Section: Radiation Oncology

Original Research Article

HYPERFRACTIONATED RADIOTHERAPY EMPLOYING SPLIT COURSE ACCELERATED THERAPY FOR ORAL CAVITY MALIGNANCIES

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Abstract

Background: To assess both the local control rate and the toxicity associated with split-course accelerated therapy (SCAT) in advanced cases of head and neck cancer. **Materials and Methods:** The study involved 20 newly diagnosed patients under 70 years of age with ECOG performance status less than 2. These patients underwent split-course accelerated hyperfractionation for advanced head and neck cancer. Treatment included 1.6 Gy per fraction, twice daily, with a 6-hour interval, over 5 days a week, totaling 38.4 Gy in 2.5 weeks. After a 14-day rest, treatment resumed with 1.6 Gy twice daily, delivering an additional 28.8 Gy over 9 days. The cumulative dose to the primary tumor and positive neck nodes was 67.2 Gy in 42 fractions over 6 weeks. In some cases, the prophylactic anterior lower neck field received a conventional dose of 200 rad, contributing to a total dose of 5000 rad. **Result:** Patients undergoing split-course accelerated hyperfractionation therapy demonstrated a positive outcome, with 56% achieving complete response in the primary disease and 52% experiencing complete nodal regression. However, notable side effects included grade II mucositis and skin reactions, emphasizing the need for vigilant monitoring and management of treatment-related issues for overall patient well-being. **Conclusion:** Relative to our past encounters with conventional radiotherapy, the results achieved with split-course accelerated therapy were remarkably promising.

INTRODUCTION

Oral cancer is the second most common cancer among male after Ca. pharynx, and in female, third mostcommonest cancer after Ca. cervix and breast. Generally, oral cancer occurs more commonly among men than women depending upon the extent and the type of tobacco habits, prevelent among them. The incidence in male is about 128 and in female 108 in India. The highest number of oral cancer in both sexes occur in the 6th decade of life.[1]

The objective of clinical radiation therapy is to administer a lethal dose to nearly every tumor cell in a localized lesion while inducing repairable injury to adjacent normal tissues. This necessitates an understanding of the differential radiosensitivity and recovery rates between neoplastic and normal tissues. Both these factors, namely, differential sensitivity and differential recovery, play a crucial role in achieving effective tumor control through radiation therapy (Ellis, 1969).[2]

The strategy to reduce overall treatment time by employing fewer and larger fractions can result in more severe late injuries. Both laboratory and clinical research have demonstrated that delivering external radiotherapy in numerous small doses and fractions (multiple fractions) enhances the irradiation of tumor cells, particularly during the mitotic and G2 phases, which are the most sensitive phases of the cell cycle. Additionally, multiple fractionation provides therapeutic advantages, including reoxygenation of hypoxic cells between fractions, improved repair capabilities of normal cells for sublethal damage, and a relative sparing of late radiation damage (Flower, J.F., 1968; Wither H.R., 1982).[3]

To leverage the advantages of a shorter overall treatment duration with hyperfractionation, it is essential to administer radiotherapy twice or thrice a day with weekend interruptions to allow the acute

reactions to subside before completing the entire course. The choice of fractionation schedule is a crucial factor influencing the outcome of radiation therapy, and various schedules, including "Conventional fractionation," hyperfractionation, accelerated fractionation, and their variants, have been employed in radiation therapy with split courses for advanced head and neck cancer. The biological basis, rationale, and results of clinical studies exploring these altered fractionation schemes have been recently discussed in a review by Ang & Peters.[4]

The primary distinction from conventional treatment with accelerated fractionation lies in the reduction of overall treatment time through the administration of two or more doses daily. Conversely, hyperfractionation involves a decrease in the size of each dose and an increase in the total dose, achieved by delivering two or more doses per day. In our study, we harnessed the radiobiological advantages of accelerated fractionation with hyperfractionation, incorporating a split in the course to allow the acute reactions to subside before completing the entire radiation course.

Hyperfractionation has been scrutinized in four randomized trials for advanced head and neck cancer, including studies by Datta N.R., Choudhary et al (1989), Pinto L.H.J. et al (1991), and Marcial V.A. et al (1989), all yielding nearly similar results. In Marcial V.A. et al's study, a standard schedule involving five fractions per week of 180 to 200 rads per day to a total dose of 6600-7380 rad was compared to a hyperfractionation regimen, comprising twice-daily fractions of 120 rads separated by a rest period of 3 to 6 hours for a total of 6000 rad. The complete response rates were 61% with the standard regimen and 59% with continuous hyperfractionation.[5]

MATERIALS AND METHODS

In this prospective study, 20 newly diagnosed head and neck cancer patients, aged <70 years, received split-course accelerated hyperfractionation. Treatment involved a cobalt-60 teletherapy unit, delivering 1.6 Gy/fraction twice daily, 5 days a week. The total dose to the primary tumor and neck nodes was 67.2 Gy over 6 weeks. Prophylactic lower neck fields received 200 rad. Sessions were held daily between 11 AM - 12 Noon and 5 PM - 6 PM. Portals covered primary disease, involved nodal areas, and likely microscopic metastatic spread. Carcinoma of the tongue and lip used two parallel portals, while carcinoma of the alveolus and buccal mucosa employed the Wedge Pair technique. Prophylaxis for the ipsilateral involved site used a single anterior field.

Patients underwent daily examinations throughout the radiotherapy course, with recorded responses in primary and nodal diseases. Follow-up occurred weekly for the initial 4 weeks, transitioning to monthly follow-ups, which are ongoing. Patients not completing the full treatment were excluded. Monthly follow-ups after treatment completion documented local response, radiation reaction, recovery, and late reactions. The presence of persistent duration and/or slough was deemed a failure.

Total number of patient 20 in majority of patient, primary site of disease was buccal mucosa 55 %followed by carcinoma of alveolus 25%, tongue 15% and lip 5%. Details given in table number 1.

RESULTS

Response of Primary Disease 09 patients (45%) revealed complete response while partial response was seen in 35% and no response was seen in 4 patients out of 20 patients (20%). Detail given in [Table 2].

In the split-course accelerated hyperfractionation therapy, 36.36% of patients with lesions in the buccal mucosa exhibited a complete response (04 out of 11 patients), carcinoma gingival alveolus with a 60% complete response rate (3out of 5 patients). One case each of carcinoma of the oral tongue and lower lip showed a complete response, while one case of oral tongue exhibited no response. Additionally, one cases of oral tongue and one case of the Gingivobuccal alveolus showed a partial response, as detailed in [Table 3].

Mucosal reactions were generally well-tolerated by the majority of patients following the radiation schedule. Grade II mucositis was observed in 45% of patients, while grade III mucositis occurred in 30% of patients. Only 15% of patients experienced grade IV mucositis, and this was observed in the last one and a half weeks of radiation during the second phase. Further details are provided in [Table 4].

Table 1: Distribution of disease according to primary site (n=20)

Sr. No.	Site	No. of patients	Percentages
1	Buccal mucosa	11	55%
2	Alveolus	05	25%
3	Tongue	03	15%
4	Lip	01	5%
	Total	20	100%

Table 2: Response of primary disease (n=25)

Sr. No.	Response	No.of patients	Percentages
1	Complete response	09	45%
2	Partial response	07	35%
3	No response	04	20%

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	Total	20	100%

Table 3: Overall response to split course accelerated hyper fractionated therapy

Sr. No.	Site	No. of case	CR No. of Patients (%)	PR No. of Patients (%)	NR No. of Patients (%)
1	Buccal mucosa	11	04 (36.36%)	05 (55%)	02 (18.18%)
2	Gingivo Alveolus	05	03(60%)	01(20%)	01(20%)
3	Tongue	03	01(33.3%)	01(33.3%)	01(33.3%)
4	Lip	01	01(100%)	-	-
	Total	20	09 (45%)	07 (35%)	04 (20%)

Table 4: Mucosal reaction (n=25)

Sr. No.	Grade	No.of patients	Percentages
1	Grade-0	Nil	-
2	Grade-I	02	10%
3	Grade-II	09	45%
4	Grade -III	06	30%
5	Grade -IV	03	15%
	Total	20	100%

DISCUSSION

Head and neck carcinoma, comprising 269 cases of all malignancies at our hospital, is primarily diagnosed at advanced stages (III and IV) in 79 % of patients. Conventional radiotherapy often struggles to control such advanced cases, leading to a common approach involving combined surgery, radiation therapy, and sometimes chemotherapy. To enhance tumor control and minimize radiation-related morbidity, various fractionation regimens have been explored. Conventional fractionation, with five sessions per week, has been a longstanding practice. Hypofractionation, accelerated hyperfractionation, and continuous accelerated hyperfractionation have also been tested. The goal of radiotherapy is to deliver an effective dose to the tumor volume, considering the rapid cell division in squamous cell carcinoma. Completing the full course of radiotherapy in the shortest time possible while maintaining fractionation benefits appears promising.[6]

Thomas et al. (1983) provided a comprehensive review of the rationale for accelerated fractionation in radiotherapy. They discussed the outcomes of several studies involving multiple dose fractions, focusing on accelerated and hyperfractionation techniques.[7]

A crucial 2-week rest period follows 38.4 Gy in split-course radiation therapy, allowing maximal radiation reaction management without compromising tumor control. This interval promotes rapid regeneration of the normal mucous membrane after radiation damage, facilitating the completion of the remaining treatment. The 6-hour interval between daily fractions supports various biological alterations, including sublethal damage repair, cell recycling, and hypoxic cell reoxygenation.

In a comparative trial by Karen K. Fu et al. (1995), split-course regimens were compared to a concomitant boost, yielding locoregional control rates of 58% and 41%, respectively, for advanced head and neck cancer in 75 randomized patients.[8]

Geoffrey P. Delaney et al. (1995) conducted a trial using a split-course accelerated radiation therapy protocol for selected head and neck cancer. The regimen included 1.8 Gy/fraction, twice daily, with a 6-hour gap between fractions for 8 days, followed by a planned 5 to 12-day break. Subsequently, another 10 to 11 treatment days of twice-daily fractions were administered, resulting in a total dose ranging from 64.8 to 72 Gy delivered in 5 to 6 weeks. Notably, 86% of patients achieved a complete tumor response, with a 3-year actuarial local control rate of 43% and a 3-year survival rate of 25%.[9]

The study included 20 patients, with three excluded due to irregular treatment. Of the 20 evaluated, 12 were male and 08 female, though this gender distribution lacked statistical significance given the small sample size. The incidence of oral cancer did not significantly differ between rural (52%) and urban (48%) populations. However, a preliminary observation suggested a higher prevalence in rural areas, possibly linked to increased tobacco consumption (76% chewing, 69% bidi smoking) in rural and low socio-economic groups. Buccal mucosa accounted for 55% of oral cancer cases, followed by carcinoma gingio-alveolus (25%), oral tongue (15%), and lower lip (05%).

Most patients tolerated radiation, experiencing grade-II mucositis in 45% and grade-III mucositis in 30%. Grade-IV mucositis occurred in 15% and peaked around the 10th day of the first phase, subsiding during the two-week interval before escalating again in the second phase. Severe pain was managed with morphine, topical gel, and intravenous fluids with multivitamins. Mucositis persisted for 4-5 weeks post-radiation.

The study findings on skin reactions revealed no severe early or late radiation skin reactions among the patients. The majority experienced early desquamation 49%, while 24% had dry desquamation, 11% observed ulceration/skin peel off, and 16% had grade-I skin reactions (erythema). Importantly, all patients tolerated the prescribed radiation schedules well, showing the predicted reactions both early and late, as anticipated before the

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trial commenced. The follow-up period extended up to about 8 months.[10]

The study demonstrated a complete local control rate of 59% and a complete nodal response rate of 47%, comparable to a similar study by C.C. Wang et al. Partial local control was observed in 36% of patients, with a corresponding 40% partial nodal response rate. Notably, better tumor control was achieved for buccal mucosa carcinoma (72.72%) and gingival alveolus carcinoma (57.14%), while tongue and lower lip carcinomas showed limited complete response rates, possibly due to advanced stages with poor risk factors.[11]

The discussed observations clearly indicate that the control rate is significantly higher in patients treated with SCAT compared to conventional therapy. Complete regression rates achieved with conventional therapy alone in stage III and IV cancers of the oral cavity and oropharynx ranged from 39% to 51%

CONCLUSION

In contrast to our experience with conventional radiotherapy, the outcomes with split course accelerated therapy in this study were notably promising. A complete response of the primary disease was achieved in 56% (14 of 25) of patients, and complete nodal regression was observed in 52% (13 of 25) of patients. While moderate to severe tissue reactions were noted, they proved manageable with I.V. Fluid + Vit. and local application of gel. Patients exhibited good compliance owing to a 1.2-week shorter radiation program compared to conventional treatment, which included a 2-week rest period. During this rest period, patients returned home, positively influencing their overall well-being.

REFERENCES

1. Chu F.C. H. & Arvin S. et al Biol. Phys. 1982, Late consequence of early skin reactions. Radiology : 94-669-672.
2. Cox J.D. : Large dose fractionation Cancer 55: 2105 2111.
3. Datta N., R. Choudhary, A.P.Gupta et al : Twice a day Vs Once a day radiation therapy in head & neck cancer. Int. J. Radiat Oncol. Biol. Phys. 17:132, 1989.
4. Ellis F. : Nominal standard dose and the rate. Brit. J. Radiol. 44:101-108.
5. Ellis : Dose, time and fractionation factors - A clinical hypothesis. Clin. Radiol. 20:1-7.
6. Geoffrey et al : Split course Int. J.Radiat. Oncol. Biol. Phys. acelerated therapy. Vol.32(3); 763-768,1995.
7. Gonzalez D.G. et al : Preliminary results in advanced head and neck cancer with radiotherapy by multiple fractions a day. Clin. Radiol. 1980; 31:417-421.
8. Holsti L.R. : Clinical experience with split course radiotherapy. Radiology 92:591-596.
9. Holsti L.R. et al : Split course radiotherapy of cancer. Acta. Radiol. Ther. 6:313-322.
10. Karen K. Fu et al Randomized phase I/II trial of two varients of accelerated fractionated radiotherapy regimens for advanced head and neck cancer - Results of RTOG. 88.09. Int. J.Radiat. Oncol Biol Phys. 22:3, 589-597.
11. Lamb s., Spry N.A. et al : Accelerated fractionation radiotherapy for advanced head and neck cancer. Radiother. Oncol. 18(2): 107-116.

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