Impacts of Radiotherapy Fractionation on Outcome in Squamous Cell Head and Neck Cancer (SQC HNC)

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SUMMARY

Although conventional fractionated (CF) radiotherapy (RT) became the most common non-surgical approach delivering 66-70 Gy in 33-35 daily fractions (fx) in 6.5-7 weeks several decades ago due to a good local control (LC) with low normal tissue complication rates, recent decades also brought altered fractionated RT regimens based on better understanding of radiobiology. Of these, split course RT is largely abandoned due to inferior results caused by the treatment gap, which led to inferior local control rates and consequently survival. Hyperfractionated (Hfx) RT and various forms of accelerated (Acc) RT had consistently shown improvement in the treatment outcome, given either alone or with concurrent chemotherapy (CHT). Hfx RT was most consistently superior to CF and frequently to Acc RT, while moderate Acc RT also holds promise to be used more often in daily clinical practice. The use of Hfx RT may face the challenge of applicability in busy radiotherapy departments around the world despite unequivocally having been proven as superior regarding both local/regional tumor control and overall survival. With concurrent CHT, although results favor it, risks of accompanying toxicity rise and should be considered when planning such intensified treatment approach.

Keywords: Altered fractionated regimens; accelerated fractionation; chemotherapy; head and neck cancer; hyper-fractionation; radiotherapy.

Introduction

At presentation, approximately 70% to 75% of the patients with squamous cell (SQC) head and neck carcinoma (HNC) have stage III or IV ("moderately advanced" or "advanced") disease. With 40% cases considered as locoregional (LR) advanced cases SQC HNC largely remains a LR disease, for which definitive LR treatments are needed. LR failure remains a predominant type of failure, although with treatment improvements and longer overall survival (OS), observed in recent decades, distant metastasis (DM) have increasingly been observed. While overall figures for HNC between 1990s and 2000s showed increase in OS from 54.7% to 65.9% at five years,[1] for LR treatments, such as surgery and/or radiotherapy (RT), five year OS were 30-35%. Conventional fractionated (CF) RT became the most common non-surgical approach delivering 66-70 Gy in 33-35 daily fractions (fx) in 6.5-7 weeks, which provided good local control (LC) with low normal tissue complication rates. However, with better understanding of 4 Rs of radiobiology (repopulation, redistribution, reoxygenation, repair) in the 1970s and 1980s of the last century, different (altered)

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fx schedules came into practice. They have been, either alone or in combination with the drug therapy, used in an attempt to intensify treatment outcome and, hopefully, the outcome.

There are several types of altered fx RT practiced in the past. One of them, namely split-course RT, had treatment interruption during which no RT is given. It had been developed in the 1970s to reduce mucosal toxicity. However, retrospective analyses showed worse LR control (LRC) and OS, with no reduction in late effects.[2,3] It was shown that outcomes depend on total dose (TD) and dose per fraction (D/fx) rather than overall treatment time (OTT). Subsequent attempts to "overcome the split" by increasing TD led to high rates of late complications and, with lacking outcome improvements, resulted in virtually being abandoned in the past few decades.[4,5] In hyperfractionation (Hfx) radiation is delivered in small dose/fx, 2-3 fx/day (bid or tid), aiming to achieve a higher biologically effective dose (BED) to the tumor in cases when α/β ratio for tumor cells is higher than α/β for dose limiting, late-responding normal tissue. Hfx induces radiosensitization through cell-cycle redistribution. There is reduction of the fraction size from 2.0 Gy to 1.1–1.2 Gy enabling 10-20% escalation in total RT dose without detectable increase in late normal-tissue injury. After an important observation that after a certain period of RT (so-called the lag phase) resistant tumor clonogens start accelerated repopulation, incremental dose of 0.6 Gy is required (i.e. four weeks) to counter accelerated repopulation to achieve tumor control. Concept of accelerated (Acc) RT requests completing the RT within 4-6 weeks to overcome accelerated repopulation. The Acc RT can broadly be divided between pure Acc aiming to reduce OTT without concurrent changes in fx size or TD while various hybrid Acc RT regimens reduce OTT with changes in other variables (fx size, TD, time distribution). The latter include either intensive short course of RT with OTT much shortened with a substantial decrease in the TD or Acc when OTT is modestly shortened but the TD is kept in the same range as a CF RT by the use of either Split Course bid fx or concomitant boost (CB) fx. Finally, there is a hypofractionation (HypoFx) which used once daily RT with slightly increased dose per fx, given in up to five times a week in shortened OTT (e.g. 3-5 weeks) to achieve similar TD like CF. HypoFx is rarely used nowadays, mostly in early laryngeal SQC carcinoma in curative attempt (TD at the upper end of the range) but is used mostly in the palliation of incurable disease (TD at the lower end of the range) of practiced RT (50-63 Gy).

MARCH Meta Analyses

The 1990s and the first half of the 2000s brought many important results from prospective randomized clinical studies (PRCTs) testing various altered fx RT regimens not only against CF RT but against other altered fx RT regimens. Due to a somewhat conflicting results and frequently observed benefit on L/R level and but not on OS, Bourhis et al.[6] underwent meta-analysis on the effects of Hfx or Acc RT in HNC (MARCH), the latter being split between Acc fx without TD reduction and Acc RT with TD reduction, all compared to CF RT. They included 15 trials with 6515 patients, which enabled 17 comparisons, with 7073 patients. Altered fx RT offered a significant OS benefit with an absolute benefit of 3.4% at five years (hazard ratio, HR, 0.92, 95% CI 0.86–0.97; p=0.003). The benefits were significantly higher with Hfx RT (8.2% at five years) than with Acc RT (2% with Acc fx without TD reduction and 1.7% with TD reduction at five years, p=0.02). Importantly, altered fx RT had no effect on cancer-unrelated deaths (HR, 1.0, 95% CI 0.93–1.22), but had it solely on cancer-related deaths. Altered fx RT offered a significant benefit on locoregional control (LRC) over CF RT (p<0.0001), which was seen in all altered Fx RT groups, although slightly more pronounced when the TD was not decreased.

Altered fx RT was especially effective in the reduction of local failure (LF) in all three groups, with a 23% reduction in the risk corresponding to an absolute benefit of 8.5% at five years. Similarly, a significant benefit on regional control (RC), although at a smaller scale, was also observed, with a 13% reduction in the risk and an absolute benefit of 1.9% at five years. Importantly, although disappointingly, despite improved LC and LRC and OS, altered fx RT did not improve distant control (DC). Additional analyses showed that there was no significant interaction between sex, performance status (PS), tumour stage, nodal stage, overall stage, tumour site, and the treatment effects on OS. However, an interaction of treatment with age was observed for OS (p=0.007), and cancer-related deaths (p=0.008), LC (p=0.002), and LRC (p=0.002). PS and treatment effects exerted a significant interaction only for LRC, LC and RC (test for trends, p<0.0001, p=0.0001, and p=0.004, respectively). The patients with good PS benefitted from altered fx RT on tumour control, but the effects of altered fx RT on tumour control were similar according to tumour stage and site. Treatment effects on locoregional failure (LRF) were better for N0 and N1 than for the N2 or N3 stage (test for trends, p=0.02). These results carried several implications for future research. The effects of Hfx RT were the same size as

the effects due to the use of CHT concomitantly with RT in HNC (i.e., 8% at five yrs).[7] Substantial acceleration was shown as being capable of only partly compensating for decreasing the TD while increasing TD in Hfx RT seemed as an attractive option since it was the only RT regimen which offered benefit both for OS and LC. The benefit on LRC was similar among trials with moderate Acc when TD was kept the same as in the CF RT. Altered fx was more effective on T than on N disease, with, however, the still unknown explanation for such an observation. Perhaps, as authors commented,[6] altered fx RT could be an appropriate approach for N0 and N1 disease (seemingly less likely to give distant metastasis) than for the N2 disease, for which, perhaps again, the more appropriate approach would be combined RT and CHT. Finally, what should not be forgotten is that a modest 3.4% OS benefit of altered fx RT at five years could be offset by an increased risk in late toxicities.

Recently, Lacas et al.[8] provided an update of the MARCH meta-analysis by adding to the initial MARCH meta-analysis [6] PRCTs carried out between Jan 1, 2009, and July 15, 2015. First comparison included CF RT vs altered fx RT (33 trials; 11 423 patients), while comparison two included CF RT+ concurrent CHT vs altered fx RT alone (five trials; 986 patients). Altered fx RT offered a significant benefit on OS (HR, 0.94, p=0.0033), which corresponded to an absolute benefit of 3.1% at five years and of 1.2% at 10 years. There was a significant interaction (p=0.051) between the type of fractionation and treatment effect, with the OS benefit, however, being restricted to the Hfx group (HR, 0.83), which corresponded to absolute differences of 8.1% at five years and of 3.9% at 10 years. Altered fx RT offered better PFS (HR, 0.90; p<0.0001), which corresponded to an absolute benefit of 3.7% and 2.3% on 5- and 10-years, respectively, without; however, the interaction between the type of fractionation and the PFS (p=0.17). Similarly to the first MARCH analysis,[5] altered fx RT led to significantly reduced cancer mortality, LF, and RF, while there was again no difference in either cancer-unrelated deaths or DM. No interaction between altered fx regimens and the effects on LC or RC were observed; Hfx, however, was associated with a reduction in LF and RF. Moderately Acc RT was only associated with a reduction in LF, while very Acc RT did not exert any effects on any of these endpoints. Many planned subgroup analyses have been performed. In N+ patients, RC was significantly improved with altered fx RT compared with CF RT (HR 0.88, p=0.017). Although this effect did not reach the level of significance according to the type of altered fx RT, it was significant

for Hfx RT. When toxicity was analyzed, a significant increase in acute mucositis (OR, 2.02) and the need for a feeding tube during treatment (OR, 1.75) with altered fx RT were observed versus CF RT. Acute dermatitis was significantly increased with altered fx RT only in the sensitivity analysis without trials responsible for the statistical heterogeneity. When late toxicities with sufficient available data were analyzed, none showed an increased prevalence when altered fx RT was used. Analysis of the second comparison in this update showed that altered fx RT alone achieved significantly worse OS than CF RT plus concurrent CHT (HR 1.22, p=0.0098), which corresponded to an absolute differences of –5.8% at 5 years and of –5.1% at 10 years, respectively. PFS was shorter with altered fx RT than with concurrent RT-CHT. A decrease in LRC was observed when altered fx RT was compared to concurrent RT-CHT, with, however, no difference in DC. No specific analysis was done for LC and RC and toxicities were not additionally analyzed due to the low number of patients in these comparisons. Updated MARCH analysis [8] reconfirmed some of the findings of initial MARCH study [6] in that Alt fx RT regimens were associated with a small (3.1% at 5 yrs). However, significant improvement in OS when compared with CF RT remained significant only in the Hfx RT group, the latter also being associated with a benefit both in LC and RC whereas Acc regimens only improved LC. In N+ pts, the interaction between Alt fx and RC was insignificant, but the effects of Alt fx RT were significant only for Hfx. Authors offered no explanation for the difference in RC favoring Hfx but speculated it might have been related to the increase in TD provided by Hfx. They also suggested that pure Acc (66–70 Gy in 5.5–6 weeks) should be considered only for pts with a low N burden. Superiority of concurrent RT-CHT over pure RT fx change modification, as well as the superiority of RT-CHT over RT alone, was clearly indicated. Consistent with MACHNC findings,[7] here, too, Alt fx RT was inferior to Platinum-based concurrent RT-CHT for OS and PFS. Hence, their conclusion that concurrent RT-CHT should remain standard of care for locally advanced N+ patients.

Due to an increasing evidence about potential superiority of RT-CHT over RT alone, several studies used various meta-analytical approaches to offer additional insight into the issue of optimal combination of RT and CHT in the setting of LA SQC HNC, including altered fx RT regimens as the part of combined treatment approach. Initial meta-analysis on chemotherapy in HNC (MAC-HNC) [9] showed that locoregional treatment (LT) with or without CHT

achieved a pooled HR of death of 0.90 (95% CI 0.85–0.94, p<0.0001), corresponding to an absolute OS benefit of 4% at 2 and 5 years for CHT. No significant benefit was detected with either adjuvant or neoadjuvant CHT, but only when concurrent CHT was given with RT significant benefits were observed. Since this meta-analysis showed only a small but significant OS benefit favoring CHT, authors called for caution in interpretation of the results and its routine use. Unfortunately, no information was provided about the effects of various fractionated RT regimens with CHT in this setting. Updated MAC-HNC [7] included 24 new trials, mostly of concurrent RT-CHT, with a total of 87 trials and 16.485 patients. The HR of death was 0.88 (p<0.0001) with corresponded to absolute benefit of 4.5% at five years for CHT. CHT reduced cancer deaths (HR, 0.78, p<0.0001) but not non-cancer deaths (HR, 0.96, p=0.62). There was a significant interaction (p<0.0001) between CHT timing and treatment with both direct and indirect comparisons showing a more pronounced benefit of the concurrent CHT as compared to induction CHT. For the former trials, the HR was 0.81 (p<0.0001), which corresponded to the absolute benefit 6.5% at fife years. Importantly, using LRF as an endpoint, concurrent CHT offered significant benefit (HR 0.74, p<0.0001), with no beneficial effect of induction CHT (HR, 1.03, p=0.43). The two HRs were significantly different (p<0.0001) favoring the concurrent CHT. Another important observation was that the benefit of concurrent CHT appeared to be similar irrespective of whether the RT was given as CF RT or using altered fx RT.

Additional Analyses Using Meta-analytical Approach

A similar magnitude of the benefit of concurrent CHT in the updated MAC-HNC [7] and that observed in MARCH,[6] respectively may have served as an impetus for several meta-analyses that followed trying to more formally, although sometimes indirectly, compare altered fx RT alone with RT-CHT, the latter sometimes including altered Fx RT regimens as part of the RT-CHT approach. In their attempt, Blanchard et al.[10] used mixed treatment comparison (MTC) meta-analysis to overcome the problem of lacking pairwise comparison between different treatment approaches, which resulted in failure to directly identify the best treatment. By doing so, simultaneous inference regarding all treatments was performed with attempts to select the best among them. MTC models were used to the MAC-HNC [7] and MARCH [6] by pooling IPD from more than 24.000 patients involved in 102 trials. Nine treatment options existed with a to-

tal of 119 comparisons, a total of 26.121 patients and 17.290 events. LT alone was compared to five treatment options (concurrent RT-CHT, induction CHT followed by LT, LT followed by adjuvant CHT, altered fx RT, and altered fx concurrent RT-CHT) using fixed-effects model and four random-effects models. Estimations of the HR of each treatment compared with LT were very similar to the five models. Alt fx concurrent RT-CHT was the best treatment in all models with a probability of >94% for four models and a probability of 84% for the model with inconsistency factors. There was a 30% reduction in the risk of death from any cause with Alt fx concurrent RT-CHT compared with LT. The authors highlighted the findings showing that concurrent CF RT-CHT was better than induction CHT and LT with an HR for OS of 0.87 and 0.85 for fixed effects and basic random effects, respectively. For the comparison between concurrent CF RT-CHT and altered fx concurrent RT-CHT, HR of OS favored altered fx concurrent RT-CHT with a ratio of 0.86 for the fixed-effects model and 0.87 for random-effects model. Authors suggested that these analyses identified altered fx concurrent RT-CHT as the one offering the best OS. When the analysis was restricted to the most recent trials with more complete data sets (platinum-based CHT), the probability that altered fx concurrent RT-CHT was the best treatment was 81.5% and concurrent conventional RT-CHT 18.5%. When compared to the full data set, HRs for altered fx concurrent RT-CHT remained the same in restricted data set. However, the efficacy of CF RT-CHT vs. LT became improved, with an HR rising from 0.80 to 0.75. Accordingly, the relative difference between concurrent CF RT-CHT and altered fx concurrent RT-CHT became smaller, with an HR dropping from 0.87 to 0.92. By incorporating indirect evidence, Blanchard et al.[10] left documented that irrespective of the model used altered fx concurrent RT-CHT was superior to other treatment approaches, as well as they showed the superiority to CF concurrent RT-CHT in more recent trials.

Gupta et al.[11] also used IPD from MAC-HNC and MARCH meta-analyses to perform an adjusted indirect comparison meta-analysis comparing different altered fx RT schedules to CF RT-CHT. Because extracted datasets from MACH-NC and MARCH meta-analyses both had CF RT as the control arm. The dataset of concurrent CF RT-CHT from MAC-HNC used in the indirect comparison comprised 4058 patients with 2676 deaths observed in 53 comparisons from 40 trials. The overall pooled HR of death in the included trials using the random-effects model was 0.76 (p<0.001) in favor of concurrent CF

RT-CHT over CF RT alone. The dataset of altered fx RT from MARCH used in the indirect comparison included 3650 patients with 2313 observed deaths in 17 comparisons from the 15 trials. The overall pooled estimate using the random-effects model favored altered fx RT (HR, 0.86; p<0.001) over CF RT. When an indirect comparison was made, the HR of death for the overall comparison of altered fx concurrent RT-CHT with CF RT-CHT was not significantly different (HR, 1.13; p=0.07)). Using the random-effects model, the corresponding HRs of death for the 3 prevalent schedules of altered fx RT were 1.01 (p=0.82), 1.22 (p= 0.13), and 1.22 (p=0.002) for Hfx RT, Acc RT without total dose reduction, and Acc RT with total dose reduction, respectively, compared to concurrent RT-CHT. Similar comparison using the fixed-effects model showed an HR of 1.10 (p=0.09) for Hfx RT confirming no significant difference in efficacy between concurrent CF RT-CHT and Hfx RT. However, both Acc RT regimens achieved inferior results since the fixed-effects model yielded an HRs of 1.18 (p<0.001) and 1.32 (p<0.001) for Acc RT without and with TD reduction, respectively when compared to concurrent CF RT-CHT. The authors concluded that any form of acceleration alone could not compensate fully for the lack of CHT, leading to inferior results.

In the most recent attempt to highlight the issue of the effectiveness of various RT and RT-CHT approaches in LA SQC HNC, including alt fx RT in both of these approaches, Liu et al.[12] performed a network meta-analysis (NMA) aiming to aid clinicians in the decision-making process about the superior treatments in this setting. They estimated the efficacy and safety of CF, CF RT-CHT, Hfx RT, Hfx RT-CHT, Acc RT, Acc RT-CHT, Hfx Acc RT (HART) or Hfx Acc RT-CHT (HACRT). OS, DFS and LRC were efficacy outcomes, whereas acute and late toxicity on skin and mucosa were safety outcomes. The authors also calculated the surface under the cumulative ranking curve (SUCRA) to help rank each treatment in each endpoint. There were 72 trials with a total of 21.868 patients. All treatments were associated with a significant OS advantage compared to CF alone, (range of HR effect sizes, 0.64-0.83), with HACRT being significantly superior to all the other treatments. The network comparisons of both HACRT vs HART (HR, 0.78) and Hfx RT-CHT vs Hfx RT (HR, 0.78) demonstrated a higher OS benefit for adding the CHT. HACRT had the best SUCRA ranking for OS and LRC, Hfx RT-CHT for DFS, HART for acute and late skin toxicity, CF RT-CHT for acute mucosal toxicity and Hfx RT-CHT for late mucosal toxicity. While the NMA results clearly indicted HACRT as the prefer-

able treatment approach due to its better rankings in all three efficacy endpoints, authors called for the cautious implementation of these results in daily clinical practice due to a high risk of acute mucositis.

Recently, however, results from several PRCTs directly comparing altered fx RT with concurrent RT-CHT started to emerge. Results were inconclusive with some of PRCTs showing the superiority of CF concurrent RT-CHT compared with altered fx RT alone, while others did not observe it. Based on this background, Gupta et al.[13] undertook a systematic review and meta-analysis of the data from 5 PRCTs with a total of 1117 patients and 627 deaths. The risk of bias in included studies was low for efficacy outcomes. There was a 27% reduction in risk of death with an overall pooled HR of death of 0.73, showing a significant advantage for CF concurrent RT-CHT over altered fx RT alone (p<0.0001). In addition, there was a 21% reduction in risk of disease progression (HR, 0.79; p=0.002) and a reduction of 29% in locoregional progression (HR, 0.71; p<0.0001) which both showed significant improvement with CF concurrent RT-CHT. The overall quality of included studies for toxicity outcomes was poor and the risk of bias was high. Analysis of the incidence of severe acute dermatitis and mucositis showed no significant differences between the two treatment approaches. However, late xerostomia was significantly increased with CF concurrent RT-CHT with the odds ratio of grade >3 toxicity being 0.59 (p=0.02). As expected, pronounced and significantly higher incidence of haematological toxicity (the mean incidence of acute grade >3 toxicity, 15.7%) and mild kidney toxicity was seen exclusively in CF concurrent RT-CHT group. Authors attempted to qualitatively summarize/grade their results and base their recommendation for the interpretation of the data based on these. The quality of evidence was graded as moderate for OS and DFS, while the quality of evidence for LRC was graded as low. Given the high risk of bias, the authors did not perform the grading of quality for toxicity.

Conclusion

The past several decades clearly indicated that alt fx RT is an important therapeutic approach in the increasing treatment armamentarium in LA SQC HNC. PRCTs and MAs unequivocally showed that alt fx RT is superior to CF RT, principally exerting its effectiveness on T rather than on N disease component, and primarily on N0-1 rather than on N2-3 disease. The data also showed that Hfx is definitely superior to various forms

of Acc RT due to superior results on OS, LC, LRC, NC and DFS, is likely to be as a consequence of the higher TD. Hfx RT also had better toxicity profile, as shown by Liu et al.[12], reconfirming of sparing of late mucosal effects Hfx was expected to achieve. Although the magnitude of the benefits of alt fx RT over CF RT, principally the Hfx, are similar to that of additional CHT,[7] majority of studies reported on the superiority of adding the CHT to either CF or alt fx RT when compared to alt fx RT alone.[8,10-13] Gupta et al.[11], however, showed that CF RT-CHT achieved similar results as Hfx RT alone with higher TD, reconfirming pivotal observation of Jeremic et al.[14] about the trade-off between added CHT and increased TD, i.e. that adding CHT to CF RT (70 Gy) results in similar results like Hfx RT alone with higher TD (77 Gy, 1.1 Gy bid), yet with less toxicity. Both Acc RT regimens seemed as inferior to Hfx RT, especially having in mind poor results very Acc RT achieved on RC.[8] Acc RT was also inferior to RT-CHT, indicating that any form of acceleration cannot efficiently compensate for missing CHT. With even more pronounced treatment intensification (e.g. Acc Hfx RT and CHT - HACRT), Liu et al.[12] documented both best results on both OS and LRC, but toxicity presented as a serious obstacle, an observation already brought by Jeremic et al.[15] in their study on Hfx RT-CHT. Obviously, improved outcomes (all but DC) are burdened by the increased risk of both acute and late toxicity, although the toxicity results need to be cautiously interpreted as some studies clearly showed the poor quality of the existing data.[13] Perhaps, limiting the CHT dose (e.g. two doses of high-dose cisplatin given in 3-4 week intervals) during the course of alt fx RT can result in better survivals achieved at the expense of less toxicity [16] when compared to weekly administration of cisplatin as recent meta-analysis showed, can be one of the ways forward.

Contrasting these, purely scientific aspects, are realities of the busy RT departments around the world. Initial criticism of alt fx RT, especially Hfx regimens (doubling the time on machines, inconveniences for staff and patients, possible cost increase), in recent years, witnessed another reason for its decreasing use in daily clinical practice. Various technological advances (e.g., intensity-modulated RT, IMRT, coupled with simultaneous integrated boost, SIB) have definitely shifted clinical practice towards more patient- and staff-friendly execution of the RT course, which all virtually became Acc fx RT. Optimized patient treatment, however, should be thoroughly considered to provide an appropriate balance between various factors in the decision-making process, which ultimately rests with the patient. This is especially so in case when treatment optimization is still facing challenges, in both non-HPV+ and HPV+ patients.[17,18] The latter brings, however, a significant challenge towards obtaining favorable therapeutic ratio and needs to be judged judiciously, again, with the patient's full understanding of the benefits and risks.

References

1. Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. Oncologist 2010;15(9):994–1001.

2. Overgaard J, Hjelm-Hansen M, Johansen LV, Andersen AP. Comparison of conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx. Acta Oncol 1988;27(2):147–52.

3. Parsons JT, Bova FJ, Million RR. A re-evaluation of split-course technique for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1980;6(12):1645–52.

4. Thames HD Jr, Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. Int J Radiat Oncol Biol Phys 1982;8(2):219–26.

5. Peters LJ, Ang KK, Thames HD Jr. Accelerated fractionation in the radiation treatment of head and neck cancer. A critical comparison of different strategies. Acta Oncol 1988;27(2):185–94.

6. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368(9538):843–54.

7. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92(1):4–14.

8. Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. Lancet Oncol 2017;18(9):1221–37.

9. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analy-

ses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355(9208):949–55.

10. Blanchard P, Hill C, Guihenneuc-Jouyaux C, Baey C, Bourhis J, Pignon JP, et al. Mixed treatment comparison meta-analysis of altered fractionated radiotherapy and chemotherapy in head and neck cancer. J Clin Epidemiol. 2011 Sep;64(9):985–92.

11. Gupta T, Kannan S, Ghosh-Laskar S, Agarwal JP. Concomitant chemoradiotherapy versus altered fractionation radiotherapy in the radiotherapeutic management of locoregionally advanced head and neck squamous cell carcinoma: An adjusted indirect comparison meta-analysis. Head Neck 2015;37(5):670–6.

12. Liu Y, Kou C, Bai W, Liu X, Song Y, Zhang L, et al. Altered fractionation radiotherapy with or without chemotherapy in the treatment of head and neck cancer: a network meta-analysis. Onco Targets Ther 2018;11:5465–83.

13. Gupta T, Kannan S, Ghosh-Laskar S, Agarwal JP. Systematic Review and Meta-analysis of Conventionally Fractionated Concurrent Chemoradiotherapy versus Altered Fractionation Radiotherapy Alone in the Definitive Management of Locoregionally Advanced Head and Neck Squamous Cell Carcinoma. Clin Oncol (R Coll Radiol) 2016;28(1):50–61.

14. Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, non-metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22(17):3540–8.

15. Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 2000;18(7):1458–64.

16. Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V, et al. Altered fractionation radiotherapy combined with concurrent low-dose or high-dose cisplatin in head and neck cancer: A systematic review of literature and meta-analysis. Oral Oncol 2018;76:52–60.

17. Jeremic B, Dubinsky P, Filipobic N, Özyiğit G. Optimal administration frequency of cisplatin concurrently with radical radiotherapy in the definitive treatment of locally advanced inoperable squamous cell cancer of the head and neck. Still obscured by clouds? Turk J Oncol 2019;34(2):133–6.

18. Jeremic B, Özyiğit G, Dubinsky P, Filipovic N. Importance of Hpv Positivity in Squamous Cell Head and Neck Cancer. Turk J Oncol 2019;34(3):204–14.