Update of MACH-NC (Meta-Analysis of Chemotherapy in Head & Neck Cancer) database focused on concomitant chemoradiotherapy

Presenter: J. Bourhis
Presenter’s Affiliation: Institut Gustave-Roussy, Villejuif, France
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Background
- In 2000, the MACH-NC performed a meta-analysis including all non-metastatic head and neck studies conducted between 1965 and 1993 randomizing patients to locoregional therapy versus locoregional therapy plus chemotherapy. The analysis demonstrated a significant survival improvement (4% at 5 years) in patients receiving chemotherapy, with an even greater benefit (8% at 5 years) observed in patients undergoing concurrent chemoradiation.
- Due to concerns over the considerable heterogeneity of the results with respect to chemoradiation versus other forms of chemotherapy regimens, the MACH-NC hesitated to draw definitive conclusions.
- In order to validate the earlier results and confirm the benefit of chemotherapy, the MACH-NC re-analyzed the data after including all studies performed between 1994 and 2000.
- Moreover, the MACH-NC sought to increase the statistical power of the study, allowing for subgroup/subset analysis.

Materials and Methods
- All trials performed between 1965 and 2000 concerning non-metastatic head and neck squamous cell carcinoma patients randomized to locoregional therapy versus locoregional therapy plus chemotherapy were analyzed.
- The log-rank test was utilized for comparison, and the hazard ratio (HR) of death was determined.

Results
- 24 trials conducted between 1994 and 2000 and totaling 5699 patients were incorporated into the meta-analysis for a total of 87 studies and 16640 individuals. The majority of the added trials included a concurrent chemoradiation arm.
- Overall, 54% of trials employed concurrent chemotherapy, 32% utilized neoadjuvant chemotherapy, and 14% included adjuvant chemotherapy.
- Median follow-up was 5.7 years.
- Primary sites in order of decreasing frequency: oropharynx > oral cavity > larynx > hypopharynx.
- There was a pooled HR of 0.88 with an absolute overall survival benefit of 5% at 5 years observed in patients receiving chemotherapy (36% vs. 31%, p<0.0001).
- When considering subsets of patients with respect to timing of chemotherapy, there was a calculated HR of 0.81 with an absolute overall survival benefit of 8% at 5 years for concurrent therapy (p<0.0001). Non-significant survival differences were detected for neo-adjuvant therapy (HR=0.96, absolute benefit of 2%, p=NS) and adjuvant therapy (HR=1.06, absolute benefit of 6%, p=NS). Ultimately, there was a significant difference in overall survival with respect to chemotherapy timing (p<0.0001).
- Concerning trials between 1994 and 2000, 85% employed concurrent chemotherapy, 5% utilized neoadjuvant chemotherapy, and 10% utilized adjuvant chemotherapy.
- Regarding all 50 trials of concurrent treatment analyzed, the survival benefit (8% at 5 years) was identical between the 1965-1993 group and 1994-2000 group. Similar benefits were observed for concurrent therapy delivered in the post-operative setting (HR=0.80), definitive setting with conventional fractionation schedule (HR=0.83), and definitive setting with altered fractionation schedule (HR=0.73). There were no significant differences with respect to anatomic site, stage,
type of locoregional therapy, or mono- versus poly-chemotherapy. There was a significantly decreased HR for death when using platinum-based chemotherapy versus other regimens (0.75 versus 0.86, p<0.01). Likewise, there was a significantly greater survival benefit for decreasing age (p<0.01).

**Author's Conclusions**
- This expanded meta-analysis validates the overall survival benefit in non-metastatic head and neck squamous cell carcinoma patients. The absolute overall survival benefit of 5% at 5 years was minimally increased versus the original meta-analysis (4% at 5 years).
- This expanded meta-analysis confirms the increased magnitude of overall survival benefit demonstrated in patients receiving concurrent chemoradiation. The absolute overall survival benefit of 8% at 5 years was identical to the original meta-analysis. Similar benefits were observed in postoperative chemoradiation, definitive chemoradiation with conventional fractionation schedules, and definitive chemoradiation with altered fractionation schedule.
- The greater statistical power of the expanded meta-analysis allowed subgroup analysis showing significant differences in results with respect to chemotherapy timing, cisplatin-based versus non-cisplatin regimens, and age.

**Clinical/Scientific Implications**
This expanded meta-analysis validates the small survival benefit observed in non-metastatic head and neck carcinoma patients while confirming the greater magnitude of benefit realized with concurrent chemoradiation. In addition, the increased statistical power of the study allowed for subset analysis. There was some concern following the original meta-analysis that not all patients required chemotherapy. However, subgroup analysis revealed no differences with regard to anatomic site, stage, or type of locoregional therapy, strengthening the hypothesis that all patients with advanced locoregional head and neck carcinoma benefit to some extent from chemotherapy. Moreover, cisplatin-containing regimens were more effective with respect to survival than those not including cisplatin. Unfortunately, limitations involved with the database precluded comparison of cisplatin and carboplatin, a topic becoming increasingly relevant due to the superior morbidity profile of carboplatin.

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