

Background

Treatment of unresectable locally advanced head and neck squamous cell carcinoma (LA-HNSCC) is based on chemoradiotherapy (CRT), the standard being concomitant cisplatin, as other drugs, such as cetuximab, have not improved the results of platinum despite their better toxicity profiles.

The aim of this study was to characterize genomic biomarkers associated with response to CRT with platinum or cetuximab for personalization of LA-HNSCC treatment.

Material and methods

An analysis of samples from the TTCC-2007-01 trial (NCT0071639122), which studied the non-inferiority of QT/RT with cetuximab (CET/RT) versus cisplatin after three cycles of induction chemotherapy (CDDP/RT), was conducted.

The sample was subclassified according to response: 1) complete or partial response "CR/PR" or 2) stabilization or progression "SD/PD".

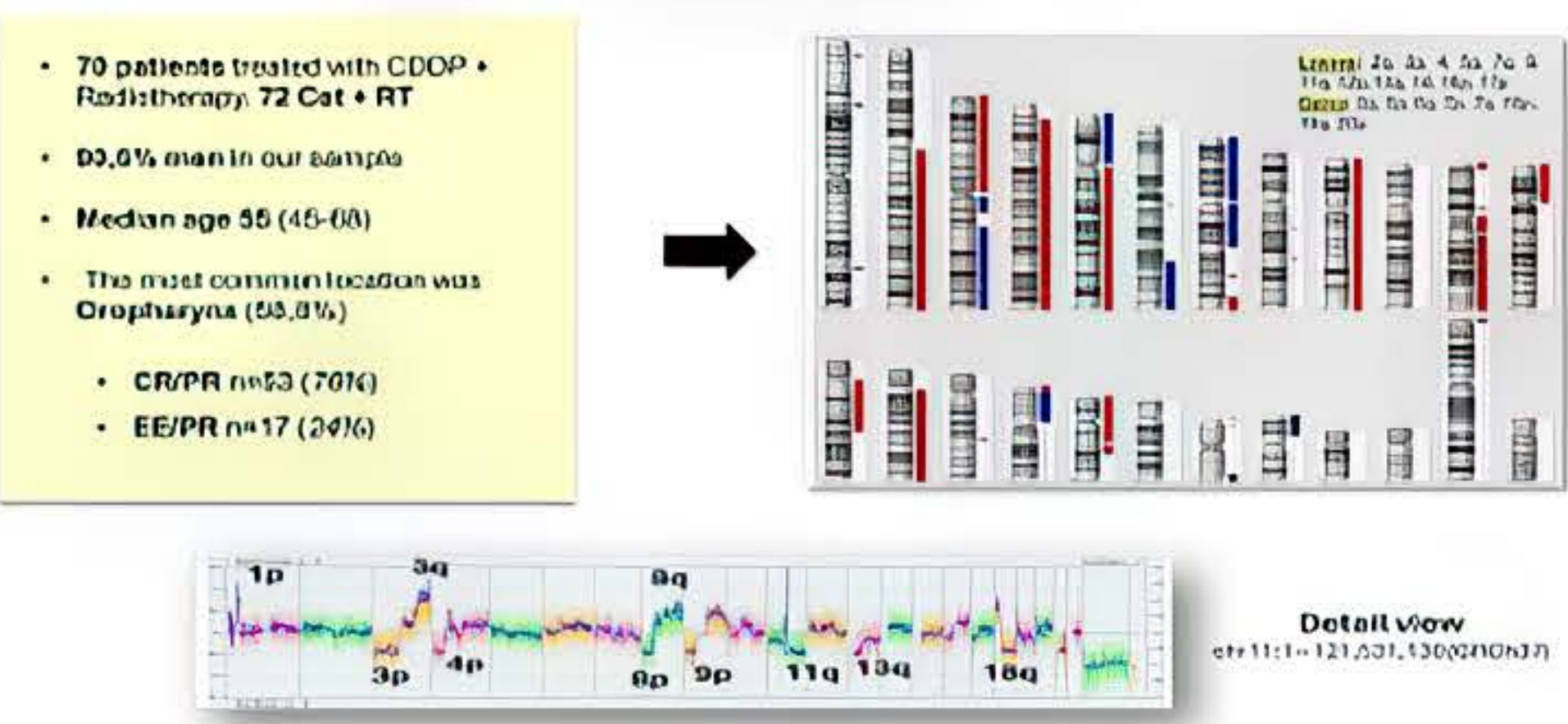


After DNA extraction with a commercial kit, it was processed with the OncoScan FFPE assay platform to determine copy number alterations (CNAs). A mutational analysis was conducted using massive targeted sequencing (TruSight Tumor26 panel).

A functional analysis of the results was conducted using WebGestalt.

Results: Baseline characteristics

Figure 1. Heterogeneous distribution of gains and losses in every individual sample



In total, 142 samples were analyzed: 70 patients received CET/RT (n=55; 76% CR/PR), and 72 patients received CDDP/RT (n=53; 76% CR/PR). The patients' mean age was 57 [29-73] years, with a predominance of males (n=127, 89.4%).

Results: Distribution of gains and losses in CNA

The CDDP/RT group associated the response with 11p- and 11q- alterations (49% vs. 17.65%; p<0.05). Focal gains in 3q11.2 (SD/PD 76.5%) and deletions in 9p22.1 (SD/PD 88.24%) were associated with non-response.

In CET/RT 2p+ and 2q+ alterations were associated with poor response (58.8% vs. 29.1%; p<0.05).

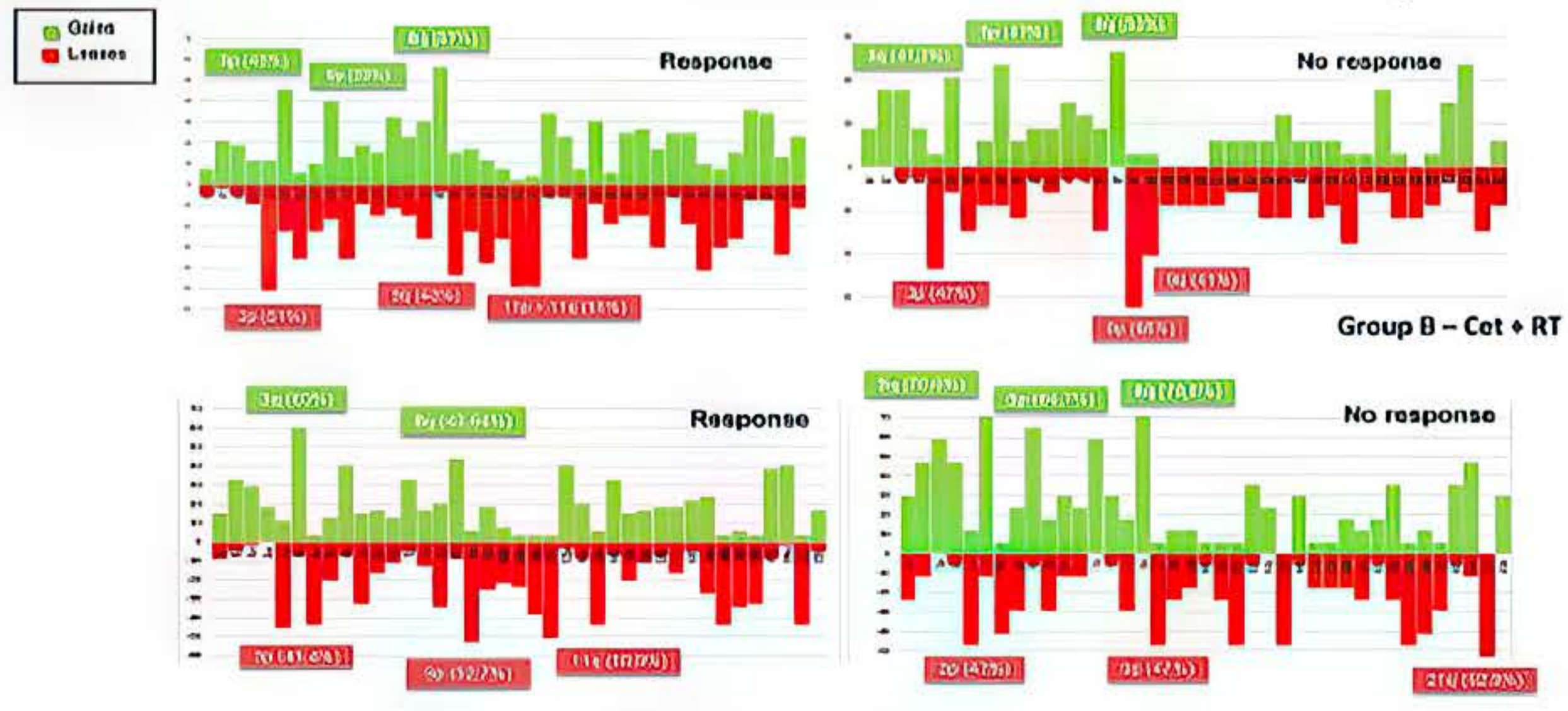
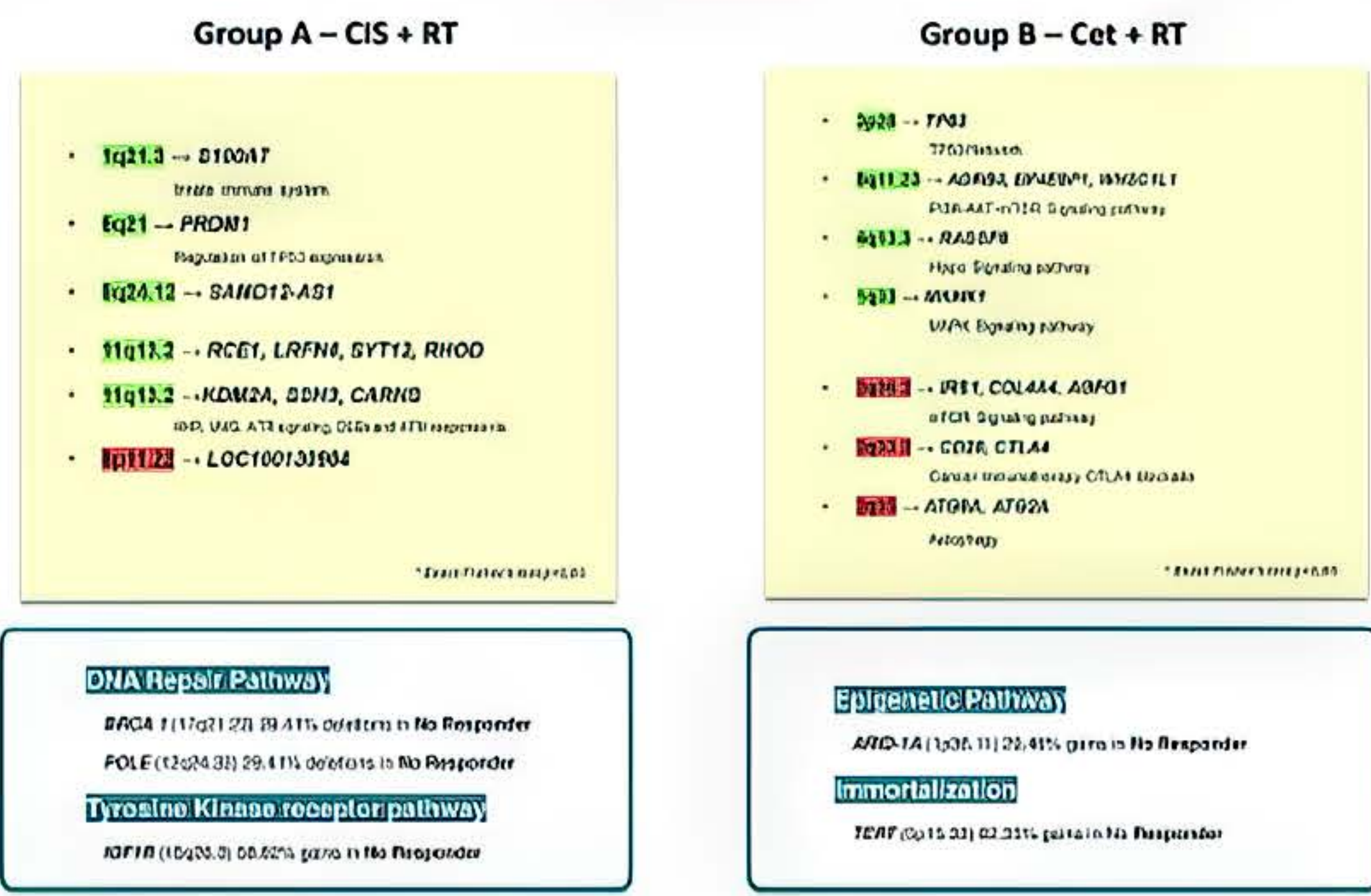


Figure 2. Analysis of CNA gains or losses for (A) Cisplatin + RT and (B) Cetuximab + RT

Mutational Profile

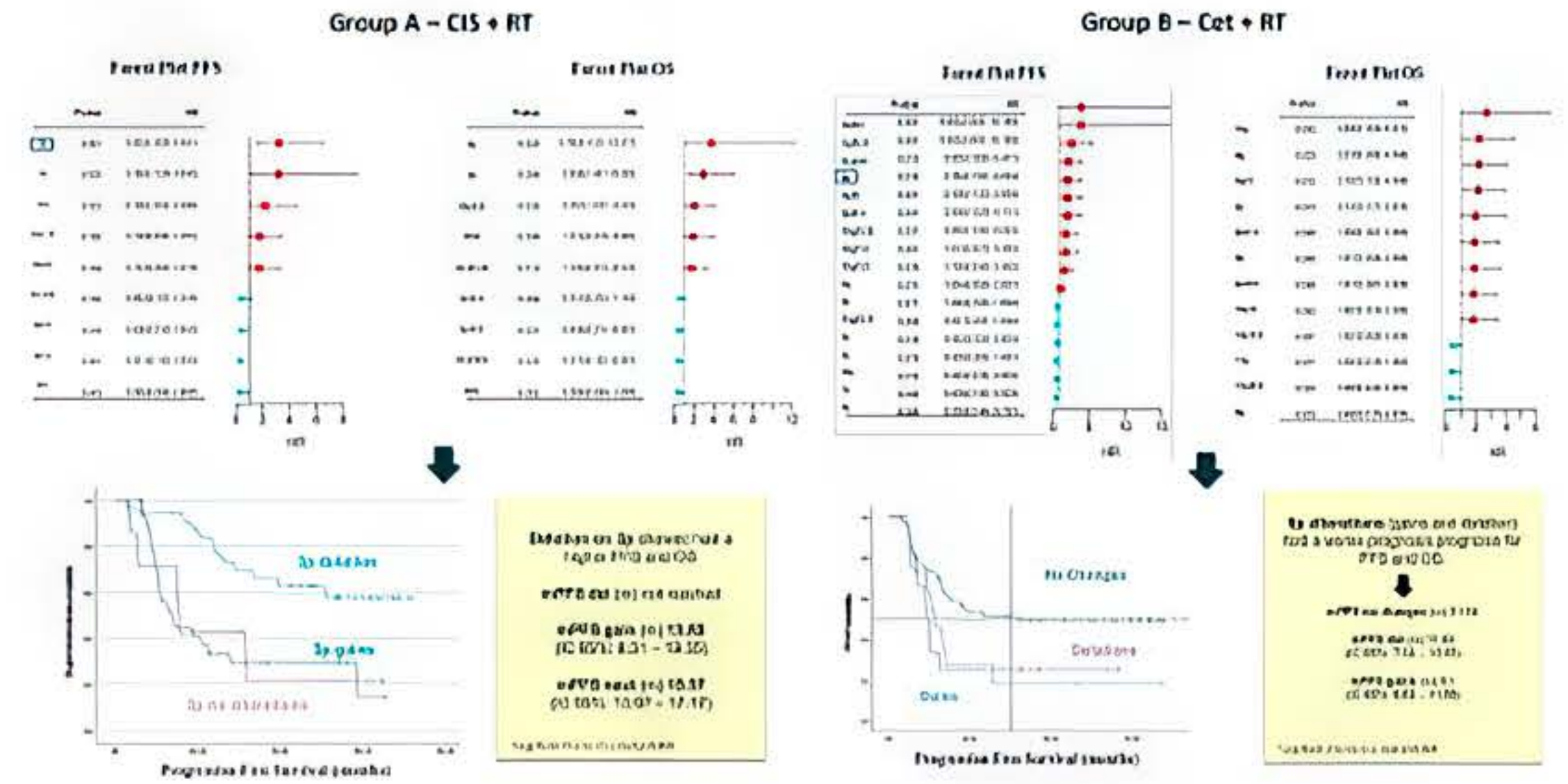
For Cis+ RT alterations in 17q21.23 or BRCA1 (CR/PR 29.4%) and 12q24.33 or POLE (CR/PR 29.4%) were associated with worse response (p<0.05). The functional analysis showed involvement of ATM and PI3KCA pathways in response.

In Cet+ RT gene alterations present on 1p36.11 ARID1A and 5p15.33 TERT, were found in non-responders (p<0.05). Functionally CET/RT-associated response to epigenetic and cellular immortalization-associated pathways.



Results: Functional analysis

Figure 3. Forest plot of PFS and OS in both groups. Clinical Outcomes based on genomic profiling data



Conclusion

- ✓ Somatic genomic alterations in genes such as ARID1A or TERT were associated with resistance to CET/RT, with the response being associated with epigenetic control pathways and cell immortality.
- ✓ These alterations may constitute genomic biomarkers predictive of response to CRT that could be used to implement precision medicine in LA-HNSCC.

References

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Contact information

Juan Carlos Redondo González
Medical Oncology Resident
University Hospital of Salamanca
Institute of Biomedical Research of Salamanca

Phone contact: +34 648078281
Mail 1: jcredondo@saludcastillayleon.es
Mail 2: jcredondogaler@gmail.com

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THE LANDSCAPE OF SOMATIC COPY NUMBER ALTERATIONS OF HEAD AND NECK SQUAMOUS CELL CARCINOMA ACROSS DIFFERENT ANATOMIC SITES



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Juan Carlos Redondo González^{1,2}, Alejandro Olivares-Hernández^{1,2}, Juan Luis García Hernández^{2,3}, Ricard Mesia Nin⁴, Jordi Rubió-Casadevall⁵, Carlos García-Girón⁶, Lara Iglesias Docampo⁶, Alberto Carral Masada⁷, Miren Taberna Sanz⁸, Luis Antonio Corchete^{1,2}, Nerea Gestoso Uza^{1,2}, Rogelio González Sarmiento^{9,10}, Juan Jesús Cruz-Hernández^{1,2,11}, Edel del Barco-Morillo^{1,2,12}, Emilio Fonseca-Sánchez^{1,2,13}

¹ University Hospital of Salamanca, ² Biomedical Research Institute of Salamanca (IBSA), ³ Salamanca Cancer Research Center (CRC), ⁴ Institut Català d'Oncologia, ⁵ University Hospital of Burgos, ⁶ University Hospital 12 de Octubre, ⁷ University Hospital La Fe, ⁸ Asturias, ⁹ University Hospital of Salamanca, ¹⁰ Biomedical Research Institute of Salamanca (IBSA), ¹¹ University Hospital of Salamanca, ¹² University Hospital of Salamanca, ¹³ University Hospital of Salamanca

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Background

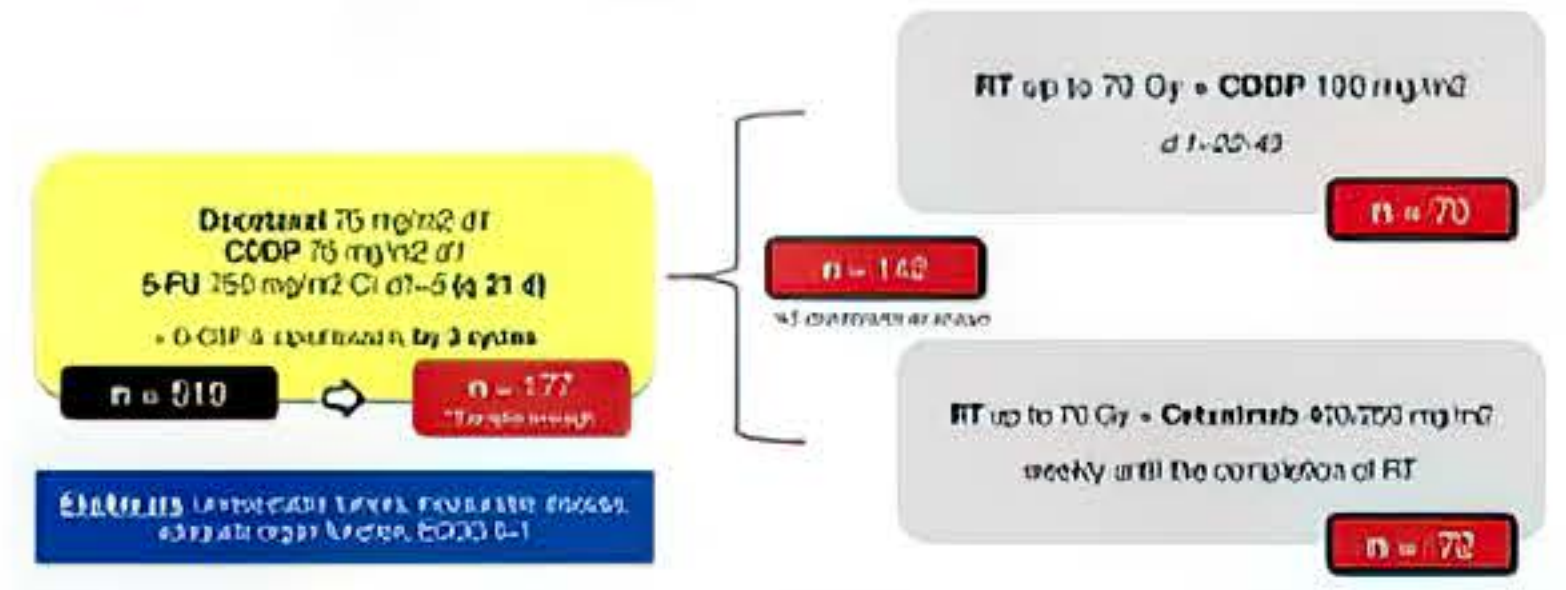
Standard treatment for locally advanced head and neck cancer (LA-HNSCC) is based on chemoradiotherapy with cisplatin regardless of its anatomical origin, although its **prognostic significance** is well known.

The **aim of the study** was the molecular characterization of these tumours according to their origin and to establish a predictive and prognostic correlation.

Material and methods

Analysis of samples from the **TCC-2007-01** trial, which assessed the non-inferiority of **cetuximab + radiotherapy** (Cet+RT) versus **cisplatin + radiotherapy** (Cis+RT).

They were classified according to location and response to treatment: complete/partial response (**CR/PR**) or stabilisation/progression disease (**SD/PD**).



Identification of **copy number alterations (CNAs)** with the **OncoScan®** platform were also classified with the CNApp tool into **global change score (GCS)**, **focal change score (FCS)** and **broad change score (BCS)**.

* Survival analysis using the Kaplan-Meier method (log-rank) with SPSSv23.0.

Results: Copy Number Alterations

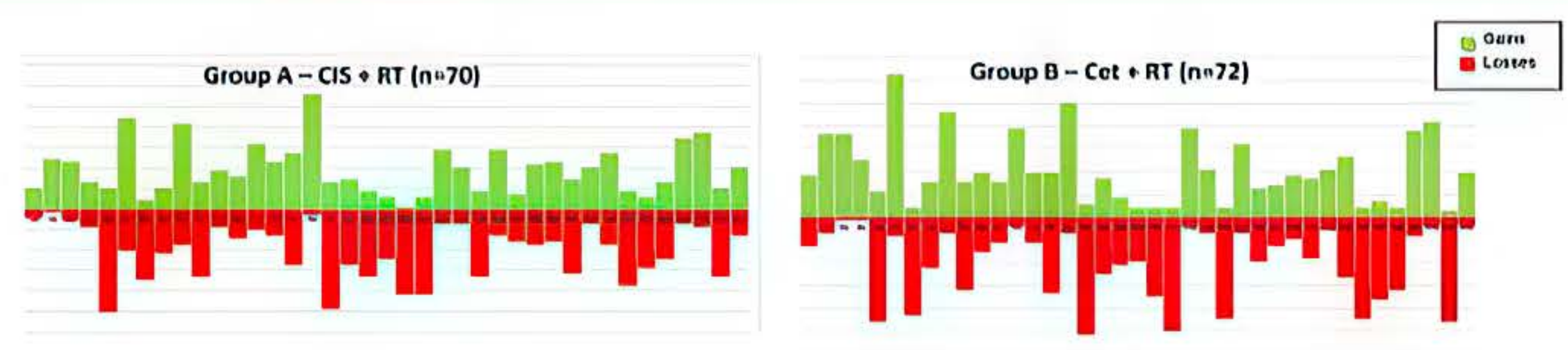
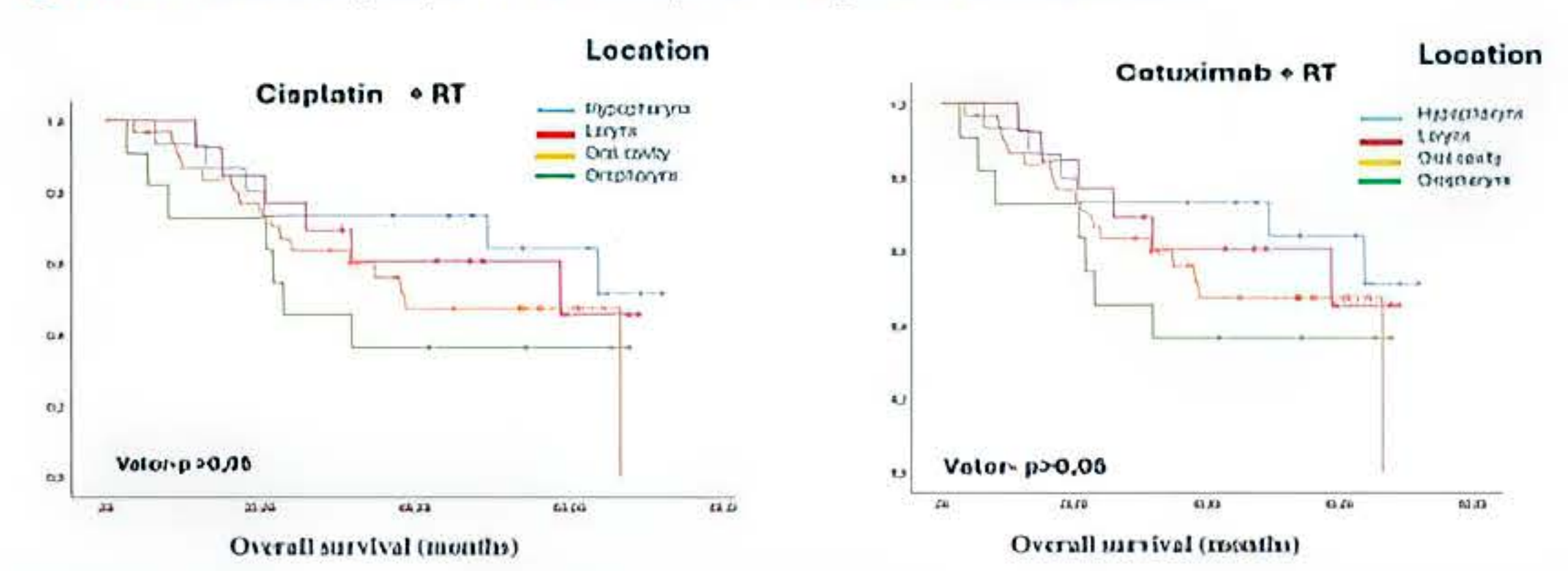
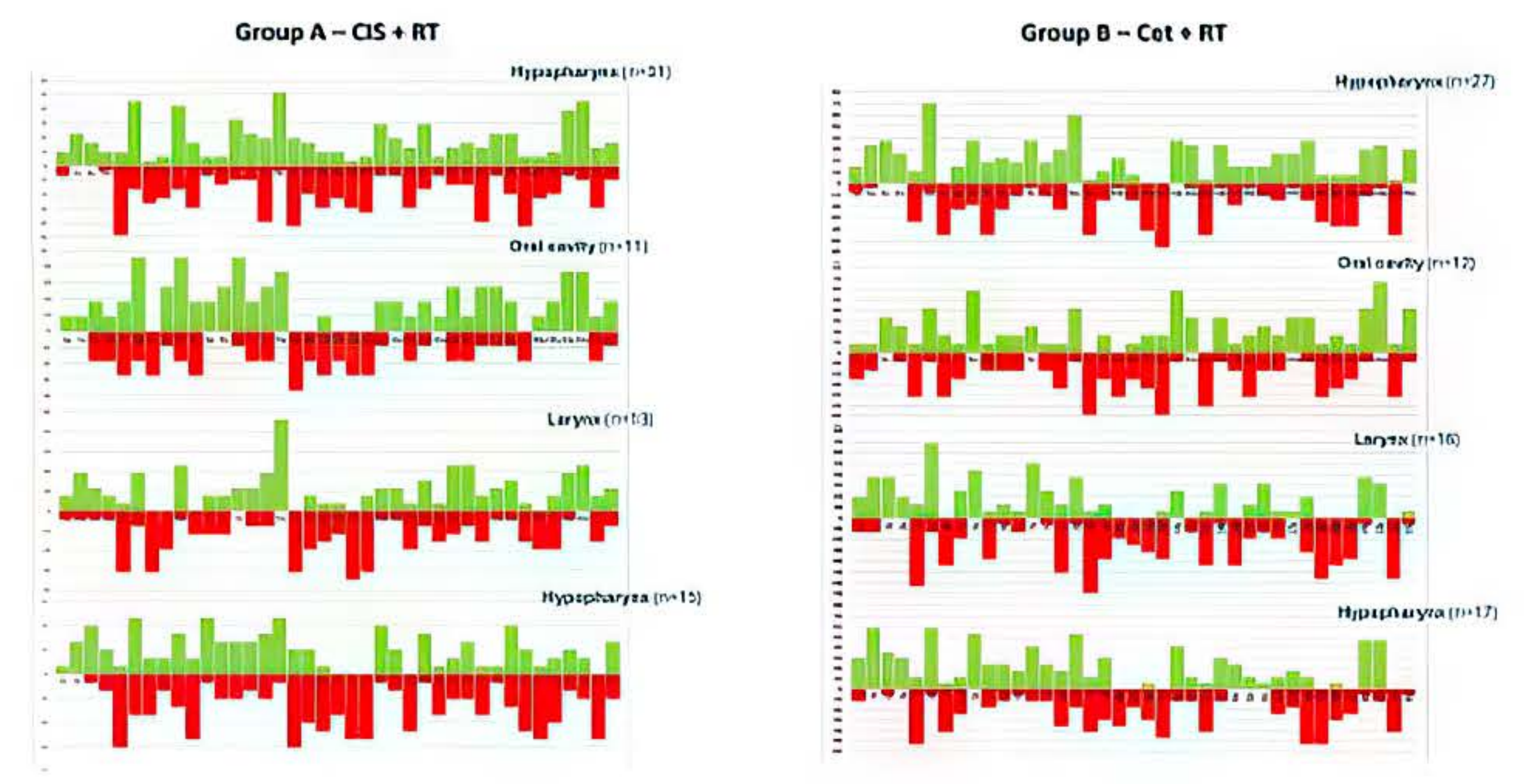


Figure 1. Overall survival of the patients in the sample according to treatment and location

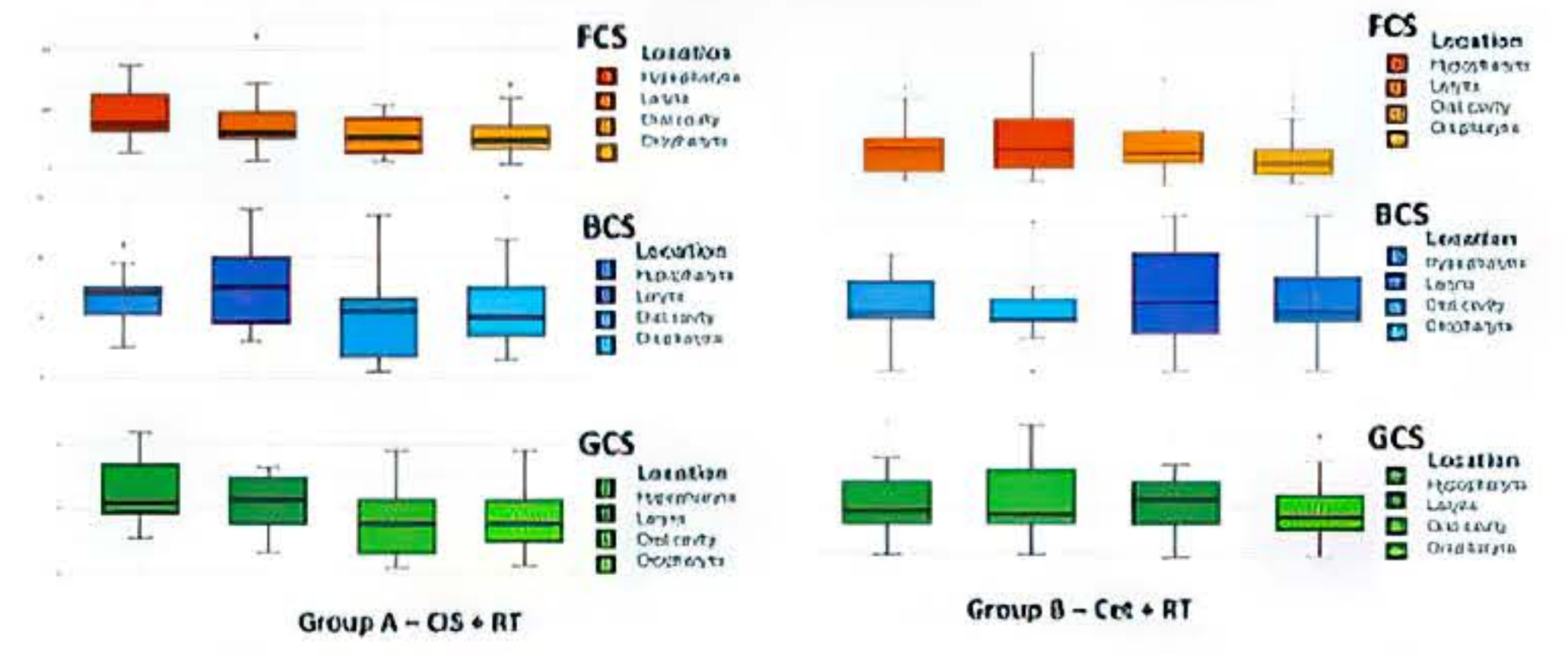


- For the Cis+RT group, in **hypopharynx**, alterations in **1q+ y 4q** implied worse response ($p < 0.05$) while deletions in **19q11** and **19q13.2** were associated with better prognosis in **oropharynx** ($p < 0.05$).
- In Cet+RT, gains in **2p** implied worse response in **larynx** and **oral cavity** ($p < 0.05$) while gains in **2q y 7q** did so in **oropharynx** ($p < 0.05$).



Results: BCS, FCS and GCS

Figure 3. Broad changes (BCS), focal changes (FCS) and global changes (GCS) by location



Cis+RT had a BCS of 11 (1-30), FCS of 133 (16-604); with lower FCS in oropharynx of 103 (16-398) $p < 0.05$.
In Cet+RT the FCS index was 140 (16-596), BCS of 11 (2-34), with lower FCS in oropharynx (120; 25-604) $p < 0.05$.

Conclusion

- ✓ **Chromosomal alterations** were identified at different levels depending on the **location** associated with **response to treatment**, although their impact on survival could not be proven.
- ✓ The data obtained could help to develop in future **new biomarkers** for HNSCC and **optimize available treatments** according to their anatomical origin.

Results: Baseline characteristics

	Cis+RT (n=70)			Cet+RT (n=72)		
	Total	CR/PR (n=53)	SD/PD (n=17)	Total	CR/PR (n=54)	SD/PD (n=18)
Sex, n (%)						
Male	63 (90)	43 (80.8)	10 (58.2)	64 (88.9)	50 (92.6)	14 (77.8)
Median age (range), years	55 (45-68)	55 (45-68)	55 (45-68)	60 (41-71)	55 (41-71)	60 (45-71)
Tumour location, n (%)						
Oral cavity	11 (15.7)	6 (11.3)	5 (29.4)	12 (16.7)	11 (20.4)	1 (5.6)
Oropharynx	31 (44.3)	21 (39.6)	10 (58.8)	27 (37.5)	19 (35.2)	8 (44.4)
Larynx	13 (18.6)	11 (20.8)	2 (11.8)	16 (22.2)	12 (22.2)	4 (22.2)
Hypopharynx	5 (7.1)	5 (9.4)	0 (0.0)	17 (23.6)	15 (27.8)	2 (11.1)
Tumour category, n (%)						
T1-2	19 (27.1)	14 (26.4)	5 (29.4)	20 (27.8)	20 (37.0)	0 (0.0)
T3-4	51 (72.9)	39 (73.6)	12 (70.6)	42 (58.3)	34 (62.8)	8 (44.4)
Unknown				1 (1.4)	1 (1.9)	
Sto status, n (%)						
St0-1	20 (28.6)	17 (32.1)	3 (17.6)	13 (18.1)	12 (22.2)	1 (5.6)
St2	42 (60.0)	31 (57.5)	11 (64.7)	42 (58.3)	34 (62.8)	8 (44.4)
St3	6 (8.6)	5 (9.4)	1 (5.9)	10 (13.9)	8 (14.8)	2 (11.1)
Unknown				1 (1.4)	1 (1.9)	
Stage, n (%)						
II	8 (11.4)	7 (13.2)	1 (5.9)	6 (8.3)	4 (7.4)	
III	50 (71.4)	38 (71.7)	12 (70.6)	51 (70.8)	39 (72.2)	12 (66.7)
IV	12 (17.1)	8 (15.1)	4 (23.5)	16 (22.2)	11 (20.4)	5 (27.8)
Unknown				1 (1.4)	1 (1.9)	
HP/other, n (%)						
HP/other	12 (17.1)	9 (17.0)	3 (17.6)	10 (13.9)	7 (12.9)	3 (16.7)
HP/other	52 (74.3)	39 (73.0)	14 (82.4)	52 (72.2)	47 (87.1)	5 (27.8)
Unknown	6 (8.6)	6 (11.3)	0 (0.0)	10 (13.9)	0 (0.0)	4 (22.2)
HP/other, n (%)						
HP/other	7 (10.0)	4 (7.5)	3 (17.6)	8 (11.1)	6 (11.1)	2 (11.1)
HP/other	12 (17.1)	8 (15.1)	4 (23.5)	17 (23.6)	15 (27.8)	2 (11.1)

142 patients were identified (Cis+RT, n=72; Cet+RT, n=70). They were subclassified into:

1. Oral cavity (n=24; 16.9%).
2. Oropharynx (n=64; 45.1%).
3. Larynx (n=26; 18.3%).
4. Hypopharynx (n=30; 21.2%).

In both groups, the **larynx** had a longer mOS: 58.07 months (95% CI: 53.14-60.2) in Cis+RT and a median not reached in Cet+RT, although without significant differences with the rest ($p > 0.05$).

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Contact information

Juan Carlos Redondo González
Medical Oncology Resident
University Hospital of Salamanca
Institute of Biomedical Research of Salamanca

Phone contact: +34 648078281
Mail 1: jcredondo@saludcastillayleon.es
Mail 2: jcredondoglez@gmail.com

