

A proposal for the stratification of the risk of locoregional failure after surgical resection, perioperative high dose rate brachytherapy, and external beam irradiation: The University of Navarre predictive model

Rafael Martínez-Monge^{1,*}, Mauricio Cambeiro¹, María E. Rodríguez-Ruiz¹, Luis I. Ramos¹, Mikel San-Julián², Juan Alcalde³, Matías Jurado⁴

¹Department of Radiation Oncology, Clínica Universitaria de Navarra, University of Navarre, Avda Pío XII s/n, Pamplona, Navarre, Spain

²Department of Orthopedic Surgery, Clínica Universitaria de Navarra, University of Navarre, Avda Pío XII s/n, Pamplona, Navarre, Spain

³Department of Otolaryngology, Clínica Universitaria de Navarra, University of Navarre, Avda Pío XII s/n, Pamplona, Navarre, Spain

⁴Department of Gynecology, Clínica Universitaria de Navarra, University of Navarre, Avda Pío XII s/n, Pamplona, Navarre, Spain

ABSTRACT

PURPOSE: To develop a simple clinical model predictive of locoregional failure after complete surgical resection followed by perioperative high-dose-rate brachytherapy (PHDRB) and external beam irradiation (EBRT).

PATIENT AND METHODS: Patients ($n = 166$) enrolled in several PHDRB prospective studies conducted at the University of Navarre were analyzed. 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 of EBRT.

RESULTS: After a median followup of 7.4 years (range, 3–12+), 50 patients have failed and 116 remain controlled at last followup. Tumor size, with a cutoff point set at 3 cm ($p = 0.041$) and margin status (positive and <1 mm vs. negative ≥ 1 mm, $p = 0.0001$) were independent predictors of locoregional control. These two parameters were used to develop a four-tiered, hierarchical scoring system that stratified patients into low-risk (negative ≥ 1 mm margins and size ≤ 3 cm), intermediate-risk (negative ≥ 1 mm margins, and size >3 cm), high-risk (positive and <1 mm margins and size ≤ 3 cm), and very high-risk categories (positive and <1 mm margins and size >3 cm). This classification yields 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. The predictive ability of the model is highly significant ($p = 0.0001$) with an area under the curve of 0.72 (0.64–0.81).

CONCLUSIONS: The risk of locoregional failure after combined surgical resection, PHDRB, and EBRT is mainly determined by the number of residual clonogens, which is inversely proportional to the status of the surgical margins and directly related to the size of the resected tumor. These two parameters generate a four-tiered predictive model that seems to be valid for a number of different common tumors and clinical settings. © 2014 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keyword: Perioperative high dose rate brachytherapy

Introduction

Perioperative high-dose-rate brachytherapy (PHDRB) is a relatively new treatment modality that closely resembles

traditional low-dose-rate brachytherapy, but with the added advantage of CT planning, dose optimization, and radiation protection.

PHDRB seems to be ideally suited to increase radiation doses in those patients who are at higher risk of locoregional failure due to the limitations of the surgical treatment or the characteristics of the tumor because PHDRB can be precisely delivered over a well-delineated area of the surgical bed that has the highest probability of containing residual tumor clonogens (i.e., positive surgical margins and/or

Received 19 February 2013; received in revised form 23 September 2013; accepted 11 November 2013.

* Corresponding author. Department of Oncology, Clínica Universitaria de Navarra, University of Navarre, Avda Pío XII s/n, Pamplona, Navarre, Spain. Tel.: +34-948-255400; fax: +34-948-255500.

E-mail address: rmartinezm@unav.es (R. Martínez-Monge).

extracapsular spread). Dose escalation with brachytherapy can be accomplished by increasing the prescription dose or by allowing a greater heterogeneity within the implant volume, resulting in a higher biologic dose.

A previous study conducted in our institution showed that the quality of the surgical margins was the main predictor ($p = 0.002$) of long-term locoregional control in 186 patients treated with PHDRB combined with external beam irradiation (EBRT) (1). Since the dose prescription was determined per protocol according to the quality of the surgical margins and the dose was prescribed to a single point (minimum target dose or the CTV90), no dose effect could be determined from that study.

The present analysis aims to determine if patients receiving the same physical dose but higher biologic doses due to more inhomogeneous PHDRB implants have an improved locoregional control compared with patients treated at the same physical dose but with lower biologic doses. From a methodological standpoint, the study requires (1) creation of a predictive model of risk of locoregional failure and (2) analysis of the impact of dose heterogeneity for each risk group. This manuscript describes a proposal for the stratification of the risk of locoregional failure after surgical resection, PHDRB, and EBRT. The analysis of the impact of dose heterogeneity for each risk group will be reported separately.

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). The majority of the patients presented with head and neck cancer (2), sarcomas (3), or gynecologic and colorectal cancer (4). A complete documentation of the status of the surgical margins was required for analysis. Other pathologic adverse features (tumor size, histologic grade, lymphovascular space involvement, perineural involvement, multiple

Table 1
Patient parameters

	<i>n</i>	%
Gender		
Female	70	42.2
Male	96	57.8
Prior treatments		
Chemotherapy	0	0
Radiation	0	0
Surgery	54	32.5

positive nodes, extracapsular spread) that have been associated with decreased locoregional control rates were documented as well (Table 2).

Treatment protocol

One hundred sixty-six patients were treated with a combination of PHDRB and EBRT. Patients with negative margins of ≥ 10 mm received a PHDRB dose of 16 Gy in 4 b.i.d. treatments in 2 days and patients with negative but < 10 mm or positive margins received 24 Gy in 6 b.i.d. treatments over 3 days. 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 (5).

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 (1). 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. For instance,

Table 2
Tumor parameters

	<i>n</i>	%
Diagnosis		
Head and neck	60	36.1
Sarcomas	67	40.4
Gyn and GI	24	14.5
Other	15	9.0
Status		
Primary	106	63.9
Recurrent	60	36.1
Surgical margins		
Negative	103	62.0
Positive ^a	63	38.0
Tumor diameter (cm)		
≤ 3	70	42.2
> 3	96	57.8
Histologic grade		
1 and 2	90	62.6
3 and 4	76	57.9
Lymphovascular space involvement	14	9.4
Perineural involvement	20	13.5
Nodal status		
pN+	45	27.1
Extracapsular spread	27	16.3
pN0	40	24.1
pNx	81	48.8

Gyn = gynecologic; GI = gastrointestinal.

^a Follows the MSKCC classification (i.e., accounts for microscopically positive and close but within 1 mm of the inked margin of resection). Patients who are extracapsular extension positive are considered margin-positive even in the absence of positive margins at the primary site.

in head and neck tumors, the implanted area usually covered the clinical target volume (CTV) around the primary tumor and the lymphatic chains with 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.

After target definition, CTV was covered with a set of plastic catheters placed as parallel as possible at 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 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 the large majority 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 (Abacus, version 3.55, Gammamed, was used from 2000 to 2006 and Brachyvision, Varian, from 2006 onward). PHDRB doses were prescribed to the minimum target dose as described in the ICRU Report No.58 (6) in the period from 2000 to 2006 and to CTV₉₀ (dose received by 90% of CTV) from 2006 onward. A Dose Homogeneity Index ([V100–V150]/V100) of at least 0.6 was required in all cases. Radiation parameters are detailed in Table 3.

Study endpoints and statistical analysis

This study aimed to develop a system for the stratification of the risk of locoregional failure after surgical resection, PHDRB, and EBRT. The first step included the univariate analysis of the effect on locoregional control of several variables: patient factors (age, gender, prior surgery), tumor

Table 3
Radiation parameters

	Value ^a
Brachytherapy	
Number of catheters	4 or 5
Surgery to brachytherapy gap (d)	4
Brachytherapy duration (d)	3
CTV (cm ³)	32.5 ± 55.5
TV 4 Gy (cm ³)	92.8 ± 113.5
TV 6 Gy (cm ³)	29.3 ± 31.3
Physical dose (Gy)	21.9 ± 3.8
External irradiation	
Physical dose (Gy)	45.2 ± 6.1
Brachytherapy + external irradiation	
Physical dose (Gy)	67.1 ± 6.7
2-Gy equivalent dose (Gy)	70.0 ± 6.6

CTV = clinical target volume; TV = treated volume.

^a Discrete parameters shown as mode; continuous variables shown as mean ± standard deviation.

factors (status, size, histologic type, grade, margins, nodal status, lymphovascular invasion, perineural involvement, extracapsular extension), and treatment-related factors (physical dose, 2-Gy equivalent dose-EQ2, CTV size, percentage of CTV within the 100% isodose-CTV100%, tissue volume within the 100% and 150% isodoses of 4Gy-TV4 Gy and TV6 Gy, respectively). Second, statistically significant variables were included in a multivariate analysis performed with the Cox Proportional Hazards Model (7). A *p*-value of <0.05 (two-tailed) was considered as statistically significant. Finally, the variables found to be significant in the multivariate analysis were used to construct a predictive model that was validated in a ROC model.

Locoregional failure was defined as any tumor regrowth occurring in the anatomic region treated (i.e., anywhere above the clavicles in head and neck tumors, the entire anatomic compartment for sarcomas, the pelvis in gynecologic tumors, and so on).

Results

At the time of evaluation, 50 patients have failed at locoregional sites at a median of 10.8 months, and 116 remain controlled at a median followup of 7.4 years (range, 3–12+). The 5-year locoregional control rate for the whole patient set was 70.3%, and the 10-year locoregional control rate was 69.3%.

Univariate analysis (Table 4) showed that two different definitions of surgical margins, tumor size, physical dose,

Table 4
Parameters analyzed

	Univariate	Multivariate
Patient factors		
Age	ns	ns
Gender	ns	ns
Prior surgery	ns	ns
Pathologic risk factors		
Tumor status ^a	ns	ns
Tumor size	0.007	0.041
Histologic type ^b	ns	ns
Histologic grade	ns	ns
Margins (negative vs. close vs. positive)	0.001	ns
Margins (negative and close ≥1 mm vs. positive and close <1 mm)	0.0001	0.0001
Nodal status (pN + vs. pN0 vs. pNx)	ns	ns
LVSI status	ns	ns
PNI status	ns	ns
ECS status	ns	ns
Treatment factors		
Physical dose	0.019	ns
2-Gy equivalent dose	0.017	ns
CTV size	ns	ns
CTV 100%	ns	ns
TV4 Gy	ns	ns

LVSI = lymphovascular invasion; PNI = perineural involvement; ECS = extracapsular extension; CTV = clinical target volume; TV = treated volume; ns = not significant.

^a Primary vs. recurrent.

^b Epithelial vs. non-epithelial.

and 2-Gy equivalent dose were statistically significant. However, in multivariate analysis, only surgical margins as per the MSKCC definition (negative ≥ 1 mm vs. positive and <1 mm) and tumor size retained statistical significance. Patients with positive and <1 mm surgical margins had a 3.4-fold (95% confidence interval [CI], 1.8–6.5) greater risk of locoregional failure than patients with negative ≥ 1 mm margins ($p = 0.0001$). The corresponding 5-year locoregional control rates for these two subsets were 55.1% and 84.6%, respectively. In addition, patients with tumors larger than 3 cm had a 1.9-fold (95% CI, 1.0–3.5) greater risk of locoregional failure than patients with smaller tumors ($p = 0.041$). Five-year locoregional control rates for tumors larger than 3 cm or ≤ 3 cm were 80.9% and 62.4%, respectively.

The combination of the two parameters allowed establishment of a hierarchical predictive model in which patients are sequentially stratified first by margins and then by tumor size (Fig. 1). This stratification generates a four-tiered risk classification of locoregional failure. The four distinct categories termed low, intermediate, high, and very high risk have 5-year locoregional control rates of 92.3%, 78%, 65.5%, and 48.0%, respectively ($p = 0.0001$). When this stratification system is plotted against locoregional failure in an ROC curve, an area under the curve (AUC) of 0.72 (95% CI, 0.64–0.81) is obtained ($p = 0.0001$) (Fig. 2).

Discussion

The success of postoperative irradiation depends on both the number of clonogens remaining after resection (quantitative component) as well as on their intrinsic radiosensitivity (qualitative component). The model proposed here is mainly quantitative, since surgical margins and tumor size are thought to be proportional to the amount of residual disease left after surgery. However, both parameters are different in the sense that surgical margin is a categorical variable (each category representing a different average of

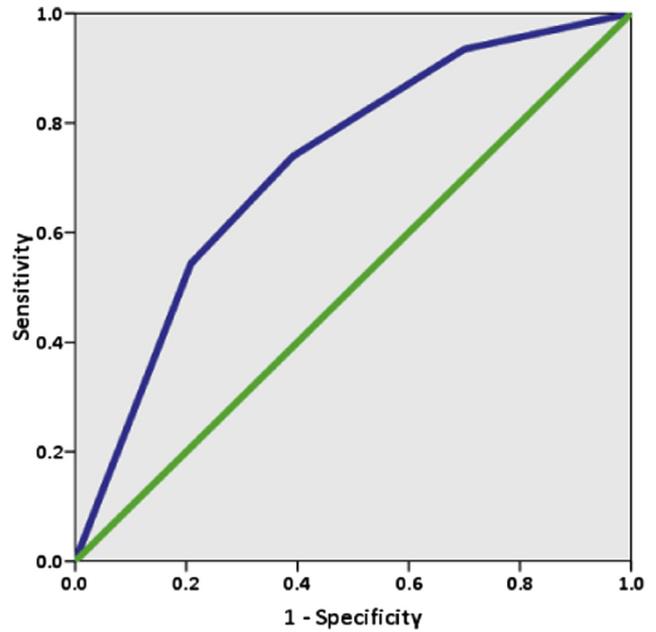


Fig. 2. Predictive ability of the model.

residual tumor burden within a presumably very broad range), whereas tumor size is a continuous variable. In clinical practice, both positive surgical margins and enlarged tumor size are predictive of increased locoregional failure in most common human malignancies including soft-tissue sarcomas, head and neck cancer, and cervical cancer among others (5). Other factors, such as lymphovascular invasion, perineural involvement, and so on, that usually portend a more aggressive clinical behavior were not statistically significant in this study. The likely explanation is that a significant percentage (more than 40%) of our patients presented with non-epithelial tumors. Non-epithelial tumors are known to have a lower propensity for either lymphovascular or perineural spread. Finally, neither primary tumor site nor tumor status affected locoregional control. All these findings show that the risk of locoregional failure primarily depends on the number of residual tumor clonogens rather than on tumor type, status, or phenotype. The present model is an obvious oversimplification of a complex phenomenon, but it seems applicable to a large number of clinical scenarios where postoperative irradiation is necessary.

The correlation between tumor size and locoregional failure throws doubt on the routine use of PHDRB in the management of large tumors. Contemporary oncologic knowledge shows that the larger the index lesion, the greater probability of residual disease after resection. In addition, the residual tumor foci can be found relatively far from the index lesion, and this distance is proportional to the size of the resected tumor (8). Hence, caution must be exercised when using PHDRB to treat large tumors, due to the risk of suboptimal CTV coverage. However, the decision to

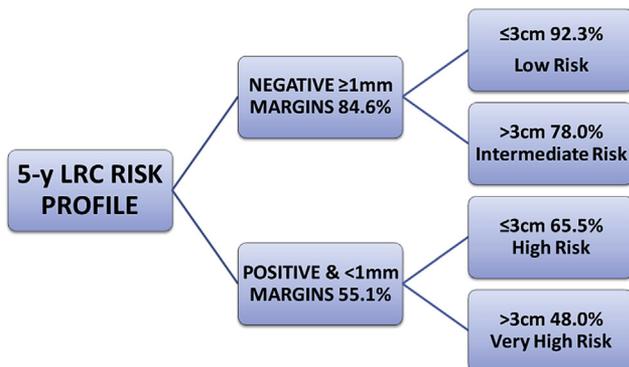


Fig. 1. Hierarchical predictive model.

use PHDRB must be made on a case-by-case basis since the inverse relationship between tumor size and locoregional control does not provide cutoff points that are sensitive enough as to predict good and poor candidates for PHDRB. For instance, the median TV4 Gy (i.e., reference volume encompassed by the 100% isodose of 4 Gy) for tumors ≤ 3 cm was 36.7 cm³; for tumors greater than 3 cm, it was 82.2 cm³. Both cases represent small boost volumes when compared with a customary EBRT conedown volume. This is extremely important when the fact that around one-third of the total physical dose was given with PHDRB (Table 3) is taken into account. Patients with large tumors in whom adequate coverage with PHDRB is questionable are probably candidates for increased EBRT doses following the same principles used in gynecologic brachytherapy.

Locoregional control rates in some patient categories remain modest. For instance, 5-year locoregional control rates in high-risk patients and very high-risk patients were 65.5% and 48.0%, despite median physical and 2-Gy equivalent doses of 69.0 Gy and 72.2 Gy, respectively. These patient categories may require dose escalation or earlier implementation of radio-potentiating agents to maximize locoregional control. A research project is underway to determine if the patients who received higher normalized doses by way of histogram-based calculation benefited from dose escalation.

Finally, the present model, although statistically significant ($p = 0.0001$) is far from being highly predictive (AUC, 0.72; 95% CI, 0.64–0.81). More research is needed to bring the predictive ability of the model nearer to AUC levels in accordance with safe clinical practices that advocate an accuracy beyond the 0.8 AUC threshold. Two independent research projects aimed at increasing the predictive ability of the model through neural network modeling and DNA profiling are currently underway. The accurate prediction of the expected 5-year locoregional control rate of a given subject has the advantage of treatment individualization that can provide superior results to a standard treatment delivery.

Conclusions

Surgical margins and tumor size determine long-term locoregional status. Locoregional outcome is mainly dependent on the number of tumor clonogens remaining after surgery and does not seem to be strongly related to other factors such as primary site, histologic type, and/or tumor phenotype.

Acknowledgments

The authors thank Mr David Carpenter for editorial assistance.

References

- [1] Martínez-Monge R, Cambeiro M, Moreno M, et al. Interaction of 2-Gy equivalent dose and margin status in perioperative high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2011;79:1158–1163.
- [2] Martínez-Monge R, Pagola DM, Cambeiro M, et al. Determinants of complications and outcome in high-risk squamous cell head-and-neck cancer treated with perioperative high-dose rate brachytherapy (PHDRB). *Int J Radiat Oncol Biol Phys* 2011;81:e245–e254.
- [3] San MI, San JM, Cambeiro M, et al. Determinants of toxicity, patterns of failure, and outcome among adult patients with soft tissue sarcomas of the extremity and superficial trunk treated with greater than conventional doses of perioperative high-dose-rate brachytherapy and external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;81:e529–e539.
- [4] Martínez-Monge R, Jurado M, Cambeiro M, et al. Perioperative high-dose-rate brachytherapy in locally advanced and recurrent gynecologic cancer: Initial results of a phase II trial. *Brachytherapy* 2006; 5:203–210.
- [5] National Comprehensive Cancer Network. Practice guidelines in oncology. 2013. www.nccn.org.
- [6] International Commission on Radiation Units and Measurements. *Dose and volume specification for reporting interstitial therapy. ICRU report 58*. Bethesda, MD: International Commission on Radiation Units and Measurements, 1997.
- [7] Cox DR. Regression models and life tables. *J R Stat Soc* 1972;34: 187–220.
- [8] Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985;56:979–990.