

ORIGINAL ARTICLE

Evaluation of planning aims and dose prescription in image-guided adaptive brachytherapy and radiochemotherapy for cervical cancer: Vienna clinical experience in 225 patients from 1998 to 2008

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ABSTRACT

Background. To assess planning aims (PAs) and dose prescription in image-guided adaptive brachytherapy (IGABT) of cervical cancer and investigate potential impact on clinical outcome.

Material and methods. Our study population consists of 225 consecutive cervical cancer patients (FIGO stages IB–IVA) treated between 1998 and 2008 at the Medical University of Vienna by external beam radiotherapy (EBRT) ± chemotherapy and IGABT. For this retrospective study, patients were stratified into two treatment groups: PA+ group, all dose constraints fulfilled for prescription; PA-, one or more dose constraints not fulfilled for prescription. The following dose constraints (EBRT+IGABT) were applied: clinical target volume (CTV)_{HR} D₉₀ ≥ 85 Gy, D_{2cm3} Rectum < 70 Gy, D_{2cm3} Bladder < 90 Gy. Differences in patient, tumor and treatment characteristics and clinical outcome (event: local failure or grade 3 + 4 toxicity) were compared between Group 1 and 2. Further, the impact of learning period (1998–2000) and protocol period (2001–2008) on the fulfillment of PAs for dose prescription and clinical outcome was analyzed.

Results. In the PA+ group there were 77 (34%) and in the PA- group 148 (66%) patients. In the PA- group, CTV_{HR} D₉₀ < 85 Gy was prescribed in 82 patients, D_{2cm3} bladder > 90 Gy was prescribed in 80 patients and D_{2cm3} Rectum > 70 Gy in 60 patients. Fulfillment of the PA for dose prescription improved from 4% in the learning period to 48% in the protocol period. The five-year event-free interval was 64% in the learning period and 84% in the protocol period (p = 0.008).

Conclusion. Fulfillment of all PAs for dose prescription is challenging – especially in patients with more advanced tumors. However, with growing experience fulfillment of PA for dose prescription can be significantly increased (learning and protocol period). Such increase in fulfilling PA for dose prescription is followed by a significant improvement in clinical outcome.

The gold standard in the treatment of locally advanced cervix cancer is radio-chemotherapy and brachytherapy [1]. Image-guided adaptive brachytherapy (IGABT) is an advanced method which is increasingly implemented in clinical practice [2,3]. By imaging of the applicator and tumor/target volume and the surrounding organs at risk (OAR), IGABT offers the possibility of dose optimization based on the individual high risk (HR) clinical target volumes (CTV) and OARs [4–7]. First clinical results indicate

a reduction in local recurrence and side effects in comparison to standard point A based brachytherapy [8–11]. Recently, dose response relationships were described in IGABT for the target volume and OARs (bladder and rectum) based on the mono-institutional Vienna cohort and also based on the large multi-center cohort RetroEMBRACE [12–15]. The observational prospective multicenter study “EMBRACE” (European study on MRI guided BRachytherapy in locally advanced CErvix cancer)

was initiated to provide further evidence on correlations between radiation dose and clinical findings. Based on such dose response relationships, in-house planning aims (PAs) and constraints were established in various centers for CTV_{HR} and intermediate risk CTV (CTV_{IR}) and OARs. Defined PAs for dose prescription are also projected for the upcoming interventional study “EMBRACE II” study. Moreover, the methodology of PAs and dose prescription has been developed within the upcoming ICRU report on cervix cancer brachytherapy (ICRU report 88) along the lines of ICRU report 83. In clinical practice of IGABT in cervix cancer, fulfillment of all PAs for dose prescription is challenging and often leads to compromises in dose distributions either for the dose prescription for target volumes or for the OARs [10].

Therefore, the aim of our study was: 1) to evaluate the fulfillment of defined PAs (representing correlations to favorable outcome [12–15] in IGABT) for dose prescription in a consecutive patient cohort; 2) to assess whether a growing level of experience with IGABT has impact on the fulfillment of such PAs for dose prescription; and 3) if an increase in fulfillment of such PAs for dose prescription translates into improved clinical outcome.

Material and methods

Patients and work up

All patients with cervical cancer FIGO IA-IVA treated with curative intent at the Department of Radiation Oncology at the Medical University of Vienna 1998–2008 were included in this study. Pre-treatment evaluation included patient history, complete physical and gynecological examination, routine laboratory tests, abdominal computed tomography (CT) or whole body positron emission tomography (PET)-CT and magnetic resonance imaging (MRI) scan of the pelvis.

Follow-up investigations were performed every three months in the first two years after treatment, then every six months in the next two years and then yearly thereafter and included gynecological examination and regular MRI scans of the pelvis and thoracic/abdominal CT scans.

Treatment

The treatment characteristics were already described in previous publications [8,9]. In short, patients were treated by external beam radiotherapy (EBRT), concomitant chemotherapy (Cisplatin 40 mg/m² of body surface per week for 5 weeks) and IGABT. EBRT was performed initially by four-field box technique and then progressively replaced by IMRT. The prescribed dose was 45 Gy in 1.8 Gy per fraction and

was increased to 50.4 Gy if concomitant chemotherapy was not delivered. At the end or after EBRT, MRI-based IGABT was performed using tandem ring applicators +/- interstitial needles, and/or combination of tandem and vaginal cylinders +/- interstitial needles. MRI-based IGABT was started between 1998 and 2000 (‘learning period’) with minor dose optimization, dose escalation and very limited use of interstitial needles whereas from 2001 to 2008 (‘protocol period’) with increasing experience more advanced dose optimization and a higher number of interstitial needles were applied.

For treatment planning and DVH-analysis all doses were calculated as EQD2 sum of all BT fractions and EBRT fractions ($\alpha/\beta = 10$ Gy for target volume and $\alpha/\beta = 3$ Gy for OARs). The following PAs were applied retrospectively for the evaluation of IGABT in the present study: CTV_{HR} D₉₀ ≥ 85 Gy, D_{2cm3} Rectum < 70 Gy, D_{2cm3} Bladder < 90 Gy.

Study design, endpoints and statistical analysis

For this study, patients were stratified into two treatment groups: Group 1, PA+: all dose constraints fulfilled for dose prescription (CTV_{HR} D₉₀ ≥ 85 Gy, D_{2cm3} Rectum < 70 Gy and D_{2cm3} Bladder < 90 Gy); Group 2, PA-: one or more dose constraints not fulfilled for dose prescription (CTV_{HR} D₉₀ < 85 Gy or D_{2cm3} Rectum ≥ 70 Gy or D_{2cm3} Bladder ≥ 90 Gy). PAs were defined based on evidence from Vienna experience [12–14] and from multicenter experience [15 and unpublished evaluations from EMBRACE] and as projected as PAs for EMBRACE II.

Furthermore, patients were stratified according to the treatment period (learning period 1998–2000 vs. protocol period 2001–2008). Differences in patient, tumor and treatment characteristics between the groups were assessed using an unpaired t-test. To reflect the full scope of treatment failure any grade 3 or 4 toxicity and local failure were scored as an event and the event-free interval was calculated and compared using the Kaplan-Meier method and log-rank test.

For time to event variables the durations were calculated from the date of biopsy until the date of event or last follow-up. Local failure was defined as any residual and progressive disease or tumor relapse in uterine cervix, uterine corpus, vagina, parametrium or pelvic wall. Late toxicity was defined as persistence of side effects after 90 days after finished treatment (EBRT + BT). It was assessed according to Late Effects in Normal Tissue-Subjective, Objective, Management and Analytic LENT SOMA scale [16], from grade 0 (without side effects) to grade 4 (severe). This study focused on severe – grade 3 or 4 – toxicity.

All statistical analyses were performed using SPSS v. 20 and a p-value of <0.05 was considered significant.

Results

Patients and outcome

Our patient cohort consisted of 225 consecutive patients with locally advanced cervical cancer. The mean age at treatment was 58 years (range 26–92). Eighty-five percent of patients had squamous cell carcinoma. The International Federation of Obstetrics and Gynecology stage (FIGO) distribution in our cohort was; stage I: 25 (11%), stage II 137 (61%), stage III 53 (24%) and stage IV 10 (4%) patients. In PA+ group were 77 (34%) and in PA- 148 (66%) patients. Details on patient characteristics are given in Table I.

Comparison of planning aim groups

In the PA+ group CTV_{HR} D₉₀ > 85 Gy, D_{2cm3} bladder < 90 Gy and D_{2cm3} Rectum < 70 Gy were fulfilled in all patients. In the PA- group, CTV_{HR} D₉₀ < 85 Gy was present in 82 patients, D_{2cm3}

bladder > 90 Gy was present in 80 patients and D_{2cm3} Rectum > 70 Gy in 60 patients resulting in 222 violations in 148 patients. The mean prescribed dose to CTV_{HR} D₉₀, D_{2cm3} Rectum and D_{2cm3} Bladder was significantly different in PA+ and PA- group (98 Gy, 60 Gy, 79 Gy vs. 85 Gy, 67 Gy, 96 Gy). Local failure was observed in 5/77 patients (6.5%) in the PA+ and 23/148 patients (15.5%) in the PA- group; of the 23 PA- patients with local failure, 20 had CTV_{HR} D₉₀ < 85 Gy, 11 had D_{2cm3} Bladder > 90 Gy and seven had D_{2cm3} Rectum > 70 Gy. Grade 4 rectal toxicity was observed in two cases in PA+ (both D_{2cm3} Rectum < 70 Gy) and one case in PA- group (D_{2cm3} Rectum > 70 Gy). Grade 3 rectal toxicity was observed in no case in PA+ and in four cases in PA- group. Grade 4 bladder toxicity was observed in no case in PA+ and in two cases in PA- group. Grade 3 bladder toxicity was observed in four cases in PA+ and in one case in PA- group. The probability of five-year event-free interval (for local failure and G4 toxicity) in PA+ and PA- group was 90% and 79.1%, respectively. The probability of five-year event-free interval (for local failure and G3 + G4-toxicity) in PA+ and PA- group was 83.9% and 75.6%, respectively (p = 0.086). There were

Table I. Patients' cohort description and comparison of PA+ (group 1) and PA- (group 2).

	All patients	Group 1 PA+ group	Group 2 PA- group	p-Value
Number of patients	225	77 (34%)	148 (66%)	
Mean age (range) years	58 (26–92)	53 (29–85)	61 (26–92)	0.002
Tumor size				
< 5 cm	83 (37%)	26 (34%)	57 (38.5%)	0.486
> 5 cm	142 (63%)	51 (66%)	91 (61.5%)	
Mean HRCTV volume (cm ³)	43 (7.6–167.3)	34 (14.6–71.3)	48 (7.6–167.3)	0.001
FIGO staging				
I	25 (11%)	14 (18%)	11 (7%)	0.015
II	137 (61%)	49 (64%)	88 (59%)	0.545
III	53 (24%)	14 (18%)	39 (26%)	0.172
IV	10 (4%)	0 (0%)	10 (7%)	0.020
Histology				
Squamous	192 (85%)	69 (90%)	123 (83%)	0.192
Adenocarcinoma	22 (10%)	6 (8%)	16 (11%)	0.472
Adenosquamous	6 (3%)	1 (1%)	5 (3%)	0.360
Others	5 (2%)	1 (1%)	4 (3%)	0.500
Grade				
1 (good)	13 (6%)	3 (4%)	10 (7%)	0.56
2 (moderate)	115 (51%)	42 (55%)	73 (49%)	0.515
3 (poor)	57 (25%)	20 (26%)	37 (25%)	0.874
Unknown	39 (17%)	11 (14%)	28 (19%)	0.537
Positive lymph nodes				
No	121 (54%)	34 (44%)	87 (59%)	0.037
Yes	104 (46%)	43 (56%)	61 (41%)	
Chemotherapy				
Yes	147 (65%)	67 (87%)	80 (54%)	<0.001
No	78 (35%)	10 (13%)	68 (46%)	
Mean dose CTV _{HR} D ₉₀ (Gy)	89 (55.1–135.5)	98 (85.5–116.7)	85 (55.1–133.5)	<0.001
Mean D _{2cm3} rectum (range)	65 Gy (31.4–104.4)	60 Gy (46.2–69.9)	67 Gy (31.4–104.4)	<0.001
Mean D _{2cm3} bladder (range)	90 Gy (51.5–181.8)	79 Gy (58.9–89.9)	96 Gy (51.5–181.8)	<0.001

several significantly confounding factors between the PA+ and PA- groups. Most relevant, more advanced tumors and a significantly larger mean CTV_{HR} volume were found in the PA- than in the PA+ group (48 cm³ vs. 34 cm³, $p = 0.001$) (Table I).

Comparison of time periods

During 1998–2000 (learning period) 71 (33%) patients were treated and 154 (68%) patients from 2001 to 2008 (protocol period). Patient characteristics of the different time periods are shown in Table II. All PAs were fulfilled in 4% of the patients in first period and in 48% in the second period. Mean CTV_{HR} was comparable in both groups. Mean CTV_{HR} D₉₀ was significantly lower in first period compared to second period, (81 Gy vs. 92.6 Gy, $p < 0.001$). There was also a significant reduction in mean D_{2cm3} for bladder in the second period (86.1 Gy versus 98.8 Gy, $p < 0.001$), but there was no significant difference in D_{2cm3} rectum. The five-year local failure-free interval was 72.8% and 91% in first and second period, respectively ($p = 0.008$). Five-year event-free interval (local failure and G4-toxicity) was 71% in first period and 88.7% in second period ($p = 0.007$). Five-year event-free interval (local failure and G3 + G4 toxicity) was 64% in first period and 84% in second period ($p = 0.008$) (Figure 1).

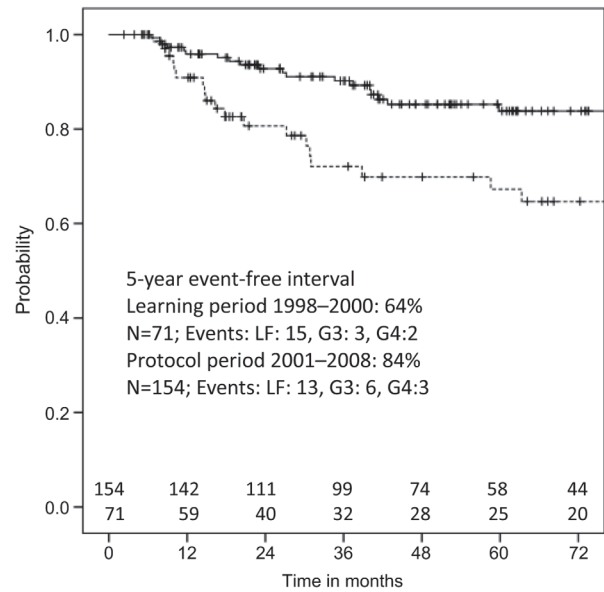


Figure 1. Comparison of 5-year event-free (local failure and G3–G4 rectal and bladder toxicity-free) survival between learning period (1998–2000) and protocol period (2001–2008).

Discussion

In this study we investigated the impact of PAs and dose prescription on the clinical outcome of IGABT. For this purpose local failure and severe – including potentially life-threatening – side effects were summarized within one category. This approach was

Table II. Comparison of treatment periods 1998–2000 and 2001–2008.

Characteristics		Period 1998–2000 (1 st period)	Period 2001–2008 (2 nd period)	p-Value
Number of patients	225	71 (32%)	154 (68%)	
Mean age (range)		60 (26–92)	58 (29–90)	0.408
Mean D90 HRCTV volume (cm ³)		42.1 (8.8–154.7)	43.6 (7.6–167.3)	0.730
Tumor size				0.085
	< 5cm	32 (45%)	51 (33%)	
	> 5cm	39 (55%)	103 (67%)	
FIGO				0.076
	I	4 (6%)	21 (14%)	
	II	46 (65%)	91 (59%)	0.418
	III	17 (24%)	36 (23%)	0.926
	IV	4 (6%)	6 (4%)	0.559
Lymph nodes				0.167
	Positive	43 (61%)	78 (51%)	
	Negative	28 (39%)	76 (49%)	
Histology				0.813
	Squamous cell	60 (85%)	132 (86%)	
	Adenocarcinoma	7 (10%)	15 (10%)	0.978
	Adenosquamous	1 (1%)	5 (3%)	0.429
	Other	3 (4%)	2 (1%)	0.168
Grade				0.879
	1 (good)	5 (7%)	8 (5%)	
	2 (moderate)	35 (49%)	80 (52%)	0.851
	3 (poor)	15 (21%)	42 (27%)	0.327
	Unknown	16 (23%)	24 (16%)	0.207
Chemotherapy				<0.001
	No	39 (55%)	39 (25%)	
	Yes	32 (45%)	115 (75%)	
Planning aims				<0.001
	Fulfilled	3 (4%)	74 (48%)	
	Not fulfilled	68 (96%)	80 (52%)	
Mean dose HRCTV D ₉₀ (Gy)		81 Gy (55.1–128.7)	92.6 Gy (56.8–133.5)	<0.001
Mean D _{2cm3} bladder (Gy)		98.8 Gy (64.1–181.8)	86.1 Gy (51.5–171.7)	<0.001
Mean D _{2 cm3} rectum (Gy)		63.7 Gy (31.4–104.4)	64.8 Gy (35.3–92.2)	0.473

chosen to mirror the full burden of treatment failure as for the individual patient likely both – a local failure and a severe side effect – will have a tremendous impact on her further life, death or major impairment in quality of life. In consequence, such an approach may be valuable to indicate the full clinical benefit of a given treatment. The possibility of delivering very focused high doses in a short time with brachytherapy is on the one hand the backbone of its high effectiveness, but it can also potentially lead to severe side effects and local failures as a result of inadequate dose distribution [17–19]. Volumetric imaging for brachytherapy treatment planning is therefore an indispensable tool to improve, adapt and individualize the dose distribution [2,3,10]. Evidence-based PAs/dose constraints for clinically relevant endpoints are becoming subsequently more and more a necessity in brachytherapy treatment planning. For IGABT of cervical cancer Dimopoulos et al. showed that if the CTV_{HR} D₉₀ is ≥ 87 Gy a local tumor control $> 90\%$ is achievable. Furthermore, the D_{2cm3} for rectum and bladder were identified as predictive toxicity parameters with an ED10 of 73 Gy for rectum and ED10 of 101 Gy for urinary bladder [12,20]. Based on these findings, PAs for dose prescription have been developed for IGABT at Vienna Medical University with lowering dose values for OARs, in particular for the bladder. The current study shows, however, that fulfillment of all PAs is overall challenging. Even in the protocol period in more than half of the patients, one or more PAs were not fulfilled for the final prescription of treatment. Main reasons might be found in the still missing prospective use of the nowadays proposed PAs, but also in high CTV_{HR} volumes and unfavorable pelvic topography. Tanderup et al. already described the strong influence of the CTV_{HR} volume on the brachytherapy dose distribution [10]. The comparison of the PA+ and PA- group confirms that in prognostic unfavorable patients fulfillment of PAs for dose prescription is in general more difficult. Therefore, a direct comparison of clinical outcome is problematic between these two groups. In addition, due to the highly heterogeneous prescribed doses, the clinical outcome of the PA-group needs to be taken with caution. The results of the PA+ group, in contrast, may be considered as potential benchmark, however, in a selected and rather favorable cohort where less patients with large tumors and unfavorable topography are represented. From a clinical point of view these results show that for patients where all PAs were fulfilled for dose prescription, there is a remaining risk of 10% to develop a major treatment failure event in terms of local recurrence or G4 morbidity. Further research will be necessary to clarify to which extent

improvements in dose distribution in patients represented by the PA- group in our study will be followed by improvements in clinical outcome.

In agreement with reports from prostate cancer brachytherapy [21–24], increasing experience seems to have a strong impact on the fulfillment of PAs for dose prescription in IGABT of cervical cancer. In the learning period 1998–2000 only 4% of the patients fulfilled all dose aims for dose prescription, whereas in the protocol period from 2001 to 2008 this number could be increased to 48%. Reasons for this overall dosimetric improvement in patients with comparable CTV_{HR} volumes (learning period: mean CTV_{HR} volume: 42cm³ vs. protocol period: mean CTV_{HR} volume: 44cm³) may be found in the increasing systematic use of interstitial needles and more advanced dose optimization techniques [25,26]. Further dose escalation for the CTV_{HR} and dose constraints for OARs could be established only after some years of experience. The more targeted dose distribution was followed by a significant improvement of the five-year event-free interval by 20% (Figure 1). The more systematic use of chemotherapy in the protocol period may also contribute to these findings, however, the absolute benefit of concomitant chemotherapy was shown to be mean 6% in a recent meta-analysis [27]. This implies that within the treatment concept of (MR-) IGABT there seems to be certain variability in local outcome and morbidity based on doses applied to the CTV_{HR} and to OARs, the degree of dose optimization and likely other clinical factors which have to be further elaborated. Recent comparisons of conventional 2D (x-ray, point A based) brachytherapy and 3D (MRI, CT) IGABT in cervical cancer showed correspondingly even larger improvements, e.g. 16–35% increase in local tumor control and overall survival in mono-institutional cohorts compared to historical treatment [28,29] and 50% reduction of side effects by IGABT in a prospective comparative study [30].

Interestingly, the improvements in clinical outcome in our study were mainly driven by the increase in local tumor control – severe toxicity did not seem to be substantially influenced by following the PAs for dose prescription (in contrast to low to moderate grade toxicity which was not subject of the current study). However, the incidence of grade 3 + 4 toxicity was overall low. In consequence, the results of the study suggest, that – if reasonably achievable – the highest priority in treatment planning should be aimed at reaching the PAs for dose prescription for the CTV_{HR}.

In conclusion, fulfillment of all PAs for dose prescription is challenging – especially in patients with more advanced tumors. However, with growing

experience fulfillment of PAs for dose prescription can be significantly increased (learning and protocol period). Such increase in fulfilling PAs for dose prescription is followed by a significant improvement in clinical outcome.

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