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New techniques in irradiation: clinical implications of perioperative high-dose rate brachytherapy

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Introduction

Brachytherapy (derived from the Greek term brachios, meaning short) is defined as the treatment of tumors through the placement of radioactive sources into or close to the malignant lesion. The main advantage of brachytherapy is based on the inverse squared law inherent to radioactive sources, which allows the delivery of a very high dose of radiation to the tumor with a substantial sparing of the surrounding normal tissues.

Historically, brachytherapy has evolved from hot loading (i.e. manual placement of radioactive devices into the patient) to remote afterloading. In remote afterloading, non-radioactive applicators are inserted into the tumor; these applicators are then loaded using mechanically driven, computer-controlled equipment after dosimetry is approved. From the radiation safety standpoint, remote afterloading eliminates the radiation hazards for both the hospital staff and visitors, and allows more convenient access to the patient.

Brachytherapy techniques, largely obscured with the advancement of modern teletherapy equipment after 1960, have received increasing attention over the last 15 years. The reasons that have contributed to this brachytherapy renaissance are multiple.

(i) Advances in brachytherapy software, particularly the integration of computed tomography (CT) image acquisition and computer-driven dosimetry, now allow a fast and meticulous analysis of the area to be treated with brachytherapy. The spatial relationship between the radiation isodoses and the volumes of interest is now visualized in a three-dimensional environment and displayed through dose volume histograms. Similarly, small imperfections in the implant quality can be corrected by changing the dwell times of the multistepping sources used in modern brachytherapy. As a result, tumor coverage is improved, and radiation dose to critical organs minimized.

(ii) Brachytherapy equipment has been improved with the design of small, stepping flexible sources with high specific activity (^{192}Ir) that can navigate through thin plastic or metal applicators of up to 5 French in diameter (1.5 mm). These sources can be designed to deliver treatments at a high dose rate (>12 Gy/h) that substantially shortens the period for which the patient remains radioactive.

(iii) Low-energy, low-activity gamma radionuclides (^{125}I, ^{103}Pd) are now available and can be used in permanent implants. These sources present a negligible radiological hazard when used for deep-seated tumors. Permanent implants have the advantage of requiring a much shorter hospital stay than other types of radiation therapy, and they are perceived by the patient as a less aggressive and more convenient type of therapy.

(iv) Finally, developments in medicine and health education have increased the number of patients with malignant tumors who are diagnosed at an earlier stage. As a result, many patients now present with small tumors that have a high probability of being organ-confined and that may be treated with organ therapies, such as brachytherapy.

Clinical indications for brachytherapy have expanded. Apart from the classical disease situations where the use of brachytherapy is undebatable, as in gynecological cancer [1], new malignant tumors are now increasingly being treated with this treatment modality. In the USA, the number of patients with low-risk prostate cancer treated with permanent brachytherapy implants [2] is almost equal to the number treated with surgery or external beam radiotherapy (EBRT), the two main standard approaches in the past. In moderate and high-risk prostate cancer, brachytherapy is also increasingly combined with EBRT to escalate the total dose delivered to the tumor, a treatment strategy which has proven superior over low-dose therapy [3]. Brachytherapy is also increasingly being used as the sole treatment modality for low-risk breast cancer. Although this approach is still experimental, initial results published worldwide report efficacy similar to standard EBRT with the advantage of reducing treatment time from 6 weeks to only 5 days [4]. Brachytherapy also plays an important role in the treatment of skin cancer [5], pediatric malignancies [6], and malignant obstruction due to lung [7], esophageal [8] and biliary duct cancer [9].

Finally, brachytherapy has been used in combination with surgical resection in the treatment of tumors that cannot be removed with wide margins. These patients are at a very high risk of relapse and usually need additional treatment with

Table 1. Prior perioperative high dose rate brachytherapy reports

Author	Institution	Journal and	Year	*n*	Comments
Höckel et al. [17]	Mainz, Germany	Cancer	1996	48	Gynecologic
Hannoun-Levi et al. [20]	Marseille, France	Eur J Surg Oncol	1997	14	Pelvic
Kwiatkowski et al. [21]	Stuttgart, Germany	Anticancer Res	1999	60	Case mix
Krull et al. [22]	Hamburg, Germany	Anticancer Res	1999	9	Head and neck cancer
Koizumi et al. [23]	Osaka, Japan	Int J Radiat Oncol Biol Phys	1999	16	Sarcomas
Petera et al. [24]	Czech Republic	Neoplasma	2004	21	Sarcomas

radiation therapy. This approach, using low-dose rate perioperative brachytherapy, has been applied extensively in the management of soft tissue sarcomas [10], but has potential for treating other tumor sites. However, the use of perioperative brachytherapy with modern high-dose rate technology remains largely unexplored. The techniques and results obtained at the University of Navarre with perioperative high-dose rate brachytherapy (PHDRB) are presented herein.

Perioperative high dose rate brachytherapy

In February 2000, we initiated a prospective, non-randomized, controlled (phase I or II) clinical study to determine whether PHDRB administered over the immediate postoperative period was useful to: (ii) safely escalate the radiation dose in well-defined areas of the surgical field that displayed high-risk features; and (ii) shorten the overall treatment time.

The successful protocol accrual, with more than 190 patients treated so far, is largely attributable to the pioneering work of Dr Calvo and colleagues with intraoperative electron beam radiotherapy at the University of Navarra. This prior experience allowed us to establish a close and friendly cooperative relationship with the different surgical teams involved in surgical oncology who were ready to face the challenges of a relatively new and unexplored treatment modality (Table 1).

Intraoperative implantation of plastic catheters into the tumor bed after surgical resection for PHDRB has several theoretical advantages over other types of radiation boosting techniques, including:

(i) accurate real-time definition of the clinical target volume (CTV) [11] surrounding the tumor bed and other high-risk areas (with the assistance of the surgical team);

(ii) CT scan-based treatment planning;

(iii) risk-adapted brachytherapy dose selection based upon the amount of residual disease described in the final pathology report; and

(iv) early delivery of fractionated radiation during the immediate postoperative period.

Materials and methods

Eligibility criteria

In general, any patient who, after preliminary evaluation, was considered a candidate for combined modality treatment with surgery and high-dose radiotherapy received a full explanation of the potential advantages of the PHDRB protocol as well as its investigational nature. Informed consent was required before study entry.

PHDRB protocol

Irradiation naïve patients. Unirradiated patients were treated with surgical resection and implantation of catheters for PHDRB. The brachytherapy dose was divided into three different levels according to the presumed amount of residual disease left as described in the final pathology report, usually available within 48 h after surgery. In R0 resections, the surgical margins were ≥10 mm. In R1 resections, surgical margins were either close (<10 mm) or microscopically positive, or extracapsular nodal extension was present. In R2 resections, gross residual disease was present.

R0 resections: brachytherapy dose = 4 Gy twice daily × 4 (16 Gy total dose)

R1 resections: brachytherapy dose = 4 Gy twice daily × 6 (24 Gy total dose)

R2 resections: brachytherapy dose = 4 Gy twice daily × 8 (32 Gy total dose)

Radiation treatment was completed with 45 Gy of EBRT in 25 treatments, 1.8 Gy daily fractions, 4–5 weeks after the surgical procedure. Total radiation doses equivalent to standard fractionation regimens delivered with 2 Gy daily fractions and calculated with the linear quadratic formulation [12] without time correction {i.e. $BED = nd[1 + d/(\alpha/\beta)]$} are shown in Figure 1).

Concomitant chemotherapy, if indicated, was added during the first and fifth weeks of EBRT.

Previously irradiated patients. Patients with recurrent disease after prior irradiation or patients with primary cancer arising in a previously irradiated field were treated with surgical resection and PHDRB. The brachytherapy dose was divided into three different dose levels according to the amount of residual disease present in the surgical bed as described in the final pathology report:

R0 resections: brachytherapy dose = 4 Gy twice daily × 8 (32 Gy total dose)

R1 resections: brachytherapy dose = 4 Gy twice daily × 10 (40 Gy total dose)

R2 resections: brachytherapy dose = 4 Gy twice daily × 12 (48 Gy total dose)

Further EBRT was not administered.

Intraoperative target definition

The surgical and the radiation oncology teams used the preoperative physical and imaging, surgical findings, frozen sections where necessary, and gross examination of the surgical specimen to jointly determine the area to be implanted.

Head and neck surgery. The CTV was all surgical field areas presumed to belong to Radiation Therapy Oncology Group (RTOG) risk category 2

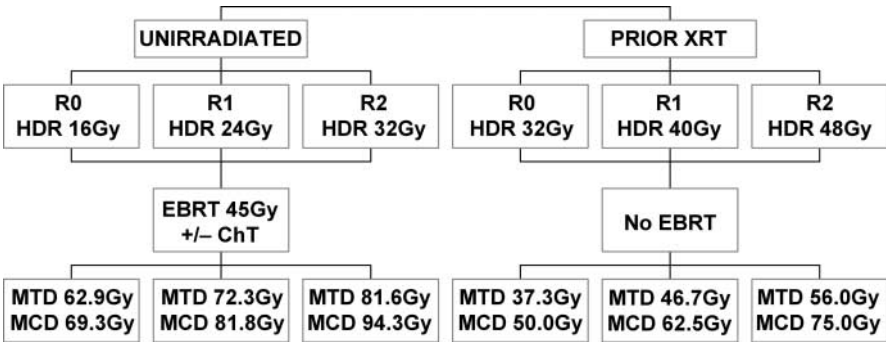

Figure 1. Treatment scheme. XRT, radiation therapy; HDR, high-dose rate brachytherapy; R0, R1, R2, type of surgical resection (see text); ChT, chemotherapy; EBRT, external beam radiation therapy; MTD, minimum target dose, 4 Gy/fraction; MCD, mean central dose, calculated at 5 Gy/fraction.

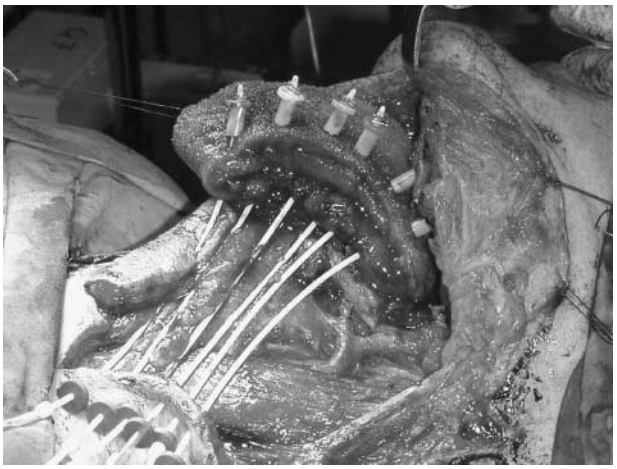

Figure 2. Squamous cell carcinoma of the right border of the tongue stage pT2N0 resected with close margins. The perioperative high-dose rate brachytherapy implant covers the surgical bed in the tongue.

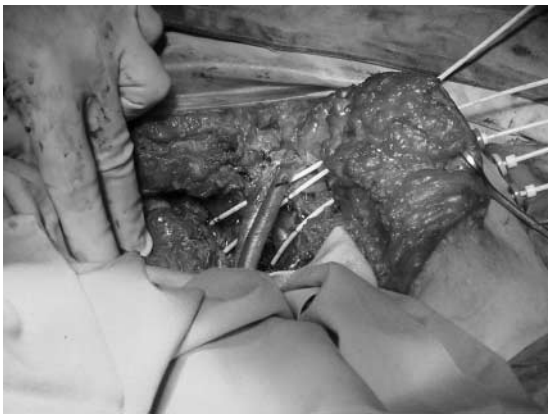

Figure 3. Recurrent clear cell carcinoma of the cervix involving the right pelvic sidewall. The perioperative high-dose rate brachytherapy implant covers the pelvic sidewall surface behind the external iliac vessels.

(i.e. two or more positive nodes or extracapsular nodal extension with negative margins) or risk category 3 (positive margins) [13] (Figure 2).

In practice, the implanted area covered the CTV around the primary tumor and the lymphatic chains with nodes >2–3 cm in diameter, which have a substantial probability of extracapsular extension [14].

Gynecological surgery. The CTV was all surgical field areas of tumor or nodal adherence to the pelvic wall(s) or lumboaortic vessels. No attempt was made to implant nodal areas at risk but clinically negative (Figure 3).

In practice, the implanted area covered the entire pelvic sidewall from the lower paravaginal space (obturator fossa) to the promontorium in pelvic locations or the lumboaortic area in paraortic nodal relapses.

Sarcoma surgery. The CTV was the entire surgical bed.

Brachytherapy technique

The CTV was covered with a set of plastic catheters placed as parallel as possible at 1–1.5 cm intervals with a margin of 1 cm in all directions. The lateral margins were provided with 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. This maneuver avoids catheter displacement and results in an improved geometry. Furthermore, the surgical surface remains catheter-free, making surgical reconstruction easier. In cases in which the catheters could not be inserted below the surface, reabsorbable sutures were used to secure the catheters onto the surgical plane. In addition, catheters were attached at the skin exit points with plastic buttons and silk sutures. The American Brachytherapy Society recommendations for brachytherapy implants in soft tissue sarcomas [15] were generally followed to develop the individual techniques for other anatomical areas. Some characteristics of individual procedures include the following.

Head and neck surgery. Single-plane implants were the preferred technique for both the primary tumor bed and the neck. In this location, the longitudinal margins were covered by setting the blind end of the catheters at 1–1.5 cm above the mucosal surface with the aid of a plastic spacer using a non-looping technique described previously [16]. Once the implant was completed, immediate reconstruction of the surgical defect was performed, if necessary, with regional flaps (infrahyoid and pectoralis major myocutaneous flaps) or microvascular free flaps including radial flap, lateral arm flap, abdominis flap and fibula.

Gynecological surgery. Single-plane implants were the preferred technique. The abdominal approach was used in the first five patients but was abandoned afterwards due to the interference of the pubic arch with the placement of catheters in low-lying tumors. In addition, in one patient a catheter became dislocated and the treatment had to be aborted. For that reason, from the sixth patient onwards, we used the perineal approach with passage of percutaneous catheters through the paravaginal or pararectal spaces to the CTV. Catheters were secured onto the surgical surface with reabsorbable sutures, because catheter tunnelization is not possible in that area. Single-plane implants were the preferred technique. Once the implant was completed, a radioprotective flap was created with the greater omentum using a technique previously described by Höckel [17].

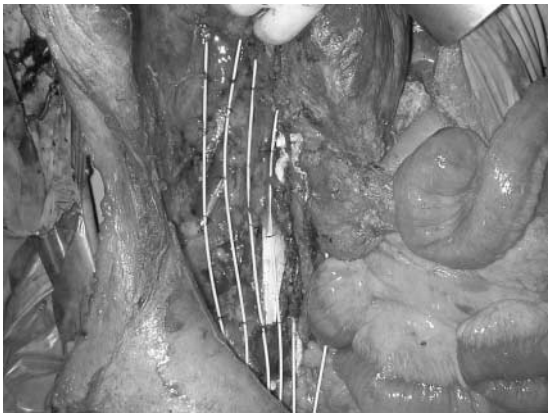

Figure 4. Recurrent retroperitoneal soft tissue sarcoma. The perioperative high-dose rate brachytherapy implant covers the right retroperitoneal surface and the anterior aspect of the inferior vena cava.

Sarcoma surgery. Single-plane implants were the preferred technique (Figure 4). The longitudinal margins were added by setting the distal and proximal ends of the catheters at 1.5–2 cm beyond the skin incision. If necessary, gelfoam or muscle flaps no more than 5 mm thick were interposed between the catheter plane and radiosensitive structures. In all cases, a sham plane reconstruction and wound closure was performed before the completion of the implant to make sure that the catheters did not overlap during closure. Once the implant was performed, the surgical team proceeded with the closure or, if necessary, with the reconstruction of the surgical defect with regional or microvascular free flaps. In abdominal or pelvic locations, an omentum or muscle flap was interposed between the implant plane and the intra-abdominal contents.

Dosimetry guidelines

A CT scan for verification was performed 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 (Abacus US module, version 3.55; Gammamed) for three-dimensional dosimetry including definition of target(s) and organ(s) at risk, source modeling, generation of dose volume histograms and evaluation of plans. The treatment planning process followed the rules of the Paris System with manual optimization for each of the CT slices. Additional rules included that the CTV be encompassed by the 4 Gy isodose line, defined as the minimum tumor dose (MTD) isodose line as per the ICRU recommendations [18]. An MTD to mean central dose ICRU ratio of not less than 70% was accepted, provided that the volume encompassed by the 6 Gy isodose (V_{150}) was not greater than 50% of the volume encompassed by the 4 Gy isodose (V_{100}). Automatic optimization algorithms provided by the Treatment Planning System were not allowed. Once the treatment plan was approved, it was transferred to the afterloader unit control console where the dwell positions and treatment times were double-checked by the radiation technologist.

Statistical analysis

Survival results were calculated using the Kaplan–Meier [19] method from the date of surgery to the last follow-up visit, and differences were evaluated with the log-rank test. Discrete variables were compared with the Fisher's exact test. Local failure was defined as the occurrence of tumor regrowth in the area treated with brachytherapy or in an adjacent region (i.e. recognition failure). Regional failure was defined as any other failure in the anatomical area treated and distant failure was defined as any other failure elsewhere.

Toxicity analysis

Acute toxicities were defined as those occurring from the date of surgery to 60 days after the completion of the treatment. Toxicities were classified as late if they occurred >60 days after the completion of the treatment. Toxicities were documented according to the RTOG morbidity scoring criteria. The scoring system was: 0 = no change; 1 = mild symptoms not requiring medication; 2 = moderate symptoms requiring occasional medication; 3 = severe symptoms requiring frequent medications and/or a minor surgical procedure; 4 = severe and persistent symptoms requiring a major surgical procedure; and 5 = treatment-related death.

Preliminary results

One hundred and eighty-three patients have been included during the study period from February 2000 to October 2004. Patient characteristics are shown in Table 2. Data analysis is based on 177 patients with at least 3 months of follow-up after PHDRB.

The average dose deviation for the 177 patients analyzed was 4.5% (Table 3). This was mainly due to a programmed reduction in the EBRT dose in growing individuals [6], as well as the need to decrease the overall target dose in some paravertebral locations where the prescription dose would

Table 2. Patient population

		n	%
Number of patients		183	100.0
Diagnosis	**Head and neck**	**69**	**37.7**
	Tongue	23	12.6
	Oropharynx	12	6.6
	Major salivary glands	11	6.0
	Floor of mouth	6	3.3
	Other	17	9.3
	Sarcomas	**57**	**31.1**
	Soft tissue	49	26.8
	Bone	8	4.4
	Abdominopelvic	**38**	**20.8**
	Gynecological cancer	23	12.6
	Colorectal	15	8.2
	Other	**19**	**10.4**
Disease status	**Primary disease**	**84**	**45.9**
	Recurrent Prior	**99**	**54.1**
	Radiotherapy	57	31.1
	No prior radiotherapy	42	23.0
Type of resection	**R0**	**36**	**19.7**
	R1	**134**	**73.2**
	Close margins	67	36.6
	Positive margins	67	36.6
	R2	**7**	**3.8**

Table 3. Protocol compliance

Category		*n*	Target dose (Gy)	Actual dose (average) (Gy)	Deviation (%)
Irradiation naïve	R0, unirradiated	31	62.9	63.7	+1
	R1, unirradiated	87	72.3	68.2	−6
Previously irradiated	R0, prior XRT	5	37.3	37.3	None
	R1, prior XRT	47	46.7	44.4	−5

Total radiation doses equivalent to standard fractionation regimens delivered with 2 Gy daily fractions and calculated with the linear quadratic formulation [12] without time correction {i.e. BED = nd[1 + d/(α /β)]}.
XRT, radiation therapy.

have exceeded the spinal cord tolerance. In addition, the PHDRB dose was reduced to the closest lower level, owing to excessive toxicity in oropharyngeal and previously irradiated pelvic tumors.

After a median follow-up of 19 months (range 3.5–54+) the 4-year local control rate was 82.5%. Local control rate correlated with the quality of the surgical margin. Patients with negative margins of resection (≥10 mm) had a 4-year local control rate of 97.1%, and patients with close and positive margins had 4-year control rates of 83.8% and 76.8%, respectively ($P = 0.04$). When compared by standardized dose [20], we observed that patients receiving a total dose of <63 Gy (average 48.2±10.3 Gy) had a control rate of 73.6% compared with 91.6% (average 73.4±4 Gy) for those patients receiving >63 Gy ($P = 0.02$) (Figure 5). This difference was even more significant in the subgroup of patients with close margins (<10 mm), with a 4-year local control of 100% for the patients who received a dose of ≥63 Gy versus 34.3% for those patients receiving <63 Gy ($P = 0.0001$). We were not able to observe any dose–response relationship in those patients with negative or positive margins. In the subgroup of patients with negative margins receiving <63 versus ≥63 Gy, the 4-year local control figures were 96.5% and 100%, respectively ($P = 0.678$). Similarly, the 4-year local control rates for the subgroup of patients with positive margins who received <63 versus ≥63 Gy were 82.1% and 75.2%, respectively ($P = 0.642$).

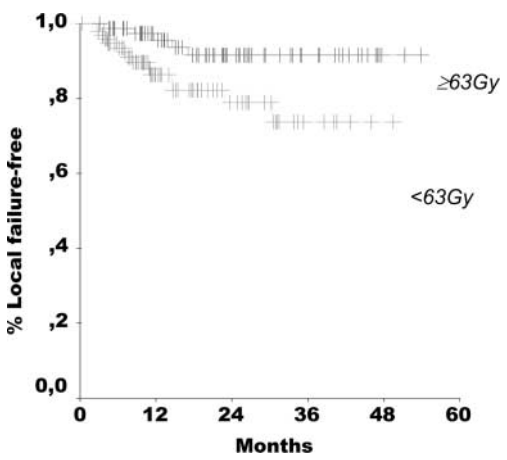

Figure 5. Four-year local control rates by standardized dose.

The 4-year regional control rate was 72.5%. Patients with negative, close and positive margins had a 4-year regional control rates of 88.9%, 76.6% and 60.8%, respectively ($P = 0.0001$). The 4-year distant control rate was 62.2%. The corresponding figures for patients with negative, close and positive margins were 79.3%, 74% and 43%, respectively ($P = 0.0001$).

RTOG 4–5 complications that occurred in the anatomical area treated (whether related to the delivery of PHDRB or not) were seen in 27 patients (15.2%). Most were surgical in nature. A detailed description of the toxicities observed is displayed in Table 4.

Conclusions

The 4-year local control results obtained with the different PHDRB protocols described exceeds 80%. This is particularly noteworthy taking into account that 54.1% of the patients received PHDRB for recurrent tumors (31.1% after prior

Table 4. Toxicity[a]

	Grades 1–3	Grade 4	Grade 5	Overall	%
Bleeding	1	2	5	8	4.5
Bone damage	3	–	–	3	1.7
Edema	2	–	–	2	1.1
Graft failure	3	3	–	6	3.4
Nerve damage	22	–	–	22	12.4
Seroma/abscess	6	–	–	6	3.4
Soft tissue necrosis	3	4	–	7	4.0
Bowel damage	4	1	–	5	2.8
Fistula	6	5	–	11	6.2
Fibrosis	2	1	–	3	1.7
Thrombosis	1	–	–	1	0.6
Ureteral damage	4	–	–	4	2.3
Wound breakdown	12	4	–	16	9.0
Technical complications	2	1	–	3	1.7

[a]More than one toxicity per patient.
Total radiation doses equivalent to standard fractionation regimens delivered with 2 Gy daily fractions and calculated with the linear quadratic formulation [12] without time correction {BED = nd[1 + d/(α /β)]}.

irradiation) and 73.2% had surgical resections with close or positive margins.

Patients with negative margins had the best 4-year local control results (97.1%) despite a lower dose as per protocol. Patients with close and positive margins had worse 4-year local control results (83.8% and 76.8%, respectively) ($P = 0.04$).

A dose–response relationship was observed in patients with close margins with a cut-off level determined at a standardized dose of 63 Gy. This dose–response effect was not seen in patients with negative or positive margins. Hence, it is uncertain that escalating the PHDRB dose may improve the local control results in patients with positive margins.

Most of the toxic events observed were surgical in nature. Toxicity mainly related to PHDRB, alone or combined with EBRT, included: four of the five cases of delayed fatal bleeding (three previously irradiated pelvic tumors and one oropharyngeal tumor); four cases of grade 4 soft tissue necrosis (three in the oropharyngeal area); and 22 cases of neuritis, mostly grade 1–2 and reversible. The toxic events observed mandated a PHDRB dose reduction to the closest lower level in oropharyngeal locations and in pelvic locations after prior irradiation.

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