# Chemo-enhanced radiotherapy in squamous cell carcinoma – Is there evidence for different regimes?

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Squamous cell carcinomas of the head and neck region (SCCHN) are the case for postoperative or definitive radiotherapy or chemo-radiation. From the results of some meta-analyses it is known that altered fractionation has some impact on local control (LC), loco-regional tumour control (LRC)and overall survival (OS) [1,2]. Radiobiology predicts a potential dose escalation by using hyperfractionated radiotherapy without running into a risk of enhanced late radiation damage. Clinical trials have unequivocally demonstrated that this hypothesis is valid. From one meta-analysis an average OS benefit of 14.2 months at 2 years has been observed from four trials which addressed the question of hyperfractionated irradiation [2]. From another meta-analysis, the hazard ratios for OS could be significantly reduced for hyperfractionated trials to 0.78 (CI: 0.69–0.89) [1]. The toxicities reported herein showed a pronounced level of acute reactions but not of late reactions when compared with conventional fractionation.

The radiobiological hypothesis of yielding better treatment results from increased dose intensity in a shorter overall treatment time was investigated in several phase III trials. Acceleration of radiotherapy was realised in three different ways: A decrease of the overall treatment time by more than 60% which required a reduction in total dose of approximately 20%. A moderate reduction of overall treatment time without a relevant compromise in total dose using split course radiotherapy regimens. A moderate reduction of the overall treatment time without a relevant compromise in total dose using six or seven fractions per week or a concomitant boost radiotherapy regimen without a split. The first two strategies were rather unsuccessful in terms of LC, LRC and OS at 2 years. The third strategy seems to be more successful. All three studies reported a significantly improved LC and in one study also, an OS benefit at 2 years. Another recently published meta-analyses based on an even broader and individual patients data set showed some conflicting results with a stated small, but still significant, OS benefit of 3.4% at 5 years for altered fractionation schemes (HR: 0.92, CI: 0.86–0.97, $P = 0.003$) [1]. However, a detailed look revealed a much larger benefit for hyperfractionated radiotherapy (8% at 5 years) than for accelerated radiotherapy without (2% at 5 years) or with total dose reduction (1.7% at 5 years). There was a beneficial effect on LRC (6.4% at 5 years, $P = 0.0001$) for the hyperfractionated (HR: 0.76, CI: 0.66–0.89) and accelerated regimens without total dose reduction (HR: 0.79, CI: 0.72–0.87). The accelerated regimens with total dose reduction could, however, not show an increase in LRC (HR: 0.90, CI: 0.80–1.02). The benefit in nodal control was also much less pronounced. The underlying hypothesis favouring concurrent chemo-radiation is some spatial cooperation at the level of the tumour target to achieve additive tumour cell kill. Concurrent chemo-radiation aims at a separation of acute and late reacting normal tissue targets and thus improvement of the therapeutic ratio. When combining radio- and chemotherapy in a neoadjuvant, concurrent or adjuvant setting, a crude OS-benefit of 5% was observed from the updated MACH-NC analysis (Bourhis J, et al. [3], Bourhis J, Pignon, ASCO Abstract 2005, J Clin Oncol). For concomitant chemo-radiation this translates into an OS-benefit of 8% for all drug combinations (hazard ratio: 0.81, CI: 0.77–0.86) and to 11% for Cisplatinum alone. Neoadjuvant and adjuvant chemotherapies had no significant impact on the OS endpoint. Cisplatinum was the most effective single drug (HR reduction of 26%) compared with other single drugs like 5-FU (HR-reduction: 10–19%) or drug combinations (HR-reduction: 20%).

From another meta-analysis 5-FU and Cisplatinum were the drugs with the highest potential of improving the median survival by a delta of 24 versus 16.2 months, respectively, compared with fractionated radiotherapy alone [2]. With standard fractionated radiotherapy and concurrent single drug chemotherapy a median increase in OS of 12 months corresponding

to an improvement of the OS-rate at 2 years of 13.3% ($P < 0.001$) was observed. With altered fractionation and a prolonged overall treatment time due to split course or rapidly alternating chemo-radiation schemes, a statistically significant, however smaller, median survival benefit of 7.9 months and a percentage OS benefit of 8.1% at 2 years were observed. With optimised hyperfractionated or accelerated radiotherapy schedules the median increase in OS amounted to 12 months corresponding to a 14.7% increase in the OS rate at 2 years. The HR reduction with concurrent chemotherapy was superior to that of altered fractionation and conventional fractionation alone. Thus concurrent Cisplatinum ± 5-fluorouracil based chemo-radiation can be considered the new standard of care for inoperable and locally advanced head and neck cancer. For patients not amenable for concurrent Cisplatinum containing chemo-radiation, either 5-FU or Taxane-based schemes or purely hyperfractionated irradiation schemes are the treatments of choice. Accelerated radiotherapy alone, particularly as split course or with decreased total dose, is not recommended. Postoperative radiotherapy is well established for head and neck cancer. The existence of different risk groups have been established during the last decade [4]. Three groups can be differentiated: Lowest, intermediate and highest risk. Many institutions worldwide have established their own risk models, where the grouping depended on the margin status (number of margins ±), ECE ±, the number of >N+ nodes and other factors. For the highest risk patients, concurrent Cisplatinum containing chemo-radiation has been conducted in three large randomised trials worldwide. After closure of two of those trials (EORTC 22931, RTOG 9501), the results show that radiotherapy and concurrent Cisplatinum can alter markedly the outcome in high-risk SCCHN, as compared with radiation therapy alone [5,6]. The 5-year survival estimates for the EORTC 22931 and the RTOG 9501 trials were comparable with each other. However, only chemo-radiation in the EORTC-trial reached a level of statistical significance at the OS endpoint in favour of Cisplatinum. When harmonising the different selection criteria from both trials by introducing multivariate Cox regression analysis for risk factor determination, namely tumour margins and extracapsular nodal spread could ultimately be established as leading risk factors. When using these two risk factors the results were comparable and reached, also for the RTOG-trial at the OS endpoint, a level of statistical significance. The German ARO 96–03 trial showed similar loco-regional relapse and and overall survival rates, which for the OS endpoint reached also a level of statistical significance after correction for prognostic factors [7]. These pivotal trials show adjuvant chemo-radiation significantly to enhance anti-tumour efficacy in the highest risk group for adjuvant treatment. Cisplatinum as single dose of $100\,mg/m^2$ in three cycles but also fractionated with $5 \times 20\,mg/m^2$ during two cycles in the first and fifth week is still the drug of choice. In future, the taxanes, EGFR-MoAb's, Bevacizumab and other small molecules should additionally be tested in phase-I through III studies, in particular in patients with intermediate risk.

## Conflict of interest statement

None declared.

## References

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