Association between event-free survival and overall survival in newly diagnosed patients with locally advanced head and neck squamous cell carcinoma ineligible for surgery

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BACKGROUND AND OBJECTIVE

- Improvement in overall survival (OS) is accepted as the gold standard in evaluation of interventions in oncology;[1] however to detect a statistical significant difference in OS between interventions, a large number of patients and an extended follow-up period is generally required, especially in earlier stages of cancer.[2]
- To facilitate drug approvals, use of surrogate endpoints (e.g. event-free survival [EFS], progression-free survival [PFS] and disease-free survival [DFS]) have been widely accepted.[1] Since these endpoints assess the time period from treatment initiation until tumor growth or recurrence, an improvement in these endpoints could predict clinical benefit in patient symptoms and longer OS.
- A comprehensive examination of EFS as a surrogate for OS in patients with LA-HNSCC was previously conducted by the investigators from the MACH-NC Collaborative Group.[4] In that study, data from 104 trials of RT with concomitant, induction, or adjuvant chemotherapy were analyzed. The study found that OS was strongly correlated with EFS and broadly established the relevance and suitability of EFS as a surrogate for OS in this population.[4]
- Our study expanded on the methods used by MACH-NC in order to estimate the correlation between EFS (and analogous outcomes to EFS) and OS in the target LA- HNSCC population ineligible for surgery.

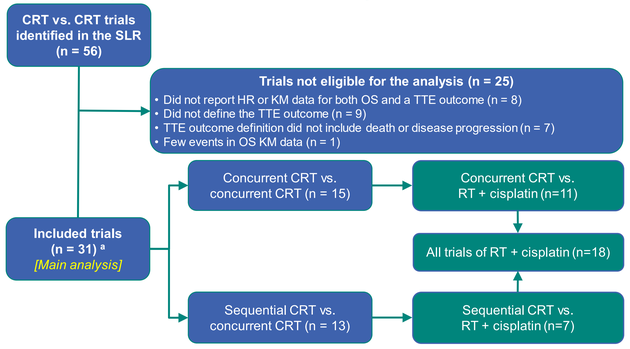
METHODS

- In the current study, results from a previous systematic literature review (SLR) in the LA HNSCC population ineligible for surgery5 was incorporated into a series of meta-analyses to estimate the correlation between EFS and OS.
- The SLR identified randomized controlled trials evaluating systemic treatments (chemotherapy or targeted therapies) administered concurrently or sequentially with RT (from here on referred to as CRT) in the target population. Trials evaluating surgical interventions were excluded.
- The SLR identified 56 trials comparing CRT regimens to one another. Trials were classified according to the timing of the administration of the systemic therapies relative to RT:
  - **Trials of concurrent CRT versus concurrent CRT:** compared systemic therapies concurrently administered with RT to one another
  - **Trials of sequential CRT versus concurrent CRT:** compared neoadjuvant/ adjuvant systemic therapies administered before/after a CRT combination versus concurrent CRT
  - **Trials of sequential CRT versus sequential CRT:** compared neoadjuvant/ adjuvant systemic therapies administered before/after a CRT combination to one another
- Trials meeting the following eligibility criteria were included in the correlation analyses:
  - Reported hazard ratios (HRs) or Kaplan-Meier (KM) data for OS and at least one other time-to-event (TTE) endpoint: EFS, PFS, DFS, and recurrence-free survival (RFS)
  - Included at least 'disease progression' and 'death due to any cause' in the definition of TTE outcome(s)
  - Reported a sufficient number of OS and other TTE events in all treatment arms.
- To assess the association between the surrogate TTE outcomes (EFS, PFS, DFS and RFS) and OS, a linear regression approach (as described in Michiels et al.[4] and Flaherty et al.[6]) was used to evaluate the relationship between the HRs of the TTE outcomes and OS.
  - This approach models the relationship between the HRs of treatments with respect to the TTE outcomes and HRs of treatments with respect to OS.
  - A weighted Pearson's correlation coefficient (R) was used as measure of the strength of the relationship between treatment effects on the TTE outcomes and OS in terms of the ln(HRs).
  - In addition, both the intercept and slope parameters resulting from the model are reported. A good surrogate relationship requires that the intercept parameter (β_0) be sufficiently close to zero and the slope parameter (β_1) be significantly different from zero.
- The main correlation analysis included simple linear regression model accounting for all CRT trials. Models including interaction terms for maximum follow-up duration and therapy type were also assessed. (**Figure 2**).
- Subgroup analyses were conducted for trials evaluating different types of CRT (**Table 1**) as well as trials with matching TTE outcome definitions that only included death and disease progression/relapse **(Figure 2**). As clinical guidelines widely recommend concurrent RT + cisplatin as the standard of care, correlation results were also summarized for this treatment group. (**Table 1**).

RESULTS

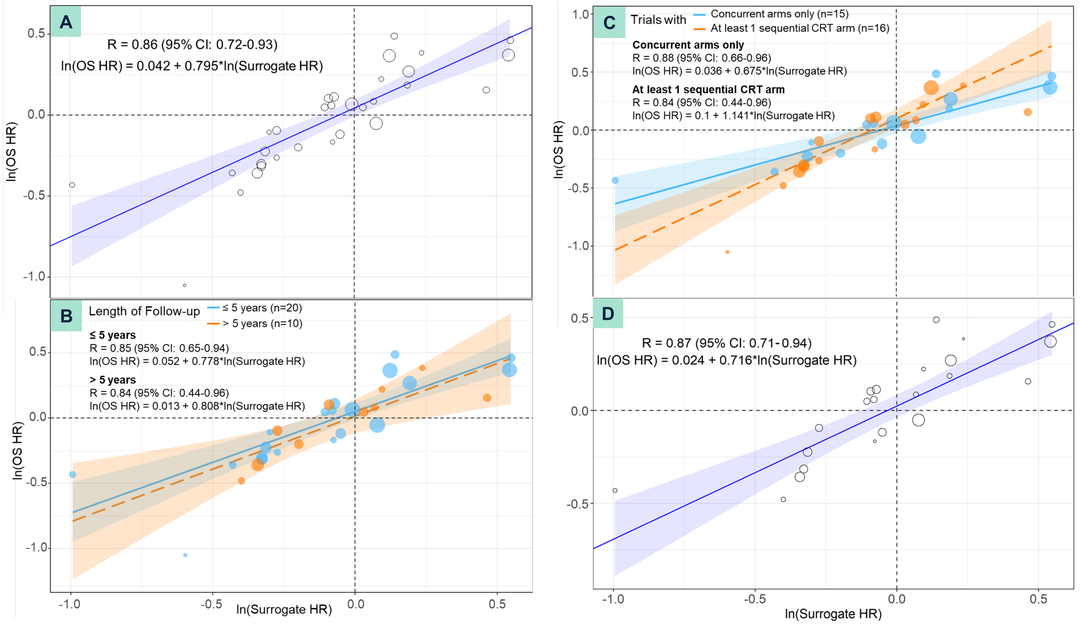
- Of the 56 trials identified in the SLR, 31 trials were included in the current study (**Figure 1**), including:
  - 15 trials of concurrent CRT versus concurrent CRT
  - 13 trials of sequential CRT vs. concurrent CRT
- RT + cisplatin was the most common studied intervention, with 11 and 7 trials evaluating RT + cisplatin, respectively, in each group.
- Among 22 trials, the TTE endpoint was consistently defined as time from randomization/treatment initiation until death or disease progression/recurrence (whichever occurred first), while the remaining 9 trials also included treatment discontinuation or second primary malignancy in the TTE endpoint.

Figure 1. Study selection for the correlation analysis



a) Three trials evaluated sequential CRT vs. sequential CRT. Due to low number of trials, this subgroup was not considered for the correlation analysis. CRT, chemoradiotherapy; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; RT, radiotherapy; TTE, time to event.

Figure 2: Relationship between the TTE outcomes and OS. A) Main analysis: all CRT trials (n=31); B) Model with interaction term for follow-up duration (n=31); C) Model with interaction term for therapy type (n=31); D) Model including trials with matching TTE outcome definitions, only including disease progression and death (n=22).



CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival; R, weighted Pearson's correlation coefficient, TTE, time to event.

Table 1: Relationship between TTE outcomes and OS by intervention type

Analysis (number of included trials)	R (95% CI)	Slope	Intercept
All CRT versus CRT (n=31)	0.86 (0.72-0.93)	0.795	0.042
Concurrent CRT versus concurrent CRT (n=15)	0.88 (0.66-0.96)	0.675	0.036
Sequential CRT versus concurrent CRT (n=13)	0.82 (0.49-0.94)	1.002	0.114
Concurrent CRT versus RT + cisplatin (n=11)	0.83 (0.46-0.95)	0.61	0.056
Sequential CRT versus RT + cisplatin (n=7)	0.87 (0.33-0.98)	1.432	0.078
All CRT versus RT + cisplatin (n=18)	0.81 (0.55-0.93)	0.649	0.053

CI, confidence interval; CRT, chemoradiation therapy; R, weighted Pearson's correlation coefficient; RT, radiotherapy; STE, surrogate threshold effect; TTE, time to event.

- A high degree of correlation (R=0.86) was observed for the main analysis including all CRT versus CRT trials. These results were consistent in the subgroup analyses factoring in trial follow-up time, intervention type, matching TTE outcome definitions, and interventions specific to cisplatin + RT (**Table 1**; **Figure 2**).
- These results were accompanied by statistically significant slopes as well as intercepts (p values not shown), suggesting a valid surrogate relationship between surrogate TTE outcomes and OS.
- The estimated R values were consistently greater than 0.81, albeit with wider 95% CIs, in the subgroup analyses, suggesting that a similar relationship existed in the evaluated subgroups of trials (**Table 1, Figure 2**).

CONCLUSIONS

- The strong relationship between TTE outcomes and OS (R=0.86, slope >0, intercept ~0) suggests these TTE outcomes are potential surrogates to OS in LA HNSCC patients ineligible for surgery.
- Our results, while limited to trial-level analyses and being conducted in a slightly different population, generally support the previous results from the MACH-NC study.
- The surrogacy relationship was weakened in the subgroup analyses due to fewer trials being included in each subgroup, leading to wider 95% CIs and indicating greater uncertainty.
- Our study was limited by lack of individual patient-level data, differences in baseline patient or trial characteristics likely impacting the estimated correlations, and heterogeneity in outcome definitions. The analyses were, however, conducted on a dataset obtained from a rigorous SLR, and the analysis methods and models that were previously established.

References: 1. U.S. Food and Drug Administration. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry. 2018. **2.** Bujkiewicz S. et al. Statistics in Medicine. 2019;38(18):3322-3341. **3.** https://clinicaltrials.gov/ct2/show/NCT03040999. **4.** Michiels S. et al. Lancet Oncol. 2009;10(4):341-350. **5.** Ramakrishnan K. et al. European Society of Medical Oncology Congress 2021; poster 880P. **6.** Flaherty K.T. et al. Lancet Oncol. 2014;15(3):297-304. **Disclosures:** C.M. Black is an employee of Merck & Co., Inc., Kenilworth, New Jersey, USA