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Tumor dose–volume response in image-guided adaptive brachytherapy for cervical cancer: A meta-regression analysis

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ABSTRACT

PURPOSE: Image-guided adaptive brachytherapy is a high precision technique that allows dose escalation and adaptation to tumor response. Two monocentric studies reported continuous dose–volume response relationships, however, burdened by large confidence intervals. The aim was to refine these estimations by performing a meta-regression analysis based on published series.

METHODS AND MATERIALS: Eligibility was limited to series reporting dosimetric parameters according to the Groupe Européen de Curiethérapie–European SocieTy for Radiation Oncology recommendations. The local control rates reported at 2–3 years were confronted to the mean D_{90} clinical target volume (CTV) in 2-Gy equivalent using the probit model. The impact of each series on the relationships was pondered according to the number of patients reported.

RESULTS: An exhaustive literature search retrieved 13 series reporting on 1299 patients. D_{90} high-risk CTV ranged from 70.9 to 93.1 Gy. The probit model showed a significant correlation between the D_{90} and the probability of achieving local control ($p < 0.0001$). The D_{90} associated to a 90% probability of achieving local control was 81.4 Gy (78.3–83.8 Gy). The planning aim of 90 Gy corresponded to a 95.0% probability (92.8–96.3%). For the intermediate-risk CTV, less data were available, with 873 patients from eight institutions. Reported mean D_{90} intermediate-risk CTV ranged from 61.7 to 69.1 Gy. A significant dose–volume effect was observed ($p = 0.009$). The D_{90} of 60 Gy was associated to a 79.4% (60.2–86.0%) local control probability.

CONCLUSION: Based on published data from a high number of patients, significant dose–volume effect relationships were confirmed and refined between the D_{90} of both CTV and the probability of achieving local control. Further studies based on individual data are required to develop nomograms including nondosimetric prognostic criteria.

Keywords: Image-guided adaptive brachytherapy; Cervix cancer; Dose–volume effect relationships; Tumor control probability; High-risk clinical target volume; Intermediate-risk clinical target volume; Meta-regression analysis

Introduction

Image-guided adaptive brachytherapy (IGABT) is a high precision technique that allows for dose escalation and adaptation to tumor response, while mastering the doses delivered to the organs at risk with dose–volume histograms (1). In 2005 and 2006, the Groupe Européen de Curiethérapie–European SocieTy for Radiation Oncology (GEC-ESTRO) published recommendations on reporting, defining clinical target volumes (low, intermediate, and high risk), and dose–volume parameters (D_{90} and D_{100}, dose received by $_{xx}$% of the volume) (2, 3), because these concepts were rapidly adopted and included in the International commission for radiation units and measurements report 89 (4, 5). According to these recommendations, the

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low-risk CTV corresponds to the external beam CTV. The high-risk CTV (CTV_{HR}), corresponds to the residual disease at the time of brachytherapy but also encompasses the whole cervix and T2-MRI visible "gray zones" (Fig. 1). The intermediate-risk CTV (CTV_{IR}) includes the CTV_{HR} with margins (0.5 cm toward the bladder and rectum, 1 cm in the parametria, and 1 to 1.5 cm of vagina and uterus), but also the disease at time of diagnosis (initial disease) (2). This last volume is therefore adapted to tumor shrinkage.

Recent series reported high local control rates with low morbidity in regard to classical data. Moreover, two monocentric series have shown a clear dose−volume effect between modern dosimetric parameters (D_{90} CTV_{HR} and D_{90} CTV_{IR}, minimal doses delivered to 90% of the corresponding CTV) and the probability of achieving local control, confirming the crucial issue of dose escalation (6, 7). However, these relationships established on limited samples of patients are burdened by large confidence intervals.

The aim of this study was to reduce these uncertainties by performing dose−volume effect analyses based on published data and a large number of patients.

Methods and materials

Series reporting the outcomes of patients treated with IGABT were identified by a PubMed search (US National Library of Medicine National Institutes of Health, Bethesda, Maryland, USA), regardless to the dose rate used. To be eligible, these series had to report their results according to the GEC-ESTRO recommendations, id est mean D_{90} of the CTV_{HR} or CTV_{IR} (2). In case of updates from the same institution, the latest report was selected. In case of simultaneous publications from the same institution (subgroup studies), the largest one was selected. To allow comparisons between series, the reporting had to include 2-Gy equivalent doses, using the linear quadratic model, with $\alpha/\beta = 10$ Gy, and a half-time repair of 1.5 hours.

The local control rates were confronted to the reported mean D_{90} using the Probit Model. The influence of each series on the dose-effect relationship was pondered according to the number of patients reported. The analyses were performed using XLSTAT 2014 (Addinsoft, Paris, France). Statistical significance was retained for $p < 0.05$.

Results

Thirteen series reporting both local control rates and mean D_{90} CTV_{HR} in a total of 1299 patients were identified (Table 1) (8−20). Their origin was Europe in eight cases, USA in three, and Asia in two. Three series were not considered since GEC-ESTRO guidelines for target definition were not applied (21−24). For the University of Vienna and Gustave Roussy, former publications were not considered (25−28). Finally, the experience from the University of Nice-Sofia was not retained since only median D_{90} was reported (29). They were all retrospective and monocentric, except the French multicentric STIC trial (Soutien Technique aux Innovations Côuteuses), comparing IGABT vs. radiograph-based brachytherapy, for which only the subgroup of patients treated with IGABT in the definitive radiotherapy arm was retained for the analyses (9). Similarly, the studies from Leiden and Aarhus universities proposed comparisons to historical cohorts, and the sole 3D groups were retained for analyzes (10, 15). Some of these series were also used, at least partly, to generate the Retro-EMBRACE (An intErnational study on Mri-guided BRachytherapy in locally Advanced CErvical cancer) cohort (universities of Vienna, Aarhus, and Utrecht, UZ Leuven, Gustave Roussy, Tata Mumbai) (20). As a consequence, the reports from this last series were not considered for analyses. Most of the patients received concomitant

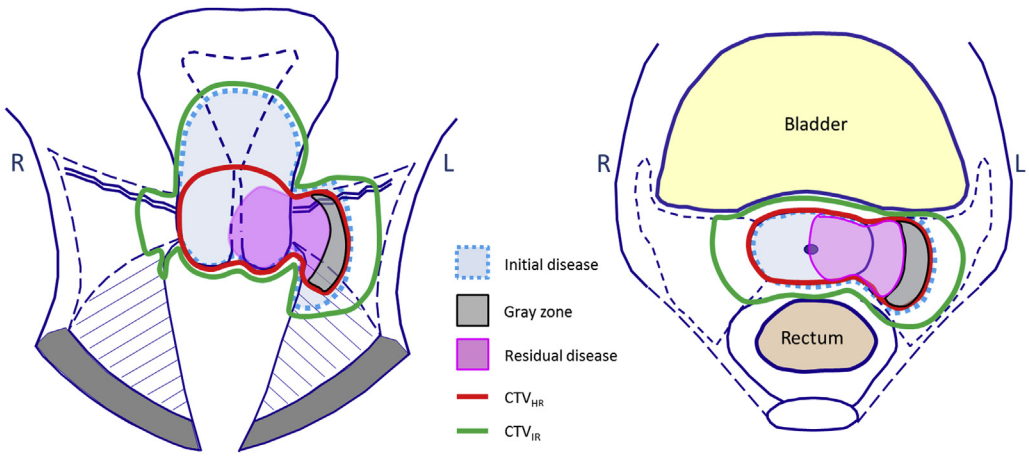

Fig. 1. Definitions of high-risk and intermediate-risk clinical target volumes (CTV_{IR} and CTV_{HR}, respectively) according to the GEC-ESTRO (Groupe Européen de Curiethérapie−European SocieTy for Radiation Oncology) recommendations. Example of a stage IIB lesion with a left distal parametrial involvement. The CTV_{HR} includes the cervix, the residual disease, and gray zones visible on T2-MRI. The CTV_{IR} encompasses the CTV_{HR} with directional margins and includes at least the initial disease. R = right; L = left.