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Case Report

Tumours of the Uterine Corpus: A Histopathological and Prognostic Evaluation Preliminary of 429 Patients

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ABSTRACT

A histopathological review preliminary of 429 patients diagnosed with tumours of the uterine corpus (TUC) cancer between 1984- 2010 in the Vigo University Hospital Complex (Spain) were evaluated prospectively for over 5 years. Of these 403 (93.9%) were epithelial tumours: 355 (82.7%) were adenocarcinomas of the endometrioid type, 5 (1.1%) mucinous adenocarcinoma, 10 (2.3%) serous adenocarcinoma, 17 (3.9%) clear cell carcinomas, 11 (2.5%) mixed adenocarcinoma, 4 (0.9%) undifferentiated carcinomas and 1 (0.2%) squamous cell carcinomas. A total 20 (4, 6%) were mesenchymal tumours: 4 (0.9%) endometrial stromal sarcoma, 7 (1.6%) Leiomyosarcoma, 9 (2%) Mixed endometrial stromal and smooth muscle tumour. A total 1 (0.2%) were mixed epithelial and mesenchymal tumours: (0.2%) Adenosarcoma 1. And 5 (1.1%) were Metastases from extragenital primary tumour (3 carcinomas of the breast, 1 stomach and 1 colon). The mean age at diagnosis from total series were 65, 4 years (range 28-101 years). Age was clearly related to histologic type: Endometrial stromal sarcoma 46.0 years, Leiomyosarcomas 57.1 years, Adenocarcinomas of the endometrioid type 65.4 years, Clear cell carcinomas 70.1 years and mixed endometrial stromal and smooth muscle tumours 71.2 years. Five-year disease-free survival rates for the entire group were: Endometrial stromal sarcoma 50%, Leiomyosarcomas 28.6%, Adenocarcinomas of the endometrioid type 83.7%, Clear cell carcinomas 64.7% and mixed endometrial stromal and smooth muscle tumours 44.4%. The 5-year disease-free survival rates of patients with Adenocarcinomas of the endometrioid type tumors were 91.4% for grade 1 tumors, 77.5% for grade 2, and 72.7% for grade 3.

In conclusion, we describe 5-year histological and disease-free survival data from a series of 429 patients with TUC, observing similar percentages to those described in the medical literature. The only difference we find with other published series is a slightly lower percentage of serous carcinomas (ESC) that the Western countries but similar to the 3% of all ESC in Japan. Our investigation is focus at the moment on construct genealogical trees for the possible identification of hereditary syndromes and to carry out germline mutation analysis.

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INTRODUCTION

The tumours uterine corpus (TUC) represents the second most common site for malignancy of the female genital system. These neoplasms are divided into epithelial, mesenchymal, mixed epithelial and mesenchymal tumours and throphoblastic tumours [1].

Endometrial cancer is the third most common cause of death among gynecological cancers, following ovarian and cervical cancer, with increasing incidence rates in several countries, and its incidence is increasing. It is the most curable of the 10 most common cancers in women and the most frequent and curable of the gynecologic cancers. Ninety-seven percent of all TUC arise from the glands of the endometrium and are known as endometrial carcinomas. The most frequently occurring histological subtype is endometrioid adenocarcinoma. The remaining 3 percent of uterine cancers are sarcomas [2,3].

Thirty years ago, Bokhman hypothesized there were two pathogenetic types of endometrial carcinomas [4]. The author presented a hypothesis that the complex of endocrine and metabolic disturbances arising long before the development of endometrial carcinoma determines the biological peculiarities of the tumor, its clinical course, and the prognosis of the disease. Type 1 is more common (70-80%), consisting of endometrioid, low grade, diploid, hormone-receptor positive tumors that are moderately- or well-differentiated and more common in obese women. Patients presenting with Type 1 tumors tend to have localized disease confined to the uterus and a favourable prognosis. In contrast, Type 2 tumors (20-30%) are more common in non-obese women, of nonendometrioid histology, high-grade, aneuploid, poorly differentiated, hormone receptor negative and associated with higher risk of metastasis and poor prognosis. While this historical system of taxonomy has been useful, substantial heterogeneity within and overlap between Type I and II cancers is now recognized. Type I and Type II designation has never been part of the formal staging nor risk stratification, and thus has no clinical utility beyond providing a conceptual framework for understanding endometrial cancer pathogenesis. Murali et al. [5]. Points out that there is substantial heterogeneity in the biological, pathological and molecular characteristics within the tumor types of both classification systems and provides an overview of the traditional and more recent genomic classifications of endometrial cancer.

Standard treatment consists of primary hysterectomy and bilateral salpingo-oophorectomy, often using minimally invasive approaches (laparoscopic or robotic). Lymph node surgical strategy is contingent on histological factors (subtype, tumour grade, involvement of lymphovascular space), disease stage (including myometrial invasion), patients' characteristics (age and comorbidities), and national and international guidelines. Adjuvant treatment is tailored according to histology and stage. Various classifications are used to assess the risks of recurrence and to determine optimum postoperative management. 5 year overall survival ranges from 74% to 91% in patients without metastatic disease. Trials are ongoing in patients at high risk of recurrence (including chemotherapy, chemoradiation therapy, and molecular targeted therapies) to assess the modalities that best balance optimisation of survival with the lowest adverse effects on quality of life [6-8].

Clarke et al. [9]. Reviews the various grading systems that have been proposed for use with endometrioid endometrial carcinoma, and discusses the recent progress in cell type assignment, including the use of immunohistochemistry as a diagnostic adjunct.

For Talhouk et al. [10]. The categorization and risk stratification of endometrial carcinomas is inadequate; histomorphologic assessment shows considerable

interobserver variability, and risk of metastases and recurrence can only be derived after surgical staging. They have developed a Proactive Molecular Risk classification tool for endometrial cancers (ProMisE) that identifies four distinct prognostic subgroups.

Hereditary endometrial carcinoma is associated with germline mutations in Lynch syndrome genes. The role of other cancer predisposition genes in endometrial carcinoma is unclear. Identification of hereditary forms of neoplasias among cancer patients is crucial for better management and prevention of other syndrome-associated malignancies for the patients and their families.

Our objective is to perform a preliminary histopathological and prognostic study of a consecutive series of 429 TUC. Subsequently, we will study the family aggregation of cancer in each of the probands with the objective of identifying hereditary syndromes associated with some of these tumors in a cohort of non-selected patients.

MATERIALS AND METHODS

Data from 429 women with TUC treated between November 1984 to September 2010 at two institutions university from Vigo (Spain): Xeral Hospital and Meixoeiro Hospital were collected diagnosed from endometrial biopsies and hysterectomy specimens received in the Department of Pathology were included in the study. All specimens were fixed in 10% neutral buffered formalin and paraffin embedded for histological examination with hematoxylin and eosin staining. The clinicopathological analysis of the cases of TUC was done with emphasis on morphology and clinical follow-up.

STATISTICAL ANALYSIS

Data were analyzed using χ^2 tests. Variables significant in the univariate analysis were subsequently entered into a multivariate analysis (MVA) using the Cox proportional hazards ratio model. Disease-free survival (DFS) and overall survival (OS) were calculated from the date of diagnosis to the date of progression, date of death, or date of last follow-up if the patient was alive. Time to any event was measured from the date of diagnosis. Kaplan-Meier curves were generated from the survival data. Statistical analysis was performed using SPSS software for Windows version 12.0 (SPSS). A P-value of < 0.05 was considered statistically significant for all tests.

RESULTS

Among the 429 TUC analyzed in the current study, the most frequent ones (93.9%) were found in epithelial tumours. Only 4.6% were mesenchymal tumours. And 5 cases (1.1%) were metastases from extragenital primary tumour: 3 carcinomas of the breast, 1 stomach and 1 colon (Table 1). In the overall study group, the median age of diagnosis was 65.4 years (range, 28 to 101 years). Endometrial stromal sarcomas affect younger women with a mean age of 46 years with ranges of 36-52 years, clearly lower than the age from global serie ($p < 0.01$)

Of these 403 (93.9%) were epithelial tumours: 355 (82.7%) were adenocarcinomas of the endometrioid type, 5 (1.1%) mucinous adenocarcinoma, 10 (2.3%) serous adenocarcinoma, 17 (3.9%) clear cell carcinomas, 11 (2.5%) mixed adenocarcinoma, 4 (0.9%) undifferentiated carcinomas and 1 (0.2%) squamous cell carcinomas. A total 20 (4.6%) were mesenchymal tumours: 4 (0.9%) endometrial stromal sarcoma, 7 (1.6%) leiomyosarcoma, 9 (2%) mixed endometrial stromal and smooth muscle tumour. A total 1 (0.2%) were mixed epithelial and mesenchymal tumours: (0.2%) adenosarcoma 1. And 5 (1.1%) were metastases from extragenital primary tumours previous: 3 carcinomas of the breast, 1 stomach and 1 colon. The mean age at diagnosis

Table 1: Number of patients and mean age in years, according to histological type.

	N° of patients	Type and histological grade		N°	Median age (DS) years
Epithelial tumours	403 (93.9%)	carcinoma the endometrioid type	Grade 1: 51 %	355	65.4 (11.4)
			Grade 2: 32 %		
			Grade 3: 17 %		
		mucinous adenocarcinoma	Grade 1: 40 %	5	61.6 (8.8)
			Grade 2: 60 %		
		serous adenocarcinoma	Grade 3: 100 %	10	67.3 (10.1)
		clear cell carcinoma	Grade 3: 100 %	17	70.1 (11.3)
		mixed adenocarcinoma	Grade 1: 20 %	11	66.8 (15.1)
			Grade 2: 40 %		
			Grade 3: 40 %		
		undifferentiated carcinomas	Grade 3: 100 %	4	70.2 (10.3)
		squamous cell carcinomas		1	54
Mesenchymal tumours	20 (4,6%)	endometrial stromal sarcoma		4	46 (6.9)
		leiomyosarcoma		7	57.1 (13.1)
		Mixed endometrial stromal and smooth muscle tumour		9	71.2 (7.3)
Mixed epithelial and mesenchymal tumours	1 (0.2%)	Adenosarcoma		1	67
Metastases from extragenital primary tumour	5 (1.1%)	Metastases from extragenital primary tumours previous (3 carcinomas of the breast, 1 stomach and 1 colon)		Breast	80
				Breast	46
				Breast	55
				Stomach	53
				Colon	82
TOTAL	429				65.4 years (DS 16.6)

from total series were 65.4 years (range 28-101 years). Age was clearly related to histologic type: endometrial stromal sarcoma 46.0 years, leiomyosarcomas 57.1 years, adenocarcinomas of the endometrioid type 65.4 years, clear cell carcinomas 70.1 years and mixed endometrial stromal and smooth muscle tumours 71.2 years.

For the different subtypes of TUC the 5-year disease-free survival rates were as follows: epithelial tumours (adenocarcinoma) 80.8%, endometrial stromal sarcoma 50%, leiomyosarcoma 28.6% and mixed endometrial stromal and smooth muscle tumour 44.4 % (Figure 1).

For the different subtypes of epithelial tumours of the uterine the 5-year disease-free survival rates were as follows: endometrioid adenocarcinoma with variants 83.4%, mucinous adenocarcinoma 80%, serous carcinoma 30 %, clear cell carcinoma 64.7 %, mixed cell carcinoma 81.8% and undifferentiated carcinoma 0% (Figure 2).

For the epithelial tumours the 5-year disease-free survival rates were 91.4% for grade 1 tumors, 77.5% for grade 2, and 72.7% for grade 3 (Figure 3).

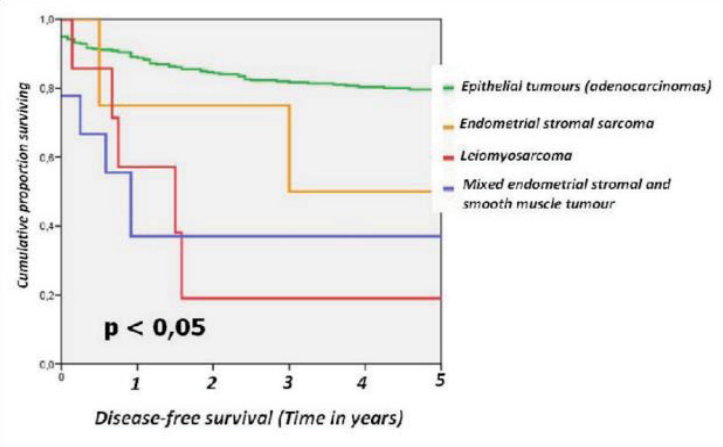

Figure 1: Disease-free survival from series endometrial epithelial tumours divided epithelial tumours, endometrial stromal sarcoma, leiomyosarcoma and mixed endometrial stromal and smooth muscle tumour.

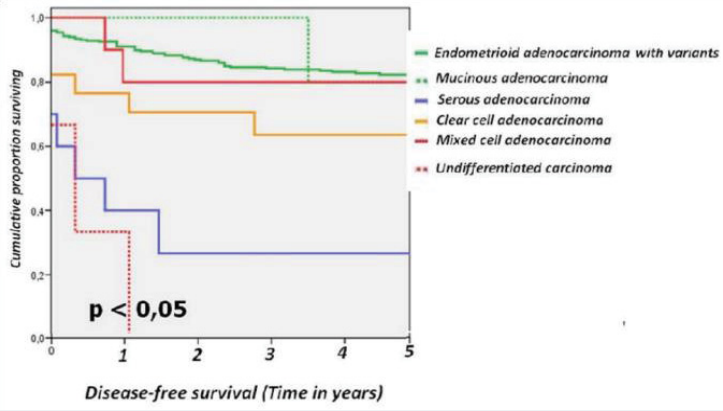

Figure 2: Disease-free survival from series epithelial tumours divided into endometrioid carcinoma and variants, mucinous adenocarcinoma, serous adenocarcinoma, clear cell adenocarcinoma, mixed cell adenocarcinoma and undifferentiated carcinoma.

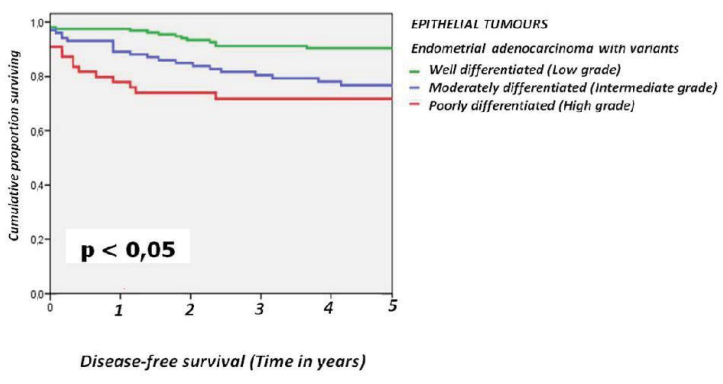

Figure 3: Disease-free survival from series endometrial epithelial tumours divided into low grade, intermediate grade and poorly differentiated endometrial adenocarcinoma.

DISCUSSION

Tumors that occur in the uterine corpus include epithelial, mesenchymal, mixed epithelial and mesenchymal, miscellaneous, lymphoid and myeloid and secondary tumors, as well as trophoblastic disease [1]. In this study, we have described the histological distribution of 429 TUC and its relation to 5-year disease-free survival. The

endometrial carcinoma is defined as a primary malignant epithelial tumour, usually with glandular differentiation, arising in the endometrium. It´s the most common malignant tumour of the female genital system in developed countries. In our series he represented the 93.9% (403 patients), which coincides with practically all published series [1,11]. Rose explains that the ninety-seven percent of all cancers of the uterus arise from the glands of the endometrium and are known as endometrial carcinomas [2]. Of the global serie of 403 epithelial tumours: 355 (82.7%) were adenocarcinomas of the endometrioid type. These carcinomas may exhibit a variety of differentiated epithelial types, when prominent in a carcinoma the neoplasm is termed a "special variant" carcinoma.

Type II endometrial carcinomas are non estrogen related, non endometrioid type. These generally occur in women a decade later than type I carcinoma, and in contrast to type I carcinoma they usually arise in the setting of endometrial atrophy. In the series of Mendivil et al. [12] the most common non-endometrioid histology is papillary serous (10%), followed by clear cell (2% to 4%), mucinous (0.6% to 5%), and squamous cell (0.1% to 0.5%). In the serie of Cirisano et al. [13] the frequency of tumors accounted were papillary serous 8%, clear cell adenocarcinoma 2%, and endometrioid carcinoma of the endometrium for 90% of cases. Some non-endometrioid endometrial carcinomas behave more aggressively than the endometrioid cancers such that even women with clinical stage I disease often have extrauterine metastasis at the time of surgical evaluation. In Western countries, the endometrial serous carcinomas (ESC) only accounts for 10% of all uterine cancers, it is responsible for 40% of uterine cancer deaths [12-16], associated with a high proportion of advanced-stage disease at diagnosis and high recurrence rates (15). The percentage of ESC in our series were 2.3% slightly lower, similar to the 3% of all ESC in Japan [17].

Several research teams have defined immunohistochemical and/or mutation profiles to aid in distinguishing EC subtypes [18-22]. In one series, a set of seven immunohistochemical markers was able to improve the distinction between high-grade EC histotypes [23] and more recently, another team demonstrated a nine protein panel improved identification of both low and high-grade EC subtypes [24].

Classification of endometrial carcinomas by histomorphologic criteria has limited reproducibility and better tools are needed to distinguish these tumors and enable a subtype-specific approach to research and clinical care. Based on the Cancer Genome Atlas, two research teams have developed pragmatic molecular classifiers that identify four prognostically distinct molecular subgroups. These methods can be applied to diagnostic specimens (e.g., endometrial biopsy) with the potential to completely change the current risk stratification systems and enable earlier informed decision making [10].

We observed 5 patients with histological proven metastatic tumor from extragenital primary tumours previous: 3 carcinomas of the breast, 1 stomach and 1 colon. Kumar and Hart [25] describe a serie of 63 cases of metastatic cancers to the uterine corpus from extragenital neoplasms.

Hereditary endometrial carcinoma is associated with germline mutations in Lynch syndrome genes. Lynch syndrome is an autosomal dominant condition caused by a mutation in the mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6* and *PMS2.* The role of other cancer predisposition genes in endometrial carcinoma is unclear [26-31]. A small proportion of endometrial carcinomas might be the result of a genetic risk condition [32]. Lynch syndrome is the main syndrome involved in such cases [33,34], although the existence of a familial site-specific endometrial carcinoma genetic entity separate from Lynch syndrome has been sugested. Differences in the prevalence of

genetic diseases are frequently observed between different populations, especially for syndromes where the penetrance is incomplete and other genetic and environmental factors might act as penetrance modifiers.

Current data on the prevalence of Lynch syndrome among unselected cases of endometrial carcinoma in North America range between 1.8% and 4.5% [35-37]. Significant differences in the prevalence of hereditary syndromes are frequently observed among different populations. Egoavil et al. [38] report a high prevalence of Lynch syndrome (4.6-6.6%) in a consecutive series of patients with endometrial carcinoma from the Spanish population, they consider that universal screening of all patients with ECs by IHC, MSI and MLH1 methylation analysis should be recommended.

In conclusion, we describe 5-year histological and disease-free survival data from a series of 429 patients with uterine body tumors, observing similar percentages to those described in the medical literature. The only difference we find with other published series is a slightly lower percentage of serous carcinomas. Our investigation is focus at the moment on construct genealogical trees for the possible identification of hereditary syndromes and to carry out germline mutation analysis.

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