Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

Comunicazioni orali 2

EXTERNAL VALIDATION OF THE HEMO-EOSINOPHILS-INFLAMMATION INDEX AS A PROGNOSTICATOR IN ANAL CANCER: A MULTICENTRIC STUDY OF THE GASTROINTESTINAL WORKING GROUP OF THE ITALIAN ASSOCIATION OF RADIOTHERAPY AND CLINICAL ONCOLOGY (AIRO)

Pierfrancesco Franco MD, PhD, MPH candidate

Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale, Novara

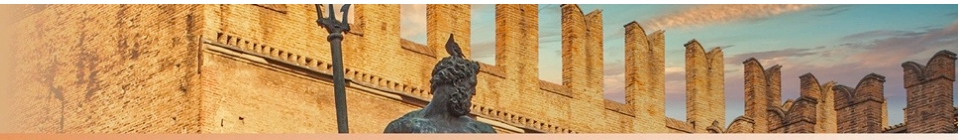
Dipartimento di Radioterapia Oncologica, AOU 'Maggiore della Carità', Novara

E-mail: pierfrancesco.franco@uniupo.it

twitter @Pier_Franco_MD

Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia



DICHIARAZIONE

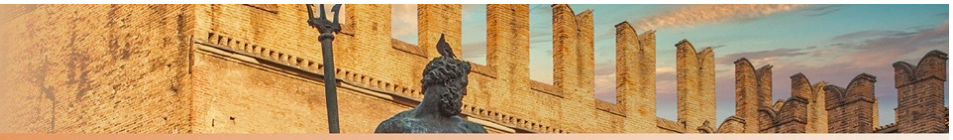
Relatore: Pierfrancesco Franco

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

Background-1

- ✓ Concurrent chemoradiation is the standard for patients with SCC of the anus
- ✓ Most patients have excellent prognosis
- ✓ However some heterogeneity exist
- ✓ Robust predictive and prognostic factors are needed in this setting to:
  - Inform research on better risk stratification for patients
  - Personalize treatment approaches
  - Introduce novel combined modality approaches



Background-2

Clinical prognostic factors
(related to patient, tumor and treatment)

- ✓ Age (older)
- ✓ Gender (male)
- ✓ T-stage (T-size)
- ✓ N-stage
- ✓ Overall treatment time
- ✓ Treatment breaks
- ✓ HPV status (and TIL)
- ✓ Hb level

Interest in the interplay between cancer, the immune system and inflammation

Different bio-humoral prognostic scores were evaluated in anal cancer:

- ✓ Absolute leukocyte and neutrophil count
- ✓ Neutrophil-Lymphocyte ratio (NLR)
- ✓ Platelet-Lymphocyte ratio (PLR)
- ✓ Systemic Index of Inflammation (SII)

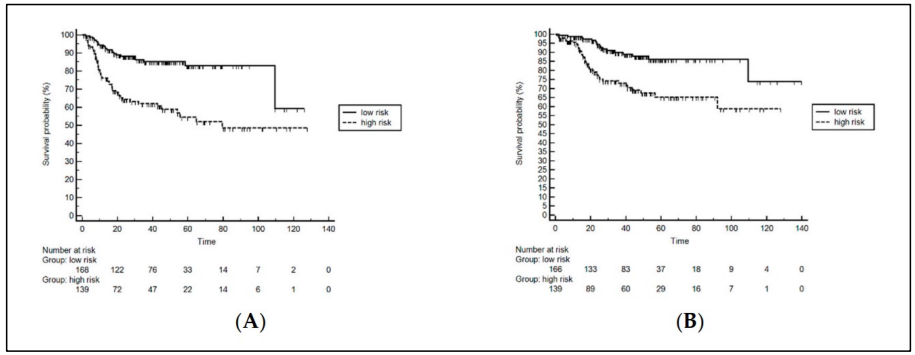
Hemo-Eosinophils Inflammation (HEI) Index in anal cancer

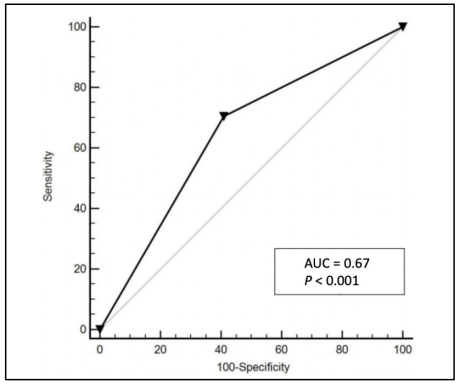
Multicentric observational study investigated the validity of a prognostic model based on the HEI Index in anal cancer patients treated with concurrent chemoradiation.

- ✓ Hb value
- ✓ Systemic Inflammatory Index (SII =Platelet x Neutrophil/Lymphocyte)
- ✓ Eosinophil count

  - All values were taken at baseline
  - Weight = 1 to each of the following variables: Hb < 12 g/dL, SII > 560 and eosinophil count ≥100/µL
  - Patients were stratified: low-risk group (0,1 negative prognostic factors) and high-risk group (2,3 negative prognostic factors)

The model was shown to predict for disease-free (DFS) and overall (OS) survival in this setting of patients.





Rimini et al; Cancers 2021

Aim of the present study

✓ To externally validate HEI as a prognostic factor in a cohort of anal cancer patients treated with concurrent chemoradiation

- RAINSTORM study: multicentric AIRO observational study to evaluate the pattern of care and clinical outcomes of anal cancer patients treated with IMRT in Italy
- Patients treated with static IMRT or VMAT
- Mostly with concurrent 5-FU/Cape and MMC (few pts with DDP)
- Mean dose to primary tumor: 55 Gy (28-30 fr); mean dose to elective volumes: 45 Gy
- Available baseline Hb, ANCs, Leukocytes, Eosinophils

Statistical plan

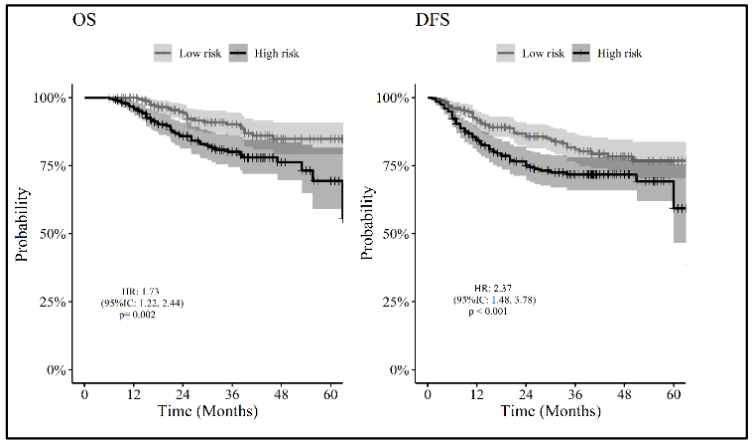
- Univ. and Multiv. Cox proportional hazards to assess impact of prognostic factors on DFS and OS
- The prognostic index (PI) $\sum_i \beta_i x_i$ was calculated
- The model calibration slope on the PI (regression coefficient) was determined in a Cox regression model in the validation set
- The coefficients (weights) of the individual variables of the PI were tested in a Cox regression in the validation cohort
- For model discrimination Harrell's c-index, Gönen & Heller K Index and the explained variation on the log relative hazard scale based on the D statistic (R^2_D)
- Predicted survival was computed according to the equation: $S(t) = S_0(t)^{e^{(PI-PI_0)}}$ following the PH assumption

Caravatta et al; Cancers 2021

Results -1

Characteristics		n	%
Age	<70 yr	269	30.5
	≥70 yr	614	69.5
Gender	Female	629	70.6
	Male	262	29.4
Stage	I-II	304	45.2
	III	369	54.8
Chemotherapy	MMC-based	592	92.1
	CCDP-based	51	7.9
HEI	Low-risk	325	51.2
	High-risk	310	48.8

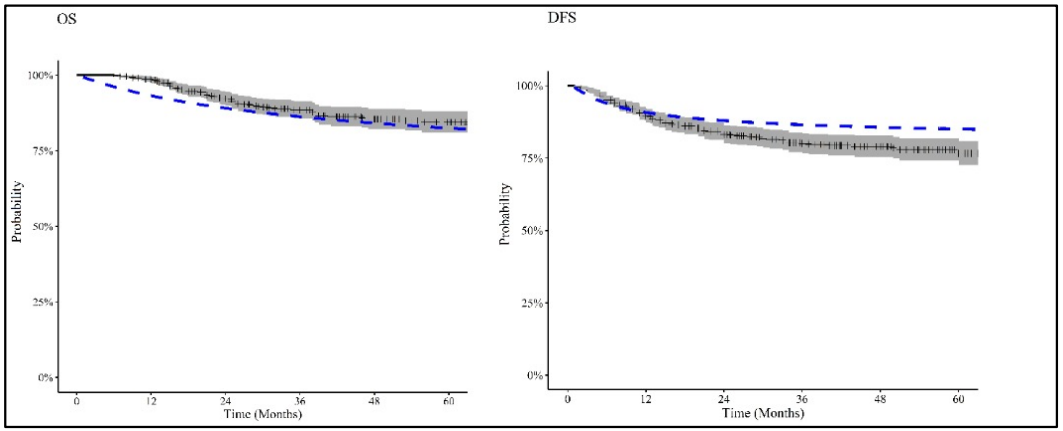
1) Validation cohort characteristics
2) KM curves for OS and DFS based on HEI risk stratification
3) Multivariate COX regression analysis



	OS		DFS	
Characteristics	Validation	Derivation	Validation	Derivation
Age (≥70 yr vs. <70 yr)	1.67(1.05, 2.64)*	1.92(0.88, 4.16)*	1.60(1.08, 2.38)*	2.25(1.19, 4.26)*
Gender (Male vs. Female)	1.60(1.01, 2.59)*	1.79(0.89, 3.58)*	1.42(0.96, 2.09)	1.19(1.43, 4.72)
Chemotherapy (CCDP-based vs.MMC-based)	0.48(0.17, 1.32)	0.25(0.08, 0.79)*	0.53(0.26, 1.10)	0.34(0.15, 0.76)*
Stage (III vs. I-II)	2.05(1.20, 3.48)*	1.97(0.87, 4.42)	2.20(1.43, 3.40)*	1.39(0.76, 2.54)
HEI (High-Risk vs. Low-Risk)	**2.02(1.25, 3.26)***	2.97(1.36, 6.50)*	**1.53(1.04, 2.24)***	2.59(1.42, 4.72)*

Results -2

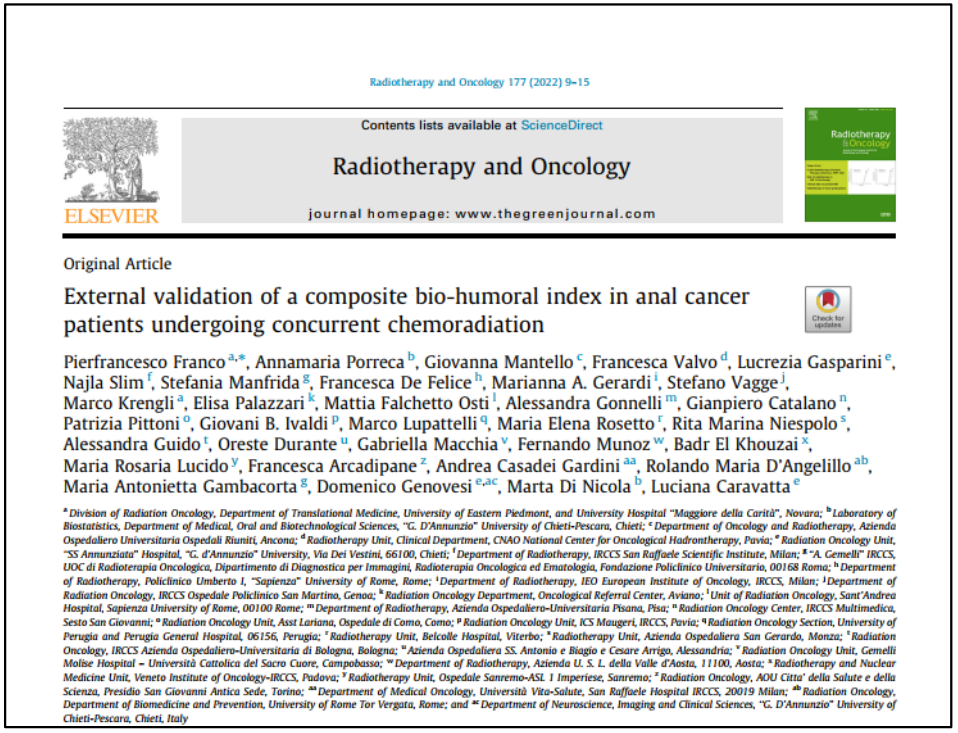
	OS		DFS	
	Validation	Derivation	Validation	Derivation
Harrell c-index (SE)	**0.68 (0.027)**	0.76 (0.054)	**0.66 (0.026)**	0.80 (0.049)
Gönen & Heller K (SE)	**0.67 (0.057)**	0.70 (0.028)	**0.71 (0.048)**	0.74 (0.021)
Explained Variation - R^2_D (SE)	**0.06 (0.403)**	0.17 (0.193)	**0.06 (0.453)**	0.21 (0.129)



1) Discrimination measures and standard error for OS and DFS for the validation and derivation datasets.
2) Estimates of the baseline survival function in the validation (grey curve) and derivation dataset (blue smoothed curve) for OS and DFS

Conclusion

- ✓ The HEI Index was confirmed to be an independent prognostic factor for OS and DFS in anal cancer patients treated with concurrent chemoradiation
- ✓ OS: similar effect size as derivation dataset; discrimination was good and calibration reliable (particularly 2-5 years after treatment)
- ✓ DFS: lower effect size compared to derivation dataset (however concordant direction); discrimination was not preserved and calibration imprecise
  - Different number of centres
  - Different patients per centre
  - Different calendar period
  - Residual confounding (HPV status, OTT, treatment compliance, comorbities not adjusted for)
- ✓ Confirmation within a prospective study is required



Radiotherapy and Oncology 177 (2022) 9–15

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

External validation of a composite bio-humoral index in anal cancer patients undergoing concurrent chemoradiation

Pierfrancesco Franco [a,*], Annamaria Porreca [b], Giovanna Mantello [c], Francesca Valvo [d], Lucrezia Gasparini [e], Najla Slim [f], Stefania Manfrida [g], Francesca De Felice [h], Marianna A. Gerardi [i], Stefano Vagge [j], Marco Krengli [a], Elisa Palazzari [k], Mattia Falchetto Osti [l], Alessandra Gonnelli [m], Gianpiero Catalano [n], Patrizia Pittoni [o], Giovani B. Ivaldi [p], Marco Lupattelli [q], Maria Elena Rosetto [r], Rita Marina Niespolo [s], Alessandra Guido [t], Oreste Durante [u], Gabriella Macchia [v], Fernando Munoz [w], Badr El Khouzai [x], Maria Rosaria Lucido [y], Francesca Arcadipane [z], Andrea Casadei Gardini [aa], Rolando Maria D'Angelillo [ab], Maria Antonietta Gambacorta [g], Domenico Genovesi [e,ac], Marta Di Nicola [b], Luciana Caravatta [e]

[a] Division of Radiation Oncology, Department of Translational Medicine, University of Eastern Piedmont, and University Hospital "Maggiore della Carità", Novara; [b] Laboratory of Biostatistics, Department of Medical, Oral and Biotechnological Sciences, "G. D'Annunzio" University of Chieti-Pescara, Chieti; [c] Department of Oncology and Radiotherapy, Azienda Ospedaliero Universitaria Ospedali Riuniti, Ancona; [d] Radiotherapy Unit, Clinical Department, CNAO National Center for Oncological Hadrontherapy, Pavia; [e] Radiation Oncology Unit, "SS Annunziata" Hospital, "G. d'Annunzio" University, Via Dei Vestini, 66100, Chieti; [f] Department of Radiotherapy, IRCCS San Raffaele Scientific Institute, Milan; [g] "A. Gemelli" IRCCS, UOC di Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario, 00168 Roma; [h] Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome, Rome; [i] Department of Radiotherapy, IEO European Institute of Oncology, IRCCS, Milan; [j] Department of Radiation Oncology, IRCCS Ospedale Policlinico San Martino, Genoa; [k] Radiation Oncology Department, Oncological Referral Center, Aviano; [l] Unit of Radiation Oncology, Sant'Andrea Hospital, Sapienza University of Rome, 00100 Rome; [m] Department of Radiotherapy, Azienda Ospedaliero-Universitaria Pisana, Pisa; [n] Radiation Oncology Center, IRCCS Multimedica, Sesto San Giovanni; [o] Radiation Oncology Unit, Asst Lariana, Ospedale di Como, Como; [p] Radiation Oncology Unit, ICS Maugeri, IRCCS, Pavia; [q] Radiation Oncology Section, University of Perugia and Perugia General Hospital, 06156, Perugia; [r] Radiotherapy Unit, Belcolle Hospital, Viterbo; [s] Radiotherapy Unit, Azienda Ospedaliera San Gerardo, Monza; [t] Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; [u] Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria; [v] Radiation Oncology Unit, Gemelli Molise Hospital – Università Cattolica del Sacro Cuore, Campobasso; [w] Department of Radiotherapy, Azienda U. S. L. della Valle d'Aosta, 11100, Aosta; [x] Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology-IRCCS, Padova; [y] Radiotherapy Unit, Ospedale Sanremo-ASL 1 Imperiese, Sanremo; [z] Radiation Oncology, AOU Citta' della Salute e della Scienza, Presidio San Giovanni Antica Sede, Torino; [ab] Department of Medical Oncology, Università Vita-Salute, San Raffaele Hospital IRCCS, 20019 Milan; [ab] Radiation Oncology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome; and [ac] Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University of Chieti-Pescara, Chieti, Italy

Thanks for your attention

Pierfrancesco Franco MD, PhD, MPH candidate

Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale, Novara

Dipartimento di Radioterapia Oncologica, AOU 'Maggiore della Carità', Novara

E-mail: pierfrancesco.franco@uniupo.it

@Pier_Franco_MD

On behalf of AIRO GI Study Group