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Commentary

Commentary: Real-World Insights into Adjuvant Immunotherapy after Esophagectomy

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The management of esophageal cancer has undergone a paradigm shift with the introduction of immune checkpoint inhibitors (ICIs) in both palliative and adjuvant settings [1-4]. Especially in the adjuvant context, following the landmark results of the CheckMate-577 trial—which demonstrated a significant disease-free survival benefit with adjuvant nivolumab in patients with residual disease after neoadjuvant chemoradiotherapy (nCRT) and surgery—ICIs have rapidly been adopted into clinical practice [5]. However, the applicability of these findings to broader, real-world populations—often more heterogeneous and medically complex than trial cohorts—remains an area of ongoing investigation. Additionally, a fundamental limitation of the CheckMate-577 trial is its use of placebo as the comparator rather than an active therapeutic agent. Although the trial conclusively demonstrated that adjuvant nivolumab prolonged disease-free survival compared to observation, it left unanswered whether immunotherapy offers a true advantage over conventional adjuvant chemotherapy (AC), especially in patients with residual disease following nCRT.

Addressing this critical gap, the recent study by Liu et al. [6] provides valuable real-world data on the effectiveness of adjuvant immunotherapy (AI), comparing it not only with no adjuvant treatment but also with AC in patients with residual disease following nCRT and surgery. Building upon the CheckMate-577 trial, this retrospective 3-arm cohort study offers insights into treatment patterns and outcomes within clinical practice, which may diverge from randomized trials due to broader patient heterogeneity, varying pathological risk profiles, and differences in reimbursement or immunotherapy accessibility.

A notable strength of the study lies in its inclusion of clearly defined subgroups, encompassing both patients who met the eligibility criteria of the CheckMate-577 trial and those with pathological nodal positivity (ypN+). By capturing a broader, real-world population—including patients with squamous cell carcinoma, varying performance statuses, and diverse treatment histories—the study enhances the external validity of current evidence and accurately reflects actual clinical decision-making in heterogeneous contexts. Furthermore, the direct comparison between AI and AC addresses an unanswered clinical question, clarifying whether immunotherapy offers a genuine advantage over established active treatment strategies, rather than merely placebo.

However, the interpretation of these findings must be tempered by the study's limited sample size, particularly within the AI group, which included only 23 patients. In stark contrast, the CheckMate-577 trial enrolled 794 patients, providing robust statistical power to detect survival

differences. The relatively small number of patients receiving AI in the current study may have limited the ability to observe a significant survival benefit, especially within subgroup analyses such as those with ypN+ disease or those meeting CheckMate-577 eligibility. Additionally, treatment allocation in this retrospective design was non-randomized and subject to selection bias, introducing potential confounding factors that could obscure true treatment effects. Thus, while the study offers important real-world context, its findings should be interpreted cautiously and ideally validated in larger, prospective cohorts.

Ultimately, this study underscores the urgent need for prospective head-to-head trials comparing AC and AI, ideally stratified by histology, PD-L1 expression, and molecular biomarkers. Although not an nCRT-based trial like CheckMate-577, the ongoing JCOG2206 (SUNRISE) trial is poised to address several key limitations unresolved by CheckMate-577 [7]. This phase III randomized controlled trial compares adjuvant nivolumab, adjuvant S-1 chemotherapy, and surgery alone in patients with esophageal squamous cell carcinoma who fail to achieve a pathological complete response following neoadjuvant chemotherapy. Until results from such trials become available, multidisciplinary discussions and individualized treatment planning remain critical for optimizing outcomes in this challenging patient population.

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Conflict of interest

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