Endometrial Cancer: Comparison of Patients with Synchronous Primary Carcinoma of the Endometrium and Ovary vs. Endometrial Carcinoma with Ovarian Metastases

Primäres simultanes Endometrium- und Ovarialkarzinom vs. Endometriumkarzinom mit Ovarialmetastasen

Authors I. Juhasz-Böss[1], T. Fehm[2], S. Becker[4], R. Rothmund[2], B. Krämer[2], A. Staebler[3], D. Wallwiener[2], E. F. Solomayer[1]

Affiliations
[1] Klinik für Frauenheilkunde, Geburtshilfe und Reproduktionsmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar
[2] Universitätsfrauenklinik Tübingen, Tübingen
[3] Institut für Pathologie, Universität Tübingen, Tübingen
[4] Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinik Frankfurt, Frankfurt

Key words
- synchronous carcinomas
- endometrial cancer
- ovarian cancer
- ovarian metastases
- outcome

Schlüsselwörter
- simultanes Karzinom
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- Ovarialmetastasen
- Outcome

Abstract

Purpose: The aim of our study was to investigate the rate of secondary carcinomas in patients with endometrial carcinoma (EC). In particular, we wanted to describe the subset of patients with endometrial and simultaneous ovarian carcinoma (OC), including outcomes. The study also compared patients with EC and ovarian metastasis with patients with EC and simultaneous OC.

Patients and Methods: Data from 251 patients with primary endometrial carcinoma who underwent surgery in the years 2005–2009 at the Department of Obstetrics and Gynaecology, University of Tübingen, were analysed retrospectively.

Results: A total of 28 patients (11.1%) had a secondary carcinoma: 18 patients (7.1%) had OC; 9 (3.5%) patients had a history of breast cancer, and one patient (0.4%) respectively had simultaneous carcinoma of the vulva or bladder. 14 patients (5.5%) had advanced stage EC with ovarian metastasis or, in one case, metastasis to the ovarian tube. Patients with ovarian metastasis had a mean age of 71.2 ± 9.2 years at primary diagnosis, making them significantly older compared to patients with EC and simultaneous OC (55.3 ± 11.8 years, $p < 0.001$). Moreover, patients with ovarian metastasis significantly more often had EC with a higher tumour grade (grade 1: 0, grade 2: 21.4%, grade 3: 78.6%) compared to patients with simultaneous EC and OC (grade 1: 11.1%, grade 2: 77.8%, grade 3: 11.1%; $p < 0.001$).

Conclusion: Almost one in 10 patients with EC had a secondary carcinoma. The most common secondary carcinoma was OC followed by breast cancer. This should be taken into account in the diagnosis and therapy of patients with EC. Patients with simultaneous EC and OC were significantly younger than patients with EC and ovarian metastasis. In addition, their tumour had better prognostic features: thus, the tumour grade of the EC was significantly lower. Overall, the prog-

Zusammenfassung

Hintergrund: Ziel unserer Arbeit ist es, die Rate an Zweitkarzinomen bei Patientinnen mit Endometriumkarzinom (EC) zu untersuchen. Insbesondere möchten wir die Untergruppe von Patientinnen mit simultanem Endometrium- und Ovarialkarzinom (OC) inklusive Outcome beschreiben. Zudem soll diese Arbeit auch Patientinnen mit einem EC mit Ovarialmetastasen mit Patientinnen mit einem EC und simultanem OC vergleichen.

Patienten und Methode: Daten von insgesamt 251 Patientinnen mit einem primären Endometriumkarzinom, die im Zeitraum 2005–2009 an der Universitätsfrauenklinik Tübingen behandelt worden sind, wurden retrospektiv untersucht.

Ergebnisse: Insgesamt 28 Patientinnen (11,1%) hatten ein Zweitkarzinom: 18 Patientinnen (7,1%) hatten ein OC, 9 (3,5%) Patientinnen hatten anamnestisch ein Mammakarzinom und jeweils eine Patientin (0,4%) hatte simultan ein Vulva- bzw. Blasenkarzinom. 14 Patientinnen (5,5%) hatten ein fortgeschrittenes EC mit Metastasierung im Ovar bzw. in einem Fall in der Tube. Patientinnen mit Metastasen im Ovar sind bei Erstdiagnose mit durchschnittlich 71,2 ± 9,2 Jahren signifikant älter als Patientinnen mit EC und simultanem OC (55,3 ± 11,8 Jahre, $p < 0,001$). Patientinnen mit Ovarialmetastasen haben zudem signifikant häufiger ein EC mit höherem Grading (Grading 1: 0, Grading 2: 21,4% bzw. Grading 3: 78,6%) als Patientinnen mit simultanem EC und OC (Grading 1: 11,1%, Grading 2: 77,8% bzw. Grading 3: 11,1%; $p < 0.001$).

Schlussfolgerung: Nahezu jede 10. Patientin mit EC hat ein Zweitkarzinom, wobei das häufigste Zweitkarzinom ein OC gefolgt vom Mammakarzinom ist. Dies sollte bei der Diagnostik bzw. der Therapie von Patientinnen mit EC mitberücksichtigt werden. Patientinnen mit einem simultanen EC und OC sind signifikant jünger als Patientin-

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Correspondence
Dr. Ingolf Juhasz-Böss
Uniklinikum Saarland
Frauenklinik Homburg
Kirrbergerstraße 100
66424 Homburg/Saar
Ingolf.Juhasz-Boess@uniklinikum-saarland.de

nosis for patients with synchronous EC and OC is better than that for patients with EC and ovarian metastasis.

nen mit einem EC und Ovarialmetastasen. Daneben weist ihr Tumor deutlich bessere prognostische Eigenschaften auf, so. z. B. ein signifikant niedrigeres Tumor-Grading des EC. Insgesamt ist die Prognose von Patientinnen mit simultanem EC und OC besser als bei EC und Ovarialmetastasen.

Introduction

Endometrial carcinoma (EC) has an incidence of between 9.9 and 15.0 for every 100 000 women in the western world, making it the most common genital cancer in women. Peak onset of disease is between the ages of 75 and 80 years, and the mean 5-year survival rate in countries with the highest incidence is between 72 and 84% [1, 2]. When taking a decision to treat it is necessary to consider the tumour stage, the patient's general state of health, and the risk factors [1, 3]. Surgery is the treatment of choice for primary cancer and should be done where possible. After the histological diagnosis has been confirmed, FIGO classification [4] prescribes operative staging, requiring exploration of the abdomen with hysterectomy and bilateral adnexectomy [1]. Depending on the histology (i.e. tumour grade, extent of myometrial infiltration), pelvic and paraaortal lymphadenectomy or omentectomy, appendectomy or the removal of diseased organs may be necessary.

Patients with EC may simultaneously present with a secondary carcinoma. The most common secondary tumours are genital carcinomas.

Simultaneous endometrial and ovarian cancer

The rate of simultaneous ovarian carcinoma (OC) in patients with endometrial cancer is between 3.3 and 10% [5–7]. The rate for patients with primary OC and a secondary carcinoma is less than 3% [8]. 2.7% of patients with primary OC have simultaneous EC [8].

Endometrial carcinoma with ovarian metastasis

There are still no clear histological and surgical criteria which would indicate whether the disease represents simultaneous malignant degeneration of the endometrium and the ovary or whether it represents an EC which has metastasised to the ovary or an OC which has metastasised to the endometrium. Because of this uncertainty the treatment offered by clinics/institutions varies and the prognosis is thus unclear. To date, information on this topic consists largely of retrospective case series with limited numbers of cases.

Recent studies have focussed on differentiating between primary EC and simultaneous OC and EC with ovarian metastasis. One important criterion proposed for the determination of primary EC with ovarian metastasis is multinodular ovarian involvement ("major criterion"), but the criteria have not yet been validated. Further indications are the presence of 2 or more "minor criteria", i.e. bilateral ovarian involvement, small ovaries (< 5 cm), deep myometrial infiltration, vascular invasion or tubal involvement [9–11]. However, these criteria may also be present with primary EC and simultaneous OC, making differentiation often difficult. Attempts to find molecular and immunohistochemical markers which would permit a better differentiation have had only limited success. Studies on molecular parameters only investigated small numbers of cases, and immunohistochemical studies often showed similar results [9, 12]. This continues to complicate attempts to differentiate between primary EC and primary OC or EC which has metastasised to the ovary. While the immunohistochemical detection of oestrogen receptor (ER), progesterone receptor (PR) and bcl-2 expression differs significantly between patients with primary EC and simultaneous OC compared to their expression in patients with EC metastasised to the ovary, parameters such as Her2Neu, Ki-67 and p53 are not suitable for any differentiation between these subgroups [9]. The most recent studies have proposed the use of additional factors such as PTEN, KRAS and β-catenin to differentiate between the tumour entities [13–15].

Patients with primary EC and OC have a better prognosis than patients with primary OC [8]. The outcome of these patients is also better compared to patients with advanced EC and ovarian metastasis [16]. It is therefore clinically relevant to know whether patients have EC with simultaneous OC or EC with ovarian metastasis [17].

The aim of our study was to investigate the rate of secondary cancers in patients with EC. In particular, we wanted to describe the subset of patients with simultaneous EC and ovarian carcinoma in more detail, including their oncological outcome. The study also aimed to compare patients with EC and ovarian metastasis and patients with simultaneous EC and OC. An overview of the current literature on this topic is given below.

Patients and Method

Retrospective analysis was done of all patients with primary EC who underwent surgery in the years 2005–2009 at the Department of Obstetrics and Gynaecology, University of Tübingen.

All patients with a histological diagnosis of EC were included in our study. The study also investigated any history of secondary carcinoma or diagnosis of secondary carcinoma found during treatment for EC.

The following characteristics were recorded and analysed for all patients: age at primary diagnosis of EC, initial FIGO stage, infiltration of the myometrium, tumour grade, lymph node status, intraoperative cytology, number and localisation of distant intraabdominal metasases, and recurrence or date of death.

All patients underwent surgery based on their tumour stage with hysterectomy, bilateral salpingo-oophorectomy and pelvic and paraaortal lymphadenectomy. Patients with advanced EC or simultaneous OC additionally had omentectomy with multiple peritoneal biopsies and appendectomy, where necessary.

Postoperatively all patients were discussed in an interdisciplinary tumour conference. Depending on the tumour stage, surgery was followed by brachytherapy and/or teletherapy or chemotherapy. All patients were regularly followed up at the clinic or by their gynaecologist.

Statistical analysis was done using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Patient population

The data of 251 patients with primary EC who underwent surgery, depending on tumour stage, in the years 2005–2009 at the Department of Obstetrics and Gynaecology, University of Tübingen, were retrospectively analysed. Patient and tumour characteristics are given in **Table 1**.

Secondary carcinoma

A total of 28 patients (11.1%) had secondary cancer in addition to EC: 18 patients (7.1%) had OC, 9 patients (3.5%) had a history of breast cancer and one patient (0.4%) respectively had simultaneous vulva or bladder cancer. The patient with bladder cancer had an additional history of breast cancer. The data of these 28 patients including information on their tumours and outcomes is summarised in **Table 2**.

Comparison of EC with ovarian metastasis and EC with OC

Out of a total of 251 patients, 14 patients (5.5%) had advanced EC with ovarian metastasis or, in one case, metastasis to the ovarian tube. These patients were compared with the 18 patients with simultaneous OC. Patients with advanced EC but without ovarian metastasis (e.g. only peritoneal metastasis or distant metastases, i.e. stage T3b or T4) were not included in the comparison. At primary diagnosis patients with ovarian metastases were significantly older (mean age 71.2 ± 9.2 years) than patients with EC and simultaneous OC (55.3 ± 11.8 years, $p < 0.001$). Moreover, patients with ovarian metastasis significantly more often had higher grade EC (grade 1: 0, grade 2: 21.4%, grade 3: 78.6%) than patients with simultaneous EC and OC (grade 1: 11.1%, grade 2: 77.8%, grade 3: 11.1%; $p < 0.001$). The data of these two subsets including myometrial infiltration, lymph node involvement, cytology, histology findings, and oncological outcome is summarised in **Table 3**.

Table 1 Patient characteristics (EC = endometrial carcinoma).

Parameter	Value
Number of patients with EC (total)	251
Age at first diagnosis of EC (years)	62.3 ± 11.8
Number of patients with secondary cancer (total)	29
Ovary	18
Breast	9
Vulva	1
Bladder	1
Tumour stage	
I	208 (83.8%)
II	14 (5.6%)
III	23 (9.3%)
IV	3 (1.2%)
Infiltration of the myometrium	
None	37 (14.7%)
< 50%	138 (55.0%)
> 50%	61 (24.3%)
Serosal involvement	7 (2.8%)
Unknown	8 (3.2%)
Tumour grade	
1	44 (17.5%)
2	159 (63.3%)
3	48 (19.1%)
Cytology	
Negative	91.7%
Positive	8.3%
Histotype	
Endometrioid	203 (80.9%)
Non-endometrioid	48 (19.1%)
▸ papillary	9
▸ tubal	8
▸ serous	6
▸ tubulopapillary	3
▸ adenosquamous	3
▸ eccrine	3
▸ clear cell	1
▸ squamous epithelial carcinoma	1
▸ adenocarcinoma without further specifications	14
Follow-up (months)	20.4 ± 14.7 (range 0–50)
Outcome	
▸ alive	210
▸ recurrence	16
▸ died	25

Discussion

Our patient population consisted of a total of 251 patients with EC, of which 18 patients had simultaneous OC and 14 patients had EC with ovarian metastasis. We thus investigated a relatively large patient population; most comparable studies had similarly large populations or patient populations of up to 100 patients [5, 6, 9, 16].

The mean age of all EC patients in our patient population was 62.3 years. Patients in our population with EC which had metastasised to the ovary were significantly younger with a mean age of 55.3 years compared to patients with primary EC and OC (mean age 71.2 years). Nishimura et al. reported similar findings with a significant difference in age between the two groups: patients with simultaneous EC and OC were significantly younger (45.2 vs. 51.2 years). It should be noted, however, that overall the patients in their study were younger than our patient population [16]. The mean age of patients with simultaneous EC and OC or EC with ovarian metastasis without differentiating between the two groups is generally reported to be 49–51 years [6, 7, 9]. 51% of patients with simultaneous EC and OC were premenopausal and 33% were nulliparous [6].

Almost 81% of patients in our total patient population had an endometrioid EC. When we examined patients with simultaneous EC and OC, the numbers for patients with endometrioid carcinoma were similar (77.8%). In the prospective study by Zaino et al., the numbers of patients (86%) with endometrioid carcinoma of the endometrium and ovary were similar to those in our study [7]. However, some studies have reported lower rates. Soliman et al. reported that only 68% of patients with either EC or OC had an endometrioid histology [6]. The rate reported by Williams et al. was even lower: in patients with simultaneous EC and OC, only 59.6% of EC and 58.1% of OC were endometrioid carcinomas [8]. The importance aspect of this study is that it evaluated the data of a total of 56 986 patients. The rate of endometrioid carcinomas in patients with only OC (= single ovarian cancer) was significantly lower with 10.6% [8].

When we studied our patients with EC and ovarian metastasis, only 64.3% had an endometrioid carcinoma. This difference was not significant compared to patients with simultaneous EC and

Table 2 Details of patients with endometrial carcinoma *and* known secondary carcinoma (EC = endometrial carcinoma, – = negative, + = positive, x = unknown).

Patient	Age (years)	Histotype EC	Grade	Myometrial infiltration	Lymph node involvement	Cytology	Secondary carcinoma	Follow-up (months)	Outcome
1	71	endometrioid adenocarcinoma	2	< 50%	–	–	breast	49	alive
2	51	tubal adenocarcinoma	2	< 50%	–	–	breast	45	alive
3	59	tubal adenocarcinoma	2	< 50%	–	–	ovary	43	alive
4	57	endometrioid adenocarcinoma	2	< 50%	–	–	ovary	43	alive
5	64	endometrioid adenocarcinoma	2	< 50%	–	–	breast	43	alive
6	63	tubal adenocarcinoma	2	< 50%	x	+	ovary	4	died
7	46	tubal adenocarcinoma	2	> 50%	–	–	ovary	41	alive
8	53	endometrioid adenocarcinoma	2	< 50%	–	+	ovary	39	alive
9	44	endometrioid adenocarcinoma	2	< 50%	x	+	ovary	37	recurrence
10	64	endometrioid adenocarcinoma	2	> 50%	–	–	vulva	36	died
11	59	endometrioid adenocarcinoma	2	serosa Involvement	x	+	ovary	1	alive
12	85	endometrioid adenocarcinoma	3	> 50%	x	x	ovary	0	alive
13	65	papillary adenocarcinoma	2	< 50%	–	x	breast	29	recurrence
14	63	endometrioid adenocarcinoma	2	< 50%	–	–	breast	27	alive
15	38	endometrioid adenocarcinoma	2	< 50%	+	x	ovary	0	alive
16	63	endometrioid adenocarcinoma	2	none	+	+	ovary	26	died
17	44	endometrioid adenocarcinoma	2	< 50%	–	–	ovary	24	alive
18	55	endometrioid adenocarcinoma	2	< 50%	–	–	breast	24	recurrence
19	57	endometrioid adenocarcinoma	1	none	–	–	ovary	22	alive
20	52	endometrioid adenocarcinoma	2	< 50%	–	+	ovary	20	alive
21	71	tubal adenocarcinoma	2	> 50%	x	–	ovary	1	died
22	52	endometrioid adenocarcinoma	2	> 50%	–	–	ovary	16	alive
23	67	endometrioid adenocarcinoma	3	< 50%	–	+	ovary	14	alive
24	42	endometrioid adenocarcinoma	2	none	–	–	ovary	14	alive
25	77	endometrioid adenocarcinoma	3	> 50%	+	+	breast	9	alive
26	65	endometrioid adenocarcinoma	1	< 50%	–	–	breast	7	alive
27	45	endometrioid adenocarcinoma	1	< 50%	–	–	ovary	7	alive
28	74	endometrioid adenocarcinoma	3	x	x	x	breast + bladder	6	recurrence

OC but it is worth considering whether this was the reason for the somewhat poorer prognosis for this subgroup in our study. Chiang et al. reported similar findings. In their study, the mean survival time for patients with the same histology (n = 15) was 63 months compared to 48 months for patients with differing histological findings (n = 12) [5]. Soliman et al. could even show that patients with a concordant endometrioid histology had a significantly better prognosis: patients with a concordant endometrioid histology had a mean survival time of 119 months, which was significantly higher than that for all other groups [6].

The most recent investigations into the pathogenesis of ovarian carcinoma indicate that these tumours originate in the tubal fimbria [18]. An early carcinoma was found in approx. 5% of adnexa investigated after resection for prophylactic reasons in women with BRCA1 or BRCA2 mutation, and 80% of these originated in the fimbria as serous tubal intraepithelial carcinoma [19]. It is not clear whether serous ovarian or peritoneal carcinomas without proven BRCA mutation also have a tubal origin. Even if we assume that the carcinoma has originated in the tube we would like to note here, with regard to our study, that in our patient population the majority of patients had an endometrioid carcinoma, both the group of patients with ovarian metastasis and the group with ovarian carcinoma.

Tumour grade is another important prognostic parameter [20]. In our study, patients with an EC which had metastasised to the ovary had a significantly higher tumour grade than patients with simultaneous EC and OC.

The majority of our patients (77%) with simultaneous EC and OC had a grade 2 tumour; only 11% had a grade 3 or grade 1 EC tumour. Zaino et al. reported that 51% of EC and OC tumours in their patient population were grade 1 [7]. However, other studies have described lower rates of grade 1 tumours; thus, in another retrospective study of 29 patients also by Zaino et al., they reported a rate of only 30% [21], and Eifel et al. described a rate of 56% [22].

When we studied our patients with EC and ovarian metastasis, 78.6% of patients had a grade 3 EC tumour and only 21.4% had a grade 2 tumour; there were no patients with a grade 1 tumour. This significantly higher rate of higher grade tumours (G2 and G3) could also be responsible for the higher rates of recurrence and death for this subgroup (**Table 3**). Similar to our findings, Zaino et al. described an increased risk of recurrence for patients with grade 2 or grade 3 tumours compared to grade 1 tumours [7]. Patients with a grade 1 tumour in both the endometrium and the ovary had a significantly lower 5-year rate of recurrence compared to patients with at least one tumour above grade 1 (8 vs. 22.4%) [7].

The rate of recurrence also depends on the extent of myometrial infiltration. 77% of patients with deep myometrial infiltration had recurrence or died [7]. In our patient population, 72.3% patients with simultaneous EC and OC either had no myometrial infiltration or the myometrial infiltration was < 50%. In the literature some authors report that up to 100% of patients had no myometrial infiltration or infiltration of < 50% [23, 24]. As expected, patients with advanced EC and ovarian metastasis are more likely to have deeper myometrial infiltration. In our patient population, 21.4% of these patients even had serosal involvement. The results of Nishimura et al. were similar to ours. Here too, the two subgroups did not differ significantly with regard to myometrial infiltration; however, it was very noticeable that patients with an EC which had metastasised to the ovary were more likely to have myometrial infiltration > 50% compared to patients with simultaneous EC and OC (48 vs. 0%) [16].

All of the criteria described above such as histological type, tumour grade, extent of myometrial infiltration and thus tumour stage are relevant for patients with simultaneous EC and OC and for patients with EC and ovarian metastasis [5]. Patients with disease limited to the uterus and the ovaries had a 5-year recurrence rate of 10% compared to 27% for patients who already had metastasis at the time of surgery [7].

It is notable that most studies reported a relatively good prognosis for patients with simultaneous EC and OC compared to patients with EC and ovarian metastasis. In what is to our knowledge currently still the only prospective investigation by Zaino et al., patients with simultaneous EC and OC had a 5-year survival rate of 85.9% and a 10-year survival rate of 80.3% [7]. Nishimura et al. reported similar survival rates. The 10-year survival rate for patients with simultaneous EC and OC was significantly better than that for the group of patients with metastasis (90.9 vs. 46.6%) [16]. In our patient population, 77.7% of patients with simultaneous EC and OC also had no recurrence, while only 42.8% of patients with EC and ovarian metastasis had no recurrence.

In summary, we could show that almost one in 10 patients with an EC had a secondary carcinoma. The most common secondary carcinoma was an OC, followed by breast cancer. This should be taken into account in the diagnosis and therapy of patients with EC. Patients with simultaneous EC and OC were significantly younger than patients with an EC and ovarian metastasis. Their tumours also had significantly better prognostic features; thus, the tumour grades for EC were significantly lower. Overall, the

Table 3 Comparison of patients with endometrial carcinoma and ovarian metastasis vs. endometrial carcinoma with simultaneous ovarian carcinoma (mean ± standard deviation).

Parameter	Ovarian metastasis	Simultaneous ovarian cancer	P
Total number of patients	14	18	
Age at primary diagnosis (years)	71.2 ± 9.2	55.3 ± 11.8	**< 0.001**
Myometrial infiltration			n. s.
▸ none	3 (21.4%)	3 (16.7%)	
▸ < 50%	4 (28.6%)	10 (55.6%)	
▸ > 50%	3 (21.4%)	4 (22.2%)	
▸ serosal involvement	3 (21.4%)	1 (5.6%)	
▸ unknown	1 (7.1%)	0	
Tumour grade			**< 0.001**
▸ 1	0	2 (11.1%)	
▸ 2	3 (21.4%)	14 (77.8%)	
▸ 3	11 (78.6%)	2 (11.1%)	
Lymph node involvement			n. s.
▸ negative	8 (57.1%)	11 (61.1%)	
▸ positive	6 (42.9%)	2 (11.1%)	
▸ unknown	0	5 (27.8%)	
Cytology			n. s.
▸ negative	7 (50%)	9 (50%)	
▸ positive	5 (35.7%)	7 (38.9%)	
▸ unknown	2 (14.3%)	2 (11.1%)	
Histotype			n. s.
▸ endometrioid adenocarcinoma	9 (64.3%)	14 (77.8%)	
▸ tubal adenocarcinoma	–	4 (22.2%)	
▸ eccrine adenocarcinoma	3 (21.4%)	–	
▸ serous adenocarcinoma	2 (14.3%)	–	
Follow-up (months)	13.4 ± 16.2 (range 0–50)	19.5 ± 15.7 (range 0–43)	n. s.
Outcome			n. s.
▸ alive	6 (42.8%)	14 (77.7%)	
▸ recurrence	2 (14.3%)	1 (5.5%)	
▸ died	6 (42.8%)	3 (16.6%)	

prognosis for patients with simultaneous EC and OC was significantly better than that for patients with EC and ovarian metastasis.

Conclusion

Almost one in ten patients with an endometrial carcinoma (EC) had a secondary carcinoma. The most common secondary carcinoma was ovarian carcinoma (OC), followed by breast cancer. This needs to be taken into account in the diagnosis and therapy of patients with EC. Patients with simultaneous EC and OC have a significantly better prognosis than patients with advanced EC and ovarian metastasis.

Conflict of Interest

The authors declare that they have no financial relationship with any company relevant for this article.

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