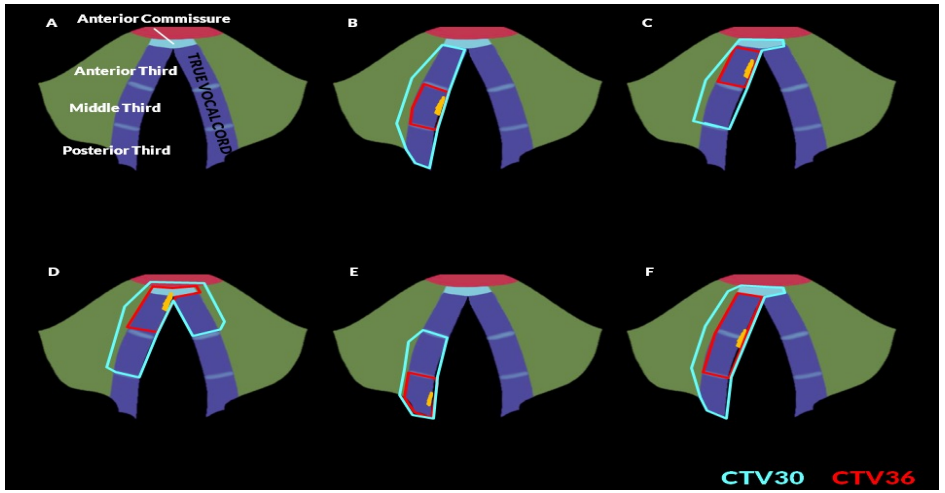
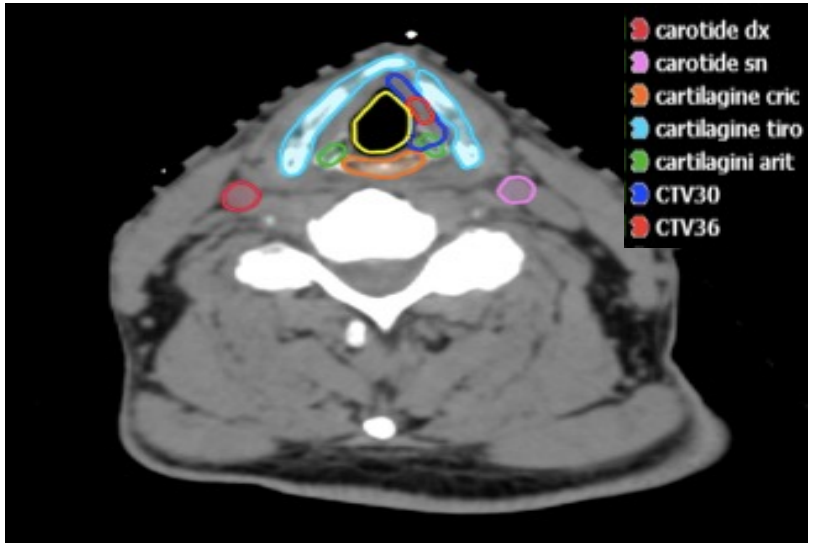
Exploring the role of SBRT for early stage glottic cancer

- Phase I/II study in T1a-T1b glottic cancer
- n=23 (01/17-08/20)
- True vocal cord (TVC) divided in thirds:
  - 36 Gy/3 fx to third(s) containing cancer
  - 30 Gy/3 fx to immediately adjacent parts
  - PTV: CTV + 3 mm (LL-AP), 5 mm (CC)
  - Thyroid, cricoid and ipsilateral arytenoid cartilages: Dmax 30 Gy to 0.1 cc





- A 3-fraction SBRT schedule is feasible
- Both acute toxicity and early functional results are promising

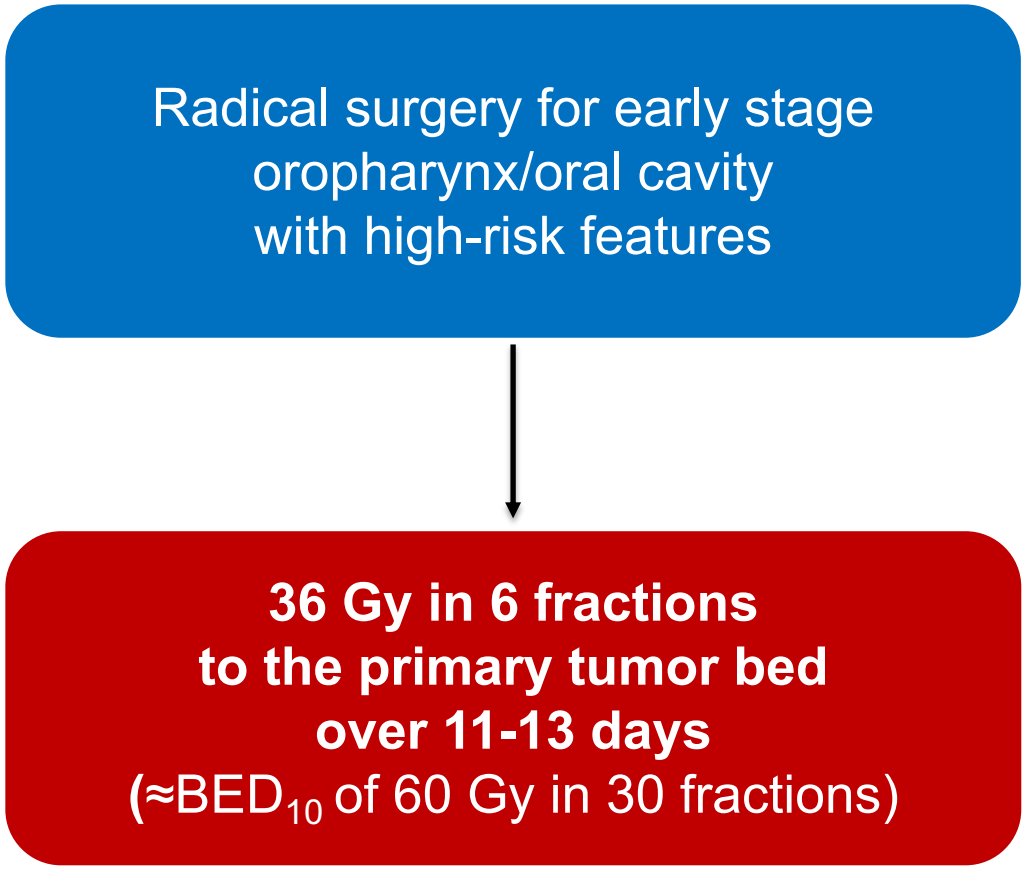
COURTESY OF GIUSEPPE SANGUINETI, IRCSS REGINA ELENA - ROME

GORTEC 2017-03 Stereo post-op phase II trial

- Open-label, single-arm phase II
- n=90 (study start: 01/18)

- pT1 or pT2 with at least one of
  - R1
  - close margin < 5 mm
  - pN0 or pN1 (no ENE)
  - PS ECOG ≤2

- **Primary endpoint:**
  - 2-year severe toxicity
    (≥G3 per CTCAE v.4.03)
    [Fleming's single stage model: reject a rate > 15%]

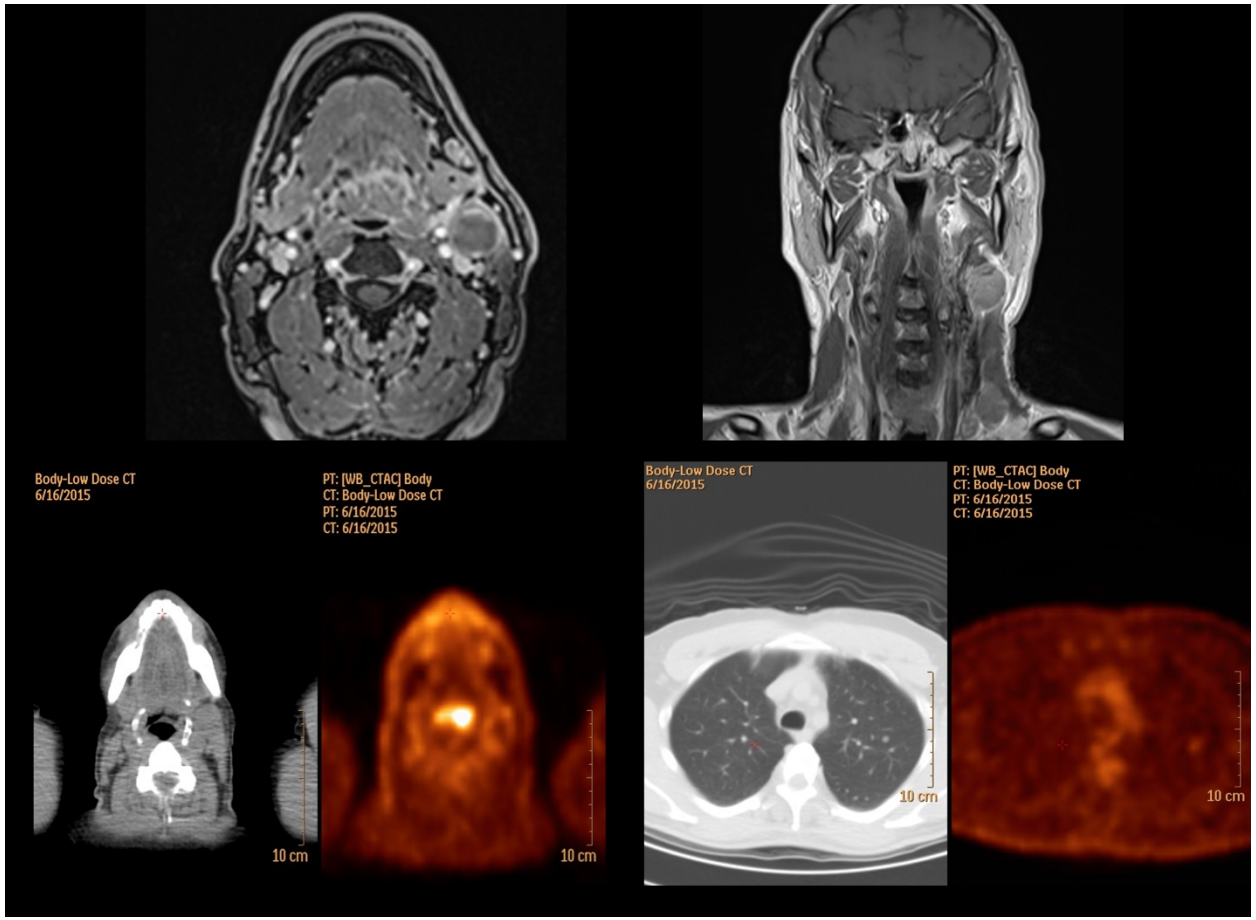


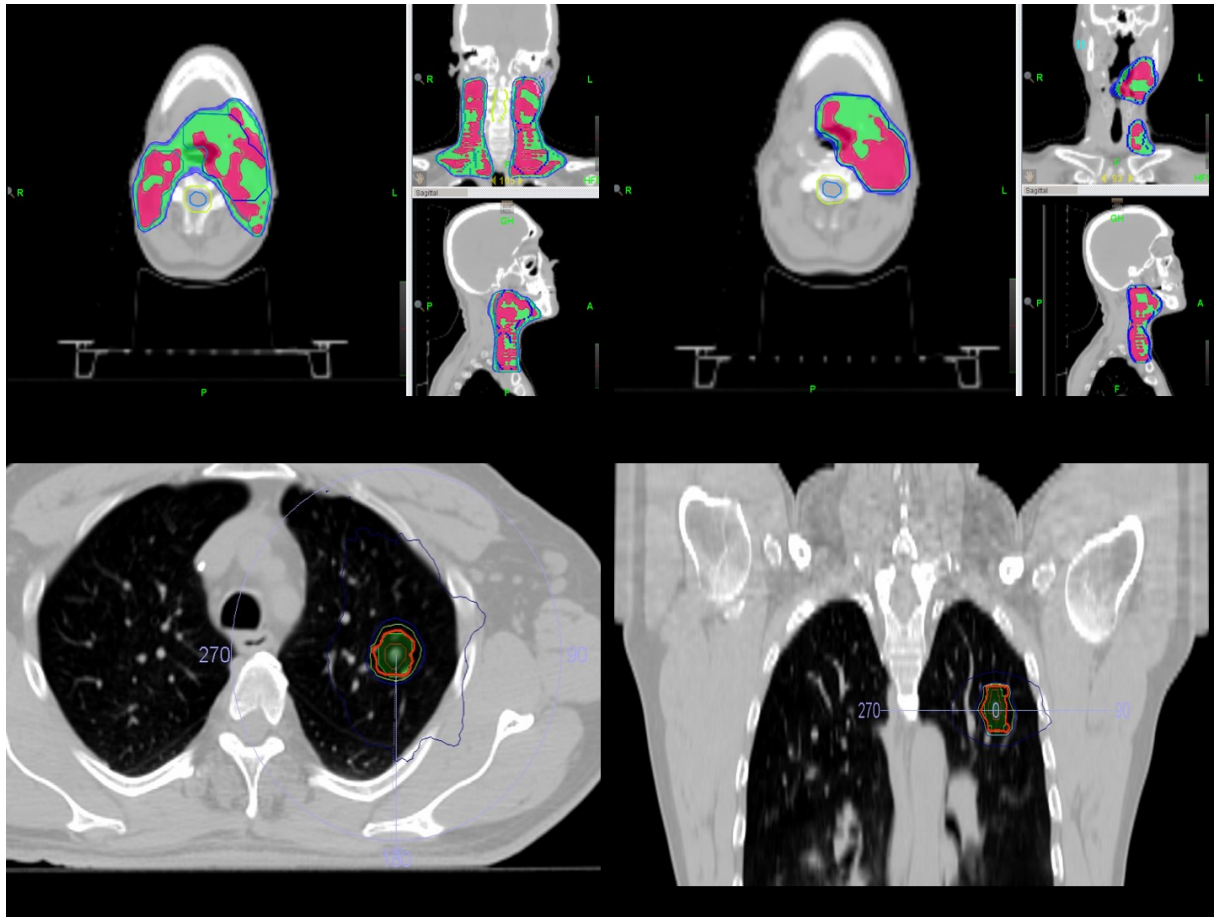
NCT03401840; primary completion date: 01/24

Biau J, BMC Cancer 2020

Oligometastatic HNSCC

- *Both base of tongue and upper left lobe nodule histologically-confirmed HPV positive: cT2N1M1*



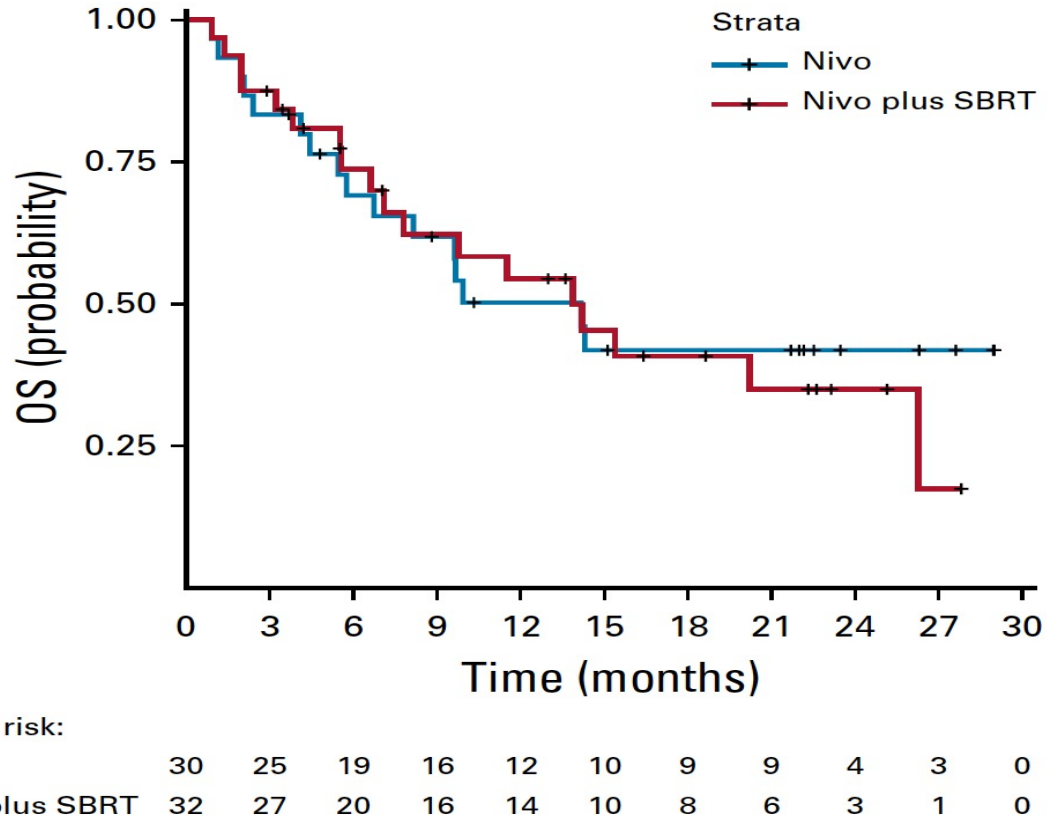


Sun XS, Future Oncol 2018; Bonomo P, Oral Oncol 2019; Bates JE, Head Neck 2019; Pasalic D, Head Neck 2020; Szturz P, Front Oncol 2020

Debunking the “urban myth” of abscopal effect in HNSCC

- n=62 with R/M HNSCC 1:1 randomized to
  - Nivolumab monotherapy or
  - Nivolumab + SBRT (9 x 3 Gy)

- Hypothesis: SBRT to boost anti-PD-1 efficacy through abscopal effect
- Primary endpoint: ORR



- No difference in ORR: 34.5% with Nivo (95% CI: 19.9-52.7) vs 29% with Nivo + SBRT (95% CI: 16.1-46.6) p=.86
- ≥G3 toxicity: 13.3% with Nivo vs 9.7% with Nivo + SBRT p=.70

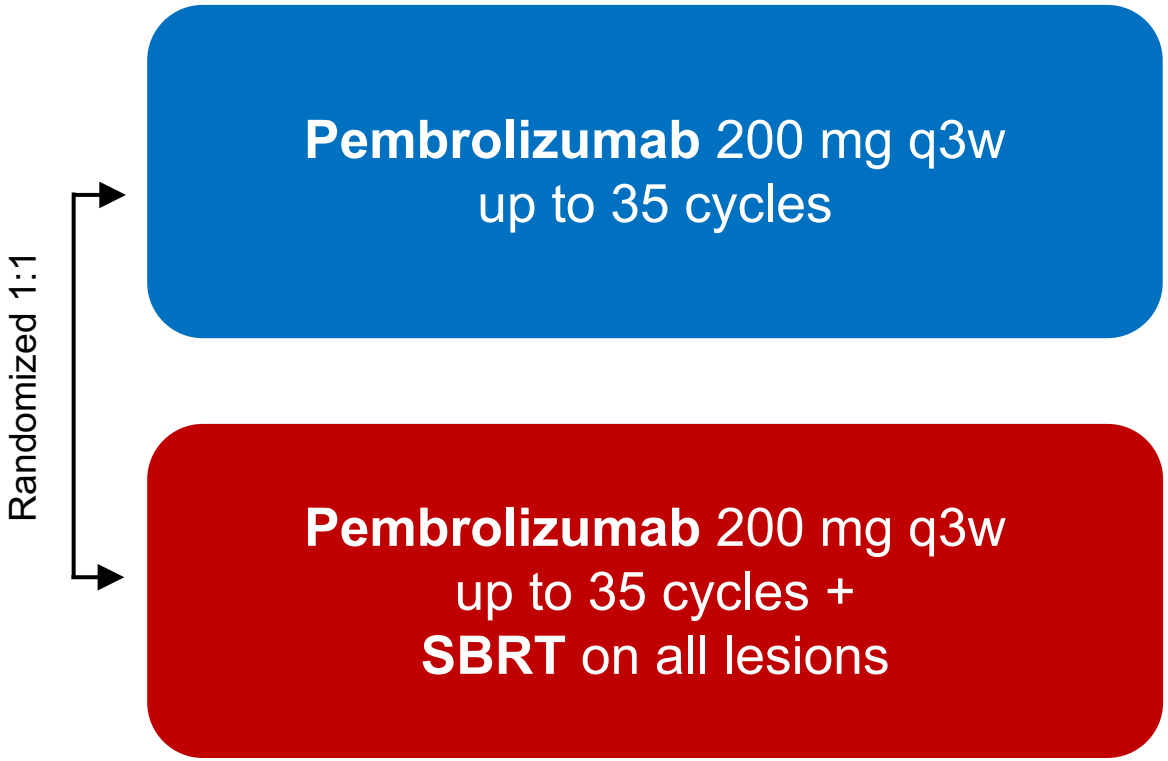
McBride S, J Clin Oncol 2020
Seiwert TY, J Clin Oncol 2020

EORTC 2014 PROLoNg randomized phase III trial

- n=200 (to be recruited in 2.5 years;
  20 sites across 4 countries)

- **Inclusion criteria**
  - Oligometastatic HNSCC (1-5 lesions)
  - PD-L1 CPS ≥1
  - Anti-PD 1 naive
- Stratified by
  - Metastatic disease at presentation
  - HPV status
  - PD-L1 CPS (<20 vs ≥20)

- **Primary endpoint:**
  - PFS



COURTESY OF PANAGIOTIS BALERMPAS, ZURICH

Stereotactic re-irradiation + immune checkpoint inhibition

Study, institution	Year	# of patients	Median SBRT dose (Gy)	Fraction and interval	Median OS (months)	Median PFS (months)	Late G3+ toxicity (%)
Diao et al., MDACC	2021	137	45	5 fx QOD	44.3	11.8	15
Vargo et al.,[17] multi-institutional	2018	414 (197 SBRT)	40	5 fx QOD	7.8		11.6
Kress et al.,[33] Georgetown	2015	85	30	5 fx daily	8.6	8.6	5.9
Vargo et al.,[39] Pittsburgh	2014	132	44	5 fx QOD	7		7
Lartigau et al.,[34] France	2013	60	36	6 fx QOD	11.8	7.1	7
Cengiz et al.,[35] Turkey	2011	46	30	5 fx daily	11.9	10.5	24.4
Roh et al.,[36] Korea	2009	36	30	3–5 fx daily	16.2		8
Siddiqui et al.,[37] Henry Ford	2009	21 recurrent	36	6 fx QOD	6.7		24

Safety of reRT with SBRT plus concurrent and adjuvant pembrolizumab in patients with recurrent or new second primary head and neck squamous cell cancer in a previously irradiated field: RTOG 3507 Foundation (KEYSTROKE)

NCT03401840; primary completion date: 01/24

Diao K, Head Neck 2021

Summary

- Non-conventional treatments in HNSCC: a word of caution
  - elective nodal irradiation is established standard of care
  - meaningful benefit to be meticulously assessed in controlled trials
- An optimistic outlook on the multifaceted landscape of HNSCC
  - cross-fertilization of technological advancements and clinical opportunities
  - promising role of particle therapy
- Proper patient selection & expertise remain crucial issues of care

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