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Time to loading and locoregional control in perioperative high-dose-rate brachytherapy: The tumor bed effect revisited

Rafael Martínez-Monge[1,7,*], Germán Valtueña[1,7], Marta Santisteban[2,7], Mauricio Cambeiro[1,7], Leyre Arbea[1,7], Luis I. Ramos[1,7], Alicia Olarte[1,7], Mikel San-Julián[3,7], Juan Alcalde[4,7], Luis Naval-Gías[5,7], Matías Jurado[6,7]

[1]*Department of Radiation Oncology, Clínica Universidad de Navarra, University of Navarre, Pamplona, Navarre, Spain*
[2]*Department of Medical Oncology, Clínica Universidad de Navarra, University of Navarre, Pamplona, Navarre, Spain*
[3]*Department of Orthopedic Surgery, Clínica Universidad de Navarra, University of Navarre, Pamplona, Navarre, Spain*
[4]*Department of Otolaryngology, Clínica Universidad de Navarra, University of Navarre, Pamplona, Navarre, Spain*
[5]*Department of Oral Surgery, Clínica Universidad de Navarra, University of Navarre, Pamplona, Navarre, Spain*
[6]*Department of Gynecology, Clínica Universidad de Navarra, University of Navarre, Pamplona, Navarre, Spain*
[7]*Instituto de Investigación Sanitaria de Navarra (IDISNA), Pamplona, Navarre, Spain*

ABSTRACT

PURPOSE: To determine whether the time to loading (TTL) affects locoregional control.
METHODS AND MATERIALS: Locoregional control status was determined in 301 patients enrolled in several perioperative high-dose-rate brachytherapy (PHDRB) prospective studies conducted at the University of Navarre. The impact of the time elapsed from catheter implantation to the first PHDRB treatment (TTL) was analyzed. Patients treated with PHDRB alone ($n = 113$), mainly because of prior irradiation, received 32 Gy in eight twice-a-day treatments or 40 Gy in 10 twice-a-day treatments for negative or close/positive margins, respectively. Patients treated with PHDRB + external beam radiation therapy (EBRT) ($n = 188$) received 16 Gy in four twice-a-day treatments or 24 Gy in six twice-a-day treatments for negative or close/positive margins followed by 45 Gy of EBRT in 25 treatments.
RESULTS: After a median followup of 6.5 years (range, 2–13.6+), 113 patients have failed (37.5%), 65 in the PHDRB-alone group (57.5%) and 48 in the combined PHDRB + EBRT group (25.5%). Patients who started PHDRB before Postoperative Day 5 had a 10-year locoregional control rate of 66.7% and patients who started PHDRB on Postoperative Day 5 or longer had a 10-year locoregional control rate of 51.8% ($p = 0.009$). Subgroup analysis detected that this difference was only observed in the recurrent cases treated with PHDRB alone (Subset 2; $n = 99$; $p = 0.004$). No correlation could be detected between locoregional control rate and TTL in the other patient subsets although a trend toward a decreased locoregional control rate after a longer TTL was observed when they were grouped together ($p = 0.089$).
CONCLUSIONS: Patients should start PHDRB as soon as possible to maximize locoregional control especially in those recurrent cases treated with PHDRB alone. The time effect in other disease scenarios is less clear.

Keywords: Time to loading; Locoregional control; Perioperative high-dose-rate brachytherapy

Introduction

Local relapse after surgical resection is the result of the interaction between the residual tumor foci and the tumor bed microenvironment. Irradiation of the tumor bed before inoculation of cells from transplantable tumors in murine models has resulted in delayed growth followed by subsequent growth at a reduced rate (1, 2). This phenomenon,

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* Corresponding author. Department of Radiation 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).

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also known as tumor bed effect (TBE), has been observed after intraoperative irradiation of tumor beds in targeted intraoperative radiotherapy-treated patients (3). Tumor bed fluids from irradiated patients show suppression of the stimulatory effect over *ex vivo* tumor cell lines when compared with fluids harvested from unirradiated patients.

TBE has been described to occur when irradiation is delivered before tumor cell inoculation (1, 2) or at the time of surgical resection (3), but it is unknown whether TBE occurs when irradiation starts a few days after resection, such as in perioperative high-dose-rate brachytherapy (PHDRB) (4). If this phenomenon is also triggered by PHDRB, the time to loading (TTL) should be taken into account because TBE has been shown to decline with time (5, 6).

Traditional brachytherapy practice advises a TTL of 5 days or more to minimize wound complications that have been observed with shorter gaps (7). However, considering the previously discussed TBE knowledge (3), one could hypothesize that a delayed TTL that allows adequate wound healing might result in a deficient TBE with a higher risk of locoregional failure.

The present study aims to elucidate the impact of TTL on locoregional control in a series of 301 patients treated with PHDRB at a single institution.

Methods and materials

Eligibility criteria

Patients treated with a complete macroscopic surgical resection followed by PHDRB and external beam radiation therapy (EBRT) or PHDRB alone between October 2000 and December 2011 were eligible for analysis of locoregional control. To ensure proper data analysis, patients with fewer than 2 years of followup were excluded unless they had previously failed locoregionally. Patients with incomplete gross resections were excluded. Most patients presented with head and neck cancer, sarcomas, gynecologic and/or colorectal cancer (Table 1). A complete documentation of the status of the surgical margins was required for analysis. Other pathologic 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 1).

Treatment protocol

PHDRB alone was used in 113 patients. Patients with prior irradiation (n = 93, 82.3%), early primary tumor not requiring EBRT, or other reasons (n = 20, 17.7%) were not given further EBRT. Patients with ≥10-mm negative margins received a PHDRB dose of 32 Gy in eight twice-a-day treatments in 4 days, and patients with negative but <10 mm or positive margins received 40 Gy in 10 twice-a-day treatments in 5 days.

Table 1
Patient parameters

	PHDRB + EBRT (n = 188)	PHDRB-alone (n = 113)	All, n = 301 (%)
Gender			
Female	83	44	127 (42.2)
Male	105	69	174 (57.8)
Diagnosis			
Sarcoma	81	37	118 (39.2)
Head and neck	66	45	111 (36.9)
Gynecologic/colorectal	25	13	38 (12.6)
Other	16	18	34 (11.3)
Prior treatments			
Chemotherapy	0	0	0
Radiation	0	93	93 (30.9)
Surgery	62	81	143 (47.5)

PHDRB = perioperative high-dose-rate brachytherapy; EBRT = external beam radiation therapy.

PHDRB combined with EBRT was used in 188 patients. Patients with ≥10-mm negative margins received a PHDRB dose of 16 Gy in four twice-a-day treatments in 2 days, and patients with negative but <10 mm or positive margins received 24 Gy in six twice-a-day 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 (8).

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 (9). 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 because of 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) has 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