TESTA COLLO
RE-IRRADIAZIONE
STEREOTASSICA

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IEO
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Arc

LOCAL AND/OR REGIONAL RECURRENCE 93%

TREATMENT OPTIONS:

- **SURGERY**
- **RE-IRRADIATION**
- **CHEMOTHERAPY**
- **BEST SUPPORTIVE CARE**

Kress M.A.S et al Head and Neck 2014
Yamazaki et al Radiother Oncol 2011
Strojan P et al Head and Neck 2014

HEAD AND NECK CANCER
RE-IRRADIATION

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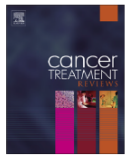

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Jon Caci
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Eur Arch Otorhinolaryngol (2014) 271:3107–3109
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EDITORIAL

When is re-irradiation in head and neck squamous cell carcinoma not indicated?

Primož Strojan · Jonath
William M. Mendenhall
Robert P. Takes · Alfio

CLINICAL REVIEW

David W. Eisele, MD, *Section Editor*

Recurrent and second primary squamous cell carcinoma of the head and neck: When and how to reirradiate

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HEAD AND NECK CANCER
RE-IRRADIATION

WHY
- SYMPTOMATIC (pain, bleeding)
- « CURATIVE»

WHEN
- UP FRONT
- AFTER SURGERY

HOW
- TECHNIQUE
- DOSE
- CONCOMITANT CT

HEAD AND NECK CANCER
RE-IRRADIATION

UNRESECTABLE DISEASE

CONVENTIONAL TECHNIQUE

- Studio GORTEC 98-03 Re- RT + CT vs CT Randomized phase III trial
  prematurely closed
- RTOG 04-21 Re-RT+ CT vs CT Randomized phase III trial
  prematurely closed

- RTOG 9610 phase II trial re-RT (1.5 bid for 4 weeks) + Hydroxyurea/5FU
  6 treatment-related deaths (7.6%), late grade ¾ toxicity at 2 and 5 yrs was 9.4%

- RTOG 9911 (200-2003) same re-RT protocol than RTOG 9610 + CDDP/Paclitaxel + GCSF
  Treatment related death 8%, Grade ¾ late adverse effect 33.8%.

Strojan P Head and Neck 2014

HEAD AND NECK CANCER
RE-IRRADIATION

UNRESECTABLE DISEASE

Conventional Technique

- OS 10-30% at 2 years.
- Late toxicity grade ¾ may occur up to 40%
- Treatment related deaths up to 10%
- Results of Surgery +/- re-PORT are better compared re-RT alone because earlier stage tumor and better patients performance status.

Strojan P Head and Neck 2014

FACTORS RELATED TO THE PATIENT

PS	Good PS > Poor PS	(Shaefer 2000, Ho 2014)
Age	Young Patients > Old Patients (60 ys)	(Shaefer 2000)
Co-morbidity	Few/None > A lot Charlson Index and Adult Comorbidity Evaluation-27 (ACE-27)	(Tanvetyanon 2009)
Organ dysfunction	Presence < Absence (Enteral nutrition, tracheotomy, soft tissue damage, radionecrosis)	(Tanvetyanon 2009)

FACTORS RELATED TO THE TUMOR

Tumour Site	Larynx,Nasopharynx > Others Hypopharynx < Others T. lateral > T. on median line	(Mendenhall 2008, Duprez 2009, Unger 2010, Ho 2014)
Hystology	Salivary gland > SCC	(Lee 2007, Davie 2014, Unger 2011)
T-Stage	rT1-rT2 > rT3-rT4	(Duprez 2009, Tanvetyanon 2009)
Volume	Small(< 25cm^3,30cc)> Extended (>60cc)	(Tanvetyanon 2009, Rwigema 2011)
Second tumour	Second primary > Local Rec.	(Kasperts 2005)

FACTORS RELATED TO THE TREATMENT

Primary treament	**Surgery plus RT > RT alone**	(Benchalal 1995, Levendag 1992)
Dose at Re-RT	**High dose > Lower dose** **>36 Gy for SBRT**	(Salama 2006, Platteaux 2010, Shaefer 2000, Lee 2007, Sulman 2009, Tanvetyanon 2009, Hungar 2010, Rwigema 2011)
RT technique	**IMRT > no IMRT** **3D vs robotic SBRT for NPC**	(Lee 2007, Ozygit 2011)
Surgery	**Operable > Inoperable**	Biaglioli 2007, Salama 2006, Platteaux 2010, Lee 2007, Duprez 2009, Unger 2010, Unger 2010)
Time Interval	**Long (≥1yrs) > Short**	Duprez 2009, Sulman 2009, Tanvetyanon 2009)
N. of LR before RT	**More than one > 1°**	(Lee 2007)
Response to re-RT	**Complete > Partial**	(Schaefer 2007, Biaglioli 2007)
Previous CT	**Worse results**	(Choe 2011,Nagar2004)

HEAD AND NECK CANCER
RE-IRRADIATION

HPV STATUS

OROPHARYNGEAL TUMOR (30 pts)
SBRT (40-50 Gy in 5 fr alternating day) + CETUXIMAB

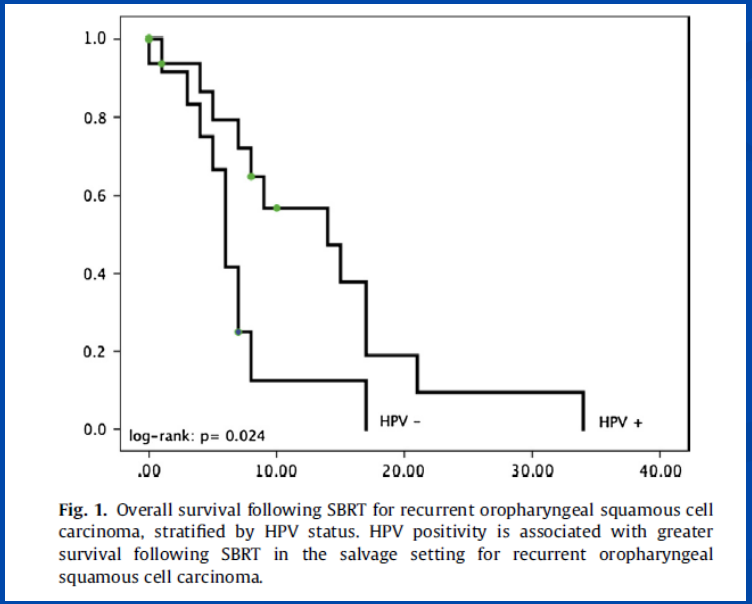


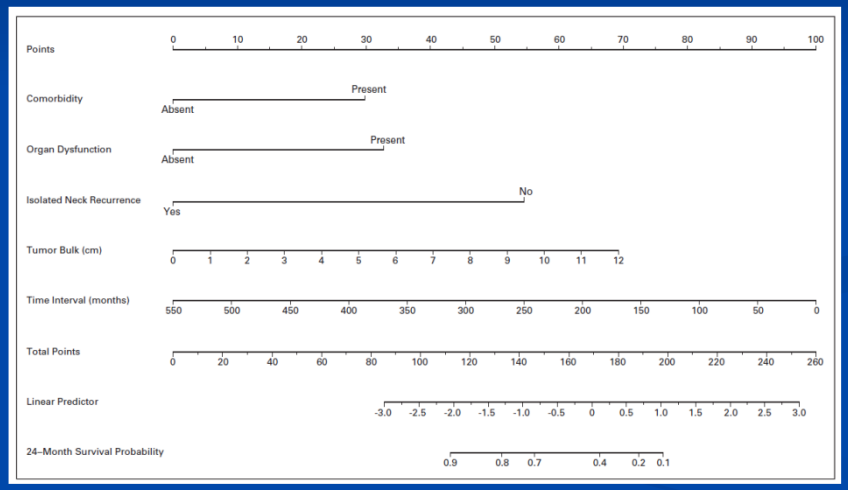
Fig. 1. Overall survival following SBRT for recurrent oropharyngeal squamous cell carcinoma, stratified by HPV status. HPV positivity is associated with greater survival following SBRT in the salvage setting for recurrent oropharyngeal squamous cell carcinoma.

Davis KS et al Oral Oncol 2014

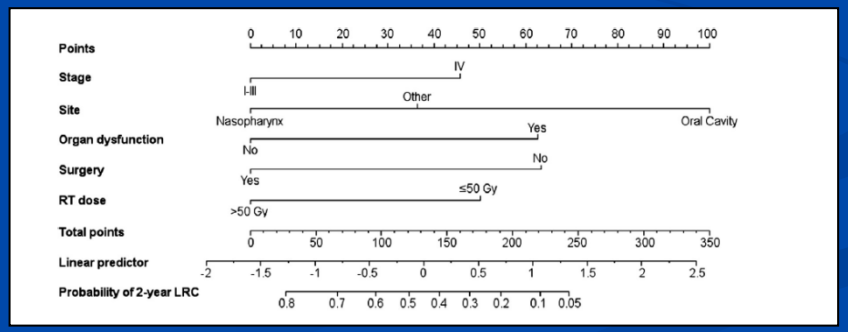
HEAD AND NECK CANCER
RE-IRRADIATION

NOMOGRAMS FOR FRACTIONATED re-RT

TO PREDICT OS



TO PREDICT LRC



TanvetyanonJCO 2009
Shikama jpn JCO 201

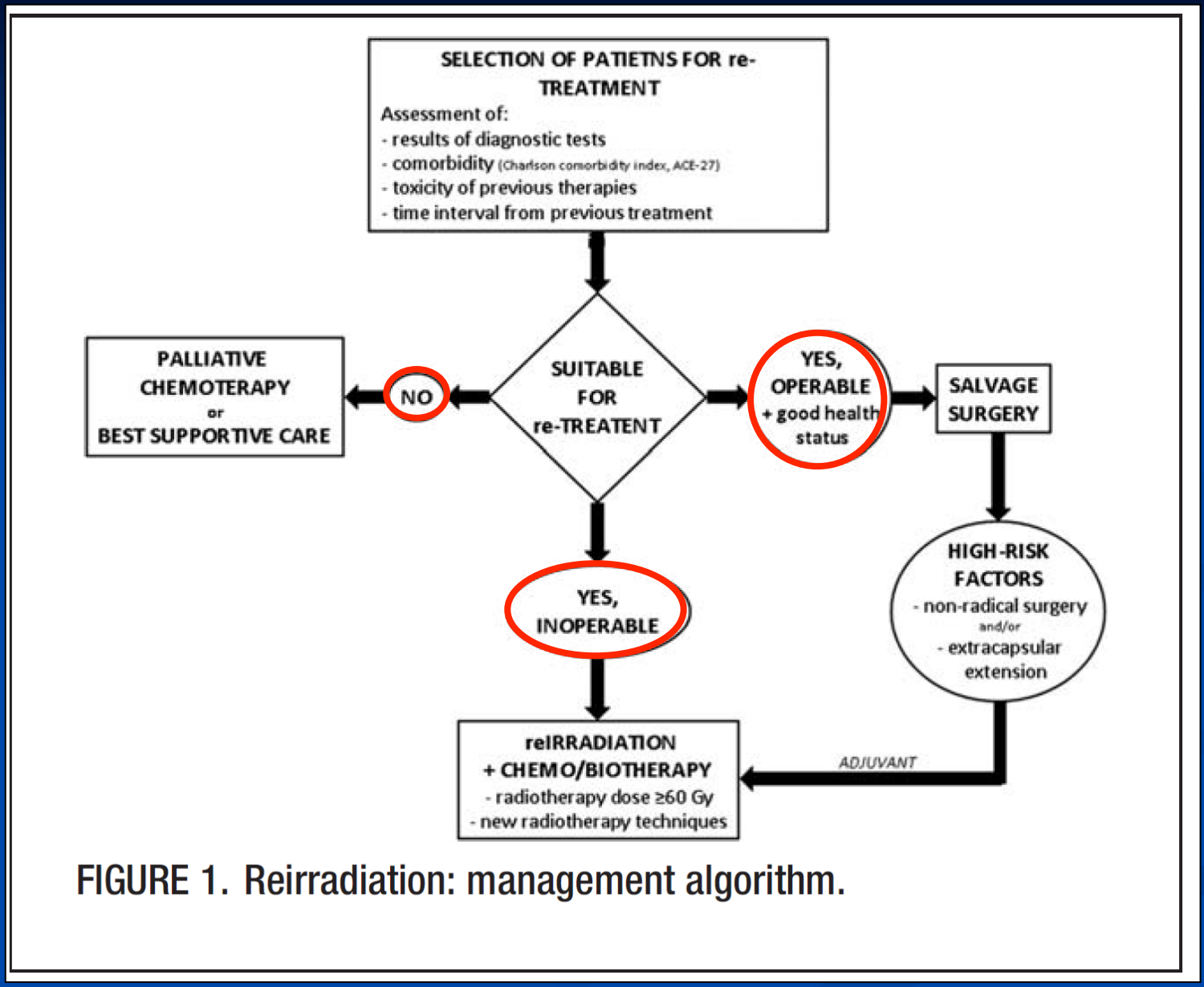


FIGURE 1. Reirradiation: management algorithm.

Strojan P Head and Neck 2014

HEAD AND NECK CANCER
POSTOPERATIVE RE-IRRADIATION

CONVENTIONAL TECHNIQUE

2008 GETTEC-GORTEC phase III trial PORT (60 Gy) +CT vs FUP

Better LRC and DFS but no difference in OS

Grade 3 and 4 late toxicity (39% vs 10% at 2 yars) and 5 treatment related deaths

- Subsequent small retrospective and prospective studies
  - High risk pts (ECE, R1)
  - Grade 3 and 4 toxicity > 30% pts
  - Up to 8% pts will die because of treatment-related toxicity
  - OS rate of 40-50% at 2 years
  - microvascular free flap may reduce incidence of severe late side effects

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HEAD AND NECK CANCER
RE-IRRADIATION

RT SCHEDULE

- FRACTIONATIONATION
  - Conventional fractionation
  - hyperfractionation (1.2-1.5 Gy x 2/die)
  - Split course regimens
  - Hypofractionation

Kress AMS et al Head and Neck 2014

HEAD AND NECK CANCER
RE-IRRADIATION

RT TECHNIQUE

IMRT/ SBRT Compared to 3D Conformal technique

- **no survival advantage using modern technique**
- **Improvement in local control can be seen despite the fact that the treated volumes sems smaller with new technique**
- **Toxicity and treatment-related deaths no conclusions**

Strojan P Head and Neck 2014

STEREOTACTIC re-RT

TABLE 5. Recent trials in head and neck reirradiation.

Study by treatment	No. of patients*	Dose, Gy, median	Response, CR, PR	LRC 1-y, 2-y	OS: median, mo 1-y, 2-y	Long-term toxicity
SBRT only						
Kress et al, 2013, retrospective	85	30	76%	57.8%, 28%	8.6 51.1%, 24%	5.9% grade 3 or higher
Comet et al,[21] 2012, prospective	40	36	79%	*	13.6 58%, 24%	10.3% grade 3
Cengiz et al,[11] 2011, retrospective	46	30	57%	83.8% at follow-up	11.9*	13.3% overall 17.8% carotid blowout
Rwigema et al,[22] 2010, retrospective	85	35	68%	51.2%, 30.7%	11.5 48.5%, 16.1%	*
Roh et al,[9] 2009, retrospective	36	30	80%	*	*52.1%, 30.9%	8.3% late complications
Heron et al, 2011, retrospective	70	40	34% to 46%	53.8%, 33.6%	17*	4.3% late grade 3
Mean		34.2	65%		13.5 mo 53%, 28%	9%
IMRT only						
Chen et al,[23] 2011, prospective	21	66 Gy	81%	72%, 65%	*65%, 40%	14.3% with toxicity; 57% gastrostomy tube dependent
Sher et al,[6] 2010, retrospective	35	60 Gy	*	67%, 67%	22.8 59%, 48%	46% grade 3 11% grade 5
Sulman et al,[7] 2009, retrospective	74	60 Gy	*	N/A, 64%	*2-y 58%	20% "severe"
Duprez et al,[5] 2009, retrospective	84	69 Gy	*	65%, 48%	13.4 54%, 35%	13.1% grade 3–4
Mean		63.8		68%, 61%	18.1 mo 59%, 45%	23%
3D conformal RT and IMRT						
Watkins et al,[24] 2009, retrospective	39	60 Gy	*	55.1%, 40.3%	13.4 60.1%, 45.1%	10.3% grade 5 acute
Popovtzer et al,[25] 2009, retrospective	66	68 Gy	*	29% at last follow-up	*2-y 40%	29% grade 3 or greater
Lee et al,[26] 2007, retrospective	105	59.4 Gy	52%	*	15 56%, 37%	15% late grade 3–4
Langer et al,[27] 2007, prospective	105	60 Gy	*	*	12.1 50.2%, 25.9%	16.9% grade 3 16.9% grade 4 3.6% grade 5
Mean		61.85			13.5 55.4%, 37%	21%

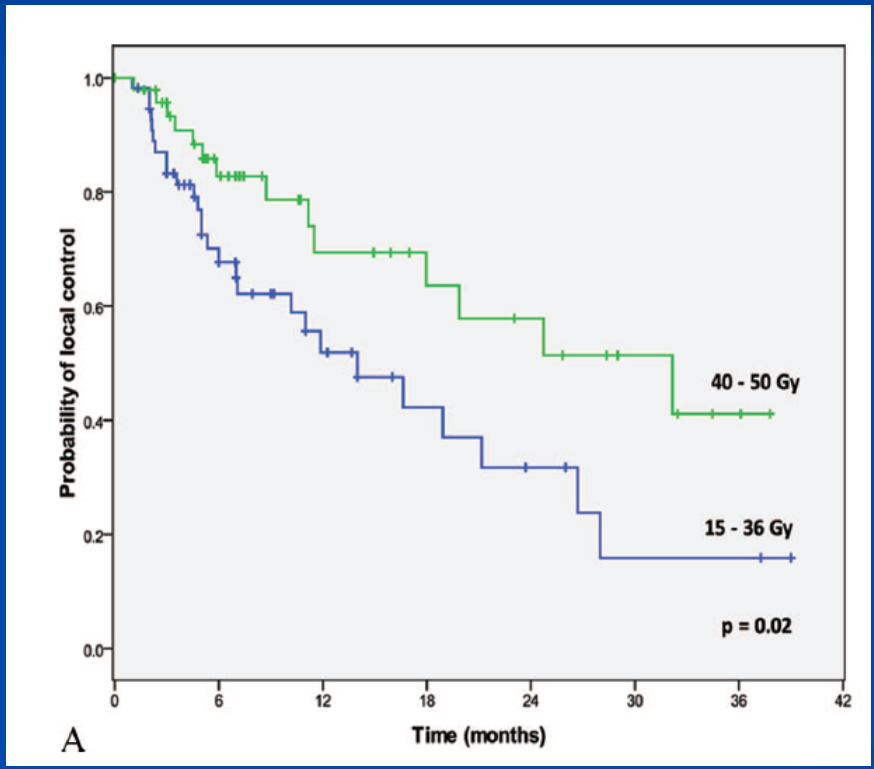
Abbreviations: Gy, Gray; CR, complete response; PR, partial response; LRC, locoregional control; OS, overall survival; SBRT, stereotactic body radiotherapy; N/A, not applicable; RT, radiotherapy; IMRT, intensity-modulated radiotherapy.
* Data not reported.

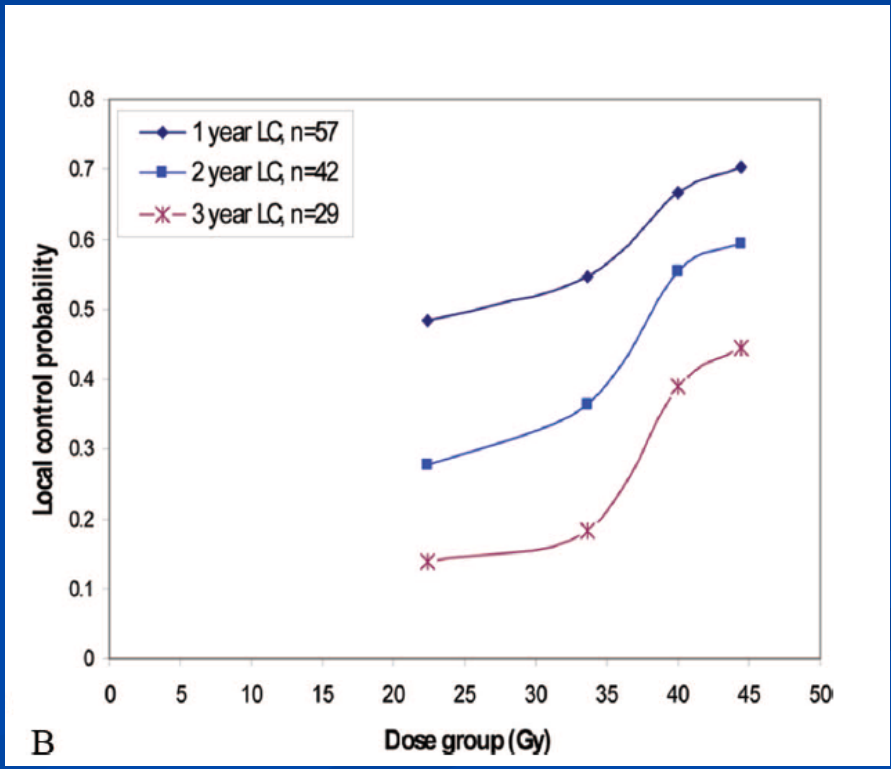
Kress MAS et al Head and Neck

STEREOTACTIC re-RT

IMPACT OF DOSES

20 Gy→ 50 Gy in 5 fr (Cyberknife, Trilogy)





Rwigema JCM et al AJCO 2011

STEREOTACTIC re-RT

IMPACT OF DOSES

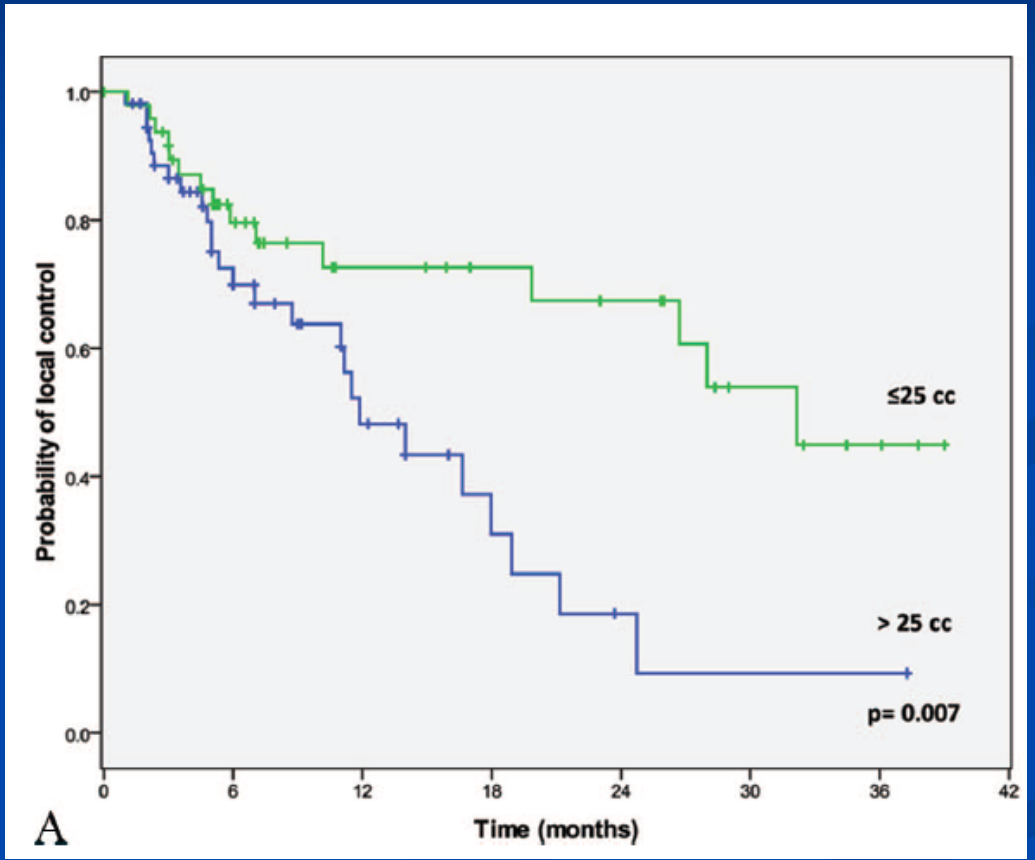
Cut-point dose suggesting an improved outcome is usually set around 60 Gy

By increasing the dose above this level, extreme caution is warranted

Strojan P Head and Neck 2014

STEREOTACTIC re-RT

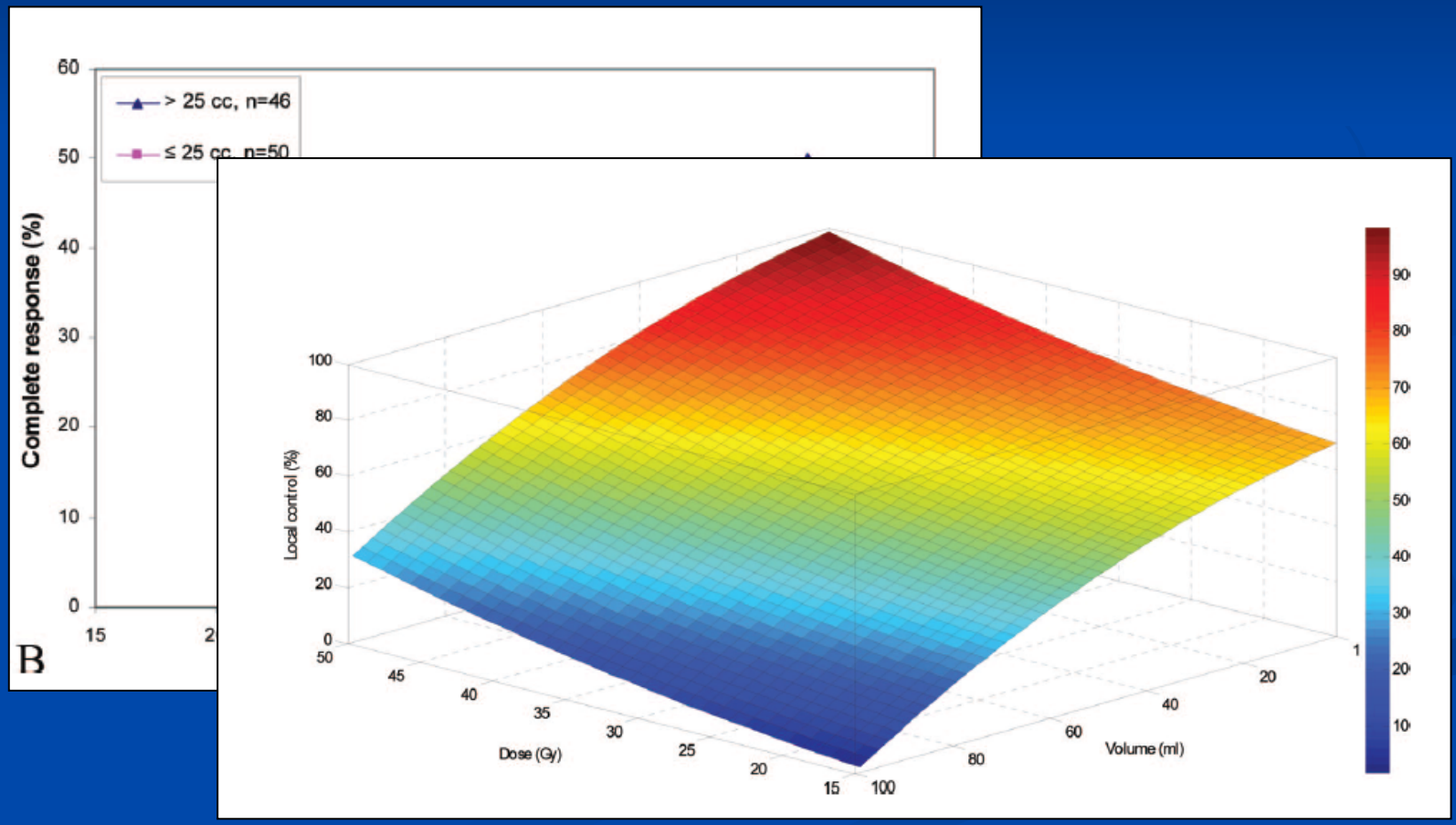
IMPACT OF VOLUME



Rwigema JCM et al AJCO 2011

STEREOTACTIC re-RT

IMPACT OF DOSE AND VOLUME



Rwigema JCM et al AJCO 2011

STEREOTACTIC re-RT

Volumes (CTV)

- CTV = GTV +0.5 cm margin. Probably benefit of FDG-PET
- Lymph nodes
  - ce CT has >94% negative predictive value after RT
  - 67% unexpected lymph node drainage in pts previously treated
  - high rate of DM and Local failures
- Elective treatment of lymph node
  - LR cN0 in pts previously treated for cN0 → low risk of N involvement
  - LR cN0 in pts previously treated for cN+ → high risk of N involvement
  - Regional R → RT only for the involved nodal levels

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STEREOTACTIC re-RT

Author (Institute)	Year (Pt No.)	Radiotherapy [Median tumor/ treatment volume]	RR	*Prognostic factors
SRS/ SRT				
[27]Siddiqui (Detroit)	2009 (21)	13-18Gy/1fr or 36-48Gy/5-8fr two to three times weekly	RR 50%/ 2yOS	
CyberKnife				
[28]Himei (Okayama Univ)	2003 (31)	15-40.3 Gy/ 1-6fr IDL44-78% (60.2%) [41.2cc]		
[29]Roh (Korea)	2008 (36)	D65-85% IDL: 30 (18-40) Gy/ 3-5fr [22.6cc]	RR80%/	
[30]Ogita (Fujimoto Hayasuzu)	2009 (58)	D95 31Gy/3-8fr [31.8cc]	2yO	
[31]Heron (Pittsburgh Univ)	2009 (25)	D90 (IDL80%) 5fr / 2week [44.8cc] Phase I: 25Gy →32Gy→36Gy→40Gy→44Gy		
[32]Rwigama (Pittsburgh Univ)	2010 (85)	D95:35 (15-44) Gy/ 5 (1-5)fr [25.1 cc] each other days	RR68%/ 2yOS	
[33]Unger (Georgetown Univ)	2010 (65)	30 Gy/5fr [75cc]	2 y Radical :MS	
[15]Kodani (Kyoto Pref. Univ)	2011 (21)	D90: 30 (19.5-42) Gy / 5 (3-8) f r [10cc]	RR	
[13]Cengiz (Turkey)	2011 (46)	IDL76.5%, 30 (18-35) Gy / 5 (1-5) fr [45cc]	RR53%	

Abbreviations: CR; complete response, PR; partial response, SD; stable disease, LC; local control, OS; o
NA; not available, IDL; isodose line, G; grade, OP; surgery, nonSQ; non squamous cell cancer
*estimated from figure, †prognostic factors for overall survival if otherwise stated

Late: bone necrosis 1, soft tissue necrosis 2

24 ulcer (41.4%)

no G3/4

2 (3%)

No G4/5

G3 : taste loss 1, Xerosto

2/21 (9.5%)

Acute 19 G1-

Late 6 G4 (9%

9 (15%)

Severe late 6

7 death

Yamazaky H, Head and Neck, 2011

STEREOTACTIC re-RT

SYSTEMIC TREATMENT

- **EFFECTIVENESS??**
- **Different CT regimens:**
  - **CDDP and 5FU-hydroxyurea most common.**
  - **Others: Bendamustine, tirapazamine, erlotinib +/- celecoxib, bevacizumab, paclitaxel+ CDDP**
  - **Cetuximab**
    - **Heron SBRT 8Gy x 5 fr every one day + CET standard doses.**
      - **Retrospective comparison with pts treated only with SBRT**
        - **2 years LC 33.6% vs 49.2% (p=0.009)**
        - **2 years OS 21.1 vs 53.3% (p=0.31)**
        - **No differences in late toxicity**

Strojan P Head and Neck 2014

STEREOTACTIC re-RT

Re-RT and Cetuximab

Cyberknife 6 Gy x 6 fr → 36Gy + CET

CTV= GTV + 5mm margins

Median follow up 11.4 months
Response rate at 3 months 58.4%
Os at 1 years 47.5%

Conclusion: effective salvage treatment with good response rate

Acute toxicity is acceptable

Lartigau EF et al Radiother Oncol 2013

STEREOTACTIC re-RT

POSTOPERATIVE re-RT + Cet

28 pts R1 or ECE
dose 40-44 Gy in 5 fr
Median FU 14 months

1 year	LRC	51%
	DC	90%
	DFS	49%
	OS	64%

TABLE II.
Acute (<90 Days) and Late (>90 Days) Physician-Recorded Toxicity.

Adverse Event	Acute <90 Days (No. of Patients = 28)	Late >90 Days (No. of Patients = 26)
Patients with no toxicity	16 (57%)	21 (80%)
Patients with ≥grade 3 toxicity	0 (0%)	2 (8%)
Incidence of ≥grade 3 toxicity events	0 (0%)	5 (19%)
Xerostomia		
Grade 1	2 (7%)	1 (4%)
Grade 2	–	1 (4%)
Dysgeusia		
Grade 1	1 (4%)	–
Grade 2	1 (4%)	–
Mucositis		
Grade 1	3 (11%)	–
Grade 2	2 (7%)	–
Dysphagia		
Grade 1	1 (4%)	–
Grade 2	1 (4%)	–
Grade 3	–	2 (8%)
Sinusitis		
Grade 1	1 (4%)	–
Pain		
Grade 1	–	–
Grade 2	2 (7%)	2 (8%)
Fatigue		
Grade 1	2 (7%)	–
Skin*		
Grade 1	4 (14%)	–
Grade 2	–	1 (4%)
Infection		
Grade 4	–	1 (4%)
Osteonecrosis		
Grade 3	–	1 (4%)
Vascular		
Grade 4	–	1 (4%)

*Fifty percent of patients with skin toxicity received concurrent cetuximab.

Vargo JA et al The Laryngoscope 2014

SIDE EFFECTS

Esophageal stenosis (Biaglioli 2007)	Bleeding (Biaglioli 2007, Duprez 2007)
Osteonecrosis of the mandible or, for nasopharynx patients, of the first cervical vertebrae or bone of the skull base (Claus 2001, Platteaux 2010, Janssen 2010, Kasperts 2005, Law 2002, Mendenhall 2008, Strojan 2014) 10%	Neurologic damage like deafness, temporal lobe necrosis, optic or base of skull nerves damages. (Claus 2001, RTOG 9610 Spencer 2008, Platteaux 2010, Mendenhall 2008 Mendenhallo 2008)
Prolonged enteral nutrition (Claus 2001, Platteaux 2010, Spencer 2008)	Soft tissues fibrosis, trismus, palatal fibrosis. (Dawson2001, De Crevoisier 200,Kasperts 2006, Chua 2006, Mendenhall 2008)
Mucosae and/or soft tissues necrosis and fistulae. (De Crevoisier 2001, Janssen 2010)	Dry eye syndrome and ocular dysfunction (keratitis, corneal ulceration) (Duprez 2009)
Pain (Spencer 2008)	Larynx damage (Spencer 2008)
Severe epistaxis (Chua 1999)	Radiation-induced sarcoma (Mendenhall 2008)
Hypopituitarism (Mendenhall 2008)	Xerostomia (Mendenhall 2008)
Vascular stenosis and trombo-embolic events (Wong 2006)	Carotid blowout syndrom 2.6% (Strojan 2014)

STEREOTACTIC re-RT

Incidence of late complication 20-40%

RISK FACTORS FOR ADVERSE EVENT

Prior RT dose
Primary site
Re-RT dose
Treatment volume
Technique

Yamazaky H, Head and Neck, 2011

BLOWOUT SYNDROME

Not hypofractionated schedule → crude rate 2.6%

Interval from start of re-RT 7.5 months (0-56 months)

76% fatal

No impact of previous salvage surgery or concurrent CT

Standard fractionation., hyperfract. < accelerated hyperfract (1.3 vs 4.5 p=0.02)

McDonald M et al Int J Radiat Oncol Biol Phys 2012
Strojan P et al Head and Neck 2014

BLOWOUT SYNDROME

Hypofractionated schedule → incidence 10-15%

Review 381 pts Cyberknife → incidence 8.4%

Median prescribed dose 30 Gy in 5 fractions (D95 in 69% pts)

Median interval 5 months

Univariate analysis: elder age, skin invasion, necrosis/infection

Multivariate analysis: skin invasion

Yamazaki H et al Radiother Oncol 2013

BLOWOUT SYNDROME

Risk factors

Carotid artery wall entrapment by the tumor → 180°

Foramen lacerum is quite vulnerable to hemorrhage

Sequential schedule > every one day schedules

Cumulative BED

Yazici et al Radiat Oncol 2013
Yamazaki et al Radiother Oncol 2013
Mc Donald et al Int J Radiat Oncol Biol Phys 2012

IEO EXPERIENCE stereotactic re-RT

1998 →2014 Re-RT Hypofractionation(>2 Gy/die) 40 pts

23 M, 17 F

Median age 58 aa (29-89 yrs)

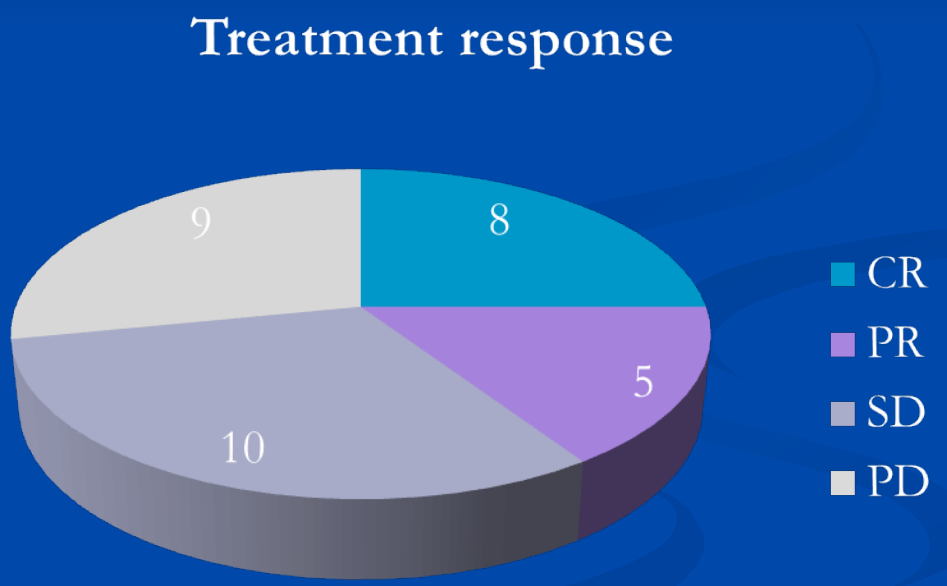
SITE	N. pts
Nasopharynx	12
Base of skull	7
Neck lymph nodes	6
Oral cavity	5
Parapharyngeal space	3
Parotid gland	3
Skin	1
Oropharynx	2
Paranasal sinus	1

IEO EXPERIENCE stereotactic re-RT

Doses range 8→ 45 Gy

1-18 Fr

Gy/fr	N. PTS
2,5	9
3	11
4	7
5	7
6	1
7	2
8	1
12	2



IEO CLINICAL CASE (1)

Nasopharynx

RW
Female
Age 54 years

Previous RT

1996
Telecobalt
61.2 Gy (1.8 Gy/fraction)

2004 Local Recurrence

interval between RT 95 months

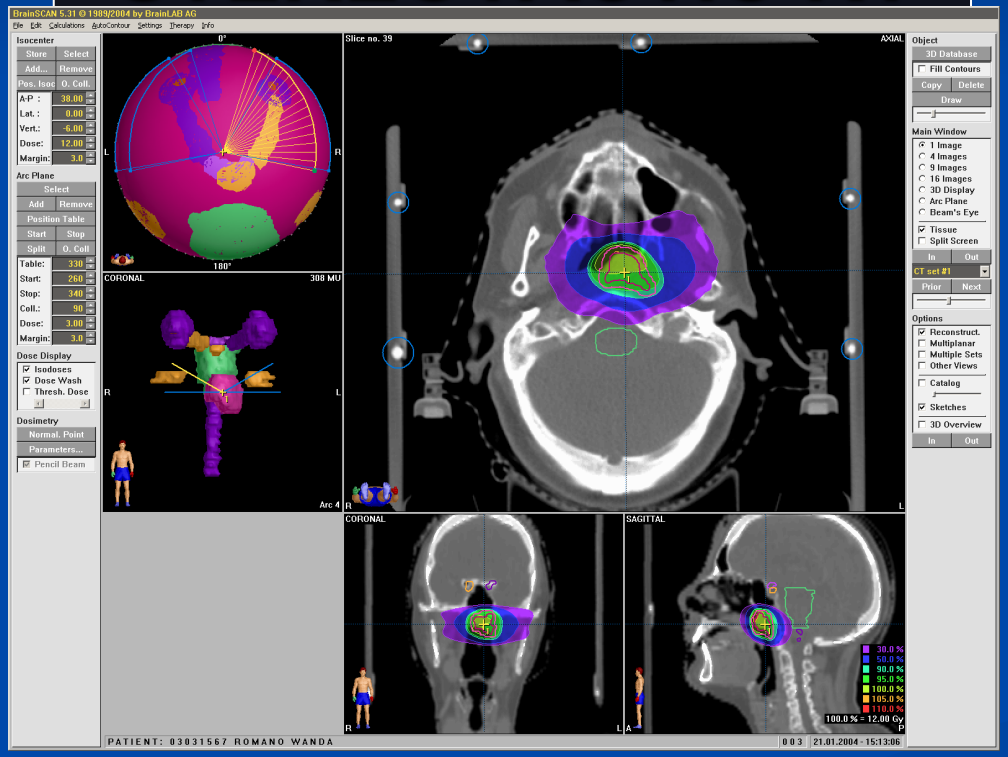
Re-irradiation

Stereotactic RT 24 Gy (12 Gy/fraction)
Brachytherapy 12 Gy (6 Gy/fr)

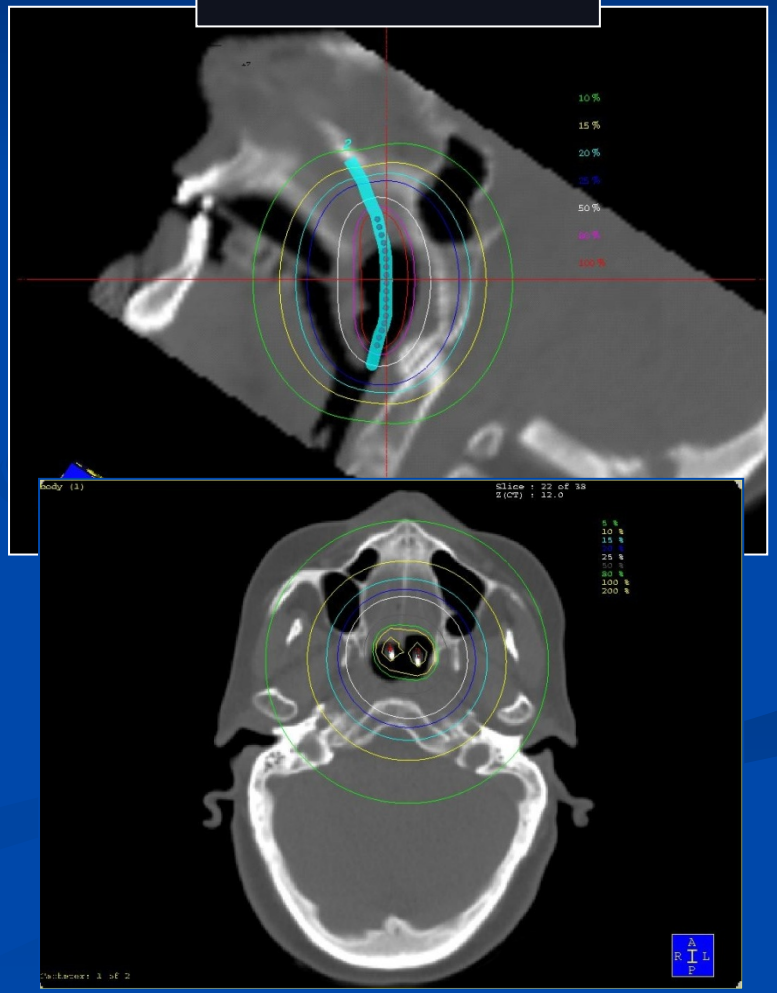
57 months Alive w/out Disease
Neck recurrence → Surgery

IEO CLINICAL CASE (1)

STEREOTACTIC RT



BRT



IEO CLINICAL CASE (2)

Nasopharynx

DM
Female
Age 29 years

Previous RT

2010
IMRT
69.96 (2.12 Gy/fraction)

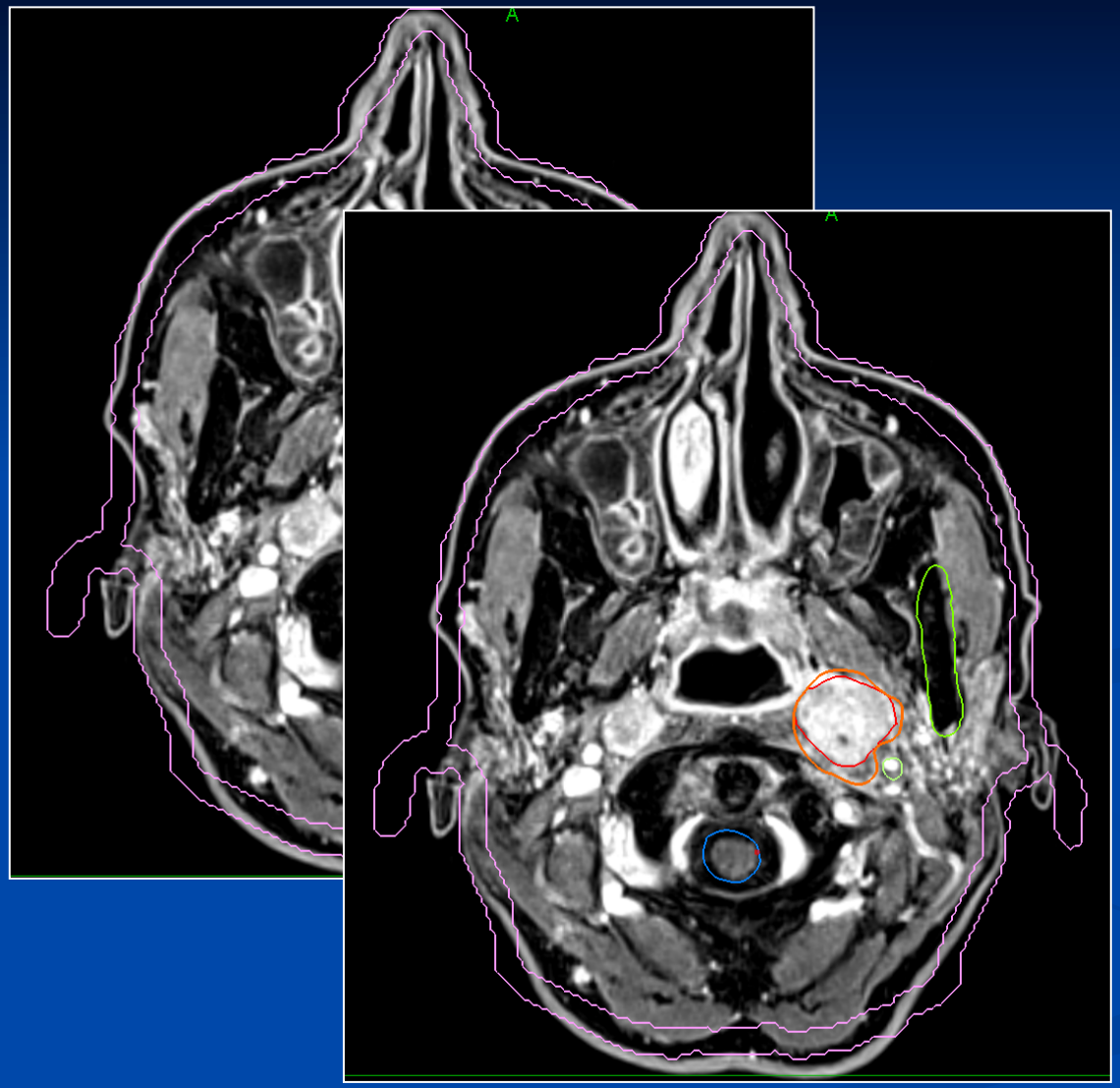
PD persistent disease

interval between RT 28 months

Re-irradiation

4/2013 Cyberknife 2.5 Gy x 16 fr → 40 Gy
5/2014 Cyberknife 2.5 Gy x 16 fr → 40 Gy

Up today stable disease
No severe late side effects



40 Gy 2.5 Gy/fr (75%)

IEO CLINICAL CASE (3)

Nasopharynx

MG
Male
Age 42 years

Previous RT

2011
IMRT
70 Gy

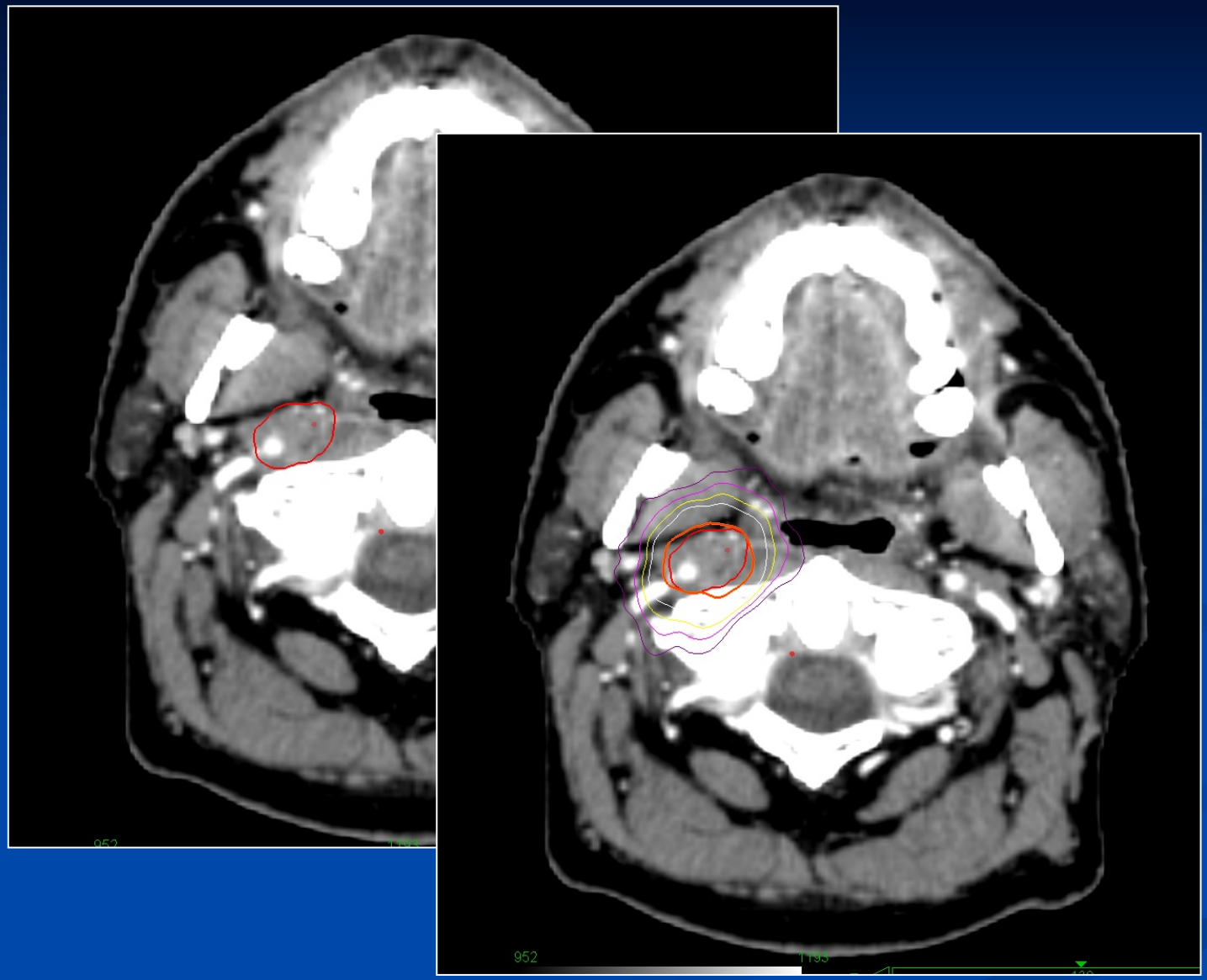
PD lymph node

interval between RT 24 months

Re-irradiation

7/2013 Cyberknife 2.5 Gy x 18 fr → 45 Gy

16 months CR
No severe late side effects



45 Gy 2.5 Gy/fr (90%)

IEO CLINICAL CASE (4)

Nasopharynx

EL
Male
Age 51 years

Previous RT

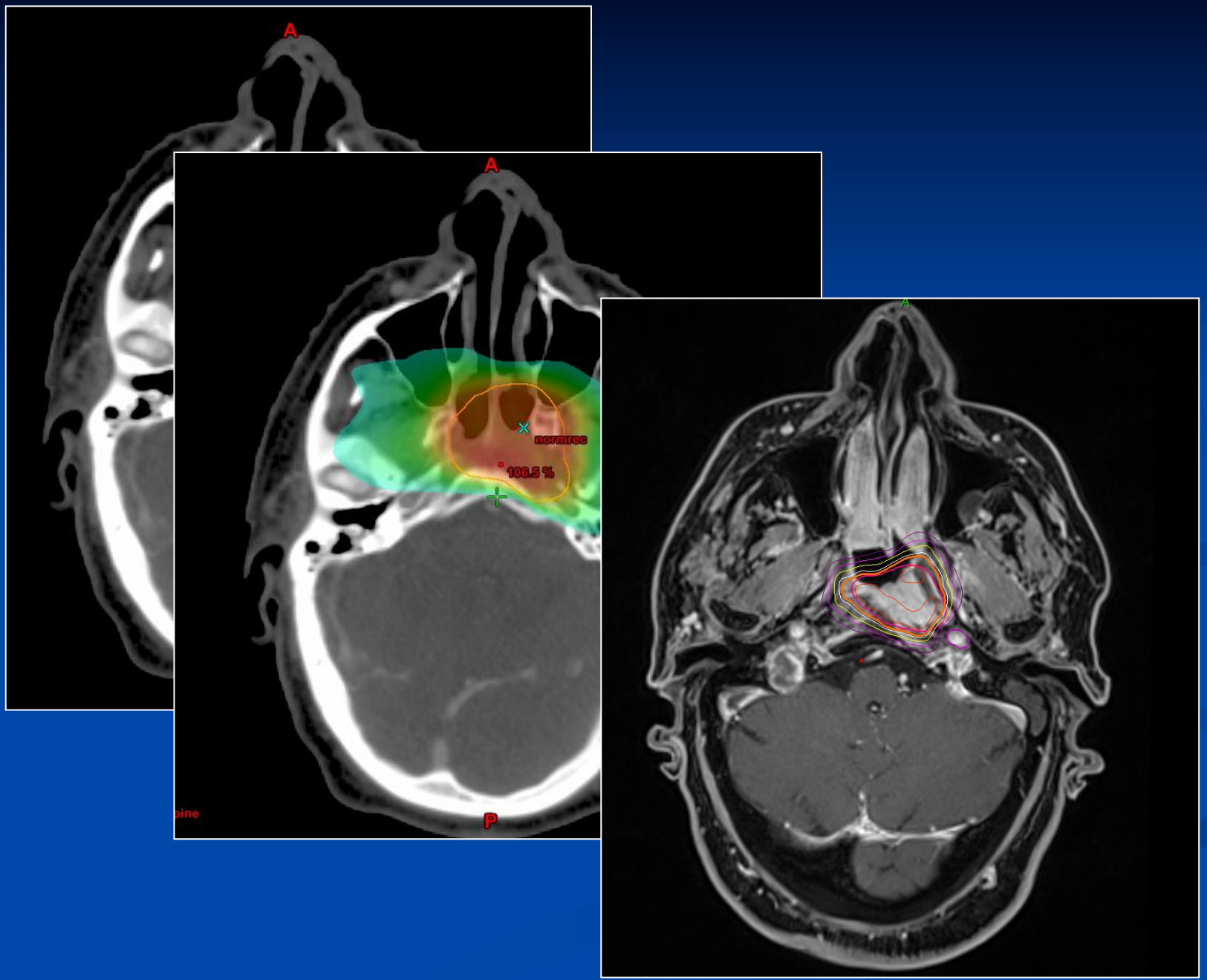
2010
IMRT
69.96 Gy

Local recurrence

interval between RT 36 months

Re-irradiation
1/2013 IMR 46 Gy 2 Gy/die
Boost Cyberknife 3 Gy x 3 fr → 9 Gy

PD T and N 12 months
No severe late side effects


A
A
normres
106.5 %
P
A

STEREOTACTIC re-RT

TAKE HOME MESSAGE

ADVANTAGES

-Personalized therapy

- Compared to 3D Conformal equivalent oncologic results
- Compared to 3D Conformal reduction of late side effects (?)

-Short duration of treatment
-Reduces expediting time to systemic therapy (for pts with DM)
-Highly conformal dose distribution
-Low hematological or systemic toxicity → pts with poor PS

McDonald M et al Int J Radiat Oncol Biol Phys 2012
Strojan P et al Head and Neck 2014

STEREOTACTIC re-RT

TAKE HOME MESSAGE

DISADVANTAGE

-High rate of some late side effects (blowout Syndrome)
-Complex treatments for patients with poor prognosis
-Wide range of CTV delineation and dose prescription

Grazie per l'attenzione

McDonald M et al Int J Radiat Oncol Biol Phys 2012
Strojan P et al Head and Neck 2014