

Facial Basal Cell Carcinomas in Elderly Frail Patients Treated with Low Total-dose Radiotherapy

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Abstract. *Aim:* A retrospective analysis was performed in our two Institutions in order to evaluate the feasibility and reliability of a hypofractionated-radiotherapy regimen in the treatment of frail elderly patients with facial basal cell carcinomas (BCCs). *Patients and Methods:* The records of elderly patients (age >75 years) with histologically-confirmed BCC, T1-2, treated to a total radiation dose of 25-30 Gy over 5-6 weeks, were retrospectively analyzed. *Results:* From February 2007-December 2010, 134 ambulatory patients with 159 BCCs were treated. Their median age was 82.5 years (range=75-103). Grade 1-2 skin acute toxicities were observed in 30.6% of patients (41/134). Complete responses were observed in 157 tumors in 132 patients. At the last follow-up, June 2014, no late toxicities had been noted; three patients had local recurrent disease. *Conclusion:* Our results seem to demonstrate both the feasibility and efficacy of curative hypofractionated radiation therapy in elderly patients with BCCs unfit for daily irradiation.

Basal cell carcinomas (BCCs) are the most common types of cancers in Europe, Australia, and the USA (1). Incidence is increasing, probably as a result of increasing age and sun exposure of the population. The median age at diagnosis is 66 years (2). For BCC, complete surgical excision with a security margin (3-5) is still the reference

therapy but the choice of treatment technique depends on various factors such as the tumor size, the general condition of the patient, and cosmetic considerations (6, 7). Radiotherapy (RT) is an option when surgery is not possible, is technically difficult, or would result in unacceptable tissue destruction, or for patients who would not be able to tolerate surgery. Despite extensive RT use in the treatment of BCC, to date the optimum dose/fraction has yet to be clearly defined (8); indeed various schemes have been reported in the literature ranging from single-fraction therapy (20-22.5 Gy/fraction) (9) to 60-70 Gy (2 Gy/day) total doses (10, 11).

The most common radiotherapy regimens, however, require so many treatment fractions and such high radiation dosages that it may be difficult or impractical to apply them for elderly patients with comorbidities. After having successfully treated a small number of patients with a single weekly lower dose schedule, we extended these lower dosages (25-30 Gy) to a larger population of patients over 75 years old. We retrospectively review the outcome of these patients and show that such hypofractionated RT may achieve long-term complete regression.

Patients and Methods

Eligibility and study parameters. Patients with one or more pathologically-proven BCCs, with stage I-II (T1-T2 N0) according to the seventh edition of the American Joint Committee on Cancer Manual for Staging of Cancer(12), age >75 years, and unfit for daily irradiation were treated using a hypofractionated RT scheme and were considered to be retrospectively reviewed for this study. Those who had had previous RT were excluded. Other requirements for eligibility were a Karnofsky Performance Status (KPS) >60, and a life expectancy >3 months.

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Key Words: Basal cell carcinoma, hypofractionated radiotherapy, skin cancer, frail patients.

Dermatologist/surgeon teams from various hospitals had evaluated all the patients. The main exclusion surgical criteria were: comorbidities (such as diabetes, dementia, and degenerative neurological disease), and BCC at sites requiring too great a reconstruction given the short life expectancy of the patient (although more than 3 months). Frailty characteristics were also evaluated using the Katz Index of Independence in Activities of Daily Living exploring six domains (each with a score of 1): bathing, dressing, toileting, transferring, continence, feeding; patients with a score of 6 are independent, whereas those scoring 0 are highly dependent (13). The Charlson age-factored comorbidity index (14) assigns a weight (score 1, 2, 3 or 6) to a list of 19 clinical conditions easily collected during the first physical examination.

Fully informed, written consent was required. Acute side-effects were graded weekly during treatment using the Common Terminology Criteria for Adverse Events v3.0 (15) The response was assessed by means of physical examination (documented by standardized digital photography) at 4 and 8 weeks post-treatment.

Treatment scheme and follow-up. Patients were treated with orthovoltage or electron beams and received 25 or 30 Gy in 5 or 6 fractions of 5 Gy, once weekly in 5 or 6 weeks. The higher total dosage was given to those with lesions thicker than 1.5 cm. Electron beam doses were specified at 90% of the maximal depth dose (Dmax). Orthovoltage x-ray doses were specified at Dmax (skin surface) to account for the relative biological difference between the two radiation modalities.

For each patient, the energy (range 55-150 kV or 4-8 MeV) was chosen based on the estimated tumour depth in order to encompass the deep margin of the tumour by at least the distal 80% (with orthovoltage beam) or 90% (with electron beam) line. The superficial extension of the planning target volume (PTV) was not less than 1 cm around the clinical extension of the tumour. A customized lead mask was constructed to fit on the skin's surface to collimate the beam. When electron beams were used, wider field margins than with orthovoltage x-rays were necessary due to the wider beam penumbra. Furthermore, bolus was also necessary to achieve adequate surface and depth dose (11). Peri-orbital tumours that needed eye shielding were treated with orthovoltage beams due to a lesser penetration of kV-beam through eye shields, whereas scalp lesions were preferably treated with electron beam in order to reduce the exit dose to the brain.

Patient records and the hospital Oncology Registry were reviewed and treatment and outcome data were recorded. Patients were followed-up by the radiation oncologist until 6-12 months after treatment and by their dermatologist afterwards. Follow-up time was defined as the time from the start of RT until the date of this analysis. The overall recurrence-free survival (RFS) was measured from the first day of irradiation to death or to the date of last follow-up; RFS distribution was estimated according to the Kaplan–Meier method.

Results

From February 2007 to May 2010, 134 outpatients with 159 BCCs were submitted to irradiation at our Departments. Their median age was 82 years (range=75-103 years). There were 40/159 (25.2%) T1 lesions and

Table I. *Patients' characteristics, baseline tumor characteristics and results in 134 lymph-node negative patients with 159 histologically-proven basal cell carcinomas deemed frail[&] and unfit for daily irradiation.*

Median age (years)	82.5 (75-103)
Gender	
Female	50 (37.3%)
Male	84 (62.7%)
T1 tumors (clinically evaluated)*	40 (25.2%)
T2 tumors (clinically evaluated)*	119 (74.8%)
Median primary tumor size (mm)	23 (9-84)
Tumor site [§]	
Nose	51 (32.1%)
Nasogenian furrow	26 (16.3%)
Eyelid-periorbital area	31 (19.5%)
Ear	9 (5.7%)
Cheek	12 (7.5%)
Forehead-temple	30 (18.9%)
Mean radiation dose/time	26 Gy/5.2weeks
Acute skin toxicity	G1/G2 41/134 (30.6%)
Complete responses	157/159 (98.7%) BCCs 132/134 (98.5%) patients
3-year RFS rate	97.3%
5-year RFS rate	92.7%

[&]Frailty was evaluated using the Katz Index of Independence in Activities of Daily Living exploring six domains (each with a score of 1): bathing, dressing, toileting, transferring, continence, feeding. Patients with a score of 6 are independent whereas those scoring 0 are highly dependent. *Imaging was rarely available due to the patients' frail conditions. [§]Scalp lesions were preferably treated with electron beams in order to decrease the exit dose to the brain, whereas periorbital tumors that needed eye shielding were treated with orthovoltage beams due a lower penetration depth of kV beams through eye shields.

119/159 (74.8%) T2 tumors; the median primary tumor size was 23 mm (range=9-84 mm); metastatic neck nodes were not observed.

The disease stage distribution was as follows: 39 stage I (29.1%), and 95 stage II (70.9%). The majority of tumours were located on the nose (51/159, 32.1%) or elsewhere on the face: eyelid-periorbital, 31/159; naso-genian fold, 26/159; cheek, 12/159; external ear, 9/159; and forehead-temple, 30/1159.

The baseline patient and tumor characteristics are summarized in Table I. All patients (n=134) had a Katz functionality index <6 and 115/134 had a Charlson age-factored comorbidity index >5, with lesions requiring a complex reconstruction. The remaining 19 patients refused surgery.

A mean (±standard deviation) radiation dose of 26 (±2.1) Gy in 5.2 (±0.5) weeks was given.

All patients completed treatment without interruptions, and no patient was hospitalized during or after irradiation



Figure 1. Photographs of lesions before and 8 weeks after treatment in two patients with locally advanced basal-cell carcinoma.

due to side-effects. No grade 3 acute toxicities occurred. Grade 1-2 skin toxicities were observed in 30.6% of patients (41/134). Complete responses were observed in 157/159 (98.7%) tumours in 132/134 (98.5%) patients. The 134 patients were followed-up for a potential median time, including those who died, of 64.5 months (range=42-88 months). At the last follow-up, on 30 June 2014, no significant late toxicities were observed; 3/134 (2.3%) patients had local recurrent disease and 124/134 patients (92.5%) had died due to causes unrelated to BCC. The 3- and 5-year actuarial RFS was 97.3% and 92.7%, respectively; the mean RFS was 6.56 years (95% confidence interval=6.29-6.82 years).

Discussion

In the present study, we report the results of a low-dose RT regimen for the treatment of head BCCs in frail elderly patients. A complete tumour response was seen in 98.5% of patients (98.7% of tumours) and there were no grade 3+ acute adverse events and no important late toxicities were reported (Figure 1). We recorded a recurrence rate as low as 2.3%, but 92.5% of our patients died from other causes during the follow-up period and therefore the incidence of recurrences may have been higher. We suggest that our excellent clinical results might derive from the use of adequate treatment-field margins (>1 cm) and from the use

of superficial beams or bolus (in the case of electron beams) to deliver irradiation, which avoids the compensation for the skin-sparing effect of electron RT alone. Indeed, BCC tends to infiltrate tissues in a three-dimensional fashion through the irregular growth of finger-like projections, which may not be obvious on visual inspection (16). For this motivation and considering the low total dosages to be delivered, we used margins >1 cm around the visible lesion.

Considering the only randomized trial in literature comparing RT and surgery (17), the poorer performances of RT in terms of cosmetic and failure outcome might be explained by the ambiguous definition of the target margin around the gross tumor used by the authors according to the three different techniques (95 patients with brachytherapy, 57 patients with contact therapy and only 20 patients with conventional therapy). In the study of Avril *et al.* (17), the extension target margins is not specified and it is not possible to know the extension of the target margins, but it is possible to speculate that they used too tight margins (less than 1 cm). Indeed, they specified that contact therapy had the largest localizer of 20 mm, and the mean diameter of treated BCC was 8.4 ± 3.2 mm. Extrapolating this means that 95% of the lesions were 14.8 mm or less, and 5% were larger. Hence, in at least 5% of patients the physical margins were less than 2.6 mm around the lesion, and the margins were under-dosed as a consequence of beam penumbra (16). This may explain their higher rate of relapse in contact therapy (6.6%) and brachytherapy (8.8%) with respect to conventional RT (5%), which usually has low technical limits in extending the margin of its radiation fields. These better results were obtained despite the fact that the largest lesions were treated with conventional RT (15.5 ± 5.8 mm) rather than with contact therapy or brachytherapy (12.9 ± 3.2 mm).

Furthermore, the higher dosage used by Avril, and also recommended by current literature (6, 11, 17), may explain the severe radio-dystrophies, radio-necrosis, and the poorer cosmetic results reported in the RT arm (17, 18).

In our study, the total radiation dosages and weekly scheduled treatments were used palliatively, at first considering the advanced age of patients. Yet the results obtained could lead radiation oncologists to reconsider the radiosensitivity of BCC and to study these low dosages for use as radical treatments in future prospective trials. Indeed, in recent retrospective trials using a weekly scheduled RT for elderly or frail patients unfit for daily irradiation, the local control rates were higher than 90% and no severe local toxicities were reported (19-21).

Finally, but no less importantly, there are cost considerations. The cost of orthovoltage or electron beam RT in six fractions is about €200.00 and €400.00 respectively (22); the cost of Mohs micrographic or conventional surgery is in excess of €1,209.00 (23), whereas the new oral-targeted

therapies, inhibiting alterations in the hedgehog signalling pathway (24) [*e.g.* Vismodegib (GDC-0449, Genentech)], has a monthly cost of €5,386.00 (25).

The limits of our study were, firstly, that it was a retrospective cohort trial and, secondly, that the high percentage of deaths related to the advanced age of the selected population reduced the length of follow-up. In conclusion, we believe that this low-dose RT regimen is advisable for unfit elderly patients or those with a short life expectancy due to the reduced need for Radiation Department visits (5 or 6 times in total), and the low mean treatment costs; furthermore, it needs to be prospectively tested in order to be validated as a curative treatment in younger patients.

Conflicts of Interest

None.

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Received April 14, 2015

Revised May 22, 2015

Accepted May 26, 2015