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Efficacy and Safety of Hypofractionated Radiotherapy in Local Advance Head and Neck Cancer Patients: Cuba Experience

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Abstract

Introduction: Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide. Conventional chemoradiotherapy remains the standard of care, but prolonged courses present challenges, especially in low-resource settings. Hypofractionated radiotherapy may offer an effective and resource-efficient alternative. **Methods:** An IAEA phase III randomized controlled clinical trial (HYPNO trial) involving the Oncology Institute of Havana, Cuba, enrolled patients from 2014 to 2018. Seventy-five patients with locally advanced HNSCC were randomized to receive conventional normofractionated radiotherapy or hypofractionated IMRT, both with concurrent low-dose chemotherapy. Outcomes included tumor response, locoregional control, survival, and toxicity. **Results:** The median age was 56.8 years, 88% were men, 59.5% reported being smokers and alcohol drinkers, and the oropharynx was the site of the highest incidence (78.7%). One month after treatment, a complete response was achieved in 91.4% of normofractionated patients versus 74.3% of hypofractionated patients. An improvement in tumor and lymph node response was observed at three months in the hypofractionated group, suggesting late but favorable tumor regression. Locoregional control at three years was 62.9% for the normofractionated arm versus 69.2% for the normofractionated arm. Overall survival at five years was 54.1% and at nine years was 48%. Late toxicity was lower in the hypofractionated group (12.8% versus 37.1%; p = 0.03). **Conclusion:** Hypofractionated radiotherapy concomitant with chemotherapy is a safe and effective option.

Keywords

Head and Neck Cancer, Hypofractionation, Radiotherapy, IMRT, Locoregional Control, Toxicity, Cuba

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide, with nearly 890,000 new cases and 450,000 deaths annually [1]. Despite therapeutic advances, approximately 47% present with regionally advanced disease at diagnosis, resulting in poor survival outcomes. Five-year survival ranges from >80% in localized disease to <40% in advanced stages [2]. Major risk factors include tobacco and alcohol consumption, as well as human papillomavirus (HPV) infection [2] [3]. The most common anatomical sites are the oropharynx, oral cavity, and larynx [2]. Radiotherapy concomitant with or without chemotherapy remains a cornerstone of treatment [4] [5]. Conventional radiotherapy, however, requires prolonged courses, which can compromise adherence and increase healthcare burden, especially in low-resource settings [6]. Hypofractionated radiotherapy shortens overall treatment duration, delivering higher daily doses while maintaining efficacy. This approach is particularly attractive in low-income countries where access to treatment is limited [7]. This study reports the Cuban experience from a phase III randomized clinical trial evaluating the efficacy and safety of hypofractionated IMRT versus conventional radiotherapy.

2. Material and Methods

Study Design and Patients

This phase III, randomized, controlled clinical trial was sponsored by the International Atomic Energy Agency (IAEA) and coordinated under the scientific direction of the University of Maryland (USA). The Institute of Oncology of Havana, Cuba, was one of the participating centers, where patient recruitment, treatment, and follow-up were performed. The study was registered under number NCT0276550 and was approved by the institutional ethics committee and conducted in accordance with the principles outlined in the Declaration of Helsinki of the World Medical Association, which ensures the protection of the rights, safety and well-being of research participants. All patients provided written informed consent prior to inclusion in the study.

Inclusion Criteria:

1) Adults ≥ 18 years of age. 2) WHO performance status: 0 - 2. 3) Stage II - IVb squamous cell carcinoma of the oropharynx, hypopharynx, larynx (excluding glottis I - II), or oral cavity.

Exclusion Criteria:

1) Distant metastasis. 2) Severe comorbidities. 3) HIV positivity. 4) Previous definitive surgery (except biopsy). 5) Synchronous cancers. 6) Pregnancy.

Before treatment started, all patients received prophylactic dental care and nutritional evaluation.

Patients were enrolled in two arms of treatment prior to randomization conducted by Maryland University.

- Normofraction arm: Total doses of 66 - 70 Gy with 2.0 Gy per fraction, in 33 - 35 fractions.
- Hypofraction arm: Total doses of 55 Gy with 2.75 Gy per fraction, in 20 fractions.

Treatment was delivered with IMRT using an Elekta Synergy system with weekly CBCT to verify the patient's position on the machine.

All patients were immobilized with a 5-point head-shoulder thermoplastic mask and subjected to a computed tomography (CT) simulation. Also, they received concomitant low dose of Cisplatin as chemotherapy treatment, 35 mg/m^2, weekly.

Endpoints and Evaluations

- Primary endpoint: locoregional control (LRC) at 3 years.
- Secondary endpoints: overall survival (OS), late toxicity, and tumor response.

Tumor response was assessed using RECIST v1.1 and toxicities using CTCAE v5.0.

Follow-up

Patient follow-up occurred weekly during treatment, at treatment completion, every three months for two years, every three months for the following two years, and annually for five and ten years. The median follow-up was 6.134 years.

Toxicity

Acute toxicity: 0 - 3 months;

Sub-Acute toxicity: 4 - 12 months;

Late toxicity: >1 - 10 years.

Statistical Analysis

Kaplan-Meier survival analysis with log-rank test, Cox regression for multivariate analysis, and chi-square tests for categorical data. Significance level: $p < 0.05$. Analyses performed with SPSS v22.

3. Results

Patient Characteristics

Median age: 56.8 years; 88% male; 69% smokers; 67% alcohol users and 59.5% had the two habits. Oropharynx was the most frequent site (78%). Most patients (83%) presented with stage III - IVa disease (Table 1).

In multivariate analysis, tobacco use was independently associated with an increased risk (HR: 2.78; 95% CI: 1.03 - 7.46; $p = 0.043$). Furthermore, oral cavity tumor location was significantly associated with an increased risk compared with other sites (HR: 5.46; 95% CI: 2.04 - 14.60; $p = 0.001$). No significant associations were found with age, sex, alcohol use, or clinical stage in the multivariate analysis ($p > 0.05$). These findings suggest that smoking and oral cavity tumor location are

independent factors influencing the outcome studied (Table 2).

Table 1. Demographic and Clinical epidemiological patient's characteristics per arm of treatment.

Variable		Normo	Hypo	Total	%
		N = 36	N = 39	N = 75	
Age	≤55	15	15	30	40
	>55	21	24	45	60
Sex	Female	5	4	9	12
	Male	31	35	66	88
Smoking	Yes	24	28	52	69
	No	12	11	23	30
Alcohol drinking	Yes	23	26	49	65
	No	12	13	25	33
Tumor site	Oral cavity	5	3	8	10
	Oropharynx and others	31	36	67	89
Clinical stage	II	4	2	6	8
	III	18	11	29	38
	IV	14	26	40	53

Table 2. Univariate and multivariate analysis of demographic and clinical epidemiological patient's characteristics.

Variable		Normo	Hypo	Total	%	Univariate			Multivariate		
		N = 36	N = 39	N = 75		HR	95% CI	p	HR	95% CI	p
Age	>55	21	24	45	60	0.584	0.308 - 1.109	0.100	0.785	0.406 - 1.515	0.470
Sex	Male	30	35	66	88	0.708	0.392 - 1.277	0.251	1.845	0.553 - 6.157	0.319
Smoking	Yes	23	28	52	69	3.504	1.460 - 8.144	0.005	2.775	1.033 - 7.455	0.043
Alcohol drinking	Yes	23	26	50	66	2.573	1.176 - 5.631	0.018	1.174	0.487 - 2.828	0.721
Tumor site	Oral cavity	5	3	8	10	4.378	1.737 - 11.032	0.002	5.460	2.041 - 14.604	0.001
Stage	III	18	11	29	38	1.124	0.320 - 3.954	0.855	0.896	0.248 - 3.238	0.867
	IV	13	26	40	53	1.773	0.518 - 6.070	0.362	1.234	0.364 - 4.180	0.735

Our findings corroborate that toxic habits, particularly alcohol and tobacco consumption, are the predominant risk factors for this type of tumor. This association in 59.5% of patients was statistically significant in this study (Figure 1).

Due to the total of patients having a local advanced tumor, they were treated with concurrent Chemoradiation under two arms: normofraction and hypofraction. In case of radiotherapy, with intensity modulated radiotherapy (IMRT) technique, due to the intention of the planning is to diminish the dose in the healthy organs or tissues of risk in comparison with the traditional treatments in the department taught with other techniques.

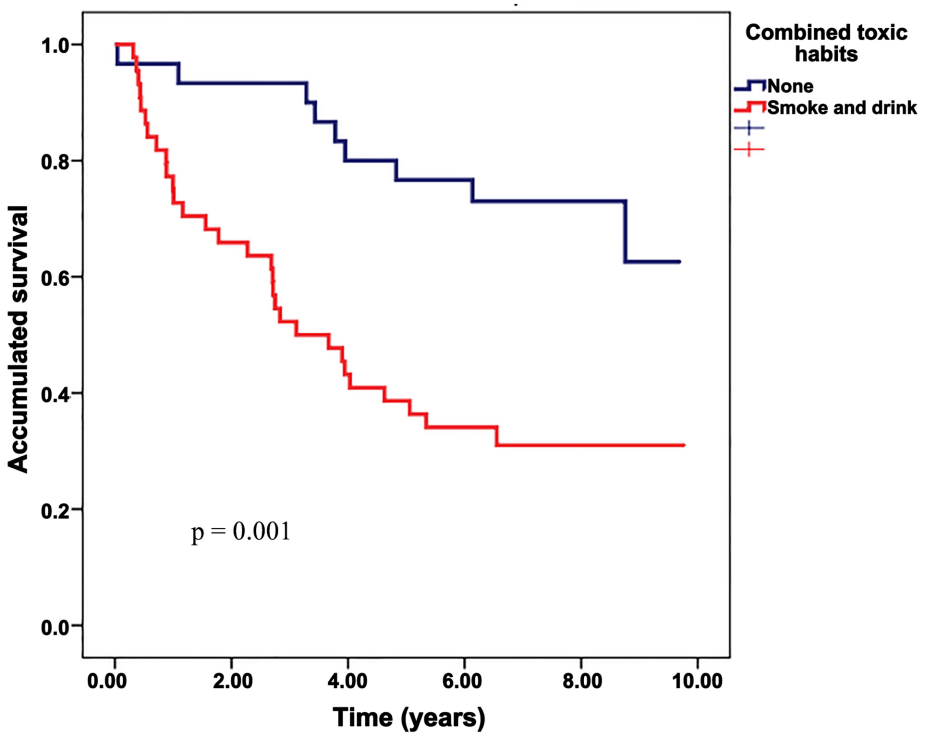

Figure 1. Survival function according to toxic habits in patients with HNSCC treated with chemoradiotherapy.

Few patients had treatment interruption 24% (18 patients) due to toxicities. 11 in normofraction arm and 7 in hypofraction arm. The average treatment discontinuation time was 5.2 days. p = 0.177.

Response to chemoradiotherapy was assessed during treatment and one month after completion. Analyzing the response in both the primary tumor and the neck lymph nodes, the following result was observed: 91.4% of patients in normofraction arm achieved a complete response in the primary tumor, while only 74.3% of those in hypofraction arm achieved a complete response. In patients with positive neck lymph nodes, the complete response rate was 71.4% in normofraction arm and 61.6% in hypofraction arm. That is, partial responses were higher for both the primary tumor and the lymph nodes in hypofraction arm. A better complete response was achieved with the normofractionated regimen, although not statistically significant (Table 3).

However, a response of both the primary tumor and positive nodes was observed for patients in hypofraction arm between one month and three months after the end of treatment. It could be associated with the delay consolidation of the disappearance of inflammation, local edema, and the immune response secondary to this type of fractionation.

Analyzing the locoregional control rates at three years in both arms, hypofraction arm had a LRC of 69.2%, higher than normofraction arm of 62.9%, for the study, which means that hypofractionated radiotherapy had better locoregional control (Table 4).

Table 3. Primary tumor and lymph node response one month after completing treatment by arm of treatment.

Tumor Response	Normofraction n = 35		Hypofraction n = 39		Total n = 74		p
	N	%	N	%	N	%	
Complete	32	91.4	29	74.3	61	82.4	0.067
Parcial	2	5.7	2	5.1	4	5.4	
Progression	1	2.9	8	20.6	9	12.2	
Total	35	100	39	100	74	100	
Node Response							
Complete	25	71.4	24	61.6	49	66.2	0.607
Parcial	8	22.9	13	33.3	21	28.4	
Progression	2	5.7	2	5.1	4	5.4	

p: Probability estimated value per chi-square; n: Number of cases; N: Number of cases with the condition; %: Percentage. Chi-square = 0.998; p = 0.607.

Table 4. Locoregional control rate three years after treatment.

Treatment Arm N = 75	LRC Rate in 3 Years	95% CI		p
		Lower	Upper	
Normofraction	62.9	44.9	80.3	0.307
Hypofraction	69.2	53.5	84.9	

LRC hypofraction arm 69.2% ≥ LRC normofraction arm 62.9%. CI: Confidence Interval; LRC: Locoregional Control.

From the start of treatment with ionizing radiation, patients progressively experience adverse events. From the fourth or fifth week of treatment, they begin to report discomfort and restlessness. These acute effects usually disappear within the first month and rarely last more than two months.

The main acute adverse events observed during treatment were similar in both groups. It was dysgeusia, radiodermatitis, mucositis, odynophagia, xerostomia, weight loss, and alopecia. Mucositis and radiodermatitis were the most frequent. No patient develops any grave event, p = 0.0001 (**Table 5**).

In the present study, 24.3% (18 patients) discontinued treatment due to Adverse Events. Clinical evaluation showed that patients in the hypofractionated treatment group (arm B) experienced acute adverse events, grade III, starting in the third week. Because this regimen is shorter, recovery from radiation damage was rapid. In contrast, conventional treatments (Normo), which showed grade II Adverse Events in the third week, required an additional three weeks to initiate recovery from radiation damage. The average treatment discontinuation time was 5.2 days.

The late events observed were the chronic xerostomia, trismus, osteoradionecrosis, and tooth loss that occurred during patient follow-up. The late adverse event rates were lower in hypofractionation arm than in normofraction arm and it was statistically significant (**Table 6**).

Table 5. Characterization of acute adverse events by treatment arm.

Adverse Event	Time	Normofraction n = 36				Hypofraction n = 39				p
		G0	G1 - G2	G3	G4	G0	G1 - G2	G3	G4	
		Adverse Event Intensity								
Mucositis	Week 3	18	17	0	0	5	34	0	0	0.0001
	Week 4	4	21	0	0	1	33	5	0	0.0001
	End of treatment	1	14	19	0	1	11	25	0	0.694
	One-month after	20	15	0	0	21	18	0	0	0.667
Radio-dermatitis	Week 3	22	12	0	0	5	34	0	0	0.0001
	Week 4	1	34	0	0	1	35	3	0	0.0001
	End of treatment	0	25	10	0	0	20	19	0	0.303
	One-month after	17	18	0	0	12	26	0	0	0.071

G0, G1, G2, G3 and G4: CTCEA V. 5.0 classification; p: Probability estimated value per chi-square; n: Number of cases.

Table 6. Three-year late adverse event rates.

Treatment n = 75	Late Adverse Event Rates	95% CI		p
		Lower	Upper	
Normofraction	37.1	19.7	54.6	0.030
Hypofraction	12.8	4.3	27.4	

Hypofraction Toxicity 12.8% ≤ Normofraction Toxicity 37.1%. CI: Confidence Interval; n: Number of cases.

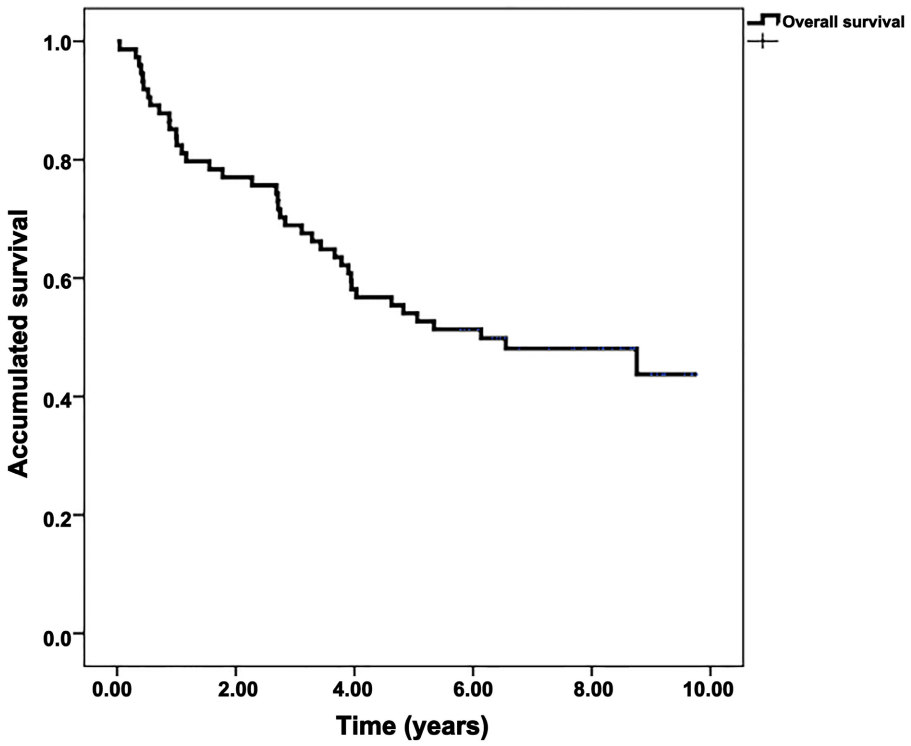

Figure 2. Overall survival function in patients with HNSCC treated with chemoradiotherapy.

The global survival in 5 years is 54.1% and 10 years 48% with a median of 6.2 years. The analysis of both arms showed a slight superiority of the hypofracioned arm over the normofractioned arm in at five years and more (Figure 2 and Figure 3).

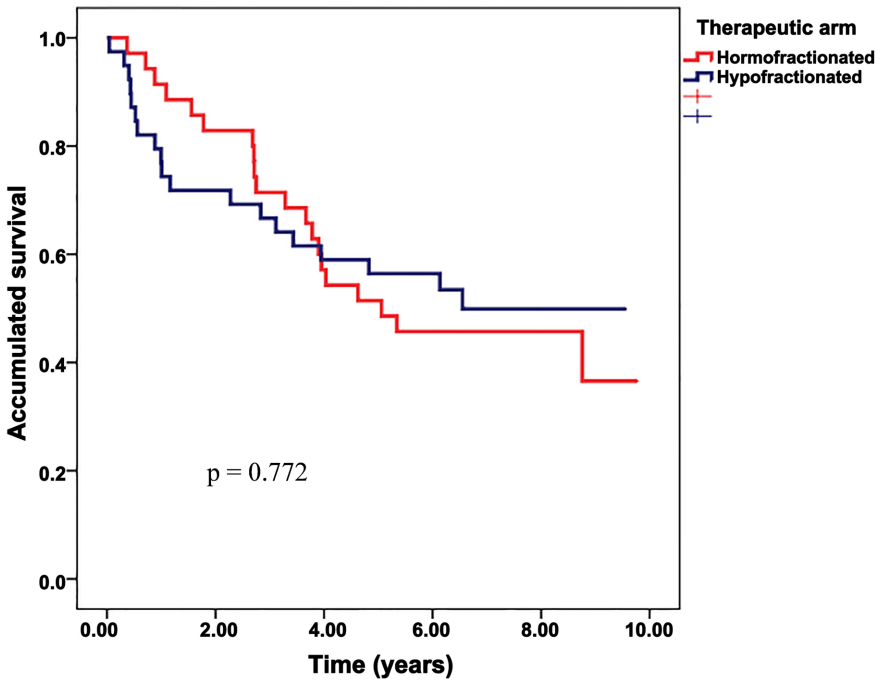

Figure 3. Survival function according to RT fractionation assignment in patients with HNSCC treated with chemoradiotherapy.

4. Discussion

Hypofractionated radiotherapy has emerged as a promising strategy for the treatment of head and neck squamous cell carcinoma, offering the advantage of shortening the overall treatment duration by administering higher doses per fraction in fewer sessions.

Matsuya *et al.* explain the radiobiological course of tumor response in hypofraction. And said it can induce a more rapid tumor response in some cases, but complete clinical or radiological disappearance of the tumor may require weeks or months post-treatment, as the cumulative effect of radiation and the immune response take time to consolidate. Furthermore, cellular repopulation and repair of damage in normal tissues can influence the time to observe a complete response. After radiotherapy, inflammation in the treated area is common. This increase in volume may suggest that the tumor persists in the early stages post-treatment, when in fact it is part of the inflammatory process [8].

Recent phase III studies, such as ELAN-RT, have demonstrated the feasibility and safety of this approach, especially in older patients, without compromising therapeutic efficacy [9]. The HYPNO trial, which the study is a part of, provides preliminary evidence of non-inferiority in tumor control with hypofractionated reg-

imens, which represents a significant advance given the impact that reduced treatment times can have on quality of life and healthcare resource capacity [10].

HYPORT phase I study (delivering 46.5 Gy in 15 fractions) has shown the feasibility and non-inferiority of hypofractionated radiotherapy compared to standard schedules [11].

A retrospective study done at The Princess Margaret Cancer Centre proposed a hypofractionated regimen in the context of the COVID-19 pandemic, in order to reducepatients' travelanalysed data from 2039 patients receiving three different radiotherapy schedules: a hypofractionated and accelerated regimen delivering 60 Gy in 25 fractions over 5 weeks, an accelerated regimen delivering 70 Gy in 35 fractions over 6 weeks and a standard chemoradiotherapy regimen delivering 70 Gy in 35 fractions over 7 weeks. A total of 324 patients received hypofractionated radiotherapy. The results showed a 3-year local control rate of 95% and distant control rate of 90% for Human papillomavirus-related (HPV+) oropharyngeal tumors (median follow-up: 4.8 years) with the hypofractionated regimen. No significant oncological differences were observed between the different treatment regimens in 2 D. patients with HPV+ oropharyngeal tumors. For HPV− head and neck tumors, the local control rate was 85%, and the distant control rate was 99% across stages I and II with the hypofractionated regimen without significant differences between the different treatment regimens. Regarding toxicity outcomes, the hypofractionated regimen did not result in any more grade 3 or higher toxicity compared to normofractionated radiotherapy. Because they were based on a retrospective study and cannot be considered as standard of care [12].

The ComPARE study, a phase III randomized controlled trial, used an adaptive multiarm approach, exclusively including patients with intermediate- and high-risk oropharyngeal cancer. The third arm of this study compared hypofractionated chemoradiotherapy regimen delivering a dose of 64 Gy in 25 fractions with standard chemoradiotherapy. A total of 257 patients were enrolled (85 in the hypofractionated treatment arm, 172 in the control arm). With a median follow-up of 36.7 months, no benefit was observed for accelerated hypofractionated chemoradiotherapy compared to standard regimen in terms of event-free survival and overall survival [13].

Gupta *et al.* demonstrated short-course hypofractionated-accelerated RT represents an attractive and suitable alternative to the more protracted regimens in non-nasopharyngeal HNSCC and can be offered in clinical practice during pandemic, which threatens to disrupt the healthcare resources and capacity globally [14].

Huang *et al.* (2020) reported that hypofractionated radiotherapy with 2.4 Gy per fraction during the COVID-19 pandemic achieved comparable outcomes and was well tolerated [15].

Jacinto *et al.* did a prospective cohort study of 20 patients, assessing the feasibility of hypofractionated and accelerated radiotherapy using three dose levels: 55 Gy in 20 fractions on macroscopic disease and 44 to 48 Gy for respectively tumor and lymph node areas at risk. Results showed that all patients received the full course

of radiotherapy, and 95% received at least three out of four chemotherapy cycles. No grade four dermatitis or mucositis was observed, but there were 30% of grade 3 dermatitis and 40% of grade 3 mucositis. All patients had complete resolution of mucositis and dermatitis within 1 month after treatment completion [16].

Mayo *et al.* (2021) also observed low toxicity rates with hypofractionated IMRT schedules [17].

The combination of hypofractionated radiotherapy with concomitant chemotherapy has shown comparable results in tumor response and toxicity compared to standard regimens in patients with unresectable locally advanced disease, supporting its potential use in diverse settings. At the same time, the integration of immunotherapy with conventional radiotherapy in studies such as GORTEC NIVOPOSTOP marks a trend toward multimodality treatments that could also be applied to hypofractionated regimens to optimize oncological outcomes [18].

However, although recent studies suggest a survival benefit with modified radiotherapy modalities, including hypofractionated therapy, the evidence is still insufficient to consolidate this approach as a standard of care. As Bocha *et al.* said in their review article, further prospective randomized studies are needed to define optimal indications and confirm long-term outcomes and safety [19].

5. Conclusion

Hypofractionated radiotherapy concomitant with chemotherapy is a safe and effective option of treatment, mainly in low- and middle-income countries. This supports its inclusion as an alternative standard in therapeutic guidelines, particularly in resource-limited settings.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations and Acronyms

IAEA: International Atomic Energy Agency.

IMRT: Intensity Modulated Radiotherapy.

CBCT: Cone Beam Computed Tomography.

Units

Gray (Gy): Unit of radiation dose, expressed as absorbed energy per unit mass of tissue.