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Original Paper

A 15-Year Overview of Management and Prognosis in Primary Fallopian Tube Carcinoma

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143 women treated in 28 departments from 1980 to 1995 were retrospectively analysed to study the impact of prognostic factors in primary carcinoma of the fallopian tube. The mean age of the patients was 62.5 years. Sixty (42%) tumours were FIGO stage I, 28 (20%) stage II, 38 (27%) stage III, 17 (12%) stage IV. Complete radical resection was achieved in 102 (71%) patients. In 122 (85%) women, surgery involved removal of the uterus, the adnexa, and/or the omentum or lymph nodes. Postoperative therapy consisted of either irradiation ($n = 40$; 28%) or chemotherapy ($n = 70$; 49%); 33 women (23%) did not receive any treatment after surgery. The 5-year survival rate for all cases was 43%. The 5-year survival rate was 59% for stages I and II and 19% for stages III and IV ($P < 0.00001$). FIGO stage, histological grade and presence of residual tumour had an independent prognostic impact in multivariate analysis. In order to investigate the role of p53 in primary fallopian tube carcinomas, we analysed the immunohistochemical expression of p53 protein regarding survival and FIGO stage in 63 patients (44%). No statistical significance was observed.

Key words: primary fallopian tube carcinoma, prognostic factors, postoperative therapy
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INTRODUCTION

PRIMARY FALLOPIAN tube carcinoma is a very rare but highly aggressive disease and accounts for 0.15–1.8% of neoplasms of the female genital tract [1–4]. A Danish study reported an incidence of 0.29 out of 100 000 women [5].

The comparison of published reports is rendered difficult by the small number of cases, heterogenous staging system and diverse methods of treatment, especially with regard to postoperative therapy [6–12]. Since the disease is a very rare entity, the literature does not provide any valid information regarding the distribution of prognostic factors or the efficacy of different treatment modalities. In order to overcome these problems, a nationwide multicentre analysis was performed, with the aim of evaluating the methods currently used to diagnose and treat primary carcinoma of the fallopian tube in Austria.

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PATIENTS AND METHODS

Cancer of the uterine tube has been registered by the Cancer Registry of the Austrian Central Statistical Office since 1980. Twenty-eight institutions of gynaecology and obstetrics and their associated departments of pathology were included in a nationwide, retrospective, multicentre analysis of fallopian tube carcinoma in Austria treated from 1980 to 1995. All institutions received standardised questionnaires which were returned to and analysed by the first author. Data concerning prognostic factors, surgical treatment and postoperative therapy were included in the analysis. Patients were followed until the control date (1 April 1997).

Pathological investigations

A modified version of the FIGO classification was used to stage the tumours [13]. Histological assessment and grading were carried out according to the criteria proposed by Hu and colleagues [14]. The departments participating in the study sent histological specimens to the study centre, where the

specimens were graded and classified by an independent pathologist.

DNA ploidy analysis was performed by image cytometry (IMC). Routine paraffin sections can be used with ICM by disaggregation of tumour cells, with the subsequent cytospin stained by the Feulgen method [15]. In ICM, a computerised optical image analysis system was used to quantitate Feulgen DNA staining in touch imprints of tumours. To ensure the validity of the distribution, at least 100–200 tumour cell nuclei were measured in each case. Lymphocytes and granulocytes were used to define the 2c peak of normal cells. Histograms of the DNA contents, 5c exceeding rates and DNA index (peak mean relative to 2c) were calculated.

P53 protein was determined in deparaffinised tissue sections using an immunoperoxidase method utilising an avidin-biotinylated horseradish peroxidase complex (Vectastatin Elite ABC; Vector Laboratories, Burlingham, California, U.S.A.). The primary monoclonal mouse anti-p53 antibody (BP53-12, Ig2a; BioGenex, San Ramon, California, U.S.A.) reacts with both wild-type and mutant forms of p53. The tissue samples were reviewed by two independent observers who were blind to the pathological stage and clinical outcome of the cases. In the event of a different assessment, the slides were reviewed by both observers together and a compromise was achieved. Staining was scored as follows 0, negative; 1, 1–10%; 2, 10–50%; 3, > 50% [16].

Furthermore, the presence of ascites, and residual tumour after surgical resection and postoperative therapy were evaluated with regard to their prognostic impact.

Statistics

The results were expressed as percentage and then subjected to a chi-square test. Survival curves were obtained using the Kaplan–Meier method, and the median survival times compared by the Mantel–Cox log-rank test [17–19]. The level of statistical significance was set at $P < 0.05$. The cox regression method was used in multivariate survival analysis to identify factors that independently influenced survival [19]. Factors that achieve statistical significance in the univariate analysis were analysed for their independent influence. Wherever feasible, hazard plots were used to assess the appropriateness of the proportional hazards assumption that underlies the Cox regression model. A log-likelihood ratio test was used to determine the significance of combinations of factors.

RESULTS

143 cases of primary cancer of the fallopian tube were included in the study. The mean age of the patients was 62.5 years (range 37.3—82.0 years). 60 (42%) patients had stage I, 28 (20%) stage II, 38 (27%) stage III and 17 (12%) stage IV tumours. After histological assessment, 25 tumours were grade 1 (17%), 49 (34%) grade 2 and 69 (48%) grade 3 (Table 1). Histology revealed the following distribution of tumour types: 75 (52%) papillary, 25 (17%) serous, 20 (14%) solid, 12 (8%) medullary and 11 (8%) mucinous carcinomas.

Surgery consisted of the following procedures: abdominal hysterectomy with bilateral salpingo-oophorectomy in 63 (44%) patients, or hysterectomy combined with bilateral salpingo-oophorectomy, infracolic resection of the omentum and pelvic lymphadenectomy in 59 patients (41%). 21 (15%) women underwent removal of one adnexum and/or laparotomy. The tumour was completely and radically resected in 102 (71%) patients, whilst 20 (14%) patients had a small (2 cm) residual tumour and 21 (15%) had a larger (> 2 cm) residual tumour mass.

70 (49%) women received postoperative chemotherapy with six cycles of a cisplatin containing regimen (75–100 mg/m^2). 40 (28%) patients were treated by irradiation (telecobalt or X-23) postoperatively; these patients received an external megavoltage irradiation exclusively to the pelvis ($n = 13$) or to the pelvis and the whole abdomen ($n = 27$). The median delivered dose was 50 Gy (range 18–56 Gy) to the pelvis and 30 Gy (range 25–32 Gy) to the abdomen. The average dosage per day was 1.8–2 Gy. Patients whose chemotherapy did not include cisplatin or patients with incomplete irradiation (dosage < 50 Gy) were excluded from the study. 33 (23%) women were given no postoperative therapy because they had stage Ia disease or because they had a performance status of 3 or 4 according to the WHO criteria. All patients with a performance status of 3 or 4 had stage IV tumours.

With regard to ascites, more than 250 ml of fluid was found intra-operatively in 31 (22%) women; the other 112 (78%) patients had no ascites.

DNA analysis was performed in 61 patients (43%) and showed the following distribution. 13 (21%) patients had a DNA index of 0.9–1.10; 33 (54%) had a DNA index of 1.11–2.00, and 15 (25%) had a DNA index of > 2.0.

Immunohistochemical detection of p53 protein expression was performed in 63 (44%) patients. No correlation with DNA ploidy as well as tumour grading was found. Twelve (19%) samples were p53 negative (tumours with < 10% of cells with nuclear staining) and 51 (81%) samples were p53 positive (tumours with > 10% of cells with nuclear staining).

The median observation period for all patients was 29 months (1–275 months). 22 patients (15%) died of an intercurrent disease not associated with fallopian tube carcinoma

Table 1. *Impact of prognostic factors on survival by univariate and multivariate analysis*

Factor	*n*	Median survival (months)	Univariate *P* values	Multivariate *P* values
FIGO				
I	60	Not reached		
II	28	137	< 0.00001	0.003
III	38	25		
IV	17	20		
Residual tumour				
0.2 cm	132	35	0.03	0.02
> 2 cm	21	11		
Grading				
Grade 1	25	73		
Grade 2	49	51	0.03	0.047
Grade 3	69	28		
Postoperative therapy				
Chemotherapy	70	35	0.195	n.s.
Irradiation	40	48		
DNA index				
0–1.1	13	34	0.83	n.s.
> 1.1	48	24		
P53 status				
Negative	12	40	0.91	n.s.
Positive	51	21		

n.s., not significant.

(myocardial infarction, accident, metachronous, secondary carcinoma, etc.). 17 patients (12%) were lost to follow-up. The median survival for all stages was 45 months (95% confidence interval (CI) 26–64) and the overall 5-year survival rate was 43%. The survival rates in FIGO I + II as well in FIGO stage III + IV did not differ statistically (Figure 1), so that they were amalgamated into two groups (I + II versus III + IV). The median survival was 137 months (95% CI 44–230) in patients with stage I and II disease ($n = 88$) and 21 (95% CI 16–26) months in those with stage III and IV disease ($n = 55$). The 5-year survival rate was 59% for stages I and II and 19% for stages III and IV ($P < 0.00001$)(Figure 1a). Patients with grade 1 tumours had a 5-year survival rate 58%, whilst those with grade 2 disease had a 5-year survival rate of 47% and those with grade 3 had a rate of 33% ($P = 0.04$) (Figure 1b).

Ascites was found in only 22% of the patients and did not have any statistically significant influence on prognosis (data not shown). In patients with a residual tumour < 2 cm the median survival was 35 months (95% CI 17–64) compared with 11 months (95% CI 7–32) in women with residual tumour > 2 cm ($P = 0.03$). Patients who received postoperative chemotherapy had a median survival of 35 months (95% CI 13–49) compared with 48 months (95% CI 31–83) ($P = 0.1954$) (Figure 2) for patients who received postoperative radiation.

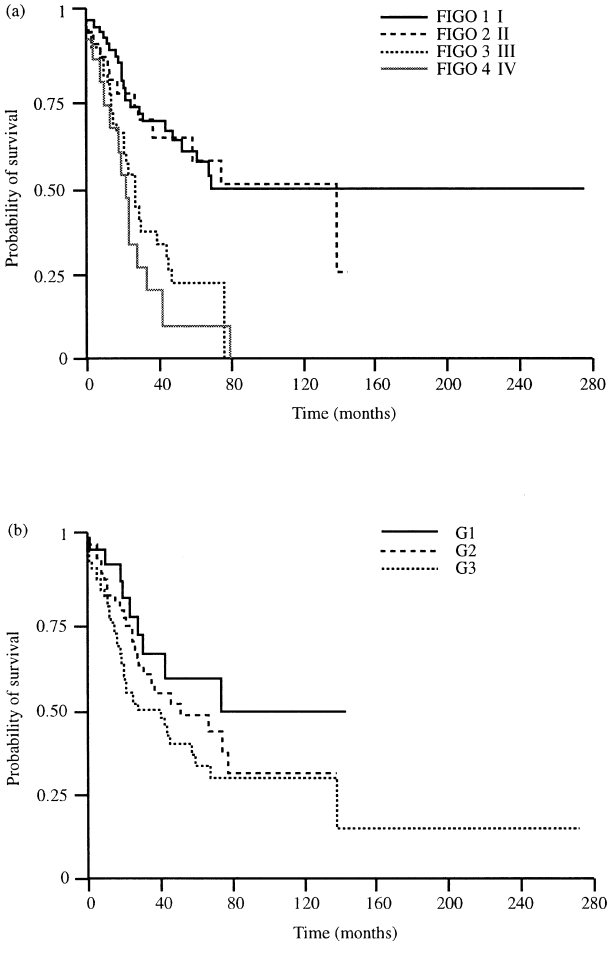

Figure 1. Overall survival analysed according to (a) FIGO stage (I, II, III, IV) and (b) histological grade (G1 versus G2 versus G3). Kaplan–Meier analysis.

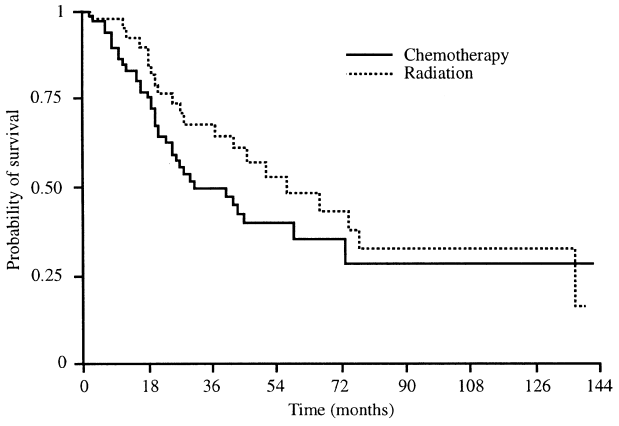

Figure 2. Overall survival analysed according to type of postoperative treatment (postoperative chemotherapy versus irradiation). Kaplan–Meier analysis.

The median survival for patients with a DNA index ≤ 1.1 was 34 months (min. 1.8; max. 126) compared with 24.5 months (min. 0.3; max. 103) for tumours with a DNA index > 1.1, but the difference did not reach statistical significance ($P = 0.83$) (Figure 3a).

The median survival for the p53 negative group (tumours with < 10% of cells with nuclear staining) was 40 months and 21 months for the p53 positive group (tumours with > 10% of cells with nuclear staining). For patients with FIGO stage I and II and negative p53 staining tumours the median survival was not reached. In these early stage tumours which were p53 positive, the median survival was 67 months. In stages III–IV the median survival time was 40 months for patients with p53

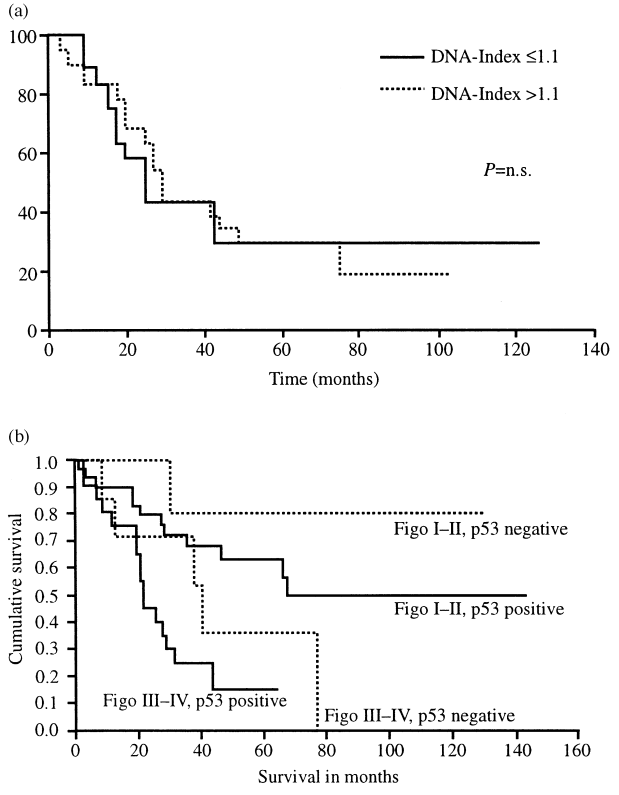

Figure 3. Overall survival analysed according to (a) DNA ploidy in 61 patients or (b) p53 expression stratified for FIGO stage, in 63 patients. Kaplan–Meier analysis.

negative tumours compared with 21 months for p53 positive tumours. However, no statistical significance was reached ($P = 0.91$) (Figure 3b).

On multivariate analysis, FIGO stage proved to be the most powerful predictor of outcome in women with fallopian tube carcinoma (for this analysis the patients were dichotomised for stage I + II versus III + IV) ($P = 0.003$). The only factors that significantly enhanced the predictive power of the FIGO stage were the amount of residual tumour (< 2 cm versus > 2 cm) ($P = 0.02$) and histological grading ($P = 0.047$). All other factors (DNA analysis, p53 determination, ascites, as well postoperative therapy) did not have any significant influence on prognosis.

DISCUSSION

The low incidence of primary cancer of the fallopian tube means only a very limited amount of data can be generated from single institutions. This makes it difficult to draw substantial conclusions on the therapy and prognosis of this malignancy. Approximately 1,500 cases have been reported worldwide, whilst no single study has reported more than 100 cases [20]. Our retrospective evaluation of data from 28 centres encompassed 143 patients. The patients' age and distribution of stages of disease in our study were similar to those reported by other authors [6, 7, 20–23].

Histologically, the tumour presents as an adenocarcinoma of various types [20, 24]. We observed a predominance of papillary (52%) and serous (17%) adenomatous structures. Solid, medullary and mucinous structures were less common. Highly differentiated grade 1 tumours were observed in 17% of patients, with 34% grade 2 and 48% grade 3 tumours. These results are in concurrence with those of McMurray and colleagues [7] (grade 1 = 39%, grade 2 = 20%, grade 3 = 43%), as well as other authors [5–7, 25]. In our study histological differentiation had a statistically significant impact on prognosis (Figure 1), as did FIGO stage (stages I–II versus III–IV, $P < 0.001$).

The early diagnosis of fallopian tube carcinoma may be explained by its frequently observed cardinal symptoms, i.e. painful tension in the tubes and an abnormal discharge of serous fluid. In some patients, these symptoms are caused by an occlusion of the abdominal ostium of the uterine tube [6, 25] which, in turn, might delay the lymphogenous and/or continuous growth of the tumour. In 1962, Green and Scully reported 5 survivors out of 18 patients in whom the lateral ostium of the tubes was occluded [26].

The overall 5 year survival rate of our patients was 43%. These findings are comparable with those reported by other authors [5, 8, 19, 24, 25, 27]. Overall, staging according to the modified FIGO system had the strongest influence on survival, both in univariate and multivariate analyses. A residual tumour mass < 2 cm in size also had a positive independent impact on survival. Ascites, a strong prognastic factor in ovarian cancer, was only observed in 22% of our patients, those with stage III and IV disease. In contrast to the influence of ascites in the presence of ovarian cancer, acites did not negatively influence the survival of patients with cancer of the fallopian tube.

As mentioned previously fallopian tube cancer is diagnosed fairly early. Therefore, in the majority of cases, the patients' condition can be stabilised by radical surgery [4]. 122 women in our series underwent radical hysterectomy including the adnexa and/or total resection of the omentum, or lymphadenectomy. Early diagnosis is invariably associated with a better outcome, and the advantage of early diagnosis is best exploited by opting for radical surgery. In keeping with the guidelines used in ovarian cancer, we recommend that resection be as radical as possible [27, 28].

Generally, fallopian tube carcinoma appears to have highly malignant potential. This is in accordance with our previous findings, which described a statistically worse outcome of patients with fallopian tube cancer in stage I and II compared with a group of women treated for ovarian cancer at the same stages [29]. In this study, we were able to show in univariate as well as in multivariate analyses in 194 primary ovarian cancers versus 68 fallopian tube carcinomas (all in stage I + II) that the predictive factor for survival was the presence of fallopian tube carcinoma [29].

The nuclear p53 tumour suppressor gene is one of the more widely mutated genes in human carcinogenesis. Immunohistochemical detection of p53 is used as a marker of p53 mutation, because only mutated protein product accumulates in the nucleus. Our finding of positive immunoreactivity in the majority (81%) of the 63 patients who were evaluated for p53 expression is not surprising, as this indicates the presence of a p53 mutation. However, the effect on patient survival still needs to be elucidated.

The role of postoperative therapy of fallopian tube carcinoma is still questionable. Due to the low prevalence of the disease and heterogeneous postoperative regimens, it is difficult to establish therapeutic guidelines. Some studies have recommended postoperative irradiation covering the pelvis and the para-aortic lymph nodes. With the introduction of new cytostatic agents, such as cisplatin, some authors favour postoperative chemotherapy, as in ovarian cancer. Although there is a trend to adjuvant and palliative cytostatic chemotherapy in the recent literature, there is no proof for a significant benefit from these regimens [6–12, 30–32].

In an early evaluation of our patients, Klein and colleagues showed improvement of prognosis by postoperative irradiation in 24 patients compared with 49 who underwent adjuvant chemotherapy [33]. Our present series, including 40 (28%) patients who received postoperative radiation and 70 (49%) who received chemotherapy who were followed for more than 2 years, failed to confirm the early results of our group. 33 (23%) patients did not receive any postoperative therapy. Although it is not possible to draw any definitive conclusions regarding the role of postoperative therapy on the basis of our retrospective data, it is questionable if results of a prospective randomised trial will ever be available due to the nature of this rare disease.

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