Tumor control and normal tissue complications in BNCT treatment of nodular melanoma: A search for predictive quantities

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ARTICLE INFO

Keywords:
Melanoma
Skin reaction
PEUD

ABSTRACT

A previous work concerning tumor control and skin damage in cutaneous melanoma treatments with BNCT has been extended to include doses, volumes and responses of 104 subcutaneous lesions from all patients treated in Argentina. Acute skin reactions were also scored for these patients, and cumulative dose-area histograms and dose-based figures of merit for skin were calculated.

Broadening the tumor response analysis with the latest data showed that the (minimum or mean) tumor dose is not a good predictor of the observed clinical outcome by itself. However, when the tumor volume was included in the model as second explicative variable, the dose increases its significance and becomes a critical variable jointly with the volume (p-values < 0.05). A preliminary analysis to estimate control doses for two groups of tumor sizes revealed that for small tumor volumes (< 0.1 cm³) doses greater than 20 Gy-Eq produce a high tumor control (> 80%). However, when tumor volumes are larger than 0.1 cm³, control is moderate (< 40%) even for minimum doses up to 40 Gy-Eq.

Some quantities based on skin doses, areas and complication probabilities were proposed as candidates for predicting the severity of the early skin reactions. With the current data, all the evaluated figures of merit derived similar results: ulceration is present among the cases for which these quantities take the highest values.

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1. Introduction

Dose data for tumor control of cutaneous melanomas and toxicity in normal skin are barely documented in BNCT. In conventional radiotherapy where a great amount of such data are available, dose distribution in tumors is highly homogeneous and tolerance doses (homogeneously distributed in the organ at risk) consider fractionation schemes. This is not the general situation in BNCT and particularly, is far from the CNEA clinical procedure with single-fraction neutron irradiation and dose prescriptions considering “the maximum point dose received in a 5 mm thick layer of skin”.

The optimization of melanoma treatments demands prescriptions of necessarily non-uniform doses that preserve normal skin while imparting therapeutic doses to tumors. In this context, we have extended a previous analysis that investigated the possible influence of tumor size and total equivalent dose on the observed local tumor response (González et al., 2006). Based on all the available data for patients treated as part of the CNEA-Roffo Phase I/II clinical trial of cutaneous melanoma and the tumor analysis results, we present a preliminary estimation of control doses for two groups of tumor sizes. Regarding normal skin, we studied different factors that may be related with observed early toxicity based on an analysis of several figures of merit (FOM) derived from the skin dose distributions. The early changes in the skin occur prior to 70–120 days post-irradiation and are consequence of the depletion of the epidermal and subpapillary microvascular cell populations (Archambeau, 1987). Since the epidermis and the subpapillary dermis vary between 50 and 300 μm, we considered superficial doses instead of distributions in a layer of skin for the
FOM-based analysis. Based on each evaluated FOM, we sort patients by ascending order. Given each ordering, we substituted the patient-assessed skin toxicity (graded as erythema and ulceration) for each patient ID. Finally, we compare the resulting orderings and discuss the consistency of our results with available reported single-fraction photon tolerance doses.

2. Materials and methods

2.1. General considerations

Since 2003, seven patients with subcutaneous nodular melanoma of the limbs were treated using the hyperthermal neutron beam of the RA-6 reactor at the Centro Atómico Bariloche, Argentina (González et al., 2004; Menéndez et al., 2009). The irradiations were performed in 10 anatomical areas comprising the thigh, calf, heel and foot sole. Since one patient was treated at two adjacent areas, namely the heel and foot sole, these areas were considered as only one for skin toxicity. The prescription dose in the skin was scaled from 16.5 to 24 Gy-Eq. Treatment planning was carried out with NCTPlan (González et al., 2002a, 2005), and tumor volumes and doses were calculated using the DVHTool System (González et al., 2002b). To study the superficial dose distribution in the skin and compute dose-area histograms, a new Matlab-based program developed by our group, named SPHERE, was employed (Gossio et al., 2009).

2.2. Tumor response analysis

Responses of 104 subcutaneous nodular lesions were analyzed with regard to different quantities such as minimum or mean photon-equivalent doses, and tumor volume. The objective response (OR) of the tumors was assessed computing tumor volumes on post treatment CT scans when possible, or by clinical inspection, external marking and photographic documentation. Local responses were graded according to WHO criteria, and complete and partial responses were considered as positive responses for the statistical analysis. A minimum follow-up of 3 months was considered for assessing responses.

A logistic regression analysis based on a generalized linear model was performed, and minimum or mean doses, either by themselves or jointly with tumor volumes, were alternatively assessed as possible predictors of the tumor response.

To preliminary estimate therapeutic doses for nodular melanomas, tumors were split into two groups according to the volume of the lesions. The division was established at 0.1 cm³, which corresponds to a spherical tumor of about 5 mm diameter.

2.3. Normal tissue analysis

As mentioned before, early skin responses are expected to be associated with superficial doses in the epidermis and subpapillary dermis rather than the dose distribution in a layer of skin. Since we were interested in these early effects, cumulative dose-area histograms (DAH) and related figures of merit were computed to investigate their possible influence on the acute skin toxicities observed in our patients (in this work, scored as erythema or ulceration). Eight figures of merit derived from DAHs were analyzed. These are maximum dose to the skin, skin area that received at least some reference dose (namely, 15, 18, and 20 Gy-Eq), mean dose in the 100 and 200 cm² of skin that received the highest doses, the normal tissue complication probability for inhomogeneous dose distributions (NTCP), and the related probability-equivalent uniform dose (PEUD) to the skin (González and Carando, 2008). Note that although all FOMs are derived from doses, and thus are correlated, they are of different nature (i.e., doses, areas and probabilities).

Reference doses used to compute skin areas were chosen based on a number of observations suggesting that doses around 18 Gy (delivered as a single fraction in fields of about 100 cm² in size) can be considered as a threshold for developing skin moist desquamation (ICRP Publication 85, 2001; Archambeau and Ines, 1984; Ellis, 1968; Douglas, 1982).

The normal tissue complication probability for inhomogeneous dose distributions was computed applying the formalism of the equivalent sub-volume model presented in González and Carando (2008), using a modified version of the NTCP model for uniform doses described by the three-parameter empirical formula (see, for example, Zaider and Amols, 1999):

\[ p(D, v) = e^{-N_0 k v D^a} \exp(-x D) \]  

where \( N_0, k \) and \( a \) are non-negative adjustable coefficients that were determined based on single-fraction photon tolerance data (Ellis, 1968; Hopewell, 1990), and \( v \) is the tissue area fraction irradiated at dose \( D \). The probability-equivalent uniform dose was also computed for all cases. Briefly, for a given dose distribution, the PEUD is the uniform dose throughout a given area (in this work, 100 cm²) that gives the same complication probability as the actual dose distribution.

3. Results and discussions

3.1. Tumors

Neither minimum nor mean equivalent doses were found to be, by themselves, good predictors of tumor response. However, when the tumor volume was incorporated as a second explicative variable in the generalized linear model, doses (minimum or mean dose) substantially increased their significance and become critical variables together with tumor volumes (\( p \)-values < 0.05).

Fig. 1 shows the distribution of volumes and minimum doses of the treated lesions together with their response. A simple analysis reveals that for small volumes (<0.1 cm³) minimum doses greater than 20 Gy-Eq produce a high tumor control (>80%). However, when tumor volumes are larger than 0.1 cm², tumor control is moderate (<40%) even for minimum doses up to 40 Gy-Eq. The present results do not substantially differ if the mean instead of the minimum dose is considered for the analysis. For tumor

![Fig. 1. Tumor size vs. minimum tumor dose on a semilogarithmic scale. Open and solid symbols indicate no response (NR) and objective response (OR), respectively.](image-url)
volumes considered “small” in this work, minimum and mean doses are almost the same. Note that if these tumors (< 0.1 cm²) were represented as spheres, their diameter would be about 6 mm or less. For larger volumes, mean doses may substantially differ from minimum doses. However, the tumor control rate for mean doses up to 40 Gy-Eq is also moderate: about 30%.

3.2. Acute skin reaction

Acute skin damage developed by our patients was classified as erythema and ulceration. While erythema was an acceptable mild toxicity, skin ulceration was considered to exceed the tolerance limit even though damage was controlled with medical treatment. Among the skin assessed areas, six out of nine developed erythema. The three patients showed that ulceration were cured within one year after BNCT. Eight FOM comprising doses, skin erythema. The three patients showed that ulceration were cured within one year after BNCT. Eight FOM comprising doses, skin erythema and ulceration. While erythema was an acceptable mild toxicity present among the cases for which FOMs take the highest values. Fig. 2 compares three different FOMs based on doses: the maximum (point) dose to the skin (Dmax), the mean dose in the 100 cm² of skin that received the highest doses (D100 mean), and the probability-equivalent uniform dose in a skin area of 100 cm² (PEUD100). Furthermore, for D100 mean and PEUD100, dose values that show the transition between the early effects appear to be consistent with the observed range of single-fraction doses for moist desquamation (i.e., between 15 and 20 Gy for 100 cm² of skin, shown as a dashed region in Fig. 2) (ICRP Publication 85, 2001; Archambeau and Ines, 1984; Ellis, 1968; Douglas, 1982). It is worthwhile mentioning that Fukuda et al. (1994) and Hopewell (1990) have reported skin reactions after BNCT treatments which are also consistent with our findings.

Fig. 2. Evaluated figures of merit based on doses. Circles and crosses indicate patients that developed erythema and ulceration, respectively.

4. Conclusions

In a previous work, minimum and mean doses to tumors were found to be, by themselves, good predictors of the observed local response. The addition of new data in the present analysis made it necessary to introduce the volume as a second explicative variable for responses. It is worthwhile noticing that in the first analysis, 39 out of 63 nodules had very small and similar volumes. With the addition of more data comprising bigger volumes, the present analysis involved a wider range of this variable.

It was stated above that tumor size affects the chances of control for a given dose. As a part of the dose prescription, tumor volume jointly with the dose will be considered for the optimization of future treatment plans.

The different figures of merit calculated to explain skin toxicities provided very similar results, (D100 mean ) and PEUD100 being those that showed transition doses between early effects consistent with the reported tolerance data for single-fraction photon irradiations. For all FOMs, patients can be roughly divided into two distinctive groups, one with mild toxicities and the other with more severe reactions. The fact that ulceration only developed in cases involving a heel or a foot sole is worthy of note. With the number of analyzed cases it is not possible to discard a particular radiosensitivity of these areas or mechanical stress as a cause.

Adding new data of normal tissue reactions to the present analysis might help to find a good predictor for the normal tissue toxicity and thus to determine a safe therapeutic dose. Since the dose distribution in the normal skin is highly inhomogeneous, an alternative quantity with more information rather than the maximum point dose to the skin will probably be considered for the new upcoming clinical trials of cutaneous melanoma. Among the candidates analyzed in this work, the mean dose in 100 cm² of skin and the probability-equivalent uniform dose were consistent with reported conventional radiotherapy tolerance data.

References


