External Beam Radiotherapy in High-risk Head-and-neck Cancers with Reduced Overall Treatment Time in Telecobalt Beam Quality

A recent study[1] highlighted the feasibility of completing 70 Gy tumoricidal dose in an overall treatment time (OTT) of 35 days, retaining 2 Gy fraction size at 7 fractions/week, without weekend gaps. The external beam radiotherapy was delivered in conventional treatments with parallel opposed fields in an old-generation model telecobalt treatment machine (Theratron 780E), without multi-leaf collimator and no automated beam modulation methods. The salient radiotherapy features were, (a) skin and mucosal sequelae were comparable for the same total physical dose 70 Gy by 6 fractions/week, 7 fractions/week repetition rate (with OTT 42 days, 6 weeks; 35 days, 5 weeks, respectively) *vis-à-vis* 5 fractions/week regimen, requiring 70 Gy in 7 weeks. Adjuvant chemotherapy remained the same in all fractionation schemes. These results were from 24 patients (6 fractions/week) and 92 patients (7 fractions/week) cohorts, compared with an earlier study[2] of 172 patients, in 5 fractions/week treatment group. All the patients had immobilization by thermoplastic molds and tissue deficiency compensation by manual custom-built individualized beam modulation filters. Treatment portals had an open window to retain dose buildup preservation of megavoltage Co-60 beam quality. A phase III two-arm clinical trial is already in progress at our center, based on the results of this pilot study, reported recently,[1] and already more than 200 patients have completed 7 fractions/week treatment protocol in a test arm, showing a lot of promise.

At the outset, these results were compared against three large series[3-5] from different investigators. These reports were from radiation therapy (RT) with 6 MV linear accelerator photon beams, 10 years earlier. Two hundred and seventy-nine high-risk oral cavity, oropharynx cancers[3] received 63 Gy total dose in 1.80 Gy fraction sizes at 7 fractions/week in 5 weeks. In randomized comparison with 5 fractions/week conventional regimen, they highlighted 60% increased confluent mucositis against 5 fractions/week treatments. This report highlighted statistically significant increased 5 years local control (74%) in 7 fractions/week against 53% in 5 fractions/week group. Another randomized study in 100 patients[4] highlighted

Table 1: Comparison of all three treatment regimens 5 fractions/week, 6 fractions/week, and 7 fractions/week and equivalent doses

Number	Biological effect end point	5 fraction/week 2 Gy/fraction	6 fraction/week 2 Gy/fraction	7 fraction/week 2 Gy/fraction	Percentage excess BED in 6 fraction/week over 5 fraction/week	Percentage excess BED in 7 fraction/week over 5 fraction/week	Equivalent dose for BED 6 fraction/week in 5 fraction/week regimen (%)	Equivalent dose for BED 7 fraction/week in 5 fraction/week regimen (%)
1	$BED_{(tumor)}$	60 Gy BED=59.4 Gy	60 Gy BED=65.7 Gy	60 Gy BED=70.2 Gy	10.6	18.2	2.15 Gy × 30=64.5 Gy(+7.5)	2.25 Gy × 30=67.5 Gy (+12.5)
2		70 Gy BED=65.1 Gy	70 Gy BED=71.4 Gy	70 Gy BED=77.7 Gy	9.7	19.4	2.13 Gy × 35=74.6 Gy (+6.6)	2.25 Gy × 35=78.8 Gy (+12.6)
3	$BED_{(acute)}$	60 Gy BED=61.5 Gy	60 Gy BED=63.3 Gy	60 Gy BED=64.5 Gy	2.8	4.9	2.04 Gy × 30=61.2 Gy (+2.0)	2.07 Gy × 30=62.1 Gy (+3.5)
4		70 Gy BED=71.8 Gy	70 Gy BED=73.5 Gy	70 Gy BED=75.3 Gy	2.4	4.9	2.036 Gy × 35=71.3 Gy (+1.9)	2.07 Gy × 35=72.5 Gy (+3.6)

BED: Biological effective dose

Table 2: Biological effective dose for different fractionations with 70 Gy physical dose

Number	Regimen (fraction/week)	N_{Total} /OTT (T days)	BED_{tumor} (α/β=10, K=0.9)	BED_{acute} (α/β=10, K=0.25)	BED_{late} (α/β=3, K=0)
1	5	35/49	65.1 Gy (0%)	71.8 Gy (0%)	116.7 Gy
2	6	35/42	71.4 Gy (>9.7%)	73.5 Gy (>2.4%)	116.7 Gy
3	7	35/35	77.7 Gy (>19.4%)	75.3 Gy (>4.9%)	116.7 Gy

BED: Biological effective dose, OTT: Overall treatment time

Table 3: Total doses and dose/fraction in 5 fraction/week, 6 fraction/week, 7 fraction/week plans

Treatment plan In head and neck RT-parallel opposed tissue Compensated fields	BED_{tumor} ($\alpha/\beta=10$)	For 6 fraction/ week total dose at 2 Gy/fraction	6 fraction/week dose for the same total number of fractions (%)	For 7 fraction/ week total dose at 2 Gy/fraction	7 fraction/week dose for the same total number of fractions (%)
60 Gy at 2 Gy/fraction 5 fraction/week 30 fractions 42 days (6 weeks)	59.4	27.4 fraction × 2 Gy/ fraction=54.8 Gy	30 fraction × 1.84 Gy/fraction=55.2 Gy (−8.0)	25.5 fraction × 2 Gy/ fraction=51.0 Gy	30 fraction × 1.93 Gy/fraction=57.9 Gy (−2.5)
70 Gy at 2 Gy/fraction 5 fraction/week 35 fractions 49 days (7 weeks)	65.1	32.4 fraction × 2 Gy/ fraction=64.8 Gy	35 fraction × 1.82 Gy/fraction=63.7 Gy (−9.0)	29.75 fraction × 2 Gy/fraction=59.5 Gy	35 fraction × 1.93 Gy/fraction=67.6 Gy (−3.5)

BED: Biological effective dose, RT: Radiation therapy

Table 4: Morbidity recorded in treated groups

Number	Treated groups (fraction/week)	Number of patients	Confluent mucositis – grades (%)				Skin reactions – grades (%)			
			I	II	III	IV	I	II	III	IV
1	5	178	Nil	Nil	47/178 (26.4)	5/178 (2.8)	Nil	Nil	19/178 (10.7)	2/178 (1.1)
2	6	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	7	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

increased incidence of (94%) confluent mucositis against 54% in 5 fractions/week cohorts. In this study, the local control was 75% in 7 fractions/week treatments against 33% in 5 fractions/week. In these two reports, the dose/fraction was kept 10% less, to account for reduction in OTT, based on linear–quadratic (LQ) model biological effective dose (BED), with α/β =10 for local tissue acute damage, and repair. Higher fraction size 2.4 Gy/fractions to achieve 60 Gy in 5 weeks, in another study,[5] showed 65% recurrence free 5-year survival in T3 N0 glottic cancers(BEDtumor=70.2 same as BEDtumor 60Gy/35days [Table 1].

In this present work, as we have maintained the same 2 Gy/fraction size, the BED_{late} (for α/β =3) is expected to remain unaltered. Unlike other reported studies[3-5] with linear accelerators with reduction to 1.8 Gy fraction size, retention of the same 2 Gy fraction size was feasible (in present work) because of good tolerance in these treatments without encountering breaks due to morbidity as reported in our own earlier study.[6] The acute-short term sequelae with α/β =10 increase 2.4% and 4.9% with 6 fractions/ week and 7 fractions/week schedule (BED10 73.5 Gy and 75.3 Gy, respectively) [Refer Table 2] against 71.8 Gy for 5 fractions/ week regimen (for k_{acute} = 0.25, which is a correction term in BED calculations in LQ biological model, for repair). A therapeutic gain in biological end point BED_{tumor} enhances by 9.7% and 19.4% (BED_{tumor} 71.4 Gy and 77.7 Gy, respectively) against 65.1 Gy for 5 fractions/week. If we express this as a ratio of BEDacute/BEDtumor relating to 5 fractions/week, 6 fractions/week, and 7 fractions/week, it could be seen that the ratio becomes 71.8/65.1 = 1.103, 73.5/71.4 = 1.029, and 75.3/77.7 = 0.969, a reversal trend is apparent at 7 fractions/ week, with about 14% effective gain factor on tumor kill against increase in acute normal tissue effect (1.103/0.969 = 1.1380). The scientific rationale for this pilot work could be appreciated from Tables 1,3 and the comparable morbidities with 5 fr/wk treatments can be seen in Table 4.

In the above context, the previous recommendations[6,7] highlighting the need for continuous use of telecobalt in radical treatments have all advantages of megavoltage photons, very much recommended for smaller interfield separation as encountered in head-and-neck RT, with simple treatment techniques, cost-effective treatment methods. The labor-intensive customized preparations of tissue compensation individualized templates are justified when we look at the clinical advantages achieved in resource-constraint situations. Automated milling methods again require, a need for making X-ray computed tomography image acquisitions, special software/hardware, and more quality assurance requirements.

It is reviewed from earlier clinical studies comparing telecobalt and linear accelerators[8,9] that cobalt photon quality has special advantages in head-and-neck cancers. In the study of 472 patients,[8] it was highlighted that neck control rates had improved for high-risk patients (extracapsular extension, more than 2 nodes positive, and/or T4 primary). Another study of 392 patients[9] analyzing the effect of beam qualities Co-60, 4 MV, 6 MV indicated that there is no significant impact on acute or late toxicity and also no significant difference in locoregional control. These data support the clinical application of cobalt machines for head-and-neck treatments. It is brought out that Linacs have definite advantages with intensity modulation and

sophistication, but with dose buildup 15 mm, more penetrations, more exit doses, make lower preference in head-and-neck RT, because the disease is not localized and aggressive. From our present results, with tissue deficit compensated treatments, buildup of dose maximum preserved, cobalt radical treatments by 7 fractions/week with less OTT may be considered by clinics where these machines are still in use. Patient hospital stay also get reduced, by adding treatments on week-ends, with better acceptability. Therefore, the recent study[1] appears an added solution in head-and-neck high-risk cancers, which is highly prevalent in low socioeconomic countries such as India. An objective analysis is separately planned, to obtain data on local control, and late effects in these cohorts of patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Received on: 15-10-2023 Review completed on: 30-10-2023
Accepted on: 31-10-2023 Published on: 05-12-2023

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Quick Response Code:

Website: www.jmp.org.in

DOI: 10.4103/jmp.jmp_142_23

How to cite this article: Ravichandran R, Kannan RR. External beam radiotherapy in high-risk head-and-neck cancers with reduced overall treatment time in telecobalt beam quality. J Med Phys 2023;48:409-11.