10.1053.paor.1999.0156 available online at http://www.idealibrary.com on IDEAL

CASE REPORT

Primary Endometrioid Carcinoma of Fallopian tube

Clinicomorphologic Study

Jerzy RABCZYŃSKI, Piotr ZIÓŁKOWSKI

Department of Pathology, Medical University of Wrocław, Wrocław, Poland

Twenty cases of primary Fallopian tube endometrioid carcinoma (PFTEC) are presented in the paper. This accounts for 42.5% of all histologic forms of primary Fallopian tube carcinoma (PFTC) found in our Department. The youngest patient was 38, and the oldest 68 years (mean: 56 years). Seven patients were nulliparas. Only two cases were bilateral. According to FIGO staging, 13 cases were evaluated as stage I, 4 as II, and 3 as stage III. Due to the histologic grading, 8 tumors were classified as well, 7 as moderately, and 5 as poorly differentiated. In the time of preparation of the manuscript, 12 women were still alive, 2 of them with recurrent disease. The follow-up of patients without recurrence ranged from 4 to 120 months (median: 63). Eight patients had died (survival time: from 4 to 65 months; median: 26). Metastases were found in 8 patients, especially to ovaries. In 14/20 cases of PFTEC various forms of tubal wall invasion were observed. Blood or lymphatic vessels involvement was found in 9 patients. Six of them had died and one is alive with the symptoms of disease. Immunohistochemical detection of the mutant form of p53 protein and oncogene product, c-erbB-2, was studied in 17 cases. Nine patients exhibited simultaneous p53 protein accumulation and c-erbB-2 expression. 2/9 of these patients are alive with recurrent tumors and 4/9 died. Endometrioid carcinoma of the Fallopian tube can be characterized by a tendency to superficial invasion of tubal wall and in a half of the cases by invasion of vessels. The majority of these tumors were diagnosed at an early stage tumors. (Pathology Oncology Research Vol 5, No 1, 61–66, 1999)

Key words: Fallopian tube carcinoma, endometrioid carcinoma, histology, immunohistology, p53 protein, c-erbB-2

Introduction

Primary Fallopian tube carcinoma (PFTC) is one of the rarest malignant tumors of the female genital tract.[1,2,5-8,10,14-16,18-20,22,25] The relatively low number of patients do not permit any conclusive statement with regard to the prognostic value of factors affecting PFTC course.[2,5-8,10,16,18,20,22] There were 47 cases seen in the Department of Pathology, in Wrocław, between 1982 and 1998. Patients histories, including follow-ups, were established in all cases from the Oncology Centre database in Wrocław. The slides with PFTC samples were reevaluated using the histologic criteria established by WHO for common ovarian epitheliomas. There were 20 primary Fallopian tube endometrioid carcinomas (PFTEC) among the examined 47 cases. Endometrioid carcinoma is generally regarded as a rather uncommon type of PFTC.[1,5,10,19]

Most series of PFTC have included no endometrioid carcinomas, but authors used the histologic classification proposed by Hu et al.[2,7,8,16,20,22] To date, only one contribution has dealt with analysis of 26 cases of primary endometrioid carcinoma of Fallopian tube (PFTEC). It seems that this histologic type of PFTC, which was reported in a single article with a 77% frequency among PFTCs, occurs more often than it was previously considered.[1,14] Since the number of contributions describing the peculiar features of PFTEC is very low, we decided to present our observations on this matter. This paper presents clinical course, and histological

Received: Nov 1, 1998; *accepted:* Jan 5, 1999

Correspondence: Piotr ZIÓŁKOWSKI, M.D., Department of Pathology, Medical University of Wrocław, ul. Marcinkowskiego 1, 50-368 Wrocław, Poland; Tel: 4871-209974, fax: 4871-3281029

 1219-4956/99/010061+06 $ 12.00/0

picture of PFTEC, as well as the results of immunohistochemical examinations that revealed p53 protein and c-erbB-2 accumulation.

Materials and Methods

Table 1. presents the clinical data of 20 patients with diagnosed PFTEC. Three to eight samples from each carcinomatous Fallopian tube were reevaluated. Two pathologists, independently, evaluated the following features: histologic grading, type and depth of tubal wall infiltration, lymphatic and blood vessels invasion and expression intensity of two markers, i.e. pathologic p53 protein and oncogene product, c-erbB-2. Immunohistochemical reactions on paraffin embedded samples were positive in 17 cases. The stage of disease was based on surgical protocols and microscopic examination of postoperative specimens using FIGO classification.[5,14,15] Immunohistochemical examinations were carried out by ABC technique (DAKO, Denmark). The expression intensity of p53 protein was not graded, because in all examined cases where the staining for this marker was positive, such expression occurred in more than 50% of nuclei. For the same reason the evaluation of local differences of p53 expression intensity within examined tumor sample was not considered.

Expression of mutant p53 protein, c-erbB-2, parity, histologic grade and stage, and vascular space invasion were compared between patients without progression of disease or died from cancer. They were analysed using the unpaired Students "t" test and the chi-square test. Overall survival curves were plotted using Kaplan-Meier method. The log rank test was used to compare curves of survival of patients with stage I and II.

Table 1. **Characteristics of patients**

Age (years)	
from – to (mean)	38-68 (56.1)
Premenopausal/postmenopausal	7/13
Paras	13
number of deliveries (mean)	1-5 (< 2)
1 delivery/2 or more/nulliparas	4/9/7
Most frequently recorded symptoms	
hypogastric pain	13
palpable tumor	9
metrorrhage	4
Preoperative diagnosis	
adnexal tumor	4
uterus myomatosus	4
ovarian cancer	3
inflammation	3
endometrial cancer	2
Treatment	
hysterectomy + adnexectomy	13
hysterectomy + adnexectomy + omentectomy	3
radiotherapy	13
chemotherapy	9
Localization	
right Fallopian tube	9
left Fallopian tube	9
bilateral	2

Results

Endometrioid carcinomas of various differentiation grades were found in 20 PFTCs. This accounts for 42.5% of total number of cases and is considered the most frequently diagnosed histological type in this series. The mean age of patients with established diagnosis of PFTEC was 56.1. The youngest patient was 38, and the oldest 68 years. Seven patients still menstruated and 13 were of postmenopausal age. Nine of 13 women who were delivered of children had at least one child (range 1 to 5). The other 7 patients (35%) were never pregnant. Four of 13 paras as well as 4 of 7 nulliparas died of PFTEC. Most frequent complaint by patients prior to diagnosis was idiopathic pain in hypogastrium, less often palpable tumor mass and metrorrhages. In only one case was the suspicion of tubal carcinoma was taken into consideration before surgery. In 4 cases an undefined adnexal tumor was considered. The other preoperative diagnoses included uterine myoma (4), ovarian carcinoma (3), uterine body carcinoma (2) and rupture of tubal pregnancy (1). The surgical treatment in 16 cases involved standard hysterectomy with adnexectomy, which in 3 cases was completed with omentectomy. In 3 cases, only the affected uterine tube was excised during the first surgical treatment. In one case bilateral adnexectomy has been performed, but this patient previously underwent hysterectomy. The tumor was diagnosed egual times in the right and the left uterine tube; in 2 cases the lesion was bilateral *(Table 1)*. Thirteen patients were then subjected to radiotherapy; 9 additionally or exclusively to chemotherapy. The clinical progression of disease according to FIGO was evaluated as stage I in 13 cases, II in 4 and III in 3 cases in the time of diagnosis. The follow-up of 20 patients with PFTEC ranged from 2 to 120 months. In the time of preparation of this manuscript 12 women were still alive, 2 of them with recurrent tumors. Eight patients had died *(Table 2)*. The follow-up of patients without tumor recurrence ranged from 4 to 120 months (average: 63 months). The two patients with recur-

Table 2. **Correlation between staging and the time of survival**

Histologic grading	*No. of patients*	*Alive without symptoms*		*Alive with symptoms*		*Died*	
		No. of patients	*Survival (median)*	*No. of patients*	*Survival (median)*	*No. of patients*	*Survival (median)*
Well differentiated	8	4	75.5 mo	1	10.0 mo	3	13.0 mo
Moderately differentiated	7	3	63.0 mo	0	0	4	14.5 mo
Poorly differentiated	5	3	80.0 mo	1	2.0 mo	1	18.0 mo

rent tumors have been observed for 2 and 10 months. Eight patients who died following tumor recurrence and/or metastases had survived from 4 to 65 months after establishing the diagnosis (mean: 26 months); see *Figure 1*. Due to the three-grade scale of histologic differentiation designed for endometrial adenocarcinoma,[24] 8 tumors were classified as well, 7 as moderately, and 5 as poorly differentiated. *Table 3* shows the analysis of survival of patients with regard to histological grade of tumor differentiation. At the time of establishing of diagnosis metastases were found in 8 patients. Six of them presented with metastases to one or both ovaries.

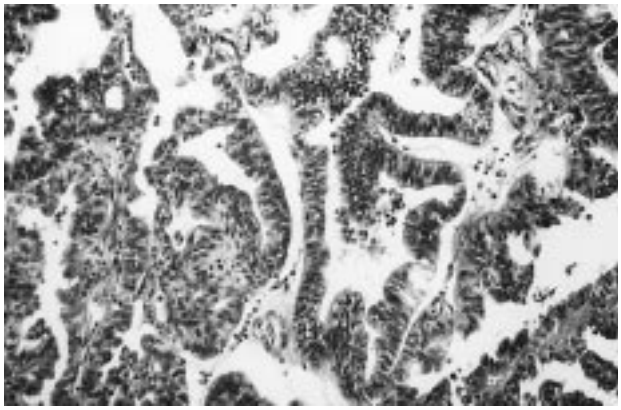

Figure 1. *Typical pattern of moderately differentiated endometrioid carcinoma of the Fallopian tube. HE, x120*

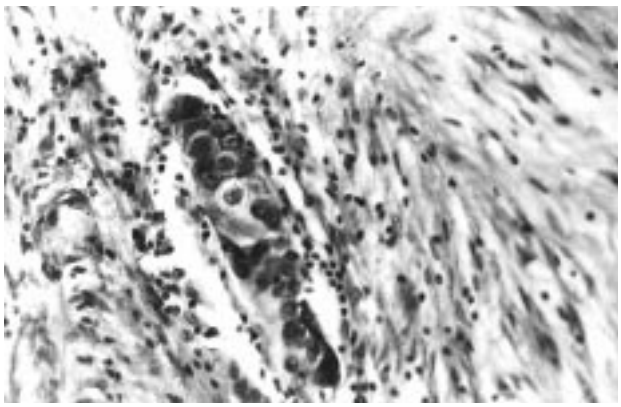

Figure 2. *Neoplastic cells in vessels of the tubal wall. HE, x250*

Two of these 6 patients also had metastases to omentum and peritoneum, one to peritoneum and one to myometrium. In six cases endometriotic foci were found in uterine body or ovaries. In 14/20 cases of PFTEC there was invasion of the tubal wall *(Figure 2)*. In 10 of these 14 cases, invasion revealed giant-nest pattern, in 4 microfocal, sometimes diffusing pattern. Seven patients who presented with various patterns of tubal wall infiltration died of recurrent tumor or metastases. Blood or lymphatic vessels involvement was found in 9 cases, including 5 cases with metastases to extratubal organs. Six of these 9 women died of PFTEC, and one patient is alive, though with PFTEC symptoms. Three of 9 paras as well as 3 of 7 nulliparas died of PFTEC.

Satisfactory results from immunohistochemical studies were obtained in 17 cases of PFTEC *(Table 4)*. Four of 9 patients with significant p53 protein and oncogene product, c-erbB-2, expression died within 4 up to 39 months after diagnosis and two are alive with recurrent tumors *(Figs 3, 4)*. Three patients with a strong expression of p53 and c-erbB-2 are free of disease – one of them for 80 months.

There was no significant correlation between groups of patients without progression of disease or dead from cancer and expression of mutant p53 protein and c-erbB-2 oncogene product, parity and histologic grade. The expression of c-erbB-2 was more common in nulliparas than in women with pregnancy in anamnesis (p=0.0095). The invasion of vascular spaces was a poor prognostic factor (p=0.001). Clinical grade of disease was a significant prognostic factor of survival (p=0.01). *Figs 5–7* show Kaplan-Meier curves *(Figure 5* presents survival for 20 patients with PFTEC; *Figure 6* shows the survival according to FIGO stages and *Figure 7* the survival according to histologic grading).

Discussion

Because of the rarity of PFTC contributions dealing with sufficient number of cases to make proper evaluation are not numerous.[2,5,7,8,10,14,16,18,20,22] The comparison of results of different studies is very difficult or even impossible, because it

Table 3. **Correlation between degree of histological differentiation and the time of survival**

FIGO stage	*No. of patients*	*Alive without symptoms*		*Alive with symptoms*		*Died*	
		No. of patients	*Survival (median)*	*No. of patients*	*Survival (median)*	*No. of patients*	*Survival (median)*
I	13	10	70.5 mo	0	0	3	24.0 mo
II	4	0	0	0	0	4	15.5 mo
III	3	0	0	2	6.0 mo	1	4.0 mo

is usually very hard to collect in one centre/clinic, within a short period of time, a large number of patients treated with a uniform protocol and diagnosed using the same methods and histological criteria for PFTC.[15] The widely used histological classification of PFTC according to Hu et al has added progress in studies of PFTC.[14,18] PFTC of endometrioid type is in our biopsy material the most often encountered histological variant of uterine tube carcinoma, (42.5%). Navani et al in 1996 reported 26 cases of PFTEC noting that prior to their study there were merely 19 case reports of PFTEC in the literature. On the other hand, there are also studies on larger number of PFTC, which show more frequent occurrence of this tumor type. Barakat et al found 77% of PFTECs in their biopsy material among treated PFTCs. Hellstrom et al found 16 PFTECs, i.e. 12.5% among 128 cases.[5] Lacy et al evaluated 6 (14%) cases as PFTECs among 43 PFTCs examined.[10] The same authors noted that both morphology and biology of PFTC is very similar to that of malignant ovarian epithelioma.[10] In different studies the number of ovarian endometrioid carcinomas among all types of ovarian cancer ranges from 11 to 25%; the same or lower occurrence of PFTEC was found among PFTCs.[3,4,9,11,26] The relatively high percentage of PFTEC in our material was, to some extent, accidental. Between 1982 and 1997 we found 36.6% of PFTECs among consulted 41 PFTC cases.[18] Among the next 6 cases diagnosed in our Department, 5 were endometroid carcinomas.

Our results confirm the high prognostic value of evaluation of PFTC progression according to FIGO classification.[5,7,8,14-16,18,20] There is a distinct correlation between the stage of clinical progression at the time of diagnosis and survival duration in our series. Among the PFTEC cases as many as 65% were classified as FIGO stage I in our material at the time of diagnosis. This percentage is similar to 69% found by Navani et al.[14] In general, this percentage is higher than that observed in previously analysed PFTC material independently of the histological type of tumor. Stage I PFTC was observed in the cited papers at a frequency of 19% to 56%.[2,5,8,10,20] In our material we have found two cases of bilateral PFTEC (10%) which is comparable to other data.[5,6,8] This, in turn, contradicts the statement that unilateral occurrence of PFTEC is typical feature of this tumor.[14]

In our series the nulliparity rate was 35%, similarly to other's finding.[15] Nulliparas with endometrial carcinoma had a poorer 5-year survival rate in comparison with patients who had 1 or more births.[21] This observation seems to be supported by our results. Among parous women 9 of 13 are alive, and among nulliparas 3 of 7.

The significance of grading of PFTEC as prognostic factor is still lacking in the literature. Results of studies on PFTCs, which express various histologic patterns, rather contradict the significance of this factor.[15,16] In our series there was no apparent correlation between grading and survival time. It is important to distinguish endometrioid

Table 4. **Correlation between accumulation of p53 protein, expression of oncogene product, c-erbB-2, and the time of survival**

Immunohistochemical staining	*No. of patients*	*Alive without symptoms*		*Alive with symptoms*		*Died*	
		No. of patients	*Survival (median)*	*No. of patients*	*Survival (median)*	*No. of patients*	*Survival (median)*
p53 (+), c-erb-2 (-)	2	2	50.5 mo	0	0	0	0
c-erbB-2 (+), p53 (-)	1	0	0	0	0	1	65.0 mo
p53 (+), c-erbB-2 (+)	9	3	63.0 mo	2	6.0 mo	4	15.5 mo
P53 (-), c-erb-2 (-)	5	5	86.0 mo	0	0	0	0

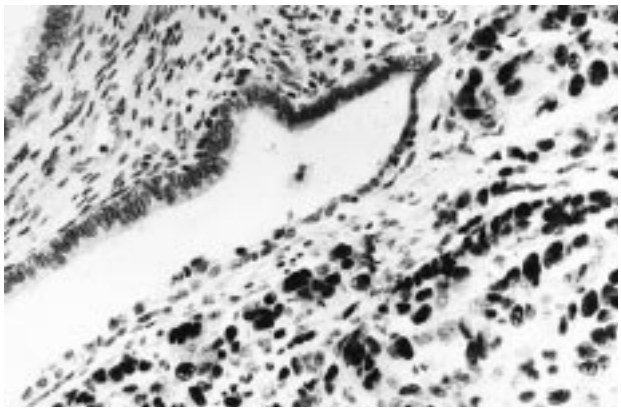

Figure 3. *Strong p53 protein accumulation in primary carcinoma of the Fallopian tube. Immunohistochemical staining, x120*

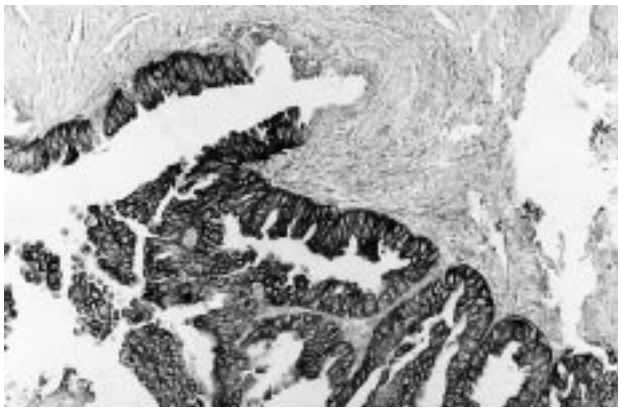

Figure 4. *C-erbB-2 oncogene product expression in primary carcinoma of the Fallopian tube. Immunohistochemical staining, x120*

carcinoma, both in uterine tubes and ovaries because of somewhat different type of invasion of surrounding tissues which resembles the primary endometrial adenocarcinoma.[14,17,19,23,26] A thin, well-vascularized tubal wall favours invasion of cancer cells into stroma and metastasising.[2,6,15] Classically, endometrial carcinoma is usually characterised by giant-nest, superficial infiltration, at least in early phase of growth.[23] Rarely, there endometrial carcinomas are found which reveal diffuse infiltration and have a worse prognosis.[13] In our material 6 PFTECs were characterised by endophytic growth (into tubal lumen) with no aggression against thinned tubal wall. In 10 cases we found focal, mostly superficial (less often deeper) invasion of tubal wall, and in 4 cases we found diffuse, tubal wall infiltration. The pattern of stromal invasion by PFTEC in our series is similar to that reported by other authors,[3,13,14,19,26] as well as to the pattern of stromal invasion in uterine and ovarian endometrioid carcinoma. The limited tendency to tubal wall infiltration was found to be a good prognostic factor in PFTEC.[14] Invasion of lymphatic and blood vessels is the other serious prognostic factor.[6,16,22] In spite of the seemingly low aggressiveness of well-differentiated carcinomas towards stroma we have found invasion of tubal wall vessels in 9 cases. In 5 of these 9 cases the metastases were noted during surgical treatment. Six patients with such a PFTEC picture died and one is still alive, with symptoms of disease. We are sure that the precise analysis of microscopic picture of affected uterine tubes with regard to the presence of cancer cells in vessels offers valuable information of indisputable prognostic significance.[15]

Endometriosis of various locations (except uterine tubes) was found in 30% of examined PFTEC cases. Microscopic analysis of PFTCs did not prove that PFTECs developed in endometriotic foci. Thus, the histogenesis of PFTEC is not related to tubal endometriosis.

The prognostic value of p53 gene mutations for apoptosis inhibition and tumor growth promotion and the expression of c-erbB-2 protooncogene in ovarian and tubal carcinomas are not yet clear. Apart from the studies, which

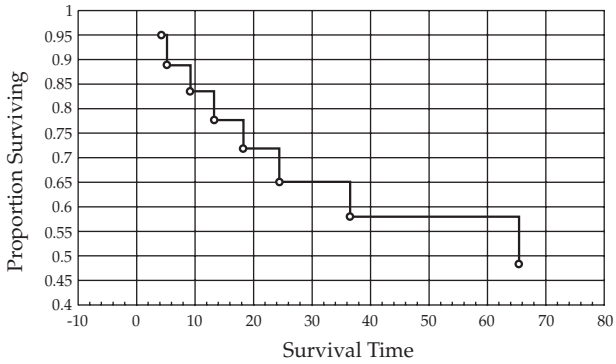

Figure 5. *Kaplan-Meier survival curve for 20 patients with primary Fallopian tube endometrioid carcinoma. Survival time – months since the time of diagnosis.*

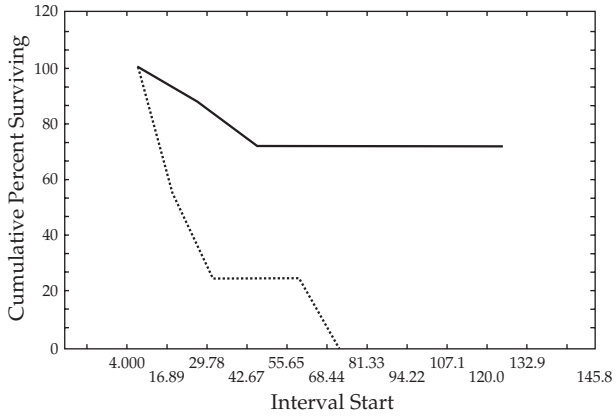

Figure 6. *Survival of patients with primary Fallopian tube endometrioid carcinoma according to FIGO stages (I _ group 1, II and III .... group 2).*

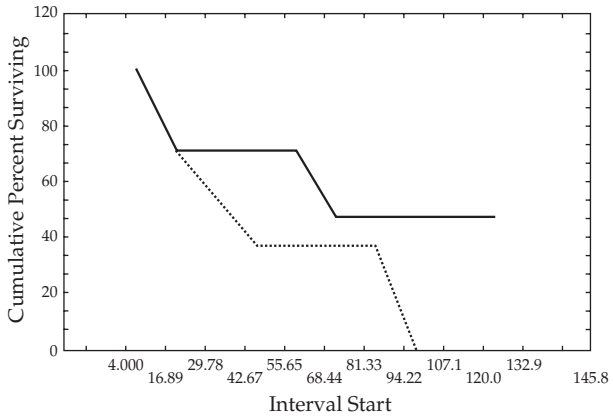

Figure 7. *Survival of patients with primary Fallopian tube endometrioid carcinoma according to histologic grading (high _ group 1, moderate and poor .... group 2).*

indicated a great prognostic value of both markers, there were contributions in which the usefulness of these markers was not decided or even denied.[4,10-12] In our series we found accumulation of pathologic p53 protein in 11 of 17, and c-erbB-2 expressions in 10 of 17 PFTECs. This is however too small number of patients and the time of follow-up in the part of the cases were too short to make generalised conclusions. Four of 9 women, showing the expression of both markers, died within the period from 3 months to 3 years after tumor diagnosis (44.4%). This percentage is comparable to results of studies on survival time in PFTC patients, independently from histologic type, differentiation grade or clinical stage.[2,8,15,16,18,20]

The analysis of our results based on 20 cases of PFTEC lets us make the statement, that this histologic type of PFTC represents an intermediate entity between endometrial carcinoma and endometrioid ovarian carcinoma. This cancer can be characterised by somewhat greater invasiveness than typical endometrial carcinoma. This unfavourable feature can be related to anatomic structure of uterine tube rather than to the biologic properties of the tumor. It should be stressed that invasion of vessels in the tubal wall correlates with metastases in the surrounding tissues. This very often takes place, although in most cases there is only a slight tendency to deep, diffuse infiltration of stroma. Therefore the majority of such tumors at the time of diagnosis can be classified as early stage tumors.

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