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Research Letter to Editor

Definitive weekly hypofractionated radiotherapy in surgery-ineligible older adults with cutaneous squamous cell carcinoma of the head and neck region

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ABSTRACT

This study intends to address the impact of weekly hypofractionated radiation therapy with curative intent for cutaneous squamous cell carcinoma of the head and neck region in the elderly population.

1. Introduction

Cutaneous squamous cell carcinoma of the head and neck region (cHNSCC) predominantly affects patients older than 65 years [1]. The standard curative treatment approach includes radical surgery followed by adjuvant radiotherapy (RT), if indicated [2]. But this management oftentimes cannot be feasibly applied to older adult patients (≥ 75 years) mainly due to their sometimes suboptimal functional status or comorbidities.

We explore the role of definitive weekly hypofractionated RT as a curative treatment for older adults with cHNSCC unfit for surgery. An update of a previous study was performed to provide insights into the long-term benefits of definitive weekly hypofractionated RT for non-metastatic cHNSCC [3,4].

2. Materials and Methods

2.1. Population

Older adults (aged ≥75 years) with histologically proven cHNSCC, unfit for surgery, and with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 3 were enrolled. The study was approved by the Institutional Review Board. All patients provided written informed consent.

Medical data were prospectively collected and included patient-, tumor- and treatment- characteristics, and follow-up data. Patients were evaluated according to the ECOG PS score and the adult comorbidity evaluation-27 (ACE-27) score [5,6]. All lesions were restaged using the 8th edition tumor-node-metastasis (TNM) system [7].

2.2. Radiation Therapy

Patients received definitive weekly hypofractionated RT, using megavoltage electrons. A total dose of 56 Gy in 7 weekly fractions of 8 Gy (in case of T1–2 lesions) or 64 Gy in 8 weekly fractions of 8 Gy (in case of T3–4 lesions) was prescribed. Bolus material was applied to reduce inhomogeneous dose distributions, when clinically appropriate. No supplemental external beam radiation was allowed.

2.3. Follow-up

After RT, patients were followed monthly. In case of complete response (CR), the evaluation was performed every three months for two years, every six months for up to five years, and included complete skin and regional lymph node exam and physician assessment of toxicity according to the Common Terminology Criteria for Adverse Events

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(CTCAE), version 5.0 [8]. Diagnostic exams, such as loco-regional ultrasound and computer tomography (CT), were recommended if clinically indicated.

2.4. Outcomes

The primary endpoint was objective response rate at three months (ORR3m), defined as the proportion of lesions with a CR or partial response (PR) at three months after RT. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), pain response within 8 weeks (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), toxicity profile, and safety. Local control and regional control were also analyzed.

DOR was defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause. OS and PFS were defined as the time in months from the end of RT to the last follow-up date, death (OS), or disease progression (PFS). Local control and regional control were defined on a "per lesion" basis, as the progression in the irradiated treatment volume.

2.5. Statistical Analysis

Statistical analysis was conducted using R-Studio version 0.98.1091 software. Standard descriptive statistics were used to evaluate the distribution of each variable. Continuous data are given as means (standard deviations [SD]) or medians (ranges), and categorical data as the numbers of observations and percentages. Survival rates were estimated using the Kaplan-Meier method.

3. Results

3.1. Patients

In total, 19 older adults with 27 cHNSCC lesions were included. Three new patients and six cHNSCC lesions were added for this updated analysis. The mean age at diagnosis was 86.7 years (range, 78–95 years) and 12 patients (63.2%) were male. Most patients ($n = 13$; 68.4%) had an ACE-27 score of ≥2. The vast majority of lesions were located in the forehead-temples ($n = 10$; 37.0%) and the scalp (n = 10; 37.0%) and were clinically staged as T3–4 ($n = 18$; 66.7%). Before RT, 10 patients (52.6%) reported local pain, and bleeding was recorded in 12 cases (44.4%).

3.2. Efficacy

In total, 19 lesions had CR (70.4%) and six had PR (22.2%). The median time to response was 1.1 (range, 0–5) months. The median DOR was 12 months (95% confidence interval [CI], 6 – NR). Resolution of bleeding and pain relief was achieved in all cases ($n = 12$ and $n = 10$, respectively).

Median survival was 25 months. The one-year and two-year PFS rates were 63.0% (95% CI, 35.2% to 81.8%) and 52.7% (95% CI, 23.6% to 75.2%), respectively. The 1-year and 2-year OS rates were 74.2% (95% CI, 44.8% to 89.5%) and 56.2% (95% CI, 25.3% to 78.5%), respectively. Four lesions recurred locally, whereas there was no evidence of regional progression. The two-year actuarial local control rate on a "per lesion" basis was 79.4% (95% CI, 53.6% to 91.9%).

3.3. Toxicity Profile and Safety

All patients received the prescribed total dose. No patients had interrupted planned treatment. All patients experienced mild to moderate acute radio-related dermatitis in the skin around the lesion. Severe toxicity was not recorded. No late toxicity was observed.

4. Discussion

To sum up, definitive weekly hypofractionated RT showed safety, durable efficacy, and promising survival outcomes in surgery-ineligible older adults with cHNSCC. The ORR was high (92.6%) with a median DOR of 12 months, complete pain relief, resolution of bleeding episodes, and a median survival of 25 months. Whether the clinical outcome differed depending on the primary lesion site could not be elucidated in this study because of the small cohort and the lack of formal assessments. However, it should be noted that those patients who developed treatment failures had lesions located on curved surfaces, including the bridge of the nose and the ear.

Our results emphasize the importance of definitive weekly hypofractionated RT for surgery-ineligible older adults with cHNSCC. The American Society for Radiation Oncology (ASTRO) recommends definitive hypofractionated RT as primary treatment for patients unfit for surgery, but different dose-fractionation schedules are recommended [9] (see Table 1). Overall, the biological effective dose (BED) ranges between 56 Gy and 88 Gy, delivered daily or 2–4 times per week.

Our weekly hypofractionated RT scheme is consistent with the results (in terms of efficacy and toxicity profile) reported in other series [10]. These are retrospective analyses of patients with non-melanoma skin cancer but details on older adults with cHNSCC are not specified. This heterogeneity limits the direct comparison, as well as the identification of the best RT scheme in terms of total dose and dose per fraction. A dose-response analysis should be investigated in the near future. We proposed a treatment regimen of 8 Gy/fraction to a total dose of 56–64 Gy to achieve the best local control with minimal treatment-related toxicity.

Hypofractionated RT has a favorable risk–benefit balance compared to radical surgery, despite surgical advantages (speed of recovery and its effectiveness). cHNSCC management should be individualized and hypofractionated RT should be proposed to older adult patients within the frame of the decision-making process.

The main limit of this study is the single-institution nature and the small number of patients. On the other hand, all lesions were treated using the same RT schedule, supporting its clinically meaningful efficacy and safety profile. Our definitive weekly hypofractionated RT schedule also suggests its potential benefit in terms of quality of life, both for patients and their families, favoring weekly transport to RT unit over daily.

To conclude, weekly hypofractionated RT has high cure rates and minimal acute morbidity in older adults with cHNSCC unfit for surgery.

Author's Contributions

Study concepts and design FDF, VT, DM; Data acquisition MS, CGC, FDG, AF, ADD, ML, EV; Data analysis, statistical analysis, manuscript preparation, editing FDF; Manuscript review all authors.

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Table 1
Dose-fractionation schedules in definitive radiation therapy treatment[*,#].

Total dose (Gy) @ Gy per fraction	Fraction per week	BED (Gy)
44 @ 4.4	4	63.4
50 @ 2.5	5	62.5
54 @ 3	4	70.2
55 @ 2.75	5	70.1
61.2 @ 3.4	5	82

Gy: Gray; BED: biologically effective dose assuming an $\alpha/\beta = 10$.
[*] Primary radical radiotherapy was given in the vast majority (> 70%) of patients.
[#] From [9].

Informed Consent

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

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 approved by the Institutional Review Board.

Declaration of Competing Interest

All authors declare that they have no conflict of interest.

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