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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Adjuvant treatment decisions for patients with endometrial cancer in Germany: results of the nationwide AGO pattern of care studies from the years 2013, 2009 and 2006

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Abstract
Purpose In 2013, 2009 and 2006, the Arbeitsgemeinschaft Gynäkologische Onkologie evaluated the therapeutic approaches for endometrial carcinoma and the adherence to their guideline in Germany. Here, the adjuvant treatment decisions were presented.
Methods A questionnaire was developed and sent to all 682 German gynecological departments in 2013 (775 in 2009 and 500 in 2006, respectively). The results of the questionnaires were compared with the recommendations of the guideline and with each other using Fisher's exact test.
Results Responses were available in 40.0 % in 2013, 33.3 % in 2009 and 35.8 % in 2006. Participants recommended external beam radiotherapy (EBRT) in 13 out of 16 requested stages and vaginal brachytherapy (VBT) in only 10 out of 16 requested stages as suggested by the guideline. Comparing the results of 2013 with 2009, less participants used EBRT and VBT in 7 out of 16 and in 6 out of 16 requested stages, respectively. Conversely, more participants offered adjuvant chemotherapy (CT) in 2013 (90.4 %) compared to 61.9 % in 2009 ($p < 0.001$) and 48.8 % in 2006 ($p < 0.001$), respectively. However, the stage-adjusted recommendations of CT were not in line with the guideline in 11 out of 15 requested stages. In total, 77.3 % of the participants use a multiple drug schedule with a platinum and a taxane compound.
Conclusions The results suggest non-adherence to the guideline concerning the stage-adjusted use of VBT and CT in endometrial carcinoma. These findings emphasize great uncertainties and the need of more clarifying trials. Furthermore, a shift from radiotherapy toward CT is observable.

Keywords Endometrial cancer · Pattern of care · Radiotherapy · Chemotherapy · Guideline

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Introduction

Endometrial carcinoma (EC) has the most favorable prognosis among gynecological malignancies; thus, treatment-related morbidity should be minimized (Robert Koch Institut 2010). However, a distinct portion of patients develops distant metastasis and is faced with low survival rates (Robert Koch Institut 2010). These patients have to be identified by correct surgical staging and require effective adjuvant treatment (AGO 2006, 2013; Emons and Kimmig 2008).

Adjuvant radiotherapy (RT) improves local control, but does not alter the development of distant metastasis or improve cancer specific or overall survival (Blake et al. 2009; Kong et al. 2012). However, various recommendations concerning indications and types of RT are given by several societies (AGO 2013; Koh et al. 2014). Conversely, adjuvant chemotherapy (CT) reduces the risk of metastasis and improves survival according to a meta-analysis driven by the Cochrane Collaboration in 2011 (Johnson et al. 2011). However, stage-adjusted recommendations are difficult to give as the results of the available trials are hampered by several conflicting factors like correct surgical staging of the included patients, broad inclusion criteria in terms of extent of disease, improper statistical analyses and different chemotherapeutical regimens within one trial (Morrow et al. 1990; Randall et al. 2006; Maggi et al. 2006; Susumu et al. 2008; Kuoppala et al. 2008; Hogberg et al. 2010; Johnson et al. 2011). Finally, the disease committee of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) has established a guideline for the management of patients with EC in Germany, which is reviewed at regular intervals (AGO 2006, 2013; Emons and Kimmig 2008).

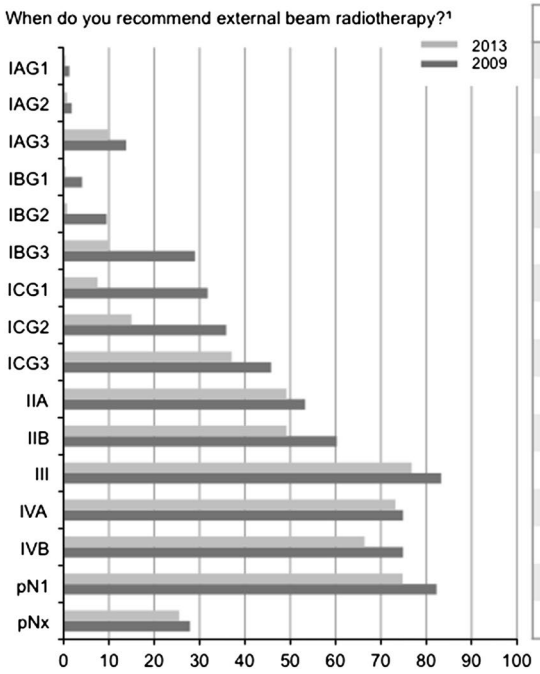
We already explored the patterns of care being delivered to German patients with EC in 2006 and 2009 and compared them with the recommendations of this guideline (Battista et al. 2013). This survey has underlined great uncertainties regarding the adjuvant treatment of EC patients (Battista et al. 2013). Therefore, we re-evaluated the current patterns of care being delivered to patients with EC using a questionnaire addressing German hospitals in November 2013. Here, we present the result concerning the adjuvant treatment decisions, whereas the results concerning the surgical procedures have been reported elsewhere (Battista et al. 2014).

Materials and methods

A questionnaire was created in order to explore the common diagnostic and therapeutic approaches in 2006 and was modified for the following surveys in 2009 and 2013. Here, we report the results of five multiple-choice questions dealing with the adjuvant treatment decisions for EC (see "Appendix"). The questions 4 and 5 were included in the 2013 survey, and the questions 1 and 2 were modified in the 2013 and 2009 survey. The questionnaire was sent to all German gynecological departments in November 2013, in August 2009 and in March 2006. A list of the addresses was provided by the German Society of Gynecology and Obstetrics (DGGG, Deutsche Gesellschaft für Gynäkologie und Geburtshilfe). A data extraction form was compiled before reviewing the questionnaires. A questionnaire was excluded from the whole analysis, if no question concerning the treatment decisions was answered. If a single question was not answered, the questionnaire was excluded from the analysis of the single question. Thereby, the reported percentages reflect the portion of participants, who answered the question and not who participated at the survey.

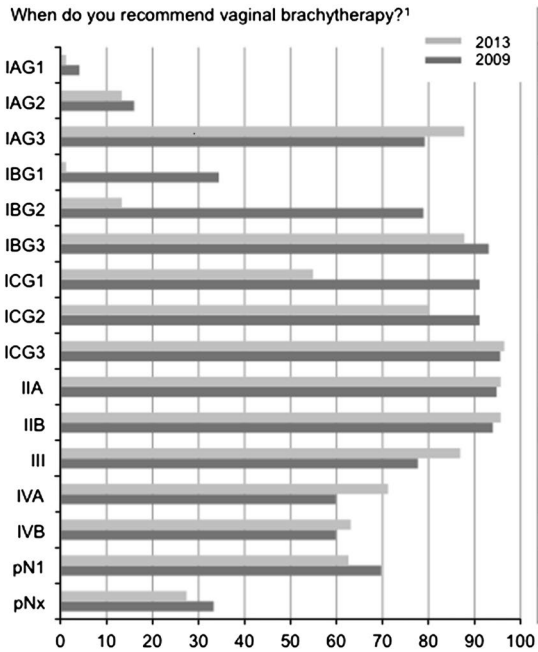
In a first step, we compared the results of the questionnaire with the recommendations of the guideline as previously described (Battista et al. 2013, 2014). Briefly, we defined a procedure as performed according to the guideline if it was performed by more than 90 % of the interviewed colleagues. Conversely, we defined a procedure as not performed according to the guideline, if it was conducted by <10 % of the participants. In cases of facultative recommended procedures, we defined the procedure as performed according to the guideline, if it was conducted by 10–90 % of the participants. The guideline from 2013 specified the recommendations concerning RT when compared with the recommendations from 2008 and 2006 (see Figs. 1, 2) (AGO 2006, 2013; Emons and Kimmig 2008). Briefly, vaginal brachytherapy (VBT) was recommended in an endometrioid EC presenting in stage FIGO IA G3 and stage FIGO IB G1 or G2, but not in stage FIGO IA G1 or G2 (AGO 2013). In endometrioid, EC presenting in stage FIGO IB G3 and stage FIGO II external beam radiotherapy (EBRT) might be added to VBT (AGO 2013). In stage FIGO III, EBRT should be used and might be combined with VBT (AGO 2013). In stage FIGO IV, EBRT might be used (AGO 2013). The revision of AGO's guideline from 2013 recommended CT in FIGO stage IB G3 and in FIGO stages II up to IV (see Table 1; AGO 2013). Thereby, AGO strengthened the recommendation for CT in stage FIGO IB G3, and stage FIGO II in comparison with the previous versions from 2011 and 2009 (AGO 2006, 2013; Emons and Kimmig 2008). In 2013, AGO specified the choice of cytostatic drugs in an adjuvant setting for the first time and recommended a multiple drug schedule with a platinum compound and paclitaxel (AGO 2013) (Table 2).

In the second step, we compared the results of the 2013, 2009 and 2006 questionnaires, in order to describe potential changes in the treatment behavior during this time period. The revised FIGO classification from 2010 was used in the current questionnaire (Creasman 2009). Obviously, the former edition of the FIGO classification was used in the questionnaires from 2009 and 2006. The results from 2013 were transformed in the former FIGO classification, in order to make the results comparable and to report on changes of treatment behavior. We compared the results of the questionnaires using Fisher's exact Test. As no statistical corrections for multiple testing were performed, all p values are descriptive measures. SPSS 21 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses.



Stage	AGO[2]	2013	2009	p-value
IA G1	-	0.4	1.3	
IA G2	-	0.8	1.8	
IA G3	-	9.9	13.8	
IB G1	-	0.4	4.1	0.007
IB G2	-	0.8	9.5	<0.001
IB G3	-	9.9	29.0	<0.001
IC G1	-	7.5	31.8	<0.001
IC G2	-	15.0	35.9	<0.001
IC G3	+/-	37.1	45.8	
IIA	+/-	49.2	53.3	
IIB	+/-	49.2	60.3	0.020
III	+	76.8	83.3	
IVA	+/-	73.2	74.9	
IVB	+/-	66.4	74.9	0.050
pN1	+	74.8	82.3	
pNx	+/-	25.5	27.9	

Fig. 1 Result of question 1: In which stage of an endometrioid endometrial carcinoma do you recommend the external beam radiotherapy? [1]The former FIGO classification from 1988 is used for all results, even if in 2009 a revised FIGO classification was published. [2]+ a positive recommendation by the AGO, − a negative recommendation and ± a facultative recommendation. *AGO* Arbeitsgemeinschaft Gynäkologische Onkologie. *FIGO* International Federation of Gynecology and Obstetrics



Stage	AGO[2]	2013	2009	p-value
IA G1	-	1.2	4.1	0.049
IA G2	-	13.3	16.0	
IA G3	+	87.8	79.2	0.011
IB G1	-	1.2	34.4	<0.001
IB G2	-	13.3	78.9	<0.001
IB G3	+	87.8	93.1	0.048
IC G1	+	54.9	91.1	<0.001
IC G2	+	80.1	91.1	<0.001
IC G3	+	96.5	95.6	
IIA	+	95.7	94.8	
IIB	+	95.7	94.0	
III	+/-	86.9	77.7	0.009
IVA	+/-	71.2	59.8	0.009
IVB	+/-	63.1	59.8	
pN1	+/-	62.7	69.7	
pNx	+/-	27.4	33.3	

Fig. 2 Result of question 2: In which stage of an endometrioid endometrial carcinoma do you recommend the radiotherapy of the vaginal vault? [1]The former FIGO classification from 1988 is used for all results, even if in 2009 a revised FIGO classification was published. [2]+ a positive recommendation by the AGO, − a negative recommendation and ± a facultative recommendation. *AGO* Arbeitsgemeinschaft Gynäkologische Onkologie. *FIGO* International Federation of Gynecology and Obstetrics

Results

In 2013, 273 out of 682 (40.0 %), in 2009, 258 out of 775 (33.3 %) and in 2006, 179 out of 500 (35.8 %) hospitals answered the questionnaire, respectively. Characteristics of the participating centers are summarized in Table 3. One questionnaire was excluded from the 2006 analysis as no question was answered.

The interviewed colleagues recommended EBRT in 13 out of 16 stages in accordance with the guideline (see Fig. 1): <10 % of the participants recommended it in 7 out of 8 stages, in which EBRT should not be performed. In total, 37.1–73.2 % of the participants recommended EBRT in the stages, in which EBRT is a possible treatment option. In the two stages (FIGO III and lymph node positive disease), in which EBRT should be performed, <90 % of the participants (76.8 and 74.8 %, respectively) recommended EBRT and therefore show non-adherence to the guideline. In comparison with the results of 2009, statistically significant less interviewed colleagues recommended the EBRT

Table 1 Results of the question no. 4: In which of the following cases do you offer chemotherapy?

	AGO	%
Endometrioid type		
Never	−	12.2
FIGO IA G3	−	4.9
FIGO IB G1	−	0.4
FIGO IB G3	+	28.1
FIGO II G1	+	13.9
FIGO II G3	+	42.2
FIGO III/IVA	+	65.8
N+	+	55.4
Always	−	1.2
Serous-papillary type		
FIGO IA	+	46.8
FIGO IB	+	67.1
FIGO II	+	79.4
FIGO III/IVA	+	90.1
N+	+	89.8
Always	+	51.1

+ a positive recommendation by the AGO, − a negative recommendation

AGO Arbeitsgemeinschaft Gynäkologische Onkologie, *FIGO* International Federation of Gynecology and Obstetrics

Table 2 Results of the question no. 5: Which chemotherapy do you use in an adjuvant setting?

	N (%)
Multiple drug CT with platinum compound and taxane compound	211 (77.3)
Multiple drug CT with platinum compound and without taxane compound	44 (16.1)
Multiple drug CT without platinum	4 (1.5)
Single drug CT with platinum	57 (20.9)
Single drug CT with anthracycline	12 (4.4)
Single drug CT with taxane	10 (3.7)
Single drug CT with another agend	6 (2.2)

Multiple answers possible

CT chemotherapy

in 7 out of 16 requested stages. In the remaining nine stages, the recommendation of the participants remained largely unchanged (see Fig. 1).

The interviewed colleagues recommended VBT in 10 out of 16 stages in accordance with the AGO guideline (see Fig. 2): It was recommended by more than 90 % of the participants in 3 out of 7 requested stages, in which this procedure should be performed. It was recommended by <10% of the participants in 2 out of 4 requested stages, in which the procedure should not be performed. The range of participants, who recommended VBT, was between 63.1 and 86.9 % in 5 out of 5 stages, in which VBT is a facultative recommended procedure. Comparing the results of 2013 with 2009, it became apparent that VBT was recommended less often in six stages and more often in three stages. In the remaining seven stages, the recommendations remained largely unchanged (see Fig. 2).

In 2013, 90.4 % of the interviewed colleagues offered adjuvant CT irrespectively of tumor stage or other risk factors as compared to 63.7 % in 2009 ($p < 0.001$) and 48.8 % in 2006 ($p < 0.001$), respectively. Conversely, the interviewed colleagues recommended CT in accordance with the guideline in 4 out of 15 requested stages in 2013 (see Table 1): 1.2 % of the participants recommended CT in all stages of an endometrioid EC. CT was recommended by less than the pre-defined 10 % of the participants in 2 out of 2 stages, in which a CT should not be performed (FIGO IA G3 and FIGO IB G1). CT recommended by more than the pre-defined 90 % of the interviewed colleagues in 1 (FIGO III/IV in serous-papillary EC) out of 11 requested stages, in which CT should be performed.

A multiple drug schedule with a platinum compound and a taxane compound was used by 77.3 % of the interviewed colleagues, followed by a single drug schedule with a platinum compound, which was used by 20.9 % of the participants (see Table 2).

Discussion

The here presented results show great diversities and non-adherence to the guideline regarding the stage-adjusted indication of CT and VBT in 2013. Conversely, the recommendations for EBRT and the choice of a multiple CT regime with a platinum and a taxane compound were in accordance with the guideline. Moreover, the here presented results suggest a shift from RT toward CT in the adjuvant treatment of EC patients in Germany.

Comparing the results of the surveys of 2013 and 2009, EBRT is recommended less often in 7 out of 16 and VBT in 6 out of 16 requested stages. This may rely to the fact that a meta-analysis and a Cochrane Collaboration review were published between our next-to-last and last survey in 2010 and 2012, respectively (Blake et al. 2009; Kong et al. 2012). Nor these two analyses nor the four available randomized trials show that EBRT improves survival even if a reduction of local recurrences is achievable (Creutzberg et al. 2000; Keys et al. 2004; Blake et al. 2009; Kong et al. 2012; Sorbe et al. 2012). Conversely, adjuvant CT became more popular among our participants over time as in 2013 90.4 % offer CT irrespectively of tumor stage or other risk factors in contrast to 63.7 % in 2009 ($p < 0.001$) and

Table 3 Characteristics of the participating centers ($n = 273$)

	N (%)
Number of beds (mean ± SD)	46 ± 21.6
Number of patients (mean ± SD)	24 ± 12.7
Type of hospital ($n = 265$)	
University hospital	30 (11.3)
Teaching hospital	169 (63.8)
Any other	66 (24.9)
Participating members of AGO	83 (30.4)
Participating centers, with at least one gynecologic oncologists	226 (86.9)

SD standard deviation, *AGO* Arbeitsgemeinschaft Gynäkologische Onkologie

48.8 % in 2006 ($p < 0.001$). This increase might reflect the emerging literature culminating in the Cochrane Collaboration review in 2011 (Morrow et al. 1990; Randall et al. 2006; Maggi et al. 2006; Susumu et al. 2008; Kuoppala et al. 2008; Hogberg et al. 2010; Johnson et al. 2011). Moreover, an increasing awareness among the gynecological oncologists might exist to cope with the risk of developing distant metastasis instead of local recurrence (Maggi et al. 2006). This shift of adjuvant treatment from RT to CT may thereby represent a shift of paradigm in the adjuvant treatment of EC.

Beside the decrease of the application of EBRT and VBT, another finding of this survey is the great diversity of the stage-adjusted recommendations of VBT. This might rely to the paucity of prospective randomized trials because only two randomized trials are available (Sorbe et al. 2009; Nout et al. 2009; Nout et al. 2010). One trial does not show any benefit in terms of survival in early EC (Sorbe et al. 2009). According to the other trial, VBT is as effective as EBRT but less toxic and therefore considered as standard of care in patients with a certain risk of local recurrence (Nout et al. 2009, 2010). On the other side, patients with local recurrence have a high chance (67–92 %) to be controlled by radical RT (Ackermann et al. 1996; Hasbini et al. 2002). Moreover, they are expected to decease in only 15 % due to local progression but in 77 % due to distant metastases (Ackermann et al. 1996; Hasbini et al. 2002). Therefore, Ackermann and Hasbini, both radio-oncologists, raise the question whether patients of stage FIGO I disease should receive adjuvant RT at all or whether RT should be reserved for patients who really develop a pelvic recurrence (Ackermann et al. 1996; Hasbini et al. 2002). In conclusion, the paucity of available literature might explain the difficulties in selecting the patients for VBT and might explain the great uncertainties among the participants of our survey.

Another key finding is that the interviewed colleagues recommended CT in only 4 out of 15 requested stages as suggested by the guideline and thereby show great uncertainty. This might rely on the available randomized trials, which have been criticized because of their incorrect surgical staging, broad inclusion criteria in terms of extent of disease, improper statistical analyses and different chemotherapeutical regimens within one trial (Morrow et al. 1990; Randall et al. 2006; Maggi et al. 2006; Susumu et al. 2008; Kuoppala et al. 2008; Hogberg et al. 2010; Johnson et al. 2011). Thereby, Johnson et al. (2011) conclude in the Cochrane Collaboration review that the selection of patients remains difficult, even if CT reduces the risk of death by a quarter.

According to the Cochrane Collaboration review and the available randomized trials, the optimal combination of CT has not been yet determined for EC (Johnson et al. 2011). Cisplatin, combined with an anthracyclin and cyclophosphamide, has been examined in JGOG 2033, a GICOG trial and a Finnish trial (Maggi et al. 2006; Kuoppala et al. 2008; Susumu et al. 2008). Cisplatin and doxorubicin have been examined in GOG 122 (Randall et al. 2006). In the pooled analysis of three trials published by Hogberg et al. (2010), several different schedules have been allowed. GOG 34 examined doxorubicin mono (Morrow et al. 1990). According to the presented results of our survey, a platinum compound combined with a taxane compound was the schedule used most frequently in Germany in 2013. One might assume that most of the participants come back to carboplatin and paclitaxel as this is an effective, well examined and tolerated combination in the treatment of ovarian cancer patients. Furthermore, several phase two studies use this schedule in advance stage or relapsed EC demonstrating response rates of 65–75 % and a progression-free survival of around 14 months (Hoskins et al. 2001; Akram et al. 2005; Sorbe et al. 2008). For sure, the determination of the incitements to use this combination is beyond the scope of this survey and remains speculative.

Watanabe et al. conducted a comparable pattern of care study among the members of JGOG using a questionnaire in 2005 with 199 participants and achieved a high return rate of 88 % (published in 2009). Naumann and co-workers did the same among the members of SGO in 1999 and 2005 (Naumann et al. 1999; Naumann and Coleman 2007). In 1999 a return rate of 42 % and in 2005 of 29 % was achieved. In contrast to our study, the non-responders were remembered by a second mail to compile the questionnaire using a tracking number, whereas our colleagues answered the questionnaire anonymously (Naumann et al. 1999; Naumann and Coleman 2007). Conclusively, our return rates of 40 % in 2013, 33.3 % in 2009 and 35.8 % in 2006 seem to be in an ordinary range. Comparing the results of these

studies to our present survey here, there is both, agreement and disagreement. Members of JGOG and our participants prefer the combination of a platinum and a taxane compound CT (Watanabe et al. 2009). Members of JGOG prefer adjuvant CT over RT; our participants increasingly use CT and refuse RT (Watanabe et al. 2009). Members of SGO prefer RT over CT, even if they decreasingly use RT (Naumann and Coleman 2007). Members of SGO and our participants prefer VBT over EBRT in early EC (Naumann and Coleman 2007). Among the members of JGOG, the lymphatic vascular infiltration is recognized as a risk factor but not the histological type, whereas our participants do the opposite (Watanabe et al. 2009). In 2007 Lee and co-workers and in 2011 Wright and co-workers performed pattern of care studies using more than 26.000 and more than 37.000 data sets out of the Surveillance, Epidemiology and End Results (SEER) database, respectively. Once again, the results of our survey are in parts comparable and in other parts not to the findings of these studies. EBRT is used more often for EC with higher stages or bad histological grade of differentiation in the two studies using the SEER database as well as in our survey (Lee et al. 2007; Wright et al. 2011). Moreover, the use of EBRT decreases over time in all surveys (Lee et al. 2007; Wright et al. 2011). In the study of Wright, the hazard ratio to receive VBT is 0.81 (0.70–0.94) in 1995–2000 and 1.40 (1.23–1.59) in 2001–2006 compared with 1988–1994 (2011). Our results suggest that VBT is recommended less often comparing 2013 with 2009. Unfortunately, data on the use of CT are not presented in the two surveys, which used the SEER database.

To the best of our knowledge, this is the first nationwide study analyzing patterns of care in more than 700 German hospitals over a time period of 7 years at three different time points. For sure, limitations inherent to questionnaire-based data must be recognized as a potential weakness of this study in contrast to clinical chart-based data or tumor registry-based data. However, the two last approaches may feature other limitations. German tumor registries, for example, do not provide information on the zytostatic drugs or which type of RT is used. Clinical chart-based data might be the most authentic source, but the effort might be exorbitant for the interviewed colleagues. Conclusively, a very low return rate and a selection bias might occur. Furthermore, one might assume that the provided list of German hospitals in 2006 was not complete as only 500 hospitals were mentioned in contrast to 775 hospitals in 2009. However, the difference of 775–682 hospitals in 2013 might be reasonable due to austerity program and a consecutive closing and pooling of German hospitals. Moreover, a certain limitation might result from the fact that it is not clear, who compiled the questionnaire in each center. Even if potential bias might occur as (1) less than a half of all German hospitals participated in all our three surveys and as (2) the answers of the colleagues might not be as realistic as data out of clinical charts or tumor registries, the advantage of a questionnaire might overbalance these problems as it allows to gather detailed information in a nationwide analysis of gynecologic departments.

In conclusion, our results suggest a shift from RT to CT in the adjuvant treatment of EC. However, the observed diversity concerning the stage-adjusted use of CT and VBT in Germany reflects the considerable uncertainty in this sector of gynecological oncology. Thus, randomized trials are urgently warranted to solve this problem.

Conflict of interest The authors declare that they have no conflicts of interests.

Appendix

1. In which stage of an endometrioid endometrial carcinoma do you recommend the external beam radiotherapy? (multiple answers possible).
   FIGO IA G1, FIGO IA G2, FIGO IA G3, FIGO IB G1, FIGO IB G2, FIGO IB G3, FIGO II, FIGO III, FIGO IVA, FIGO IVB, N+ , Nx.
2. In which stage of an endometrioid endometrial carcinoma do you recommend the radiotherapy of the vaginal vault? (multiple answers possible).
   FIGO IA G1, FIGO IA G2, FIGO IA G3, FIGO IB G1, FIGO IB G2, FIGO IB G3, FIGO II, FIGO III, FIGO IVA, FIGO IVB, N+ , Nx.
3. Do you offer chemotherapy in an adjuvant setting? Yes or No
4. In which of the following cases do you offer chemotherapy?

   I do not offer chemotherapy in an endometrioid EC. Yes or No
   I offer chemotherapy in a case with an endometrioid EC and a…
   … FIGO IA, G3. Yes or No
   … FIGO IB, G1. Yes or No
   … FIGO IB, G3. Yes or No
   … FIGO II, G1. Yes or No
   … FIGO II, G3. Yes or No
   … FIGO III/IVA. Yes or No
   … lymph node positive disease. Yes or No
   I offer chemotherapy in every endometrioid EC. Yes or No
   I offer chemotherapy in a serous-papillary EC and stage …
   ... FIGO IA. Yes or No
   … FIGO IB. Yes or No

… FIGO II. Yes or No
… FIGO III/IVA. Yes or No
… lymph node positive disease. Yes or No
I offer chemotherapy in every serous-papillary EC. Yes or No

5. Which chemotherapy do you use in an adjuvant setting? (multiple answers possible)

I use 6 courses of a …
… multiple drug chemotherapy with a platinum and a taxane compound. Yes or No
… multiple drug chemotherapy with a platinum compound without a taxane compound. Yes or No
… multiple drug chemotherapy without a platinum compound. Yes or No
… single drug chemotherapy with a platinum compound. Yes or No
… a single drug chemotherapy with an anthracycline compound. Yes or No
… a single drug chemotherapy with a taxane compound. Yes or No
… a single drug chemotherapy with another compound. Yes or No.

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