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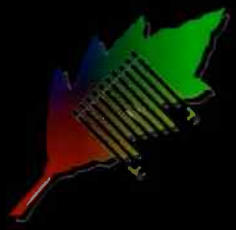
Correlation of Dosimetrical Variables and Cytokines in NSCLC Patients Treated with IG-IMRT

Avanzo M, Trovò M, Furlan C, et al.

CRO Aviano



Background

Post RTOG 0617 era. Improving outcome in locally advanced NSCLC:

- Radiobiology - alterated fractionations
- New systemic agents
- Biology

SBRT era. Widespread use of high ablative dose; the number of patients eligible for SBRT is likely to increase. New challenges:

- interpretation of lung changes vs. PD
- foreseeing high risk patients for severe lung toxicity

Background

As part of Biology: cytokines!

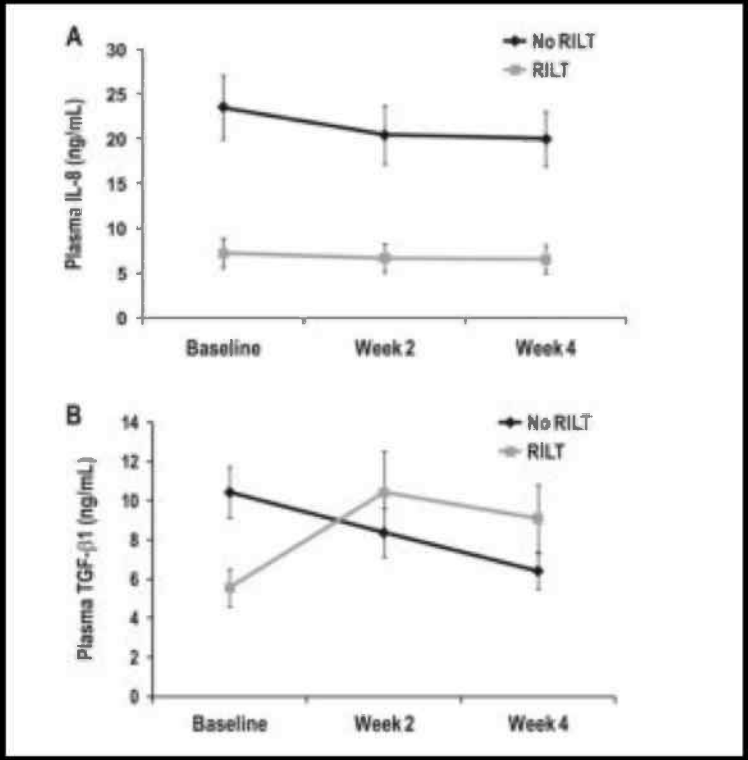
Possible biomarkers:

- in the identification of patients at high risk for the development of radiation fibrosis
-differential diagnosis fibrosis vs. PD in SBRT

-in the identification of patients that might / might not benefit from dose-escalation
-surrogates of response

Rationale

A correlation exists between plasma levels of cytokines and side effects of RT to the lung



Int J Radiat Oncol Biol Phys. 2012 October 1; 84(2): e217–e222.

Rationale

Research has been conducted in this field with limitations:

- different studies assessed the role of ***single*** cytokines

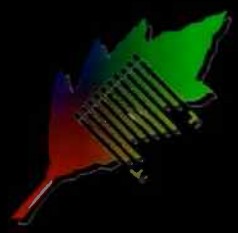
- few molecules investigated

- no current endpoints (clinical –G2/4 pneumonitis)

- no conclusive results

Purpose

to investigate if a correlation exists between dosimetrical variables of the RT treatment and plasmatic levels of multiple cytokines in NSCLC patients treated with IG-IMRT.

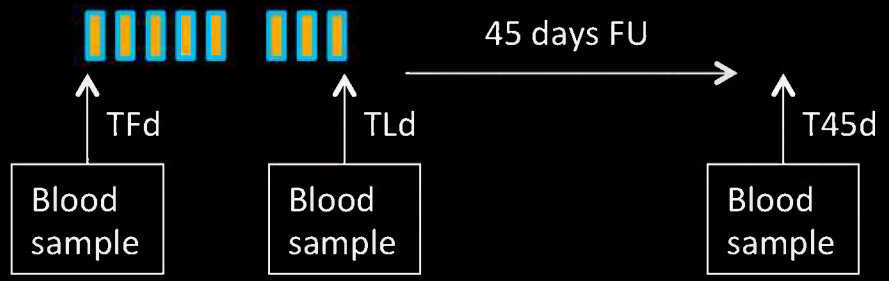


Methods and Materials

Ethics Committee Approval
Between May and December 2011

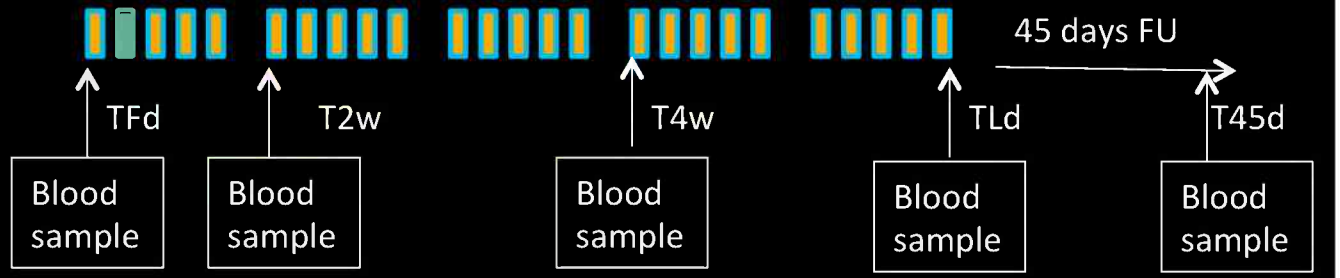
Early-stage:

SBRT 52 Gy/
8fr
15 patients



Locally-advanced:

IMRT 60 Gy/
25fr
13 patients



TFd: Time first day of RT; TLd: Time last day of RT; T45d: Time 45th day of follow-up; T2w: Time second week RT

Methods and Materials

A multiplex parametric technology was used for quantification of the following cytokines:

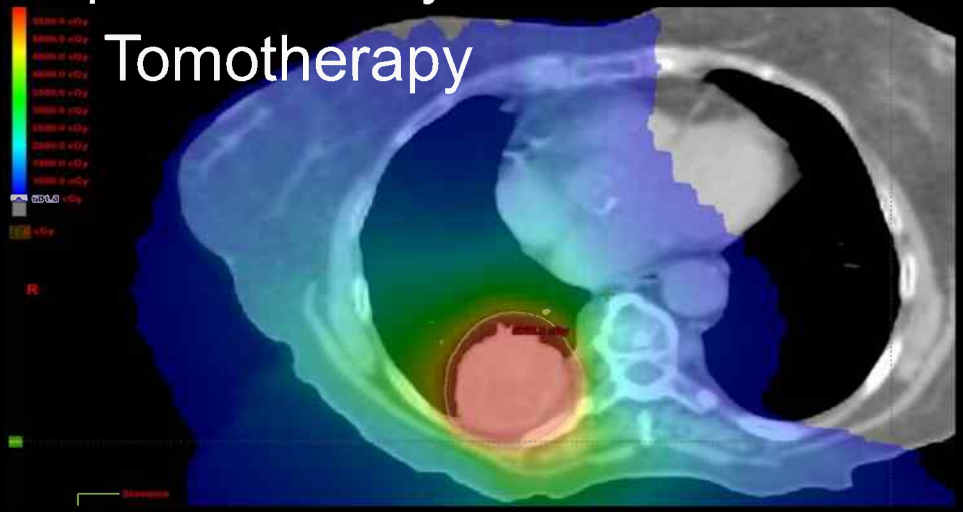
IL-1, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17,

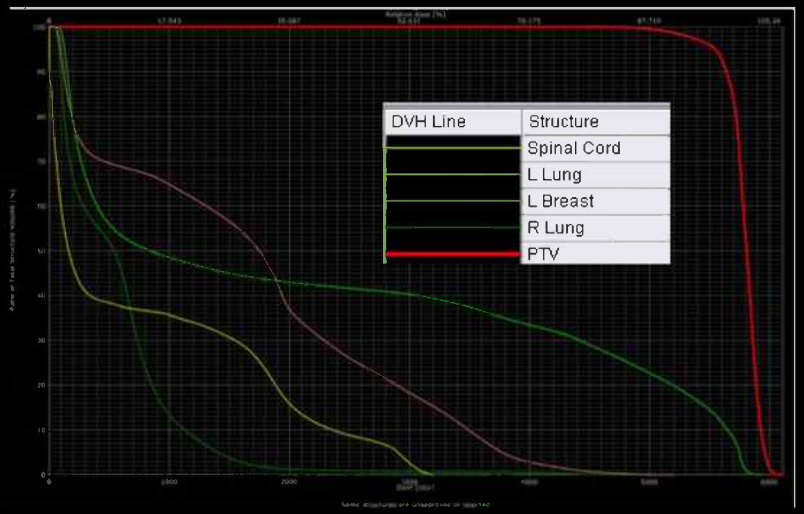
EGF, FGF-2, INF-γ, MIP-1α, MIP-1β, TGF-α, VEGF, PDGF-α, PDGF-β

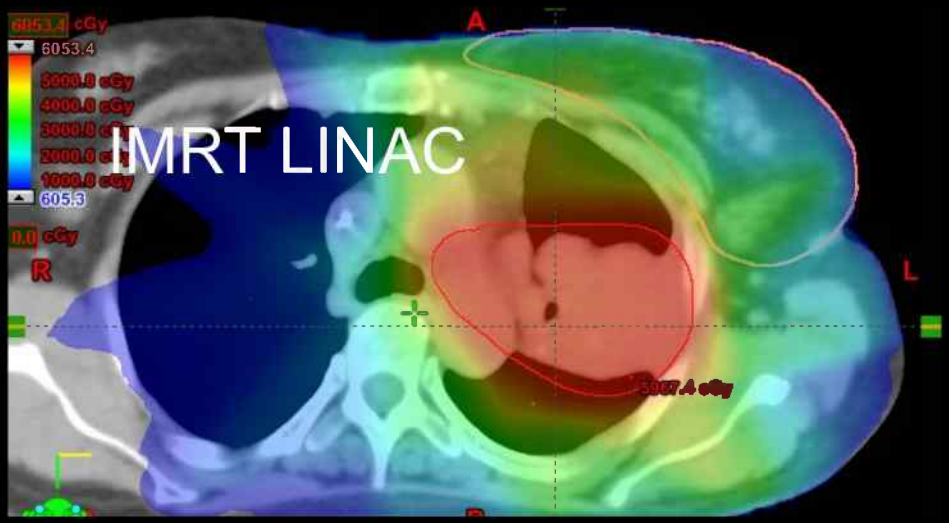
Bortolin MT. Cytokine. 2012 Oct;60(1):90-5

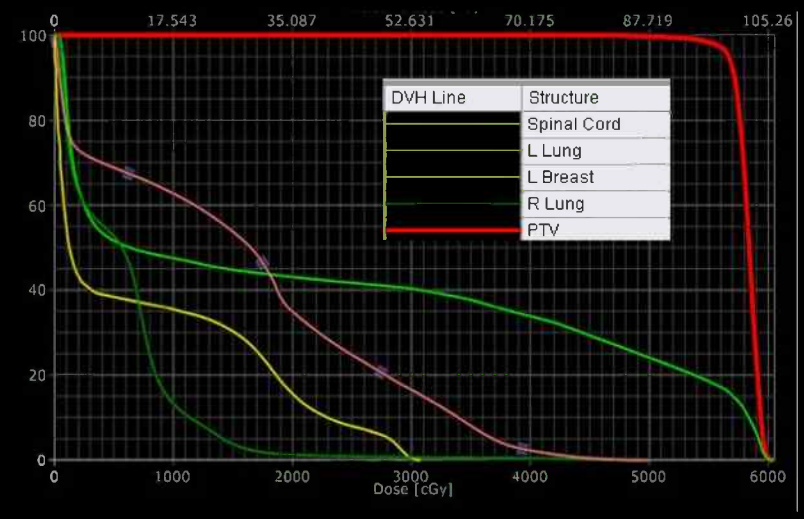
Methods and Materials

IMRT was delivered with the Tomotherapy Hi-Art II System or with a Varian LINAC (RA). Tomotherapy plans were exported to Eclipse for analysis.









Methods and Materials

The following dosimetrical parameters were extracted:

Variables related to ipsilateral lung:
Mean lung dose (MLD): 17.2 Gy (95% CI 3.7 - 30.1)
V20: 32.4 (95% CI: 6.1 - 59.1)
V5: 59.3 (95% CI: 16.3 - 94.6)

Variables related to PTV:
Size of PTV: 281.1 cc (95% CI: 25.4 – 975)
Average dose to PTV: 58.2 Gy (95% CI: 53.4 - 63.2)

Variables related to fractionation:
Average dose / fraction to PTV: 5.9 (95% CI: 2.4 - 10.9)
Number of fractions: 5,8, 25

Statistical analysis

Ccorrelations between dosimetric parameters and cytokines was performed using the Pearson linear correlation coefficient and the associated *p*-values computed using a Student's t distribution.

A matrix of p-values, showing only $p<0.05$ was calculated to identify significant correlations

Dosimetrical variables

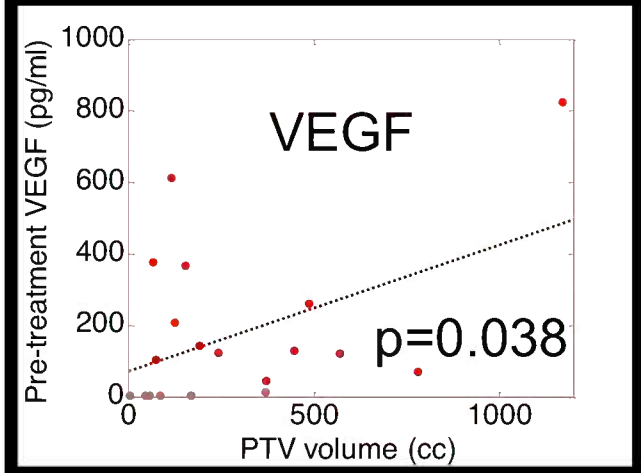
Measured Cytokines

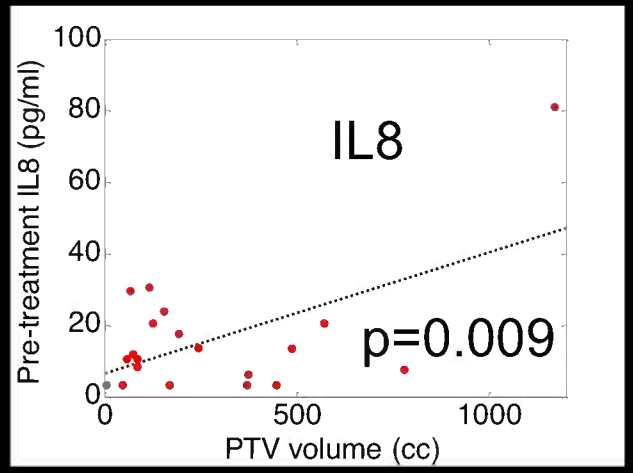
	PTV size (cc)	V20 (Gy)	V5 (Gy)	MLD (Gy)	PTVave (Gy)	fractions	dose / fx (Gy)
IL1_0							
IL1ra_0							
IL2_0							
IL4_0							
IL5_0	0.009						
IL6_0							
IL7_0							
IL8_0	0.009						
IL10_0							
IL12_0							
IL13_0							
IL15_0							

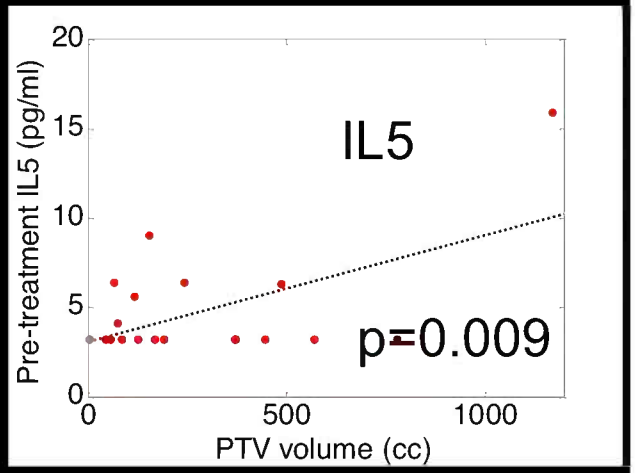
Results (1)

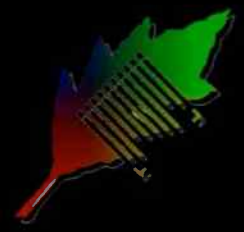
Statistically significant correlations were found between some absolute values of cytokines and dosimetric variables:

PTV size (cc) was related to pre-treatment values of IL 5, IL 8 and VEGF



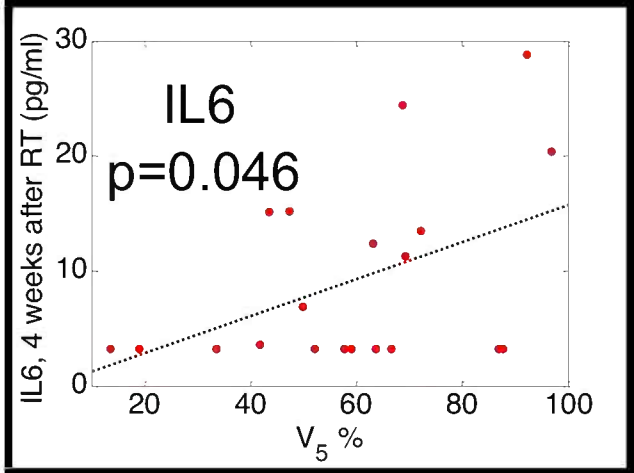


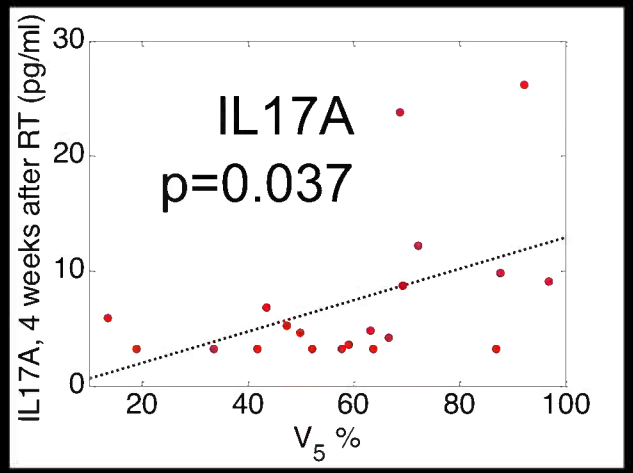


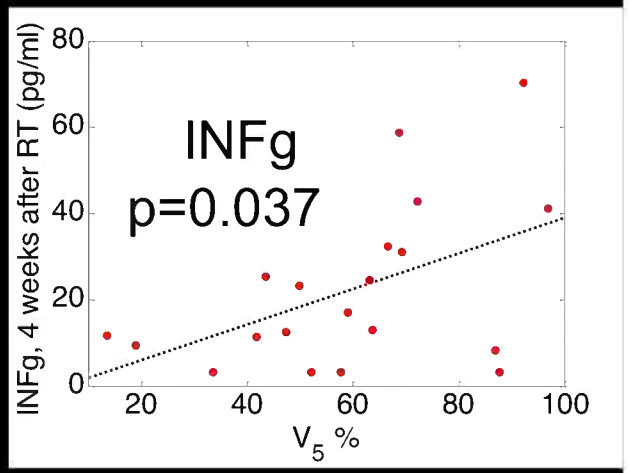


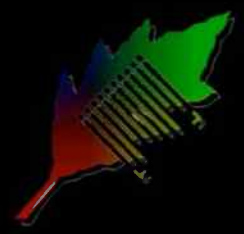
Results (2)

Ipsilateral Lung V5 was related to plasmatic value of IL6, IL17A and INFg measured at 45 days after RT



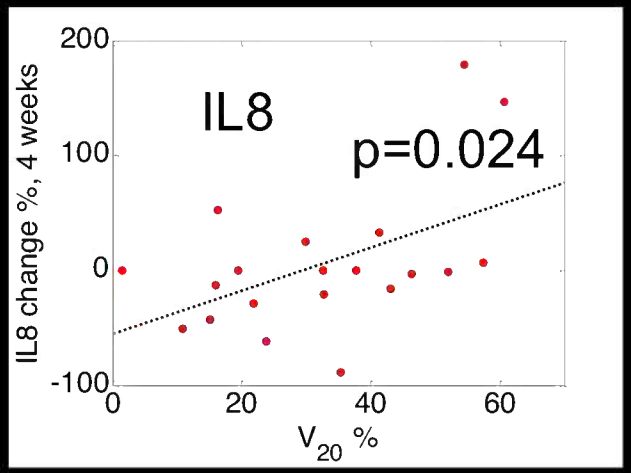


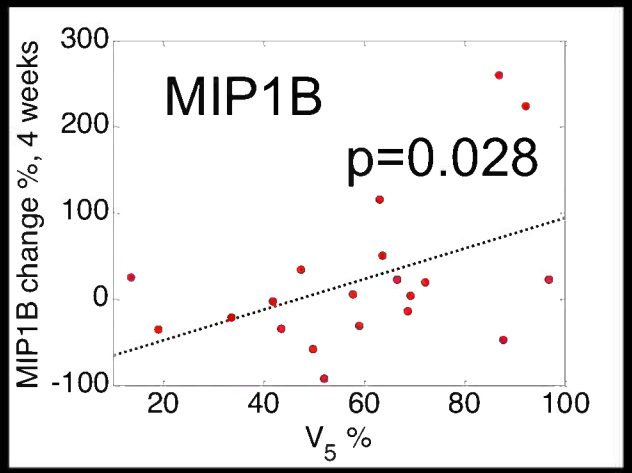


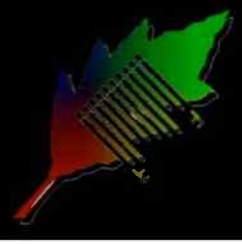


Results (3)

Ipsilateral Lung V5 and V20 were also related to relative change in MIP1B and IL-8 45 days after RT







Conclusions

- PTV volume was related to some baseline cytokines values (IL-5, IL-8, VEGF).
- Dosimetrical lung variables (V5 and V20) were related to cytokines levels after completion of RT.
- All correlations were positive: an increase in dosimetrical parameters corresponded to an increase in cytokine plasmatic level
- No ”fractionation effect” on cytokine levels.