

Non-melanoma Skin Cancer at Facial Sites Treated with Varian HDR Surface Applicators

Yüz Yerleşimli Melanom Dışı Cilt Tümörlerinde Varian Yüksek Doz Hızlı Brakiterapi Uygulamaları

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ABSTRACT

Objective: Non-melanoma skin cancer (NMSC) is the most common cancer type worldwide. Surgery is the mainstay of treatment. High Dose Rate Brachytherapy (HDR-BT) is an effective alternative method when surgery is contraindicated or when there is cosmetic concern. This study aimed to report our clinical outcomes consisting local control and toxicity rates in patients treated with HDR-BT.

Method: Patients with squamous cell cancer (SCC) and basal cell carcinoma (BCC) treated with HDR-BT from May 2021 to April 2022 were included in the study. Medical reports including pathologic and radiologic reports and photos were retrospectively reviewed. Radiation toxicity was graded using the Radiation Therapy Oncology Grading (RTOG) acute toxicity scale. Local control and toxicity rates were evaluated for all patients.

Results: All 7 patients, including 3 BCCs and 4 SCCs, with 7 lesions were treated with definitive intent. Prescribed dose was 40 Gray (GY) in 8 fractions in all cases. Local control was 100%. Both overall survival and progression free survival was 100%. Skin toxicity was seen in 4 patients with grade 1 and in 3 patients with grade 2 and resolved in 3 months time.

Conclusion: HDR -BT provides excellent cosmetic outcomes without compromising local control both for curative intent. Considering short interval local control rates, long term follow up is necessary.

Keywords: BCC, brachytherapy, SCC, skin cancer

Öz

Amaç: Melanom dışı cilt kanseri dünyadaki en yaygın kanser türüdür. Cerrahi, bu kanser türünde ana tedaviyi oluşturmaktadır. Yüksek doz hızlı brakiterapi (High Dose Rate [HDR] Brachytherapy) özellikle kozmetik olarak cerrahinin doku kaybı yaratacağı bölgelerde en etkili cerrahi alternatiftir. Bu çalışmanın amacı; kesin HDR brakiterapi ile tedavi edilmiş hastaların erken yan etki sonuçlarını ve lokal kontrol verilerini sunmaktır.

Yöntem: Çalışmaya, Mayıs 2021 ve Nisan 2022 tarihleri arasında yüz bölgesinde skuamöz hücreli ve bazal hücreli cilt tümör olan yedi hasta dahil edildi. Hasta raporları, radyolojik ve patoloji raporları retrospektif olarak incelendi. Radyasyon erken toksisite değerlendirilmesi "Radiation Therapy Oncology Grading (RTGO)" sistemine göre yapıldı. Lokal kontrol, erken sağkalım ve toksisite tüm hastalarda değerlendirildi.

Bulgular: Hastaların tamamı, üç bazal hücreli kanser ve dört skuamöz hücreli kanser olarak tedavi edildi. Tüm hastalara kesin doz olarak sekiz fraksiyonda 40 Gy tanımlandı. Lokal kontrol %100 olarak görüldü. Sağkalım ve progresyonsuz sağkalım %100 idi. Cilt toksisitesi grade 1 dört hastada ve grade 2 toksisite üç hastada görüldü. Bu toksisitelerin hepsi üçüncü ayda iyileşti.

Sonuç: HDR brakiterapi mükemmel kozmetik sonuç ve hastalığın lokal kontrolünü sağlamaktadır. Uzun takipler gerekmele birlikte cerrahiye özellikle yüz bölgesinde önemli bir alternatif tedavidir.

Anahtar kelimeler: Bazal hücreli kanser, brakiterapi, cilt tümörü, skuamöz hücreli kanser

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INTRODUCTION

Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC) are the most common neoplasms worldwide with increasing incidence over the last decade.^[1] Non-melanoma skin cancer (NMSC) is often managed with surgical excision with excellent local control rates. Radiotherapy (RT) and topical agents are alternative therapeutic options. Over the last years, systemic agents such as hedgehog pathway inhibitors for BCC and check point inhibitors for SCC have been approved when the tumor is not amenable to local therapies.^[1] RT is generally employed as an efficacious curative treatment method when radical excision is limited by the proximity of essential anatomic structures or patients comorbidities, adjuvant radiotherapy is also indicated for patients having positive surgical margin or high risk of recurrence.^[2,3] Superficial X-rays, electron beam, megavoltage photons, and low (LDR) or high-dose rate (HDR) brachytherapy (BT) can be applied in various settings with the common goal of achieving durable disease control while maintaining functional and cosmetic outcome. Optimal treatment technique is determined by the physician mostly based on institutional resources. Given the excellent local control rates and less invasive nature, HDR-BT is an appealing treatment modality; however, there are limited number of clinical studies on the use of HDR-BT for early stage NMSC.^[4-7] Rapid dose fall-off at the target periphery with HDR-BT ensures better sparing of organs at risk and reduce risk of late radiation-related toxicity.^[7] Reported toxicity profile is also not severe which makes it favorable especially for patients wanting to preserve cosmesis in the head and neck area [6]. Using hypofractionated regimens, it enables shorter treatment times. Considering that the incidence of NMSC increases with advanced age, limiting visits to hospital is essential for old and fragile patients.^[8]

In the present study, it was aimed to present the clinical outcomes and posttreatment radiation toxicity associated with iridium-192 (192Ir)-based HDR-BT in patients treated for NMSC retrospectively.

METHOD

A total of 7 patients with treated with HDR-BT using standard Varian surface applicators for biopsy confirmed superficial NMSC between May 2021 and April 2022 were reviewed retrospectively. All patients were aged over 18 years. Data were collected retrospectively. Local ethics approval was granted (protocol no: 2022/137).

Patients for whom surgery might be accompanied with cosmetic or functional deficits and who had significant comor-



Figure 1. The Varian Surface Applicator Set 10, 15, 20, 25, 30, 35, 34mm round and 20 and 25mm oval

bidity for surgery were included in the study. Exclusion criteria included prior RT to the same site and deep infiltration. A diameter of 8 mm and a maximum depth of 4 mm was the highest limit to be eligible to apply HDR-BT. In the curative setting, ultrasound imaging was applied to assess tumor depth.

Lesions exhibiting a smooth contact surface were generally preferred for treatment. Gross tumor volume was assessed visually by the treating radiation oncologist. Well circumscribed lesions were predominantly chosen. Treatment dose was prescribed at 3mm for lesions with a depth of 3 mm or less, and 4 mm for those between 3mm and 4 mm in depth. Intact lesion planning target volume (PTV) consisted of the macroscopic lesion plus a 5 mm margin. Based on the planning target volume size, appropriate applicator (20 or 15 mm) was used for coverage. High accuracy in tumor depth measurement is critical due to the high dose gradient. To ensure accurate applicator positioning, all treatments were delivered under the supervision of radiation oncologist. Some examples of applicators and treatment set up are illustrated on Figures 1-3. When required, ex-



Figure 2. The application of the Varian surface applicator with 20mm cone

ternal eye shields were used. Generally, a total dose of 40 Gy in 8 fractions prescribed to the appropriate depth (≤ 4 mm) was given twice weekly with a minimum interval of 48 hours between fractions. Dosimetry was calculated with a CT scan. Dosimetry was initially carried out according to

the Paris System on 85% isodose. Typical prescription to 3mm, the surface dose will reach approximately 120–130%. Toxicity descriptions were made by physicians and graded according Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer Criteria (EORTC) criteria.^[9]

Statistical Analysis

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, UT, USA) program was used for all statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used in evaluating data. Paired samples t-test was used for the comparison of normally distributed quantitative variables for BCC and SCC.

RESULTS

A total of 7 patients were treated between 2021 January and 2022. Baseline demographics, pathologic and therapeutic data are summarized in Table 1. Median patient age was 70 (range 63–85) years. Of the 7 patients, 3 were younger than 65 years old (42.8%). There were 4 (57.1%) females and 3 (42.8%) males. The proportion of histological subtypes were as follows: BCC in 3 (42.8%), SCC in 4 (57.1%) patients. All 7 lesions were located on the head and neck. Treatment intent was definitive radiotherapy in 7 of the cases.

Lesions were treated with a total dose of 40 Gy, using 8 fractions (5Gy/fraction; twice weekly mostly) all of the cases. All patients successfully completed treatment.

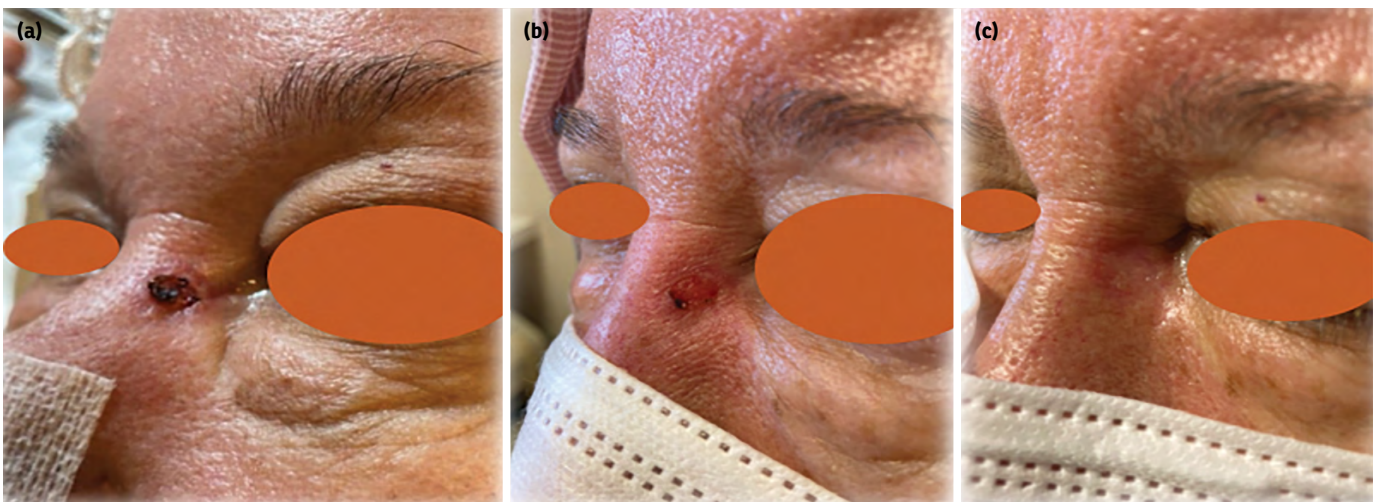


Figure 3. The changes of the skin lesion over time with brachytherapy. **(a)** Before brachytherapy, **(b)** 1.5 months after brachytherapy, **(c)** 3 months after brachytherapy

Table 1. Baseline demographics and pathologic and therapeutic data

Number	Age	Sex	Type of skin cancer	Location	Tumor diameter/ invasion depth	RTOG Toxicity (Grade)	Total Dose (Gy)/BED ₃
1	63	F	SCC	Left side of the nose	5 mm/3mm	2	40/110
2	81	F	BCC	Left infraorbital region	5 mm/3mm	1	40/110
3	77	F	SCC	Right nasal ala	4 mm/2mm	1	40/110
4	66	F	BCC	Left nasal ala	8 mm/3mm	2	40/110
5	63	M	BCC	Left forehead	7 mm/4mm	2	40/110
6	70	M	SCC	Left malar	8 mm/3mm	1	40/110
7	85	F	SCC	Left malar	5 mm/3mm	1	40/110

RTOG: Radiation Therapy Oncology Group; SCC: Squamous cell carcinoma; BCC: Basal cell carcinoma; F: Female; M: Male

Median follow-up was 5 months (range: 3–12). None of the lesions showed signs of residual tumor after 3 months of therapy. (Fig. 3) There have been no recurrences reported to date.

The treatment was well tolerated in all cases. The highest acute skin toxicity was grade 2 based on RTOG criteria, Grade 2 acute radiation dermatitis was observed in 3 lesions (42.8%), grade 1 in 4 (57.1%), having resolved with topical treatment at 3 months in all cases. There were no grade 3 or higher late adverse events at any time.

DISCUSSION

NMSC is the most frequent cancer diagnosis made in both sexes. Patients may experience impairment in their quality of life.^[10] Although mortality is low, more than 5400 people worldwide die of NMSC every month.^[11] Current treatment recommendations are in favor of surgical management.^[12] Surgery may be contraindicated due to certain tumor or patient determined factors such as cosmetic limitations or patients' comorbidities. When surgery is inadequate or inappropriate, multiple radiotherapy techniques are available on definitive and adjuvant settings. Superficial X-rays, megavoltage X-rays, orthovoltage X-rays, LDR-BT, HDR-BT, Electronic BT electron beam irradiation are used. Equivalent recurrence rates, cosmetic and functional outcomes can be achieved with HDR-BT compared to EBRT and surgery, albeit available data are based on mostly single center experiences.^[13] There are no randomized controlled trials regarding this approach, hence ESTRO recommends to tailor HDR-BT when tumor cannot be removed by surgery safely.^[14] We advocate that when surgery or re-surgery is accompanied with functional and cosmetic deficits, HDR-BT should be a part of the decision making process for whom the benefit/risk ratio for radiotherapy considered to be favorable.

To date, we have achieved excellent durable local control with minimal toxicity in agreement with the available literature. In a study by Delishaj et al.,^[15] the authors have reported that 96.25% of the patients treated with HDR-BT with definitive intent showed complete response with minimal toxicity and all patients were free of recurrences at 12 months follow up period. Taylor and colleagues have yielded 95% local recurrence free survival with a median 7.2 months follow up period.^[16] We have not witnessed any recurrence up to now within early follow up period. Numerous papers have documented recurrences patterns of NMSC. Chren has shown that basal cell carcinoma and cutaneous squamous cell carcinoma recurrences may occur 4 years after treatment, and additionally, Rowe and colleagues have found that 10-year recurrence rate is twofold than of the 2-year recurrence rate, furthermore 18% of recurrences appear between the fifth and tenth year following treatment.^[17,18] Considering all of these together, it should be interfered with caution that longer follow up periods are needed to address the efficacy of HDR-BT.

Secondary carcinogenesis due to radiation therapy is a major concern especially after a latency of 10 years.^[19] Given the carcinogenic effect of radiation exposure in a group of diseases that are curatively treated by surgery such as NMSC, it seems more rational not to recommend brachytherapy as a standard primary treatment when surgery is feasible, principally for young and having long life expectancy patients.^[20] The literature states that the mean age of diagnosis is 63 years for BCC and 71 years for SCC. In our data, median age of diagnosis was 66 for BCC and 70 for SCC, which is consistent with literature.^[21]

Numerous dosing and fractionation schemes might be used when applying BT, majority of centers report to prefer 40 Gy in 8 fractions as we applied or even more hypofractionated

schedules. This hypofractionated course, 2–3 times a week, allows for fewer visits to the clinic without hospitalization.^[22] During the Covid-19 pandemic, NMSC treatment was negatively affected.^[23] Considering this group of patients, the vast majority of whom are elder, fragile and have comorbidities, when feasible, HDR-BT should be major component of shared decision making process in the Covid-19 era.

The main aspect of treatment in NMSC is minimizing recurrence while maintaining functional and cosmetic outcome. There remains controversies about implementing BT as the first line treatment since surgery is safe and highly effective.^[24] We have not offered HDR-BT as the primary treatment modality to any of the patients and references were made by the surgeon when there was a contraindication for surgery/re-surgery, thus our data consisted of mostly postoperative patients. There is conflicting data about the management of close and positive surgical margin in NMSC in daily practice. Some authors claim that the presence of positive margins may mislead to predict recurrence.^[25] In a prospective study, researchers have found residual tumor in only 33% of the patients who were reoperated due to surgical margin positivity.^[26] Alcalay and colleges have shown even 25% of preoperatively biopsied NMSC disappeared in the debulking specimen.^[27] Several studies have also shown that adjuvant radiotherapy reduces risk of recurrence^[28] and considering a close or positive margin might increase recurrence rates up to %40.^[29] Wolf et al.^[30] have found that a minimum margin of 4 mm is necessary for the complete removal of the tumor in more than 95% of cases for BCC with a diameter less than 2 cm, and this approach is also accepted by current NCCN guideline.^[31] Robinson and colleges have shown that delayed re-excision can result in more extensive surgery in recurrent BCC.^[32] Moreover, recurrences may not always be salvageable. Thus, we believe that immediate complete eradication of the tumor should be our goal and immediate adjuvant HDR-BT at least should be an option in the shared decision-making process for the patients having high probability of recurrence. In our daily practice, when further surgery accompanies with cosmetic and functional deficits or patients' performance status is not suitable for second surgery, we advocate adjuvant HDR-BT, and results are excellent with outstanding cosmesis as mentioned.

Small sample size is the major limitation of our data; however, we believe that in an emerging treatment modality, every single experience is essential to build up available data. Short follow up period and retrospective nature of the analyses are other limitations.

CONCLUSION

HDR-BT is a well tolerable and effective treatment modality for NMSC both in definitive and adjuvant setting with minimal side effect. Personalized decision-making process is essential within a multidisciplinary team. Aesthetic results obtained with HDR-BT without compromising local control makes it valid alternative to surgery, albeit extended follow up periods and further prospective trials are required to address the optimal treatment strategy.

Disclosures

Ethics Committee Approval: The study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (No: 2022/137, Date: 18/04/2022).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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