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Typ nowotworu w prognozowaniu przeżycia chorych na raka endometrium

Tumor type in prediction of survival in patients with endometrial cancer

Streszczenie

Wstęp. Kluczowym czynnikiem w terapii raka jest możliwość przewidywania przeżycia.

Cel. W pracy oceniono wpływ typu raka endometrium na 5-letni czas przeżycia wolny od choroby.

Materiał i metoda. Do badania zakwalifikowano 218 chorych leczonych operacyjnie. Wyniki terapii porównano pomiędzy typem I i II raka endometrium.

Wyniki. Wśród 218 leczonych chorych u 174 stwierdzono typ I raka endometrium, a u 44 typ II. Pięcioletni czas przeżycia wolny od choroby dla chorych z typem I raka wynosił 72%, natomiast dla typu II 34% ($p<0.001$). Pięcioletni czas przeżycia wolny od choroby w I stopniu zaawansowania klinicznego typu I raka wynosił 92%, w II stopniu 70%, a w III stopniu 13%, w porównaniu z 60%, 45% i 0% typu II ($p<0.001$ i $p=0.86$). Wykazano, że zróżnicowanie histologiczne jest istotnym czynnikiem w typie I raka endometrium i koreluje z czasem przeżycia wolnym od choroby.

Wnioski. Zaawansowanie kliniczne jest istotnym czynnikiem prognostycznym w nowotworach endometrium typu I. Typ II raka endometrium wiąże się z niepomyślnym rokowaniem, nawet w I stopniu zaawansowania klinicznego.

Słowa kluczowe: typ raka endometrium, czas wolny od choroby.

Abstract

Introduction. An ability to predict survival is of crucial importance in determining the need for cancer therapy.

Aim. The purpose of this study was to evaluate whether updated tumor type predicts 5-year disease free survival (DFS) for patients with endometrial cancer.

Material and methods. Two hundred and eighteen patients who received primary surgical treatment for endometrial cancer were enrolled in this study. The clinical outcomes were compared among the patients with type I and II of endometrial cancer.

Results. Among 218 patients in 174 cases were confirmed type I endometrial cancer and in 44 cases were type II. The 5-year DFS of the entire group was 72% in patients with type I tumors and 34% in patients with type II endometrial cancer ($p<0.001$). The 5-year DFS was 92% for patients with stage I, 70% for patients with stage II and 13% for stage III in type I endometrial cancer compared with 60%, 45% and 0% for those with type II, respectively ($p<0.001$ and $p=0.86$, respectively). Tumor grade are the most important factors in type I endometrial cancer and correlated with DFS ($p=0.0072$).

Conclusions. Clinical stage is the most important prognostic factor in type I endometrial cancer. Type II of endometrial cancers is associated with poor prognosis even when at stage I.

Key words: type of endometrial cancer, disease free survival.

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INTRODUCTION

Cancer of the uterus is the seventh most commonly diagnosed cancer that occurs in women, with 189.000 new cases and 45.000 deaths occurring worldwide each year. About 60% of these occur in more developed countries. The highest incidence rates are in the USA and Canada. The age-adjusted incidence rate in the USA was 23.3 per 100 000 women per year [1]. In other regions, with age-standardized rates in excess of 10 per 100.000 include Europe, Australia and New Zealand, the southern part of South America, and the Pacific Island nations. Low rates occur in Africa (Uganda 3.3 per 100 000) and Asia (China 3.8 per 100 000) [2]. In Poland, the age-adjusted incidence was 13.7 per 100 000 women per year [3].

In general, the prognosis for most patients with endometrial carcinoma is relatively good with an overall 5 year survival rate of 73.4%. This is in contrast to many other cancers, including gynecological malignancies. The main reason for this is related to the early symptoms of postmenopausal or intermenstrual bleeding which lead women to seek medical consultation soon after the first episode. Moreover, this tumor is generally contained for long periods of time by the myometrium, and spreads late to the lymph nodes. It is therefore not surprising that approximately 73% of patients with endometrial cancer present with stage I disease. However, endometrial carcinoma is a heterogenous disease. In the majority of cases, the neoplasm is histologically diagnosed as an endometrioid type (Type I) and its stage, at the time of diagnosis, is established as I (FIGO). The second major group of endometrial cancer is histologically classified as serous carcinoma (Type II) [4].

The most common type I arises in younger, obese women with a history of hyperestrogenism and coexisting endometrial hyperplasia. The type II tends to occur in older, slender women, and is not associated with endometrial hyperplasia. On the contrary, it generally arises adjacent to atrophic endometrium. Younger patients tend to have better differentiated tumors (G1 or G2), superficial invasion of the myometrium, high levels of estrogen and progesterone receptors, and favorable prognosis. The second group of patients with a poor prognosis tends to have G3 tumors, deep myometrial invasion, lymph node metastasis, and low sensitivity to progestagens [4,5].

AIM

The purpose of this study is to evaluate whether updated tumor type predicts outcome for patients with endometrial cancer.

MATERIAL AND METHODS

A total of 218 patients with endometrial cancers (aged 48-79 years; median value – 64.5 years), who underwent a total abdominal hysterectomy with bilateral salpingoophorectomy at the Department of Gynecology of the Medical University of Bialystok and District Hospital in Bialystok between 1996 and 2004, were included in this study. Clinical data were collected by reviewing the medical records, correspondence with the primary physicians and from the National Cancer Registry. All patients had primary cancers and were receiving first surgical treatment. Adjuvant radiation therapy was recommended for all patients with myometrial tumor infiltration without distant metastases. Intravaginal radiation was given to women with highly or moderately differentiated tumors infiltrating less than half of the myometrium. For some patients, however, advanced age or recurrent disease resulted in less aggressive treatment, and gestagens were given as part of the primary treatment to some of them. Patients were informed and gave their consent for the study. All tumors were staged according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO). Disease-free survival (DFS) was defined as the time elapsed from diagnosis to disease recurrence or cancer-related death. The protocol was previously approved by the Bioethical Committee of the Medical University of Bialystok (R-I-002/152/2009).

Statistical analysis

Statistical analysis was performed using Statistica software version 8.0 (StatSoft, Inc., StatSoft Polska Sp. z o.o., Poland). Data are expressed as mean ±SD. Fisher's exact test was used to determine significance between the two groups. A chi-square test was used to evaluate the relationship between categorical variables. A p-value of <0.05 was considered as statistically significant.

RESULTS

Table 1. Patients characteristics.

Characteristics Menopausal status	no. (%)
Pre-menopausal	34 (15.6)
Post-menopausal	184 (84.4)
Stage	
I	62 (28.4)
II	118 (54.2)
III	38 (17.4)
Grade	
G1	96 (44.0)
G2	44 (20.2)
G3	78 (35.8)
Post-operative treatment	
None	57 (26.3)
Intravaginal radiation	66 (30.2)
External radiation	56 (25.6)
Hormonal	39 (17.9)

The patient's characteristics are listed in Table 1. The tumors were classified as follows: 174 cases were type I (endometrioid endometrial carcinomas) and 44 cases were type II (therein 38 cases of serous and 6 of clear-cell carcinomas). Among patients with type I endometrial cancer, 52 had tumors classified as stage I, 98 patients had tumors classified as stage II, and 24 patients were classified as stage III.

The type II tumors were classified as follows: 10 cases were in stage I, 20 cases were in stage II and 14 cases were in stage III. The samples were grouped by histological grade: 96 endometrial cancers type I were classified as grade 1, 44 were grade 2 and 34 were grade 3. All 44 type II tumors were in grade 3.

The 5-year DFS of the entire group was 72% in patients with type I tumors and 34% in patients with type II endometrial cancer (Table 2). As seen in Table 3, the most significant factor correlated with DFS was disease stage. The 5-year DFS was 92% for patients with stage I, 70% for patients with stage II and 13% for stage III in type I endometrial cancer compared with 60%, 45% and 0% for those with type II, respectively ($p<0.001$ and $p=0.86$, respectively). As shown in Table 4 tumor grade are the most important factors in type I endometrial cancer and correlated with DFS ($p=0.0072$). Type II endometrial carcinomas are high-grade aggressive neoplasms regardless of stage (Table 3). The stage is the most important prognostic factor in low-grade type I endometrial cancer, while type II are associated with poor prognosis even when at stage I (Table 2 and 4).

TABLE 2. Comparison of 5-years DFS between patients with type I and II endometrial cancer.

	No. of cases	5-years DFS no. (%)
type I	174	125 (72)
type II	44	15 (34)
p value		<0.001

TABLE 3. Comparison of 5-years DFS between patients with type I and II endometrial cancer of different FIGO stage.

	No. of cases	5-years DFS no. (%)
	type I	
stage I	52	48 (92)
II	98	69 (70)
III	24	3 (13)
p value		< 0.001
	type II	
stage I	10	6 (60)
II	20	9 (45)
III	14	0 (0)
p value		0.86

TABLE 4. Comparison of 5-years DFS between patients with type I endometrial cancer of different histopathologic grades.

	No. of cases	5-years DFS no. (%)
	type I	
grade G_1	96	91(95)
G_2	44	30 (68)
G_3	34	4 (12)
p value		0.0072

DISCUSSION

Generally, long-term survival of patients with endometrial cancer is clearly related to their surgical stage and substage. Representative 5-year survival rates by stage are 90% for stage I, 60% for stage II, 40% for stage III, and 5% for stage IV [6,7,8]. Because most patients have stage I disease and because there is a wide variation in survival based on risk profile within this stage, most research into post-operative adjuvant therapy is aimed at subsets of stage I patients. It is anticipated that the routine use of surgical staging will result in a more homogenous subgrouping of similar-risk patients and allow a more reliable prediction of survival potential.

The outcome in our study confirms results of Maneschi et al. and Wolfson et al. who have reported the 5-year disease-free survival as 90% for stage I, 83% for stage II, and 43% for stage III [9,10].

Although endometrial cancer is the most common type of gynecological cancer in the developed world, the details of its carcinogenesis are still not well known. The histological type is one of the most important predictors of the biological behavior of endometrial cancer. There are two main types of endometrial cancer which differ in their pathogenesis, clinical course and histology.

A subset of endometrial carcinoma patients with an excellent outcome can be identified based on endometrioid type or type I. Type II tumors represent about 10% of endometrial carcinomas. These tumors typically occur in postmenopausal women and are unrelated to estrogen exposure, developing from atrophic endometrium or occurring in endometrial polyps or from the putative precancerous lesion (endometrial intraepithelial carcinoma). They are very aggressive, often with myometrial or lymphovascular invasion, and carry a poor prognosis. In fact, in a recent series, up to 70% of women have been shown to have extrauterine disease. Even patients with stage I type II endometrial carcinomas have an overall survival of 30% ranging from 54% to 72% and from 27% to 59% in stage I and stage II tumors, respectively. These tumors are responsible for 50% of all relapses that occur in endometrial carcinomas and surgical staging is extremely important as up to 58% of clinically stage I tumors may be upstaged surgically [11].

Tumor differentiation (grade) has strong prognostic implications and is one of the most sensitive indicators of survival. The value of the FIGO grading system was demonstrated in a study by Zaino et al. in a univariate analysis of more than 600 patients, who had clinical stage I, or occult stage II endometrioid carcinoma. In the above study, the 5-year relative survival was 94% for patients with grade 1 tumors, 84% for those with grade 2 tumors, and 72% for those with grade 3 tumors [12].

It has been found that recurrences developed in 7.7% of grade 1 endometrial tumors, 10.5% of grade 2, and 36.1% of grade 3. The rates for patients with grade 1 and 2 tumors were 92% and 86% respectively for 5 year disease-free survival, in contrast to 64% for patients with grade 3 tumors [13].

This system categorized patients into three prognostic and therapeutic groups: those patients with low-stage and low-grade tumors, with an excellent 100% 5-year survival rate; those with higher stage and low-grade tumors and those with high-grade tumors confined to the myometrium, with a 5-year survival rate of 67% to 76%; and finally those with advanced-stage high-grade tumors, with only a 26% 5-year survival rate [14]. These dependences are confirmed by our own studies.

CONCLUSIONS

1. Stage is the most important prognostic factor in type I endometrial cancer.
2. Type II of endometrial cancers is associated with poor prognosis even when at stage I.

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