Efficacy, cosmesis and skin toxicity in a hypofractionated irradiation schedule for cutaneous basal cell carcinoma of the head and neck area

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Abstract

Aim
To evaluate efficacy and acute and chronic toxicity of a hypofractionated irradiation schedule in elderly patients with basal cell carcinoma (BCC) of the skin.

Materials and methods
Between February 2005 and November 2011, 42 retrospectively selected patients diagnosed with skin BCC of the head and neck area were treated with three-dimensional conformal radiotherapy (3DCRT) as an adjuvant therapy. Radiotherapy schedule was 5 × 600 cGy once weekly. Acute and late radiotherapy skin toxicity and cosmetic outcome were assessed in long-term follow up according to European Organization Research Treatment of Cancer/Radiotherapy Oncology Group (EORTC/RTOG) criteria, while cosmesis was evaluated by a plastic surgery expert

Results
Patients’ median age was 78 years, while median follow up was 15 months. Only two local recurrences were observed at 15 and 32 months, respectively. Post-3DCRT. Grade I, II and III acute skin toxicity was observed in 30/42, 9/42 and 2/42 patients, respectively. Late toxicity as grade I and II was observed in 14/42 and 2/42 patients, respectively. ‘Excellent’ or ‘good’ cosmesis was achieved in 30/42 and 12/42 patients, respectively.

Conclusion
Our irradiation schedule achieved very high local control rate with very good cosmetic and functional results, and it could be an alternative radiotherapy treatment for elderly patients with BCC of the head and neck area.

Introduction
Basal cell carcinoma (BCC) is the most common skin malignancy in the United States. It is diagnosed more often in men (4:1) and the median age of appearance is 68 years. The most common predisposing factor is ultraviolet (UV) exposure and previous radiotherapy (RT), although chronic irritation, trauma, occupational exposure, and genetic disorders can play an important role.

This malignancy is growing very slowly and presents with metastases very rarely.

While surgical approach is the standard treatment, some patients are appropriate candidates for radiation therapy due to poor performance status for surgery or when positive or close margins or residual disease remain following excision or when there is a high risk for recurrence. Hypofractionated schedules have been already used in clinical practice for BCC with satisfactory results. The aim of our study was to investigate the efficacy and long-term side effects using a hypofractionated irradiation weekly schedule with special attention to the cosmetic and functional outcome.

Materials and methods
This is a retrospective study evaluating hypofractionated irradiation schedule as a treatment in BCC patients either at ATTIKON or Aretaieion University Hospital in Athens. Between February 2005 and November 2011, 38 retrospectively selected patients diagnosed with skin BCC of the head and neck area received adjuvant RT using a hypofractionated schedule of 5 × 600 cGy once weekly. The median age was 78 years. The selection criteria for the relevant patients were satisfied if three or more of the following were met:

- Area of cheeks, forehead, scalp and neck with a tumour diameter of more than 10 mm
- ‘Mask Area’ of the face (central face, eyelids, eyebrows, periorbital, nose, lips, chin and mandible) >6 mm
- Poorly defined
- Recurrent
- Immunosuppression
- Site of prior RT
- Perineural involvement
- Aggressive growth pattern

Patient characteristics are shown in Table 1. Pre-treatment evaluation included pathology review, computed tomography (CT) or magnetic resonance imaging (MRI) for the assessment of the lesion and studying the regional lymph node involvement, clinical examination, palpation and a high resolution ultrasound. Patients were staged using TNM classification system.
The anatomical sites of the lesions are shown in Table 2, along with the high risk cases according to National Comprehensive Cancer Network (NCCN) criteria. Median tumour diameter was 13 mm (range 11–25 mm).

Before treatment initiation, all patients signed an informed consent form concerning the side effects of irradiation. Each patient underwent a virtual CT-simulation, in supine position, using a thermoplastic mask. Planning CT scan of the region of interest was then performed with 0.3-cm spacing between slices. CT datasets were transferred either to the Prosoma® Virtual simulation and contouring system or PLATO contouring system through the DICOM network. All contouring of target volumes and normal structures (organs at risk, OAR) were performed. The following structures were delineated: clinical target volume (CTV) and planning target volume (PTV), according to the ICRU criteria.

The volume to be irradiated included the tumour (CTV) with a margin of 10–15 mm (PTV). Eleven patients were treated with 6 Mev electron beam, while the remainder were treated with a 6 MV photon beam with a 1 cm bolus on the skin. Multiple weighted beams, wedges and/or compensating filters were used as necessary to improve dose homogeneity. In case of photons, the fields were isocentrically placed, while the dose calculation was performed and normalized to the isocenter. For the treatment technique, histograms were generated; a number of parameters, including mean, median and maximum dose, were evaluated. Patient setup was weekly monitored using portal films. Individual shielding of normal tissues (contralateral part of the nose, external ear and eye) was performed as and when necessary. Thermoplastic mask was used for immobilization.

A total dose of 30 Gy was prescribed in 5 weekly fractions of 6 Gy per fraction. All patients were treated either on a VARIAN CLINAC 2100C or 600C or Siemens Oncor linear accelerator.

We used the linear-quadratic (LQ) modelling to equate the hypofractionation schedule to the normalised total dose (NTD) if delivered in 2 Gy-fractions. Thus, NTD represents the dose given in 2 Gy fractions that would give an equivalent biological effect to the new hypofractionated dose:

\[
NTD_{new} = \frac{D_{new} + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}}
\]

where, \(D_{new}\) and \(d_{new}\) are the total dose and dose per fraction, respectively, for a suggested hypofractionation scheme. NTD was calculated and tabulated for low proliferating tumours and late reacting tissues (\(\alpha/\beta = 3\) Gy) as well as for skin cancer (\(\alpha/\beta = 8.5\) Gy). The total physical dose was 30 Gy. Considering that \(\alpha/\beta = 3\) Gy and \(\alpha/\beta = 8.5\) Gy, NTD was 55 Gy and 49.7 Gy, respectively.

Dose calculations were performed using the treatment planning system.
Endpoints
The primary endpoint was the treatment efficacy, while the secondary endpoints included acute and late toxicity as well as cosmetic results. Efficacy was based on the rate of local recurrence. Treatment feasibility was also evaluated in terms of the successful delivery of the prescribed dose following the intended treatment schedule. Cosmesis was rated on excellent, good, fair or poor using the standardized cosmesis scale grading between: poor, fair, good, excellent. Excellent was defined as no changes to slight induration or pigmentation change or loss of subcutaneous fat. Good was defined as patch atrophy, moderate telangiectasia, total hair loss, moderate fibrosis but asymptomatic, slight field contracture with <10% linear reduction. Fair was defined as marked atrophy, gross telangiectasia, severe induration, or loss of subcutaneous tissue, or field contracture >10% linear measurement. Poor was defined as ulceration and necrosis.

Efficacy
All patients were weekly evaluated during treatment and reviewed every month later on, after the completion of the RT, to assess acute/late toxicities. Data at diagnosis (baseline), end of radiation treatment and at all monthly follow up visits 6 months after finishing RT were analysed in this study. Symptoms occurring in the interval between the start of RT and 90 days after this time point were classified as ‘acute’. Symptoms occurring 6 months after the end of treatment were defined as ‘late’. Toxicity was graded according to the European Organization Research and Treatment of Cancer / Radiotherapy Oncology Group (EORTC/RTOG) criteria.

To evaluate the dose constraints for normal tissues, we used the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) trial corrected for hypofractionation.

Discussion
BCC is the most common skin cancer in the US. As shown in Table 1, the nodular subtype is the most common, in accordance with the current literature. There are specific characteristics that define BCC as either low or high risk for recurrence. The treatment of choice remains tumour excision, especially by Mohs’ technique. New pharmacological agents, such as immunomodulators, topical chemotherapeutic agents and photodynamic therapy, have shown promising results. Many prospective, randomized studies of either Eclipse (Varian Associates, Palo Alto, CA) or PLATO (Nucletron, The Netherlands) to deliver the prescribed dose to the International Commission on Radiation Units and Measurements (ICRU) reference point.

Statistical methods
Local recurrence free survival (RFS) rates were calculated from the onset of RT. RFS was calculated using Kaplan–Meier method. All analysis was performed using SPSS version 10 software.

Results
All patients had good performance status according to the Eastern Cooperative Oncology Group performance score of 0–1. Median follow-up duration was 15 months (range, 0–36 months).

All patients underwent successful completion of treatment with the prescribed dose according to the treatment plan. All lesions were treated with 30 Gy in 5 fractions of 6.0 Gy each once weekly. There were no patients with severe (grade 4) toxicities. Only two local recurrences were observed at 15 and 32 months post-three-dimensional conformal radiotherapy (3DCRT), respectively, while after re-excision, the patients have been disease free to date. The Kaplan–Meier curve for RFS is shown in Figure 1. At the end of RT, grade I, II and III acute skin toxicity was observed in 30/42, 9/42 and 2/42 patients, respectively. Toxicity score details are shown in Table 3. Late toxicity as grade I and II was observed in 14/42 and 2/42 patients, respectively. ‘Excellent’ or ‘good’ cosmesis was achieved in 30/42 and 12/42 patients, respectively.

Figure 1: Kaplan–Meier curve for RFS. The local control rate was 95.23%.
controlled studies have established the efficacy of imiquimod for superficial BCC\textsuperscript{19}.

However, topical irradiation remains a considerable treatment choice for BCC\textsuperscript{20,21}. The goal of primary treatment of BCC is curing the tumour and maximal preservation of function and cosmesis. In certain patients at high risk for multiple primary tumours, increased surveillance and consideration of prophylactic measures may be indicated.

In general, RT is typically recommended for primary and recurrent lesions of the central face, when they exceed 5 mm and for large lesions (>2 mm) that would potentially have poor functional and cosmetic outcomes after Mohs’ excision. RT is indicated post-operatively when there are positive margins, perineural invasion of a named nerve, lesion >3 cm, extensive skeletal muscle invasion and bone/cartilage invasion. According to the NCCN guidelines, post-operative adjuvant conventional RT refers to 50 Gy in 20 fractions or 60 Gy in 30 fractions\textsuperscript{8}.

The main advantage of RT in treating BCC is that normal tissue adjacent to the tumour can be preserved. This is especially relevant for tumours of the head and/or face. Cosmesis is usually good or very good and most functional results are excellent. RT produces only low skin morbidity; it is not painful and requires no anesthesia\textsuperscript{21}.

On the contrary, RT is contradicted when a patient is <50 years, the lesion exists as a post-irradiation recurrence, the area is prone to trauma with poor blood supply (below knees/elbows) and in high sun exposure\textsuperscript{22}. In our study, all patients were elderly and the NCCN criteria for irradiation were met.

In this retrospective study, a hypofractionated schedule of 5 weekly fractions of 6.0 Gy was evaluated. Fractionation in RT was initiated to spare normal tissue (by repair of sublethal damage and repopulation from surviving cells) and also to increase the damage to the tumour (by reoxygenation of hypoxic cells and redistribution of cells along the cell cycle). Along with radiosensitivity, the aforementioned radiobiological processes represent the foundation of fractionation in RT under the 5R’s of radiobiology\textsuperscript{23}. Repair and repopulation confer resistance to the tissue between two radiation doses, while redistribution and reoxygenation are expected to make the tissue more sensitive to a subsequent dose\textsuperscript{11,22}. The main factors influencing the design of an altered fractionation schedule include the following: dose per fraction, number of fractions, time interval between subsequent fractions and overall time and dose. The main intention of altered fractionation was the need to improve loco-regional control and survival and to reduce the treatment cost\textsuperscript{24}. A guide to the appropriate adjustment was based on the formula for the biologically effective dose delivered from linear-quadratic cell survival model\textsuperscript{11,24}. Apart from this, hypofractionation is an attractive fractionation regimen in terms of both logistics and patients’ convenience and may allow dose escalation/treatment acceleration without an increase in the cost associated with accelerated hyperfractionation\textsuperscript{25,26}.

RT is an effective treatment modality as an adjuvant therapy as well as for previously untreated and recurrent BCC. It has a reported 5-year local control rates of over 90%\textsuperscript{27}.

In the current literature, there are reports for overall 5-year cure rates of 91%–93% for previously untreated BCCs, while the complete response rates are 96% for smaller BCCs at low risk for recurrence\textsuperscript{22,24,28–32}. However, for patients with recurrent BCCs, the response rates are lower, (between 86% and 91%)\textsuperscript{22,29–31}. Recurrent BCCs post-RT may behave more aggressively than those recurring after surgical procedures, with higher rates of second recurrence and distant metastasis\textsuperscript{32}.

Previous reports with lower level of RT-techniques showed a poor outcome with RT alone for larger or more deeply invasive tumours (i.e., those involving cartilage, bone and/or muscle), while in the era of 3DCRT, there are higher control rates with good cosmesis and functional outcomes. Normally, 3- to 5-year loco-regional control rates were 86%–91% for large and/or locally advanced BCCs with RT\textsuperscript{22,24,28,30,32}.

Generally, rapidly proliferating tumours have been managed with rather aggressive treatment in the form of accelerated RT. Slowly growing tumours such as BCC, with an α/β = 8.5 Gy (highly proliferated tumours), normally require larger fraction sizes by means of hypofractionation. Thus, the suggested hypofractionated schedule seems relevant to the current radiobiological and clinical data\textsuperscript{24}.

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Hernández-Machín et al. reported a retrospective study of 604 patients with recurrence and a 5-year response rate of up to 94.4%. Recurrence was highly associated with tumour location on the nasolabial fold and tumour size >10 mm. The authors suggested that RT is an effective treatment for BCC and should be considered as a treatment of choice.

Van Hezewijk et al. reported on the efficacy of RT for BCC in 332 patients that were treated with electron beam and received either 54 Gy in 18 fractions or 44 Gy in 10 fractions. Three-year local recurrence free rates were similar, with 97.0% for 54 Gy and 93.6% for 44 Gy. The authors concluded that electron beam irradiation is safe and effective, while a hypofractionated schedule involving 44 Gy in 10 fractions can be regarded as the RT schedule of choice.

In our case, the local control rate was 95.23%, and only two patients presented with local recurrence. The above reported rate is in accordance with the current literature for conventional or hypofractionated schedule, thereby validating the efficacy of the irradiation suggested scheme of 5 weekly fractions of 6 Gy per fraction. Additionally, the low toxicity rate along with the good cosmetic results should not be underestimated.

Conclusions
Our study showed that 3DCRT is a feasible and safe modality, allowing for hypofractionation of up to 30 Gy in 5 weekly fractions. This study demonstrates that in elderly patients requiring adjuvant RT and unfit for daily irradiation, it is possible, in an alternative manner, to deliver hypofractionated 3DCRT to the BCC lesions with an acceptable acute and late toxicity rate and a lower cost in terms of the Linac workload. However, safe results could not be extracted because of the non-randomized retrospective nature of the current study. Thus, a randomized prospective study comparing the hypofractionated and conventional irradiation schedule is necessary for confirming our results.

References


