Percutaneous parametrial dose escalation in women with advanced cervical cancer: feasibility and efficacy in relation to long-term quality of life

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Background. We analyzed long-term quality of life (QoL) and prognostic factors for QoL as well as clinical outcome in patients with advanced cervical cancer (ACC) treated with primary radiochemotherapy (RChT) consisting of external beam radiotherapy (EBRT) with or without sequential or simultaneous integrated boost (SIB) to the parametria, intracavitary brachytherapy and concomitant chemotherapy (ChT).

Patients and methods. Eighty-three women were treated with primary RChT between 2008 and 2014. Survival of all patients was calculated and prognostic factors for survival were assessed in univariate and multivariate analysis. In 31 patients QoL was assessed in median 3 years (range 2–8 years) after treatment. QoL was compared to published normative data and the influence of age, tumour stage, treatment and observed acute toxicities was analyzed.

Results. Thirty-six patients (43.4%) died, 18 (21.7%) had a local recurrence and 24 (28.9%) had a distant progression. Parametrial boost (p = 0.027) and ChT (p = 0.041) were independent prognostic factors for overall survival in multivariate analysis. Specifically, a parametrical equivalent doses in 2-Gy fractions (EQD2) > 50 Gy was associated with improved overall survival (OS) (p = 0.020), but an EQD2 > 53 Gy did not further improve OS (p = 0.194). Tumour size was the only independent prognostic factor for local control (p = 0.034). Lymph node status (p = 0.038) and distant metastases other than in paraaortic lymph nodes (p = 0.002) were independent prognostic factors for distant progression-free survival. QoL was generally inferior to the reference population. Age only correlated with menopausal symptoms (p = 0.003). The degree of acute gastrointestinal (p = 0.038) and genitourinary (p = 0.041) toxicities correlated with the extent of chronic symptoms. Sexual/vaginal functioning was reduced in patients with larger tumours (p = 0.012). Parametrial EQD2 > 53 Gy correlated with reduced sexual/vaginal functioning (p = 0.009) and increased sexual worry (p = 0.009). Whether parametrial dose escalation was achieved by sequential boost or SIB, did not affect survival or QoL.

Conclusions. Primary RChT is an effective treatment, but long-term QoL is reduced. The degree of acute side effects of RChT correlates with the extent of chronic symptoms. Patients benefit from parametrical SIB or sequential boost, but an EQD2 > 53 Gy does not further improve survival and negatively affects QoL.

Key words: cervical cancer; parametrial boost; quality of life; radiotherapy
Introduction

Primary radiochemotherapy (RChT) with external beam radiotherapy (EBRT), intracavitary brachytherapy (ICBT), and concomitant chemotherapy (ChT) remains a frequently used treatment for advanced cervical cancer (ACC). However, local tumour control requires comparatively large doses, which in turn may lead to relevant treatment-related morbidity.\textsuperscript{1,2} In recent years, image guided adaptive brachytherapy (IGABT), based on magnetic resonance imaging (MRI) and combined interstitial / intracavitary brachytherapy (IBT/ICBT), has been successfully implemented as the new standard of care for local dose escalation and substantial reduction of therapy-related morbidity.\textsuperscript{3-5}

However, access to IGABT is limited at many brachytherapy facilities. Therefore, despite evidence of the inferiority of percutaneous boosting in terms of organ sparing and target coverage, another approach has been to combine ICBT with modern radiotherapy (RT) techniques, such as intensity-modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) to the parametria, for percutaneous local dose escalation.\textsuperscript{6,7} There is a low incidence of acute toxicities after SIB, but clinical outcome and QoL of these patients have not been investigated so far.\textsuperscript{7} Due to limited access to IGABT at many brachytherapy facilities and the unknown effects of SIB in terms of chronic morbidity, IMRT with sequential boost remains a widely used method for parametrial dose escalation. Given the comparatively young age of patients with cervical cancer and improving prognosis, long-term quality of life (QoL) and extent of chronic morbidity become increasingly important issues.

Therefore, we conducted this study to analyze feasibility and efficacy of a percutaneous parametrial boost in relation to long-term QoL as well as to assess tumour- and treatment-related prognostic factors for long-term QoL and outcome in women with ACC.

Patients and methods

Between 2008 and 2014, eighty-three women with ACC underwent primary treatment at our department. Patients' data were acquired from the institutional electronic patient charts and the institutional follow-up database. Median age at first diagnosis was 57 years (range 32–90 years; Table 1). Due to the substantially differing fractionation schedules, all reported doses were recalculated as equivalent doses in 2-Gy fractions with $\alpha/\beta = 10$ (EQD\textsubscript{2}}) for the tumour and $\alpha/\beta = 3$ (EQD\textsubscript{3}}) for the organs at risk (OARs). OAR doses were documented for volumes of 0.1 cm\textsuperscript{3} (D0.1cc), 1 cm\textsuperscript{3} (D1cc) and 2 cm\textsuperscript{3} (D2cc). They were calculated as the sum of the individual doses received from all brachytherapy fractions and the EBRT plan.\textsuperscript{8}

Survival was plotted according to Kaplan and Meier. Overall survival (OS) was defined as the time between first diagnosis and death. Local progression-free survival (LPFS) was defined as the time between first diagnosis and occurrence of any local progression. Since patients with distant metastases (cM1a and cM1c) at first diagnosis were in-
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Three years (median; range 2–8 years) after treatment, patients were approached during clinical follow-up examinations and asked to fill-in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer Patients 30 (QLQ-C30) and the Cervical Cancer Module (QLQ-CX24). Thirty-one women agreed to participate. The difference between patients’ QoL items scores and published German reference values was analyzed with the t-test (9). Possible prognostic factors for QoL (age, stage, tumour size, lymph node status, distant metastases status, histological grading, histology, RT techniques, applied RT doses, OAR doses, ChT, treatment duration, observed acute toxicities, anemia during RChT, number of transfusions during RChT) were investigated with an analysis of variances and the t-test. Age was used as a covariate. A p-value ≤0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS version 24.0.

This study was conducted in accordance with the declaration of Helsinki and was approved by the responsible independent ethics committee on 22 October 2012 (#S-513/2012). The requirement of informed consent was waived by the ethics committee, due to the retrospective nature of the study.

Results

Treatment and dose-volume histogram analysis

RT was conducted as EBRT (69.9% IMRT, 30.1% 3D-conformal RT), with or without sequential boost / SIB to parametria and involved pelvic / paraaortic lymph nodes (43.4% no boost, 37.3% sequential boost, 19.3% SIB), and high-dose-rate (HDR) ICBT boost (tandem and ring applicator). Median EBRT EQD2 to the whole pelvic (and paraaortic) planning target volume (PTV) was 44 Gy (range 35–51 Gy) and median parametrial EQD2 was 53 Gy (range 38–67 Gy). Including ICBT boost, as prescribed to point A, with a median EQD2 was 40 Gy (range 10–50 Gy), the median prescribed primary tumour EQD2 was 84 Gy (range 54–95 Gy). Seventy-one patients (85.5%) received con-
comitant ChT with 4–6 cycles of cisplatin 40 mg/m² weekly (Table 2).

Mean bladder D0.1cc, D1cc and D2cc were 130.2 Gy (± SD 31.7 Gy), 105.6 Gy (± SD 14.2 Gy) and 97.1 Gy (± SD 9.9 Gy), respectively. Mean sigmoid D0.1cc, D1cc and D2cc were 71.9 Gy (± SD 10.6 Gy), 64.1 Gy (± SD 7.9 Gy) and 61.1 Gy (± SD 6.9 Gy), respectively. Mean rectum D0.1cc, D1cc and D2cc were 89.8 Gy (± SD 23.1 Gy), 74.3 Gy (± SD 12.8 Gy) and 68.8 Gy (± SD 9.4 Gy), respectively.

**Survival analysis**

Thirty-six patients (43.4%) died, 18 (21.7%) had a local progression and 24 (28.9%) developed new distant metastases during follow-up. Calculated 3- / 5-year LPFS, DPFS and OS were 80.5% / 73.2%, 76.7% / 65.3% and 66.5% / 53.2%, respectively.

In univariate analysis (Table 3), Fédération Internationale de Gynécologie et d’Obstétrique (FIGO) stage (I/II vs. III/IV; p = 0.015), tumour size (T1/2 vs. T3/4; p = 0.036), parametrial boost (yes vs. no; p = 0.037), parametral dose (EQD210 < 50 Gy vs. > 50 Gy; p = 0.020 and EQD210 < 53 Gy vs. 53 Gy vs. > 53 Gy; p = 0.017), simultaneous ChT (yes vs. no; p = 0.004), total treatment duration (6–8 weeks vs. ≥ 9 weeks; p = 0.027), anemia during therapy (minimal hemoglobin < 10 g/dl vs. ≥ 10 g/dl; p = 0.039) and number of erythrocyte concentrate transfusions (≤ 2 vs. > 2; p = 0.007) were prognostic factors for OS. Histological grading showed a tendency towards statistical significance (G1/2 vs. G3; p = 0.053). Importantly, a percutaneous dose escalation in the parametria beyond an EQD210 of 53 Gy did not further improve survival (p = 0.194; Figure 1). For DPFS, only tumour size (T1/2 vs. T3/4; p = 0.034) was a prognostic factor. Lower FIGO stage (FIGO I/II vs. III/IV; p = 0.072) and conductance of a parametrial boost (yes vs. no; p = 0.095) showed a tendency towards improved LPFS. DPFS was prolonged in patients without lymph node metastases (N0 vs. N1; p = 0.038) and in patients without distant metastases other than in paraaortic lymph nodes (M0 vs. M1a vs. M1c; p = 0.002) as well as in patients with low or intermediate histological grading (G1/2 vs. G3; p = 0.037). In none of three endpoints we found any difference in outcome between patients receiving SIB or sequential boost.

In multivariate analysis (Table 3), parametrial boost (yes vs. no, HR 0.417 [95%CI 0.192–0.900], p = 0.027) and simultaneous ChT (yes vs. no, HR 0.382 [95%CI 0.152–0.961], p = 0.041) remained as independent prognostic factors for OS. Advanced tumour size was the only independent prognostic factor for LPFS (T3/4 vs. T1/2, HR 2.668 [95%CI 1.032–6.896], p = 0.043). Regarding freedom from distant progression (DPFS), presence of pelvic lymph node metastases (N1 vs. N0, HR 4.383 [95%CI 1.003–19.154], p = 0.05) as well as distant metastases other than in the paraaortic lymph nodes at initial diagnosis (M1c vs. M0/M1a, HR 4.646 [95%CI 1.466–14.719], p = 0.009) were independent prognostic factors.

**Quality of life analysis**

We found the values of the functioning and symptoms scores in our cohort to be significantly worse in comparison those from the normative population (Table 4). Generally, age must be considered when looking at quality of life and we used age as a covariate for our analyses, however age only correlated with menopausal symptoms (p = 0.003) in our analysis and did not affect global health status or any of the other functioning or symptom items scores from the QLQ-C30 or QLQ-CX24 questionnaires in our cohort.

The doses to bladder, sigmoid and rectum did not correlate with any of the QoL item scores. However, we found a statistically significant correlation between the degree of observed acute gastrointestinal (GI) and genitourinary (GU) toxicities with chronic symptom experience (p = 0.038 and p = 0.041), which can be considered an indicator for the known dose-volume dependence of...
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Chronic morbidity. Patients with higher degree of observed acute GI toxicity also complained more about chronic diarrhea (p = 0.053). Since most of our patients underwent IMRT and all of them received HDR ICBT, we found no difference in QoL between RT techniques. Importantly, we could show, that a parametrial EQD210 > 53 Gy statistically significantly correlated with reduced sexual/vaginal functioning (p = 0.009) and increased sexual worry (p = 0.009). Additionally, these patients also suffered more from chronic constipation (p =

### TABLE 3. Prognostic factors for survival

| OS | Univariate analysis (log-rank test) | Mean (months) | p-value |
|----|------------------------------------|---------------|---------|
|    |                                    |               |         |
| FIGO stage | | | |
| FIGO I/II | | 72.6 | 0.015 |
| FIGO III/IV | | 50.8 | |
| Tumour size | | | |
| T1/2 | | 69.2 | 0.036 |
| T3/4 | | 50.4 | |
| Grading | | | |
| G1/2 | | 72.4 | 0.053 |
| G3 | | 50.5 | |
| Parametrial boost | | | |
| yes | | 69.9 | 0.037 |
| no | | 51.2 | |

| Parametrial dose in EQD2 (α/β = 10) | | | |
| ≤ 50 Gy | | 50.7 | 0.020 |
| > 50 Gy | | 71.5 | |
| ≤ 53 Gy | | 59.5 | 0.194 |
| > 53 Gy | | 64.1 | |
| Chemotherapy | | | |
| yes | | 67.4 | 0.004 |
| no | | 32.1 | |
| Total treatment duration | | | |
| 6–8 weeks | | 71.6 | 0.027 |
| ≥ 9 weeks | | 44.7 | |
| Anemia during therapy | | | |
| min. Hb < 10 g/dl | | 52.1 | 0.039 |
| min. Hb ≥ 10 g/dl | | 70.3 | |
| Transfusions | | | |
| ≤ 2 ECs | | 67.6 | 0.007 |
| > 2 ECs | | 41.6 | |

| LPFS | Mean (months) | p-value |
|------|---------------|---------|
| FIGO stage | | | |
| FIGO I/II | | 85.9 | 0.072 |
| FIGO III/IV | | 66.7 | |
| Tumour size | | | |
| T1/2 | | 85.7 | 0.034 |
| T3/4 | | 64.1 | |
| Parametrial boost | | | |
| yes | | 84.1 | 0.095 |
| no | | 56.1 | |

### DFPS

| Mean (months) | p-value |
|----------------|---------|
| Lymph node status | | |
| N0 | 85.6 | 0.038 |
| N1 | 61.0 | |
| Distant metastases | | |
| M0/M1a | 75.2 | 0.002 |
| M1c | 37.1 | |
| Grading | | |
| G1/2 | 84.6 | 0.037 |
| G3 | 59.8 | |

### Multivariate analysis (Cox regression)

| OS | HR | 95% CI | p-value |
|----|----|--------|---------|
| Parametrial boost | | | |
| yes | 0.417 | 0.192-0.900 | 0.027 |
| no | Reference | |
| Chemotherapy | | | |
| yes | 0.382 | 0.152-0.961 | 0.041 |
| no | Reference | |
| Tumour size | | | |
| T1/2 | Reference | |
| T3/4 | 2.668 | 1.032-6.896 | 0.043 |

### LPFS

| Mean (months) | p-value |
|----------------|---------|
| Lymph node status | | |
| N0 | Reference | |
| N1 | 4.383 | 1.003-19.154 | 0.05 |
| Distant metastases | | |
| M0/M1a | Reference | |
| M1c | 4.646 | 1.466-14.719 | 0.009 |

DPFS = Distant progression-free survival; ECs = erythrocyte concentrates; EQD2 = equivalent doses in 2-Gy fractions; FIGO = Fédération Internationale de Gynécologie et d’Obstétrique; Hb = haemoglobin; LPFS = Local progression-free survival; OS = overall survival.
0.057). Whether parametrial dose escalation was achieved by sequential boost or SIB did not affect QoL. Sexual/vaginal functioning was statistically significantly worse in patients with T3/4 tumours compared to those with T1/2 tumours (p = 0.012). Details are shown in Table 5.

**Discussion**

The objective of this study was to analyze the feasibility and efficacy of a parametrial boost in relation to long-term QoL of patients with ACC. Secondly, we aimed to assess tumour- and treatment-related prognostic factors for long-term QoL and clinical outcome.

Currently, for the QLQ-CX24 items, there are only reference populations from 2 Korean studies available and possible social or cultural differences prevent these cohorts from being reference populations for European studies. Therefore, we were unable to compare the QLQ-CX24 items scores of our patients and we can only report on the comparison between our patients’ QLQ-C30 items scores and German normative data. Compared to the reference population, the patients in our cohort had significantly worse functioning and symptoms item scores. Similar results have been reported in a large population-based study from the United States. They found health-related QoL in survivors of cervical cancer to be worse than in the normal population as well. In women treated with IGABT within the “European and international study on MRI-guided brachytherapy in locally advanced cervical cancer” (EMBRACE), after a median follow-up of 21 months, functioning and general QoL returned to levels of the reference population, but several clearly treatment-related symptoms, e.g. diarrhea and sexual dysfunction, did develop or persist in those patients during follow-up as well. While we, probably due to the small cohort, were unable to show a significant correlation between the doses received by the OARs and any of the QoL item scores, others have found a significant dose-volume effect relationship for late rectal and urinary morbidity. Particularly, patients with bladder D2cc > 95 Gy and rectum D2cc ≥ 75 Gy are at risk for severe late toxicities. It has been shown that chronic bladder and rectal morbidity can be further reduced by IGABT. Therefore, in the ongoing EMBRACE-2 trial, the planning aims / limits for the prescribed EQD2 to rectum (D2cc < 65 / < 75 Gy) and bladder (D2cc < 80 / < 90 Gy) are substantially lower than the mean dose values achieved in

| TABLE 4. Quality of life of patients compared to reference populations (EORTC QLQ-C30) |
|---------------------------------|---|---|---|---|
| **Global health status**        |   |   |   |
| Reference                       | 1309 | 74.5 | 15.5 | 0.001 |
| Patients                        | 30   | 60.3 | 21.7 |
| **Physical functioning**        |   |   |   |
| Reference                       | 1309 | 91.5 | 15.5 | < 0.001 |
| Patients                        | 30   | 73.6 | 19.6 |
| **Role functioning**            |   |   |   |
| Reference                       | 1309 | 89.9 | 20.6 | < 0.001 |
| Patients                        | 31   | 58.1 | 33.0 |
| **Emotional functioning**       |   |   |   |
| Reference                       | 1309 | 83.2 | 19.3 | 0.001 |
| Patients                        | 31   | 65.1 | 26.7 |
| **Cognitive functioning**       |   |   |   |
| Reference                       | 1309 | 93.4 | 14.6 | < 0.001 |
| Patients                        | 31   | 73.2 | 28.4 |
| **Social functioning**          |   |   |   |
| Reference                       | 1309 | 93.3 | 17.1 | < 0.001 |
| Patients                        | 31   | 69.9 | 29.0 |
| **Fatigue**                     |   |   |   |
| Reference                       | 1309 | 16.4 | 21.4 | < 0.001 |
| Patients                        | 31   | 51.6 | 28.0 |
| **Nausea / Vomiting**           |   |   |   |
| Reference                       | 1309 | 2.4  | 9.6  | 0.030 |
| Patients                        | 31   | 11.3 | 21.7 |
| **Pain**                        |   |   |   |
| Reference                       | 1309 | 17.0 | 24.2 | 0.025 |
| Patients                        | 31   | 26.9 | 24.2 |
| **Dyspnea**                     |   |   |   |
| Reference                       | 1309 | 7.2  | 18.7 | 0.020 |
| Patients                        | 30   | 18.9 | 25.8 |
| **Insomnia**                    |   |   |   |
| Reference                       | 1309 | 13.0 | 23.6 | < 0.001 |
| Patients                        | 31   | 40.9 | 36.2 |
| **Appetite loss**               |   |   |   |
| Reference                       | 1309 | 4.2  | 13.9 | 0.002 |
| Patients                        | 31   | 21.5 | 27.7 |
| **Constipation**                |   |   |   |
| Reference                       | 1309 | 3.1  | 12.1 | < 0.001 |
| Patients                        | 31   | 22.6 | 27.7 |
| **Diarrhea**                    |   |   |   |
| Reference                       | 1309 | 2.9  | 12.7 | < 0.001 |
| Patients                        | 31   | 29.0 | 30.7 |
| **Financial difficulties**      |   |   |   |
| Reference                       | 1309 | 4.8  | 16.3 | < 0.001 |
| Patients                        | 31   | 29.0 | 29.5 |

EORTC = European Organization for Research and Treatment of Cancer; QLQ-C30 = quality of life questionnaire for cancer patients 30
Consequently, the QLQ-CX24 symptom experience score was higher in our patients compared to those treated within the EMBRACE study (18.1 ± SD 16.4 vs. 12.1 ± SD 11.9; p = 0.063) after 36 months of follow-up. As a further indicator for the dose-volume-dependence of chronic morbidity, we found the degree of RT-related acute GI and GU toxicities in patients with ACC to statistically significantly correlate with the extent of chronic symptoms and we have already shown this correlation in a previous study from our institution on women with endometrial cancer. In that study we also demonstrated an improved global health status and fewer chronic GI symptoms by reduction of acute toxicities with IMRT. Since most of the patients in our current analysis were treated with IMRT, we were unable to demonstrate such a benefit in terms of long-term QoL. Apart from the dose-volume-relationship found in both, acute and late toxicities, chronic toxicities may be consequential to acute damage, thus amelioration of the acute response to irradiation may be a useful approach to minimize late side effects.

Our analysis showed a significant impairment of sexual/vaginal functioning, significantly increased sexual worry, and a trend towards more chronic constipation in patients exceeding an EQD2 of 53 Gy in the parametria. This was equally true for patients with SIB or sequential boost. The required dose to the parametria for adequate local tumour control has not been established and dose prescriptions vary greatly among radiation oncologists. In patients with traditional midline-shielding, parametrial boost resulted in a significantly higher incidence of radiation proctitis and enterocolitis when > 54 Gy were applied, and this technique has been described to substantially contribute to rectum, sigmoid and bladder doses. In the times of IMRT and SIB to the parametria, studies have shown, that local dose escalation can be achieved with a relevantly reduced incidence of acute toxicities. So far, no study has ever looked at percutaneous parametrial dose escalation regarding QoL and chronic morbidity. Particularly, chronic vaginal morbidity after EBRT boost has not been the focus of research so far. The Vienna group has provided important evidence, that IGABT delivers superior outcome and can reduce vaginal morbidity significantly, but sexual dysfunction remained a problem in patients treated within the EMBRACE trial as well. It is assumed that vaginal toxicity may be further reduced with IGABT by decreasing dwell times in the ovoid/ring and increasing dwell times in tandem/needles. In this context it is important to state that the ongoing EMBRACE-2 trial limits percutaneous IMRT boost as SIB to involved lymph nodes and does not allow a parametrial IMRT boost. At our institution, MRI-guided IGABT with combined IBT/ICBT was recently implemented and we are currently planning a study with longitudinal QoL assessment in these patients. Certainly, it should be the ultimate goal to enable access to IGABT at all brachytherapy centers and EBRT boost remains a widely

### TABLE 5. Prognostic factors for patients’ long-term quality of life (EORTC QLQ-C30, QLQ-CX24)

|                          | n | mean | SD  | p-value |
|--------------------------|---|------|-----|---------|
| **Diarrhea**             |   |      |     |         |
| Acute GI 0               | 11| 12.1 | 16.8| 0.053   |
| Acute GI I/II            | 15| 35.6 | 32.0|         |
| Acute GI III/IV          |  5| 46.7 | 38.0|         |
| **Constipation**         |   |      |     |         |
| Parametria ≤ 53 Gy*      | 19| 14.0 | 23.1| 0.057   |
| Parametria > 53 Gy*      | 11| 33.3 | 29.8|         |
| **Symptom experience**   |   |      |     |         |
| Acute GI toxicity 0      | 11|  9.4 | 8.6 | 0.038   |
| Acute GI toxicity I/II   | 14| 20.6 | 15.9|         |
| Acute GI toxicity III/IV |  5| 30.3 | 22.7|         |
| Acute GU toxicity 0      |  5| 14.3 | 12.9| 0.041   |
| Acute GU toxicity I/II   | 22| 22.4 | 9.7 |         |
| Acute GU toxicity III/IV |  3| 38.4 | 33.5|         |
| **Menopausal symptoms**  |   |      |     |         |
| ≤ 49 years               |  7| 57.1 | 25.2| 0.033   |
| 50–59 years              | 12| 36.1 | 36.1|         |
| 60–69 years              |  7| 14.3 | 26.2|         |
| ≥ 70 years               |  4|  8.3 | 16.7|         |
| **Sexual / vaginal functioning** | | | | |
| T1/2                     |  9| 93.5 | 11.6| 0.012   |
| T3/4                     |  3| 41.7 | 52.0|         |
| Parametria ≤ 53 Gy*      |  8| 96.9 |  6.2| 0.009   |
| Parametria > 53 Gy*      |  4| 47.9 | 44.2|         |
| **Sexual worry**         |   |      |     |         |
| Parametria ≤ 53 Gy*      | 17| 15.7 | 26.6| 0.009   |
| Parametria > 53 Gy*      |  9| 51.8 | 37.7|         |

EORTC = European Organization for Research and Treatment of Cancer; GI = gastrointestinal; GU = genitourinary; QLQ-C30 = quality of life questionnaire for cancer patients 30; QLQ-CX24 = quality of life questionnaire cervical cancer module

*expressed as equivalent dose in 2-Gy fractions (EQD2) with α/β = 10
used method for parametrial dose escalation. This underlines the importance of our investigation.

While survival rates were generally adequate in our study and in line with previously published data from randomized controlled trials on RChT in patients with ACC, a comparison of our results to data on IGABT is quite challenging because our cohort consists of mostly advanced stage patients. The RetroEMBRACE study, a multicenter retrospective observational study, found substantially better 5-year pelvic control and overall survival rates (84% vs. 73.2% and 65% vs. 53.2%), but their cohort contained much more stage I and far less stage IV patients than our study (16.8% vs. 2.4% and 3.1% vs. 31.3%) (23). A Dutch retrospective analysis on 46 patients treated with IGABT found a 3-year regional control rate of 86% and a 3-year overall survival rate of 65%. Similarly, Pöter et al. found pelvic control and overall survival to be 91% and 68% after 3 years, respectively. The patient cohorts in these two studies were very similar to the collective of the RetroEMBRACE study. Therefore, our results, despite the large proportion of stage IV patients and the negligible amount of stage I patients, are not inferior in terms of overall survival and seem comparable with respect to local pelvic control. However, primary tumour control was remarkably high with 93% after 3 years in the Vienna series. Furthermore, an analysis from the RetroEMBRACE study comparing IGABT with IBT/ICBT to ICBT only showed the feasibility of local dose escalation without an increase in dose to organs at risk as well as a 10% higher 3-year local control rate with IBT. These results clearly demonstrate the advantage of MRI-based IGABT with combined IBT/ICBT for local dose escalation.

Nevertheless, our analysis showed a statistically significant overall survival benefit from a parametrial boost and this was equally true for patients with SIB or sequential boost, but exceeding an EQD2 of 53 Gy with this technique does not further improve survival and has a negative impact on QoL. Therefore, the conductance of a percutaneous parametrial boost has to be seen very critically with respect to local tumour control and long-term QoL. MRI-guided IGABT with combined IBT/ICBT certainly is the gold standard for local dose escalation in ACC.

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