

Spatial Fractionation: Partial Tumor Irradiation

Dr. Tubin Slavisa

ASS. PROFESSOR AT ALBERT EINSTEIN COLLEGE OF MEDICINE NEW YORK
DIRECTOR OF CLINICAL RADIOBIOLOGY, SCIENTIFIC CO-DIRECTOR
MEDAUSTRON CENTER FOR ION THERAPY AND RESEARCH



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Disclosures

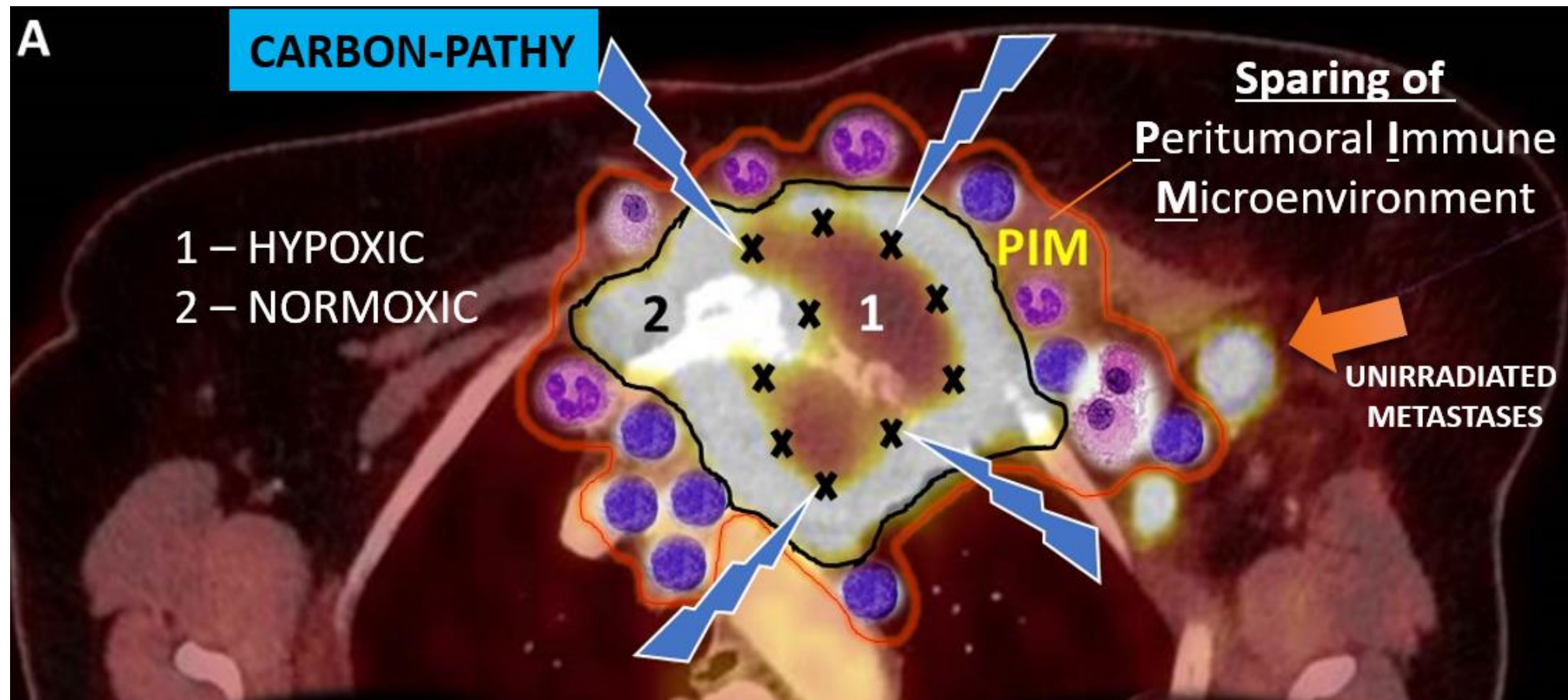


I have no relevant financial relationships with ineligible companies to disclose.

„PATHY“ Approach

- PATHY: Partial Tumor irradiation targeting Hypoxic segment
- Novel, unconventional, immunomodulatory approach
- Designed for exploitation of the non-targeted effects of RT:
bystander and abscopal.
- ***SBRT-PATHY*²⁰¹⁵ / *Particle-PATHY* / *CARBO-PATHY*²⁰²⁰**

- **CARBO-PATHY** = **CARBON** ion-based **PA**rtial **Tu**mor irradiation targeting **HY**poxic segment
 - IMMUNOGENEICITY = CARBON ions + highly heterogeneous dose + HYPOXIC target + IMMUNE-SPARING.



-PATHY:

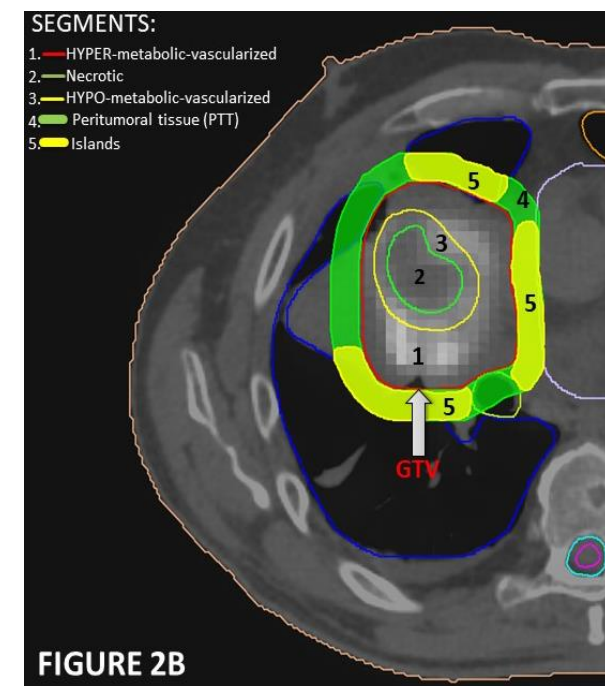
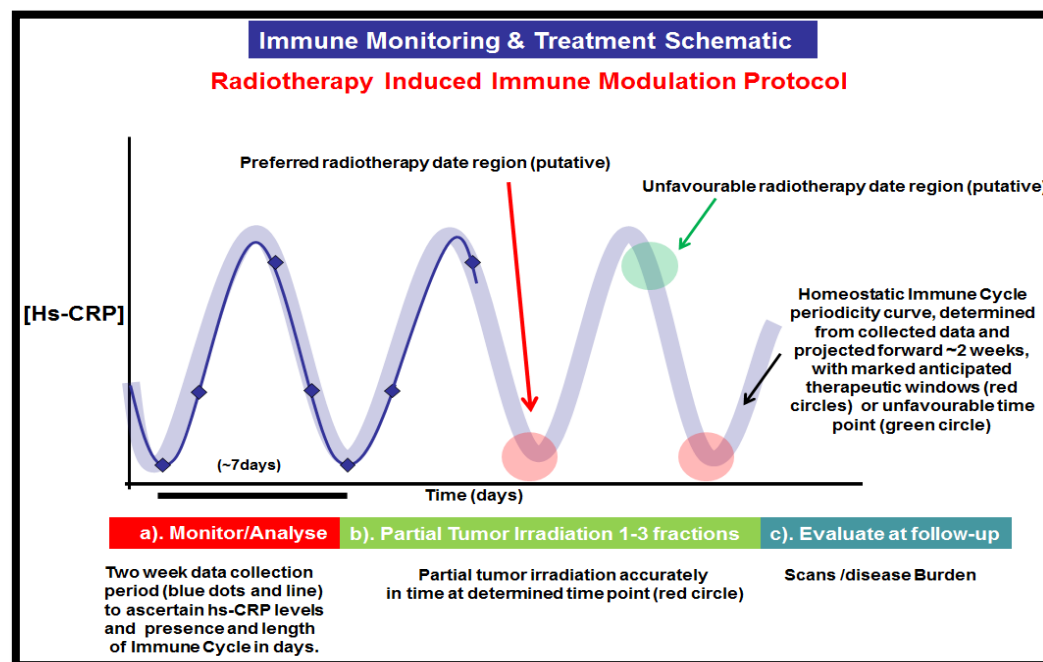
Partial Tumor irradiation targeting Hypoxic tumor segment

- 3 key-components of -PATHY:

1.) PARTIAL TUMOR IRRADIATION TARGETING HYPOXIC SEGMENT


2.) SPARING OF PERITUMORAL IMMUNE MICROENVIRONMENT (NEW OAR)

3.) TIME-SYNCHRONIZED IMMUNE-GUIDED TUMOR IRRADIATION



TARGET-VOLUME: HYPOXIC TUMOR SEGMENT

1. Tumor hypoxia is a potent immunosuppressor (abolished IFN-1 β response, enhances expression of immunosuppressive proteins),
2. Hypoxic tumor cells stronger abscopal inductor.



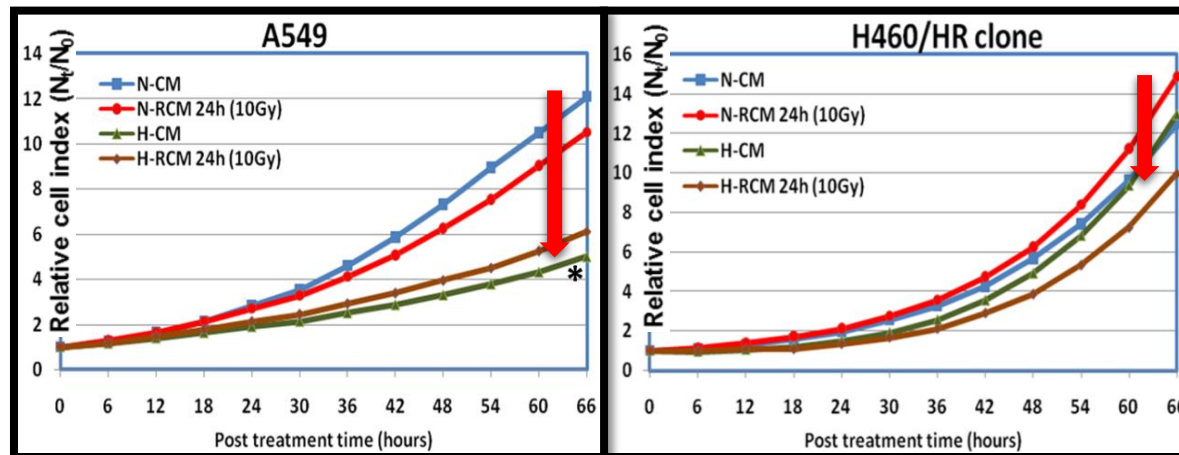
ORIGINAL ARTICLE
Radiation and hypoxia-induced non-targeted effects in normoxic and hypoxic conditions in human lung cancer cells
 Slavisa Tubin^{a*}, Mansoor M. Ahmed^b and Seema Gupta^{a†}
^aDepartment of Radiation Oncology, Sylvester Comprehensive Cancer Center, University of Miami Leonard Miller School of Medicine, Miami, FL, USA; ^bDivision of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Radiotherapy Development Branch, Radiation Research Program, Rockville, MD, USA

2010-2011 Translational Oncology Research



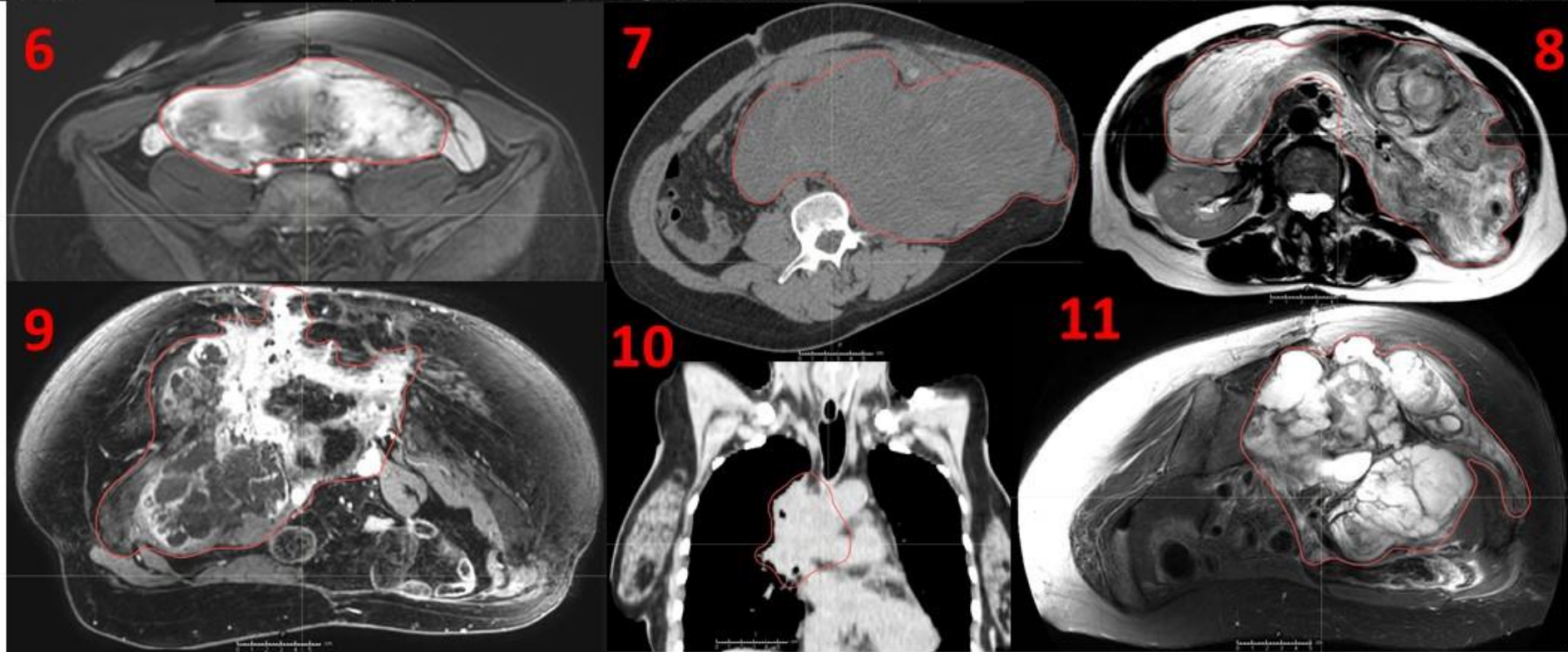
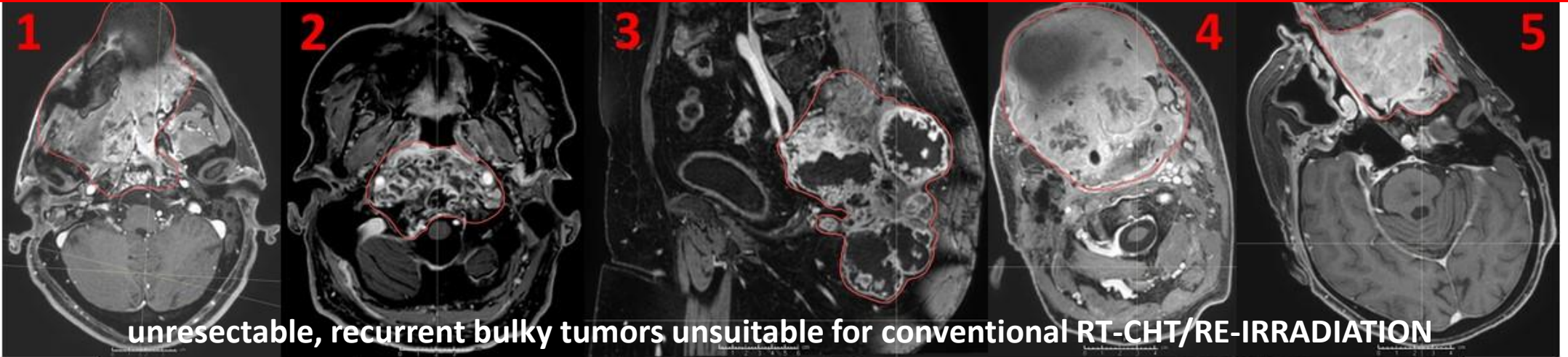
PRECLINICAL RESULTS ON BYSTANDER/ABSCOPAL EFFECT-INDUCTION:

10Gy SINGLE DOSE irradiation of the HYPOXIC (vs. normoxic) tumor = stronger bystander effect!



TUMOR GROWTH after induction of abscopal effect with 10Gy x 1 to the hypoxic tumor

INDICATIONS

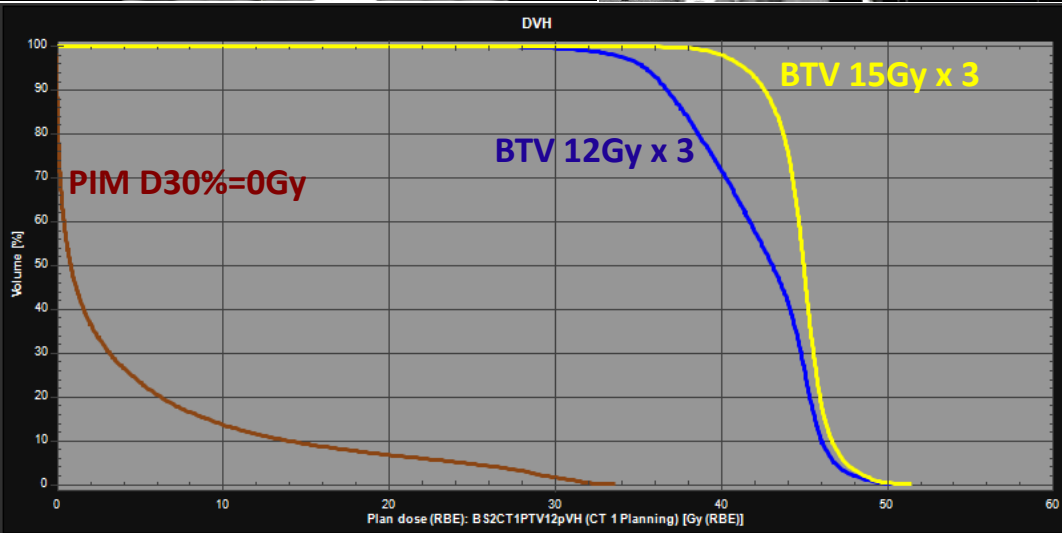
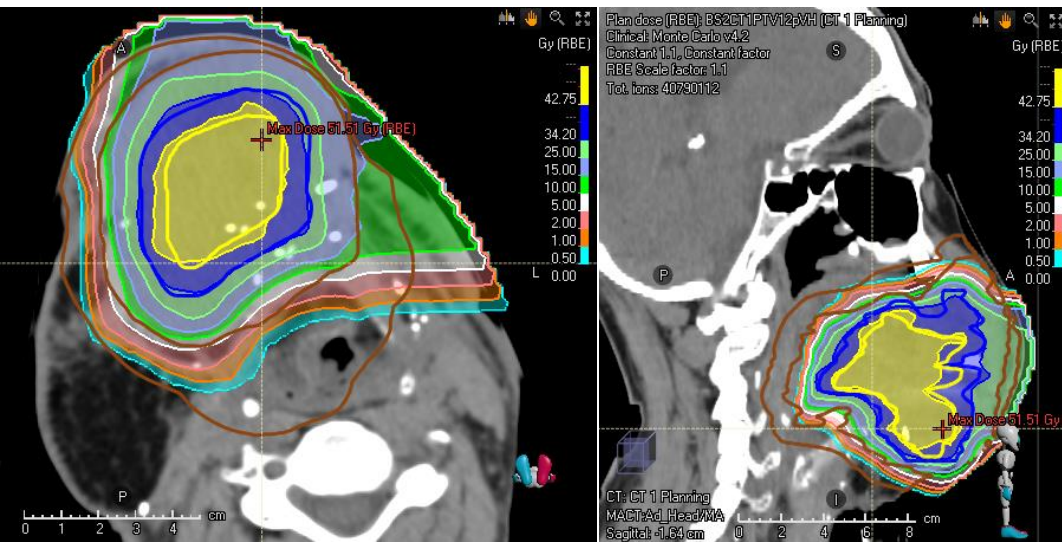


DOSE: HIGH, HETEROGENEOUS, GRADIENTS

Prescription of heterogeneous dose(-gradients):

INITIAL: 10-12Gy x 1 to 60-70% (2015)

ESCALATED: 15Gy x 3 to 60-70% (2020)

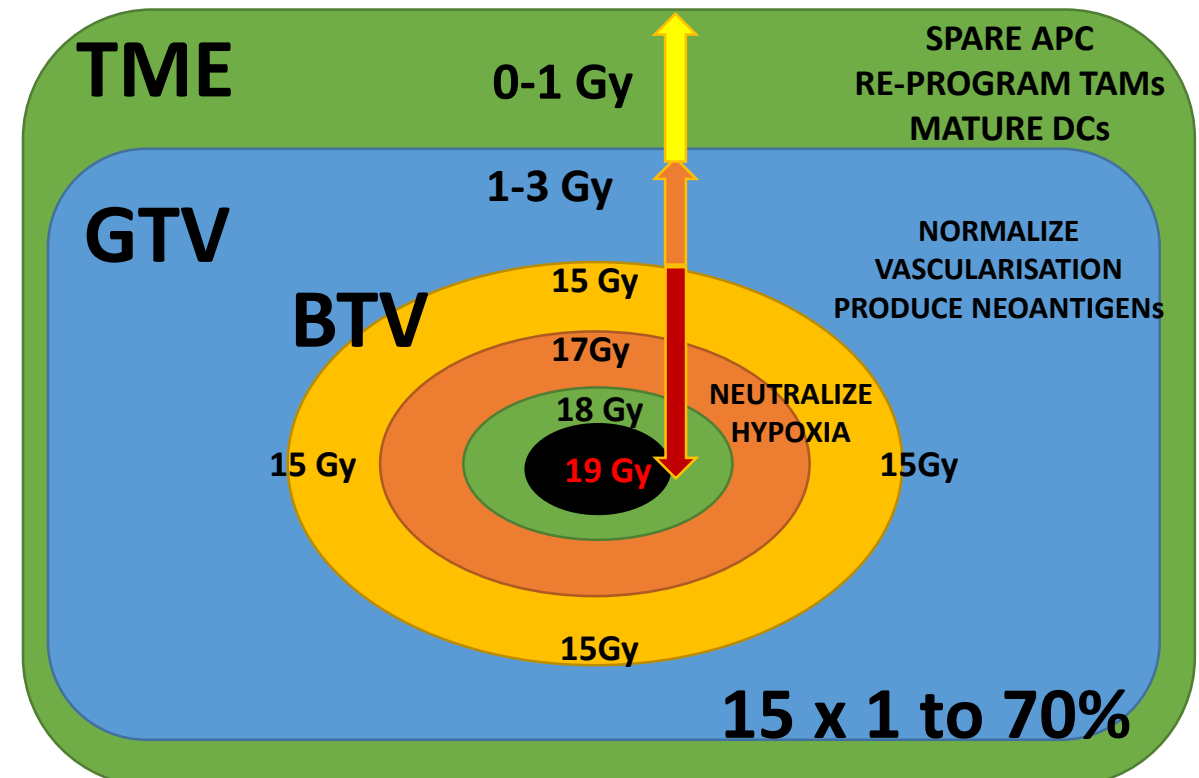


Dose axis: Absolute Relative max Relative dose [Gy (RBE)]: Volume axis: Relative Absolute

Beams (Current) Energy layer (Current) BEV (Current)
 Dose Statistics Clinical Goals Biological Response Plan Fraction Schedule

ROI statistics POI statistics

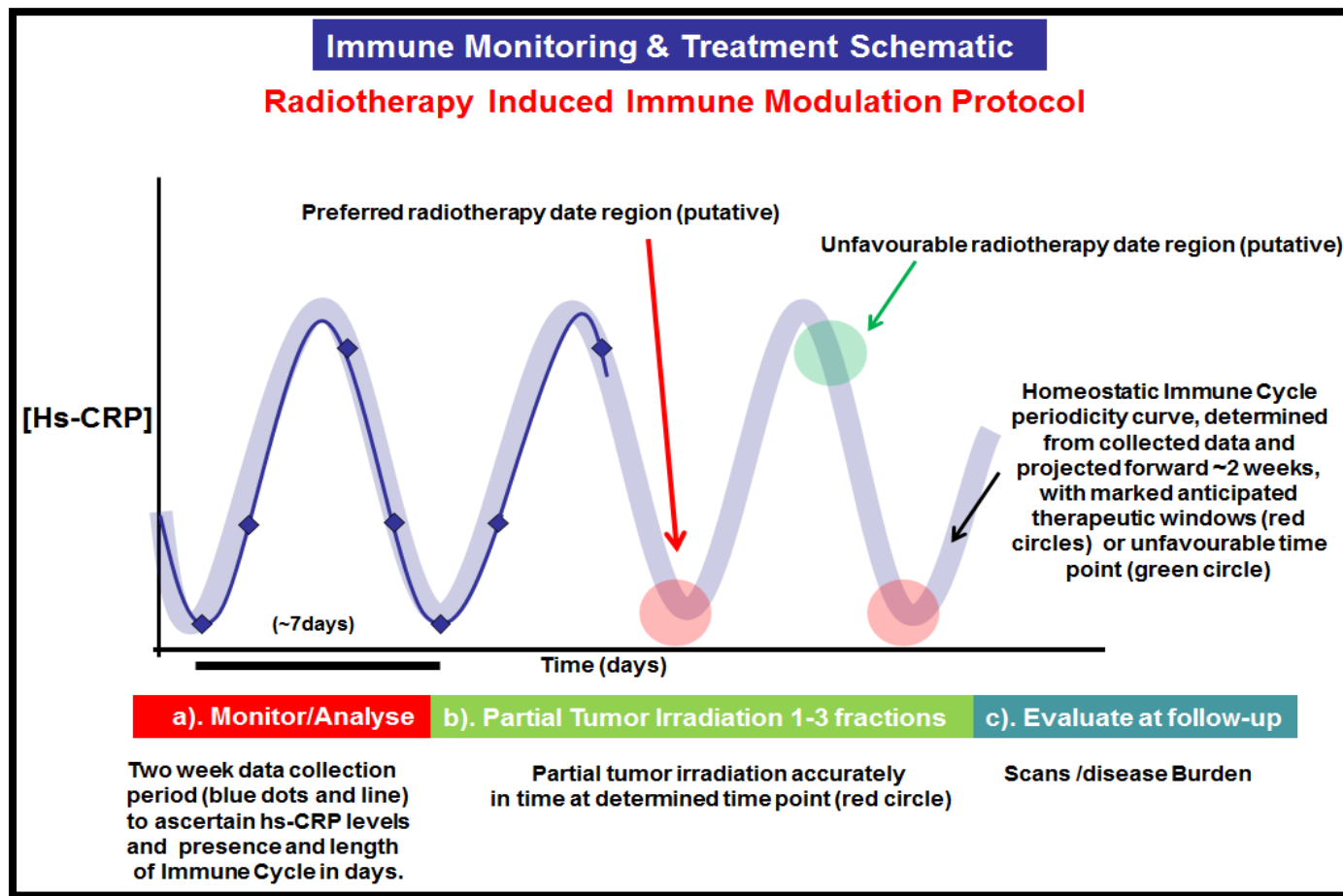
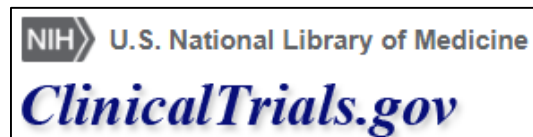
Dose	ROI	ROI vol. [cm ³]	Dose [Gy (RBE)]							% of
			D99	D98	D95	Average	D50	D2	D1	
Plan dose (RBE): BS2C...	■ BTV 12Gy RBE x 3	163.49	31.68	33.51	35.42	42.14	43.08	47.97	48.76	0 %
Plan dose (RBE): BS2C...	■ BTV 15Gy RBE x 3	81.30	39.05	39.95	41.41	44.80	45.00	48.64	49.15	0 %
Plan dose (RBE): BS2C...	■ PIMnew	274.37	0.00	0.00	0.00	4.19	0.83	29.28	30.81	0 %



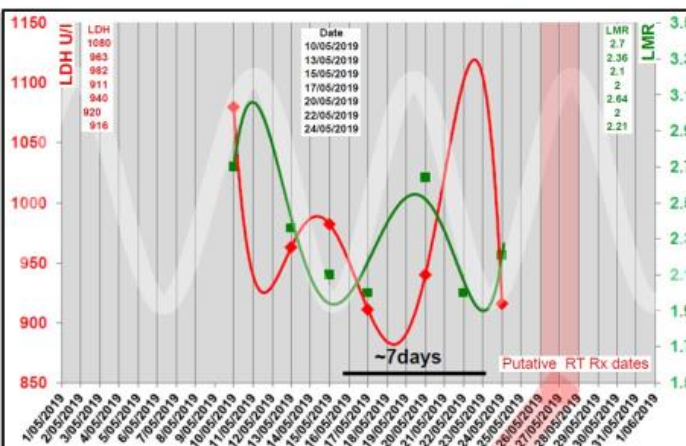
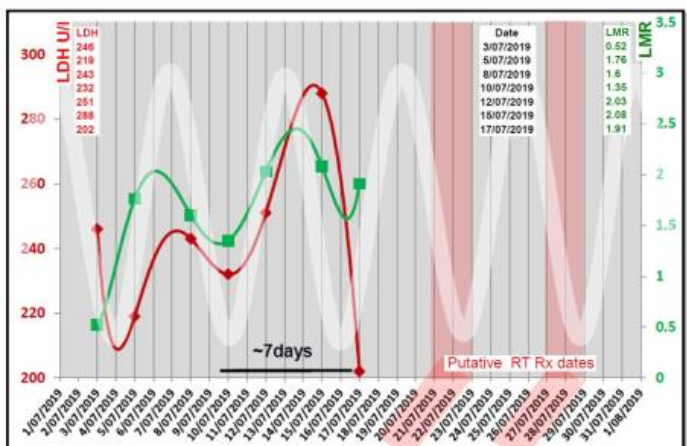
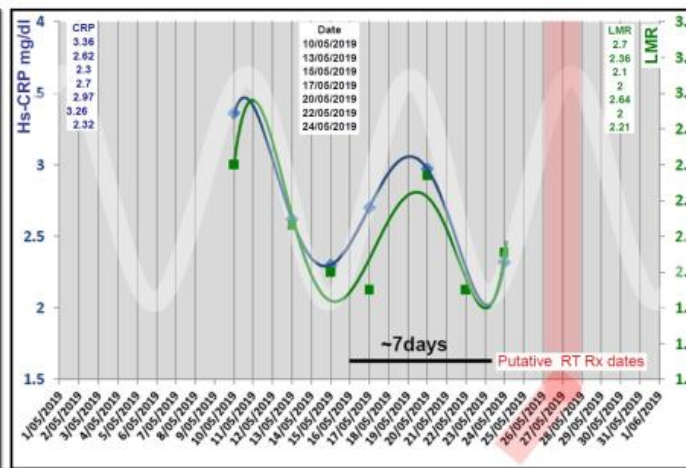
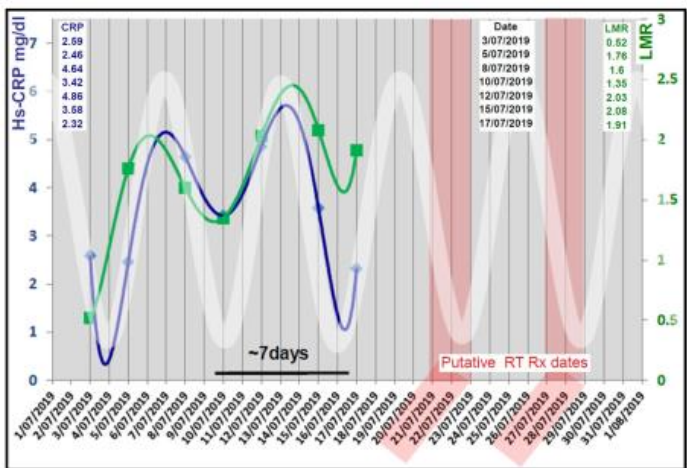
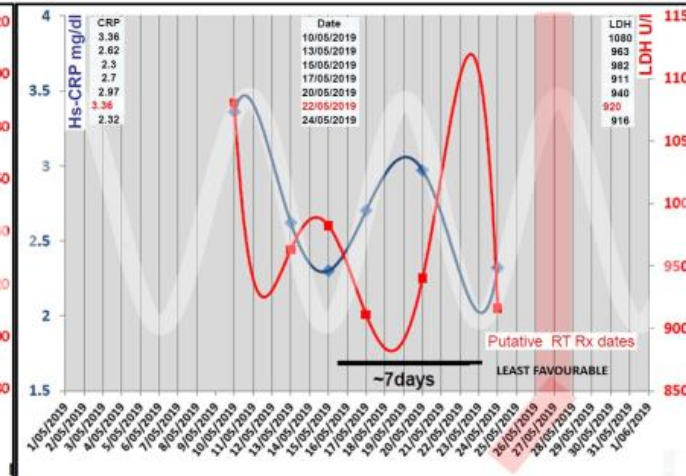
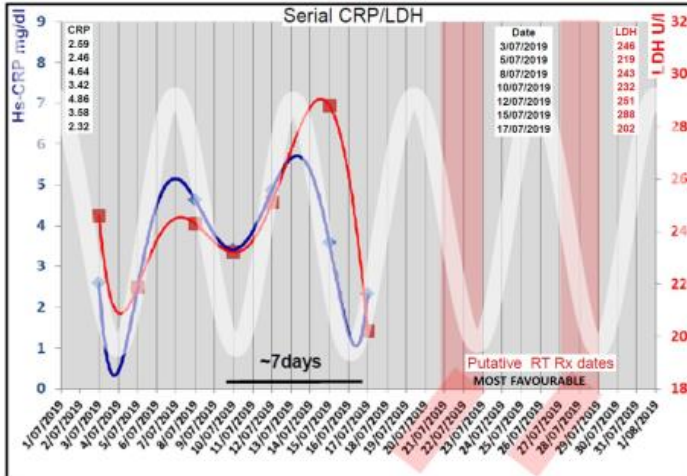
TIMING

TIME-SYNCHRONIZED IMMUNE-GUIDED SBRT-PATHY

ClinicalTrials.gov Identifier: NCT04168320



CRP, LDH, IL-2, IFNg and Lymphocyte/Monocyte analyzed for levels and cyclical fluctuations to determine each patient's idiosyncratic immune cycle's periodicity and then each patient's time-position of initiation of treatment and response to therapy.



Median follow-up: 12 months (4–22).

Optimally synchronized SBRT-PATHY with the favourable immune cycle period was associated with improved clinical outcomes (three complete responses plus significant abscopal effects in 3 patients).

Time-synchronized immune-guided SBRT partial bulky tumor irradiation targeting hypoxic segment while sparing the peritumoral immune microenvironment

Slavisa Tubin¹, Martin Ashdown² and Branislav Jeremic³

PUBLISHED
DATA

120 patients

Time-synchronized immune-guided SBRT partial bulky tumor irradiation targeting hypoxic segment while sparing the peritumoral immune microenvironment. 2019
Tubin S, Ashdown M, Jeremic B.

Mono-institutional Phase 2 Study of Innovative Stereotactic Body RadioTherapy targeting Partial Tumor HYpoxic (SBRT-PATHY) Clonogenic Cells in Unresectable Bulky Non-Small Cell Lung Cancer: Profound Non-Targeted Effects by Sparing Peri-Tumoral Immune Microenvironment.
Tubin S, Khan M.M, Salerno G, Mourad W.F, Weisi Y, Jeremic B.

Novel stereotactic body radiation therapy (SBRT)-based partial tumor irradiation targeting hypoxic segment of bulky tumors (SBRT-PATHY): improvement of the radiotherapy exploiting the bystander and abscopal effects.
Tubin S¹, Popper HH², Brcic L².

International Journal of **Radiation Oncology** ASTRO
biology • physics

Re-Treatment of Recurrent Bulky Lesions with High Single Dose Partial Irradiation Targeting the Hypoxic Tumor Segment (PITH): Case Series
M. Massaccesi • N. Dinapoli • L. Boldrini • ... G.C. Mattiucci • M.A. Gambacorta • V. Valentini •

88
CLINICAL

2 PRECLINICAL

Radiation and hypoxia-induced non-targeted effects in normoxic and hypoxic conditions in human lung cancer cells
Slavisa Tubin, Mansoor M. Ahmed & Seema Gupta

Hunting for abscopal and bystander effects: clinical exploitation of non-targeted effects induced by partial high-single-dose irradiation of the hypoxic tumor segment in oligometastatic patients
Slavisa Tubin and Wolfgang Raunik

Manipulation of radiation-induced bystander effect in prostate adenocarcinoma by dose and tumor differentiation grade: In vitro study
Slavisa Tubin¹, Maurizio Valeriani¹, Gerardo Salerno², Stefano Bracci¹, Antonella Stoppacciaro³, Patrizia Cardelli⁴, Mattia Falchetto Osti¹, Vitaliana De Sanctis¹, Giuseppe Minniti¹ & Riccardo Maurizi Enrici¹

A Case Report on Metastatic Thyroid Carcinoma: Radiation-induced Bystander or Abscopal Effect?
Slavisa Tubin*, Franco Casamassima, Claudia Menichelli, Gabriella Pastore, Alessandro Fanelli and Rossana Crisci
Istituto Ricerche Cliniche Ecomedica, Empoli, Florence, Italy

Shifting the Immune-Suppressive to Predominant Immune-Stimulatory Radiation Effects by SBRT-Partial Tumor Irradiation Targeting Hypoxic Segment (SBRT-PATHY)
Slavisa Tubin^{1,*}, Seema Gupta², Michael Grusch³, Helmut H. Popper⁴, Luka Brcic⁴, Martin L. Ashdown⁵, Samir N. Khlif⁷, Barbara Peter-Vörösmarty³, Martin Hyden⁶, Simone Negrini⁷, Piero Fossati¹ and Eugen Hug¹

Novel Carbon Ion and Proton Partial Irradiation of Recurrent Unresectable Bulky Tumors (Particle-PATHY): Early Indication of Effectiveness and Safety
Slavisa Tubin^{1,*}, Piero Fossati, Antonio Carlino, Giovanna Martino, Joanna Gora, Markus Stock and Eugen Hug





Novel Carbon Ion and Proton Partial Irradiation of Recurrent Unresectable Bulky Tumors (Particle-PATHY): Early Indication of Effectiveness and Safety

Slavisa Tubin ^{1,*}, Piero Fossati, Antonio Carlino, Giovanna Martino, Joanna Gora, Markus Stock and Eugen Hug

Review

Shifting the Immune-Suppressive to Predominant Immune-Stimulatory Radiation Effects by SBRT-Partial Tumor Irradiation Targeting Hypoxic Segment (SBRT-PATHY)

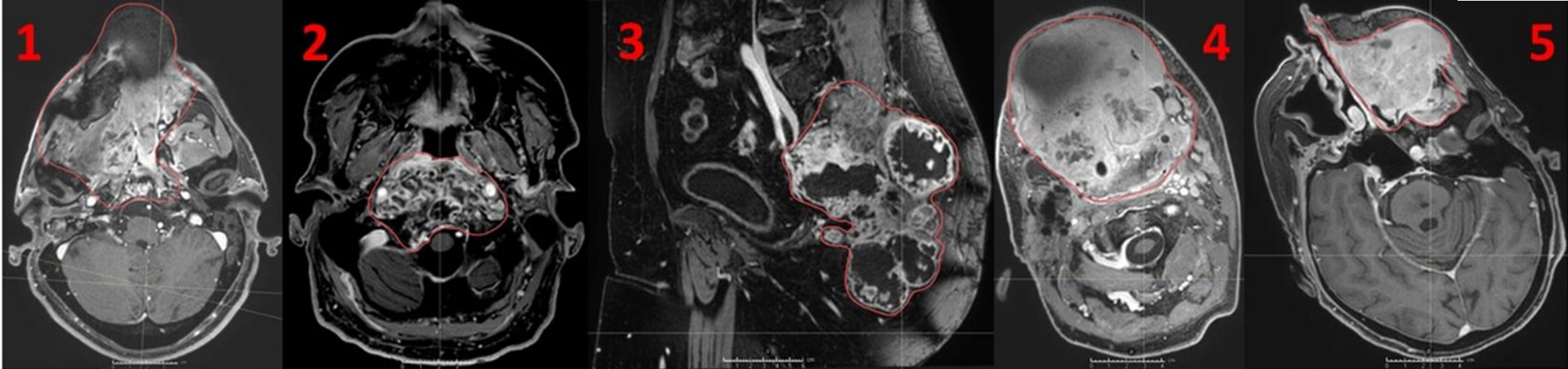
Slavisa Tubin ^{1,*}, Seema Gupta ², Michael Grusch ³, Helmuth H. Popper ⁴, Luka Brcic ⁴, Martin L. Ashdown ⁵, Samir N. Khleif ², Barbara Peter-Vörösmarty ³, Martin Hyden ⁶, Simone Negrini ⁷, Piero Fossati ¹ and Eugen Hug ¹

Table 1. Treatment characteristics of the selected studies.

Authors (year of publication) [reference]	Tubin et al. (2017) [21]	Tubin et al. (2019) [37]	Massaccesi* et al. (2019) [38]	Tubin et al. (2019) [39]	Tubin** et al. (2020) [40]	Tubin et al. (2019) [41]	Tubin** et al. (2020) [42]
Type of study	Retrospective	Retrospective phase II	Retrospective	Retrospective	Retrospective	Prospective	Prospective phase I
			case series (re-irradiation)				
Number of patients underwent SBRT-PATHY	7	20	8	23	3	8	20
Median follow up (months)	6 (2-9)	13 (4-27)	7 (1-15)	9.4 (4-20)	5.3 (3-7)	11.8 (4-22)	9 (4-12)
Local control (bystander effect)	100%	95%	83%	96%	67%	75%	73%
Abscopal response	28.6%	45%	Not evaluable	52%	Not evaluable	50%	47%
Symptom relief	100%	80%	100%	96%	67%	88%	82%
Treated symptoms	Dyspnea, pain.	Dyspnea, pain, cough, hemoptysis.	Pain, bleeding	Dyspnea, pain, cough.	Pain, Dysphagia.	Dyspnea, pain, cough.	Dyspnea, pain, cough, haemoptysis, edema-extremities, dysphonia.
Toxicity	none	Fatigue G1 (15%)	none	none	none	none	Fatigue G1 (20%)
Hematological toxicity/leucopenia	none	none	none	none	none	none	none
Median total dose/dose-fraction (Gy)	10/10	10-30/10	10/10	10-30/10	36/12	30/10	30/10

RADIOBIOLOGICAL EFFECTS OF PATHY

Large spectrum of malignancies: lung, H&N, kidney, liver, pancreas, rectum, brain, prostate, adrenal etc.



PATHY: safety

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Type of study	Retrospective	Retrospective phase II	Retrospective case series (re-irradiation)	Retrospective	Retrospective	Prospective	Prospective phase I
Toxicity	none	Fatigue G1 (15%)	none	none	none	none	Fatigue G1 (20%)
Hematological toxic- ity/leucopenia	none	none	none	none	none	none	none

- The only side effects observed were flu-like symptoms -

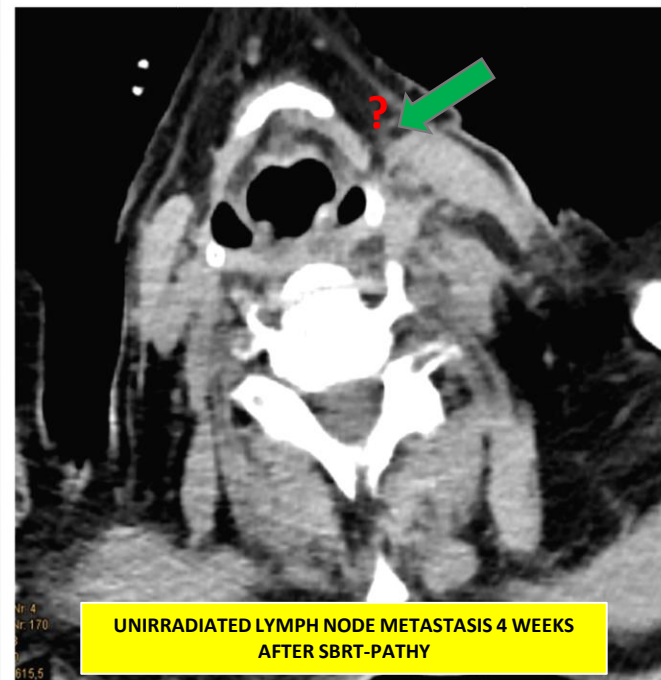
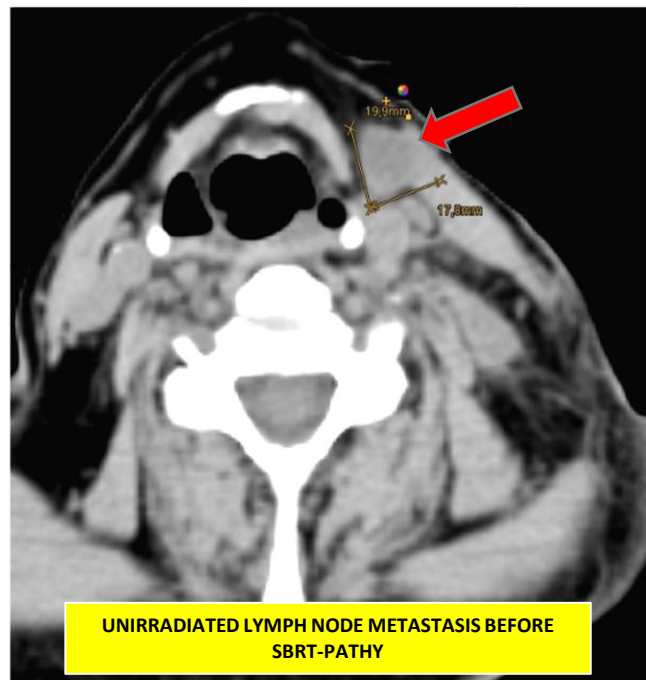
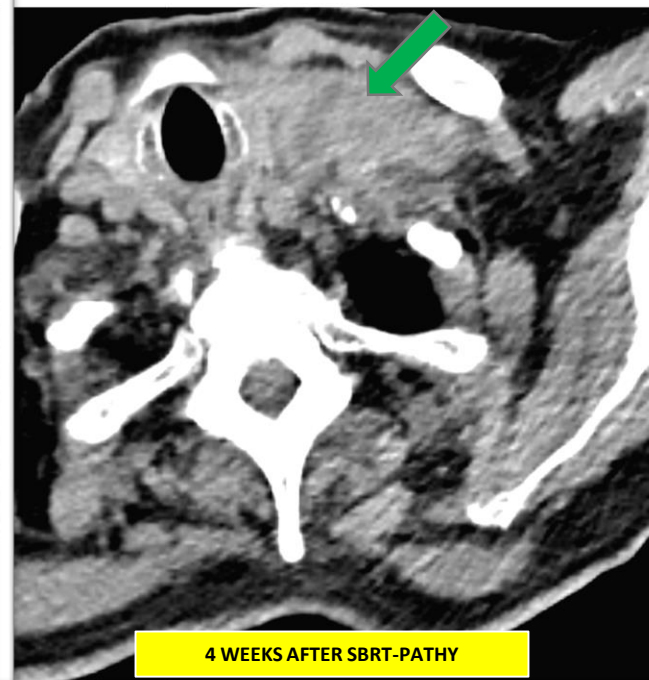
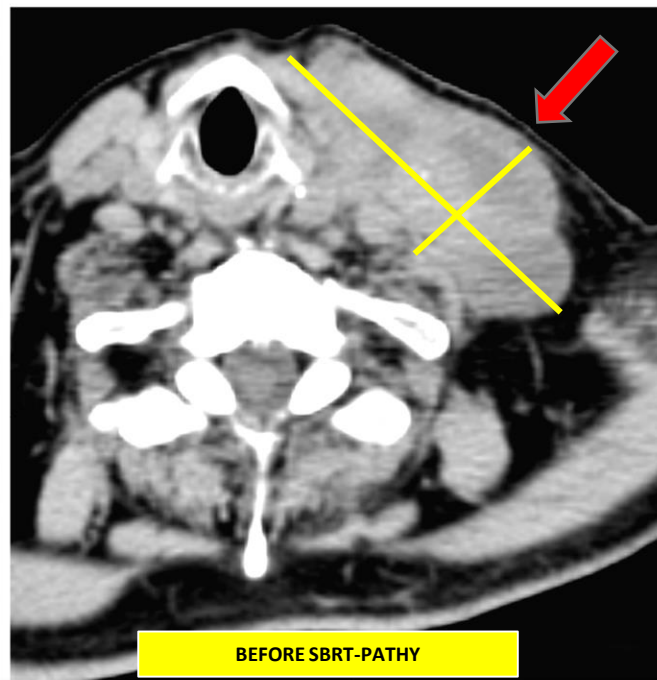
SINGLE FRACTION

METASTATIC MELANOMA

Progressive under immunotherapy

DOSE: 10Gy x 1 to 70%

Disease free till death (2 years)



BYSTANDER EFFECT

PATHY:
immunogenic
effects

ABSCOPAL EFFECT

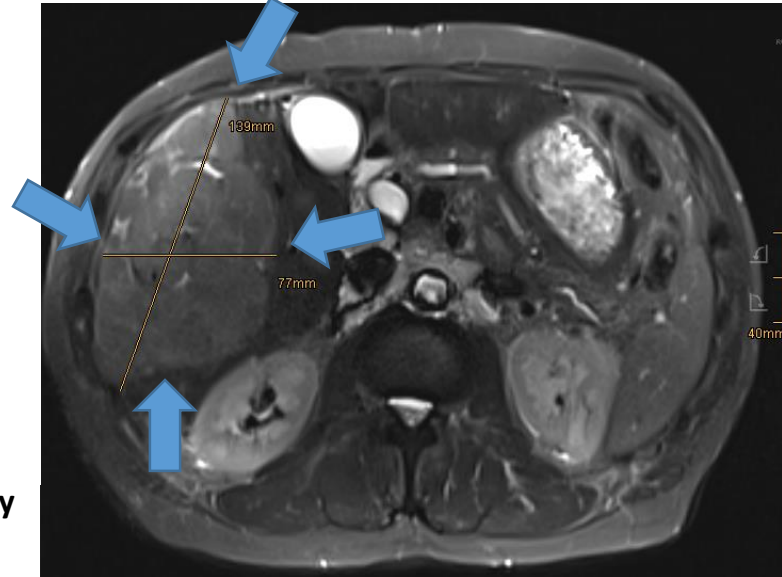
THREE FRACTION

HCC

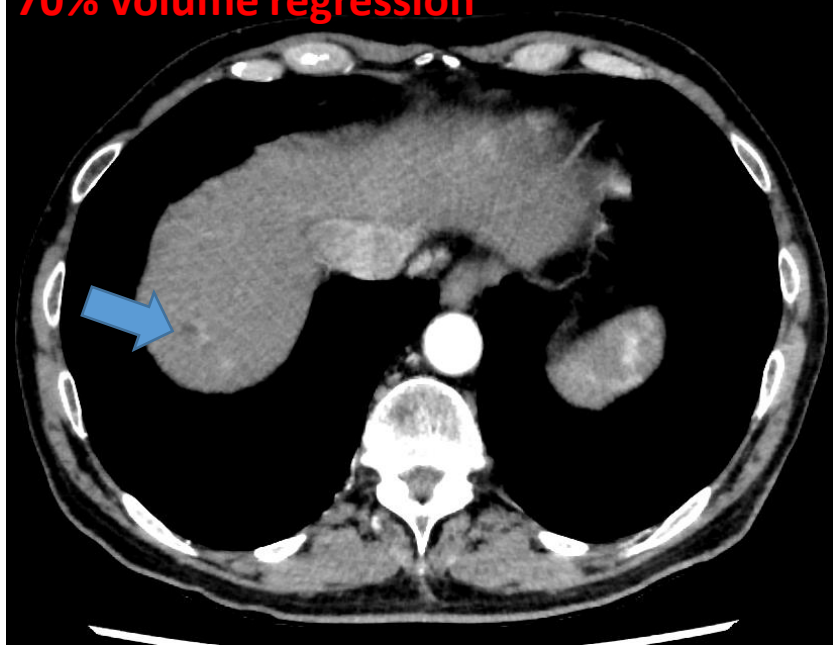
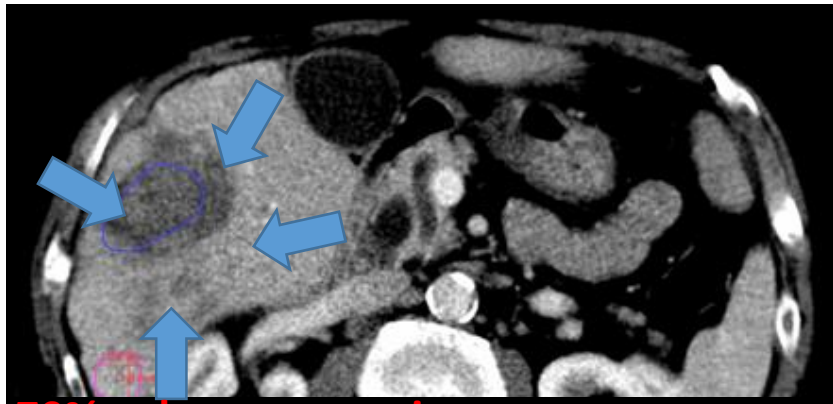
Progressive under immunotherapy

DOSE: 10Gy x 3

BEFORE PATHY



1 MONTH AFTER PATHY



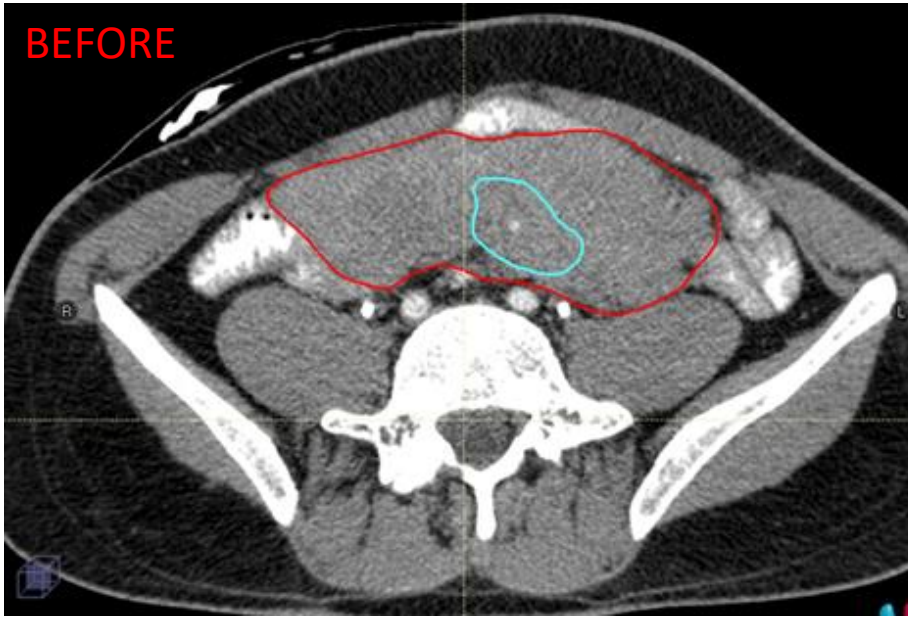
BYSTANDER EFFECT

PATHY:
immunogenic effects

ABSCOPAL EFFECT

HOT

BEFORE



90% volume regression

AFTER

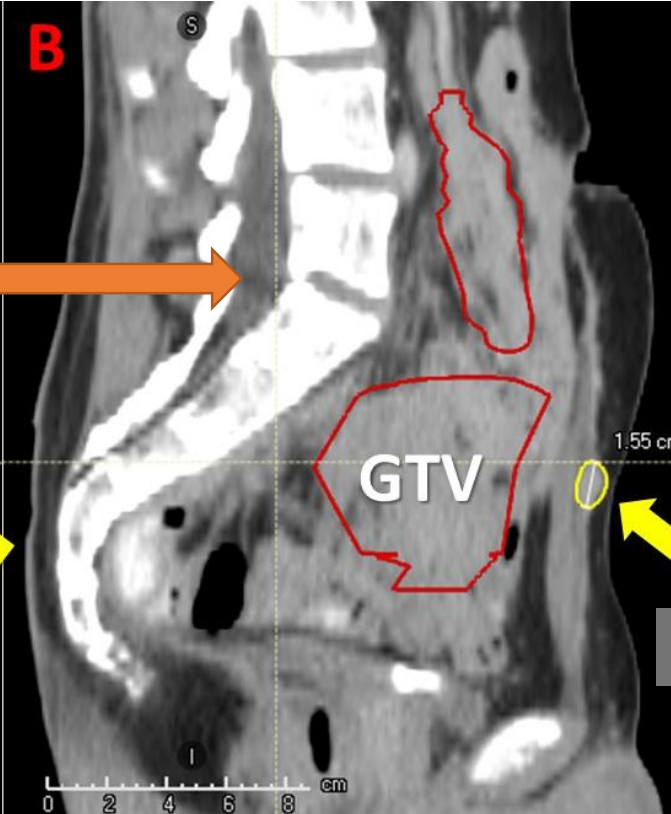
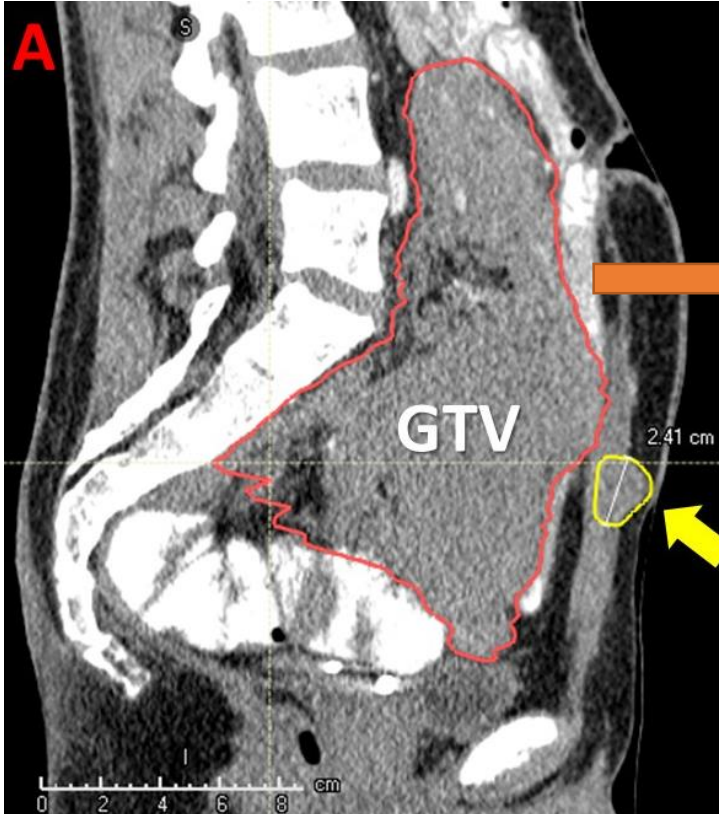


BYSTANDER EFFECT

DESMOID

Progressive under
IMMUNO Tx

DOSE: 10Gy x 3



ABSCOPAL EFFECT

COLD

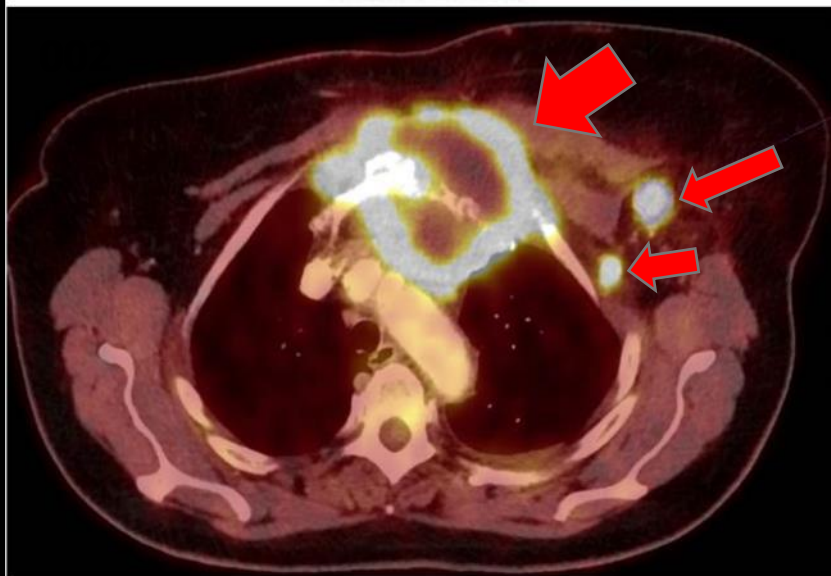
NED / clinical complete response

BREAST (cM1)

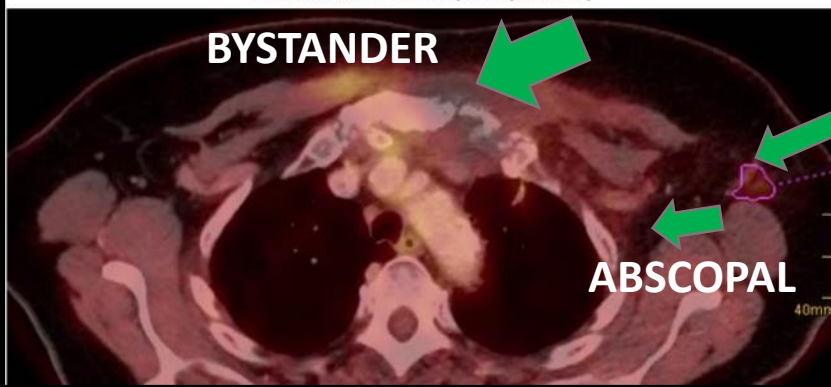
Progressive under CHT

DOSE: 10Gy x 3

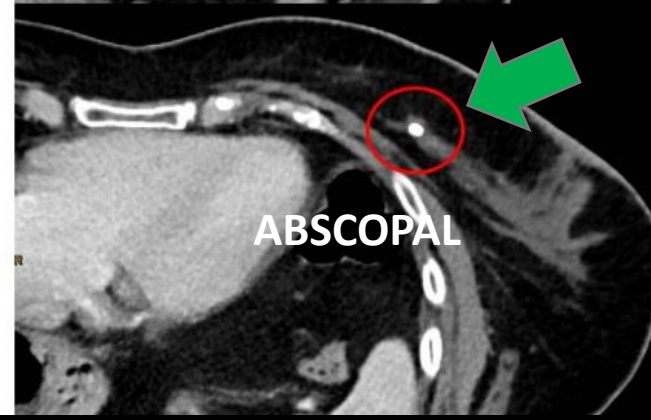
12 cm large sternum bulky metastasis of the primary breast cancer: before SBRT-PATHY; Axillar nodal metastases unirradiated



Sternum bulky metastasis 5 months after SBRT-PATHY (partial irradiation): complete response also at unirradiated nodal sites (abscopal effect)



Unirradiated primary breast cancer: before (up) and after (down) SBRT-PATHY: complete response due to the abscopal effect;



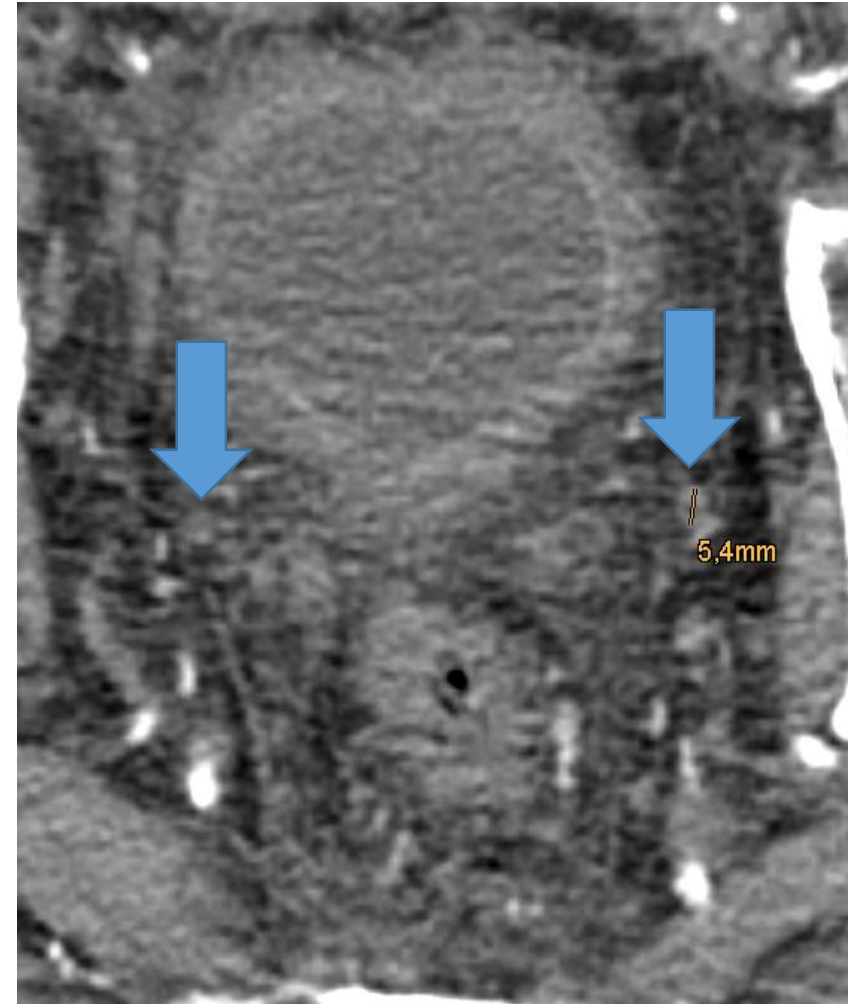
SYNCHRONOUS ABSCOPAL

BEFORE PATHY

2 MONTH AFTER PATHY

RECTUM

DOSE: 10Gy x 3



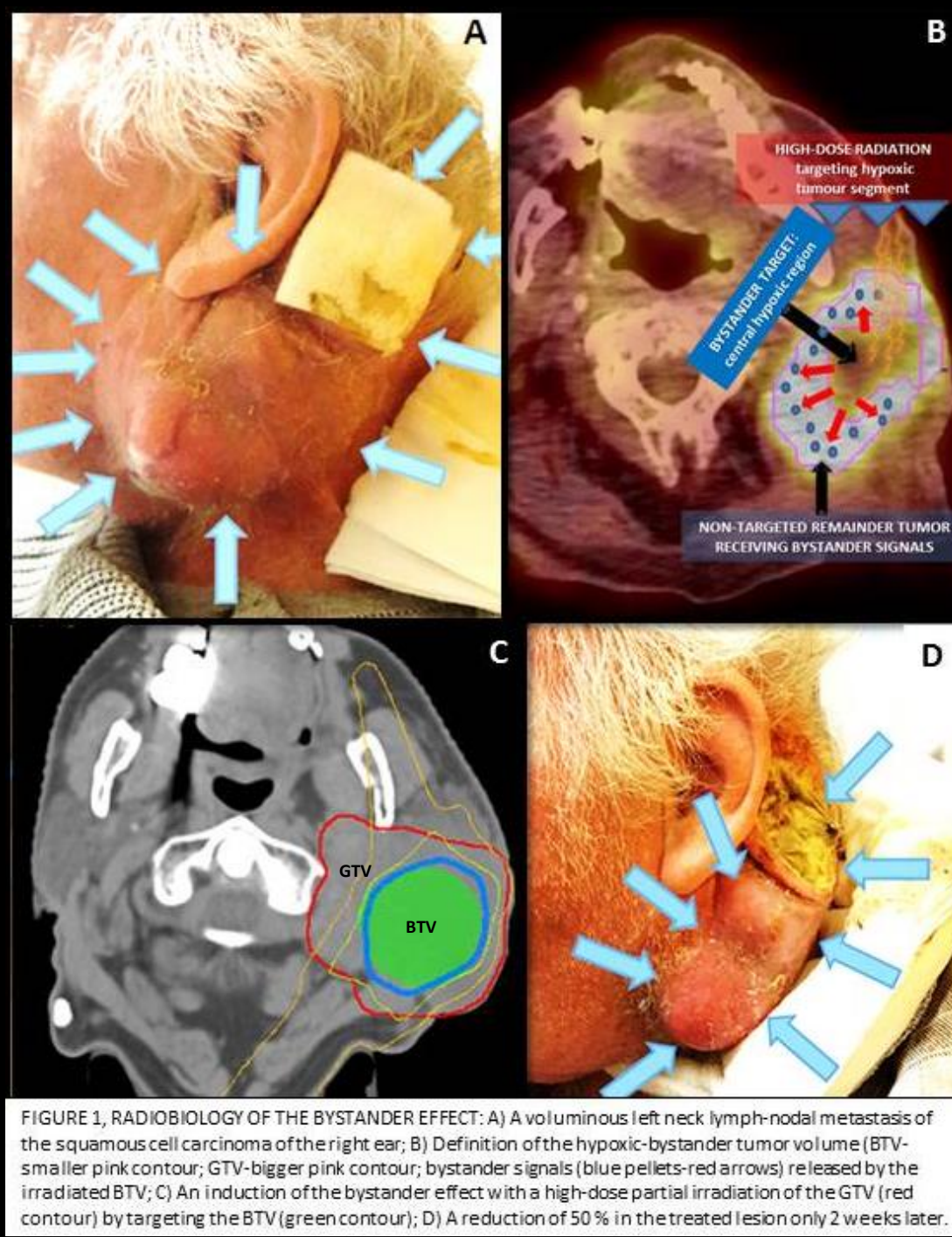
Synchronous colon cancer

70% volume regression

**RESPONSE
DYNAMIC:
AFTER 2 WEEKS!!**

**LYMPH NODE METASTASIS OF
THE SQUAMOUS CELL H&N**

DOSE: 10Gy x 1 to 70%



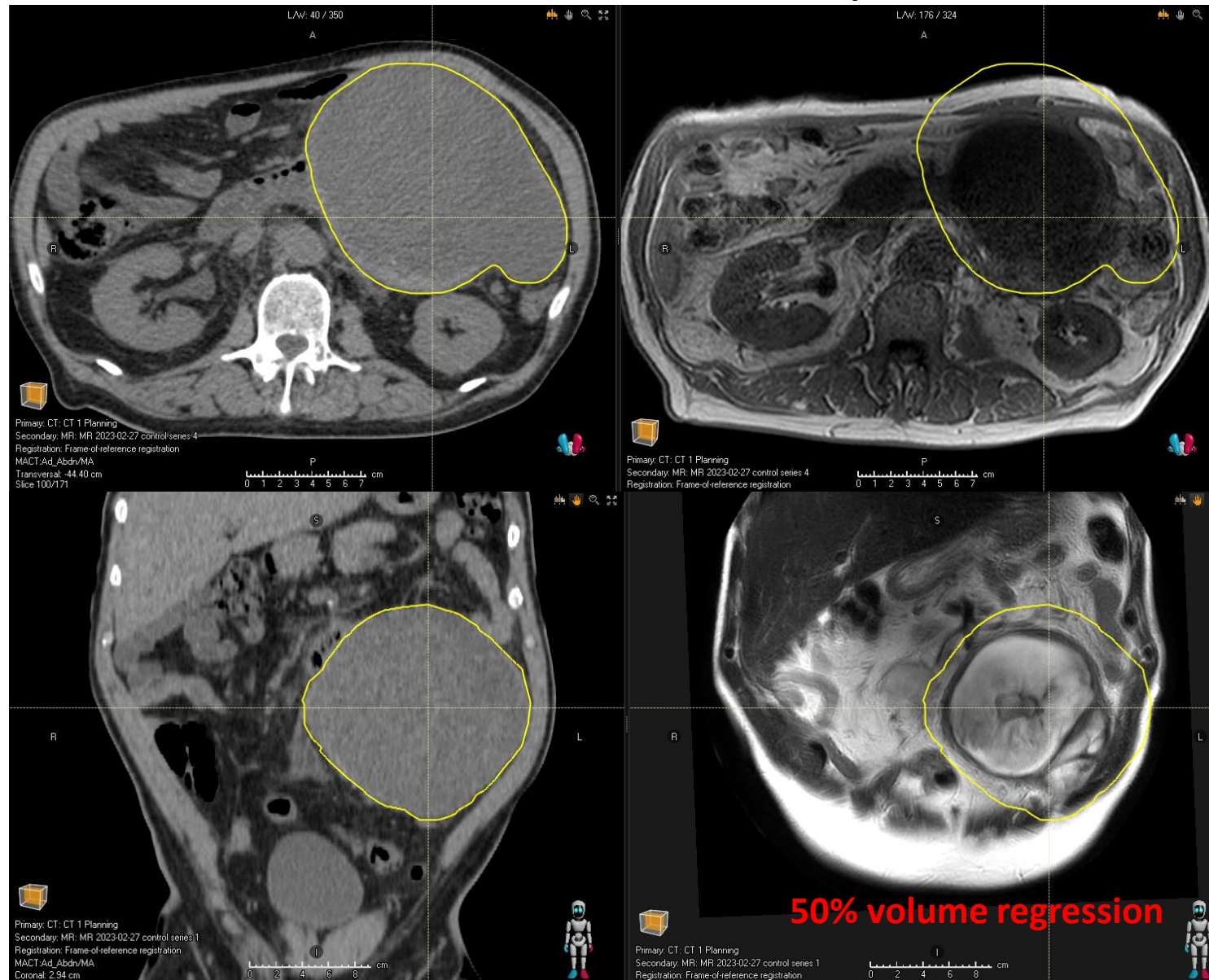
50% volume regression

DEDIFFERENTIATED LIPOSARCOMA

Before CARBO-PATHY

5 months after partial tumor irradiation

**AFTER
5 MONTHS**



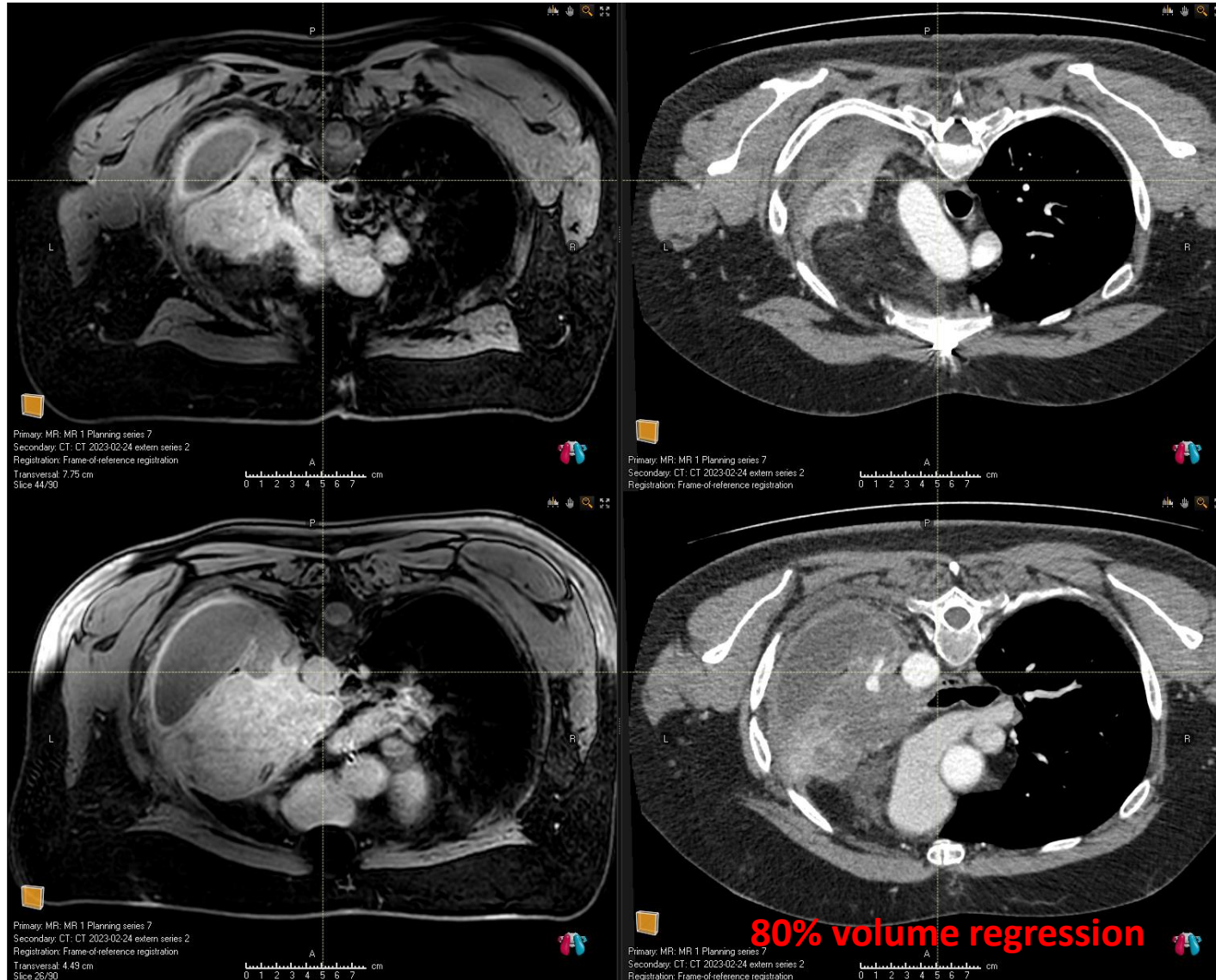
RADIO-RESISTANT TUMORS

DOSE: 15Gy x 3

ADENOID-CYSTIC CARCINOMA OF LUNG

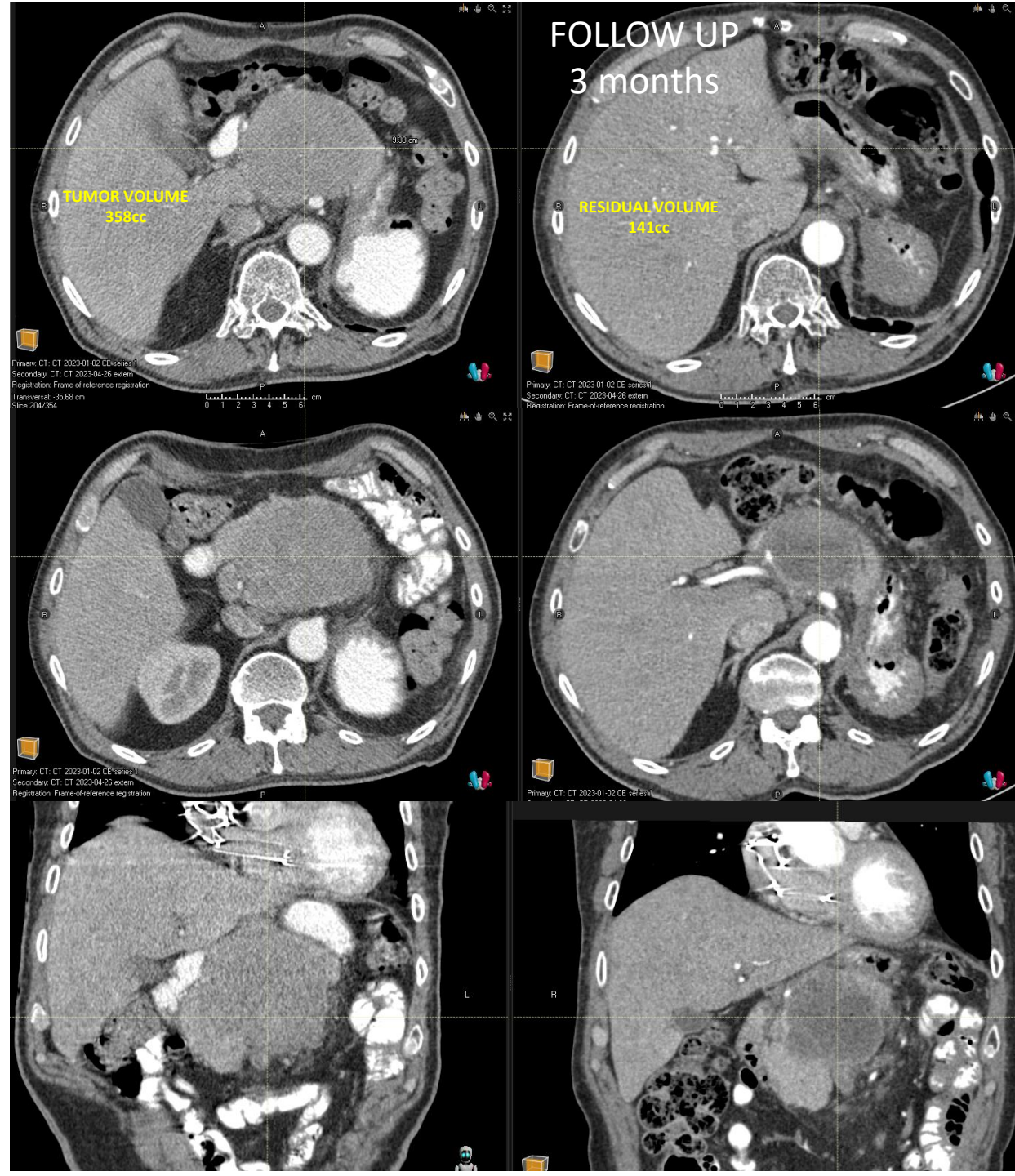
Before CARBO-PATHY

1 month after partial tumor irradiation



RADIO-RESISTANT TUMORS

FOLLOW UP
3 months



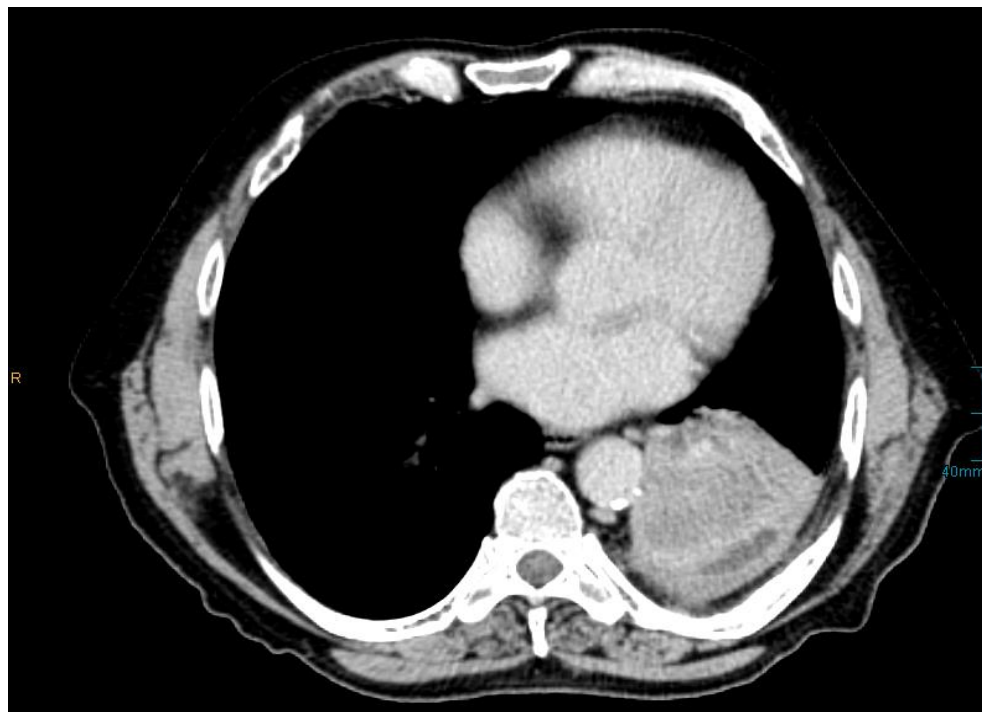
60% volume regression

G2 LIPOSARCOMA

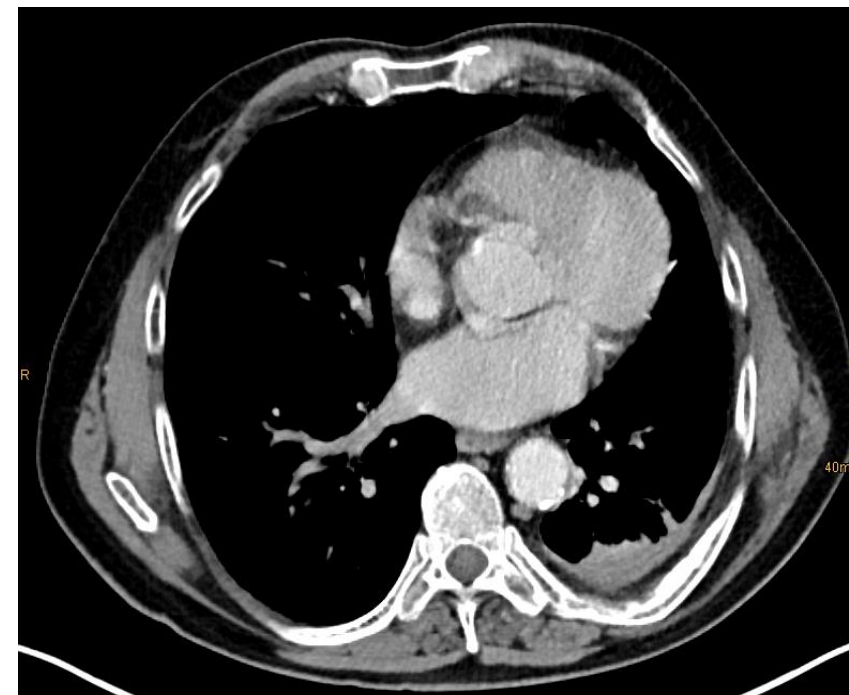
DOSE: 15Gy x 3

COMPLETE RESPONSE

Before SBRT-PATHY



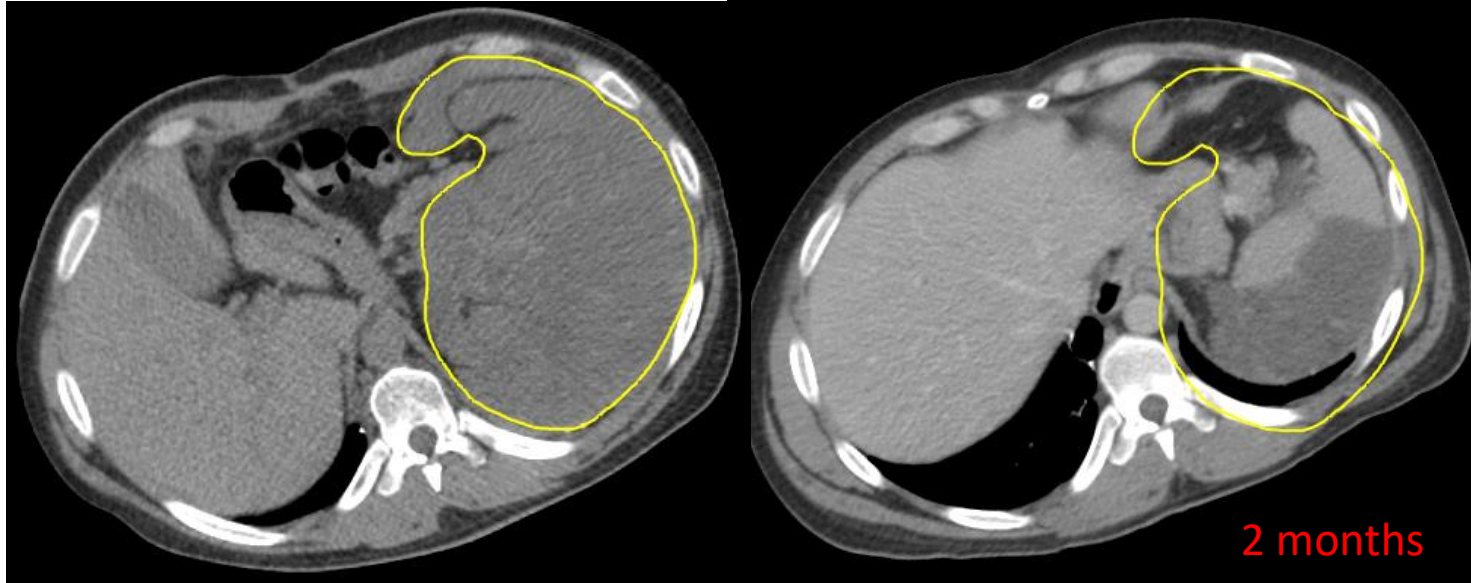
PRIMARY ADC OF THE LUNG



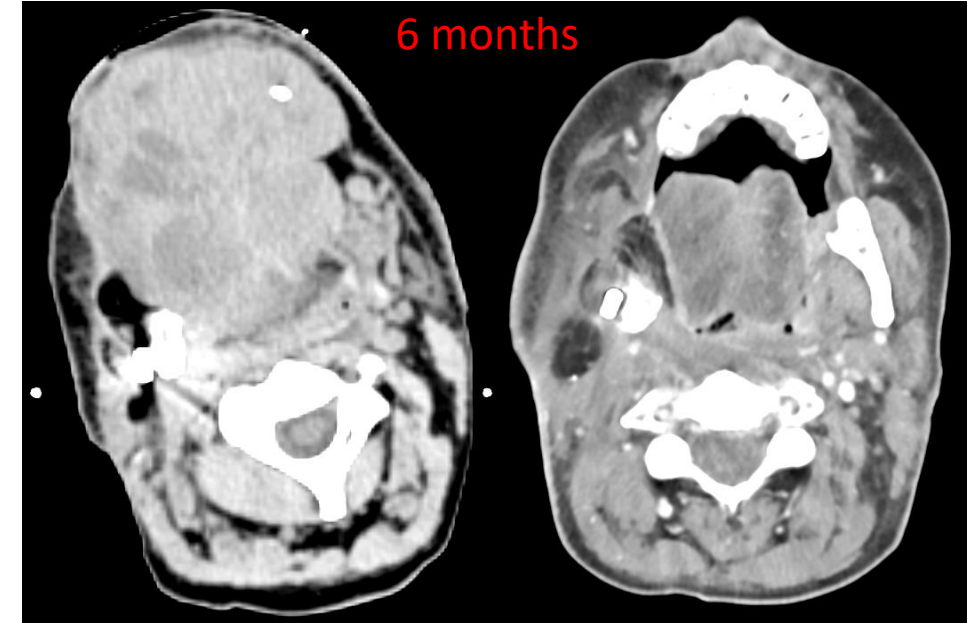
**7 months after partial tumor irradiation
10Gy x 1 to the 70%**

LONG- and SHORT-lasting RESPONSES

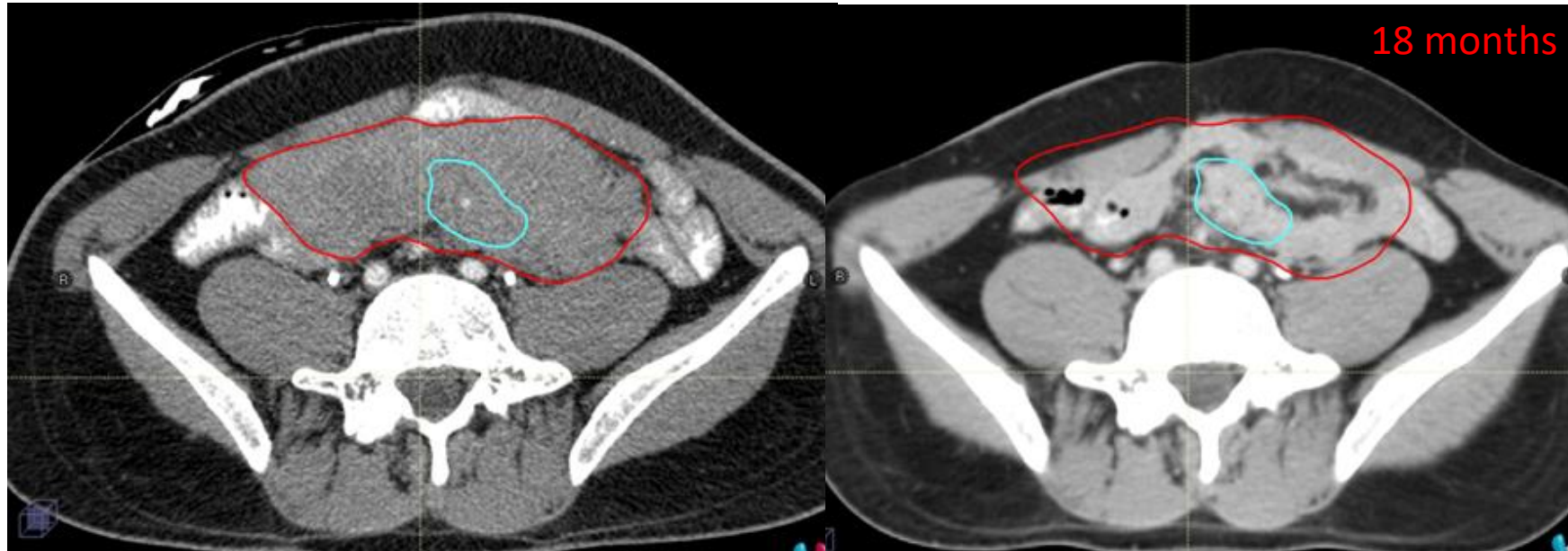
SECONDARY GERMINOMA, 10Gy x 3



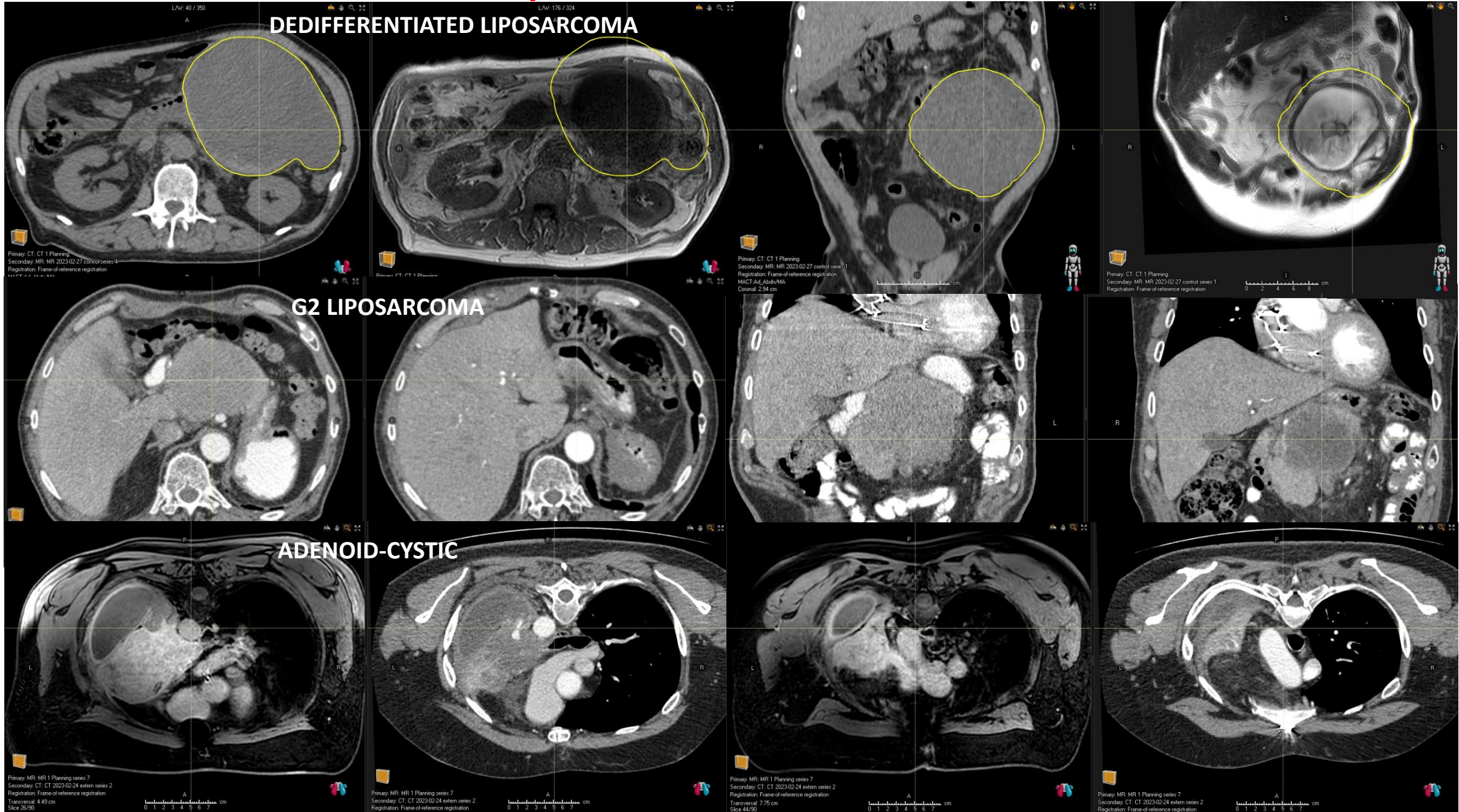
SCC FLOOR OF MOUTH, 15Gy x 3



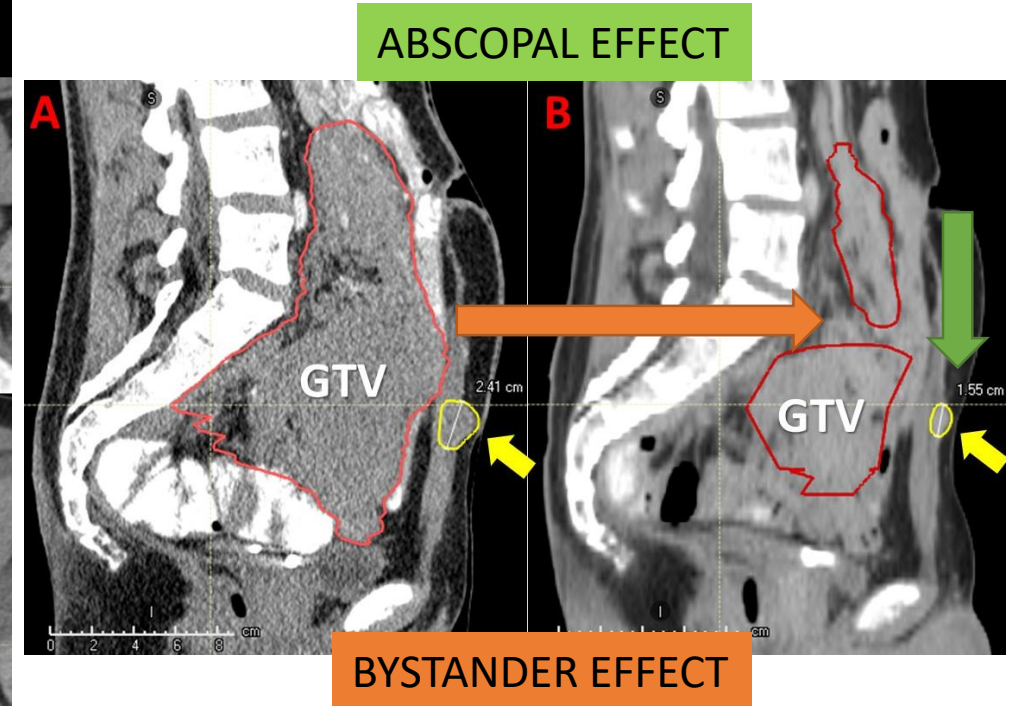
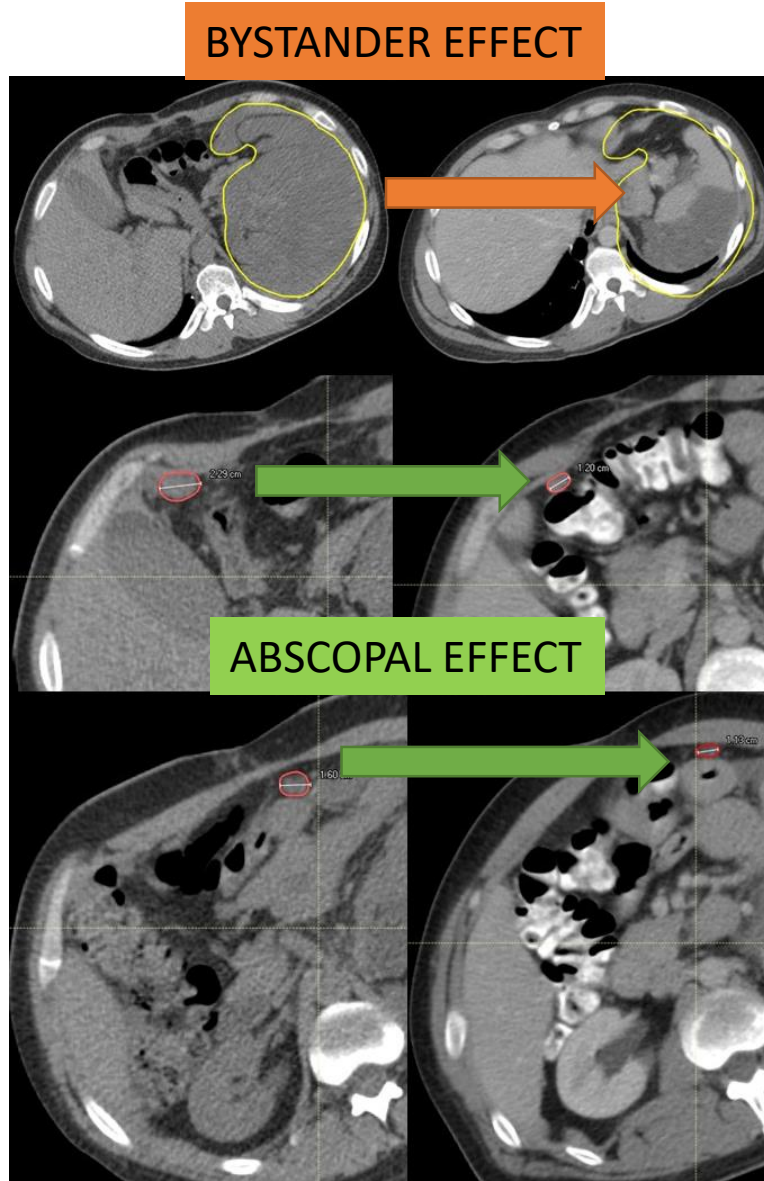
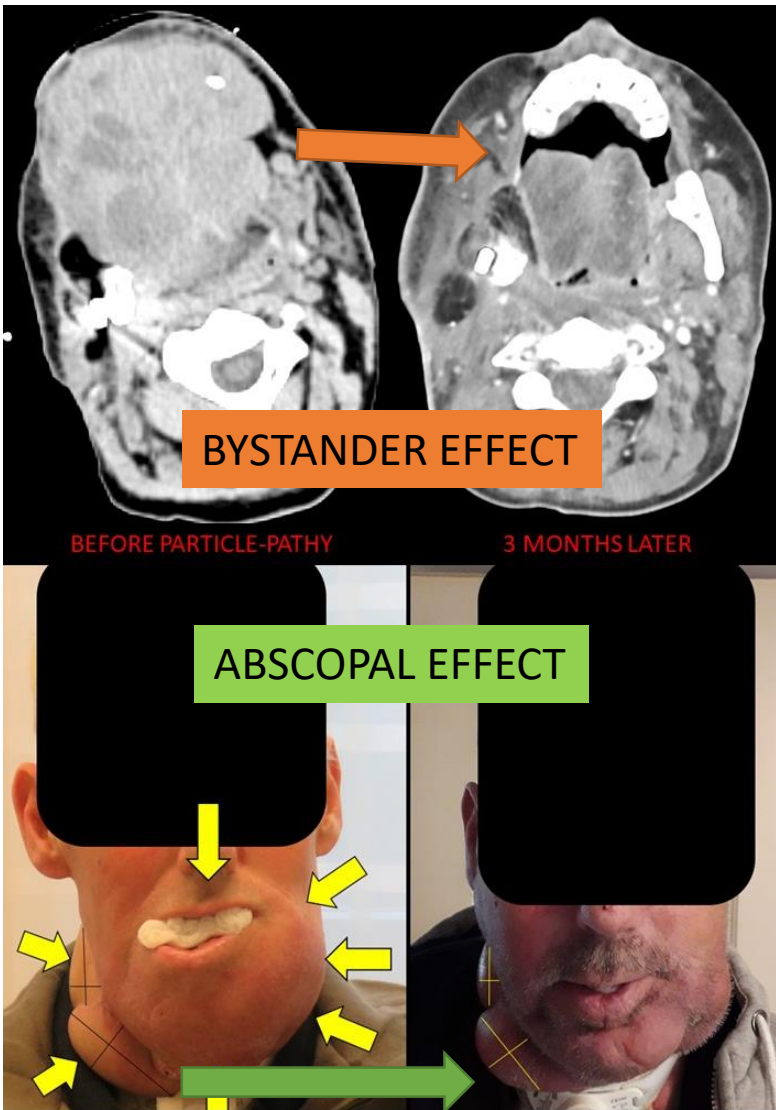
DESMOID
10Gy x 3



NEOADJUVANT POTENTIAL by UNRESECTABLE RADIORESISTANT BULKY TUMORS

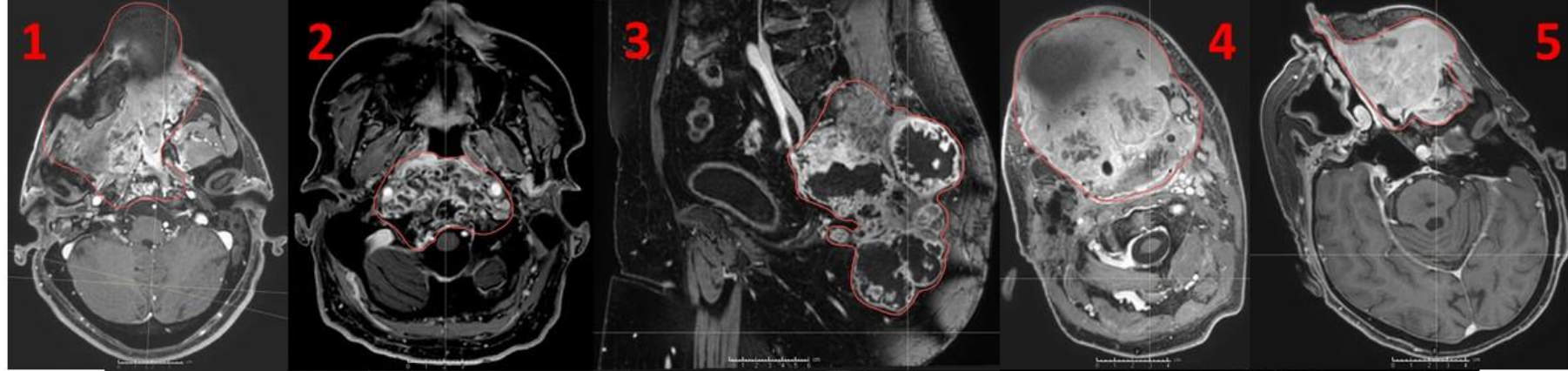


Prediction of abscopality



Predictive by the local response: $\geq 50\%$

SURVIVAL UNDER PATHY



LIFE EXPECTANCY

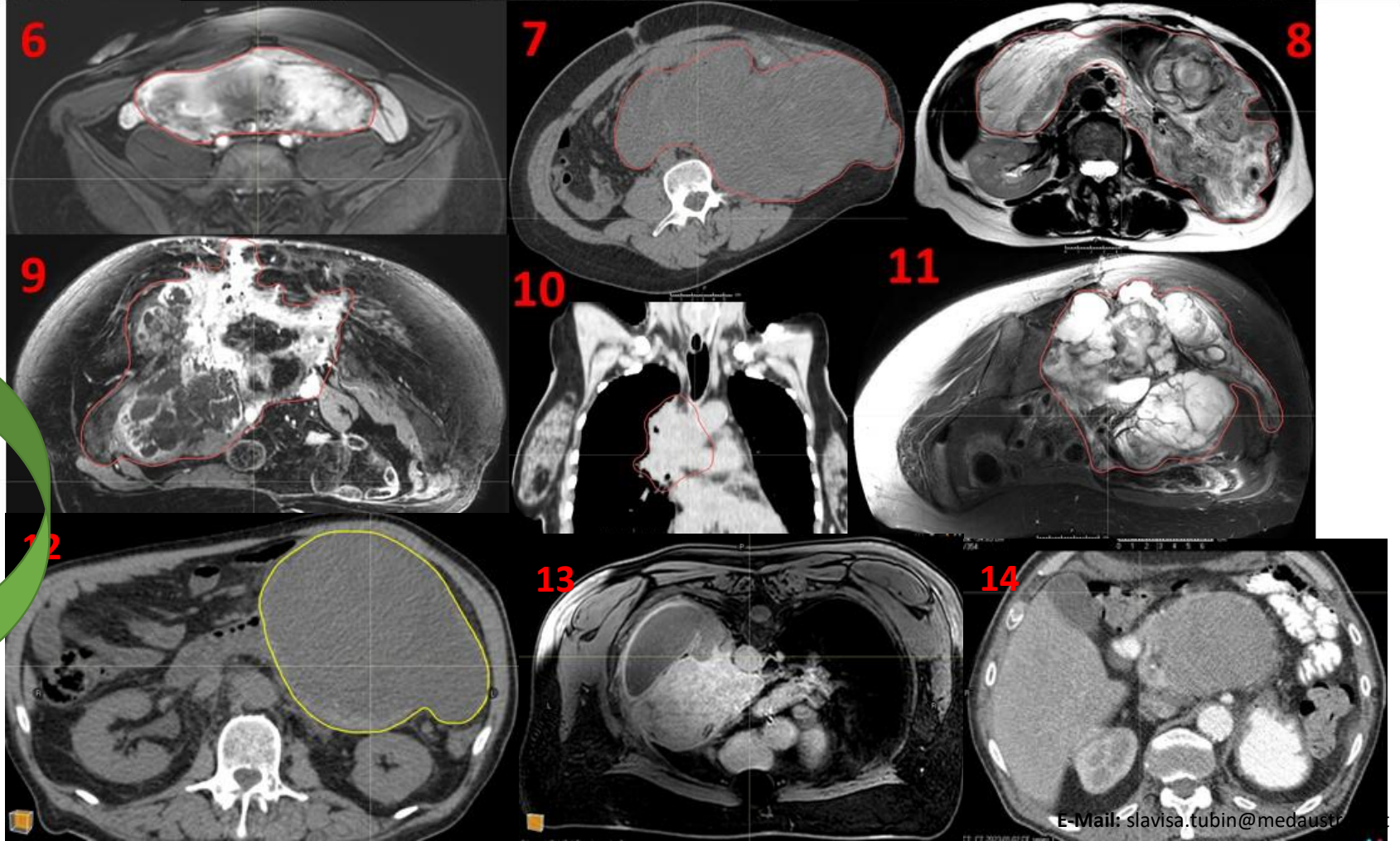
- Palliative Prognostic Index: <2months!



PATHY (only 1 course)



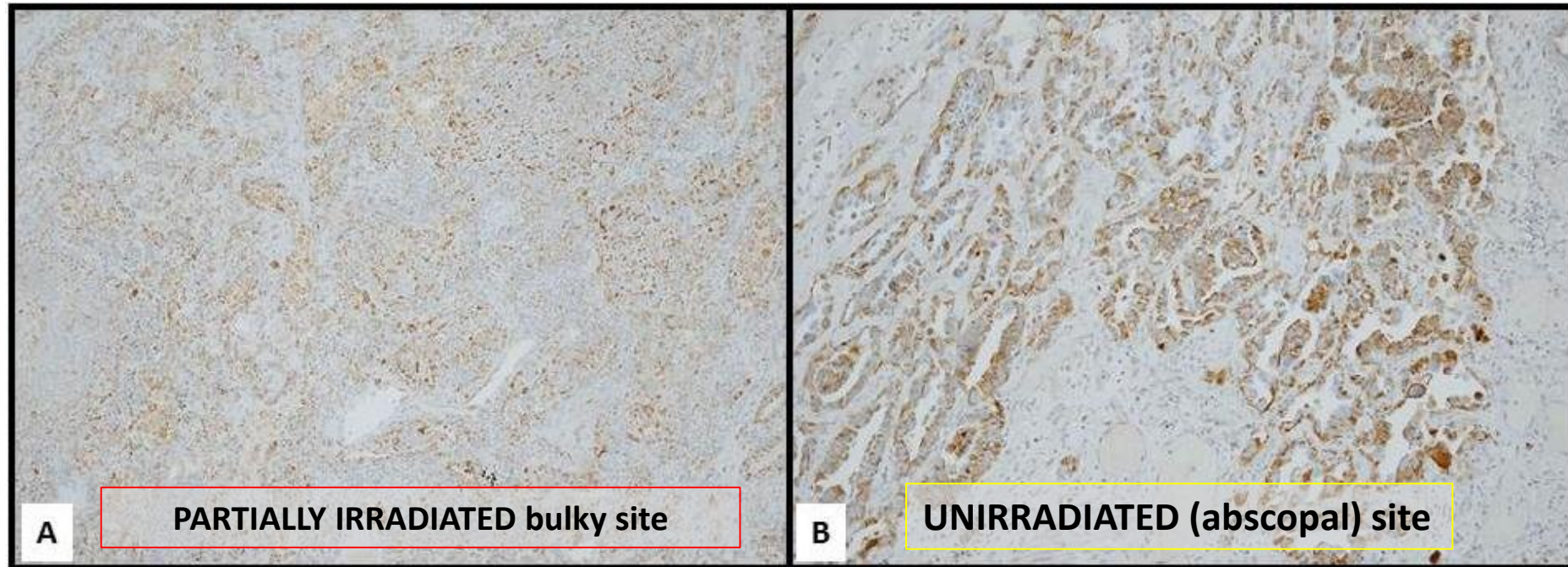
**OVERALL SURVIVAL
8 months**





Immunohistochemistry

- **Immunohistochemistry** was performed using antibodies for **apoptosis-inducing factor (AIF)**, CD3, CD4, CD8, CD20, CD56, CD14, CD15, and S100 protein to explore for the activation and modifications within the tumor microenvironment.
- **Gene analysis** focused on the expression of **cell death and immune activation-related genes** in the necrotic tumor, PIM and abscopal sites. Specific regions were identified from H&E stained sections cut in parallel and dissected from the slides to isolate RNA. RNA was reverse transcribed and qPCRs were run on a Biorad CFX 96 Real-Time System.



AIF was massively upregulated in the partially irradiated bulky, but also at abscopal tumor sites.

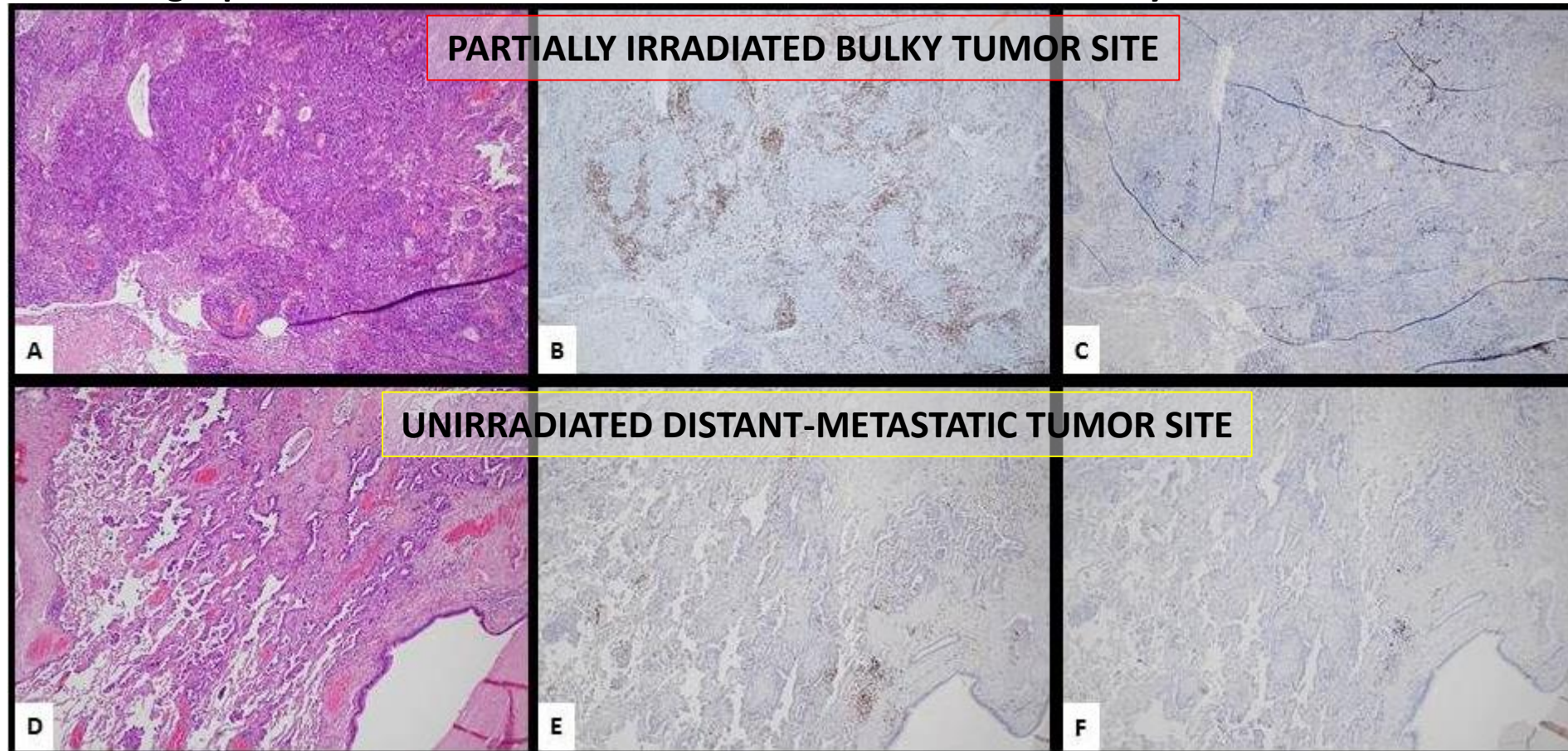
MECHANISMS BEHIND THE NON-TARGETED EFFECTS



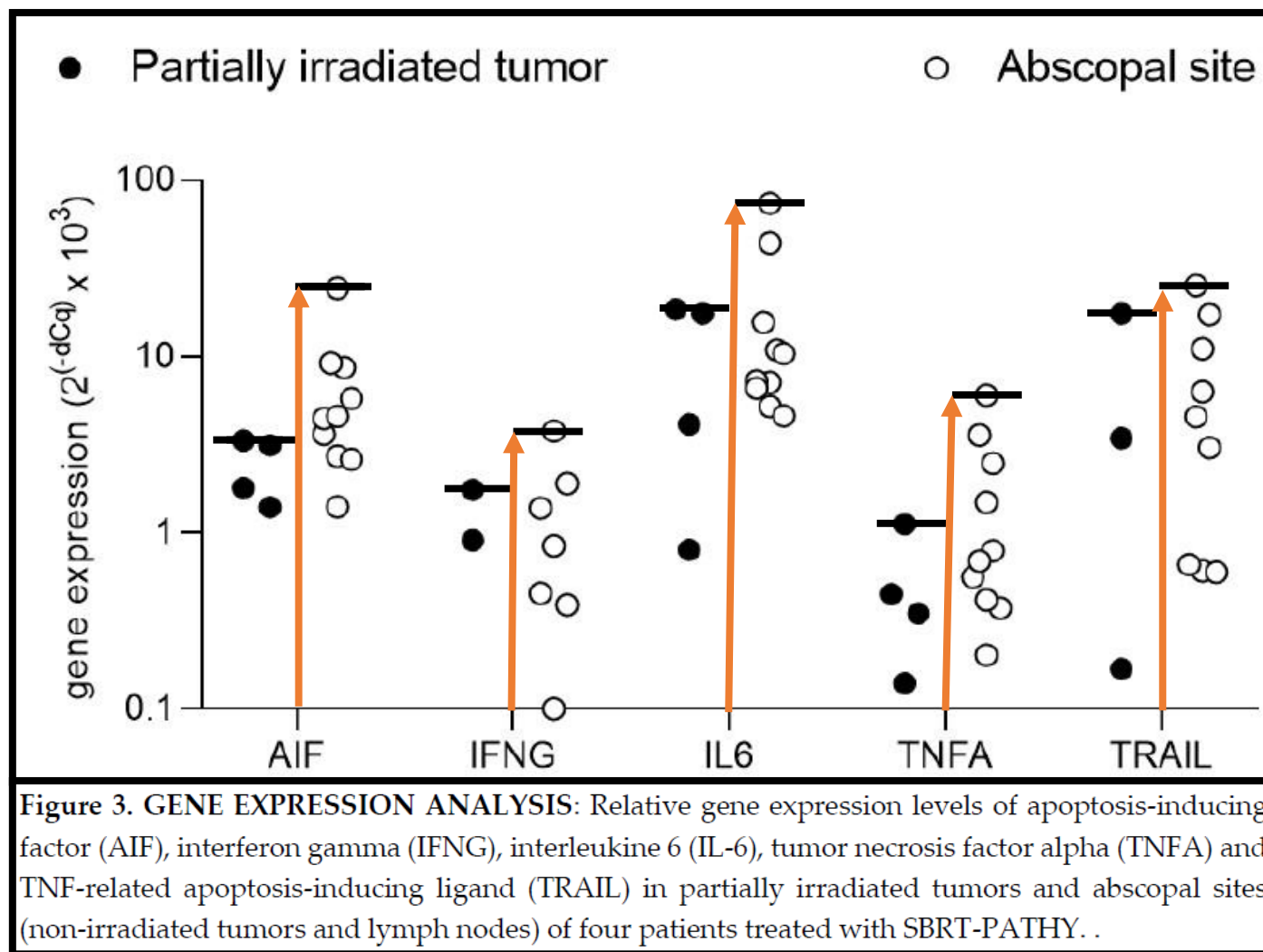
cancers Tubin et al. 2020

Immunohistochemistry

Abundant infiltration of the CD20+ B-lymphocytes, CD3+/CD8+ T-lymphocytes was observed, indicating a possible anti-tumor-directed-activation of the immune system!



- The same signs of immune system activation at abscopal site were clearly absent.



Despite absent immune infiltration those apoptotic abscopal sites showed a **strong expression of the cell death-inducing cytokines!**

For **AIF**, **IL-6** and **TNFA**, abscopal sites had higher expression levels compared to the partially irradiated tumors!

suggesting an abundance of potentially cell death-inducing signals not only in the partially irradiated tumors but even more so in non-irradiated abscopal sites.

Conclusions

- RT has great immunogenic potential, can brake tolerance, convert cold into hot environments!
- PARTIAL T Rx resulted in **effective**, **safe** and **well tolerated** treatment.
- **Improvement in symptoms** and **quality of life** without associated treatment related toxicity.
- PATHY resulted in varying degrees of **tumor downsizing (neoadjuvant effect!)**.
- Optimum patient selection and definition of most suitable disease characteristics are currently explored in an ongoing, prospective study.

1.) **MedAustron**
 U.S. National Library of Medicine
ClinicalTrials.gov

Particle-based Partial Tumor Irradiation of Unresectable Bulky Tumors (**PARTICLE-PATHY**)

Recruitment Status: Recruiting

Hypothesis-generating study on the mechanisms behind radiation-hypoxia-induced abscopal response

2.) **KABEG Klinikum Klagenfurt**
 ClinicalTrials.gov Identifier: NCT04168320
ClinicalTrials.gov

SBRT-based PARTIAL Tumor Irradiation of HYpoxic Segment (**SBRT-PATHY**)

Recruitment Status: Recruiting