HER2-Positive Endometrial Cancer Subtype Carries Poor Prognosis

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Abstract

Endometrial cancer (EC) is a hormone-dependent, most frequent malignancy of the female genital tract, yet no molecular subtype classification based receptor status (estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 [HER2]) has been established so far. Assuming that molecular subtypes might differ fundamentally in EC, we analyzed expression levels of ER, PR, and HER2 with immunohistochemistry and aimed to determine clinical significance of four molecular subtypes: ER+/PR+/HER2+; ER+/PR+/HER2−, ER−/PR−/HER2+, and ER−/PR−/HER2−. The study included 400 formalin-fixed paraffin-embedded primary tumor EC samples which covered all stages of endometrial carcinoma, from IA to IVB. ER−/PR−/HER2+ subtype correlated with the poorest outcome, ER+/PR+/HER2− subtype was associated with the most favorable prognosis ($p = 0.002$). Molecular subtype division remained an independent prognostic factor in multivariate analysis, accompanying parameters such as diabetes, hypertension, stage, myometrial infiltration, and metastases, all of which yielded hazard ratios between 1.39 and 2.23. ER+/PR+/HER2+ and ER+/PR+/HER2− subtypes had low average TP53 and TOP2A expression levels when compared with ER−/PR−/HER2+ and ER−/PR−/HER2− (both $p < 0.00001$). Molecular subtypes in EC do show diversity in terms of prognosis, clinicopathological, and molecular characteristics. ER−/PR−/HER2+ subtype exhibit is exceptionally aggressive tumor characteristics. Subtype differentiation might aid prediction of treatment response in EC. Clin Trans Sci 2014; Volume 7: 482–488

Keywords: molecular subtypes, estrogen receptor, progesterone receptor, HER2 receptor, endometrial cancer

Introduction

Endometrial cancer (EC) is a hormone-dependent, most frequent malignancy of the female genital tract in the Western world, with approximately 90,000 new cases registered each year in the European Union.[1] Despite the high prevalence of EC, no molecular subtype classification based on receptor status (estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor 2 [HER2]) has been established thus far.

Molecular subtypes have been primarily proposed in breast cancer as the result of high-throughput gene expression analysis, which yielded several substantially different groups: luminal A, luminal B (HER2−), luminal B (HER2+), HER2+ (nonluminal), triple negative (basal-like).[2] The elucidated subtypes differed in epidemiological risk factors, natural histories, and responses to systemic and local therapies.[3] Especially, the latter was of utmost importance as the findings implied that clinicians who manage breast cancer patients should tailor the treatment according to molecular subtypes. As gene expression array information was not feasible in most of the cases, a simplified classification, based on immunohistochemistry (IHC), has been adapted.[4] Consequently, luminal A subtype was characterized as ER and/or PR+, HER2−; luminal B (HER2−) as ER and/or PR+, HER2−; luminal B (HER2+) as ER and/or PR+, HER2 overexpressed or amplified; HER2+ (nonluminal) as ER and PR absent, HER2 overexpressed or amplified; and triple negative (basal-like) as ER and PR absent, HER2−.[3]

Reports concerning receptor status classification in EC characterize triple-negative phenotype only.[5,6] Assuming that molecular subtypes might differ fundamentally also in EC, we analyzed the expression levels of ER, PR, and HER2 with IHC and aimed to determine the clinical significance of four molecular subtypes: ER+ and/or PR+, HER2+ (ER+/PR+/HER2+); ER+ and/or PR+, HER2− (ER+/PR+/HER2−); ER− and PR−, HER2+ (ER−/PR−/HER2+); ER− and PR−, HER2− (ER−/PR−/HER2−). Proposed classification has been compared with clinicopathological characteristics, survival, and molecular data. Molecular characterization of the studied subtypes included protein expression analysis of mutated TP53 (tumor protein p53) and TOP2A (DNA topoisomerase II α 170 kDa), also measured by IHC.

Patients and Methods

Patients and tissues

The study included 400 formalin-fixed paraffin-embedded (FFPE) primary tumor samples retrospectively collected from a cohort of consecutive EC patients who were operated in the Department of Gynecology, Gynecological Oncology and Gynecological Endocrinology (Medical University of Gdansk) between 2000 and 2010. Samples included in the study were the total sum of eligible cases with available tissue material. Each patient was primarily treated by surgery, with the possible option of radiotherapy and/or chemotherapy administration. The inclusion criteria were operable EC (IVB stage patients underwent cytoreductive surgery) confirmed by histological examination and a signed consent form. The study was accepted by the Independent Ethics Committee of the Medical University of Gdansk (NKEBN/269/2009). Procedures involving human subjects were in accordance with the Helsinki Declaration.

The tumor samples included all stages of endometrial carcinoma, from benign IA to metastatic IVB cancer, as distinguished by FIGO in 2009 (International Federation of

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Variable	Number of cases (%)
Menopausal status	
Premenopausal	28 (7.0%)
Perimenopausal	26 (6.5%)
Postmenopausal	345 (86.3%)
Missing data	1 (0.3%)
Age	
≤50 years	42 (10.5%)
50 years	358 (89.5%)
Obesity	
Absent	197 (49.3%)
Present	202 (50.5%)
Missing data	1 (0.3%)
Diabetes	
Absent	300 (75.0%)
Present	100 (25.0%)
Hypertension	
Absent	140 (35.0%)
Present	260 (65.0%)
Histology	
Endometroid	293 (73.3%)
Nonendometroid	105 (26.3%)
Missing data	2 (0.5%)
Stage (FIGO*)	
IA–IB	277 (69.3%)
II	55 (13.8%)
IIIA–IIIC	47 (11.8%)
IVA-IVB	16 (4.0%)
Missing data	5 (1.3%)
Grade	
I	191 (47.8%)
II	148 (37.0%)
III	49 (12.3%)
Missing data	12 (3.0%)
Cervical invasion	
Absent	300 (75.0%)
Present	95 (23.8%)
Missing data	5 (1.3%)
Myometrial infiltration	
≤1/2	198 (49.5%)
1/2	197 (49.3%)
Missing data	5 (1.3%)
Metastases	
Absent	262 (65.5%)
Present	125 (31.3%)
Missing data	13 (3.3%)
ER status	
Positive	337 (84.3%)
Negative	63 (15.8%)
PR status	
Positive	323 (80.8%)
Negative	77 (19.3%)
HER2 status	
Positive	147 (36.8%)
Negative	253 (63.3%)

*FIGO = International Federation of Gynecology and Obstetrics.

Table 1. Clinicopathological data (*N* = 400).

Gynecology and Obstetrics).[7] All primary carcinomas of the uterine corpus were analyzed and divided into endometrioid and nonendometrioid subtypes. The latter included serous, clear cell, and mucinous adenocarcinomas. The patients' characteristics are summarized in *Table 1*. The median age was 64 (range 26–89 years). Patients with a body mass index higher than 30 were classified as obese.[8] A survival analysis was performed for 397 (99.3%) patients, 3 patients were lost to the follow-up. After a median follow-up of 72 months (range: 0–158), 113 (28.5%) patients had died. The last follow-up data were collected in September 2013. The study was performed in accordance with the REMARK criteria.[9]

IHC on tissue microarrays (TMA)

Samples were collected by surgical excision prior to any systemic treatment and were fixed in 10% (v/v) neutral buffered formalin for up to 24 hours, dehydrated in 70% ethanol, and embedded in paraffin. FFPE tissue blocks were stored at room temperature for up to 14 years. The percentage of tumor cells in each FFPE specimen was evaluated by hematoxylin and eosin staining reviewed by a certified pathologist. TMAs were constructed from FFPE surgical resection tumor specimens and control samples, as previously described.[10] Four 1.5-mm-diameter cores from each tumor were obtained from the most representative areas using tissue-arraying instrument (MTA-I, Beecher Instruments, Sun Prairie, WI, USA), and then reembedded in microarray blocks. Punches of normal tissues were added to the each array to introduce built-in internal controls to the system. Consecutive 4-µm-thick TMA sections were cut and placed on charged polylysine-coated slides (Superfrost Plus, BDH, Menzel, Germany) for subsequent IHC analysis.

Protein expression was examined by IHC on TMA blocks using the following antibodies: ER—clone SP1 (Roche, Basel, Switzerland, dilution: ready to use, RTU), PR—clone 1E2 (Roche, dilution: RTU), HER2—clone 4B5 (Roche, dilution: RTU), TOP2A—clone Ki-S1 (DAKO, Glostrup, Denmark, dilution: 1:200), TP53—clone BP-53-11 (Roche, dilution: RTU). The staining has been performed in accordance with manufacturers' guidelines. Protein expression was evaluated by two pathologists blinded to clinical data (HM and JG). ER and PR evaluation of the nuclear staining was performed based on Allred score.[11] HER2 receptor status was determined based on the criteria of

HercepTest (DAKO) according to the manufacturer's guidelines. TOP2A expression was assessed based on the percentage of the stained nuclei (1: 0–5%, 2: 6–25%, 3: 26–50%, 4: 51–75%, 5: 76–100%). TP53 expression evaluation included staining intensity (0—negative, 1—weak, 2—intermediate, 3—strong) and the percentage of stained cells (0: negative, 1: up to 10%, 2: 11–25%, 3: 26–50%, 4: 51–75%, 5: 76–100%), which accounted for the score ranging from 0 to 8. Cutoff point determination of expression positivity, based on results' distribution, was performed with the use of Cutoff Finder Web Application[12] and yielded values: ≥4 for ER and PR, and ≥2 for HER2. The assumed values were similar to those reported in the literature.[5,6]

Statistical analysis

STATISTICA software (Statsoft Co., Tulsa, OK, USA, version 10) was used for all calculations. The tests that were used and their applications were as follows: testing normality of the data set—Shapiro–Wilk test; comparison of the tumor subtypes with clinicopathological data of the patients—crosstabs statistics with Pearson's chi-square test; correlations between the tumor subtypes and assessed markers—Kruskal–Wallis test; ER, PR, and HER2 status in the context of clinicopathological data—crosstabs statistics with Pearson's chi-square test; TOP2A and TP53 expression in the context of clinicopathological data—Mann–Whitney test. TOP2A and TP53 expression analysis were performed on continuous measurements in order to avoid information loss introduced by marker dichotomization.[9] The Kaplan–Meier estimator was employed for survival analysis, and the generated curves were compared with the log-rank test. The endpoint for the study was overall survival (OS). OS was defined as the time from sample collection to death from any cause or censoring. Censoring was defined as loss of follow-up or alive at the end of follow-up. Cox proportional hazards regression analysis was used to identify the independent predictors of OS. Statistical significance for all the aforementioned calculations was assumed when $p \leq 0.05$. Univariate predictors significant with a value of $p \leq 0.10$ were entered into a stepwise multivariate model to identify those with independent prognostic information. Missing data were not included into statistical analysis.

Results

Flow of samples

Constructed TMA blocks collectively included 406 patients. Information concerning the expression level of all three receptors simultaneously (ER, PR, HER2) was available for 400 (98.5%) cases. Within the group of 400 samples, 399 (99.8%) and 400 (100.0%) had their TOP2A and TP53 status assessed, respectively.

Correlation of molecular subtypes with clinical and pathological data

ER+/PR+/HER2+ subtype included 129 (32.3%) samples, ER+/PR+/HER2−: 224 (56.0%), ER−/PR−/HER2+: 18 (4.5%) and ER−/PR−/HER2−: 29 (7.3%). Clinicopathological characterization of the molecular subtypes is presented in *Table 2*. Patients classified as ER−/PR−/HER2+ or ER−/PR−/HER2− had higher stage of the disease, higher grade, histology type II, myometrial infiltration, cervical invasion, and metastases more frequently but were rarely obese. No statistically significant correlations between the subtypes and parameters such as age, menopausal status, or diabetes have been observed.

Survival analysis

ER−/PR−/HER2+ subtype correlated with the poorest outcome, ER+/PR+/HER2− subtype was associated with the most favorable prognosis ($p = 0.002$), as presented in *Figure 1*. Univariate analysis performed for ER−/PR−/HER2+ subtype *versus* ER+/PR+/HER2− yielded hazard ratio of 3.49 (95% CI, 1.87–6.54, $p = 0.00009$). All of the studied parameters, excluding obesity, carried negative prognostic information in univariate analysis. Molecular subtype division remained an independent prognostic factor for overall survival in multivariate analysis, accompanying parameters such as diabetes, hypertension, stage, myometrial infiltration, and metastases, all of which yielded hazard ratios between 1.39 and 2.23. The results of univariate and multivariate analysis of all the studied parameters are presented in *Table 3*.

Molecular characterization of the elucidated subtypes

ER+/PR+/HER2+ and ER+/PR+/HER2− subtypes had lower average TP53 and TOP2A expression levels when compared with ER−/PR−/HER2+ and ER−/PR−/HER2− (both $p < 0.00001$), as presented in *Figure 2*.

Clinical and pathological data in the context of the studied proteins

Correlations between ER, PR, HER2 status, and clinicopathological data are presented in *Table 4*. ER and PR loss and HER2 overexpression correlated with more aggressive tumor characteristics. TOP2A and TP53 expression has been presented in *Figure 2*. High levels of TOP2A and TP53 correlated with more aggressive tumor characteristics.

Discussion

The distinction of molecular subtypes in breast cancer has introduced valuable information about underlying tumor biology and made advances have already begun to translate into treatment individualization. Molecular subtypes in EC, similarly to breast cancer, do differ fundamentally in terms of prognosis, clinicopathological, and molecular characteristics. The greatest distinction was observed between ER−/PR−/HER2+ subtype exhibiting exceptionally aggressive tumor characteristics and ER+/PR+/HER2− subtype being the most benign. ER−/PR−/HER2+ subtype was characterized by the shortest overall survival, often falling into the categories of histology type II, advanced stage or grade, and frequently showing signs of cervical invasion, myometrial infiltration, or metastases. ER−/PR−/HER2+ subtype remained an independent prognostic factor for overall survival in multivariate analysis. Furthermore, it had the highest TOP2A and mutated TP53 protein expression of all four subtypes. ER+/PR+/HER2− subtype was the exact opposite of ER−/PR−/HER2+. The difference in survival between ER−/PR−/HER2+ and ER+/PR+/HER2− subgroups was 37% (41% vs. 78%, respectively) what gives the power of 82% with two-sided α of 5%. Thus, our study is powered enough to detect the claimed difference in survival.

The other subtypes, ER−/PR−/HER2− and ER+/PR+/HER2+, have fallen in the middle of the molecular distinction, showing intermediate clinicopathological, prognostic, and molecular characteristics, with ER−/PR−/HER2− subtype classified as the second least favorable and ER+/PR+/HER2+ subtype—the second most favorable.

Lack of ER and PR expression and high expression of HER2 are treated as indicators of poor survival and aggressive tumor

Variable	Molecular subtype				*p* Value
	ER/PR+, HER2+ *N* = 129 (32.3%)	ER/PR+, HER2− *N* = 224 (56.0%)	ER/PR-, HER2+ *N* = 18 (4.5%)	ER/PR-, HER2− *N* = 29 (7.3%)	
Menopausal status					
Premenopausal	11 (39.3%)	14 (50.0%)	1 (3.6%)	2 (7.1%)	0.88
Peri- and postmenopausal	118 (31.8%)	210 (56.6%)	16 (4.3%)	27 (7.3%)	
Age					
≤50 years	14 (33.3%)	25 (59.5%)	1 (2.4%)	2 (4.8%)	0.80
>50 years	115 (32.2%)	199 (55.6%)	17 (4.8%)	27 (7.5%)	
Obesity					
Absent	68 (34.5%)	94 (47.7%)	14 (7.1%)	21 (10.7%)	0.0006
Present	61 (30.2%)	129 (63.9%)	4 (2.0%)	8 (4.0%)	
Diabetes					
Absent	102 (34.0%)	159 (53.0%)	15 (5.0%)	24 (8.0%)	0.20
Present	27 (27.0%)	65 (65.0%)	3 (3.0%)	5 (5.0%)	
Hypertension					
Absent	50 (35.7%)	67 (47.9%)	6 (4.3%)	17 (12.1%)	0.01
Present	79 (30.4%)	157 (60.4%)	12 (4.6%)	12 (4.6%)	
Histology*					
Type I	82 (29.9%)	179 (65.3%)	6 (2.2%)	7 (2.6%)	<0.000001
Type II	46 (37.1%)	45 (36.3%)	12 (9.7%)	21 (16.9%)	
Stage (FIGO*)					
IA–IB, II	104 (31.3%)	198 (59.6%)	9 (2.7%)	21 (6.3%)	0.00006
IIIA–IIIC, IVA–IVB	23 (36.5%)	24 (38.1%)	9 (14.3%)	7 (11.1%)	
Grade					
1, 2	112 (33.1%)	201 (59.5%)	11 (3.3%)	14 (4.1%)	<0.000001
3	13 (26.5%)	18 (36.7%)	7 (14.3%)	11 (22.5%)	
Cervical invasion					
Absent	98 (32.7%)	176 (58.7%)	8 (2.7%)	18 (6.0%)	0.004
Present	29 (30.5%)	46 (48.4%)	10 (10.5%)	10 (10.5%)	
Myometrial infiltration					
≤1/2	62 (31.3%)	122 (61.6%)	6 (3.0%)	8 (4.0%)	0.02
>1/2	65 (33.0%)	100 (50.8%)	12 (6.1%)	20 (10.2%)	
Metastases					
Absent	87 (33.2%)	157 (59.9%)	3 (1.2%)	15 (5.7%)	0.00001
Present	39 (31.2%)	58 (46.4%)	15 (12.0%)	13 (10.4%)	

*For statistical analysis "type II" included grade 3 tumors in addition to nonendometroid carcinomas. FIGO = International Federation of Gynecology and Obstetrics.

Table 2. Comparison of molecular subtypes with clinicopathological data.

behavior in EC.[13,14] This explains why ER−/PR−/HER2+ subtype seems to be the most unfavorable subtype, whereas ER+/PR+/HER2− subtype—the least. Works on molecular subtypes in EC focus on triple-negative phenotype being the indicator of poor prognosis.[5,6] Our data also point to triple-negative phenotype having rather short overall survival and unfavorable tumor characteristics (high grade, advanced stage, type II histology, myometrial invasion), however it is ER−/PR−/HER2+ subtype, which determines exceptionally poor prognosis.

Data obtained on molecular subtypes in EC are in high concordance with subtype characterization in breast cancer. In terms of occurrence frequency, basal-like (mostly ER−/PR−/HER2−) and HER2-positive (often ER−/PR−/HER2+) tumors constitute a minority of cases when compared with luminal A (mostly ER+/PR+/HER2−) and B (usually ER+/PR+/HER2+) tumors. Similarly to EC, of the four subtypes, luminal A breast tumors are characterized by good prognosis, with high survival and low recurrence rates. Also, women

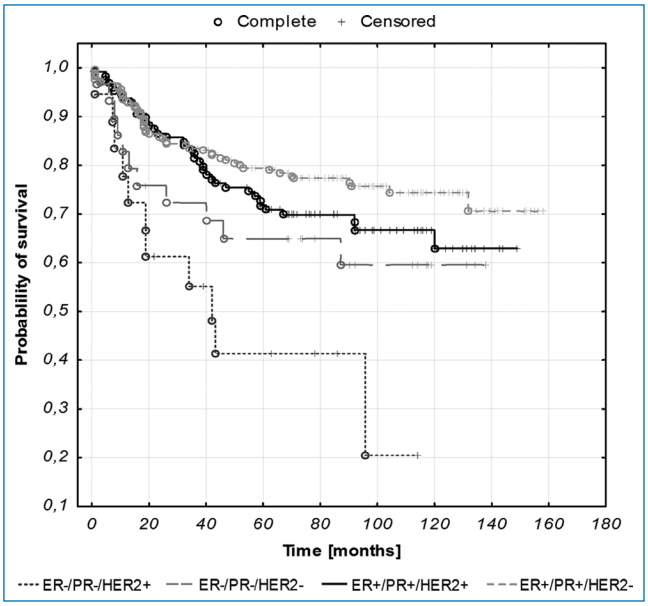

Figure 1. Kaplan–Meier curves illustrating overall survival of EC patients stratified against molecular subtypes ($p = 0.002$).

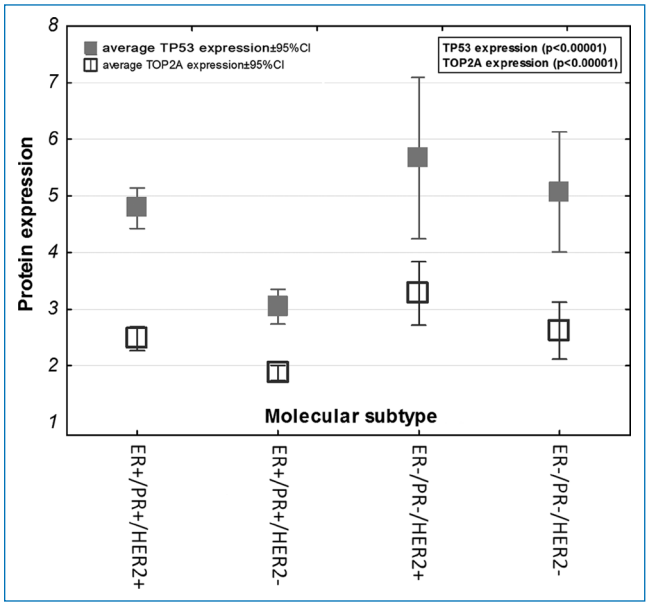

Figure 2. TP53 and TOP2A expression level within the studied subtypes.

Analyzed parameter	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* Value
Menopausal status (postmenopausal vs. peri- and premenopausal)	1.84	1.04–3.25	0.04	Not significant		
Age (>50 vs. ≤50 years)	4.04	1.49–10.95	0.006	Not significant		
Obesity (present vs. absent)	1.18	0.81–1.70	0.39			
Diabetes (present vs. absent)	1.77	1.21–2.60	0.004	1.74	1.16–2.60	0.007
Hypertension (present vs .absent)	1.98	1.29–3.06	0.002	1.89	1.21–2.93	0.005
Histology* (type II vs. type I)	1.71	1.18–2.48	0.005	not significant		
Stage (3, 4 vs. 1, 2)	1.97	1.62–2.39	<0.0000001	1.39	1.09–1.78	0.008
Grade (3 vs. 1,2)	1.37	1.09–1.74	0.008	not significant		
Cervical invasion (present vs. absent)	2.52	1.72–3.69	0.000002	not significant		
Myometrial infiltration (>1/2 vs. ≤1/2)	2.40	1.62–3.56	0.00001	1.79	1.19–2.68	0.005
Metastases (present vs. absent)	3.74	2.57–5.46	<0.0000001	2.23	1.39–3.58	0.0009
Molecular subtype (ER/PR–, HER2+ vs. ER/PR+, HER2–)	3.49	1.87–6.54	0.00009	2.07	1.07–4.02	0.03

*For statistical analysis "type II" included grade 3 tumors in addition to nonendometroid carcinomas.

Table 3. Univariate and multivariate analysis of clinicopathological and subtype data as prognostic factors in EC.

with luminal B tumors have fairly high survival rates, yet not as high as those with luminal A. Few luminal A tumors but many basal-like tumors have TP53 mutations.[15–17] Additionally, also similarly to EC, no correlation between the subtypes and patients' age is observed.[18]

One of the limitations of the study was relatively short follow-up period. Another problem was small sample size in ER+/PR+/HER2– and ER–/PR–/HER2– subgroup. Additionally, Ki67 expression status, often taken into account in molecular subtype determination in breast cancer, was unavailable. Ergo, we decided to include TOP2A expression as a surrogate of a proliferation marker, as proposed in the literature.[19]

In our study, TOP2A expression was higher in ER–/PR–/HER2+ and ER–/PR–/HER2– subtypes when compared to ER+/PR+/HER2+ and ER+/PR+/HER2–. High TOP2A expression has also been observed in triple-negative breast cancer.[20] Our study showed that TOP2A expression correlated with more aggressive tumor characteristics. Similar results were

Variable	ER status		PR status		HER2 status	
	Number of positive samples (%)	*p* value	Number of positive samples (%)	*p* value	Number of positive samples (%)	*p* value
Menopausal status						
Premenopausal	24 (85.7%)	0.86	21 (75.%)	0.42	12 (42.9%)	0.45
Peri- and postmenopausal	316 (84.5%)		303 (81.2%)		135 (35.8%)	
Age						
≤50 years	38 (90.5%)	0.25	34 (81.0%)	0.95	15 (35.7%)	0.92
>50 years	302 (83.7%)		290 (80.6%)		133 (36.5%)	
Obesity						
Absent	159 (79.9%)	0.02	146 (73.7%)	0.0007	82 (41.0%)	0.07
Present	180 (88.7%)		177 (87.2%)		66 (32.2%)	
Diabetes						
Absent	252 (83.2%)	0.25	237 (78.5%)	0.06	118 (38.6%)	0.12
Present	88 (88.0%)		87 (87.0%)		30 (30.0%)	
Hypertension						
Absent	116 (81.7%)	0.28	105 (75.0%)	0.04	57 (39.9%)	0.29
Present	224 (85.8%)		219 (83.6%)		91 (34.6%)	
Histology						
Type I	251 (91.6%)	<0.000001	243 (88.7%)	<0.000001	88 (32.0%)	0.007
Type II	88 (69.3%)		80 (63.5%)		59 (45.7%)	
Stage (FIGO*)						
IA, IB, II	295 (88.1%)	0.00002	278 (83.7%)	0.0004	114 (33.9%)	0.02
IIIA, IIB, IIIC, IVA, IVB	42 (66.7%)		42 (64.6%)		32 (49.2%)	
Grade						
1, 2	301 (88.8%)	<0.000001	287 (84.9%)	<0.000001	123 (36.2%)	0.56
3	30 (58.8%)		27 (54.0%)		21 (40.4%)	
Cervical invasion						
Absent	267 (88.4%)	0.0002	250 (83.1%)	0.03	107 (35.3%)	0.42
Present	70 (72.9%)		70 (72.9%)		39 (39.8%)	
Myometrial infiltration						
≤1/2	178 (89.0%)	0.02	167 (84.3%)	0.06	69 (34.3%)	0.39
>1/2	159 (80.3%)		153 (76.9%)		77 (38.5%)	
Metastases						
Absent	241 (91.3%)	<0.000001	224 (85.5%)	0.0002	91 (34.5%)	0.15
Present	90 (71,4%)		88 (69.3%)		54 (41.9%)	

*FIGO = International Federation of Gynecology and Obstetrics.

Table 4. ER, PR, HER2 status in the context of clinicopathological data (crosstabs statistics with Pearson's Chi-square test).

reported for nasopharyngeal carcinoma.[21] We also assessed TP53 expression, as this marker is commonly studied in the context of breast cancer molecular subtypes[22,23] and TP53 is frequently found overexpressed in uterine carcinomas.[24] TP53 overexpression correlated with more aggressive tumor characteristics and its level was higher in ER–/PR–/HER2+ and ER–/PR–/HER2– subtypes. TP53 overexpression as a determinant of the poor course of the disease is well documented in the literature, also in EC where it is typical for histology type II tumors.[25]

Conclusion

In EC molecular subtypes based on ER, PR and HER2 status differ fundamentally in terms of prognosis, clinicopathological, and molecular characteristics. The proposed classification might serve as a clinically valid molecular marker and IHC could be a fast and simple method of its determination. Continued investigation of the elucidated groups, especially in the aspect of targeted therapies, is necessary as the increasing body of evidence supports the use of ER, PR, and HER2 as markers of treatment response. However, their assessment is not a routine practice in EC.[26,27]

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Conflict of Interest

The authors declare that they have no conflict of interest.

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