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Original article

Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including MRI guided brachytherapy of locally advanced cervical cancer

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ABSTRACT

Background and purpose: Currently, there is no consensus on dose prescription in image guided adaptive brachytherapy (IGABT) in locally advanced cervical cancer. The purpose of this study was to provide evidence based recommendations for tumor dose prescription based on results from a multi-center patient series (retroEMBRACE).

Materials and methods: This study analyzed 488 locally advanced cervical cancer patients treated with external beam radiotherapy ± chemotherapy combined with IGABT. Brachytherapy contouring and reporting was according to ICRU/GEC-ESTRO recommendations. The Cox Proportional Hazards model was applied to analyze the effect on local control of dose-volume metrics as well as overall treatment time (OTT), dose rate, chemotherapy, and tumor histology.

Results: With a median follow up of 46 months, 43 local failures were observed. Dose (D90) to the High Risk Clinical Target Volume (CTV_{HR}) ($p = 0.022$, HR = 0.967 per Gy) was significant for local control, whereas increasing CTV_{HR} volume ($p = 0.004$, HR = 1.017 per cm^3), and longer OTT ($p = 0.004$, HR = 1.023 per day) were associated with worse local control. Histology ($p = 0.084$), chemotherapy ($p = 0.49$) and dose rate ($p = 1.00$) did not have significant impact on local control. Separate analyses according to stage of disease showed that dose to CTV_{HR}, residual gross tumor volume (GTV_{res}), and Intermediate Risk CTV (CTV_{IR}) has significant impact on local control.

Conclusion: CTV_{HR} dose of $\geqslant$85 Gy (D90) delivered in 7 weeks provides 3-year local control rates of >94% in limited size CTV_{HR} (20 cm^3), >93% in intermediate size (30 cm^3) and >86% in large size (70 cm^3) CTV_{HR}. CTV_{IR} and GTV_{res} dose of $\geqslant$60 Gy and $\geqslant$95 Gy (D98) leads to similar local control. A dose of 5 Gy (CTV_{HR}) is required to compensate an increase of OTT by one week. Increased CTV_{HR} volume by 10 cm^3 requires additional 5 Gy for equivalent local control.

Worldwide, cervical cancer is one of the most common malignancies in females. While early detection and prevention through screening and vaccination are available, there is still a lack of comprehensive programs in many regions, in particular in countries with limited resources. Effective therapeutic strategies for cervix cancer are therefore of utmost importance over the next decades. Early cervical cancer may be treated with surgery alone, while the standard of care for locally advanced disease is radiochemotherapy including brachytherapy. Classical radiochemotherapy is highly efficient in limited disease [1]. Yet, advanced disease and treatment related morbidity have represented significant challenges [2]. After a long period with little technological development in gynecological brachytherapy, MRI based image guided adaptive brachytherapy (IGABT) resulted in a major change in treatment paradigm during the last decade [3]. IGABT is being implemented in a growing number of centers, and evidence of improved clinical outcome is accumulating [4–9].

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The GEC ESTRO recommendations facilitated IGABT by introducing a novel adaptive target concept which forms the basis of the ICRU/GEC-ESTRO report 89 [10]. Differential BT targets are defined according to tumor response and risk of recurrence: Intermediate-Risk CTV (CTV_{IR}), High-Risk CTV (CTV_{HR}), and residual GTV (GTV_{res}) [11]. However, significant variation in dose prescription between institutions remains. In the transition phase from 2D to 3D image guided brachytherapy, many institutions have stayed close to their 2D practice in terms of dose prescription. Traditional point A dose prescriptions have varied widely for decades in terms of fractionation and total biologically equivalent dose [12]. Current common schedules such as 45 Gy external beam radiotherapy (EBRT) combined with HDR of 2 fractions of 9 Gy, 5 fractions of 5.5 Gy, or 4 fractions of 7 Gy correspond to total equivalent dose in 2 Gy fractions using $\alpha/\beta = 10$ ($EQD2_{10}$) of 73 Gy, 80 Gy, and 84 Gy, respectively ($\alpha/\beta = 10$). So far, it has not been possible to establish consensus on dose prescription for IGABT, although mono-institutional dose and overall treatment time effect analyses have been published [13,14]. In order to establish evidence-based dose-prescription schedules for the new treatment paradigm of IGABT there is currently a major need to provide evidence for dose effects from large multicenter patient series.

In 2008 the GEC-ESTRO Gyneacology network initiated the "International study on MRI based brachytherapy in cervical cancer" (EMBRACE, www.embracestudy.dk). The purpose of EMBRACE was to benchmark MRI based IGABT in a prospective multicenter setting (1320 patients until 6/2015). Furthermore, the GEC-ESTRO group initiated a retrospective collection of data (retroEMBRACE) on 852 patients from 12 centers treated with IGABT before starting EMBRACE (www.retroembrace.com). The purpose of retroEMBRACE was to compile retrospective IGABT outcome data until mature prospective data became available e.g. from the EMBRACE study. The retroEMBRACE series represents by far the largest patient series with an IGABT treatment strategy and with mature disease outcome [15].

The purpose of this paper is to quantify the effect of tumor dose and volume as well as overall treatment time (OTT) on local control in the sub-cohort of retroEMBRACE patients treated with MRI guided BT and from this analysis to provide recommendations for evidence based IGABT dose prescription.

Materials and methods

The eligibility criteria for retroEMBRACE were: (1) diagnosis of locally advanced cervical cancer and (2) treatment with curative intent with IGABT based on MRI or CT [15]. For the analysis presented in this paper, centers were only included if BT was systematically based on MRI, and if EBRT midline block or pre-operative IGABT was not used. The following centers/patients from the retroEMBRACE database of 852 patients were excluded: 3 centers doing mainly CT based dose planning (153 patients), 2 centers not reporting dose and volume parameters (50 patients), 53 patients receiving pre-operative IGABT, and 42 patients receiving mid-line block EBRT. The remaining 554 patients from 7 institutions were consecutive (6 centers) or represented all patients who were treated with MRI guided brachytherapy (1 center) in the given period. Data were missing on local control or CTV_{HR} dose or volume in 66/554 patients. Consequently, a total number of 488 patients were available for CTV_{HR} dose-volume effect analysis. GTV_{res} and CTV_{IR} contouring and reporting were not systematically performed by all institutions, and was available in 267 patients (4 centers) and 345 patients (5 centers), respectively. The distribution of patients between the 7 centers is shown in Table 1.

Patients were treated between 2/1998 and 12/2009. EBRT was combined with MRI based BT. Concomitant chemotherapy was delivered after its systematic introduction in 1999. BT was administered as high dose rate (HDR) in 2 centers and pulsed dose rate (PDR) in 5 centers. MRI was performed with the brachytherapy applicator in situ for each applicator insertion. In case of several fractions delivered on one implantation, the imaging was not necessarily repeated for each fraction. Imaging, contouring of target volumes, applicator reconstruction, and dose reporting followed the GEC ESTRO recommendations [11,16–18]. Furthermore, ICRU rectum and bladder dose was reported as well as point A dose for patients receiving intracavitary treatment. Combined intracavitary-interstitial (IC/IS) brachytherapy was applied according to institutional practice, mainly in patients with significant residual disease at the time of brachytherapy. BT dose optimization and dose prescription were according to the policy in each institution. D90 and D100 were reported for GTV_{res}, CTV_{HR}, and CTV_{IR} for each BT fraction. All doses were normalized to total biologically equivalent dose in 2 Gy per fraction (EQD2) using the linear-quadratic model with $\alpha/\beta = 10$ Gy for tumor [16]. For PDR, a repair half time of 1.5 h was used. Total $EQD2_{10}$ for EBRT and BT was obtained by summation of prescribed EBRT dose ($EQD2_{10}$) and fractional BT doses ($EQD2_{10}$) [16]. Direct summation of fractional BT doses was performed under the assumption that cold-spots remained in the same position for all BT fractions. Follow up was performed according to institutional guidelines at regular intervals. In general this was a 3-month interval for the first year, a 6-month interval for years 2 and 3, and annually thereafter. The data were submitted by each institution through access to a joint online database.

Table 1
Overview of patient inclusion, dose rate, fractionation schedules and EBRT dose.

Institution	# patients (% of cohort)	Dose rate	Number of BT fractions	EBRT dose
Aarhus	66* (14%)	PDR	2–3	45 Gy or 50 Gy
Leuven	54 (11%)	PDR	1	45 Gy or 50 Gy
London	30 (6%)	HDR	3	50 Gy
Ljubljana	43 (9%)	PDR	2	45 Gy or 50 Gy
Paris	108** (22%)	PDR	1–2	45 Gy
Utrecht	45□ (9%)	PDR	2	45 Gy
Vienna	142□□ (29%)	HDR	4	45 Gy, 48 Gy or 50 Gy

* Patients have been included in a previous publication on dose and outcome [5].
** Patients have been included in a previous publication on dose effect [14].
□ Patients have been included in previous publication on dose and outcome [6].
□□ Patients have been included in a previous publication on dose effect [13].

Univariate and multivariate Cox Proportional Hazards regression (SPSS Statistics, version 20) was applied to evaluate the impact on local control of CTV_{HR} D90, CTV_{HR} volume, CTV_{IR} D90, GTV_{res} D100, OTT, dose rate (HDR versus PDR), stage, histology (squamous cell versus adeno and adeno-squamous carcinoma) and administration of chemotherapy. Cox regression was performed in all patients as well as in the subset of patients who received chemotherapy. Patients were censored at the end of follow up, at death, and at regional or systemic failure. Factors associated with p-values <0.1 in the univariate analysis were included in the multivariate analysis. Volumes of GTV_{res} and CTV_{IR} were not reported in the retroEMBRACE database, and therefore it was not possible to perform regression on both dose and volume for GTV_{res} and CTV_{IR}. In order to partly compensate for volume bias, a stage-wise dose–effect analysis including OTT was performed using Cox Proportional Hazards regression in three stage groups: IB, IIA + IIB, and IIIA + IIIB + IVB. Statistical significance was defined by a p-value below 0.05.

Results

The median patient age was 54 (23–91) years. The FIGO stage distribution was IB (19%), IIA (7%), IIB (50%), IIIA (3%), IIIB (18%),

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