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Comparison of Primary Tumor Size in Stage I and III Epithelial Ovarian Cancer

EDGAR PETRU[1], CAROLA HUBER[2], EVA SAMPL[3] and JOSEF HAAS[1]

[1]*Department of Obstetrics and Gynecology, Division of Gynecology, LKH University Hospital Graz, Graz, Austria;*
[2]*Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria;*
[3]*Department of Internal Medicine, LKH Kirchdorf, Kirchdorf, Austria*

Abstract. *Background: Two studies have found primary ovarian carcinomas in stage I disease to be larger than those in stage III. Thus, these stages may represent different tumor entities. Materials and Methods: The clinical data from 553 patients operated on between 1985 and 2012 for epithelial ovarian cancer were retrospectively analyzed. Results: Primary lesions including invasive, borderline and benign components were significantly larger in stage I compared to stage III disease (p<0.001). However, the maximum diameter of invasive components in those with stage III disease were significantly larger than in those with stage I disease (p=0.001). The size of the invasive component was not associated with the largest size of intraperitoneal metastasis. Conclusion: We were only, in part, able to reproduce the data from the two smaller published studies. The prognosis of patients with stage III disease strongly depends on the size of intraperitoneal metastases.*

Primary tumors in International Federation of Gynecology and Obstetrics (FIGO) stage I ovarian cancer might be expected to be smaller than those in stage III disease. One study on 110 patients reported tumors in those with FIGO stage I and II disease being significantly larger than those in FIGO stage III and IV (1). Thus, 'early' and 'late' stage disease might in fact represent different clinical entities.

The aim of the present study was to analyze the primary tumor size in FIGO stage I and III disease in a larger patient population treated at our Institution. If previous findings by Horvath *et al.* (1) were confirmed, this might have a clinical impact on the diagnosis and treatment of ovarian cancer.

Correspondence to: Carola Huber, Medical University of Graz, Auenbruggerplatz 14, 8036 Graz, Austria. Tel: +43 31638581082 (E. Petru), e-mail: carola.huber@stud.medunigraz.at

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Materials and Methods

In this study, 553 consecutive patients with primary epithelial ovarian cancer in stage I and III disease, operated on between 1985 and 2012 at the University Hospital for Gynecology and Obstetrics in Graz, were identified from the local tumor registry. They were retrospectively analyzed. Patients and disease characteristics are given in Table I. Primary tumors and intraperitoneal metastases were removed surgically in all cases, with the exception of a minority deemed inoperable or anesthetically critical. A chart review was performed and data on macroscopic and microscopic histopathology were extracted (96%). In the remaining 4% in which no resection of metastases was performed, the size of the largest intraperitoneal metastasis was estimated on the basis of the surgical report. The microscopic findings with regard to the size of the primary tumor with its invasive, borderline and benign components were recorded.

Patients had to meet all of the following criteria to be included in this study: Primary epithelial ovarian cancer, FIGO stage I or III disease, primary surgery at the Department of Obstetrics and Gynecology of the Medical University of Graz, information on follow-up available.

Patients with at least one of the following criteria were excluded from this study: epithelial ovarian cancer in stage II or IV disease, borderline tumor of the ovary, non-epithelial ovarian cancer (carcinosarcoma, germ cell tumor, malignant stromal tumor), relapsed ovarian cancer, undergoing neoadjuvant chemotherapy, primary surgery at another institution.

Data were evaluated using the statistical program SPSS 15.0 (SPSS Inc., Chicago IL, USA). For statistical analysis, a level of α=0.05 was used as the significance limit. A significant difference was stated in cases with a *p*-value less than 0.05. Survival at 5 and 10 years was calculated using the Kaplan–Meier method.

Results

In our study, significantly more patients had FIGO stage III disease than stage I disease (Table I). Histologically, primary lesions containing invasive, borderline and benign components had a significantly larger maximum diameter in FIGO stage I than in FIGO stage III disease (Figure 1). In contrast, invasive lesions in stage III disease were significantly larger than those in stage I disease (Figure 2).

Table I. *Tumor and patient profiles for the 553 (100%) patients who were diagnosed with primary epithelial ovarian cancer in International Federation of Gynecology and Obstetrics (FIGO) stage I and III disease.*

Characteristic	FIGO stage I		FIGO stage III	
Number of patients	177 (32%)		376 (68%)	
Age, years				
Mean (range)	59 (26-91)			
<60 Years	99 (56%)		192 (51%)	
>60 Years	78 (44%)		184 (49%)	
Maximum size of the primary ovarian cancer, n (%)				
<5 cm	13 (7%)		90 (24%)	
5-10 cm	63 (36%)		139 (37%)	
>10-20 cm	72 (41%)		129 (34%)	
>20 cm	29 (16%)		18 (5%)	
Maximum diameter of primary ovarian tumor, cm				
Median (95% CI)	12.8 (11.9-13.8)		9.7 (9.2-10.2)[a]	
Maximum size of invasive component, n (%)				
<5 cm	85 (48%)		132 (35%)	
5-10 cm	56 (32%)		124 (33%)	
>10-20 cm	30 (17%)		107 (29%)	
>20 cm	6 (3%)		13 (3%)	
Maximum diameter of invasive component, cm				
Median (95% CI)	6.7 (5.8-7.5)		8.3 (7.8-8.9)[b]	
Histological subtype, n (%)				
Serous	69 (39%)		244 (65%)	
Non-serous	108 (61%)		132 (35%)	
Mucinous	41 (23%)		13 (3%)	
Endometrioid	37 (21%)		43 (11%)	
Clear-cell	25 (14%)		36 (10%)	
Other histology*	5 (3%)		40 (11%)	
Differentiation grade, n (%)				
1	69 (39%)		48 (13%)	
2	49 (28%)		74 (20%)	
3	47 (27%)		237 (63%)	
Unknown	12 (6%)		17 (4%)	
Median maximum size of lesion by histological subtype, cm	Serous	Non-serous	Serous	Non-serous
Primary	11.0	14.1[c]	8.9	11.4[d]
Invasive component	6.7	6.6[e]	7.5	10.0[f]
Type of primary surgery, n (%)				
TAH+BSO+OM+LA**	67 (38%)		207 (55%)	
TAH+BSO+OM	110 (62%)		149 (40%)	
Exploratory laparotomy	0 (0%)		20 (5%)	
Residual disease, n (%)				
None	177 (100%)		129 (34%)	
<1.0 cm	0 (0%)		45 (12%)	
1.1-2.0 cm	0 (0%)		74 (20%)	
>2.1 cm	0 (0%)		128 (34%)	

TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, OM: omentectomy; LA: lymphadenectomy. Significantly different at: [a]$p<0.001$, [b]$p=0.001$, [c]$p=0.003$, [d]$p<0.001$ from stage I disease; [e]$p=0.678$, [f]$p<0.001$ from serous component. *Stage I disease: Large cell carcinoma, adenocarcinoma not otherwise specified, undifferentiated carcinoma; stage III disease: Small cell carcinoma, adenocarcinoma not otherwise specified, anaplastic carcinoma, undifferentiated carcinoma. **Pelvic with/without para-aortic lymphadenectomy.

In FIGO stage I disease, most patients had non-serous tumors (61%), whereas in FIGO stage III disease, mainly serous tumors (65%) were diagnosed. Serous ovarian carcinomas were significantly smaller than those of other histological subtypes. This was shown in both FIGO stage I and III disease for primary lesions, as well as for the respective invasive tumor components (Table I).

In FIGO stage I disease, most patients had grade 1 or grade 2 lesions. In FIGO stage III disease, most lesions were undifferentiated. Similar results have been reported in the literature (2).

Maximum size of intraperitoneal metastasis in ovarian cancer in stage III disease (n=354) is shown in Table I and detailed in Figure 3. The median maximum diameter of

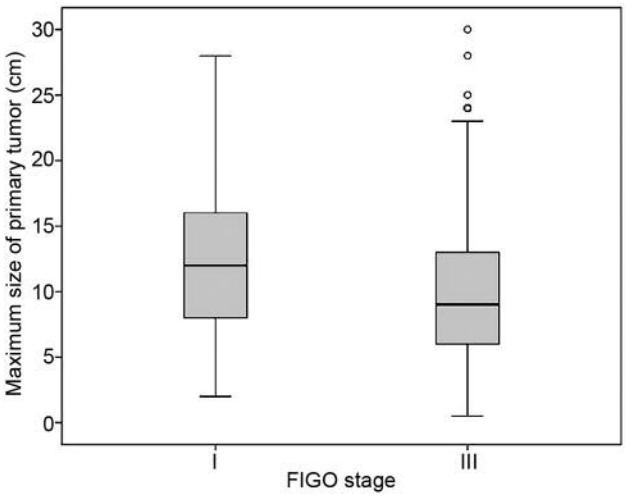

Figure 1. *Distribution of the maximum size of the primary lesion of the ovary including invasive, borderline and benign components in International Federation of Gynecology and Obstetrics (FIGO) stage I (n=177) and stage III disease (n=376) (p<0.001).*

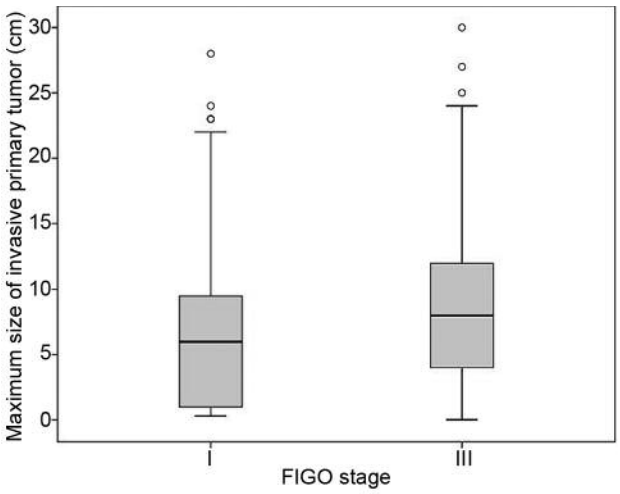

Figure 2. *Distribution of the maximum size of the invasive component of the epithelial ovarian cancer in International Federation of Gynecology and Obstetrics (FIGO) stage I and III disease (n=553) (p=0.001).*

metastasis of epithelial ovarian cancer in FIGO stage III disease (n=354) was 5.8 cm (95% confidence interval=5.1-6.6 cm; Table II). There was no correlation between the size of the invasive component of the primary lesion and the intraperitoneal metastasis (Figure 4).

A larger size of metastasis was associated with the presence of ascites and bowel involvement (data not shown). Retroperitoneal lymphadenectomy was performed more often in patients with smaller intraperitoneal metastases and in those in whom tumor resection to less than 2 cm was achieved.

Overall 5-year survival was significantly higher in patients with stage I than stage III disease (75% *vs*. 26%, respectively). Similar results were obtained for 10-year survival (72% *vs*. 17%, respectively). Relapse-free survival was significantly higher in patients with FIGO stage I disease than in those with FIGO stage III disease. In stage I disease, survival was not significantly different between the subgroups according to tumor size (log-rank test: p=0.839)

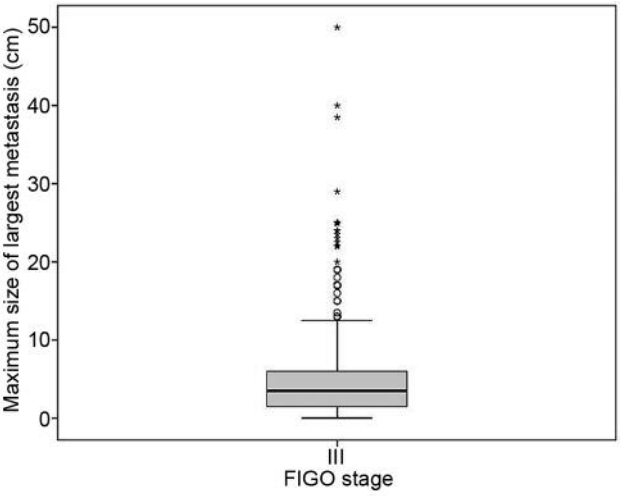

Figure 3. *Distribution of the maximum size of the largest intraperitoneal metastasis of patients with International Federation of Gynecology and Obstetrics (FIGO) stage III epithelial ovarian cancer (n=354).*

Table II. *Largest intraperitoneal metastasis in relation to the maximum size of the invasive component of the epithelial ovarian cancer in International Federation of Gynecology and Obstetrics stage III disease (n=354).*

Size of intraperitoneal metastasis	Number of patients	Size of invasive component		
		≤5 cm	5-10 cm	≥10 cm
0.1-2.0 cm	129	33 (26%)	44 (34%)	52 (40%)
2.1-5.0 cm	117	56 (48%)	36 (31%)	25 (21%)
>5.0 cm	108	36 (33%)	39 (36%)	33 (31%)

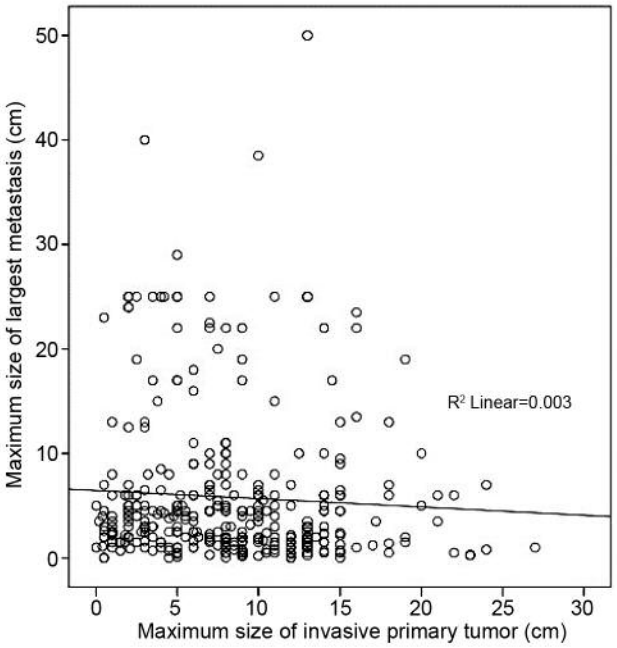

Figure 4. *Distribution of the maximum diameter of the largest intraperitoneal metastasis compared to the maximum invasive primary ovarian tumor size in stage III disease (n=354). Note that several carcinomas were only microscopic but were associated with significantly larger intraperitoneal metastases (p=0.003).*

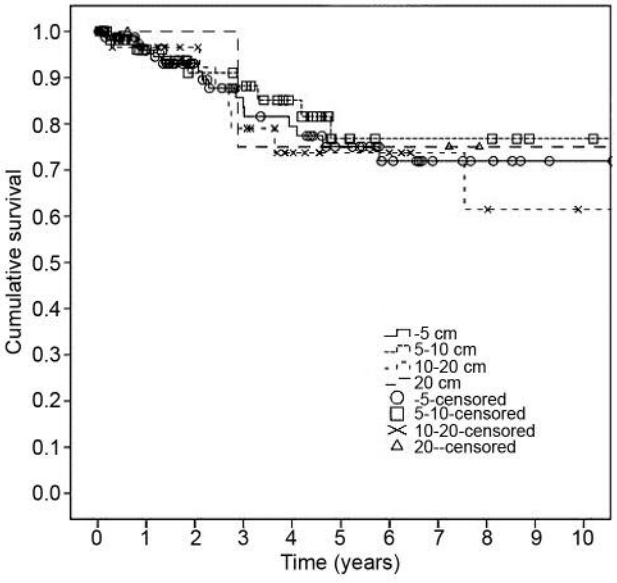

Figure 5. *Overall survival of patients with stage I ovarian cancer based on the maximum size of the invasive tumor component.*

(Figure 5). Similar results were found for FIGO stage III disease (log rank test: p=0.661) (Figure 6).

Discussion

Primary lesions of ovarian tumors with invasive, borderline and benign components in FIGO stage I disease had a larger median maximum diameter than those in FIGO stage III disease (12.8 *vs*. 9.7 cm, respectively; p<0.001; Figure 1). In contrast, the median maximum diameter of the invasive tumor component was higher in FIGO stage III disease than that in stage I disease (8.3 *vs*. 6.7 cm, respectively; p=0.001; Figure 2). Thus, it might be hypothesized that some invasive carcinomas in stage III disease may develop from stage I lesions. This might be caused by the overgrowth of benign or borderline tumor components by more aggressive invasive tumors (3).

Due to the relatively large tumor size in stage I disease, the tumor might have been diagnosed earlier due to earlier occurrence of symptoms, gynecological palpation and ultrasound (4). In stage III disease, the maximum size of the primary lesion differed only slightly from that of the invasive tumor component (9.7 *vs*. 8.3 cm; not statistically significant; Figures 1 and 2). These data suggest different pathology in stage

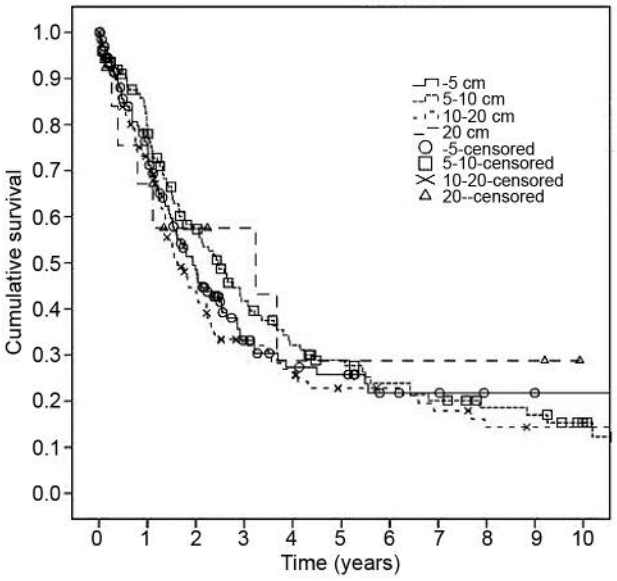

Figure 6. *Overall survival in patients with stage III ovarian cancer based on the maximum size of the invasive tumor component.*

I and III ovarian cancer. With the help of molecular genetic analyses including rat sarcoma (*RAS*), B-rapidly accelerated fibrosarcoma (B-RAF), human epidermal growth factor receptor 2 (*ERBB2*) and p53 mutation, additional important characteristics of both tumor entities might be identified (5, 6).

Horvath *et al*. reported that primary tumors in FIGO stage I are larger than those in stage III disease (1). We were able to confirm these findings only for primary ovarian lesions including invasive, borderline and benign components. In our series, the invasive tumor components were significantly smaller in FIGO stage I than in FIGO stage III disease (Table I and Figure 2).

The median size of the maximum diameter of intraperitoneal metastasis of the epithelial ovarian cancer in stage III disease was 5.8 cm. There was no correlation between the size of the invasive component of the primary ovarian tumor and the size of intraperitoneal metastases in stage III disease. Regression analysis showed no relationship between the size of the primary ovarian cancer and the size of metastases (Figure 3). This finding confirms previous hypotheses that coelomic epithelium *per se* represents 'at risk' tissue for a widespread neoplastic field giving rise to peritoneal and the more common ovarian or tubal serous type neoplasms. They may represent the origin of malignant transformation and this process may take place independently of the development of primary ovarian cancer (7). Survival analyses of our patient groups are consistent with those reported in the literature (8-12).

In summary, patients with stage I disease had larger primary ovarian lesions than those with stage III disease, mainly due to concomitant non-invasive or benign components. There was no correlation between the invasive primary tumor size and the size of metastases in stage III disease.

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