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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)