

EP09.09: In-field and out-of-field responses after PATHY in first-line thoracic malignancies: an institutional five-case series

G. Suay¹, A. Pouptsis¹, E. Nadal¹, M. Piqueras², A. Armero², E. Alemany², M. Benet², F. Aparisi¹, O. Juan-Vidal¹, A. Lahoz², R. Chicas¹

¹University and Polytechnic La Fe Hospital, Valencia, Spain ²La Fe Health Research Institute, Valencia, Spain

Correspondence: guillermo_suay@iislafe.es

INTRODUCTION

Bulky thoracic tumours are hypoxic, radioresistant and immunosuppressive. Whole-tumour irradiation also depletes the peritumoral immune microenvironment (PIM) and circulating lymphocytes — the effectors of anti-tumour immunity.

PATHY (Partial Tumour irradiation targeting the HYpoxic segment) delivers a high dose only to the hypoxic, hypovascularised junctional zone — the bystander tumour volume (BTV) — sparing the PIM and the rest of the lesion.

Rationale: shifting radiation effects from immune-suppressive to immune-stimulatory should generate tumour-cell death in the non-irradiated part of the treated lesion (bystander effect) and in distant, non-irradiated lesions (abscopal effect).

Evidence gap: clinical experience is limited to small series and case reports, almost all without concurrent systemic therapy; data with first-line chemoimmunotherapy are essentially absent.

Objective: to report our early institutional experience with PATHY during first-line chemoimmunotherapy in advanced NSCLC, focusing on the concordance between in-field and out-of-field responses.

METHODS

Design. Retrospective, single-centre, consecutive case series (Hospital Universitari i Politècnic La Fe, Valencia), in routine clinical practice.

Population. Consecutive patients treated with PATHY at our centre. The primary analysis was restricted to **first-line** cases with at least one post-PATHY radiological assessment → **5 evaluable patients**.

PATHY delivery. Partial irradiation of the hypoxic tumour segment (BTV), defined on contrast-enhanced CT ± 18F-FDG PET as the hypovascularised–hypometabolic junctional zone between the necrotic core and the hypermetabolic periphery. Dose 15–18 Gy. Nodal and metastatic sites were left un-irradiated. Delivered during ongoing first-line platinum-based chemoimmunotherapy.

Endpoints. Best response of the irradiated lesion (in-field) and of the non-irradiated lesions (out-of-field); concordance between the two; immune-related adverse events (irAEs) requiring interruption of immune checkpoint inhibition (ICI); progression and survival status.

Assessment. Response was taken from the treating team's routine radiological reports; **no centralised radiological review** was performed. Descriptive analysis only.

A. PATHY concept — partial irradiation of the hypoxic tumour segment

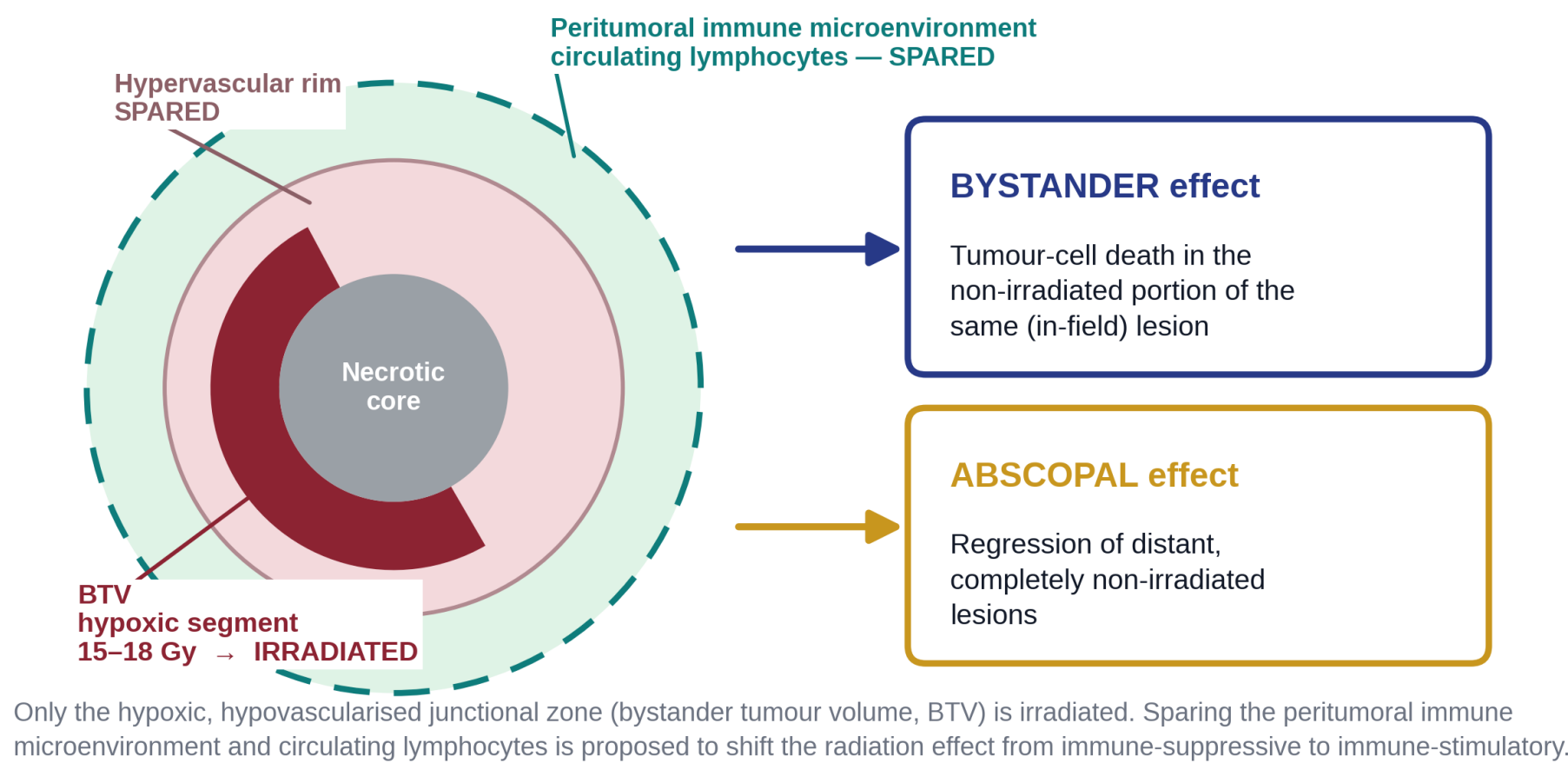


Figure 1. The PATHY concept: only the hypoxic segment is irradiated; the peritumoral immune microenvironment is spared.

DISCUSSION AND CONCLUSION

KEY FINDINGS

PATHY was feasible during first-line chemoimmunotherapy in routine practice, in patients with high comorbidity and polypharmacy. No toxicity attributable to PATHY was recorded.

In-field and out-of-field best responses were concordant in 5/5 cases — four concordant partial responses and one concordant progression. Regression of completely non-irradiated lesions in 4/5 patients is the clinically notable signal, consistent with an abscopal-like effect.

The single progressor (C05) had the highest comorbidity burden, NSCLC-NOS histology, CNS involvement during follow-up and a non-platinum-doublet partner drug — a phenotype worth capturing in future selection criteria.

LIMITATIONS

Retrospective, uncontrolled series of five patients with heterogeneous clinical scenarios; response was not centrally reviewed and was not formally RECIST-adjudicated.

Chemoimmunotherapy alone produces systemic responses. The independent contribution of PATHY cannot be isolated in an uncontrolled design; the observations are hypothesis-generating, not evidence of efficacy.

Whether PATHY modifies irAE risk is unknown; 2/5 patients required ICI interruption, within the expected range for this regimen.

CONCLUSION

PATHY may represent a feasible immunomodulatory radiotherapy approach in selected first-line thoracic malignancies. The concordant in-field and out-of-field responses seen here are **hypothesis-generating and warrant prospective evaluation** with standardised RECIST assessment, a pre-specified out-of-field endpoint and translational correlates.

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RESULTS

5 evaluable first-line cases	4/5 in-field partial response (80%)	4/5 out-of-field partial response (80%)	5/5 in-field / out-of-field CONCORDANCE	2/5 irAE requiring ICI interruption	7.9 median months of follow-up after PATHY
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Table 1. Baseline characteristics of the five evaluable first-line cases. Median age 65 years (range 49–74); all male; four of five were smokers.

Case	Age / Sex	PS	Smoking (pack-yr)	Histology	Genomic alteration	PD-L1	Stage	First-line regimen	Comorbid. (n)	Co-med. (n)
C01	74 / M	1	Never	Adenocarcinoma	TP53	Positive	IVA (T4N3M1a)	Carboplatin–pemetrexed–pembrolizumab	4	9
C02	49 / M	1	33	Adenocarcinoma	KRAS G12D	Negative	IVA (T4N3M1a)	Carboplatin–pemetrexed–nivolumab–ipilimumab	2	4
C03	65 / M	2	20	Adenocarcinoma	BRAF (non-V600E)	Negative	IVA (T4N3M1b)	Carboplatin–pemetrexed–cemiplimab	2	3
C04	64 / M	0	25	Adenocarcinoma	KRAS G12C	Positive	IVA (T4N3M1b)	Carboplatin–pemetrexed–cemiplimab	2	2
C05	71 / M	1	50	NSCLC-NOS	MET	Positive	IIIA (T3N2M0)	Carboplatin–vinorelbine–cemiplimab	6	10

Table 2. PATHY delivery and outcomes. Median 12 cycles of chemo-immunotherapy (range 7–14); median follow-up 7.9 months from PATHY.

Case	PATHY site	Dose	Diagnosis → PATHY (mo)	Cycles of chemo-IO	In-field response	Out-of-field response	Concordant	irAE (grade) / ICI stopped	Progression	Follow-up from PATHY (mo)	Status
C01	Lung	18 Gy	6.3	12	PR	PR	Yes	None	Yes (3.3 mo)	7.8	Alive — on trial
C02	Lung	18 Gy	2.6	14	PR	PR	Yes	Skin G3 — yes	No	8.1	Alive
C03	Hepatic hilar node	18 Gy	4.0	13	PR	PR	Yes	None	No	7.9	Alive
C04	Lung	15 Gy	2.0	8	PR	PR	Yes	Renal G2 — yes	No	4.1	Alive
C05	Lung	18 Gy	2.6	7	PD	PD	Yes	None	Yes (1.9 mo)	3.2	Died

B. Individual patient course (n = 5)

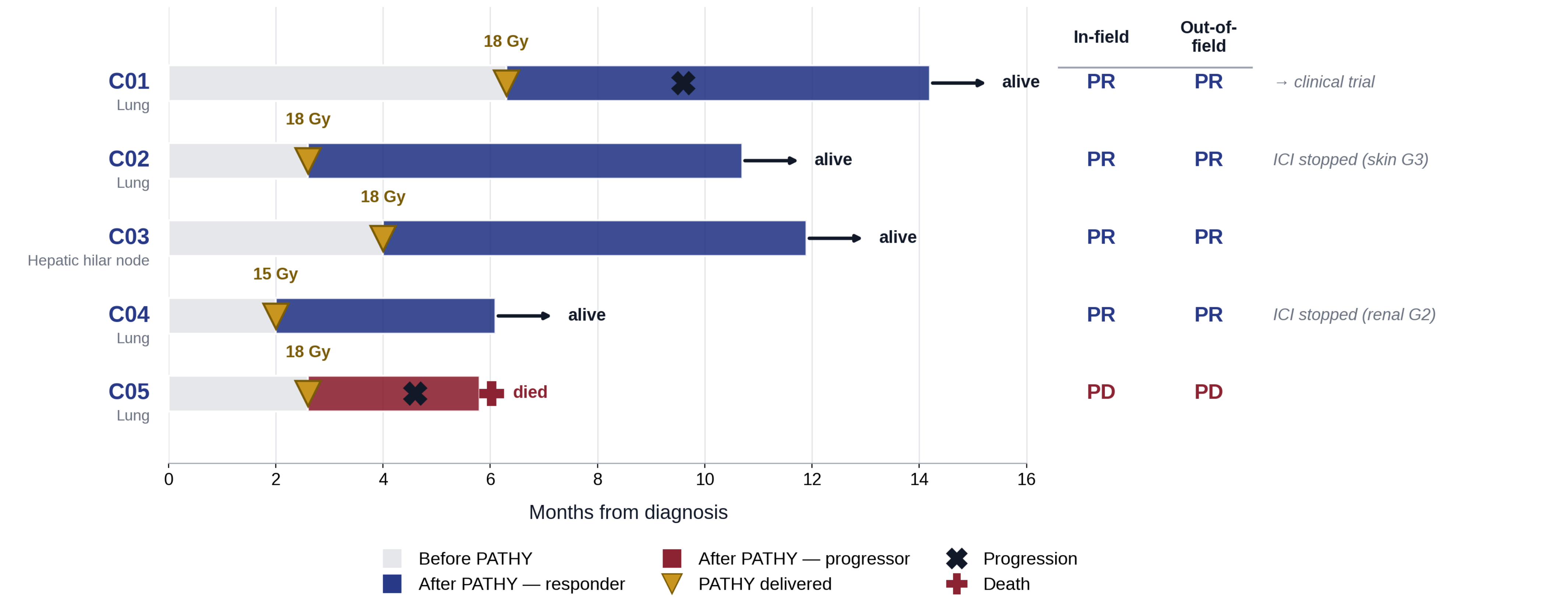


Figure 2. Individual patient course from diagnosis. PATHY was delivered a median of 2.6 months after diagnosis (range 2.0–6.3), during ongoing first-line chemoimmunotherapy. In-field and out-of-field best responses were concordant in every case. C05, the only progressor, developed brain metastases during follow-up.