



Short Communication

Ki-67 Reactivity in Primary Fallopian Tube Cancers

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Abstract. Forty-four cases of primary cancer of the fallopian tube (PFTC) were analyzed as to Ki-67 expression, grade, stage and the cancer histological type. Among patients with an average age of 57.5 years (range 38–70 years), 27 patients were FIGO I, 7 were FIGO II and 10 were FIGO III. Histological classification of PFTC revealed 18 cases of endometrioid type, 9 serous, 7 undifferentiated, 6 urothelial, 2 clear-cell and 2 of other type. Histological grading revealed 11 cases of G1, 16 of G2 and 17 of G3 tumors. The quantity of Ki-67 positive cells was counted on 300 cancer cells in random high-power fields (10×40) and recorded as the labeling index (LI, %). Positive staining for Ki-67 was shown in the nuclei in all cases. Ki-67 LI values ranged from 14.2 to 97.2% (median 36.1). Ki-67 LI values were graded as $\geq 36.1\%$ as high and $<36.1\%$ as low. We did not find any significant differences in Ki-67 LI values among tumors of various clinical stages, histological grades and histological types. The p value was statistically significant only for stage as a prognostic factor.

Key words: primary cancer of fallopian tube; Ki-67.

Introduction

The evaluation of the biological aggressiveness of cancer cells might be used as a prognostic factor in a wide variety of tumors. One of the methods useful for the estimation of proliferative activity is the detection and evaluation of Ki-67 positive cells^{3–6, 10–12, 15, 16, 23, 24}. The Ki-67 antigen is the molecule that begins its expression in mid G1, increases in level through S and G2 and peaks in the M phase of the cell cycle. This molecule is decomposed rapidly at the end of the M phase¹⁰. In many neoplastic diseases, research on the relationship between cell proliferative activity and other parameters has revealed good correlation among these parameters. The investigation of Ki-67 expression in proliferative cells showed correlation with the staging of disease, histological grading and type of the tumors and progression of differentiation and was considered

as prognostic factor for patient survival^{3–6, 10, 12, 15, 16, 23, 24}. Primary fallopian tube cancer (PFTC) is a rare malignant neoplasm in the female genital tract^{1, 2, 7–9, 13, 14, 17, 18, 20–22, 25} and is associated with a very poor prognosis, especially in advanced stages of the disease^{1, 2, 8, 9, 13, 14, 18–22}. Only the clinical stages of this disease have true prognostic value^{8, 18, 19, 20, 22}. In this study, we have investigated the correlation between expression of Ki-67 and stage, histological grade and type and the survival of a group 44 patients with PFTC.

Materials and Methods

Patients. The material was obtained from 44 patients with primary PFTC who were being consulted in the Department of Pathological Anatomy of the University Medical School of Wrocław between 1981 and

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1997. The age of the patients ranged from 38–70 years, with an average age of 57.5 years. The patients underwent hysterectomy and bilateral oophorosalingectomy (42 patients) or bilateral oophorosalingectomy (2 patients). After surgery, adjuvant radiotherapy (34 patients) and/or chemotherapy (41 patients) were applied. Histological classification PTFC was performed according to the WHO ovarian epithelial tumor classification and the clinical stage of disease was based on the FIGO classification of fallopian tube cancer^{8, 14}. Histological classification of the tumors revealed: 18 endometrioid type, 9 serous, 7 undifferentiated, 6 urothelial and 2 of another type (intestinal, squamous cell). Twenty-seven patients were FIGO I, 7 FIGO II and 10 FIGO III stage. Seventeen patients died with recurrence of disease after 3–84 months from diagnosis (mean survival 29.1 months). Among the 27 patients still alive 4–120 months from diagnosis (mean 44.8 months), 24 survived without symptoms of neoplastic disease and 3 are alive with recurrence of the tumor.

Tissue samples, immunohistochemical staining and scoring Ki-67 labeling index. The paraffin – embedded tissue samples were cut into 4- μ m sections. Immunostaining for Ki-67 was performed using the avidin-biotin peroxidase complex method with the antigen retrieval technique by heating the tissue section in a microwave oven. The primary antibody against Ki-67 nuclear antigen was the monoclonal NCL-Ki67-MM1 (Novocastra Lab. Ltd.). The sections were counterstained lightly with hematoxylin. Negative controls were obtained by omission of the primary antibody. The computed quantitation of Ki-67 positive cells was counted in 300 cancer cells in random high-power fields (10 $\times$ 40) and was recorded as the labeling index (LI, %).

Statistical analysis. Analysis of variance was used to analyze the statistical differences between the clinicopathologic variables and the factor expressed as a continuous variable (Ki-67 LI). The overall survival curves were estimated by the Kaplan-Meier method and statistical significance was analyzed by log rank statistics. The Cox's proportional hazards model and Scheffe test were used in multivariate regression analyses of survival data. Differences were considered to be statistically significant when the probability value was under 0.05.

Results

Positive staining for Ki-67 was identified in the nuclei in all cases. Ki-67 LI values ranged from 14.2–97.2% (mean $\pm$ SD: 36.5 $\pm$ 16.65%, median 36.1). Ki-67 LI values $\geq$ 36.1% were grade as high Ki-67 LI (Fig. 1)

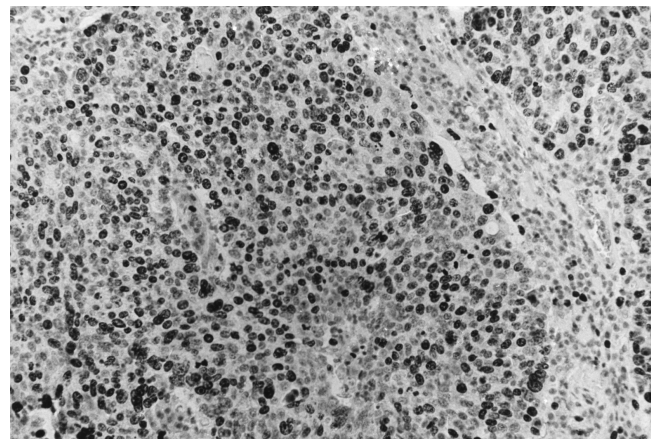


Fig. 1. PTFC. Immunostaining for Ki-67; Ki-67 LI value $\geq$ 36.1% (high)

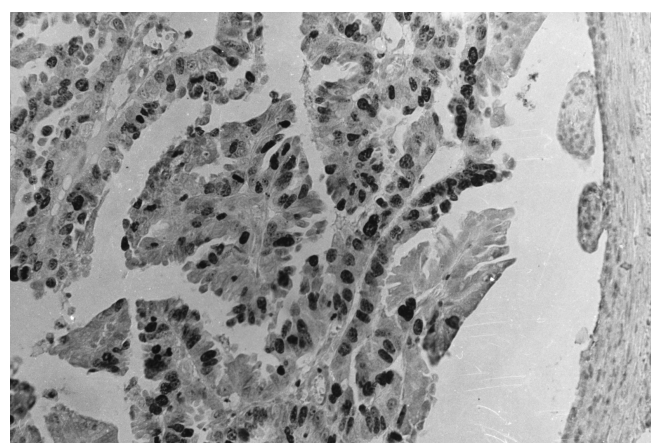


Fig. 2. PTFC. Immunostaining for Ki-67; Ki67 LI value < 36.1% (low)

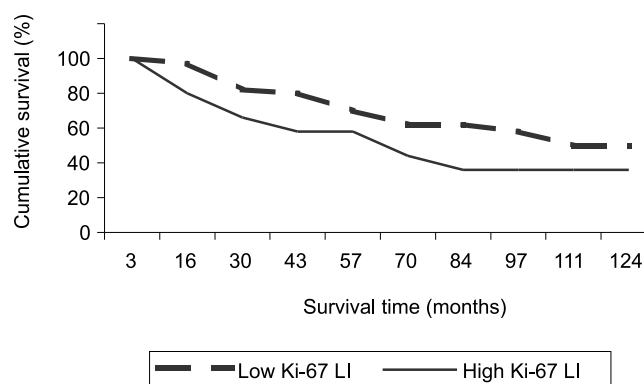


Fig. 3. Survival curve by Ki-67 LI value (interval method)

and those with Ki-67 values < 36.1% were grade as low Ki-67 LI (Fig. 2). The correlations between the staging, histological grading, histological type and Ki-67 LI are summarized in Table 1. We did not find any significant differences in Ki-67 LI values between tumors at various clinical stages, histological grades and histological types. Multivariate p value analysis was statistically

Table 1. Ki-67 LI in various histological type of PFTC

Histologic type of PFTC	Other n=2	Clear cell n=2	Endometrioid n=18	Undifferentiated n=7	Serous n=9	Urothelial n=6
Ki-67 LI	27.8 ± 15.4	38.0 ± 0.7	39.6 ± 22.8	29.8 ± 7.6	37.7 ± 12.8	35.7 ± 9.7

Table 2. Relationship between the clinicopathologic findings and Ki-67 labeling index (LI). Analysis of variance

Variables	Number of cases	Ki-67 LI (mean ± SD)	Analysis of variance
Stage according to FIGO			
I	27	36.7 ± 15.2	not significant
II	7	31.9 ± 10.5	
III	10	39.2 ± 23.4	
Histological type			
endometrioid	18	39.6 ± 22.8	not significant
serous	9	37.7 ± 12.9	
undifferentiated	7	29.8 ± 7.6	
urothelial	6	35.7 ± 9.7	
clear cell	2	38.0 ± 0.7	
another	2	27.8 ± 15.4	
Histological grading			
I	11	35.6 ± 10.4	not significant
II	16	40.5 ± 23.9	
III	17	33.3 ± 10.6	
Survived	27	37.3 ± 19.9	not significant
Dead	17	35.2 ± 9.8	

significant only for stage as a prognostic factor (Table 2). No statistically significant differences were found between the survival of patients with high and low Ki-67 LI (Fig. 3).

Discussion

Primary fallopian tube carcinoma is relatively rare and is associated with a poor prognosis^{7–9, 13, 17–19}. From the various prognostic factors for patients with PFTC, only the staging of the disease at the time of diagnosis has an established value^{7, 8, 14, 19, 21, 22}. To estimate the biologic aggressiveness of cancer cells and establish new prognostic factors, oncogenes, tumor suppressor genes and the nuclear DNA content were examined^{3–7, 10–13, 15–17, 21, 23–25}. Ki-67 staining is easy, inexpensive and can be performed using formalin fixed and paraffin embedded specimens^{3–5, 10–12, 15, 16, 23, 24}. Counting the Ki-67 LI provides more reliable information about the growth fraction of the cancer cell population^{3–5, 10–12, 15, 16, 23, 24}. In various forms of neoplasm, also localized at various sites labeling of Ki-67 positive cancers cells was used as a prognostic factor^{3–6, 10–12, 15, 16, 23, 24}.

We had 44 patients with PFTC observed from 3 to over 120 months from diagnosis. Seventeen patients died because of recurrence and dissemination of the primary disease. In another study we confirmed that

staging of the disease had unquestionably been a prognostic factor^{17–19}. Other authors reported that the histologic type of PFTC and histological grade are closely correlated with patient survival^{7, 8, 17, 18, 21, 22} and showed that the median Ki-67 labeling index in PFTC was high. The studies on cancers of the extrahepatic bile ducts (29%), renal cell carcinoma (13%), invasive cervical carcinoma (34%), lung adenocarcinomas (27.1%), transitional cell carcinoma of the bladder (28%), esophageal squamous cell carcinoma (48–66%), endometrial cancer (39%) the ovarian cancer (16%) reported lower or higher median Ki-67 labeling indexes^{3, 5, 10, 11, 15, 16, 23, 24}. It is particularly interesting that ovarian cancers had a lower Ki-67 labeling index than PFTC⁶.

The comparison of the biologic behaviors of ovarian carcinomas and PFTC has shown that the histologic types of PFTC were similar to those seen in ovarian carcinomas^{17–19} and that the differences in clinical behavior between the serous and endometrioid types of ovary and fallopian tube carcinomas were similar^{17, 18}. Other authors confirmed these findings by research on the Ki-67 labeling index⁶. In our study, the endometrioid type of ovarian and fallopian tube carcinoma had a higher value of Ki-67LI than the serous type carcinomas, similar to cancers of the endometrium¹⁵. A high level of the Ki-67 labeling index is associated with poor outcome in cases of PFTC, similar to cancers located

elsewhere, i.e. esophageal, lung, extrahepatic bile duct^{10, 11, 23}. Better prognosis is associated with the endometrioid type of PFTC than with the serous one¹⁸. The proliferative activity of the PFTC cells is a good marker in grading every histological type of cancer, but can not be used as a single independent and significant prognostic marker^{3, 5, 10, 11, 15, 16, 23, 24, 26}.

The investigations on the balance between proliferation and cell loss in the progression of hepatocellular cancer suggest that tumor progression depends on a disturbance in the cell kinetic balance caused not by a decrease in the absolute amount of cell loss, but in the chaotic balance between cell loss and cell proliferation²⁷.

The proliferative properties of PFTC cells are evident, but they not determine the course of disease^{4, 18}. The prognosis in PFTC patients closely depends on the clinical stage at the time of diagnosis^{14, 18}.

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