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Original Article

Evolution of characteristics of women with endometrial cancer during a 40 years study period

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ABSTRACT

Objectives: The aim of our work was to investigate changes in presentation and endometrial cancer (EC) types frequencies thorough a 40 years study period.
Patients and methods: The patient group consisted of consecutive women undergoing surgery for endometrial cancer in our institution between 1975, and 2014. Clinical data included age, BMI (Kg/m2), histological data from surgical staging and survival data.
Results: 842 patients with the final diagnosis of endometrial cancer were enrolled. BMI was overweight rising through study decades. Age of diagnosis was also in constant augmentation since 1975. Type II EC proportion was 9.2% in the seventies and 27.9% after 2000. Overall survival was stable over time. Women with BMI < 18 kg/m^2 had lower overall survival when compared to women with other BMI categories ($p < 0.0001$).
Discussion and conclusion: An analysis on a larger population of underweight women with EC is needed to identify specific factors. A trend to develop more type II EC can partly explain these results. We identified a clear trend of augmentation of type II EC, known to have a poor prognosis while necessitating specific surgical management. Histologic analysis standardisation, surgical strategy and amelioration of adjuvant treatments permitted to maintain a stable overall survival for the whole population despite this augmentation.

Introduction

Endometrial cancer (EC) is the first gynaecological cancer affecting women in western countries with 382.069 new cases and 89.929 deaths worldwide in 2018 [1–4]. In France, 6852 new cases and 2148 specific deaths occurred in 2012 versus 8360 new cases and 2340 specific deaths in 2017 [5–12]. A growing incidence was noticed in France with 68 per 100.000 in 1989–1993 moving to 75 per 100.000 in 2005–2010 [13].

Most ECs are diagnosed at early stages (75% stage I) with generally only surgery as therapeutic management conferring an image of a "good prognosis" cancer with a 5-year overall survival of 81% for all stages combined [13–21]. However, it is well known that EC is a heterogeneous entity with various histological types. ECs are broadly classified into two major types based upon clinico-pathologic features: 1) Type I ECs are low grade endometrioid ECs (International Federation of Gynecology and Obstetrics (FIGO) grades 1 end 2) which comprise the majority of all ECs (70–80% of cases), almost present at an early stage, and have a good prognosis [14–22], 2) Type II ECs include FIGO grade 3 endometrioid ECs and the nonendometroid histologies: serous (10% of cases), clear cell (<5% of cases), mixed cell, undifferenciated and carcinosarcomas (or malignant mixed mullerian tumors<5% of cases). They are high grade and have a poor prognosis, even though surgery and adjuvant treatments permitted the reduction of locoregional recurrence rate [22–30]. They seem to occur in a different population than the one concerned by endometrioid ECs: type I ECs are stimulated by estrogen and are associated with prolonged exposure to endogenous or exogenous estrogen unopposed by progesterone, causing continuous proliferation of the endometrium, then endometrial hyperplasia and subsequent carcinoma.

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Typically, type II ECs are not estrogen sensitive and often occur in the presence of an atrophic endometrium [14–22].

What we propose in the present work is to study modifications in patient's characteristics, histological types and their impact on overall survival among patients with endometrial cancer managed in our institution through the last four decades.

Patients and methods

Women referred for endometrial cancer at the tertiary oncological referral center of Tours (France) were prospectively entered into a multidisciplinary team meeting register between October 1975 and June 2014. With the authorization of the institutional review board we retrospectively reviewed this prospective database.

Inclusion criteria were: women with EC managed between October 1975 and June 2014 with available histological data. Exclusion criteria were: women with uterine sarcoma (leiomyosarcoma, endometrial stromal sarcoma or adenosarcoma).

Individual records of all patients were reviewed and analysed from the medical records held by our institution on a computerized database. Variables included patient demographics, histological and survival data. Patients with known Body Mass Index (BMI) were categorized as: underweight (BMI < 185 kg/m^2), normal (185 ≤ BMI ≤ 249 kg/m^2), overweight (25 ≤ BMI ≤ 299 kg/m^2) and obese (BMI ≥ 30 kg/m^2).

In the first part of "results" section, patient's age, BMI, were treated as continuous variables.

Survival data were extracted from medical files when available, if not, the birthplace (city hall) of each patient was contacted to consult survival data of the birth registry. The date of death was noted on the marginal notes on the birth certificate. In the absence of a marginal mention of death, the patient was considered alive.

In the absence of a mentioned birthplace, the residence city hall or departmental archives made it possible to find survival data. Overall survival (OS) was calculated.

As stated in the introduction, ECs are classified into two major types based upon clinicopathologic features. Bokhman in 1983, [31] was the first who hypothesized that there are two types of ECs driven by different metabolic and endocrine signals: type I being more common, consisting of endometrioid, low grade, diploid, hormone-receptor positive tumors that are moderately- or well-differentiated and more common in obese women. Type II ECs are more common in non-obese women, of non-endometrioid histology, high grade, aneuploidy, poorly differentiated, hormone receptor negative and associated with higher risk of metastasis and poor prognosis. This historical system has been useful but overlap between type 1 and 2 is now well recognized.

For numeric data, results are reported as mean and median values ± standard deviation (SD). The Fischer exact and χ^2 chi-square tests were used to compare categorical values. Characteristics of women and tumors were analyzed using Chi-square statistics or Fisher's exact test for categorical variables and *t*-test or analysis of variance (ANOVA) for continuous variables. Values of $P < 0.05$ were considered to denote significant differences. Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analyzed using the R 3.0.2 software, available online. For the survival analysis, survival curves were generated (in months) using the method of kaplan-meier, based on the interval from the date of diagnosis to the date of last contact or death from any cause. The log-rank test was used to compare differences between survival curves.

Results

From 1th October 1975 to 30th June 2014, 842 women were managed for an endometrial cancer in the university teaching hospital of Tours. Mean age at diagnosis was 64.7 years ± 10.6 (range: 27–93).

Table 1, report characteristics according to the decade of management. There was a significant difference in age at diagnosis; women diagnosed after 2000 were significantly older than women diagnosed in other decades ($p < 0.0001$). There was no difference in parity ($p = 0.46$), with 15.5% of nulliparous women during the study period. There was no difference in age at diagnosis between women having type I EC and women having type II EC (64.32 vs 65.95 years, $p = 0.15$).

Mean BMI of the whole population was 27.5 kg/m^2 ± 6.9 [13–71]. Characteristics of women with known BMI are reported on Table 2. Women diagnosed in the 2000s had significantly higher BMI than women diagnosed in other decades ($p < 0.0001$). BMI was not statistically different according to histological type (27.5 kg/m^2 for type 1 versus 27.39 kg/m^2 for type 2, $p = 0.58$).

Histological repartition changed during the study period (Fig. 1). Proportion of histological type II increased with a factor of 3 in 40 years ($p < 0.0001$), representing more than 1 cancer on four in the 2000s versus less than 10% in the 1970s.

The increase of histological type II proportion was not traduced by a difference in overall survival according to the decade of diagnosis ($p = 0.16$) Fig. 2.

There was a significant difference in overall survival according to histological subtype $p = 0.0002$ (Fig. 3). Women with normal weight had better overall survival than other BMI categories (Fig. 4).

We performed two-by-two comparison confirming these findings:

Normal weight/underweight ($p < 0.001$)

Normal weight/obese ($p = 0.002$)

Normal weight/overweight ($p = 0.002$)

There we no statistical difference when we compared OS of obese women to women with overweight ($p = 0.52$)

We also found a significant statistical difference when we compared OS of underweight women to obese women ($p < 0.0001$) and to overweight woman ($p < 0.0001$)

Discussion

The rising incidence of EC in western countries these last decades is thought in literature to be due to an augmentation in the incidence of endometrioid EC. Between 1994 and 2006, Evans et al found in a study concerning 6867 EC patients, an augmentation in type I EC incidence (12.0 versus 16.3 for 100.000, $p < 0.001$). The incidence of type II EC was considered sTable (2.5 versus 2.2 for

Table 1
Characteristics of the whole population.

Characteristics (n = 842)	1970s n=76	1980s n=315	1990s n=139	2000s n = 312	p
Age (years)	63.7 ± 8.6 [46-84]	62.9 ± 9.9 [27-87]	62.6 ± 9.6 [39-85]	67.5 ± 8.6 [28-93]	<0.0001
BMI (kg/m^2)	27.1 ± 8.1 [13-62.5]	26.1 ± 5.5 [15.6-48.5]	26.8 ± 6.1 [17.1-47]	29.3 ± 7.9 [14-71]	<0.0001
Histological type II (%)	7 (9.2%)	42 (13.3%)	31 (22.3%)	87 (27.9%)	<0.0001

Table 2
Population characteristics according to BMI category.

	Underweight	Normal	Overweight	Obese	p
1970s (n = 50)	7 (14%)	16 (32%)	10 (20%)	17 (34%)	<0.0001
1980s (n = 268)	7 (2.6%)	118 (44%)	95 (35.4%)	48 (18%)	
1990s (n = 133)	3 (2.2%)	59 (44.4%)	33 (24.8%)	38 (28.6%)	
2000s (n = 277)	13 (4.7%)	78 (28.1%)	72 (26%)	114 (41.2%)	
Type I (n = 578/674)	22 (3.8%)	216 (37.4%)	169 (29.2%)	171 (29.6%)	0.83
Type II (n = 150/167)	8 (5.3%)	55 (36.7%)	41 (27.3%)	46 (30.7%)	
Type I/II in the 1970s	Type I: 6 (85.7%)	Type I: 15 (93.7%)	Type I: 8 (80%)	Type I: 15 (88.2%)	
	Type II: 1 (14.3%)	Type II: 1 (6.3%)	Type II: 2 (20%)	Type II: 2 (11.8%)	
Type I/II in the 1980s	Type I: 7 (100%)	Type I: 100 (84.7%)	Type I: 85 (89.5%)	Type I: 42 (87.5%)	
	Type II: 0 (0%)	Type II: 18 (15.3%)	Type II: 10 (10.5%)	Type II: 6 (12.5%)	
Type I/II in the 1990s	Type I: 1 (33.3%)	Type I: 46 (77.9%)	Type I: 24 (72.7%)	Type I: 32 (84.2%)	
	Type II: 2 (66.7%)	Type II: 13 (22.1%)	Type II: 9 (27.3%)	Type II: 6 (15.8%)	
Type I/II in the 2000s	Type I: 8 (61.5%)	Type I: 55 (70.5%)	Type I: 52 (72.2%)	Type I: 82 (71.9%)	
	Type II: 5 (38.5%)	Type II: 23 (29.5%)	Type II: 20 (27.8%)	Type II: 32 (28.1%)	

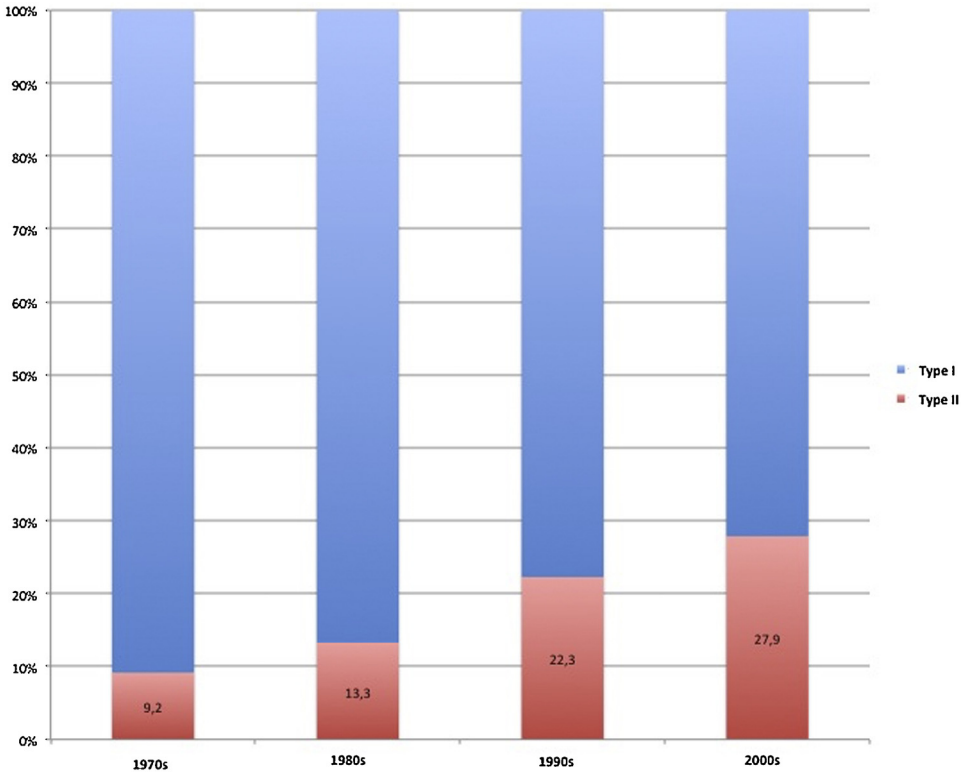

Fig. 1. Histological type proportions according to the decade of diagnosis.

100.000) [32,33]. Duong et al, confirmed these results in a study with 145 922 type I and 15 591 type II ECs [34].

Boll et al, found an augmentation in the incidence of types I ECs. In a study with 32.332 ECs of which 80% were of endometrioïd type [8]. They also found in 3618 women with type II EC a diminution in the incidence between 1989 and 2008 (30 versus 13 per 100.000). This corresponded to a diminution in the incidence of serous

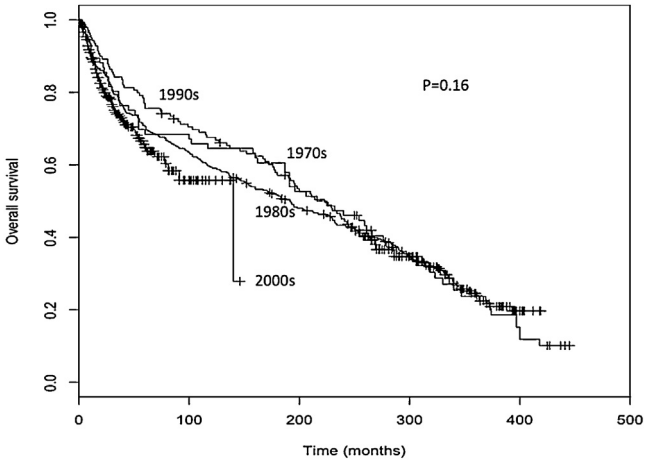

Fig. 2. Overall survival according to the decade of diagnosis.

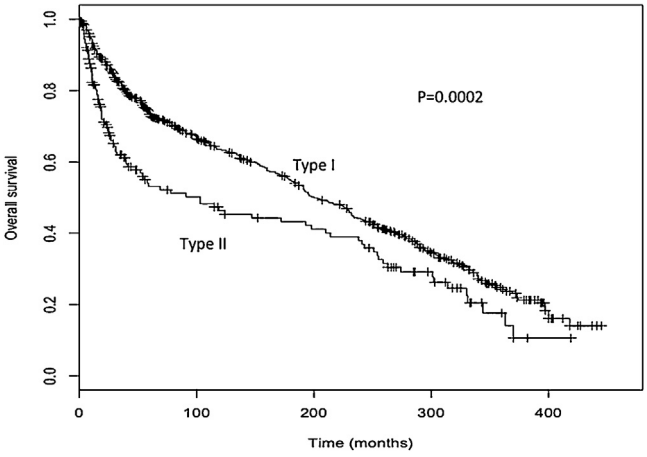

Fig. 3. Overall survival according to histological subtype.

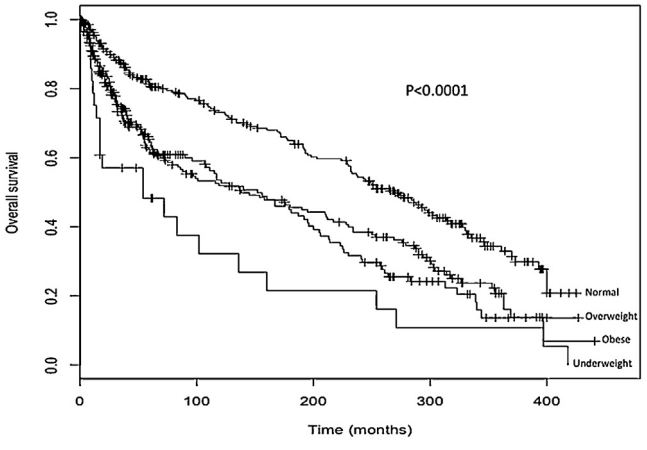

Fig. 4. Overall survival according to BMI categories.

histological subtype (68% of type II EC) from 22 to 7.1 per 100.000, clear cells ECs incidence was stable [29].

An analysis of 48.150 patients extracted from the SEER database (Surveillance, Epidemiology, and End Results) between 1988 and 2001, found a proportion of 83.7% of type I EC. Rates of type II ECs progressed over time with 14.7% in the 1990s to 17.3% in the 2000s ($p < 0.001$). Serous histological subtype increased from 5.8% to 6.7% [35].

The augmentation in type II EC proportion was more important in our population, with 9.2% in the 1970s to 27.9% in the 2000s. Our study period concerned 40 years that permitted a global view of evolving tendencies of minority histological subtypes. The augmentation was marked in the 1980s. During that decade, advances in immunochemistry and molecular biology contributed to a more precise and specific detection of tumours, particularly for type II EC. On another hand the university hospital centre of Tours was identified as a tertiary referral in the late 1970's that might partially explain the high incidence of type II EC. There was no real evolution of the gynaecological surgery team or neither in the modalities of patient's recruitments nor in the administrative region

The comparison with literature data is more delicate because of adjunction of grade 3 endometrioid EC to type II EC during the study period, because they are considered as having similar prognosis [35,36]. When performing our analyses, grade 3 endometrioid EC was included in type II ECs as reported in the latest recommendations.

Despite emergence of more aggressive histological subtypes, overall survival remained stable whatever the decade of management. Boll et al found a significant rise in 5-year overall survival for type I EC from 83% in 1990 to 85% in 2007 ($p < 0.001$) [8], and in parallel a diminution in 5-year overall survival from 15 to 18% for type II EC [29].

In the present study we did not found any difference between age at diagnosis between women with type I EC and women having type II EC (64.32 vs 65.95 years, $p = 0.15$), but when considering the whole population, women diagnosed in the 2000s were significantly older than the others ($p < 0.0001$). This is in line with the majority of published studies. For type I EC, the incidence increases for women aged $\geq$60 years at diagnosis ($p < 0.001$) [8]. Duncan et al, found a constant augmentation in incidence for women aged 60–64 years from 44.8 to 72.8 per 100.000 between 1985 and 2008. The incidence diminished for women aged less than 55 years, with a new rise in the 2000s [9].

We also found that BMI were higher in the 2000s when compared to BMIs of other decades of diagnosis ($p < 0.0001$). French population count 15% of obese and 32.3% of overweight persons [37]. Obese women represented 41.1% of the whole study population; this report is lower than American women affected by EC. Kamal et al found a mean BMI of 34.3 kg /m^2 and a proportion of 46.8% for obese women treated for a type I EC [38]. Our results are similar to previous French reports [39].

The proportion of type II EC diminished with the augmentation of BMI. Literature report the same pattern for type I EC with less aggressive histological features associated with the augmentation of BMI (myometrial invasion and LVSI) [40].

The augmentation of BMI is largely associated to EC risk. Lindermann et al, showed that EC risk raised linearly with BMI. In comparison with women with normal BMI, relative risk of developing an EC was 6.36 (95%CI; 3.08–13.16) when BMI $\geq$ 40 kg /m^2 and 0.53 (95%CI ; 0.19–1.47) when BMI < 20 kg/m^2 [41]. In another study on 1 036 877 women in Norway, overweight and obese women, in comparison to women with normal BMI, had a relative risk of 1.36 (95%CI: 1.29–1.42) and of 2.51 (95%CI: 2.83–2.66) [42]. Each augmentation of 5 kg/m^2 in BMI confers 1.6-fold higher risk of developing a type I EC when compared to women with normal BMI. In Europe, it is thought that weight excess is responsible of the occurrence of 60% of new cases of EC [43].

The effect of BMI on survival of EC patients still a matter of debate in literature [44]. Arem et al, reported an augmentation in specific cancer mortality for women with BMI $\geq$ 35 kg/m^2 (HR = 3.00, 95%CI 1.59–5.67) [45]. In the ASTEC population study [44,46],

Crosbie et al, did not found any influence of BMI category on overall and disease free survival [40]. This was in line with Park's results who showed no difference in survival when comparing women with BMI $< 25\,kg/m^2$ to those with BMI $\geq 25\,kg/m^2$ (47). Other studies showed the same results when comparing survival of obese EC patients to non obese patients [39].

We found poorer overall survival in underweight women with EC when compared to women with other BMI categories. Cachexia and sarcopenia are clinical entities, which negatively impact on the outcome of cancer patients. The international consensus conference defined cancer cachexia as a multifactorial syndrome characterized by an ongoing loss of squeletic muscle with or without fat mass that cannot be fully reversed by conventional nutritional support [48]. The weight loss is associated with muscle wasting or sarcopenia that occurs across all weight groups, including those of normal, overweight and obesity. In terms of prognosis, the use of BMI along with weight loss is a very powerful predictor for overall survival in patient with advanced cancer whatever the type [49].

Conclusion

An analysis on a larger population of underweight women with EC is needed to identify specific factors. A trend to develop more type II EC can partly explain these results. We identified a clear trend of augmentation of type II EC, known to have a poor prognosis while necessitating specific surgical management. Histologic analysis standardisation, surgical strategy and amelioration of adjuvant treatments permitted to maintain a stable overall survival for the whole population despite this augmentation.

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