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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

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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.

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

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

Table 1
Patient parameters

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

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

	n	%
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.