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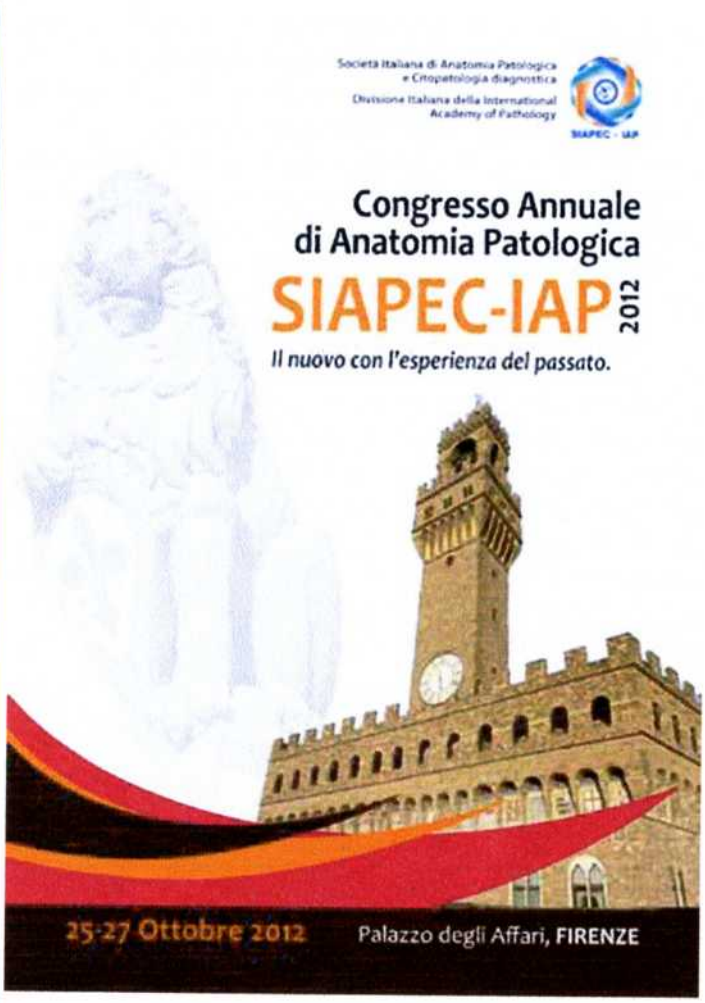

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Sala Botticelli – ore 17,36-18,30

ENDOCRINO

Epidemiological analysis of the histopathological features of testicular tumour in patients living in a high-risk environmental area

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Background/Aim. Testicular tumour is the most common form of neoplasia in young or middle-aged men (0-39 years), representing the 17.8% of all tumours diagnosed among men of this age range, in 2003-2005. The age-specific prevalence rates indicate that the number of cases increases quickly starting from adolescence, reaching higher values around 25-29 years. From 30th year onwards, the prevalence decreases steadily [1]. The testicular tumor epidemiologic pattern suggests etiologic factors that may be congenital, racial, and geographic. Risk factors for testicular tumor include cryptorchidism, a prior history of tumour in one testis (the contralateral testis is at increased risk), and a family history of testicular tumour. This tumour is sometimes linked to other rare conditions which do not allow testes to develop normally. Furthermore, the incidence of testicular tumour varies markedly according to ethnicity, with geographic variations across the world [2].

Most testicular tumours begin in germ cells (testicular germ cell cancers, TGCC). Despite a common cell of origin, TGCC are histologically and clinically classified in seminoma (S) and non-seminoma (NS). Among patients with a history of cryptorchidism and affected by testicular tumour, S accounts for more than half of tumours, and the only distinct subtype is the spermatocytic seminoma. NS includes many histological subtypes, such as yolk sac tumour, choriocarcinoma, embryonal cell carcinoma, teratoma [2]. Other histopathological variants of testicular tumour include tumours of paratesticular soft tissue (i.e. sarcomas), tumours of the gonadal stroma (Leydig cell tumour, Sertoli cell tumour), and lymphoid/haematopoietic tumours. Data from the Italian Cancers Registries showed that the most frequent form is represented by S (50%), followed by embryonal carcinomas (17%), non specified malignancies (7%), teratocarcinomas (6%), and teratomas (3%). Cryptorchidism is reported in the 6% of testicular tumours [3]. In some cases of TGCC-NS, the contemporary presence of different histotypes within the same tumour has been reported, but there are no data on the association of S with NS tumors. It has been suggested that testicular tumour derives from a precocious lesion, the *in situ* carcinoma of the testis, also named intratubular germ cell neoplasia (IGCN) or testicular intraepithelial neoplasia (TIN) [4]. Prevention and treatment make the 5 years survival very high (95%). The mortality trend remains stable between 1998 and 2005 [5].

Testicular tumour prevalence has been increasing over the past several decades in many developed countries, although the reason for this increase is not clear. Some studies suggest that in utero or in early childhood exposures, may play a relevant role in the individual risk level. In Denmark, a temporal decrease of the sperm output associated with an increased testicular tumour prevalence has been observed. This increase is associated with urogenital malformations such as cryptorchidism and hypospadias and/or reduced testicular volume. In other countries, like Finland, the opposite occurs. The geographical difference in the incidence of these diseases suggests an etiopathogenetic role of environmental factors [6-10]. Recent evidences showed that the non classical membrane G-protein coupled estrogen receptor (GPER/GPR30) mediates the effects of both estrogens and xenoestrogens through rapid non genomic activation of signal transduction pathways in various human estrogen dependent cancer cells (breast, ovary, endometrium). GPER is expressed by human normal adult testicular germ cells, specifically overexpressed in seminoma tumours and it is able to trigger seminoma cell proliferation in vitro [11].

Few years ago, it was suggested that some male reproductive disorders, such as cryptorchidism, hypospadias, reduced sperm quality, and TGCC, are interlinked and originate from an abnormal intrauterine testicular development [12]. This hypothesis has been defined testicular dysgenesis syndrome (TDS), and suggests that the prenatal period is a highly vulnerable phase, in which the impairment of testicular differentiation, genetic diseases, polymorphisms, exposure to environmental toxins, lifestyle or disorders intrauterine growth, may cause permanent adverse effects [13 14].

In Sicily, there is an industrial area, the so-called Melilli-Priolo-Augusta (SR) triangle, which has been declared of national interest (L. 426/98, art.1) as "area at high risk of environmental crisis" (D.L. 30/11/1990). The finding that an increased prevalence of urogenital tract malformations (hypospadias) has been reported in this area [15 16] lead us to evaluate whether this correlated with the presence of testicular tumour in the same area. Preliminary data from a study conducted in men living in Melilli's urban area indicate a high prevalence of asthenozoospermia and teratozoospermia [17 18]. Hence, this study aimed to evaluate the occurrence and the histopathological features of testicular tumours in this area, and in the overall Eastern Sicily, through the analysis of hospital discharge records.

Materials and methods. The Integrated Cancers Registry database, sections of Syracuse (SR), Catania (CT), and Messina (ME), was searched. The data relate to the period 2003-2005. All incident cases over these three years, for each province, were analyzed. A subgroup of cases from the industrial area (IA) was identified. We examined age at diagnosis, topography, and histological finding.

Results. Number (N) and age (mean ± SD) of patients, a positive history for cryptorchidism (C) (n, % of N), and an overview of histological categories (n, % of N) are reported in Table I.

Testicular tumours in IA were the 25.8% of all those reported

Tab. I.

	N	Years	C	TGCC-S	TGCC-NS	Others	No data
SR, all	31	36.1±15.5	1 (3.2%)	19 (61.2%)	11 (35.4%)	1 (3.2%)	-
SR, IA	8	30.6±4.3	-	5 (62.5%)	3 (37.5%)	-	-
CT	102	35.2±15	8 (7.8%)	38 (37.2%)	52 (50.9%)	7 (6.8%)	5 (4.9%)
ME	57	31.8±10.9	6 (10.5%)	28 (49.1%)	23 (40.3%)	2 (3.5%)	4 (7.0%)

Tab. II.

	TCGC-S			TCGC-NS						
	S	AS	SS	G	NS	EC	MT	TC	YS	CC
SR, all	16	1	1	1	-	2	-	3	-	-
SR, IA	4	-	-	-	-	-	-	2	-	-
CT	37	-	1	3	1	17	2	3	1	1
ME	26	1	1	-	1	7	-	3	-	-

S: seminoma; AS: anaplastic seminoma; SS: spermatocitic seminoma; G: germinoma; NS: non seminoma; EC: embrional carcinoma; MT: malignat teratoma; TC: teratocarcinoma; YS: Yolk sac tumor; CC: choriocarcinoma

in the province of SR. In two cases (25%), the occurrence of a second tumour was reported. Others tumours were: liposarcoma (1 SR; 1 CT), Leydig cells tumour (1 CT), non-Hodgkin's lymphoma (2 CT; 1 ME), plasmacytoma (1 CT), B-cells malignant lymphoma (1 CT; 1 ME), follicular lymphoma (1 CT). Table II shows the histopathological variants distribution of testicular tumours.

Altogether, 34 out of 190 (17.8%) patients had mixed forms of testicular tumours, divided into seminoma + non-seminomatous (S+NS) (N = 19), and more than one variant of non-seminomatous (MNS) (N = 15). Tab. III shows these data, with the mean ± SD age of the affected patients.

Tab. III.

	N	% of all testicular cancer	S+NS (n,%)	Age	MNS (n,%)	Age
SR, all	5	16.1	2 (40%)	32±4.2	3 (60%)	30±5.5
SR, IA	2	25	2 (100%)	32±4.2	-	-
CT	19	18.6	10 (52.6%)	29±4.4	9 (47.3%)	30.7±13.1
ME	10	17.5	7 (70%)	28.7±11.3	3 (30%)	31.6±7.0

Conclusions. Our data showed a higher prevalence of TGCC-NS for the province of Catania, in contrast with the national data and with data from other provinces. Seminomas are more frequent in patients from IA, but a relevant percentage (25%) of these subjects develop a second tumour. Interestingly, in this area was found the same percentage of testicular tumours with mixed histopathologic variants, and all of these presented seminomatous elements. Also for the province of Messina, was found a higher percentage of S+NS. Furthermore, we did not find a relationship between seminoma and cryptorchidism in all the provinces examined. These findings suggested the potential etiopathogenetic role of environment in the development of testicular tumours.

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KI-67 heterogeneity in gastroenteropancreatic neuroendocrine tumors

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Introduction. Prediction of survival is difficult in gastroenteropancreatic (GEP) neuroendocrine tumors (NET), due to their highly variable clinical course [1]. In order to determine a parameter that correlates with survival and optimizes patient management, the European Neuroendocrine Tumour Society (ENETs) introduced a proliferation-based three-tiered grading system that uses either mitotic count (G1: < 2/10 HPF; G2: 2 to 20/10 HPF, G3: > 20/10 HPF) or Ki67 labeling index (G1: < 2%; G2: 3-20%; G3: > 20%) [2,3]. This grading system has been incorporated into the new WHO 2010 classification of GEP NETs [4]. It is known that proliferation varies within the tumor, indeed, ENETs/WHO recommend that at least 40 to 50 HPF should be counted for mitoses and areas of highest labeling (so called "hot spots") should be identified to determine the Ki67 index (percentage of positively stained tumors cell nuclei on a 2000 cell count). When there is discordance between mitotic rate and the Ki67 index the highest dictates the final grade [5].

Many Authors have proved the reliability of the new grading system with survival in many cohorts of patients [6-8], but to date many concerns exist on the heterogeneity of Ki67 in the same tumor or in metastatic disease.

Our aim was to retrospectively study a series of GEP NETs with clinical follow-up, and evaluate Ki67 index in order to establish whether there is significant variability in different samples of the same lesion. Moreover, we studied the variability of Ki67 index in a group of patients with multiple primitive NETs on first diagnosis. Finally, we wanted to verify if in recurrent disease, local or distant, the Ki67 index is different from the primary tumor.