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Predictive factors of adverse events onset in GEPNET patients treated with PRRT

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AIM

To predict real-life adverse events occurrence in a series of consecutive GEPNET patients treated with PRRT.

MATERIALS AND METHODS

G1-G2 metastatic GEPNETs patients treated in our centre with PRRT (177Lu-Oxodotreotide, 4 administrations, 7.4 GBq/each) from April 2019 to December 2020 were considered. Patients were all previously treated with SSA followed by radiological disease progression (PD). Haematopoietic, liver and renal toxicities were collected every 14 days during PRRT and graded according to CTCAE v5 (G0, G1-G2, G3-G4). The population was subdivided as midgut/foregut and G1/G2, according to WHO 2019. Patients were categorical grouped according with ECOG-PS, number of metastatic sites, previous treatment lines (1 or ≥2) and the therapies received before PRRT (splenectomy, Everolimus, alkylating chemotherapy). To test independence between CTCAE onset and patient characteristics Pearson/Fisher and Wilcoxon's test were assessed. The last was applied to continues variables. Logistic regression with Firth correction *(R Puhr, Stat Med 2017*) and bootstrap were performed to determine predictability of clinical features and previous therapies for CTCAE onset.

Age	n= 87
Mean (± SD)	62.8 (± 12.2)
> 60 ys (n,%)	52 (59.8)
Gender	**n (%)**
Male	41 (47.1)
Female	46 (52.9)
ECOG PS	
0	69 (79.3)
1_2	18 (20.7)
Grading (WHO 2019)	
G1	33 (37.9)
G2	54 (62.1)
Primary tumor	
Midgut	56 (64.4)
Foregut	31 (35.6)
Distant metastasis localisation	
Liver	70 (80.5)
Nodal	40 (46)
Bone	24 (27.6)
Mesenteric	12 (13.8)
Peritoneal	8 (9.2)
Lung	2 (2.3)
Other localisations	11 (12.6)

Tab 1:
Whole study population (N=87)

PRRT administrations	
I	87 (100)
II	76 (87.3)
III	72 (82.7)
IV	61 (70.1)
PRRT line of treatment	
2nd	62 (71.3)
3rd	16 (18.4)
4th or further	9 (10.3)
Previous Therapies	
Surgery	64 (73.6)
Loco-regional (TACE, TARE)	15 (17.2)
Splenectomy	11 (12.7)
Alkylating Chemotherapy	16 (18.4)
mTOR inhibitor (Everolimus)	14 (16.1)
MetNET protocol	5 (5.7)

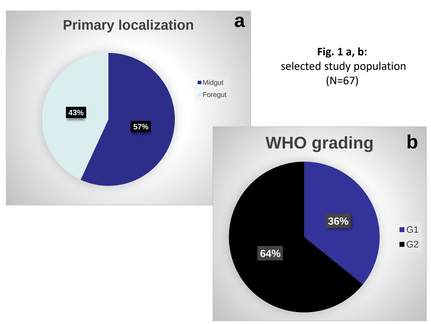

Fig. 1 a, b:
selected study population (N=67)

ADVERSE EVENTS	G1-G2, n(%)*	G3-G4, *n*(%)	Total CTCAE, n(%)
Leukopaenia	**30 (44.8)**		**30 (44.8)**
midgut	19 (63.3)		19 (63.3)
foregut	11 (36.7)		11 (36.7)
Neutropaenia	16 (23.9)	2 (3)	18 (26.9)
midgut	9 (56.3)	1 (50)	11 (28.9)
foregut	7 (43.7)	1 (50)	7 (24.1)
Anaemia	**46 (68.6)**	1 (1.5)	**47 (70.1)**
midgut	26 (56.5)	1 (100)	27 (57.5)
foregut	20 (43.5)		20 (42.5)
Thrombocytopaenia	**32 (47.8)**	2 (3)	**34 (50.7)**
midgut	21 (65.6)	1 (2.6)	22 (64.7)
foregut	10 (31.3)	1 (3.5)	11 (32.4)
ALT/GPT increase	21 (31.3)	1 (1.5)	22 (32.8)
midgut	10 (47.6)		10 (45.4)
foregut	11 (52.4)	1 (100)	12 (54.5)
AST/GOT increase	17 (25.4)		17 (25.4)
midgut	8 (47.1)		8 (47.1)
foregut	9 (52.9)		9 (52.9)
GGT increase	12 (17.9)		12 (17.9)
midgut	3 (25)		3 (25)
foregut	9 (75)		9 (75)
Total bilirubin increase	17 (25.4)		17 (25.4)
midgut	8 (47.1)		8 (47.1)
foregut	9 (52.9)		9 (52.9)
Albumin decrease	4 (6)		4 (6)
midgut	2 (50)		2 (50)
foregut	2 (50)		2 (50)
INR increase	6 (9)	1 (1.5)	7 (10.5)
midgut	2 (33.3)	1 (2.6)	3 (42.9)
foregut	4 (66.6)	-	4 (57.1)
Creatinine clearance	16 (23.9)		16 (23.9)
midgut	10 (62.5)		10 (62.5)
foregut	6 (37.5)		6 (37.5)
eGFR decrease*(n:58)***	**44 (75.9)**		**44 (75.9)**
midgut (n: 31)	21 (47.7)		21 (47.7)
foregut (n: 27)	23 (52.3)		23 (52.3)

Tab. 2: Occurred CTCAE. *Percentage are calculated in accordance with the number of patients (n=67). **eGFR alteration was assessed in 58 patients, in accordance with age cut-off

Explanatory Variables	*Leukopaenia*	*Neutropaenia*	*Anaemia*	*Thr-paenia*	*ALT increase*	*AST increase*	*GGT increase*	*Bil increase*	*Alb decrease*	*INR increase*	*Creatinine increase*	*eGFR decrease*
*Age (p)**	0.5886	0.5473	0.2547	0.7569	0.5723	0.4835	0.7755	0.7576	0.1586	0.8753	0.4357	**0.0316**
Gender (p)	0.219	0.583	**0.003**	0.028	0.298	1	0.524	0.269	0.329	0.696	0.011	0.378
ECOG-PS (p)	1	0.72	0.091	0.539	1	0.715	0.678	1	0.144	0.6	**0.029**	0.322
Grading (p)	1	0.567	0.405	0.131	1	1	1	0.574	1	0.407	1	0.118
Liver (p)	1	0.069	0.511	1	0.538	1	0.328	1	1	1	0.423	0.428
Nodal (p)	1	0.592	1	0.627	0.792	0.386	0.755	0.168	**0.036**	1	0.574	1
Mesenteric (p)	0.199	1	0.282	0.34	0.48	0.053	1	1	1	0.323	0.438	0.673
Peritoneal (p)	0.692	0.375	0.094	0.259	0.416	1	1		0.669	1	1	1
Bone (p)	0.608	0.773	0.402	1	0.005	0.547	1	0.56	0.113	0.221	0.77	0.338
Lung (p)	0.448	1	1	0.493	1	1	1	1	1	1	1	1
PRRT line (p)	0.082	0.166	0.102	0.504	0.718	0.116	**0.047**	0.645	0.398	0.062	0.628	0.714
Chemotherapy (p)	0.759	0.312	0.315	0.765	0.499	0.715	0.228	0.725	1	0.127	1	0.424
Everolimus (p)	0.759	0.736	0.74	0.369	1	0.465	1	0.158	0.167	0.614	0.274	0.691
MetNET (p)	0.65	0.116	1	0.197	0.316	0.588	0.216	0.099	1	0.081	1	0.563
Splenectomy (p)	**0.017**	0.714	1	**0.006**	**0.024**	1	0.099	1	1	1	0.274	0.424

Tab 3: Chi square/Fisher and Wilcoxon test were applied to evaluate the association between CTCAE and the independent variables. Thr-paenia: thrombocytopaenia.

	Anaemia	Thrombo-cytopenia	Leukopaenia	Neutro-paenia	INR_ increase	AST_ increase	ALT_ increase	GGT_ increase	Creatinina_ increase	EGFR_ increase	Bilirubine_ increase	Albumine_ decrease
Gender	1.889	0.870	0.915	0.167	0.138	0.000	0.170	0.066	2.114	0.593	0.413	0.269
Age	0.020	0.035	0.005	0.007	0.011	0.005	0.006	0.044	0.091	0.175	0.036	0.079
WHO grading	0.091	0.944	0.022	0.005	0.292	0.179	0.125	0.371	0.258	0.460	0.226	0.000
PRRT line	2.658	0.743	0.812	0.783	0.214	0.878	0.038	2.712	0.541	0.265	0.332	0.183
Tumor primary location	0.164	0.047	0.102	0.045	0.352	0.071	0.662	1.104	0.529	1.306	0.244	0.088
ECOG-PS	1.263	0.135	0.061	0.059	0.207	0.037	0.106	0.274	0.333	0.123	0.005	2.247
Chemotherapy	0.192	0.068	0.411	0.015	0.360	0.619	0.759	0.586	0.351	0.295	0.057	0.118
Everolimus	1.468	0.773	0.461	0.231	0.149	0.191	0.082	1.733	1.461	0.708	0.764	0.854
METNET	1.263	0.540	0.106	0.564	1.185	0.199	0.856	0.069	0.056	0.111	0.937	0.071
Splenectomy	0.121	3.050	2.044	0.364	0.343	0.041	1.812	0.809	0.654	0.011	0.097	0.069
n° metastatic sites	0.078	0.035	0.057	0.017	0.037	0.324	0.884	0.042	0.053	0.021	0.067	0.087

Tab 4: mean absolute effects of the covariates arisen from subsampling

RESULTS

Eight-seven patients were treated **(Tab 1**) from April 2019 to December 2020. Twenty were excluded due to ongoing PRRT therefore 67 (31(46.3%) males, 36 (53.7%) female, mean age 63) were selected. Thirty-eight (56.7%) were classified as midgut, 29(43.3%) as foregut, 24 (35.8%) G1 and 43 (64.2%) G2 (**Fig 1a,b**). Alkylating chemotherapy and Everolimus were the previous treatments in 13 (19.4%) patients, in both cases. Patients were treated with PRRT as third or further lines in 34.3% (23) of the whole population, 48.3% (14) of foregut cohort. All the patients showed at least one G1-G2 CTCAE during PRRT, in particular anaemia, thrombocytopaenia and leukopaenia. G3-G4 were rare events, in particular haematological alterations were reported (**Tab2**). G3-G4 CTCAE were transitional. No G3-G4 renal toxicities were reported. The results of Chi square/Fisher and Wilcoxon test are shown in **Tab3**. Line of PRRT administration, age, gender and ECOG-PS were the main predictors of CTCAE, according to Firth regression. The mean absolute effect of covariates is shown in **Tab 4.** The model performance, expressed by AUC, was > 65% for anaemia, creatinine and eGFR.

CONCLUSIONS

The application of FLIC model can be useful to improve GEPNET decision-making, allowing clinicians to identify the better therapeutic sequence to avoid adverse events PRRT-related, on the of base of patient characteristics and previous treatment lines. Internal validation confirmed the performance of the model for anaemia, creatinine and eGFR.

CONFLICT OF INTEREST and FINANCIAL TRASPERENCY → The authors have nothing to declare and the didn't receive any founding to develop the study