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Volume of high-dose regions and likelihood of locoregional control after perioperative high-dose-rate brachytherapy: Do hotter implants work better?

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ABSTRACT

PURPOSE: To determine whether perioperative high-dose-rate brachytherapy (PHDRB) implants with larger high-dose regions produce increased locoregional control.

METHODS AND MATERIALS: Patients ($n = 166$) enrolled in several PHDRB prospective studies conducted at the University of Navarre were analyzed. The PHDRB was given to total doses of 16 Gy/4 b.i.d. or 24 Gy/6 b.i.d. treatments for negative or close/positive margins along with 45 Gy/25 Rx of external beam radiation therapy. The histogram-based generalized equivalent uniform dose (EUD) formulism was used to quantify and standardize the dose−volume histogram into 2-Gy equivalents. The region of interest analyzed included: tissue volume encompassed by the prescription isodose of 4 Gy (TV_{100}). Routine dose reporting parameters such as physical dose and single-point 2-Gy equivalent dose were used for reference.

RESULTS: After a median followup of 7.4 years (range, 3−12+), 50 patients have failed, and 116 remain controlled at last followup. Overall, EUD was not different in the patients who failed compared with controls (89.1 Gy vs. 86.5 Gy; p = not significant). When patients were stratified by risk using the University of Navarre Predictive Model, very high-risk patients (i.e., tumors ≥3 cm resected with close <1 mm/positive margins) had an improved locoregional control with higher EUD values ($p = 0.028$). This effect was not observed in low-, intermediate-, and high-risk University of Navarre Predictive Model categories.

CONCLUSIONS: In very high-risk patients, enlarged high-dose regions can produce a dose−response effect. Routine dose reporting methods such as physical dose and single-point 2-Gy equivalent dose may not show this effect, but it can be revealed by histogram-based EUD assessment.

Keywords: Perioperative; High-dose rate; High-dose regions; Locoregional control

Introduction

Perioperative high-dose-rate brachytherapy (PHDRB) is an example of extremely inhomogeneous dose distribution that leads to an asymmetrical fractionation. In a typical PHDRB treatment, about one-third of the target volume receives a dose per fraction that is equal to or greater than 150% of the prescription isodose. Traditional standards in good brachytherapy practice advise minimizing the size of the high-dose regions through disciplined technical execution and meticulous planning. However, the volume of the high-dose regions will remain enlarged in some instances, such as when the geometry of the implant is suboptimal and a shrinkage of the high-dose regions would jeopardize target coverage; and/or when there is a deliberate attempt to escalate the dose by creating high-dose

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regions in areas where the tumor cell density is presumed (or confirmed) to be greater.

In a former study, our group developed a four-tiered, hierarchical scoring system (University of Navarre Predictive Model [UNPM]) that stratified patients treated with surgical resection, PHDRB, and external beam radiation therapy (EBRT) into low- (negative margins ≥1 mm and tumor size ≤3 cm), intermediate- (negative margins ≥1 mm and tumor size >3 cm), high- (positive margins <1 mm and tumor size ≤3 cm), and very high-risk categories (positive margins < 1 mm and tumor size >3 cm) (1). This classification yielded 5-year locoregional control rates of 92.3%, 78.0%, 65.5%, and 48.0% for low-, intermediate-, high-, and very high-risk categories, respectively. This system was strongly related to the status of the surgical margins as well as to the size of the tumor and was independent of other common factors such as the treatment-related factors, primary site, histologic type, and/or tumor phenotype. The predictive ability of the model was highly significant ($p = 0.0001$) with an area under curve (AUC) of 0.72 (95% confidential interval = 0.64−0.81).

The present study aims to elucidate whether the dose escalating effect produced by enlarged high-dose regions translates into improved locoregional control rates in each of the four UNPM categories.

Methods and materials

Eligibility criteria

Patients treated with a complete macroscopic surgical resection followed by PHDRB and EBRT between October 2000 and October 2010 were eligible for analysis of locoregional control. To ensure proper data analysis, patients with fewer than 3 years of followup were excluded unless they had previously failed locoregionally. Patients with incomplete gross resections, prior radiation therapy, or treatment with PHDRB as a single modality were excluded (Table 1). Most patients presented with head and neck cancer, sarcomas, gynecological cancer, or colorectal cancer (2). A complete documentation of the status of the surgical margins was required for analysis. Other pathological adverse features (tumor size, histological grade, lymphovascular space involvement, perineural involvement, multiple positive nodes, and extracapsular spread) that have been associated with decreased locoregional control rates were documented as well (Table 2).

Treatment protocol

A total of 166 patients were treated with a combination of PHDRB and EBRT. Patients with negative margins of 10 mm or greater received a PHDRB dose of 16 Gy in 4 b.i.d. treatments in 2 days, and patients with negative margins lesser than 10 mm or positive margins received 24 Gy in 6 b.i.d. treatments over 3 days. The PHDRB was followed by 45 Gy of EBRT in 25 daily treatments 4 weeks later. Site-appropriate concurrent chemotherapy was administered following currently accepted treatment guidelines for each disease situation (3).

PHDRB technique

The implantation procedure and the general guidelines of the target definition process for each disease site and for several specific clinical situations have been previously described. Briefly, the surgical and the radiation oncology teams used the preoperative physical examination and imaging, surgical findings, frozen sections where necessary, and gross examination of the surgical specimen to jointly determine the area to be implanted. This area usually included the aspect of the surgical bed with the highest probability of residual disease owing to inadequate resection margins. For instance, in head and neck tumors, the implanted area usually covered the surgical bed around the primary tumor and the soft tissue around neck nodes greater than 2−3 cm in diameter, which have a substantial probability of extracapsular extension; in sarcomas, the implanted area was the whole surgical bed, although in recent years, the definition of the clinical target volume (CTV) evolved toward a more focused delineation around the areas of the surgical bed with closer margins. Our current CTV definition policy includes the placement of at least four gold fiducial markers in the four cardinal points of a single-plane surgical bed. In more complex brachytherapy procedures (i.e., volume implants), additional gold markers are used. These fiducial markers allow for accurate recognition of the CTV during brachytherapy planning. The CTV is created by adding a 5-mm margin to the clip-delineated ellipsoid. In addition, these fiducial markers are extremely useful in those patients who require post-brachytherapy image-guided external irradiation because they are fully visible under kilo- or megavoltage conditions.

After target definition, the CTV was covered with a set of plastic catheters placed as parallel as possible at

Table 1
Patient parameters

Parameters	Low risk ($n = 39$)	Intermediate risk ($n = 46$)	High risk ($n = 31$)	Very high risk ($n = 50$)	All ($n = 166$), n (%)
Gender					
Female	16	22	10	22	70 (42.2)
Male	23	24	21	28	96 (57.8)
Prior treatments					
Chemotherapy	0	0	0	0	0
Radiation	0	0	0	0	0
Surgery	13	14	10	17	54 (32.5)

Table 2
Tumor parameters

Parameters	Low risk ($n = 39$), n (%)	Intermediate risk ($n = 46$), n (%)	High risk ($n = 31$), n (%)	Very high risk ($n = 50$), n (%)	All ($n = 166$), n (%)
Diagnosis					
Gyn & GI	2 (5.1)	10 (21.7)	5 (16.1)	7 (14.0)	24 (14.5)
HNC	18 (46.2)	8 (17.4)	20 (64.5)	14 (28.0)	60 (36.1)
Other	2 (5.1)	3 (6.5)	2 (6.5)	8 (16.0)	15 (9.0)
Sarcoma	17 (43.6)	25 (54.3)	4 (12.9)	21 (42.0)	67 (40.4)
Status					
Primary	26 (66.7)	34 (73.9)	19 (61.3)	27 (54.0)	106 (63.9)
Recurrent	13 (33.3)	12 (21.1)	12 (38.7)	23 (46.0)	60 (26.1)
Histological grade					
1 and 2	18 (46.2)	22 (47.8)	20 (64.5)	30 (60.0)	90 (54.2)
3 and 4	21 (53.8)	24 (52.2)	11 (35.5)	20 (40.0)	76 (45.8)
Lymphovascular space involvement	2 (5.1)	2 (4.3)	5 (16.1)	5 (10.0)	14 (8.4)
Perineural involvement	4 (10.3)	1 (2.2)	7 (22.6)	8 (16.0)	20 (12.0)
Nodal status					
pN+	6 (15.4)	3 (6.5)	19 (61.3)	17 (34.0)	45 (27.1)
Extracapsular spread	—	—	13 (41.9)	14 (28.0)	27 (16.3)

Gyn & GI = Gynecological and gastrointestinal; HNC = Head and neck cancer; pN+ = positive nodes.

1.0−1.5 cm intervals with a margin of 1 cm in all directions. The lateral margins were covered using additional catheters extending beyond the CTV. Catheters were inserted no more than 5 mm deep into the tumor bed to avoid underdosage of the surgical surface. In cases in which the catheters could not be inserted below the surface, reabsorbable sutures were used to secure the catheters onto the surgical surface. Single-plane implants were used in most of the cases. Once the implant was completed, any necessary reconstruction of the surgical defect was performed immediately.

A CT scan was performed for verification, usually during the second or third postoperative day, once the patient was in stable condition and ready for transportation. The CT study was transferred to the radiation treatment planning system for dosimetry (Gammamed's Abacus, version 3.55, was used from 2000 to 2006 and Brachyvision v.8.0, Varian, Palo Alto, CA from 2006 onward). The PHDRB doses were prescribed to the minimum target dose (MTD) as described in International Commission on Radiation Units and Measurements Report No. 58 (4) in the period from 2000 to 2006 and to the D_{90} (dose received by 90% of the CTV) from 2006 onward. A dose homogeneity index (DHI) ($[V_{100} - V_{150}]/V_{100}$) of at least 0.6 was required in all cases. Radiation parameters are detailed in Table 3.

Table 3
Radiation parameters for UNPM groups and outcome

Parameters	Low risk ($n = 39$)	p-Values	Intermediate risk ($n = 46$)	p-Values	High risk ($n = 31$)	p-Values	Very high risk ($n = 50$)	p-Values
Brachytherapy								
Number of catheters	5	ns	5	ns	5	ns	5	ns
Surgery to brachytherapy gap (d)	3	ns	5	ns	5	0.043	5	ns
Brachytherapy duration (d)	3	ns	3	ns	3	ns	3	ns
TV 4 Gy (cm^3)	45.5	ns	121.4	ns	59.7	ns	124.1	ns
TV 6 Gy (cm^3)	15.1	ns	37.5	ns	21.3	ns	37.6	ns
Physical dose (Gy)	20.1	ns	20.7	ns	23.5	ns	23.4	ns
D_{90} (Gy)	3.65	ns	4.04	ns	4.18	ns	4.09	ns
V_{100} (%)	89.8	ns	86.1	ns	95.5	ns	86.2	ns
V_{150} (%)	36.9	ns	40.0	ns	52.6	ns	40.6	ns
V_{200} (%)	11.8	ns	19.7	ns	21.2	ns	23.0	ns
CTV (cc)	15.7	ns	62.1	ns	8.5	ns	30.1	ns
DHI	0.64	ns	0.66	ns	0.63	ns	0.67	ns
External irradiation								
Physical Dose (Gy)	44.3	ns	43.9	ns	46.6	ns	46.3	ns
Brachytherapy + external irradiation								
Physical Dose (Gy)	64.4	ns	64.6	0.038	70.1	ns	69.7	ns
SP-based EQD2 (Gy)	67.1	ns	67.3	ns	73.2	ns	72.7	ns
H-based EUD TV_{100} (Gy)	83.5	ns	82.9	ns	93.0	ns	90.6	0.028

ns = not statistically significant; UNPM = University of Navarre Predictive Model; TV = treated volume; SP-based EQD2 = single-point 2-Gy equivalent dose; H-based EUD $TV100$ = histogram-based equivalent uniform dose in the tissue volume encompassed by the 100% isodose.

Study endpoints and statistical analysis

This study aimed to investigate the relationship between the size of the high-dose region and the probability of locoregional control in patients with the same UNPM risk category. Locoregional failure was defined as any tumor regrowth occurring in the anatomical region treated (i.e., anywhere above the clavicles in head and neck tumors, the entire anatomical compartment for sarcomas, the pelvis in gynecological tumors, and so on).

Physical dose, single-point 2-Gy equivalent dose (SP EQD2) and generalized histogram-based equivalent uniform dose (EUD) were calculated in each patient. Physical dose was calculated by addition of the prescription doses of the EBRT and the PHDRB courses. The SP EQD2 was calculated with the linear−quadratic model formulism (5) using an alpha/beta ratio of 10. The dose to the isocenter was used as single point for the EBRT course, and the minimum target dose International Commission on Radiation Units and Measurements No.58 or the CTVD_{90} were used as single-point for the PHDRB course. Finally, the EUD was calculated with the generalized formulation of Niemierko (6) (Fig. 1). In each of the UNPM risk categories, an ROC analysis was performed to determine the impact of EUD as well as the rest of the variables shown in Table 3 on locoregional control; in those patients with a p-value lower than 0.05, the difference was considered significant and the null hypothesis rejected (i.e., the differences were attributed to radiation dose effect).

Results

After a median followup of 7.4 years (range, 3−12+), 50 patients have failed and 116 remain controlled at last follow-up. The locoregional failure rate by UNPM group was 7.7%, 21.7%, 35.5%, and 52.0% for low-, intermediate-, high-, and very high-risk groups, respectively ($p = 0.0001$).

The EUD values for low-, intermediate-, high-, and very high-risk patients were 83.6, 82.9, 93.0, and 90.6 Gy, respectively (Table 3). Patients with high- and very high-risk tumors had greater average EUD values than patients with low- and intermediate-risk tumors (91.6 vs. 83.2 Gy; $p < 0.0001$) because the guidelines of the PHDRB protocol assigned a higher dose level to patients with close/positive margins.

We were unable to find a correlation between increasing EUD values and improved locoregional control in low-risk patients (AUC = 0.435; p = not significant [ns]), intermediate-risk patients (AUC = 0.386; p = ns), and high-risk patients (AUC = 0.473; p = ns). However, there was a significant correlation between increasing EUD values and improved locoregional control in very high-risk patients (AUC = 0.681; $p = 0.028$) with the best cutoff point set at an EUD of 89.5 Gy (AUC = 0.697; $p = 0.017$). When the data for very high-risk patients were split by cutoff point and entered into a Kaplan−Maier model, the difference was highly significant ($p = 0.002$; Fig. 2).

$$EUD = \left(\frac{1}{N}\sum_i D_i^a\right)^{\frac{1}{a}}$$

Fig. 1. Generalized EUD formulism. EUD = equivalent uniform dose.

Discussion

The relationship between generalized EUD and outcome has been analyzed in only a few studies, most of them dealing with permanent prostate implants (7−9). In the prostate reports referenced, the use of EUD did not reveal information additional to that provided by routine single-point parameters such as D_{90} or V_{100} (%); although in the study by Miles *et al.* (8), the correlation between EUD and biochemical relapse-free survival was greater ($p = 0.008$) than that of D_{90} ($p = 0.020$) and V_{100} (%) ($p = 0.017$). In a recent report, Stewart *et al.* (10) described a positive association between EUD and hyperpigmentation and telangiectasia in patients receiving partial breast irradiation using the Mammosite applicator. No other reports attempting to establish a relationship between EUD and outcome parameters were found in the PHDRB literature (11−18).

The present analysis shows that very high-risk patients (i.e., those with tumors larger than 3 cm resected with close <1 mm/positive margins) have improved locoregional control rates with increasing EUD values (Table 4). This dose−response effect was modest but statistically significant (AUC = 0.681; $p = 0.028$) and was not observed in the other risk groups, probably owing to the lack of statistical power to detect differences in strata with an anticipated low number of events. Dose escalation with

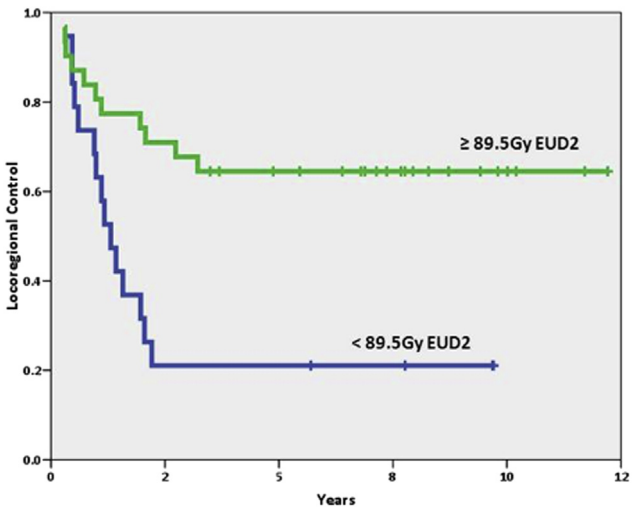

Fig. 2. Locoregional control by EUD in University of Navarre Predictive Model very high-risk patients. EUD = equivalent uniform dose.

Table 4
Outcome and H-based EUD TV_{100} values by risk group

Risk group	Controlled, *n* (%)	EUD, Gy	Failed, *n* (%)	EUD, Gy	*p*-Value
Low risk ($n = 39$)	36 (92.3)	83.3	3 (7.7)	85.7	ns
Intermediate risk ($n = 46$)	36 (78.3)	81.9	10 (21.7)	86.5	ns
High risk ($n = 31$)	20 (64.5)	92.8	11 (35.5)	93.6	ns
Very high risk ($n = 50$)	24 (48.0)	92.8	26 (52.0)	88.6	0.028

EUD = equivalent uniform dose; ns = not statistically significant; H-based EUD TV100 = histogram-based equivalent uniform dose in the tissue volume encompassed by the 100% isodose.

PHDRB, therefore, seems to be especially useful in those patients with the highest probability of locoregional failure. This finding is in agreement with other dose escalation studies (19) in which the magnitude of the benefit increases with the risk of the patient.

The improved locoregional control observed in very high-risk patients treated at higher doses was seen only when doses were calculated using the EUD formulism and not when the more common dose reporting methods such as physical dose or SP EQD2 were used (Fig. 3). This probably occurred because EUD accounts for the entire brachytherapy dose distribution and is highly dependent on the DHI. For instance, a combination of 24 Gy of PHDRB in 6 b.i.d. fractions with a DHI of 0.7 followed by 45 Gy of EBRT in 25 treatments results in an EUD of 89.5 Gy. Using the same combination, the use of optimal implants with a DHI of 0.8 would result in lower EUD values of less than 83 Gy, whereas suboptimal implants with a DHI of only 0.6 would result in EUD values of 96 Gy or more. Because similar physical doses or SP EQD2 values result in a wider range of EUD values, we recommend that PHDRB implants be evaluated with the EUD formulism in addition to other methods in routine practice (Fig. 4).

The use of histogram-based methods of dose standardization in brachytherapy seems necessary to analyze the overwhelming amount of data contained in the entire dose distribution. The histogram-based analysis is relatively simple and reliable with current computational technology and should be provided along with routine dose parameters and clinical data. The brachytherapy community should make a consensus effort to establish commonly accepted histogram-based surrogate parameters.

Conclusions

The UNPM very high-risk patients defined as those with tumors larger than 3 cm resected with microscopically positive margins or close margins of less than 1 mm have improved locoregional control rates with increased EUD values. This effect was not observed in low-, intermediate-, and high-risk patients. This dose–response effect is only evident if brachytherapy dose is calculated with the EUD formulism and may be overlooked if routine calculation methods are used.

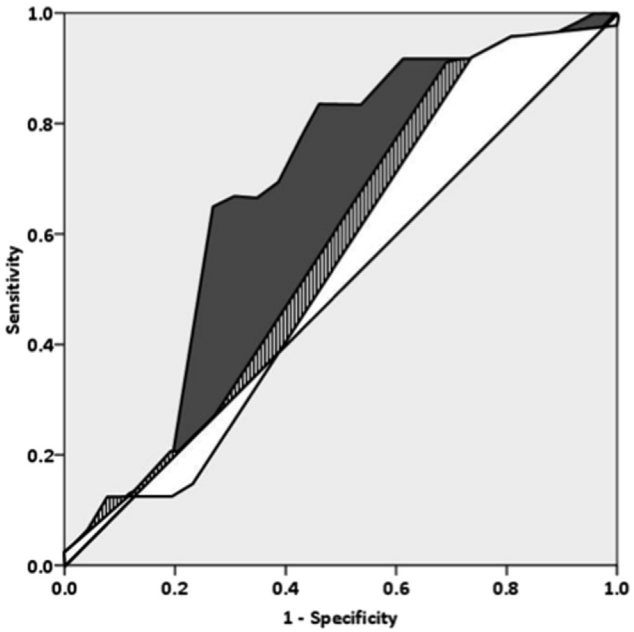

Fig. 3. Receiver operating characteristic curve by dose definition for very high-risk patients (physical dose, white; single-point 2-Gy equivalent dose, stripes; equivalent uniform dose, solid gray).

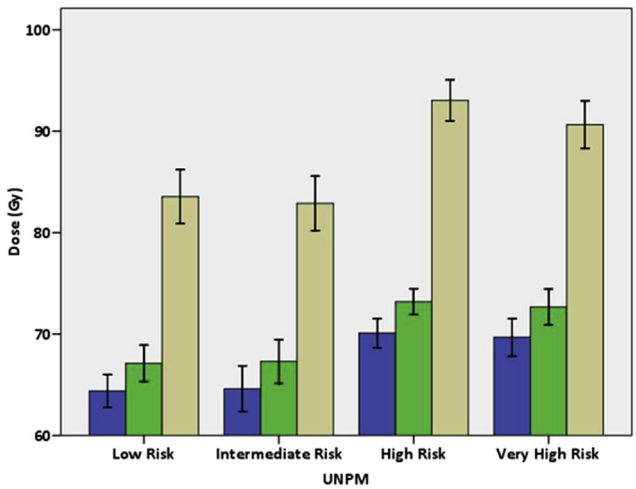

Fig. 4. Average physical dose (left, dark), single-point 2-Gy equivalent dose (center, dotted), and equivalent uniform dose (EUD; right, white) for each of the UNPM Groups. Error bars indicate that dose variability (95% confidence interval) is greatest after EUD calculation. UNPM = University of Navarre Predictive Model.

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