Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

TOSSICITÀ E RISULTATI CLINICI NEI PAZIENTI ANZIANI CON CARCINOMA ANALE TRATTATI CON RADIOTERAPIA AD INTENSITÀ MODULATA: UNA ANALISI DI SOTTOGRUPPO DI UNO STUDIO MULTICENTRICO DEL GRUPPO DI STUDIO AIRO PER LE PATOLOGIE GASTROINTESTINALI

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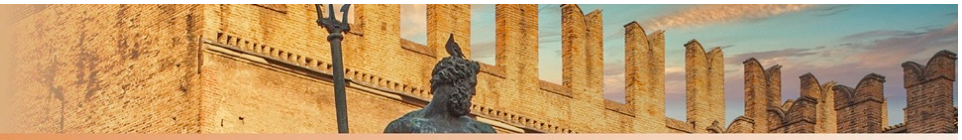

DICHIARAZIONE

Relatore: LUCIANA CARAVATTA

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

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

For **elderly patients**' treatment needs often to be modified. Alternative treatment strategies are not described in guidelines and little evidence is available in the literature.

Background-2

RAINSTORM (Radiotherapy with Intensity-Modulated Techniques in the Treatment of Anal Carcinoma) retrospective study

- ❑ **987** consecutive non-metastatic AC patients treated within 25 different Italian centers between 2007–2019
- ❑ 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 fractions); mean dose to elective volumes: 45 Gy

Multivariate analysis:

- ✓ **Lymph node involvement** negatively affected **all clinical outcome** measures (LC, CFS, OS, PFS and EFS).
- ✓ **Age > 68.5** (cut-off set at 68.5 years as median age of population study) and **pathological grade 3** were confirmed as **negative prognostic factors for PFS (p = 0.019) and LC (p = 0.032)**, respectively

*Caravatta L. Cancers **2021**, 13, 1902. https://doi.org/ 10.3390/cancers13081902*

Background-3

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

877 patients available for laboratory inflammation parameters (Hemo-Eosinophils-Inflammation index, including baseline hemoglobin level, systemic inflammatory index and eosinophil count).

Proportional hazards were adjusted for **age**, gender, tumor-stage, and chemotherapy.

Table 3
Hazard Ratios and relative 95% Confidence Interval for OS and DFS resulted from multivariate Cox regression analysis.

Characteristics	OS		DFS	
	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 vsMMC-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 Index (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)*

Legend: CDDP: cisplatin; MMC: Mitomicyn C; OS: overall survival; DFS: disease-free survival; HEI: Hemo-Eosinophils Inflammation.
* $p < 0.05$ derived from Cox regression analysis.

*Franco P. Radiotherapy and Oncology **2022**. https://doi.org/10.1016/j.radonc.2022.10.015*

Aims and Methods

- ✓ To compare acute and late adverse events and clinical outcomes of older (≥ 70 years) and younger patients with anal cancer treated with curative radio-chemotherapy.

- ✓ A subgroup analyses of RAINSTORM retrospective cohort according to the distribution of variables in Age subgroups (<70 years, n=694 and ≥70 years, n= 283) was conducted.

- ✓ The univariate Cox proportional hazards model reported the hazard ratio (HR) and the 95% confidence interval (95% CI) for Age (<70 vs. ≥70), ECOG PS (≥1 vs. 0), HIV (Yes vs. No), HPV (Yes vs. No) and baseline Haemoglobin level (Hb <10 vs. ≥ 10) as independent factors impacts on clinical outcomes: Overall Survival (OS) and Disease-Free Survival (DFS).

Results

Distribution of **variables** in Age subgroups. The association between categorical variables was assessed using the chi-square test, and the p-value was reported, indeed, the Mann U Whitney test was used to assess median differences.

Older patients:

- worse baseline performance status (PS 1-2 vs 0) (35.3% vs. 15.7%, p <0.001)
- similar stage

	Age		
	<70	**≥70**	*p-value*
	N=694	N=283	
Gender			*0.139*
Male	206 (29.7%)	70 (24.7%)	
Female	488 (70.3%)	213 (75.3%)	
Baseline ECOG performance status			***<0.001***
0	582 (83.9%)	181 (64.0%)	
1-2	109 (15.7%)	**100 (35.3%)**	
NR	3 (0.4%)	2 (0.7%)	
TNM Stage			*0.740*
T1-T2, N0	236 (34.05%)	91 (32.03%)	
T3-T4, N0	70 (10.06%)	32 (11.39%)	
Any T, N+	388 (55.89%)	160 (56.58%)	
Baseline Haemoglobin level			*0.247*
<10 g/dl	20 (2.88%)	10 (3.53%)	
≥10 g/dl	456 (65.7%)	170 (60.1%)	
NR	218 (31.4%)	103 (36.4%)	

Results

Distribution of **variables** in Age subgroups. The association between categorical variables was assessed using the chi-square test, and the p-value was reported, indeed, the Mann U Whitney test was used to assess median differences.

Older patients:

- less concomitant chemotherapy (88.0% vs. 97.4%, p <0.001)

	Age		
	<70	**≥70**	*p-value*
	N=694	N=283	
Concomitant chemotherapy			***<0.001***
No	236 (34.05%)	91 (32.03%)	
Yes	70 (10.06%)	32 (11.39%)	
Concomitant chemotherapy (schedule)			***0.003***
MMC+5FU	472 (68.05%)	**188 (66.67%)**	
MMC + Capecitabine	116 (16.72%)	**37 (13.25%)**	
CDDP+5FU	18 (2.37%)	7 (2.41%)	
CDDP+Capecitabine	54 (7.84%)	17 (6.02%)	
MMC	2 (0.30%)	0 (0.00%)	
CDDP	2 (0.30%)	1 (0.40%)	
5FU	2 (0.30%)	**6 (2.41%)**	
Capecitabine	14 (2.07%)	**17 (6.02%)**	
Dose fraction			*0.069*
≤ 200	463 (66.72%)	171 (60.35%)	
> 200	231 (33.28%)	112 (39.65)	

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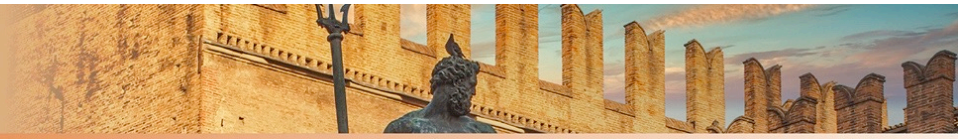

Results

Distribution of **toxicities** in Age subgroups. The association between categorical variables was assessed using the chi-square test, and the p-value was reported, indeed, the Mann U Whitney test was used to assess median differences.

		<70 YEARS (N=694)	≥70 YEARS (N=283)	*p value*
ACUTE TOXICITY	**Grade**	%	%	
Skin	0	9.08	9.19	*0.154*
	1	14.1	12.7	
	2	47.7	54.8	
	3	27.5	20.8	
	missing	1.59	2.47	
Intestinal	0	21.2	23.0	*0.701*
	1	38.6	34.6	
	2	32.0	33.6	
	3	6.63	6.36	
	missing	1.59	2.47	
Urogenital	0	54.5	53.4	*0.601*
	1	34.4	32.5	
	2	9.22	11.0	
	3	0.43	0.71	
	missing	1.44	2.47	
Hematologic	0	41.5	38.9	***0.005***
	1	28.8	22.6	
	2	**11.0**	**17.3**	
	3	9.37	7.07	
	missing	9.37	14.1	
TREATMENT COMPLIANCE				
>5 days interruption for toxicity	No	81.3	81.3	*0.929*
	Yes	18.7	18.7	
Median overall treatment time (days)		44.0 [38.0;50.8]	43.0 [38.0;49.0]	*0.111*

		<70 YEARS (N=694)	≥70 YEARS (N=283)	*p value*
LATE TOXICITY	**Grade**			
Skin	0	77.2	70.3	*0.151*
	1	17.0	21.9	
	2	0.86	1.41	
	3	0.29	0.00	
	missing	4.61	6.36	
Subcutaneous	0	81.4	77.4	***0.022***
	1	**11.8**	**16.6**	
	2	1.87	0.00	
	3	0.29	0.35	
	missing	4.61	5.65	
Intestinal	0	66.0	57.6	*0.074*
	1	18.7	25.1	
	2	6.63	5.65	
	3	1.59	2.47	
	missing	7.06	9.19	
Urogenital	0	86.5	82.7	*0.330*
	1	6.05	7.77	
	2	1.15	1.77	
	3	0.58	0.00	
	missing	5.76	7.77	

- median follow-up of 28 months (range 6–138)
- **No statistically significant increase** has been reported in **grade ≥3 acute and late toxicities** in older patients
- **similar compliance** in terms of overall treatment **times** and **treatment interruptions.**

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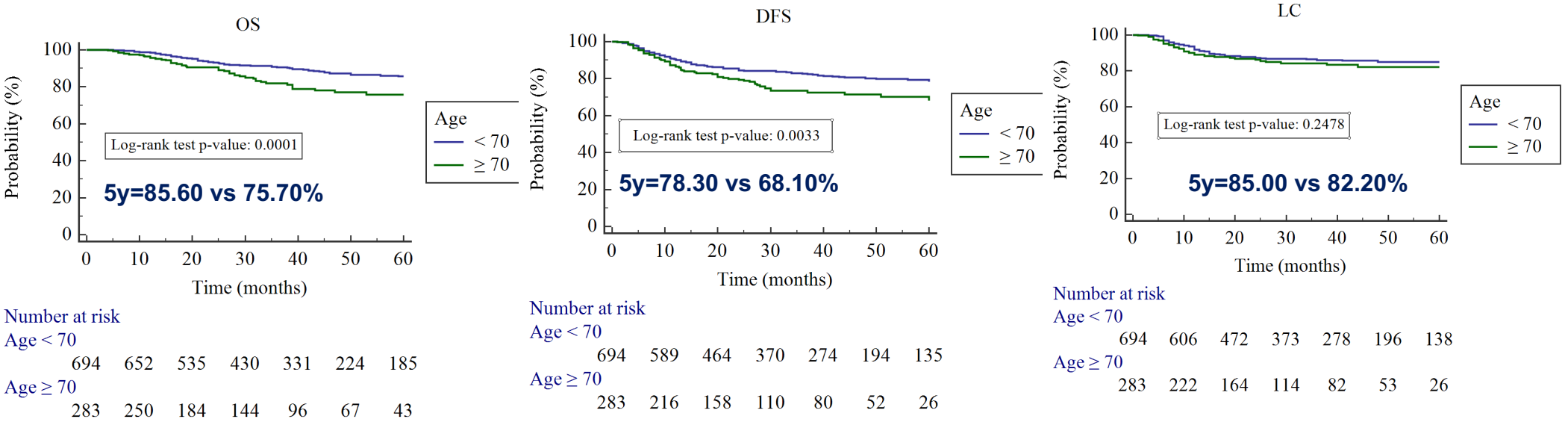
Results



OS and DFS resulted significant **lower in patients** with age ≥70 years.

Baseline **haemoglobin level <10 gm/dl** resulted predictive of **worse OS and DFS**, suggesting that a supplement supportive therapy in elderly patients may be considered.

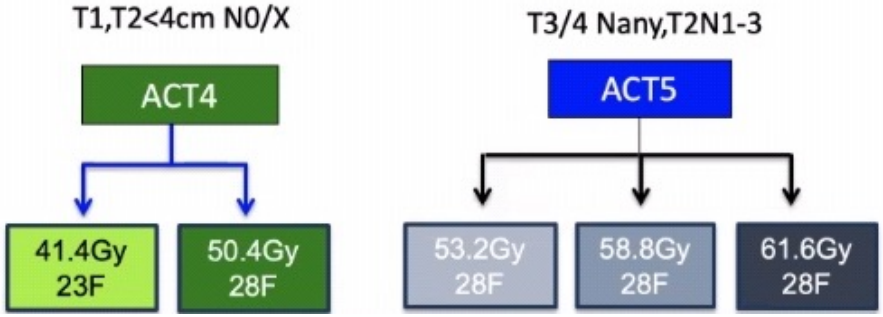
Conclusions

- ✓ In our analysis **older patients** (≥ 70 years) who underwent CRT showed the **same rates of grade ≥ 3 acute and late toxicities compared to younger patients**.
- ✓ **OS and DFS, but no LC, resulted significant lower in patients with age ≥70 years.**
- ✓ **Chemotherapy adaptation** (dose and/or regimen) may be necessary related to higher haematological toxicity.
- ✓ Baseline **haemoglobin level <10 gm/dl** resulted predictive of **worse OS and DFS**, suggesting that a supplement supportive therapy in elderly patients may be considered.
- ✓ Our data suggest, as in other retrospective series, that **fit older patients** with anal cancer should receive standard treatment similarly to their younger counterparts.

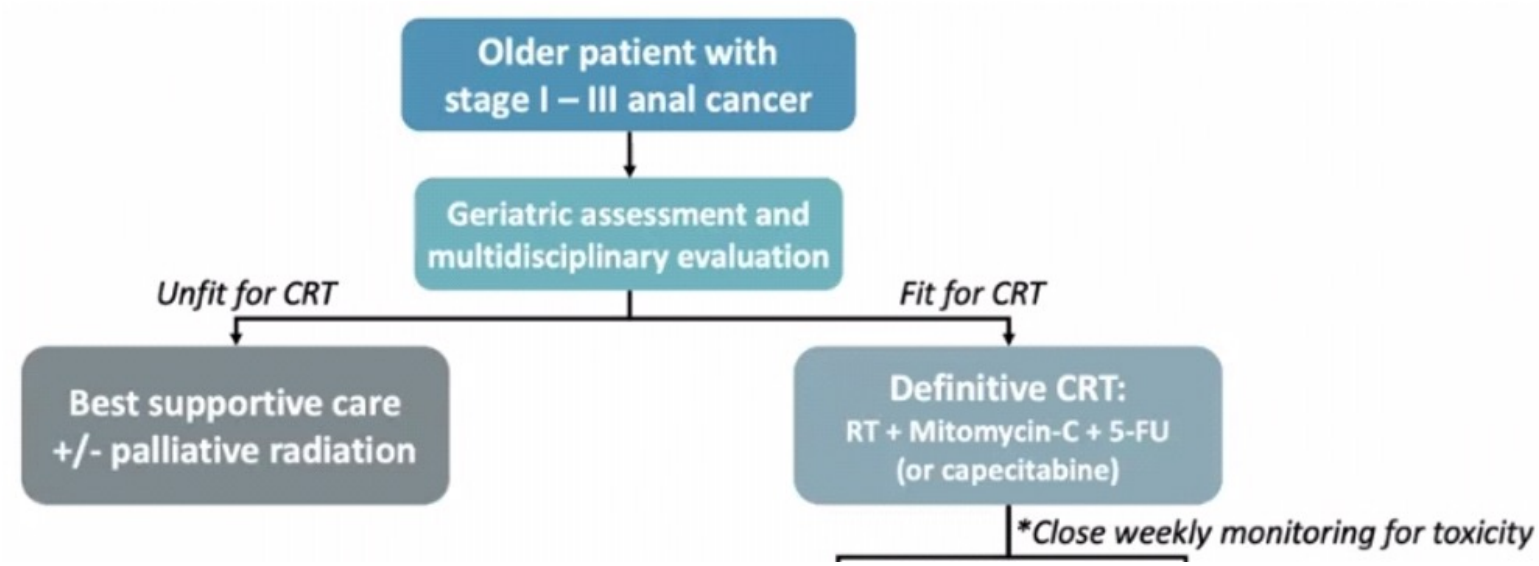
PLATO recruitment

ACT 3, ACT 4 & ACT 5
PLATO
PersonaLising Anal cancer radioTherapy tOne

- ACT 5 Phase II (RT dose escalated) – oldest patient recruited was 77 years (median age 60 years)
- ACT 4 (RT dose reduced) – oldest patient recruited was 87 years (median age 66 years)



A **multidisciplinary and comprehensive team approach** could be offered to ensure improved outcomes and maintenance of quality of life, and the **geriatric assessment** should be a key component in the evaluation of every older patient with anal cancer.



Martinez-Cannon BA, et al. Anal cancer in older adults: A Young International Society of Geriatric Oncology review paper. J Geriatr Oncol. 2022

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… and thank you for your attention

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