Relationship Between Event-Free Survival and Overall Survival in Newly Diagnosed Patients With Resectable Locally Advanced Head and Neck Squamous Cell Carcinoma

Dandan Zheng[1*]; Ali Mojebi[2]; Yuexin Tang[1]; Braden Hale[2]; Sanjay Merchant[1]; Coco Liu[2]; Sam Keeping[2]

[1]Value and Implementation, Outcomes Research, Merck & Co., Inc., Rahway, NJ, USA; [2]Evidence Synthesis, Precision AQ, Vancouver, BC, Canada

Background and objective

- Surgery followed by adjuvant radiotherapy (RT) or chemoradiotherapy for tumors at low or high risk of postoperative recurrence, respectively, is the standard of care for patients with resectable locally advanced (LA) head and neck squamous cell carcinoma (HNSCC).[1,2] The addition of neoadjuvant and/or adjuvant systemic treatments, including immunotherapy, to this standard of care is being investigated in this population[3-5]
- For trials in oncology, overall survival (OS) is the gold standard outcome and is the most relevant outcome from a regulatory and reimbursement perspective.[6] To assess new oncology treatments in patients in early cancer stages, long-term follow-up of trial participants is often needed for OS data to mature, which delays access to new therapies
- The use of a surrogate end point that matures faster can help reduce the time to patient access for new therapies.[7] Prior studies have suggested that event-free survival (EFS) may be a suitable surrogate end point for OS in the broader population with LA HNSCC[8] as well as the subgroup of patients with unresectable tumors[9]
- The objective of the current study was to estimate the trial-level correlation between EFS and OS in newly diagnosed patients with resectable LA HNSCC who undergo surgery with neoadjuvant and/or adjuvant treatments, based on published data from randomized controlled trials (RCTs)

Methods

- A systematic literature review (SLR) was conducted on April 29, 2024, to identify RCTs evaluating neoadjuvant and/or adjuvant treatments in newly diagnosed patients with resectable stage III-IV LA HNSCC receiving surgery. Trials were of interest if they reported hazard ratios (HRs) or presented Kaplan-Meier curves for OS and EFS
- Consistent with the approach described in the previous surrogacy analyses in LA HNSCC[8,9]
  - A linear regression analysis was conducted to measure the association between the ln(HR)s of EFS and OS
  - A regression equation with an intercept parameter (β_0) sufficiently close to 0 and a slope parameter (β_1) significantly different from 0 indicated a good surrogate relationship
  - A weighted Pearson correlation coefficient (*R*) was calculated to measure the strength of the relationship between the natural logarithms of HRs for EFS and OS
  - *R*≥0.75 suggested strong trial-level associations
  - Leave-one-out validation analysis was performed to assess the robustness of the models
- Base case
  - The base case was restricted to trials comparing neoadjuvant treatment followed by surgery (± adjuvant therapy) vs surgery (± adjuvant therapy)
- Sensitivity analyses
  1. '*All-trials*': To maximize the amount of data feasible to incorporate into the models, a sensitivity analysis included all trials meeting the eligibility criteria of the SLR
  2. '*All-trials excluding E3311*': To exclude an outlier study (ECOG-ACRIN E3311 [NCT01898494]) that was entirely conducted in patients with human papillomavirus (HPV)-positive oropharyngeal cancer and used an older edition of the AJCC criteria to determine their tumor staging. Of note, patients with HPV-positive oropharyngeal cancer have been downstaged in the AJCC staging 8th ed due to having considerably more favorable prognosis[10]
  3. '*2005+ trials excluding E3311*': To further restrict to trials published in or after 2005, withthe assumption that these trials generally administered the currently recommended risk-adapted standard of care post-surgery

Results

- The SLR included 19 trials,[11-29] which were included in the base case (n=5 trials), as well as the all-trials (n=19), all-trials excluding E3311 (n=18), and 2005+ trials excluding E3311 (n=12) sensitivity analyses. Analysis results are presented in **Table 1**
- In the base case (**Figure 1A**; **Table 2**), a strong trial-level correlation (*R*=0.91) was observed between EFS and OS, while both the slope and the intercept met the surrogacy requirements. In the associated leave-one-out analysis, models were able to predict OS HRs with acceptable accuracy (**Figure 2**)
- In the *all-trials* scenario (**Figure 1B**), the slope was not statistically different from 0 and therefore did not meet the surrogacy requirements. The outlier observation at the bottom of the regression plot corresponded to the ECOG-ACRIN (E3311) trial, which was exclusively conducted in patients with HPV-positive oropharyngeal cancer
- In the sensitivity analyses that excluded ECOG-ACRIN (E3311), ie, *all-trials excluding E3311* (*R*=0.78; **Figure 1C**) and *2005+ trials excluding E3311* (*R*=0.76; **Figure 1D**), the estimated *R* values were more consistent with that of the base case, while both the slope and the intercept met the surrogacy requirements

Table 1. Estimated trial-level correlations between ln(HR)s of EFS and OS

Scenario	Description of included trials	Trials (comparisons)	R (95% CI)	Intercept (95% CI)	Slope (95% CI)
Base case	Neoadjuvant + adjuvant vs adjuvant (n=4)[11-14] Neoadjuvant vs surgery alone (n=1)[15]	5 (6)	0.91 (0.36, 0.99)	0.00 (-0.15, 0.15)	1.07 (0.38, 1.77)
All-trials	Neoadjuvant + adjuvant vs adjuvant (n=4)[11-14] Neoadjuvant vs surgery alone (n=1)[15] Neoadjuvant vs neoadjuvant (n=2)[16,17] Adjuvant vs adjuvant (n=11)[18-28] Adjuvant vs surgery alone (n=1)[29]	19 (21)	0.41 (-0.03, 0.71)	-0.05 (-0.24, 0.13)	0.79 (-0.05, 1.64)
All-trials excluding E3311	Neoadjuvant + adjuvant vs adjuvant (n=4)[11-14] Neoadjuvant vs surgery alone (n=1)[15] Neoadjuvant vs neoadjuvant (n=2)[16,17] Adjuvant vs adjuvant (n=10)[19-28] Adjuvant vs surgery alone (n=1)[29]	18 (20)	0.78 (0.52, 0.91)	-0.01 (-0.08, 0.05)	0.77 (0.47, 1.07)
2005+ trials excluding E3311	Neoadjuvant + adjuvant vs adjuvant (n=3)[12-14] Neoadjuvant vs surgery alone (n=1)[15] Neoadjuvant vs neoadjuvant (n=2)[16,17] Adjuvant vs adjuvant (n=6)[23-28]	12 (14)	0.76 (0.39, 0.92)	-0.02 (-0.10, 0.05)	0.71 (0.33, 1.09)

CI, confidence interval.

Table 2. Randomized controlled trials included in the base case

Trial	Design	Region	Interventions	N	Age, median (range)	Male, %	Tumor location, %
Paccagnella 1994 (NCT01542931)[11]	Phase 3	Italy	Cisplatin + 5-FU + surgery + RT	118	57.0 (31-69)	92.4	HP, 25.4; OP, 59.3; OC, 15.3
			Surgery + RT	119	56.0 (38-70)	90.8	HP, 28.6; OP, 54.6; OC, 16; PS, 0.8
IT-MATTERS (NCT01265849)[12]	Phase 3, OL	International (23 countries)	Leukocyte IL + CTX + indomethacin + zinc + surgery + RT ± cisplatin	395	Mean, 56.6	79.3	OC, 100
			Leukocyte IL + indomethacin + zinc + surgery + RT ± cisplatin	134			
			Surgery + RT ± cisplatin	394			
EAGLE (NCT01434394)[13]	Phase 3, OL	China	Cetuximab + cisplatin + docetaxel + surgery + RT	138	—	—	OC + OP, 100
			Surgery + RT	136			
Zhong 2013[14]	Phase 3, OL	China	Docetaxel + cisplatin + 5-FU + surgery + RT	128	56.0 (26-75)	68.8	OC, 100
			Surgery + RT	128	55.0 (29-74)	71.1	OC, 100
Chaukar 2022[15]	Phase 2, OL	India	Cisplatin + 5-FU + docetaxel + surgery	34	46.0 (27-62)	97.1	OC, 100
			Surgery	34	49.5 (27-68)	85.3	OC, 100

5-FU, fluorouracil; CTX, cyclophosphamide; HP, hypopharynx; IL, interleukin; OC, oral cavity; OL, open-label; OP, oropharynx; PS, paranasal sinuses.

Figure 1. Relationship between ln(HRs) of EFS and OS

(A) The base case (n=5), **(B)** All-trials (n=19), **(C)** All-trials excluding E3311 (n=18), and **(D)** 2005+ trials excluding E3311 (n=12).

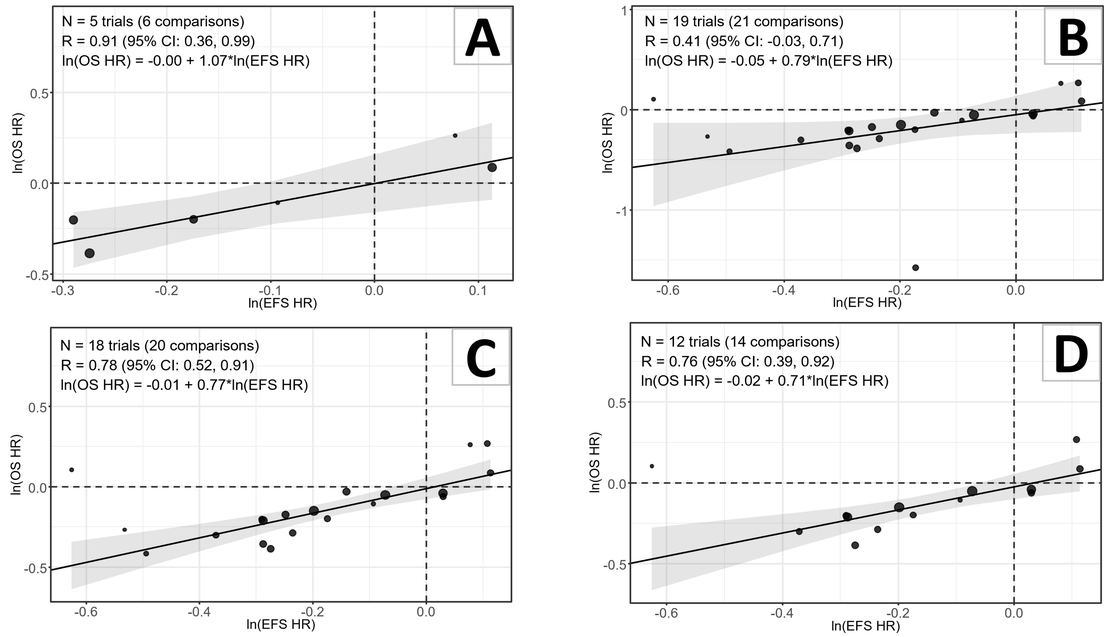
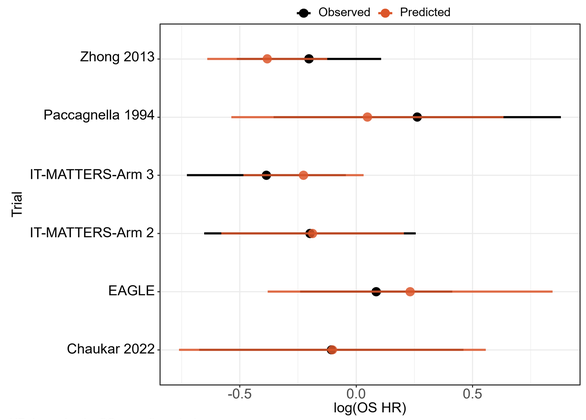


Figure 2. Leave-one-out validation analysis for the base case



HR, hazard ratio; OS, overall survival.

Discussion

- The surrogacy requirement for a non-zero slope was met in all but one scenario, which was due to an outlier trial that was exclusively conducted in a population with more favorable prognosis. Removing that trial in the subsequent analyses resulted in strong correlations (*R*≥0.75) that met the surrogacy requirements
- Our analysis, which was informed by a comprehensive SLR, followed the established methodology used in previous surrogacy models in the LA HNSCC population. Complementing findings from those analyses (*R* range, 0.79-0.93 in the broader population[8] and *R*=0.85 in the subgroup with unresectable tumors[9]), our results (*R* range, 0.76-0.91) show strong trial-level correlations between EFS and OS in the subgroup with resectable tumors
- Only 5 trials met the eligibility criteria of the base case analysis, which led to a wide 95% CI around the estimated R. Despite this, the leave-one-out analysis suggested that the model was robust and could reliably predict OS
- As individual patient-level data were not available for the included RCTs, there may have been differences in baseline study and population characteristics of the included RCTs that potentially modified the estimated correlations but could not be adjusted for

Conclusions

Based on the strong trial-level associations observed between EFS and OS, EFS is a valid surrogate for OS in newly diagnosed patients with resectable LA HNSCC.

References

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) - Head and Neck Cancers; Version 2.2025
2. Machiels J-P, et al. *Ann Oncol.* 2020;31(11):1462-1475.
3. Klochikhin A, et al. *Eur J Surg Oncol.* 2023;49(1):e9.
4. Patel SA, et al. *Cancer.* 2023;129(21):3381-3389.
5. Rosenberg AJ, et al. *JAMA Oncol.* 2024;10(7):923-931.
6. Driscoll JJ, et al. *Cancer J.* 2009;15(5):401-405.
7. Bujkiewicz S, et al. NICE DSU TSD 20. 2019. Available from: www.nicedsu.org.uk.
8. Michiels S, et al. *Lancet Oncol.* 2009;10(4):341-350.
9. Black CM, et al. *Front Oncol.* 2022;12:868490.
10. Amin MB, et al. *CA Cancer J Clin.* 2017 Mar;67(2):93-99.
11. Paccagnella A, et al. *J Nat Cancer Inst.* 1994;86(4):265-272.
12. Talor E, et al. *J Clin Oncol.* 2022;40(suppl 16):6032.
13. Zhong L-P, et al. *Ann Oncol.* 2022;33(suppl 7):S848-S849.
14. Zhong L-P, et al. *J Clin Oncol.* 2013;31(6):744-751.
15. Chaukar D, et al. *J Clin Oncol.* 2022;40(3):272-281.
16. Le et al. *Clin Cancer Res.* 2022;20:20.
17. Yi J, et al. *Oncotarget.* 2017;8(27):44842-44850.
18. Ferris RL, et al. *J Clin Oncol.* 2022;40(2):138-149.
19. Bernier J, et al. *N Engl J Med.* 2004;350(19):1945-1952.
20. Cooper JS, et al. *N Engl J Med.* 2004;350(19):1937-1944.
21. Laramore GE, et al. *Int J Radiat Oncol Biol Phys.* 1992;23(4):705-713.
22. Smid L, et al. *Int J Radiat Oncol Biol Phys.* 2003;56(4):1055-1062.
23. Harari PM, et al. *J Clin Oncol.* 2014;32(23):2486-2495.
24. Harrington K, et al. *J Clin Oncol.* 2015;33(35):4202-4209.
25. Kiyota N, et al. *J Clin Oncol.* 2022;40(18):1980-1990.
26. Laskar SG, et al. *Eur J Cancer.* 2023;181:179-187.
27. Machtay et al. *Int J Radiat Oncol Biol Phys.* 2023;117.4:e1.
28. Tobias JS, et al. *Lancet Oncol.* 2010;11(1):66-74.
29. Kokal WA, et al. *J Surg Oncol.* 1988;38(2):71-76.

Presented at ISPOR; Montreal, Canada; May 13-16, 2025.

https://bit.ly/4jw0udX