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Perspectives

Resource-sparing curative-intent hypofractionated-accelerated radiotherapy in head and neck cancer: More relevant than ever before in the COVID era

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ABSTRACT

The incidence of head and neck squamous cell carcinoma (HNSCC) is increasing worldwide, with over three quarters of cases now diagnosed in low and middle-income countries (LMICs) with resource-constraints. Loco-regional recurrence remains the predominant pattern of failure mandating adequate local therapy for acceptable loco-regional control and survival. There is high-quality evidence that intensification of treatment by either by adding concurrent chemotherapy or by altering radiotherapy (RT) fractionation improves outcomes in the curative-intent management of loco-regionally advanced HNSCC. Even conservative estimates indicate that > 50% of patients in LMIC are unlikely to get access to timely RT, which will only get compounded with the coronavirus disease (COVID)-19 pandemic. The radiation oncology community has been systematically testing altered fractionation schedules in several solid cancers (breast, lung, and head-neck), given the cost-effectiveness, convenience, and compliance to short-course RT regimens. Radiobiological modelling suggests that standard fractionation of 6–7 weeks in HNSCC can be compressed safely into a 4-week schedule to counter accelerated repopulation by increasing the dose per fraction and delivering 5 fractions per week which is currently being tested in the ongoing multicentric trial of hypo- vs normo-fractionated accelerated RT (HYPNO study). Herein, we discuss the radiobiological basis of curative-intent hypofractionated-accelerated RT schedule delivering 55 Gy in 20 fractions over 4 weeks in HNSCC followed by critical appraisal of the published literature on such regimens with concurrent systemic therapy and its inherent resource-sparing potential applicable across large parts of the world particularly in the context of the ongoing COVID-19 pandemic.

Introduction

Head and neck squamous cell carcinoma (HNSCC) constitutes nearly 7% of the global cancer burden with an estimated worldwide incidence of over 600,000 new cases annually [1,2]. Over three quarters of such cases are now seen in low and middle-income countries (LMICs), where they commonly present with loco-regionally advanced stage disease [2]. The rising incidence of HNSCC is largely driven by lifestyle related factors such as tobacco and alcohol consumption [2,3], although human papilloma virus (HPV)-associated oropharyngeal cancer has emerged as a distinct entity and is being increasingly reported from high-income countries [2,4]. Loco-regional recurrence remains the predominant pattern of failure mandating adequate local therapy in the form of surgery and/or radiotherapy (RT) for acceptable loco-regional control and survival. Recent emphasis on organ-preservation has spurred more widespread the use of definitive non-surgical approaches [5,6], particularly for cancers of the larynx and pharynx. Traditionally, this was accomplished by radical RT using conventional fractionation typically defined as delivery of 1.8–2 Gy per fraction, one fraction per day, 5 fractions per week to a total dose of 66–70 Gy in 33–35 fractions over 6–7 weeks [7,8].

Treatment intensification in HNSCC

There is now consistent and robust high-quality evidence that intensification of treatment either by combining with chemotherapy [9,10] or altering the fractionation schedule [11,12] improves outcomes in the curative-intent radiotherapeutic management of loco-regionally advanced HNSCC. Schedules of altered fractionation were generally designed to increase dose-intensity by delivering a higher total dose in the same overall treatment time (hyperfractionated RT), the same total dose in lesser (5–6 weeks) time (accelerated RT without total dose reduction), or a lesser total dose in even shorter (3–4 weeks) time (accelerated RT with total dose reduction). Accelerated RT where typically doses above the conventional 10 Gy per week are delivered has been shown to be associated with an improved benefit-risk ratio

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relative to standard normofractionated RT (2 Gy/fraction) in HNSCC, provided a careful balance between total dose, dose per fraction and overall treatment time is chosen [7,13]. The Danish Head and Neck Cancer Group (DAHANCA) and the International Atomic Energy Agency (IAEA) reported significant improvements in loco-regional control using normofractionated-accelerated RT delivering 2 Gy/fraction, 6 fractions per week for total dose of 66–70 Gy in 33–35 fractions over 5.5 weeks compared to conventionally fractionated RT, delivering similar total dose (66–70 Gy) in 5 fractions per week over 6.5–7 weeks in large pivotal phase III randomized controlled trials [14,15]. Radiobiological modelling suggests that this can be further compressed in 4-week schedule to counter accelerated repopulation by increasing the dose per fraction and delivering 5 fractions per week. Such a hypofractionated accelerated RT schedule delivering 55 Gy in 20 fractions over 4 weeks is currently being tested in the ongoing IAEA multicentric trial of hypo- vs normo-fractionated accelerated RT in non-nasopharyngeal HNSCC (HYPNO study), registered at clinical trials.gov (NCT0765503). Herein, we discuss the radiobiological basis of curative-intent hypofractionated-accelerated RT schedules in HNSCC followed by critical appraisal of the published literature on such regimens combined with systemic therapy and its inherent resource-sparing potential applicable across large parts of the world, particularly in the context of the ongoing coronavirus disease 19 (COVID-19) pandemic.

Radiobiological modelling

A systematic overview analysing 14 paired comparisons of altered fractionation RT (test arm) versus conventionally fractionated RT (control arm) from several phase III trials with a combined sample size of 6229 patients was conducted (unpublished data). Within each trial, a linear-quadratic (LQ) model with correction for overall treatment time was fitted to the observed tumor control data and the parameters were synthesized across trials using standard meta-analysis methodology. The best-fit estimates of the model parameters with 95% confidence interval (CI) provided an α/β ratio of 6.4 Gy (95%CI: 2.7–10.2 Gy) and Dproliferation = 0.65 Gy/day (95%CI: 0.55–0.76) to counter accelerated repopulation after 4-weeks. These estimates are roughly in agreement with previously data, but have narrower CI, particularly for the time factor, with added theoretical advantage of being derived only from randomized trials. Fractionation sensitivity of HNSCC is quantified by the parameter α/β (in Gy) and the estimate derived from this systematic overview is somewhat lesser than the often quoted 'textbook' value of α/β = 10 Gy [16]. This suggests that hypofractionated schedules could be associated with a slightly higher efficacy than estimated using conventional values. Radiobiological modelling and exploratory calculations suggest that a hypofractionated-accelerated schedule delivering 55 Gy in 20 fractions over 4 weeks (2.75 Gy per fraction, 5 fractions per week) could radiobiologically represent an attractive alternative to other altered fractionation regimens in HNSCC.

Comparison of fractionation schedules

The current standard fractionation schedule in HNSCC comprising 70 Gy in 35 fractions over 7 weeks (2 Gy/fraction, 5 fractions per week) is compared for tumor control (α/β = 10 Gy) and late effects (α/β = 3 Gy) in terms of equivalent doses in 2 Gy-fractions (EQD2) with three altered fractionation RT schedules used for treating HNSCC (Figure 1). The DAHANCA schedule of 66 Gy in 33 fractions over 5.5 weeks (2 Gy per fractions, 6 fractions per week); the Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) [17] schedule of 54 Gy in 36 fractions over 12 days (1.5 Gy per fraction, 3 fractions per day 4–6 h apart, 7 fractions per week); and the hypofractionated-accelerated schedule of 55 Gy in 20 fractions over 4 weeks (2.75 Gy per fraction, 5 fractions per week) are included for comparison. Both CHART and DAHANCA are corrected for incomplete recovery between fractions delivered in the same day, assuming 6-hour inter-fraction interval and half-life for repair ($T_{1/2}$) of 4.4 h. Acceleration is assumed to kick in before 26 days after the first fraction of RT. As shown in the bar-chart (Fig. 1), both DAHANCA and hypofractionated-accelerated RT regimens are very nearly equivalent with respect to biological effect on tumor and more efficient than 70 Gy using standard fractionation. Details of bio-effect modelling for the control arm (normofractionated-accelerated RT) as well as the test arm (hypofractionated-accelerated RT) of HYPNO study for tumor control (α/β = 10 Gy) and late normal tissue effects (α/β = 3 Gy) are provided in an online supplementary file (S1). If the actual α/β for HNSCC is 6.4 Gy, i.e. the best estimate from the systematic overview and meta-analysis, then the hypofractionated-accelerated schedule of HYPNO trial would be marginally hotter with expectedly lesser late-effects than DAHANCA and be near as well tolerated as the CHART regimen.

Discussion

As per conservative estimates by IAEA [18], over 50% of patients in LMICs are unlikely to get access to timely RT, which will get further compounded by the COVID-19 pandemic. The radiation oncology community has been at the forefront of systematically testing altered fractionation schedules not only to improve the therapeutic index, but also to promote the safe and evidenced-based use of hypofractionation in several solid cancers (breast, lung, and head-neck), given the fact short-course RT is associated with cost-effectiveness, patient/care-giver convenience and better compliance. Short-course RT (40 Gy in 15 fractions over 3 weeks) is now well established as the contemporary standard of care in the post-operative radiotherapeutic management of early breast cancer [19]. However, the COVID-19 pandemic has prompted the breast oncology community to offer even shorter regimens (5-fraction RT) such as 28.5 Gy/5 fractions (5.7 Gy/fraction), once weekly over 5 weeks (FAST protocol) and 27 Gy/5 fractions (5.4 Gy/fraction) or 26 Gy/5 fractions (5.2 Gy/fraction), once daily in one week (FAST-Forward) for early stage node-negative breast cancer in clinical practice [20]. The European Society for Radiation Oncology (ESTRO)-American Society for Radiation Oncology (ASTRO) consensus statement provides pragmatic, graded, and balanced practice recommendations for thoracic RT in patients with lung cancer including judicious and appropriate use of hypofractionated regimens in order to address the challenges of the COVID-19 pandemic [21]. In head-neck cancer, hyperfractionated RT [11,12] appears to be the best form of altered fractionation and is associated with an 8% improvement in overall survival compared to conventionally fractionated RT. However, hyperfractionation is more resource-intensive (delivering 2 fractions per day with no reduction in overall treatment time) that makes it impractical and undesirable, particularly in the current context of the COVID-19 pandemic, wherein the underlying principle is to reduce the number of fractions/visits to the hospital to reduce the risk-exposure to patients and staff, as well as to allow more efficient utilization of resources [22–24]. The recently published ASTRO-ESTRO consensus statement [25] on practice recommendations for risk-adapted head and neck cancer RT during COVID-19 pandemic turns out to be overly conservative towards altered fractionation schedules. There was strong agreement (oropharynx) and agreement (glottis and larynx) to stay with conventional dose-fractionation for definitive and even palliative head-neck RT in early pandemic scenario. Reassuringly, in the later pandemic stage, there was strong agreement to switch to more hypofractionated regimens for all sub-sites; unfortunately, without recommending any specific schedule. Panellists considered it unsafe to combine chemotherapy with higher (> 2.5–2.8 Gy) dose per fraction, despite evidence for its safety. The resource-sparing potential of hypofractionated-accelerated schedule such as 55 Gy in 20 fractions over 4 weeks would make it the most suitable alternative for HNSCC in the present scenario.

Studies using hypofractionated-accelerated RT (55 Gy in 20 fractions over 4 weeks) with concurrent systemic therapy are summarized

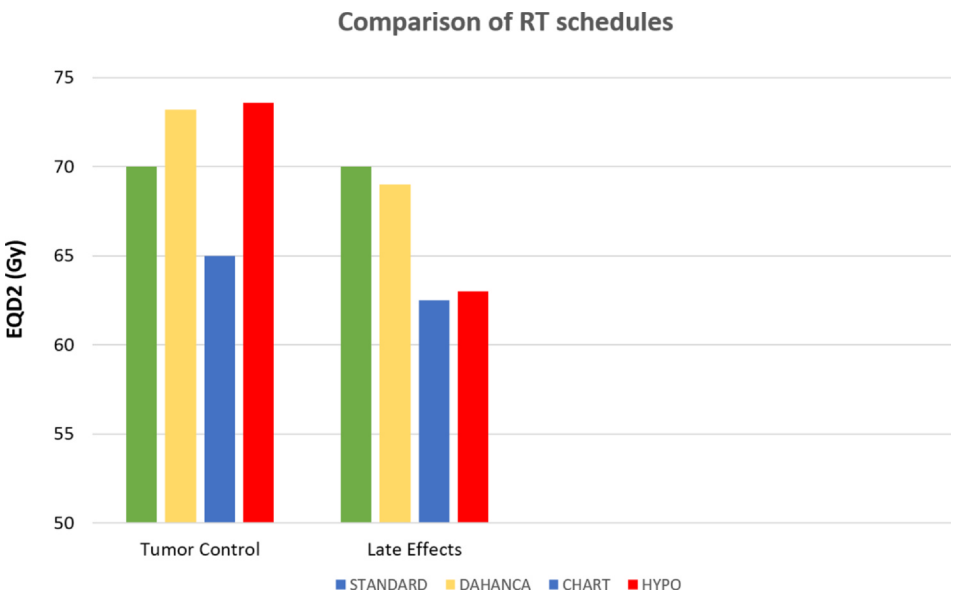

Fig. 1. Estimated equivalent dose in 2-Gy fractions (EQD2) of DAHANCA, CHART, and Hypofractionated-accelerated (HYPO) schedules of radiotherapy for tumor control (α/β = 10 Gy, Dproliferation = 0.65 Gy/day, and start of accelerated repopulation at 28 days) and late normal tissue toxicity (α/β = 3 Gy and no impact of overall treatment time) compared to STANDARD (70 Gy in 35 fractions over 7 weeks) fractionation in head and neck cancer.

in Table 1 [26–32]. Safety and efficacy outcomes of these short-course regimens are largely similar to the usually more protracted schedules. Given the clinical equipoise, there should not be much hesitation in offering such short-course hypofractionated-accelerated regimens in clinical practice in the context of the ongoing pandemic. COVID-context regimens need not necessarily be based on high-quality (level I) evidence from randomized trials, but could be supported by prospective phase II data, retrospective studies, or even personal/institutional experience. A few years ago, the Royal College of Radiology (RCR) in the UK, had omitted hypofractionated-accelerated RT (55 Gy in 20 fractions over 4 weeks) as an option for definitive curative-intent RT of HNSCC in their updated dose-fractionation guidelines [33]. Notably, the recent RCR advisory [34] enlists the same hypofractionated-accelerated regimen as one of the evidence-based and preferred therapeutic options in the definitive curative-intent management of HNSCC during the COVID-19 pandemic. There may be some scope to further tweak this schedule to derive the most optimal regimen by striking the right balance between tumor control probability (TCP) and late normal tissue complication probability (NTCP). Based on mathematical and optimized radiobiological modelling [35], a regimen delivering 54 Gy in 18 fractions over 3.5 weeks (3 Gy per fraction, 5 fractions per week) was recently predicted to substantially increase the TCP, particularly for late-stage disease (from 35% to 49% for advanced stages) while decreasing severe late NTCP (from 13% to < 2%) compared to standard-fractionation (70 Gy in 35 fractions over 7 weeks). The authors further reported that any regimen delivering > 3 Gy per fraction though associated with marginally increased TCP was predicted to be suboptimal due to the unacceptably high late NTCP. Several attempts have been made to model the contribution of chemotherapy given concomitantly with RT in terms of BED for squamous cancers of various sites including HNSCC [36–38] that would lead to resultant improvement in TCP. Although this can vary somewhat based on the model used, it is widely accepted that concurrent chemotherapy adds between 4.5 and 6.8 Gy (EQD2) for squamous cell carcinoma [37,38]. Such chemo-potentiation has not been included in the radiobiological modelling of equivalent doses in the HYPNO study protocol as concurrent weekly cisplatin is optional in the study, which is attempting to answer a pure fractionation question. Identifying the optimal hypo-fractionated-accelerated RT regimen in loco-regionally advanced HNSCC continues to remain an area of active research. One of the four experimental arms in an ongoing phase III randomized controlled trial 'Comparing Alternative Regimens for Escalating treatment of intermediate and high-risk oropharyngeal cancer' (ComPARE) uses 64 Gy in 25 fractions over 5 weeks with concurrent cisplatin (either 100 mg/m^2 three-weekly or 40 mg/m^2 weekly) against standard-fractionation RT (EudraCT No: 2014-003389-26).

Challenges of hypofractionated-accelerated schedules

The use of short-course regimens using a higher dose per fraction comes with its unique set of challenges. While it is easier to compensate for missed treatments in the standard schedule by either delivering it on the weekend or by giving 6 fractions in the week following the missed fraction, the same cannot be done easily for hypofractionated-accelerated schedules, to keep the delivered dose per week within safe and acceptable limits. Rapid shrinkage of a tumor, particularly a large nodal mass, due to the higher dose per fraction may increase the perceived need for adaptive re-planning with resultant unfavourable impact on workflow and resources. There exist due concerns of an increased risk of acute and possibly even late toxicity of such short-course regimens, particularly when combined with concurrent chemotherapy; however, many of these concerns are mostly theoretical and largely unfounded. Nonetheless, it is important to remember that such schedules are just about at the limits of acute normal tissue tolerance, precluding the use of concurrent high-dose three-weekly cisplatin, otherwise considered as standard of care in HNSCC. In any case, most head and neck oncologists would presently prefer avoiding high-dose three-weekly cisplatin concurrently with RT during the ongoing pandemic. However, the addition of concurrent weekly low-dose cisplatin is much safer, less resource-intensive, and can be left to the discretion of the treating physician. Nonetheless, addition of any such concurrent chemotherapy should not compromise the delivery of definitive RT.

Conclusion

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 the ongoing pandemic which threatens to disrupt the healthcare resources and capacity globally.

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Table 1
Studies using hypofractionated-accelerated radiotherapy (55 Gy/20 fx/4wk) with concurrent systemic therapy in head and neck squamous cell carcinoma.

Author [ref] (year)	Number of pts (N)	Disease stage	Radiotherapy regimen	Concurrent systemic therapy	Median FU	Loco-regional control & survival	Acute toxicity	Late toxicity
Sanghera [26] (2007)	81	Stage II-IV	55 Gy/20 fx/4wk	Methotrexate (100 mg/m^2) D1 & 14 Or Carboplatin (AUC = 4.5) on D1 & 21	24 mth	2-yr LRC = 75.4% 2-yr DFS = 68.6% 2-yr OS = 71.6%	Grade 3/4 mucositis = 65 (80%) Prolonged grade 3 mucositis = 7 (9%) Grade 3 dysphagia = 44 (54%)	1-year feeding tube dependency = 11%
Jegannathen [27] (2010)	43	Stage II-IV	55 Gy/20 fx/4wk	Cisplatin (80–100 mg/m^2) wk 1 & 4 Or Carboplatin (AUC = 5) week 1 & 4 Or Methotrexate (100 mg/m^2) wk 1 & 3 Or Capecitabine (500 mg/m^2) twice daily	3.9 yr	3-yr LRC = 70% 3-yr DFS = 60% 3-yr OS = 60%	Grade 3 mucositis = 39 (90%) Prolonged grade 3 mucositis = 24 (56%) Prophylactic tube feeding = 11 (26%) Reactive tube feeding = 25 (58%)	1-year feeding tube dependency = 14%
[$]Tobias [28] (2010)	212	Stage III-IV	55 Gy/20 fx/4wk	Vincristine, Bleomycin, Methotrexate and Fluorouracil	10 yr	RT + Sim CT 5-yr DFS = 42% 5-yr OS = 50%	Hospitalization for supportive care during RT + Sim CT = 28%	Significant late (> 6-month) toxicity = 6%
Chan [29] (2011)	150	Stage II-IV	55 Gy/20 fx/4wk	Carboplatin (at median dose AUC = 4)	25 mth	2-yr LRC = 78.3% 2-yr DFS = 67.2% 2-yr OS = 74.9%	Grade 3/4 mucositis = 121 (81%) Prolonged grade 3 mucositis = 9% Grade 3 dermatitis = 58 (39%)	1-year feeding tube dependency = 9%
Jegannathen [30] (2011)	50	Stage III-IV	55 Gy/20 fx/4wk	Capecitabine (450–550 mg/m^2) twice daily	6 yr	3-yr LRC = 78% 3-yr DFS = 62% 3-yr OS = 72%	Grade 3/4 mucositis = 47 (96%) Feeding tube = 22 (44%)	1-year feeding tube dependency = 6%
Beniaghat [31] (2014)	85	Stage II-IV	55 Gy/20 fx/4wk	Carboplatin at AUC of 4 on D1 & 21 (n = 69) Or Cetuximab 400 mg/m^2 (loading dose 1wk before RT), 250 mg/m^2 once weekly (n = 16)	26 mth	2-yr LRC = 68% 2-yr OS = 80%	Grade 3 mucositis = 85 (100%) Prolonged grade 3 mucositis = 9 (11%) Grade 3 dermatitis = 36 (43%) Prophylactic tube feeding = 36 (43%) Reactive tube feeding = 8 (17%)	1-year feeding tube dependency seen only in one patient
Jacinto [32] (2018)	20	Stage III-IV	55 Gy/20 fx/4wk	Cisplatin (35 mg/m^2) once weekly	NR	ORR = 95% at 2 mth CR at primary = 85% CR at nodes = 40%	Grade 3 mucositis = 6 (30%) Grade 3 dermatitis = 8 (40%) Median weight loss = 7.8% Reactive tube feeding = 15 (75%)	1-year feeding tube dependency = 1 (5%)

Pts = patients, RT = radiotherapy; fx = fractions; FU = follow-up; wk = weeks; mth = months; yr = years; AUC = area under curve; D = day; LRC = loco-regional control; DFS = disease-free survival; OS = overall survival; Sim = simultaneous; CT = chemotherapy; NR = not reported; ORR = overall response rate; and CR = complete response.

[$] Outcome data includes all patients treated with definitive RT with simultaneous CT in the UKHAN1 trial. Hazard ratios (HR) with 95% confidence intervals (CI) of survival for simultaneous chemoradiotherapy vs RT alone (in patients without surgery) was 0.77 (95%CI = 0.56–1.07) for conventional fractionation regimen; 0.83 (95%CI = 0.51–1.33) for Christie's regimen; and 0.55 (95%CI = 0.35–0.87) for Manchester/Birmingham regimen (same as HYPNO schedule). In all regimens, the CI included the overall HR of 0.72 indicating no evidence of a differential treatment effect according to the RT fractionation.

Declaration of Competing Interest

All the authors are involved as Investigators from Tata Memorial Centre, Mumbai, India on an international multicentric randomized controlled trial comparing accelerated hypofractionated vs normofractionated RT (HYPNO study) in loco-regionally advanced head and neck cancer which has received financial support from the International Atomic Energy Agency (IAEA), Vienna, Austria.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2020.105045.

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