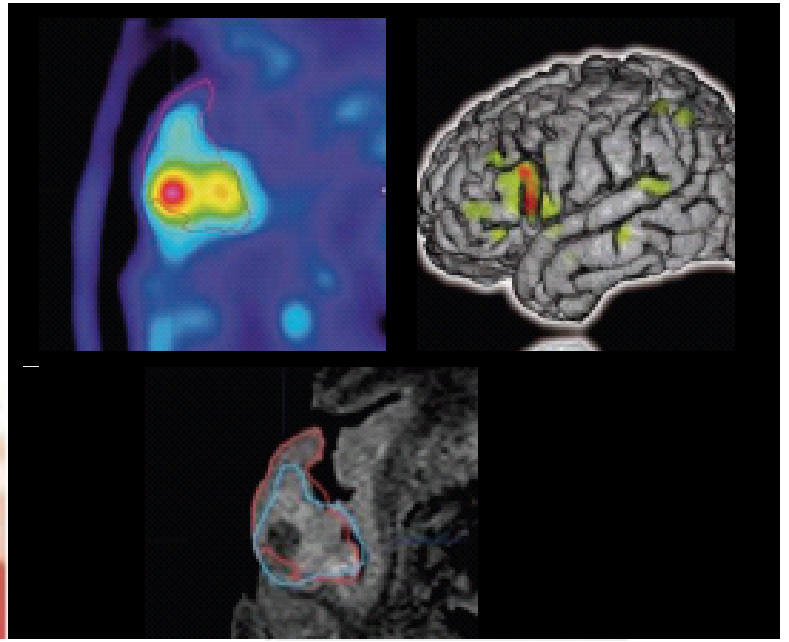
NEW ADVANCES IN NEURONCOLOGY

Humanitas University and Research Hospital
Milan, Italy 28-29 June 2019



Role of Radiation Therapy in Lower Grade Glioma

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AIOM Associazione Italiana di Oncologia Medica
AIRO Associazione Italiana Radioterapia e Oncologia clinica
HU HUMANITAS UNIVERSITY
SINCH SOCIETÀ ITALIANA NEUROCHIRURGIA

Lower Grade Glioma (LrGG)

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LrGG — Grade II-III glioma

2016 WHO CNS — Re-evaluation biologic heterogeneity molecular make-up

Some LGG behave → like GBM

Anaplastic Glioma → like LGG

These molecular biomarkers — Prognostic factors

Predictive markers

Drive therapeutic decision making

RT in Low Grade Glioma (LGG)

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Radiation Therapy (RT) controversial modality in LGG

Prolonged natural history and potential late toxicity from RT

Several prospective randomized trials to define WHO benefit from RT

Limitations: all types of resection and multiple histologies included

Some populations higher risk of recurrence

A risk stratification needed to point out who treat in up-front setting

RT in Low Grade Glioma (LGG)

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Trial	Adjuvant Therapy	5-y PFS (%)	5-y OS
EORTC 22844	45 Gy	47	58%
	59.4 Gy	50	59%
NCCTG 86-72-51	50.4 Gy	55	72%
	64.8 Gy	52	64%
EORTC 22845	Observation	35	66%
	54 Gy	55	68%
RTOG 9802	Observation (nonrandomized low-risk arm)	48	93%
	54 Gy	72	63%
	54 Gy + PCV	84	72%
RTOG 0424	54 Gy/TMZ (nonrandomized)	46	60%
EORTC 22033	50.4 Gy/TMZ (12 cycles)		

RT in Low Grade Glioma (LGG)

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Prospective phase III dose-escalation studies

NCCTG 86-72-51 trial

203 patients

RT doses 50.4 Gy *vs* 64.8 Gy

No OS differences (p=0.48)

EORTC 22844

379 patients

RT doses 45 Gy *vs* 59.4 Gy

No OS or PFS differences (p=0.73; 0.94)

Grade 3-5 toxicity

doubled in the higher dose arm (p=0.04)

Suggestions
RT doses 45-50.4 Gy
No role for dose escalation

Limitations
CT scan only
Old RT techniques employed

RT in Low Grade Glioma (LGG)

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EORTC 22845 trial or "non-believer's trial"

Optimal timing of RT — up-front *vs* at progression

311 patients enrolled — 290 patients assessable

Median FU time — 7.8 years

Biopsy or Resection → up-front RT 54 Gy

Biopsy or Resection → observation-delayed 54 Gy

No formal QoL or Neurocognitive/neurologic functions performed

Van de Bent JCO 2005

RT in Low Grade Glioma (LGG)

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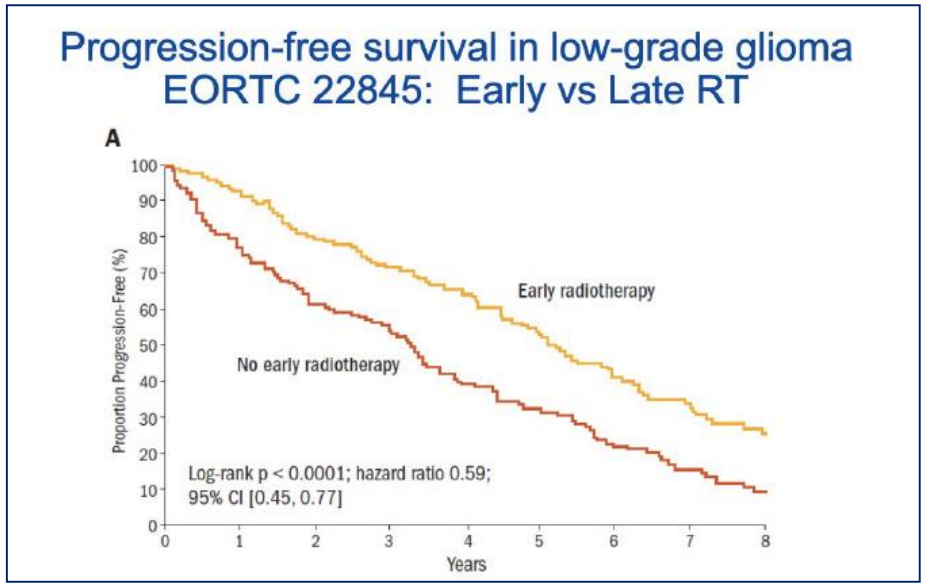

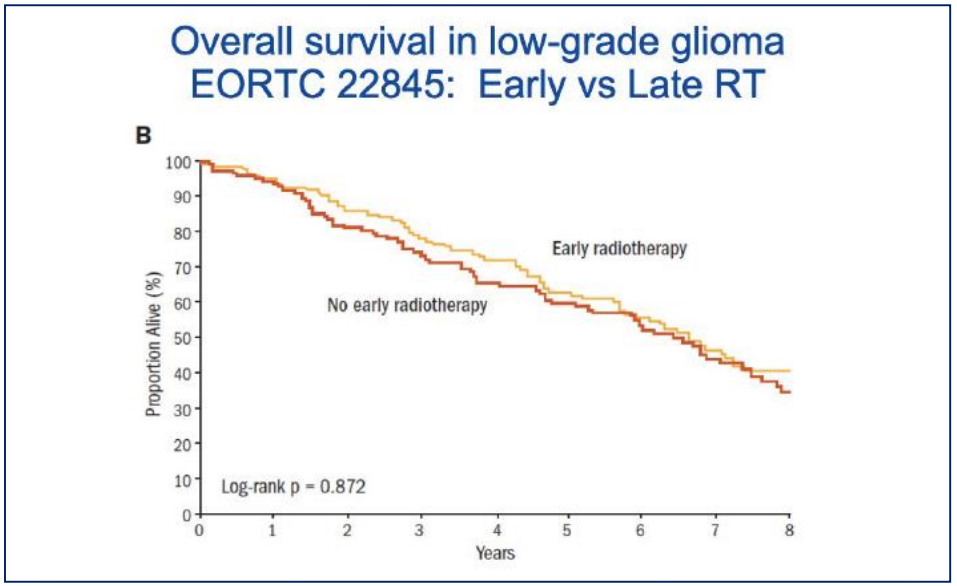

mPFS 5.3 years *vs* 3.4 years (p=0.0001)

mOS 7.4 years *vs* 7.2 years

Seizure at 1year 25% *vs* 41% p=0.03

RT could be safely performed

Limitations did not assess differences between risk groups and QoL

RT in Low Grade Glioma (LGG)

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RTOG prognostic factors	EORTC prognostic factors
Unfavorable • Age >40 years • Tumors > 5 cm • Astrocytoma histology • Surgery < GTR	Unfavorable • Age >40 years • Tumors≥6 cm • Tumor crossing midline • Astrocytoma histology • Neurologic symptoms

Observation in low risk patients

Radiation therapy in high risk patients

RT in Low Grade Glioma (LGG)

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Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

Brigitta G Baumert, Monika E Hegi*, Martin J van den Bent, Andreas von Deimling, Thierry Gorlia, Khê Hoang-Xuan, Alba A Brandes, Guy Kantor, Martin J B Taphoorn, Mohamed Ben Hassel, Christian Hartmann, Gail Ryan, David Capper, Johan M Kros, Sebastian Kurscheid, Wolfgang Wick, Roelien Enting, Michele Reni, Brian Thiessen, Frederic Dhermain, Jacoline E Bromberg, Loic Feuvret, Jaap C Reijneveld, Olivier Chinot, Johanna M M Gijtenbeek, John P Rossiter, Nicolas Dif, Carmen Balana, Jose Bravo-Marques, Paul M Clement, Christine Marosi, Tzahala Tzuk-Shina, Robert A Nordal, Jeremy Rees, Denis Lacombe, Warren P Mason, Roger Stupp**

Lancet Oncol 2016; 17: 1521–32

487 patients
250 RT
237 TMZ

Aim PFS and identification of molecular factors predictive outcome

2 Arms RT alone 50.4 Gy *vs* TMZ dose dense alone

Median FU 48 months

Median PFS RT 46 months TMZ 39 months p=0.22

IDH mutation/1p19q- better PFS in RT arm p=0.0043

Worse outcome in both arms in case of IDH wild type

Baumert, Lancet Oncology 2016

RT in Low Grade Glioma (LGG)

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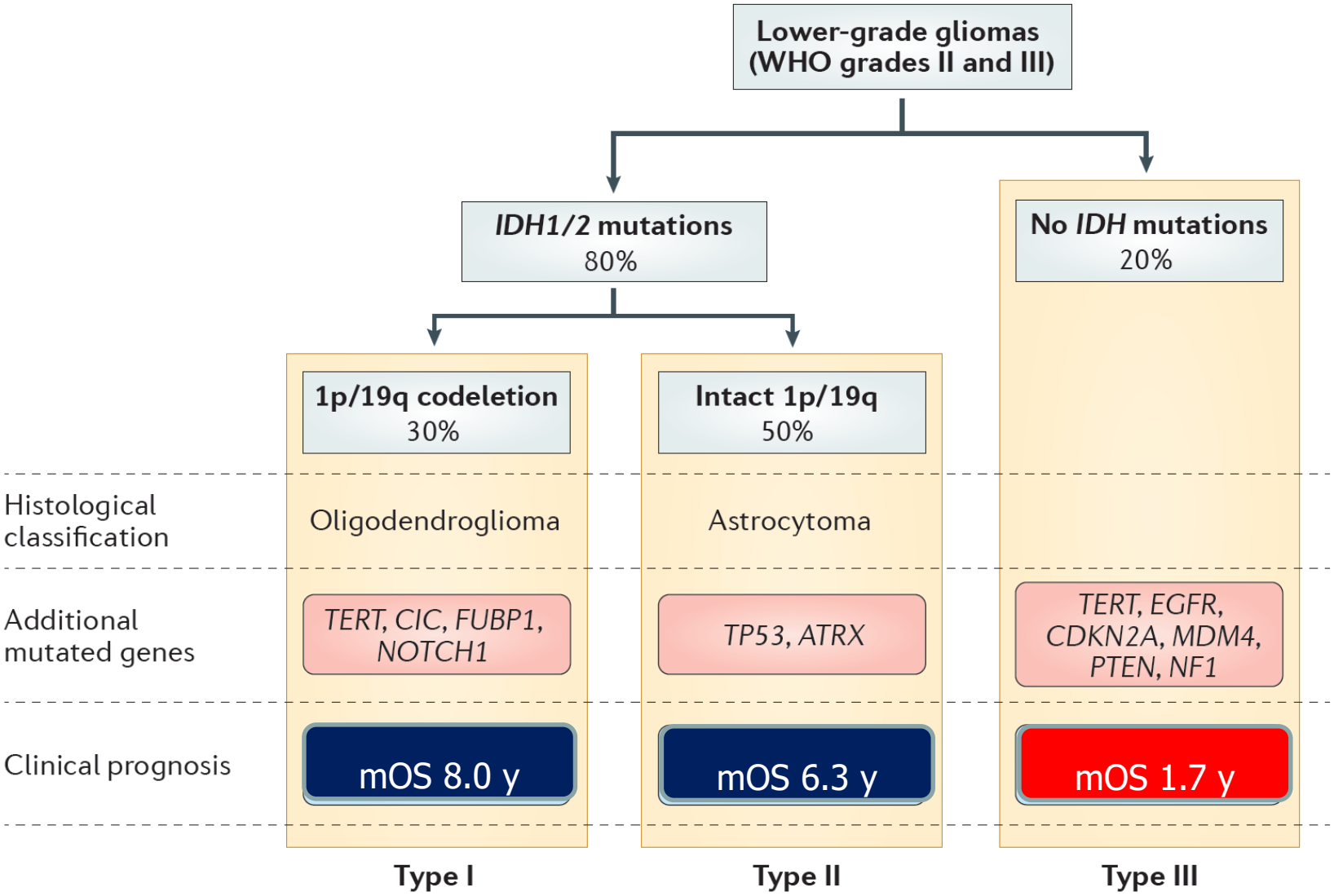

RT in Low Grade Glioma (LGG)

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Ann Neurol 1994; 36:48-54

Cognitive Functions and Quality of Life in Patients with Low-Grade G… The Impact of Radiothe…

M. J. B. Taphoorn, MD,* A. Klein Schiphorst, MA,† F. J. Snoek, PhD,† J. G. Wolbers, MD,‡ A. B. M. F. Karim, MD,§ P. C. Huijgens, MD,¶ a…

Lancet 2002; **360:** 1361–68

ARTICLES

Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study

Complications of Cancer Therapy ***Tissue Necrosis***

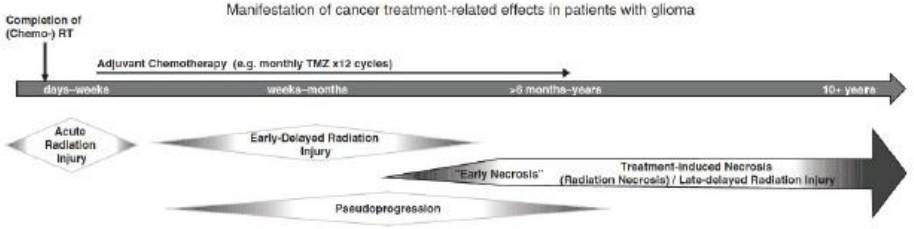
Neuro-Oncology

XX(XX), 1–13, 2019 | doi:10.1093/neuonc/noz048 | Advance Access date 4 March 2019

Treatment-induced brain tissue necrosis: a clinical challenge in neuro-oncology

Sebastian F. Winter, Franziska Loebel, Jay Loeffler, Tracy T. Batchelor, Maria Martinez-Lage, Peter Vajkoczy, and Jorg Dietrich

Manifestation of cancer treatment-related effects in patients with glioma



…col (2017) 134:9–18
…007/s11060-017-2503-z

CrossMark

…REVIEW

…or-related neurocognitive dysfunction in patients with diffuse …na: a systematic review of neurocognitive functioning prior …ti-tumor treatment

…van Kessel[1] · Anniek E. Baumfalk[1] · Martine J. E. van Zandvoort[1,2] · …. Robe[1] · Tom J. Snijders[1]

RT in Low Grade Glioma (LGG)

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Supporting Studies	Non–supporting Studies
• Limited number of pts • Retrospective studies • High RT doses • Wide target volumes *Down L Lancet neurology 2002;* *Olson JD Neurology 2000;* *Surma-aho O Neurology 2001;* *Postma TJ Neurology 2002;* *Correa DD J Neurooncol 2008*	• Prospective studies • Two with more than 100 pts • Limited target volumes • Evaluation using standardized test batteries *Klein M Lancet 2002;* *Laack NN IJROBP 2005;* *Vigliani MC IJROBP 1996;* *Amstrong CL Neurology 2002;* *Brown PD JCO 2003;* *Torres IJ Neurology 2003*

NO RANDOMIZED STUDIES

RT in Low Grade Glioma (LGG)

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Neurocognitive decline → Multifactorial genesis

- Patients
  - age
  - presence of comorbidities — *Down L Lancet neurology 2002*
- Disease
  - site and size of tumor
  - seizure — *Klein M Lancet 2002; Klein M Ann Neurol 2003*
- Treatments
  - surgery
  - chemotherapy
  - radiotherapy — *Reijneveld JC Neurology 2001; Brown PD Neuro Oncol 2003; Lesser GJ Sem Rad Oncol 2001*

RT in Low Grade Glioma (LGG)

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DOSE REDUCTION

Doses	50.4 Gy (EORTC) or 54 Gy (RTOG)
Advantages	* not exceed brain stem or optic tolerances * tolerable for large tumor volume * with a low risk of radiation necrosis
Doses	45 Gy
Advantages	* very large treatment volumes * involvement of particular brain regions * such as dominant temporal lobes or hippocampus * predispose to late cognitive sequelae

RT in Low Grade Glioma (LGG)

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APPROPRIATE IMAGING FOR TARGET VOLUME DELINEATION

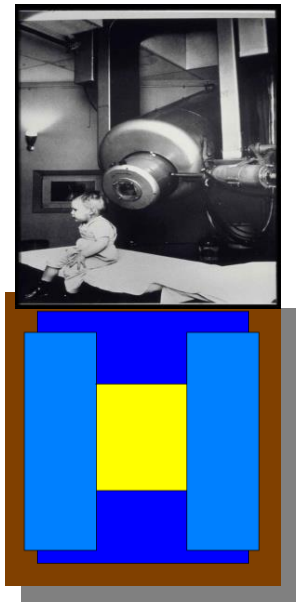
MRI is mandatory	T2 sequences
	FLAIR sequences
	diffusion or perfusion weighted imaging
CT scan	For treatment planning
[11C]METCTPET	Astrocytoma

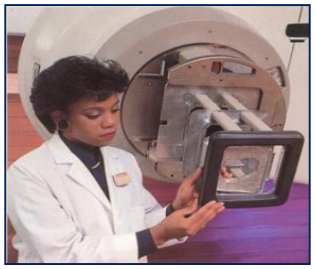
MARGIN REDUCTIONS

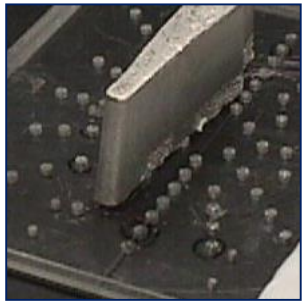
Smaller tumor margins are acceptable in LGG from 2 cm to 5 mm

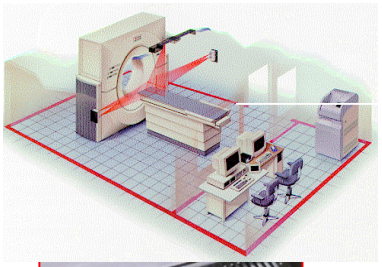
NEW RT TECHNOLOGIES

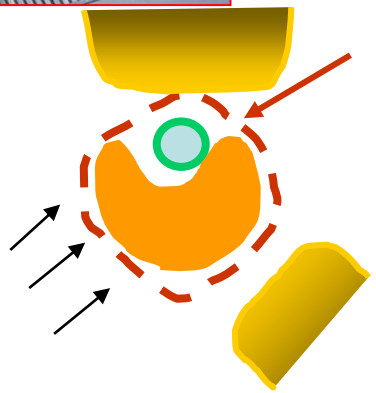
2D → 3DCRT → IMRT/VMAT

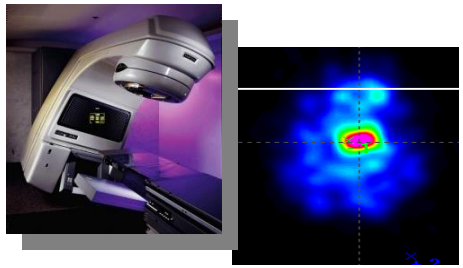


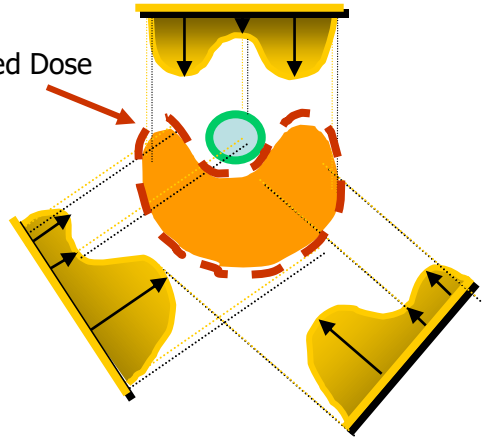












RT in Low Grade Glioma (LGG)

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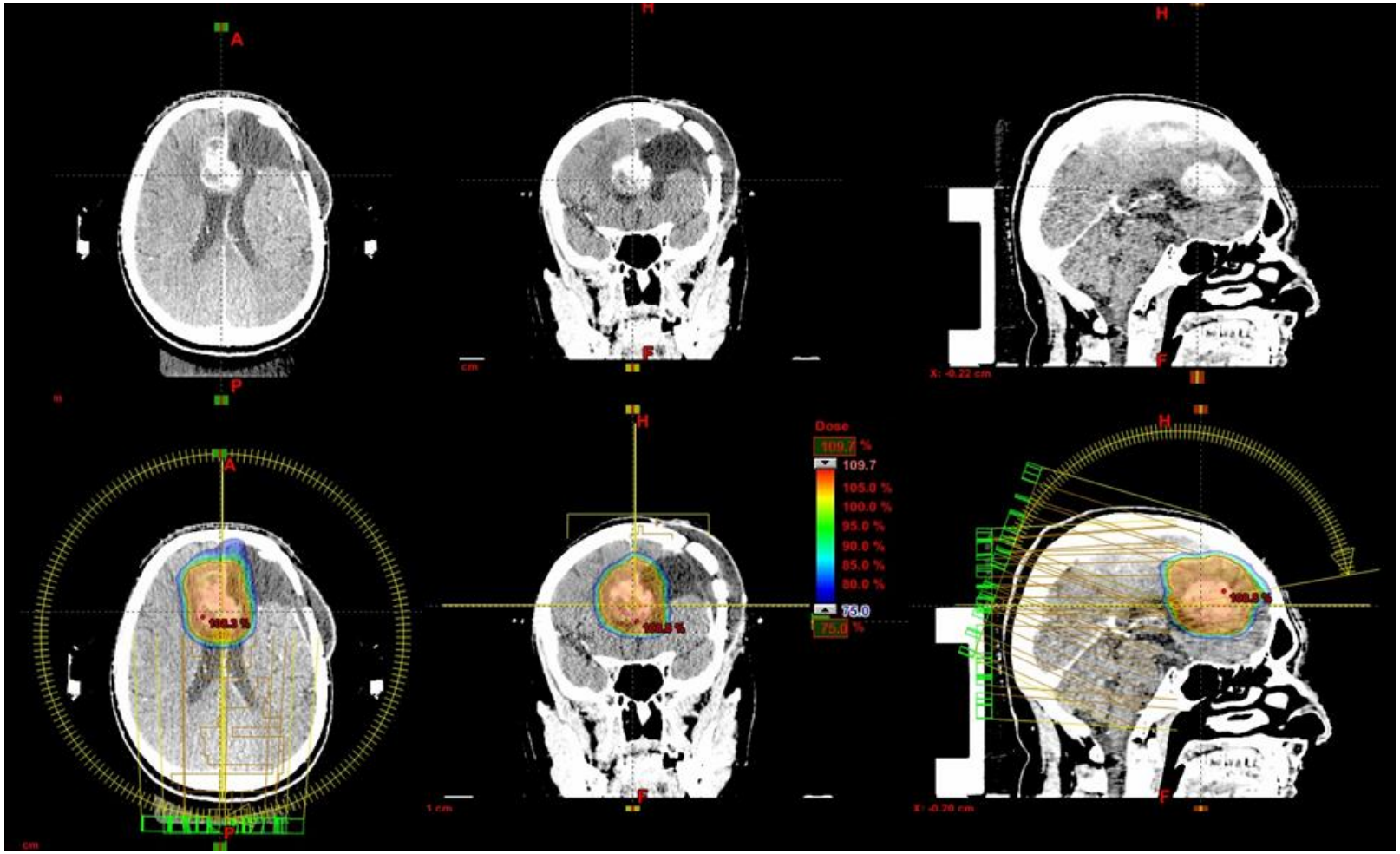
NEW RT TECHNOLOGIES: VMAT



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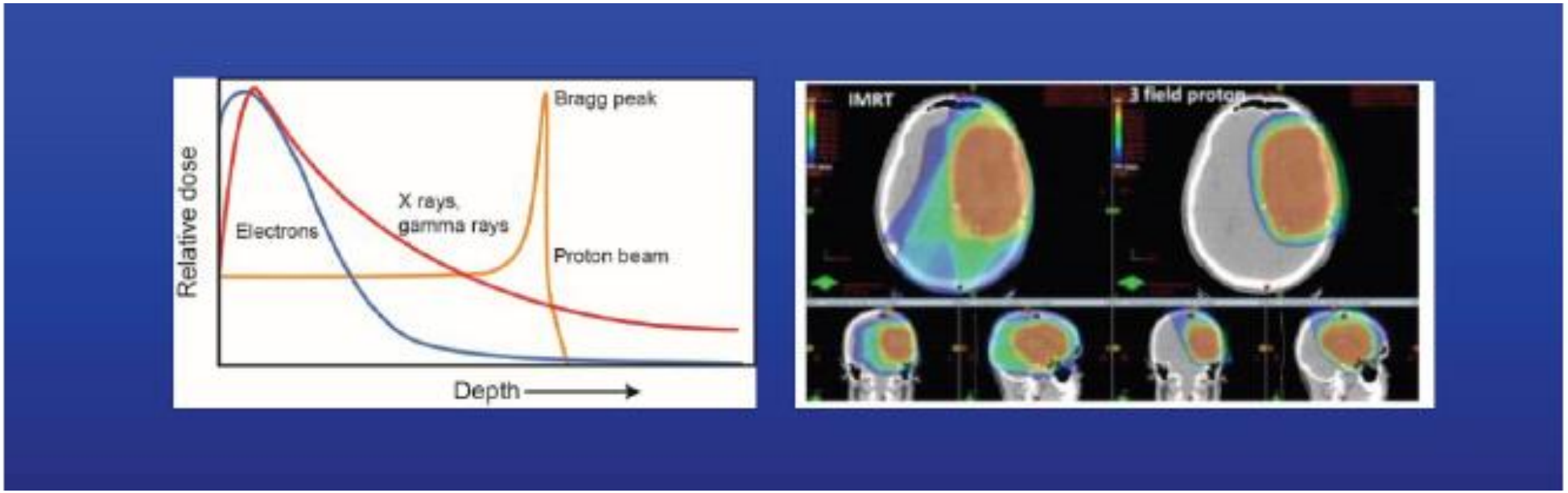
NEW RT TECHNOLOGIES: PROTON vs PHOTON



RT in ANAPLASTIC GLIOMA (old Grade III)

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Adjuvant RT is the standard treatment in anaplastic glioma

Two randomized trials published at the end of 70s showed

SUPERIORITY

SURGERY+RT compared to SURGERY alone

(p=0.005)

Higher doses are needed → 60 Gy in 30 fractions

RT in ANAPLASTIC GLIOMA (old Grade III)

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In some selected cases with favorable molecular profile

Adjuvant RT can be discussed

→ oliodendroglioma histology (1p19q-codeleted)

younger age

IDH mutated

MGMT methylated

GTR also of FLAIR abnormalities

RT in ANAPLASTIC GLIOMA (old Grade III)

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NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide

W.Wick, JCO 2009,2016

Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

MJ. Van de Bent,JCO 2013

Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402

G.Cairncross, JCO 2013

CHT ASSOCIATED TO RT

CATNON TRIAL
ASCO 2019

CODEL ONGOING

RT in ANAPLASTIC GLIOMA (old Grade III)

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NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide

W.Wick, JCO 2009

RT vs PCV vs TMZ"

318 patients anaplastic glioma

Time to treatment failure (TTF)

Median TTF, PFS, OS	similar for arms
Initial radiotherapy or chemotherapy	achieved comparable results

RT in ANAPLASTIC GLIOMA (old Grade III)

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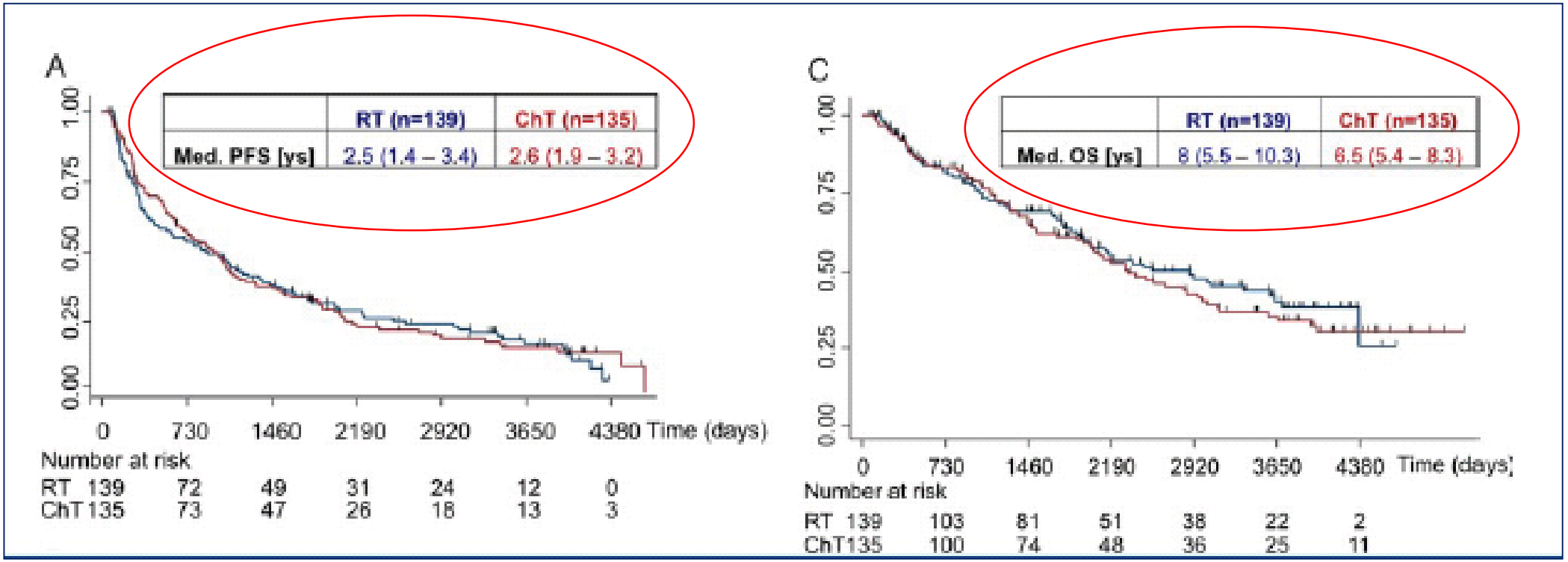
Long term results of NOA-04 showed that Chemotherapy (PCV or TMZ) is not superior to Radiation Therapy



Wick W et al NO 2016

ROLE of RT in LOWER GRADE GLIOMA

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TAKE HOME MESSAGE

- In high risk LGG adjuvant radiation therapy is a valid treatment option
- An advanced imaging for tumor volume delineation and RT planning is needed
- New RT technological improvements allow to perform an effective treatment with maximum sparing of OARs and normal brain preserving neurocognitive functions

- RT is always recommended in case of anaplastic glioma
- In selected cases RT can be delayed
- A multidisciplinary evaluation is mandatory


Thank you