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Updates from medicine

Definitive weekly hypofractionated radiotherapy in cutaneous squamous cell carcinoma: response rates and outcomes in elderly patients unfit for surgery

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Abstract

Introduction The optimal definitive radiotherapy (RT) scheme in cutaneous squamous cell carcinoma (cSCC) remains controversial, especially in elderly patients.

Methods Data of elderly patients with cSCC lesion(s) treated with weekly hypofractionated RT (8 Gy per week per 7-8 weeks) were analyzed.

Results Eighteen patients (median age 89 years) with 23 cSCC lesions have been identified including nine males (50%) and nine females (50%). The most common tumor localization was the head and neck region (n = 21; 91.3%), and the majority of lesions (n = 15; 65.2%) was stage ≥ III. At diagnosis, pain and bleeding were ascribed in 13 (56.5%) and eight (34.8%) cSCC, respectively. Compliance with weekly hypofractionated RT was excellent. The overall response rate at 12 weeks after treatment was 95.7%. Bleeding and pain relief were achieved in all cases. Severe toxicity was not recorded. The 1-year overall survival was 66.0%. The 1-year progression-free survival was 58.7%.

Conclusions Weekly hypofractionated RT provides a safe, efficient, and cost-effective treatment in elderly cSCC patients with minimal side effects.

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common type of nonmelanoma skin cancer, and its incidence continues to increase by about 7% per year in elderly population.[1] Since comorbidities, functional losses, cognitive impairment, and physiologic changes rise steeply with age, cSCC elderly patients will become more vulnerable to surgical approach—the standard of care—and postoperative recovery. In this context, an attenuated management is necessary, and radiation therapy (RT) should be a valid option to guide treatment decisions among those patients. Here, we reported our experience in cSCC elderly patients treated with weekly hypofractionated RT with megavoltage electrons. The aim was clearly to minimize treatment toxicity and maintain good clinical oncologic outcomes.

Materials and Methods

Patient population

This retrospective analysis included elderly patients (aged ≥75 years) with cSCC treated at the Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome, between January 2016 and March 2021. The diagnosis of cSCC was established by biopsy of the cutaneous lesions. All lesions were (re-)staged using the 8th TNM staging system. The study was approved by the Institutional Review Board and patients signed an informed consent. All patients referred to the multidisciplinary elderly board and were judged unfit for surgery. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) score and the adult comorbidity evaluation-27 (ACE-27) score were used to assess PS and comorbidities, respectively.[2,3]

Radiation therapy

All patients were treated with definitive RT. As previously described,[4] based on tumor characteristics—shape, margins, thickness, and anatomic location—and surrounding normal tissue considerations, the physical properties of MeV electron therapy—rapid dose falloff sparing deeper structures—were preferred. Based on tumor (T) stage, a total dose of 56 Gy in 7 weekly fractions of 8 Gy (T1-2) or 64 Gy in 8 weekly fractions of 8 Gy (T3-4) was prescribed. This solution—56-64 Gy in 7-8 Gy/fraction given once a week—

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was arrived at by considering the longer overall treatment time. To evaluate this possibility, we completed the calculations for tumor biological effective dose (BED), using the 7th LQ formula allowing for cell proliferation[5]: BED = [total dose x RE] minus [ln2(T–Tk)/αTp]. We assumed α/β = 10 Gy, α = 0.35 ln/Gy, T = 56 days, Tk = 21 days, and Tp = 3 days (as in head and neck tumors), resulting in BED = 82.8 Gy (for 56 Gy in 7 weekly fractions) and BED = 92.1 Gy (for 64 Gy in 8 weekly fractions). Due to the uncertainties involved in the extreme hypofractionated (≥6 Gy) dose, we prescribed 8 fractions to be sure to reach a curative intent in ≥T3 lesions.[6]

A single appositional field using an electron energy was chosen so that the lesion was encompassed by 95% of the dose at the deep margin. Bolus material was applied to reduce inhomogeneous dose distributions, when clinically adequate. Radiation oncologist performed weekly visual confirmation of surface coverage before treatment.

Follow-up

After treatment, all patients were monitored by physical examination, including complete skin and regional lymph node exam at 4-week intervals. If clinical evidence of disease was absent, evaluation was then performed every 3 months for 2 years and then every 6 months thereafter. Diagnostic exams to evaluate for loco-regional and distant metastatic disease were recommended if clinically indicated.

Statistical analysis

Statistical analysis was performed using R-Studio, version 0.98.1091, software. Standard descriptive statistics were used to evaluate the distribution of each variable. Continuous variables are presented as the median and range, and dichotomous variables are presented as percentages. The primary endpoint was overall response rate at 12 weeks (ORR12w) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[7] ORR12w was defined as the proportion of lesions which have a partial or complete response to therapy and was assessed 12 weeks from the completion of RT. Secondary endpoints included toxicity profile, RT response self-reported pain score, overall survival (OS), and progression-free survival (PFS). Toxicity was scored using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.[8] Pain response within 8 weeks was defined as at least 2-point decrease on a 0 to 10 pain score scale from baseline, without an increase in analgesics use or a decrease in analgesics of ≥25% without an increase in pain score. OS and PFS were calculated in months from the date of the end of RT to the first event, including the date of the last follow-up examination or death (OS) and/or disease progression (PFS). OS and PFS were estimated using the Kaplan–Meier method.

Results

Patient and lesion characteristics

Overall 18 consecutive elderly patients were included in the present study. In 18 patients with cSCC, a total of 23 lesions were observed. The patient and lesion characteristics are listed in Table 1. The median age at diagnosis was 89 years (range, 76-97 years), and all patients had an ACE-27 score of ≥1. Overall, 17 patients were qualified for home health care, and one patient lived in a nursing home. The vast majority of lesions (n = 21; 91.3%) were located in the head and neck region. Thirteen patients (72.2%) referred local pain at diagnosis and bleeding lesion was evident in 8 cases (34.8%).

Response rate

All patients were treated with a hypofractionated RT and received the prescribed total RT dose. The ORR12w was 95.7%. Complete response rate and partial response rate were 65.2% (n = 15) and 30.4% (n = 7), respectively. Only one

Table 1 Patient and lesion characteristics

Characteristics	*n* (%)
Patient	18 (100)
Gender	
Male	9 (50.0)
Female	9 (50.0)
Age	
75-80	3 (16.7)
81-85	3 (16.7)
86-90	5 (27.8)
>90	7 (38.8)
Performance status	
1	8 (44.5)
2	9 (50.0)
3	1 (5.5)
ACE-27 score	
0	0 (0.0)
1	8 (44.5)
2	7 (38.8)
3	3 (16.7)
Lesion	23 (100)
Histology squamous cell carcinoma	23 (100)
Tumor stage	
1	1 (4.4)
2	7 (30.4)
3	14 (60.8)
4	1 (4.4)
Site	
Zygomatic area	2
Ear, pre-, retroauricular region	3
Cheek	1
Forehead-temples	5
Scalp	10
Extremities	2

ACE-27, adult comorbidity evaluation-27.

patient experienced progressive disease (n = 1; 4.4%). Details are presented in Figure 1.

Clinical outcomes

RT was not interrupted for acute toxicity. Mild to moderate acute dermatitis in the skin around the lesion was reported in all cases (n = 23, 100%). Of the 13 patients who referred local pain at diagnosis, all cases reported a complete pain response within 8 weeks after RT. Bleeding relief was achieved in all those lesions that bled before treatment. Overall, severe acute and late toxicity were not recorded.

Survival outcomes

The follow-up data were updated in May 2021. At the date of analysis, nine patients (50%) had died, of whom one (11.1%) had died of cSCC. Other major causes of death were related to coexisting medical conditions (n = 8; 88.9%). Overall, five patients (27.8%) had relapsed either locally (n = 1), regionally (n = 2) or at the metastatic level (n = 2). The 1-year and 2-year OS rates were 66.0% (95% confidence interval [CI], 0.350-0.848) and 26.4% (95% CI, 0.043-0.568), respectively. The 1-year and 2-year PFS rates were 58.7% (95% CI, 0.265-0.807) and 23.5% (95% CI, 0.038-0.526), respectively.

Discussion

Our series shows that vulnerable elderly patients with cSCC achieve an optimal response rate (95.7%) with a low toxicity profile after 7-8 weekly fractions of 8 Gy per fraction with megavoltage electrons. All patients who had developed pain or bleeding before treatment had achieved symptom relief. Only a minority of patients (11.1%) had died of the disease. The efficacy of the hypofractionation RT is therefore of the utmost importance for tumor control and patient quality of life.

These clinical results are consistent with those reported in literature. Actually there are few studies that tested the therapeutic effects of definitive hypofractionated RT and, thus, it is difficult to precisely determine its significance.[9] Generally, the cure rate is

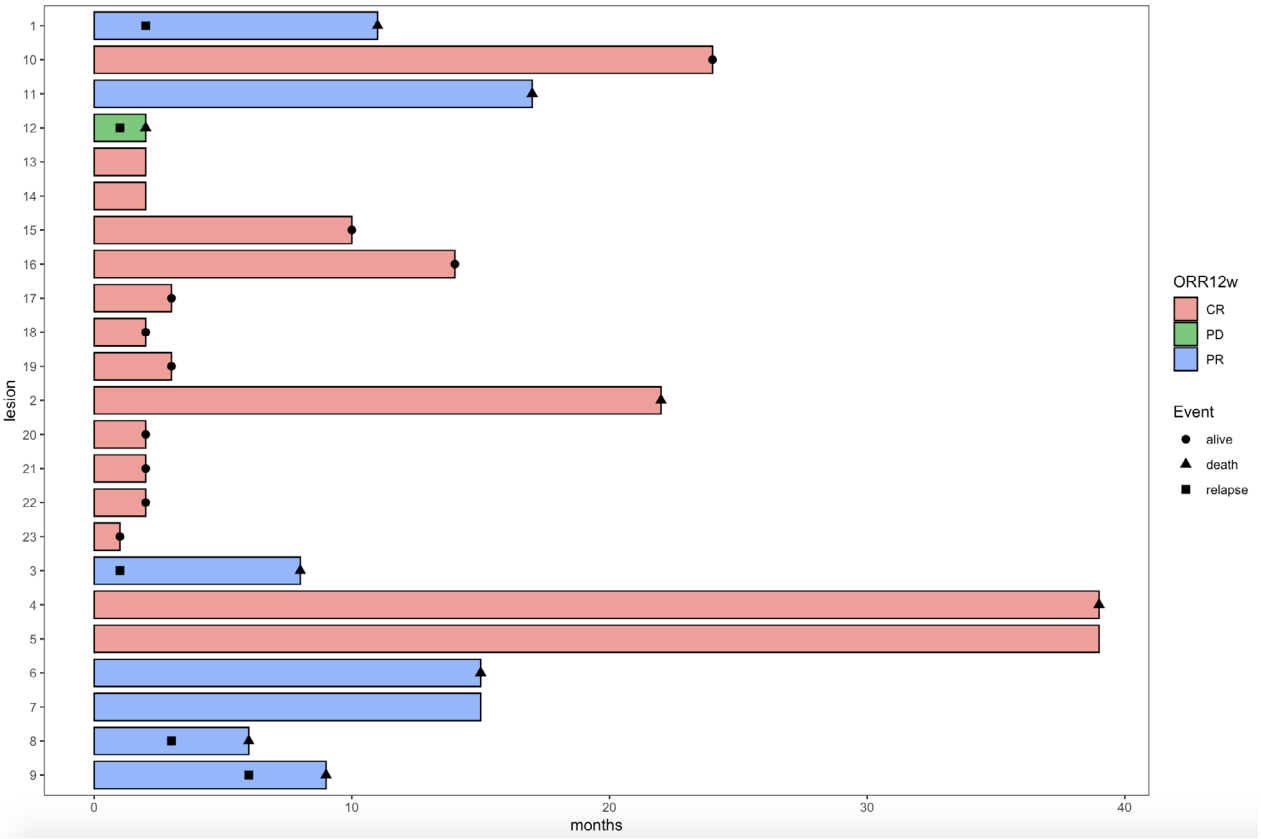

Figure 1 Swimmer plot showing patients and lesions evolution. ORR12w: overall response rate at 12 weeks after radiotherapy; CR, complete response; PD, progressive disease; PR, partial response. Horizontal bars represent each lesion (total number = 23). Each bar shows the length of follow-up period for each treated lesion. Colors express overall response rate at 12 weeks (ORR12w) for each lesion. While geometrical shapes refer to patients (total number = 18) and are utilized to display additional information, including event of death, relapse of disease, or alive. In this context, for patients with multiple lesions, geometrical shapes will be just displayed in the first bar lesion (for instance, lesions 12, 13, and 14 refer to the same patient and thus event is only shown in the bar 12)

reportedly 90%.[9] However, outcomes and patient population are not uniform, limiting a precise comparison of the effect of RT schedule per se. It is important to emphasize that the variety of methods used in many studies as well as the heterogeneity of the results precluded any quantitative analysis. The recent review by Gunaratne et al. represents a descriptive synthesis of the available data and documented that hypofractionated RT delivered either daily, alternative daily, or once weekly represents a highly effective treatment with acceptable toxicity.[10]

At present, there is no standard of care for non-resectable cSCC. Despite the moderate-quality evidence, the American Society for Radiation Oncology (ASTRO) convened to strongly recommend a definitive RT in cSCC patients who cannot undergo surgical resection.[11] Different appropriate dose-fractionation schedules, including both conventional fractionation and hypofractionation options, are provided. Generally a total dose of 70-80 Gy at 2 Gy/fraction or an equivalent regimen has been prescribed in existing series with over 100 patients treated with definitive RT.[11] Overall, these schemes offer a versatility in treatment strategy but, as authors recognized, they are not all-inclusive. For instance, there is no mention of a weekly approach. We believe that the choice of a weekly hypofractionated regimen using electron beam therapy without three-dimensional planning should be considered a valid option in vulnerable elderly patients, mainly due to logistics and cost-effectiveness issues. In our series, all patients were qualified for home health care or nursing home, making daily transportation to an RT unit difficult. Our weekly hypofractionated scheme offers an opportunity to propose a patient-centered management, merging optimal response rate and clinical outcomes to an adequate life quality, both for patient and his/her family.

Actually, these findings are broadly in keeping with the conclusions of several retrospective studies documenting the clinical efficacy of hypofractionated schedule in the setting of elderly patients.[10,12,13] As an example, both Valeriani et al. and Pampena et al. agreed to safely prescribe hypofractionated regimes in elderly frail patients, mainly because of patient's quality of life advantages.[12,13]

During the last years, various sequences and combinations of multiple and novel systemic treatment have extremely changed the field of oncologic therapy in different human malignancies.[14–16] New knowledge is accumulated concerning immune checkpoint blockade in the treatment of cSCC as tumor with a high mutational burden.[17] The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently approved the immune-checkpoint inhibitor cemiplimab for patients with an advanced form of cSCC.[18,19] However, despite remarkable advance has been made with the introduction of cemiplimab, the quality of evidence is limited as cemiplimab has not been investigated in randomized controlled trials, and its approval is based on two early-phase clinical trials.[18,19] A real-life experience of cemiplimab use in cSCC exhibited a worse safety profile than in clinical trials, with more treatment discontinuation, especially in older patients (> 65 years old).[20] Therefore, a mixed treatment including weekly hypofractionated and cemiplimab should be conscientiously evaluated. It could be a good option in well-selected elderly patients with a good PS and minor comorbidities.

The limitations of this study are mainly related to the retrospective coding of patients and the relatively limited sample size, providing hypothesis generating rather than confirmatory results. Our results would ideally be confirmed in a randomized trial. Nevertheless, this study could help guide clinical decision-making in elderly cSCC patients. For sure, in elderly patients, treatment strategy becomes a question of trade-offs. Therapy should be individualized and shared between clinicians, patients, and their family to balance clinical benefit, toxicities, costs, and personal preferences. It is paramount to establish whether a patient is fit, vulnerable, or frail in order to properly select the best management. A better quality and quantity of life as well as a less treatment time should be prioritized.

The proposed hypofractionation schedule is a safe, effective, and reliable treatment approach for elderly cSCC patients who are not surgical candidates. This study further adds to the literature and warrants a prospective clinical trial to improve the level of evidence.

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Ethical approval and ethical standards

Collected data were anonymized and protected during the study. This study has been conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board.

Informed consent

Informed consent was obtained from participants included in the study, allowing authors to exploit data anonymously.

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