

Telecobalt megavoltage radiotherapy in head and neck Cancers with Aluminum Tissue Compensation - A Pilot study to increase local control by reducing overall treatment time (OTT)

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Abstract

Introduction: In north eastern India, head and neck cancers form as high as 50%. Radiotherapy (RT) with tele-cobalt beam using Aluminum tissue compensators (ATC) has shown reduction in skin sequelae in head and neck treatments, as indicated by the pattern of care during last 5 years in our clinic. As the failure in local control of head and neck tumors is due to accelerated tumor growth beyond overall treatment time (OTT) >28 days, a study is undertaken to reduce cumulative inter-fraction interval (CIFI) to aim at better local control. **Methods:** A clinical trial in RT of high-grade head and neck malignancies by 6 fractions/wk and 7 fractions/wk, 2 Gy/fraction, in Theratron 780E telecobalt machine was undertaken. In 7f/wk protocol, 57(62%) completed without gap and 35(38%) with gaps. 7f/wk group completed total dose 70Gy in a mean period of 38 days and median period 36 days. In 6f/wk regimen 14(58%) completed total dose in OTT 40-41 days; 9(38%) in >41 days; and 1(4%) patient completed in 56 days. 17/24 completed 35 fractions, 3/24 completed 30-34 fractions, 4/24 completed 36-40 fractions including gap corrections. **Results:** The morbidities observed in 7f/wk group were, 0/92(Gr IV), 15/92(16%) (Gr III), 23/92(25%) (Gr II), 43/92(47%) (Gr I) skin reactions; and 0/92(Gr IV), 24/92(26%) (Gr III) 35/92(38%) (Gr II) and 29/92(32%) (Gr I) Mucositis. For 6f/wk group, skin reactions were 0/24(Gr IV), 4/24(17%) (Gr III), 6/24(25%) (Gr II) 14/24(58%) (Gr I); and mucositis 1/24(4%) (Gr IV) 10/24(42%) (Gr III) 11/24(46%) (Gr II) and 2/24(8%) (Gr I). A comparison of 5f/wk (n=178) and 7f/wk (n=92) showed Skin reactions were 2/178 (1.1%) Gr IV in 5f/wk against Nil/92 in 7f/wk arm. Gr III skin reactions were 15/92 (16%) in 7f/wk arm against 19/178(11%) in 5f/wk group. Gr IV mucositis was 0/92 in 7f/wk against 5/178 in 5f/wk; Gr III mucositis 24/92(26%) in 7f/wk arm against 47/178(26.4%) in 5f/wk arm. **Conclusion:** Our results show that, skin and buccal mucosa sequelae have less incidence by using ATC. Experience with 7Fr/wk showed feasibility to achieve 70Gy in 5weeks OTT. Cobalt 60 treatments give an edge to linac beam, because of increased tolerance with simple beam directed cobalt treatment and ATC; less dose build up against 6 MV linac beam; advantageous situation in head and neck treatments. Objective follow up on treatment outcome in these cohort is necessary in terms of dose adjustments and resultant local control.

Key words: head and neck, reduction in OTT, changed fractionation, biologically effective dose, telecobalt

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Introduction

In the north eastern parts of the Indian sub-continent, there is high incidence of head and neck cancers, and form as high as 50% of the total number of patients receiving radiotherapy. Tele-cobalt megavoltage machines continued to be in clinical radiotherapy infrastructure almost more than six decades. Radiation skin reactions are more common in head and neck patients, preventing completion of treatment in planned total time. There is an urgent need to overcome the problem of skin reactions as well as completing treatments in planned overall treatment time. (OTT).

In head and neck radiotherapy, we introduced custom built aluminum tissue compensation (ATC) technique during 2016 [1]. An objective evaluation of skin morbidity highlighted reduction in skin sequelae with Tissue compensated (TC) RT [2], in two groups of total 178 patients (89 in each) treated with and without TC [2]. It was also highlighted that in conventional fractionation of 5Fr/wk, a total dose up to 70 Gy could be delivered without any increase in OTT.

Many studies have found that, in radiotherapy of squamous cell head and neck cancers, a reduction in local control by 1-2% can result per day extension in overall treatment time (OTT) beyond

42 days [3,4]; due to reduced Equivalent Tumor Dose (ETD) for total regimen. The linear quadratic (LQ) model on fractionated radiotherapy indicates estimates of biological effective dose (BED) using Equation (1), by using total no. of fractions (N), dose per fraction d (Gy/fr), for tumors, early and late reacting tissues (to represent dose related cell killing, tissue damage, repair and the survival fractions after dose delivery).

$$BED_{\text{tumor}} = Nd[1 + d/(\alpha/\beta)] - k_t (T - T_k) \quad \text{---(1)}$$

The OTT is represented by T (days). A correction on kicks off time (T_k) represents the tumor repopulation during T, which is negligible till 4 weeks (viz. $T_k = 28$ days). The commonly used values of multiplication factors are $k_t = 0.9$; $\alpha/\beta = 10$ for tumor. For acute effects of normal tissues, the BED_{acute} is evaluated by equation (2) where $\alpha/\beta = 10$ for early reacting tissues like skin and $k_{\text{acute}} = 0.25$ with $T_k = 0$.

$$BED_{\text{acute}} = Nd[1 + d/(\alpha/\beta)] - k_{\text{acute}} (T) \quad \text{---(2)}$$

For late reacting tissues $k=0$ and $\alpha/\beta = 3$ (for normal tissues no kick of time like tumors, and radiation effects accumulate, without inter-fraction repair probability). Calculations using Eq. (1) show that a reduction in local control as high as 75% is envisaged, when the OTT get increased from 6 to 10 weeks. As the failure in local control in these tumors are mainly due to accelerated tumor growth > 28 days, local control could be further improved by reducing OTT. A recent report from us [5] brought out that physical dose of 80-84 Gy could be administered in head and neck RT, when we compensated for missed treatment days (due machine failure).

It is observed in general, the head and neck treated patients complete treatments with increased OTT than planned. Bahl et al [6] reported an OTT 52.9 ± 22.8 days for conventional RT, and 48.2 ± 5 days for Simultaneous Integrated Boost-Volume modulated Arc Therapy (SIB-VMAT). These authors highlighted that treatment breaks 4.7 ± 8.2 days was observed invariably in conventional RT. At our institute, the tissue compensated head and neck RT patients definitely have OTT less than what was reported by the above report [6].

Some reports are available showing inclusion of sunday treatments as 7 Fr/wk [7,8]. Between 2001-2004, 279 patients of oral cavity, oropharynx high risk squamous cancers [7], received 63 Gy in 1.80 Gy fractions in 5f/wk and 7f/wk in randomized allotment. They reported acceptability of late and acute toxicity in continuous 7f/wk arm. Confluent mucositis was higher (60%) compared to conventional 5f/wk arm, in this series. Their 3 years local control rate was statistically significant in 74% for 7f/wk arm against 53% for 5f/wk group. Another report [8] summarized their 5 year results of randomized study, in 100 patients treated by 7f/wk against 5f/wk (to achieve 2 weeks shorter OTT). An increase of local control 75% in 7f/wk group against 33% in conventional 5f/wk is reported. These researchers also brought out that confluent mucositis was significantly higher (94%) against 53% of 5f/wk control arm. Another study [9] in a cohort 70 patients with T_3N_0 glottic cancers, reported 60 Gy dose delivered in 5 weeks at 2.4Gy/Fr achieving

65% recurrence free 5-year survival. A study is undertaken to reduce OTT (as 6Fr/wk and 7Fr/wk regimens), with an objective to reduce CIFI.

Materials and Methods

Clinical Trials at CCHRC was carried out in 2019-2021. We initiated



Fig. 1: Head & Neck status (RT with Tissue Compensation) at 70Gy, 35fr, @ 5fr/wk completed (no interruption)



Fig. 2: Head & Neck status (RT without Tissue Compensation) at 50Gy, 25fr, @ 5fr/wk (interrupted mid-way)

clinical trials of 6f/wk and 7f/wk RT with ATC in Head and Neck malignancies (except Nasopharynx). Clearance from Institute Research Board (IRB) was obtained vide approval No. CCHRC/IRB/008/2020 dated 6th October, 2020. This was based on our earlier results [1] (Figs.1 and 2) showing efficacy of cobalt radiotherapy with ATC. Theratron 780E (MDS Nordion, Canada) cobalt machine and custom-built ATC were used for RT. Our center did not have linac and cobalt-60 machine is the only modality. Totally 92 patients completed 7 f/wk schedules to a total dose of 70 Gy; and 24 patients in 6f/wk schedules to a total tumor dose 70 Gy.

Comparison of Biologically Effective Doses (BEDs)

From Eqn.1, the calculated BED values for tumor and for early reacting tissues(acute) are shown in Table-1. For 70 Gy total dose, BED_{tumor} values for tumor are 65.1Gy₁₀, 71.4Gy₁₀, 77.7Gy₁₀ for 5fr/wk, 6fr/wk and 7fr/wk respectively. From Eq.2 BED_{acute} values are 71.8 Gy₁₀, 73.5 Gy₁₀ and 75.3 Gy₁₀ for 5fr/wk, 6fr/wk and 7fr/wk respectively. BED_{late} for late reacting tissue is 116.7Gy for all these fractionations, as fractions size is kept same as 2 Gy/fr. From Table-1 it is seen that when the late effect of tissues remaining same (116.7 Gy), tumor and normal tissue acute effects tissue show increased biological damage for 6f/wk and 7f/wk; 9.7% and 19.4% (for tumor) and by 2.4% and 4.9% (for acute tissue effects) respectively, against 5f/wk. In Table-2 BED values and equivalent physical dose estimates for 5fr/wk, for 6 fr/wk and @7 fr/wk treatments. Equivalent doses 7.5% and 12.5% for 60 Gy; and 6.6% and 12.6% for 70 Gy are realised. Normal tissue acute effect doses increased only 2% to 3.5%.

Table-1: BED for different fractionations with 70 Gy physical dose

No.	Regimen	N _{total} / OTT Days	BED_{tumor} $\alpha/\beta = 10$ K=0.9	BED_{acute} $\alpha/\beta = 10$ K=0.25	BED_{late} $\alpha/\beta = 3$ K=0
1	5fr/week	35/49 days	65.1 Gy (0%)	71.8 Gy (0%)	116.7 Gy
2	6fr/week	35/42 days	71.4 Gy (>9.7%)	73.5 Gy(>2.4%)	116.7 Gy
3	7fr/week	35/35 days	77.7 Gy(>19.4%)	75.3 Gy(>4.9%)	116.7 Gy

High grade head and neck tumors were included for 6fr/wk or 7fr/wk tissue compensated parallel opposed radiotherapy. Bigger field size included spinal cord upto a dose of 45 Gy; and later re-planned to include only primary infiltrating tumor volume. Computerized tomography (x-ray CT) localization is used for RT planning. 24h inter-fraction interval is maintained for allowing repair in normal tissues and including Saturday and Sunday fractions. Adjuvant chemotherapy is maintained in most of the cases without dose adjustments. In Table-3 the change of dose/fraction for same number of total fractions and change of number of fractions for 2 Gy fractions are brought out. It could be observed that when 6f/wk regimen is considered ($BED_{6f/wk}$), the physical dose of 70 Gy in 5 fr/wk is only 63.7 Gy (-9.0%). When 7f/wk regimen is considered ($BED_{7f/wk}$) the physical dose of 70 Gy in 5 fr/wk is equivalent of 67.6 Gy (-3.5%).

Results

Patients and Treatments

92 patients were in 7Fr/wk group. They completed 70Gy in a mean period of 38 days and median 36 days. Out of 92, 57 patients took full course of RT without gaps. 35 received with gaps. 26 patients had >35 fractions; 2 of them <35fractions. 24 completed 35 fractions in >35days OTT. 18 of total 92 had 5 cycles chemotherapy (CT) in 35 fractions; 6 of them <5 CT in 35 fractions; Without CT only radiotherapy were 20 number. 5 patients expired due to reasons not attributed to radiation treatments.

29 patients in 6f/wk group. Out of them 6 defaulted, 1 died. 24 completed treatments. 17 received 35 fractions; 3 completed 30-34 fractions; 4 completed 36-40 fractions accounting for gap corrections. 14 of them completed in OTT 40-41 days; 9 completed in >41 days OTT; 1 patient completed in 56 days. In 6f/wk group 12 patients received 6 cycles CT; 7 patients 5 cycles CT; 2 patients only 4 and 2 cycles CT.

Tolerance to RT

In Table-4 a summary of observed morbidities in 6f/wk group and 7f/wk group are presented. The morbidities in 7f/wk group were; skin reactions 0/92(Gr IV), 15/92(Gr III), 23/92(Gr II), 43/92(Gr I); Mucositis 0/92(Gr IV), 24/92 (Gr III) 35/92(Gr II) and 29/

92(Gr I) were recorded. In the other 6f/wk group; skin reactions were 0/24(Gr IV), 4/24(Gr III), 6/24(Gr II) 14/24 (Gr I) and mucosal reactions 1/24 (Gr IV) 10/24(Gr III) 11/24(Gr II) and 2/24(Gr I). A comparison of 5f/wk (178 patients) and 7f/wk (92 patients) arms recorded, Gr IV mucositis 5/178 in 5f/wk against 'Nil' in 7f/wk; 47/178(26.4%) Gr III mucositis in 5f/wk arm compared to 24/92(26.1%) Gr III mucositis in 7f/wk arm. Skin reactions were 2/178 (1.1%) Gr IV in 5f/wk arm compared to Nil/92 Gr IV in 7f/wk arm. Gr III skin reactions were 19/178(10.7%) in 5f/wk group and 15/92(16.3%) in 7f/wk group. From the percentage occurrence of mucositis and skin reactions it was observed that both 6f/wk and 7f/wk treatments the morbidities were not much different from 5f/wk conventional arm treatments.

Discussion

Continuation of telecobalt beam quality for radiotherapy was recommended in literature with particular reference to highly populated low-socioeconomic countries [10,11]. In the north eastern parts of India, head and neck cancers forms as high as 50% of radiation therapy treatments [1]. Entrance dose pattern of cobalt beam and 6MV linear accelerator beams are different. Most of the reports on head and neck treatments from western countries are based on linear accelerators and multi-leaf treatment plans. To achieve correct dose in the shallow depths, presence of thermo-plastic material have to be retained with linac in the path of the beam. A previous work [6] has highlighted that invariably breaks are encountered in head and neck RT because of tolerance issues. Preservation of skin sparing in cobalt beam in tangential incidence with neck and chin entrance radiation field by cut open thermo-plastic material and aluminum tissue deficit compensation for absence of tissues, are unique modifications built in our cobalt treatment plans [1]. In the above circumstances, we could achieve planned dose delivery in high-risk head and neck malignancies.

In altering fractionations, usually the caution is to have 'Normal Tissue Effects' as well as 'Late Effects' within tolerance. Radiobiological recommendations indicate, normal cell recovery takes place within 6 - 24h, so that inter-fraction interval may be retained as 1 day. However, in conventional fractionation (5Fr/wk), week-end 2 days non-treatment adds to about 10 days in 6 weeks period, being included in calculating BED equivalence, by

Table-2: Comparison of all 3 treatment regimens 5fr/wk, 6fr/wk,7fr/wk and equivalent doses

No.	Biological Effect End Point	5 Fr/Wk, 2Gy/ Fraction	6 Fr/Wk, 2Gy/ Fraction	7Fr/Wk 2Gy/ Fraction	%Excess BED in 6Fr/wk over 5Fr/wk	%Excess BED in 7Fr/wk over 5Fr/wk	Equivalent Dose for BED 6Fr/wk in 5Fr/wk regimen	Equivalent Dose for BED 7Fr/wk in 5Fr/wk regimen
1	BED (tumor)	60Gy BED= 59.4Gy	60Gy BED= 65.7Gy	60Gy BED= 70.2Gy	10.6%	18.2%	2.15Gy x30=64.5 Gy (+7.5%)	2.25Gy x30=67.5 Gy (+12.5%)
2		70Gy BED= 65.1Gy	70Gy BED= 71.4Gy	70Gy BED= 77.7Gy	9.7%	19.4%	2.13Gy x35=74.6 Gy (+6.6%)	2.25Gy x35=78.8 Gy (+12.6%)
3	BED (acute)	60Gy BED= 61.5 Gy	60Gy BED= 63.3Gy	60Gy BED= 64.5Gy	2.8%	4.9%	2.04Gy x30=61.2Gy (+2.0%)	2.07Gy x30=62.1Gy (+3.5%)
4		70Gy BED= 71.8 Gy	70Gy BED= 73.5Gy	70Gy BED= 75.3Gy	2.4%	4.9%	2.036Gy x35=71.3 Gy (+1.9%)	2.07Gy x35=72.5 Gy (+3.6%)

Table-3: Total Doses and dose/fr in 5fr/wk,6fr/wk,7fr/wk Plans

Treatment Plan In Head & Neck RT-Parallel opposed Tissue Compensated Fields	BED _{tumor} ($\alpha/\beta = 10$)	For 6 Fr/Wk Total Dose @ 2Gy/Fr	6Fr/Wk Dose for Same total No.of Fractions	For 7 Fr/Wk Total Dose @ 2Gy/Fr	7Fr/Wk Dose for same total No.of Fractions
60Gy@ 2Gy/Fr 5 Fr/Week 30 Fractions 42 Days (6 Wks)	59.4	27.4Fr x 2 Gy/Fr = 54.8Gy	30Fr x 1.84Gy/Fr =55.2Gy (-8.0%)	25.5Fr x 2 Gy/Fr =51.0Gy	30Fr x 1.93Gy/Fr =57.9Gy (-2.5%)
70Gy @ 2Gy/Fr 5 Fr/Week 35 Fractions 49Days (7 Wks)	65.1	32.4Fr x 2 Gy /Fr = 64.8Gy	35Fr x 1.82Gy/Fr =63.7Gy (-9.0%)	29.75Fr x 2Gy/Fr =59.5Gy	35 Fr x 1.93 Gy/Fr =67.6Gy (-3.5%)

Table-4: Morbidity recorded in treated groups

No.	Treated Groups	No. of patients	Confluent Mucositis - Grades				Skin Reactions - Grades			
			I	II	III	IV	I	II	III	IV
1	5f/wk	178	Nil	Nil	47/178 (26.4%)	5/178 (2.8%)	Nil	Nil	19/178 (10.7%)	2/178 (1.1%)
2	6f/wk	24	2/24 (8.3%)	11/24 (45.8%)	10/24 (41.7%)	1/24 (4.1%)	14/24 (58.3%)	6/24 (25%)	4/24 (16.7%)	Nil
3	7f/wk	92	29/92 (31.5%)	35/92 (38.0%)	24/92 (26.1%)	Nil	43/92 (46.7%)	23/92 (25%)	15/92 (16.3%)	Nil

Eqn.1. The BED values in Table-2 has brought out that reduction in OTT by increasing fractionations by adding Saturdays and Sundays, will have advantageous situation increasing equivalent physical dose at the same time smaller change in normal tissues acute effect doses. Table 3 compares the 60Gy physical dose equivalence in 6f/wk and 7f/wk scales. It could be understood indirectly that higher effective dose is administered in a curative intent. In Table-4 our results showed that mucositis and skin reactions are comparable in 7f/wk regimen and 5f/wk regimens. This tries to highlight confirming that 24 hours inter-fraction interval itself is sufficient to give repair in acute reacting tissues. From Table-1 the calculated BED_{acute} (5th column) is increased in 7f/wk regimen; but as per Table-4 the actually encountered confluent mucositis and skin morbidity are comparable to 5f/wk, which corroborates with least effect on equivalent physical dose with reference to normal tissue acute effects. Two earlier large series [7,8] have recommended a reduction of 10% in daily planned dose @ 1.80 Gy/fraction, delivering 63 Gy in 35 fractions 5 weeks continuous irradiation schedule. Our calculated values of 1.82 Gy/fraction, total dose 63.7 Gy (Table-3) is in agreement their reduction in dose due to change of fractionation to 7f/wk.

It is also brought out that due to Covid 19 pandemic situation, there was interruptions became inevitable in some of our patients. We found that the aggressive treatments (with less OTT) could be feasible with cobalt beam quality; cobalt-60 gives an edge to linac beam, because it is felt 15mm build up of linac is disadvantageous in head and neck treatments. Also tolerance is much better with cobalt beam after tissue compensation and simple beam directions. We have to follow up these cohort of patients objectively and make dose adjustments in future trials.

As the TC plates are mounted away from patients' skin at least beyond 35 cm, the skin sparing effect of mega-voltage beam is preserved. These cohort of patients have given both feasibility of the 6 and 7 Fr/wk treatment delivery, as well as tolerance related information; and our results from the clinical trials have given much less morbidity compared to earlier series on 7 Fr/wk in head and neck radiation treatments [7,8]. Encouraged by this clinical data, we started following 7Fr/wk in many patients for RT in head and neck malignancies. From these results, the authors strongly recommend use of tele-cobalt beam in head and neck radical radiotherapy with custom-built tissue compensators. When the OTT gets reduced by 2 weeks, the possibility to increase total number of annual patients in the cobalt machine is envisaged.

Conclusion

Our results show that, skin and buccal mucosa sequelae have less incidence by using ATC. Experience with 7Fr/wk showed feasibility to achieve 70Gy in 5weeks OTT. Cobalt 60 treatments give an edge to linac beam, because of increased tolerance with simple beam directed cobalt treatment and ATC; less dose build up against 6 MV linac beam; advantageous situation in head and neck treatments. Objective follow up on treatment outcome in these cohort is necessary in terms of dose adjustments and resultant local control.

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