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Radiotherapy of basal cell carcinoma of the face and head: Importance of low dose per fraction on long-term outcome

Radiotherapie des Basalzellkarzinoms im Gesichts-/Kopfbereich: Bedeutung einer niedrigen Einzeldosis für das Langzeitsergebnis

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Keywords
- basal cell carcinoma
- radiotherapy
- radiotherapy dose fractionation
- treatment outcome

Summary
Background: Radiotherapy plays an important role in the treatment of basal cell carcinoma of the face and head and achieves cure rates of 92-96 %. Different fractionation concepts of radiotherapy have been described. This study investigates the efficacy, as well as acute and chronic toxicity, of a slightly hypofractionated radiotherapy schedule.
Patients and Methods: 85 patients with 104 tumors underwent radiotherapy for basal cell carcinoma of the face and head. The radiotherapy schedule was 5×3 Gray/week up to a total dose of 57 Gray in 95 % of patients. Acute and late radiotherapy toxicity and cosmetic outcome were evaluated in long-term follow-up.
Results: No recurrence was observed. In 87 % of tumors, only low acute toxicity occurred at the end of radiotherapy. Late toxicity, if observed, was low in most patients. "Excellent" or "good" cosmesis was achieved in 94 % of tumors at last follow-up.
Conclusions: Our radiotherapy schedule achieves a very high local control rate and very good cosmetic and functional results. This fractionation can be recommended as a standardized radiotherapy treatment for basal cell carcinoma of the face and head.

Schlüsselwörter
- Basalzellkarzinom
- Radiotherapie
- Radiotherapie-Fraktionierung
- Behandlungsergebnisse

Zusammenfassung
Hintergrund: Die Radiotherapie spielt eine wichtige Rolle in der Behandlung des Basalzellkarzinoms des Gesichts-/Kopfbereichs und erreicht Heilungsraten von 92–96 %. Verschiedene Radiotherapie-Fraktionierungsschemata sind beschrieben worden. Die vorliegende Arbeit untersucht die Wirksamkeit und (akute und chronische) Nebenwirkungen eines moderat hypofraktionierten Bestrahlungsschemas.
Patienten und Methodik: 85 Patienten mit 104 Tumoren erhielten eine Radiotherapie bei einem Basalzellkarzinom des Gesichts-/Kopfbereiches. In 95 % aller Patienten erfolgte eine Fraktionierung von 5x3 Gray/Woche bis zu einer Gesamtdosis von 57 Gray. Untersucht wurden akute und späte Radiotherapie-Nebenwirkungen sowie das kosmetische Ergebnis.
Ergebnisse: Es wurde kein Lokalrezidiv beobachtet. In 87 % aller Tumoren fanden sich zum Bestrahlungsende nur geringgradige akute Nebenwirkungen. Spätnebenwirkungen waren bei den meisten Patienten ebenfalls geringgradig ausgeprägt. In 94 % aller Tumoren konnte ein „exzellentes" oder „gutes" kosmetisches Ergebnis erreicht werden.

Schlussfolgerungen: Das verwendete Bestrahlungsschema erzielt eine sehr hohe lokale Kontrollrate und („sehr") „gute" kosmetische (und funktionelle) Ergebnisse. Die verwendete Fraktionierung kann insgesamt als standardisierte Behandlung für ein Basalzellkarzinom des Gesichts-/Kopfbereiches empfohlen werden.

Introduction

Basal cell carcinoma (BCC) is the most common human malignancy and non-melanoma skin cancer. Incidence ranges from around 100 per 100,000 people in Europe to 900 per 100,000 in Australia [1]. Under certain high-risk conditions, the lifetime probability to develop a basal cell carcinoma can reach 33 % [1]: Ultraviolet radiation is the most important environmental carcinogen causing mutations in cellular DNA, which lead to unrestricted growth and cutaneous malignancies such as BCC. Nearly 80 % of cases arise on the sun-exposed skin of the head and neck, and of those 30 % are found on and around the nose [2]. Most BCC (nearly 90 %) grow slowly, but if untreated, almost all tumors may invade and destroy the surrounding (deeper) normal tissues. This can lead to severe mutilation especially in the face and head region. Therefore treatment is almost always indicated after histological confirmation has been obtained. The major goal in the treatment of BCC is the eradication of the tumor and additionally an excellent to at least acceptable functional and cosmetic outcome. Functional and cosmetic considerations are very important in treating tumors of the head, especially the face, as they involve aspects of public appearance and self-imaging.

For many decades, external beam radiotherapy (RT) has been proven as an effective treatment modality which achieves cure rates of 92–96 % [3-6]. At the same time, RT yields excellent functional and usually good cosmetic results. Therefore, RT is a proven alternative to many invasive, i.e. surgical, treatment modalities. Mohs micrographic surgery [7], the most effective invasive method which is often applied in regions where cosmesis is important, can reach local control rates of up to 99 % [2, 7].

The aim of our study was to investigate the efficacy and long-term side effects using a slightly hypofractionated irradiation schedule. Special attention was given to the cosmetic and functional outcome [8].

Material and Methods

From April 1998 to October 2002, 85 patients with 104 basal cell carcinomas of the head were treated with RT. Median age was 77 years (range 47–98 years). 40 patients were men and 45, women. 102 of the 104 tumors (98 %) were primary tumors, while 2 were local recurrences following previous surgery. 96 of the 104 tumors (92 %) had been diagnosed histologically. In 86 of these 96 histologically-proven tumors (90 %), treatment was started within 0-2 months after biopsy. In accordance with the literature [2, 7], the nodular subtype was most common representing 45 % (43 of 96 tumors); most of the tumors (34 of 104/ 33 %) were found on the nose, followed by forehead (20 %) and the temples (17 %). Median tumor diameter was 12 mm (range 3–45 mm).

The volume to be irradiated was assessed by detailed clinical examination, palpation and high-resolution ultrasound. It included the tumor with a margin of 10-15 mm around the entire lesion, depending on the individual tumor size and configuration. RT dose was prescribed to the skin-tumor surface, while the RT energy was chosen dependent on the tumor thickness. Individual shielding of normal tissues (contralateral part of the nose, external ear, and eye) was performed whenever necessary. All patients, excluding three, were irradiated with low energy photons (50–100 kilo volts (Gulmay orthovoltage unit, Chertsey, UK). Three patients underwent RT with megavoltage electrons (5–7 million electron volts, Siemens linear accelerator, Concord, CA., USA) due to the size and location of the tumor. In 83 of the 104 lesions (80 %), the applied photon energy was 70–75 kV. All tumors were irradiated with the same slightly hypofractionated (in contrast to a standard fractionation of 5×2 Gray per week) schedule of 5×3 Gray (Gy) per week. 99 of the 104 tumors (95 %) received a total dose of 57 Gy. In 4 patients, total dose was limited to 54 (51) Gy due to marked acute radiogenic skin toxicity (> CTC Grade 2), and in 2 patients total dose was increased to 60 Gy due to a longer treatment break. The follow-up of the irradiated patients consisted thorough physical examination of the irradiated region at 3 month intervals with photographic documentation and the option of a re-biopsy in case of suspected tumor recurrence. Treatment outcome was defined as the clinical absence or the histological confirmation of a local recurrence. Acute radiogenic skin toxicity was evaluated at the end of RT and 6 weeks after RT by use of the Common Toxicity Criteria (CTC) Score [9] (Table 1).

Table 1: CTC score for the evaluation of acute cutaneous (subcutaneous) RT-induced toxicity.
Tabelle 1: CTC-Score zur Beurteilung akuter Strahlentherapie-induzierter Nebenwirkungen an der Haut und am Unterhautgewebe.

Grade 0	No change
Grade 1	Follicular, faint or dull erythema; epilation; dry desquamation; decreased sweating
Grade 2	Tender or bright erythema; patchy moist desquamation; moderate edema
Grade 3	Confluent, moist desquamation other than skin folds; pitting edema
Grade 4	Ulceration, hemorrhage, necrosis

Table 2: Modified LENT-SOMA score for the evaluation of late cutaneous (subcutaneous) RT-induced toxicity.
Tabelle 2: Modifizierter LENT-SOMA-Score zur Beurteilung von Strahlentherapie-induzierten Spät-Nebenwirkungen an der Haut und am Unterhautgewebe.

	Grad 1	Grad 2	Grad 3	Grad 4
Subjective				
Scaliness/roughness	Present/ asymptomatic	Symptomatic	Requires constant attention	
Sensation	Hypersensitivity, pruritus	Intermittent pain	Persistent pain	Debilitating dysfunction
Objective				
Edema	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Alopecia (scalp)	Thinning	Patchy, permanent	Complete, permanent	
Pigmentation change	Transitory, slight	Permanent, marked		
Ulcer/ Necrosis	Epidermal only	Dermal	Subcutaneous	Bone exposed
Telangiectases	Minor	Moderate <50%	Gross >50%	
Fibrosis/ Scar	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Atrophy/ Contraction (depression)	Present/ asymptomatic	Symptomatic/ <10%	Secondary dysfunction/ 10-30%	Total dysfunction/ >30%
Management				
Dryness			Medical intervention	
Sensation		Intermittent medical intervention	Continuous medical intervention	
Ulcer			Medical intervention	Surgery/ amputation
Edema			Medical intervention	Surgery/ amputation
Fibrosis/ Scar			Medical intervention	Surgery/ amputation
Analytic				
Color photographs	Assessment of changes in appearance			
(Modified from: Pavy J, Denekamp J, Letschert J, et al. Late effects toxicity scoring: SOMA scale. Int J Radiat Oncol Biol Phys 1995;31:1043-1047)				

Late radiogenic side effects (>90 days after RT) were evaluated at last follow-up by use of the Late Effects of Normal Tissues- Subjective, Objective, Management, and Analytic Categories- (LENT-SOMA) Score [10] (Table 2).
Cosmetic outcome was measured objectively according to the scale introduced by Lovett [11] that is based upon the amount of telangiectases, pigmentary change and skin fibrosis (Table 3).
The evaluation of cosmetic outcome and of late radiogenic side effects were repeated yearly; the reported data are the most recent ones.
In addition, each patient received a questionnaire to state the degree of satisfaction with the therapy and its result in three categories: a) "very satisfied", b) "satisfied" and c) "not satisfied". Each patient was also asked, whether or not he would repeat this therapy if necessary.

Results

Median follow-up period was 37 months (range 12-77 months), with a minimum follow-up of 24 months for those surviving. During the long-term follow-up, 10 patients died due to other age-related diseases. No local recurrence has been observed, resulting in a local control rate of 100 %. At the end of RT, maximum acute skin toxicity reached CTC Grade 1 in 90 (87 %), and CTC Grade 2 in 14 (13 %) lesions. Six weeks after RT, acute skin toxicity had changed to CTC Grade 0 in 56 (54 %), and CTC Grade 1 in 48 (46 %) lesions (see also Table 4).
The predominant late toxicities were pigmentation changes (LENT-SOMA Grade 2 in 53 (51 % of all) and Grade 1 in 43 (41 % of all) lesions), telangiectases (LENT-SOMA Grade 2 in 10 (10 % of all) and Grade 1 in 55 (53 % of all)

Table 3: Lovett score for the evaluation of cosmesis.
Tabelle 3: Lovett-Score zur Beurteilung des kosmetischen Ergebnisses.

"Excellent" cosmesis	No telangiectases, pigment change or fibrosis
"Good" cosmesis	Mild telangiectases or slight pigment change
"Fair" cosmesis	Severe telangiectases or pigment change or mild to moderate fibrosis
"Poor" cosmesis	Severe fibrosis or skin contracture

lesions), fibrosis (LENT-SOMA Grade 1 in 45 (43 % of all) lesions), and skin atrophy (LENT-SOMA Grade 1 in 76 (73 % of all) lesions).
"Excellent" cosmesis was achieved in 39 of 104 tumors (38 %), "good" cosmesis in 58 of 104 tumors (56 %), and "fair" cosmesis in only 7 tumors (6 %).
65 of 85 patients were "very satisfied" (77 %), 19 were "satisfied" (22 %), and one patient was "not satisfied" (1 %) due to a localized alopecia. 76 of 85 patients (89 %) stated that they would repeat radiotherapy, if necessary.
In 49 of 85 patients (58 %), topical therapy with dexpanthenol or silver sulfadiazine was necessary for 2–8 weeks after treatment.
During follow-up, 19 of the 85 patients (22 %) developed 35 new tumors in other locations of the skin, well in accordance with literature [2]. 24 new tumors were treated by RT, 11 underwent surgery. At this point, no local recurrence after treatment of these secondary tumors has been seen (100 % local control rate).

Table 4: Own results.
Tabelle 4: Eigene Ergebnisse.

1. Treatment outcome:
• 100% local control, no recurrences
2. Acute toxicity profile (6 weeks after RT):
• CTC-Grade 0: 54% of all lesions
• CTC-Grade 1: 46% of all lesions
3. Late toxicity profile:
• Pigmentary change: LENT-SOMA Grade 1 and 2 in 92% of all lesions
• Telangiectases: LENT-SOMA Grade 2 in 10% of all lesions
• Fibrosis: LENT-SOMA Grade 1 in 43% of all lesions
• Atrophy: LENT-SOMA Grade 1 in 73% of all lesions
4. Cosmetic evaluation:
• "Excellent" cosmesis in 38% of all lesions
• "Good" cosmesis in 56% of all lesions

Discussion

RT has been used for nearly a century in the treatment of cutaneous malignancies. Primary curative RT, postoperative curative RT for incompletely excised lesions, and primary palliative RT for advanced or even metastatic BCC are the main treatment indications. Most patients are treated with primary curative intention. Primary RT should be used in situations where it can produce superior cosmetic and/or functional results and at the same time achieve at least equivalent tumor control rates in comparison to other modalities [13]. The main advantage of RT in treating BCC is that normal tissue adjacent to the tumor can be preserved. This is especially relevant for tumors of the head and even more so for the face. Another advantage is the high effectiveness of RT. Cosmesis usually is good or very good, and most functional results are excellent. RT produces only low skin morbidity, is not painful, and requires no anesthesia. Possible disadvantages of RT include: margins are not routinely controlled by histopathology, time expenditure for patient and radiotherapist, treatment costs, possible radionecrosis in tumors located close to bone, and possibly decreased cosmesis over time [1, 7].
Ideal indications for primary RT are tumors of the face, especially around the nose, external ear, and eyelid, where surgery could result in moderate to severe functional or cosmetic impairment. Other possible indications for RT are significant concomitant medical problems, patient preference, advanced age, use of anticoagulation, and special situations such as extensive superficially spreading BCC, recurrent BCC, or multiple BCCs [1, 2, 7, and 14].
In the literature relying on studies of the last two decades with more than 700 patients, RT has yielded very high local control rates of 93–96 % (Table 5) [4, 5, 12, 15, and 16].
The results of our study conform well to the literature. As 65 % or more of recurrent BCC appear within the first 3 years after treatment [6, 16], our median follow-up period of 37 months is sufficient for a long-term assessment, as many other treatment methods are routinely evaluated at one year or less.
The following four figures (Figures 1–4) demonstrate the clinical course of irradiated BCCs in two of our patients:
Superficial irradiation up to the above mentioned dose usually leads to an intensive local erythema within the irradiated

Table 5: Results of RT in the treatment of BCC in studies larger than 700 patients within the last two decades.
Tabelle 5: Ergebnisse der Radiotherapie in der Behandlung des BCC: Studien der letzten 2 Jahrzehnte mit mehr als 700 Patienten.

Authors, year	Number of patients	Local cure rate
Fitzpatrick et al., 1984 (4)	1062	95%
Abbatucci et al., 1989 (12)	742	96%
Suter et al., 1990 (15)	1083	93%
Silverman et al., 1992 (16)	862	93%
Finizio et al., 2002 (5)	1863	96%

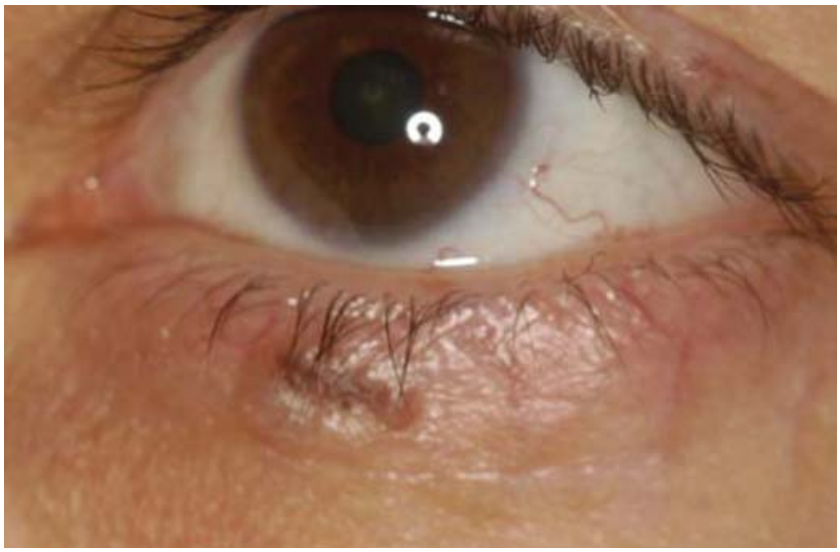

Figure 1: Patient with a nodular BCC of the left lower eye lid before RT.
Abbildung 1: Patient mit einem nodulären BCC des linken Augenunterlids vor RT.

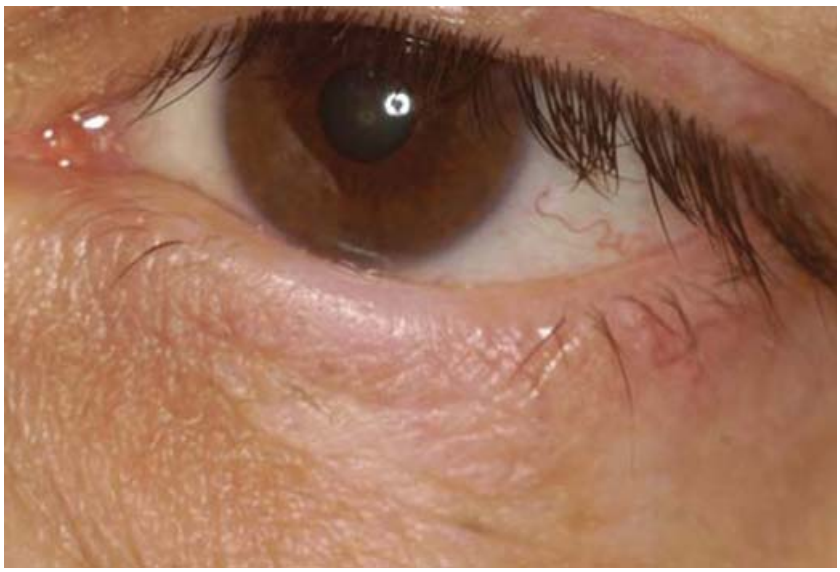

Figure 2: Same patient as Figure 1 in complete remission with excellent cosmesis (only circumscribed alopecia) 20 months after RT.
Abbildung 2: Patient aus Abbildung 1 in kompletter Remission mit „exzellentem" kosmetischen Ergebnis (nur umschriebene Alopezie) 20 Monate nach RT.

field sometimes associated with a moist desquamation (CTC Grade 1). Acute cutaneous toxicity is highest at the end of the RT series. Nevertheless, only 13 % of the irradiated lesions developed a CTC Grade 2 acute toxicity. Within a period of six weeks, the skin in 54 % of the irradiated lesions healed completely (CTC Grade 0). Unfortunately, a comparison of our results regarding analysis of acute RT-associated cutaneous toxicity with the literature data is not possible due to a lack of information from those former studies concerning the acute toxicity profile. Thus, we recommend a systemic evaluation of acute radiogenic skin toxicity to optimize quality assurance in the RT treatment concepts of BCC.

Evaluation of the radiogenic late effects of the skin is very important. The second endpoint referring to the local control rate was "excellent" and furthermore "good" or at least "fair" cosmetic and functional outcome. An ideal RT treatment would yield a very high cure rate, a very low recurrence rate and an "excellent" cosmesis.

Fraction size of RT (i.e. dose per fraction) is the main factor influencing the development of late radiogenic effects. Many clinical and experimental animal studies have shown that large dose fractions are associated with an increase in the severity of radiogenic late effects. The repair of sublethal damage in late-responding tissues such as the human skin is improved by using many small doses instead of few large dose fractions [18]. The impact of dose per fraction cannot be compensated by reduction of total dose of RT or protraction of overall treatment time. Currently, most fractionation calculations include treatment

time, single dose and fractionation factors (TDF dose concept). This allows a comparison between standard RT regimens using 2 Gy per day for 5 days per week versus other radiation regimens. Historically, RT of human skin cancer triggered the development of this standardized dose concept [7, 18].

The literature concerning fractionation of RT indicates a wide range of single and total doses from 20 Gy as a single dose to total doses of 50 Gy in 20 fractions and 60 Gy in 30 fractions [5, 12, 13, and 19]. While no large differences in local control were observed, impressive differences in late radiogenic effects were seen. RT regimens using > 10 Gy per fraction up to a total dose of 50 Gy induced cutaneous and subcutaneous necrosis rates of 34 % or more, while schedules using 5 Gy per fraction up to a total dose of 45 Gy produced a lower rate of 5 % [13].

This radiobiological background and previous clinical experience led us to lower the fraction size to 3 Gy per day for 5 days per week, and to deliver a total dose of 57 Gy (19 treatments). Using the TDF dose concept, we so reached an isoeffective dose (in comparison to standard fractionation) of approximately 70 Gy, which is recommended for definitive RT of BCC in the German guidelines for treatment of cutaneous malignancies [20].

A standard fractionation schedule is only necessary in very large BCC or in BCC of the extremities due to a more protracted healing process in such locations. In these cases, we usually prescribe a total dose of 66(–70) Gy (33–35 × 2Gy).

Careful analysis of late skin toxicity detected only slight pigmentation changes, minor telangiectases, and mild asymptomatic cutaneous atrophy resulting in maximum LENT-SOMA scores of 2 and lower. The only LENT-SOMA Grade 2 toxicities seen were pigmentary change (51 % of lesions) and telangiectases (10 % of lesions). No ulcer or skin necrosis was observed. A comparison of these results with the literature is not possible, since the application of the LENT-SOMA system in the evaluation of late RT-associated toxicity was not employed in the past. LENT-SOMA appears to be a valid tool in the systemic long-term evaluation of late RT toxicity, but it should be used consistently. This allows the documentation and comparison of toxicity profiles for the optimization of quality assurance in the RT of BCC between different studies.

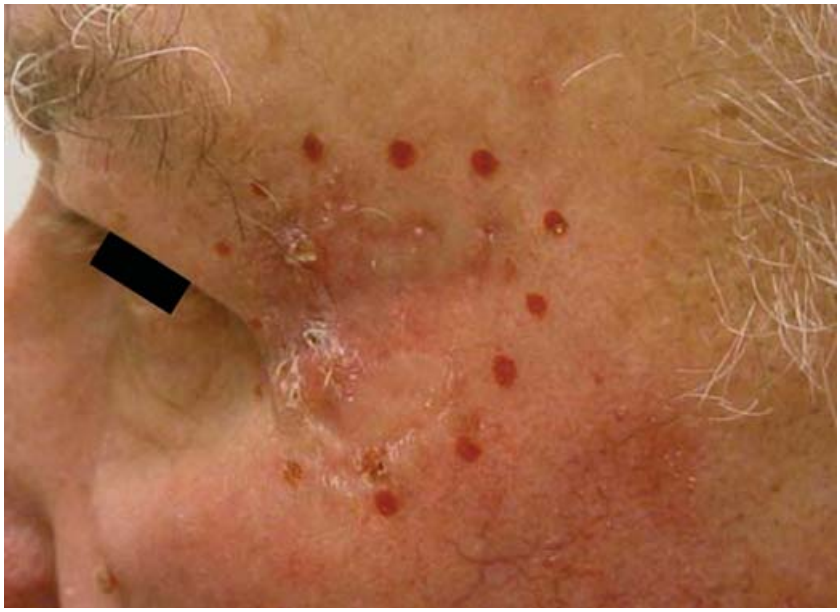

Figure 3: Patient with a large nodular BCC of the left periorbital region before RT.
Abbildung 3: Patient mit einem ausgedehnten nodulären BCC der linken Perorbitalregion vor RT.

In most patients, “excellent” or “good” cosmesis was noted, which is consistent with the reference literature [11] with 97 % rate of excellent or good cosmesis: In 38 %, cosmetic results were “excellent” with complete normalization of the irradiated skin in comparison to the surrounding tissue. Literature data reveal a wide range in the rates of "good cosmesis" from 40–61 % [20] to 93.4–97 % [5, 11]. The use of different scoring systems, subjective judgment and possible intraobserver bias make it difficult to compare older literature data with our own results. In the past, poor cosmetic results occurred when RT schedules were applied using a higher dose per fraction. Our results with “excellent” or “good” cosmesis underline the advantage of a slightly hypofractionated schedule.

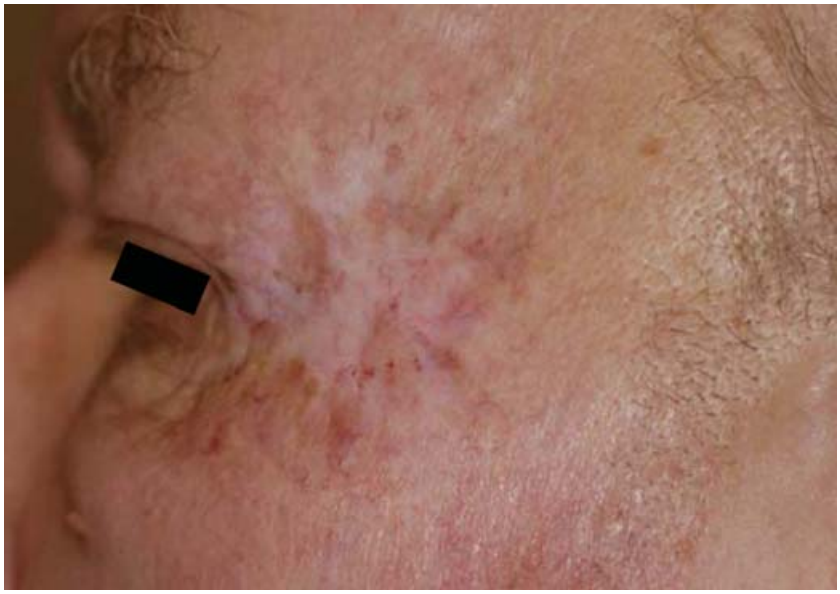

Figure 4: Same patient as Figure 3 in complete remission with good cosmesis (mild fibrosis, atrophy, telangiectases, and hypopigmentation) 38 months after RT.
Abbildung 4: Patient aus Abbildung 3 in kompletter Remission mit gutem kosmetischen Ergebnis (mäßiggradig ausgeprägte Fibrose, Atrophie, Teleangiektasien und Hypopigmentierung) 38 Monate nach RT.

Further follow-up is required to evaluate future changes in cosmesis, because some "excellent" or "good" results may deteriorate over the next decades. The very high satisfaction rates of our patients with the treatment and outcome and the high willingness and compliance to repeat RT underline the acceptance of our treatment approach. Even very old patients tolerated and accepted the overall treatment period of 19 treatment days (about four weeks) well.

Results of this and a previous study [22] from our clinic (99 patients with 127 BCC, treated from 1986 to 1998) are comparable. Both studies have the same median follow-up (36 vs. 37 months), local cure rates were 98 % in the previous study vs. 100 % currently, and rates of excellent and good cosmesis 98 % in the preceding study vs. 94 % currently. In contrast to our present study, multiple fractionation schedules were used and only 67 of 127 BCCs were irradiated with 3 Gy per day for 5 days per week. Many patients were irradiated with 2.5–3 Gy per day for 3–4 days per week and received a total dose lower than 57–60 Gy, which increases the risk of a reduced tumor control. Some patients were treated with larger doses per fraction (4–5 Gy). Such fractionation led to high CTC Grade 3 toxicity in about 30 % of the irradiated patients at the end of RT in the previous study (vs. 0 % currently).

Conclusion

Our RT concept meets the requirements of an ideal RT treatment; it produces a very high local control rate and, at the same time, provides good or very good cosmetic and functional results with low long-term toxicity. The only disadvantages may be related to the higher costs of this RT schedule (about 650,- Euro) and the availability of the orthovolt equipment. Nevertheless, this treatment concept can be recommended especially for BCC of the head as a standardized treatment option, which can be readily performed by most RT departments worldwide.

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