Retooling treatment in oligometastatic oesophageal cancer

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The existence of a true oligometastatic disease (OMD) state and its optimal management across solid tumours remains controversial.[1] As long-term survival improves in oesophageal squamous cell carcinoma (ESCC), primarily due to the use of immune checkpoint inhibitors (ICB), gauging the benefit of adding local treatment of metastases over systemic therapy becomes a clinically relevant question.[2,3]

Liu Q. and colleagues address the treatment of OMD in ESCC in the phase 2, randomised, ESO-Shanghai 13 trial. The study enrolled patients with low-volume metastatic (1-4 lesions) ESCC and a primary tumour controlled by chemoradiotherapy or surgery to receive either palliative systemic therapy alone or combined with local ablative approaches. The local therapy arm outperformed the systemic therapy arm meeting the primary endpoint of the study, progression-free survival (PFS) (stratified HR 0.26, 95% CI 0.16-0.42, p<0.0001), with no significant differences in severe adverse events or quality of life. Overall survival (OS), a secondary endpoint, was also improved but the benefit appeared attenuated in patients receiving immunotherapy. Predictably, the pattern of treatment failure was different with new lesions occurring more frequently in the local therapy arm. However, this group achieved good (83%) and durable local control (median not reached after a median follow-up time of 30.5 months), with around 30% of complete responses to ablative treatments.

Overall, the ESO-Shanghai 13 trial provides valuable preliminary evidence that upfront local treatment may benefit selected ESCC patients with metachronous OMD. That ablative treatments could improve the survival outcomes of patients with OMD is not new, following the results of both disease-agnostic and disease-specific trials, despite differences in OMD chronology, histology, and radiotherapy schemes.[4-8] Liu Q. and colleagues take a step further showing that this paradigm may be applicable also in a disease like ESCC with a renowned dismal prognosis and limited post-progression treatment options. With only a few patients receiving immunotherapy, this data requires validation in larger studies to understand if more active systemic strategies could overcome the benefits of local treatments of metastatic foci. Lower baseline tumour burden may anticipate greater benefit from ICB.[9,10] The identification and stratification by predictive biomarkers of response to systemic therapy would then help refine patients' selection.

Heterogeneity in inclusion criteria and treatment interventions made ESO-Shanghai 13 a pragmatic trial with timely alignment to changes in treatment practice. Yet, interpreting the outcomes of mixed cohorts poses substantial methodological challenges. First, the adoption of non-uniform staging techniques could introduce a selection bias. In the ESO-Shanghai 13 trial, a PET-FDG was performed in 38% versus 49% of patients in the local and systemic treatment arms, respectively. The final OS advantage in the experimental arm may be then diluted due to the inclusion of patients with undetected metastases. Second, despite incorporating the use of ICB, the lack of PD-L1 expression data reporting complicates result interpretation. Lastly, unblinded PFS assessment may be a weak primary endpoint in relatively small, open-label study, enrolling patients at different treatment stages. That metastatic sites treated with ablative treatments would not progress while those treated only with systemic therapy would become resistant is a self-fulfilling prophecy and does not clarify if a combined approach upfront can offer a meaningful survival benefit over salvage therapy, although the OS data are encouraging in this direction.

The definition of OMD remains largely arbitrary relying on expert panel consensus and the feasibility of approaching the disease with local ablative treatments.[11,12] Liu Q. et al. study provides supportive evidence

for the existence of an ESCC subset with a more indolent course. With most of the subjects having a controlled primary and an oligo recurrence, not surprisingly the survival outcomes exceeded those seen even in the control arms of the most recent randomised clinical trials.[2,3] This may explain why sequential treatment with consolidation with systemic therapy worked in this study. Further data is required to clarify if OMD could be truly described by a 'one-size-fits-all' definition or requires disease-specific adjustments where additional clinical and molecular factors can eventually sit in the equation. Risk stratification by treatment of the primary tumour, number, location and pattern of occurrence of the metastatic foci, PD-L1 expression, and the recognition of molecular features are key to ascertain the added benefit of local approaches and offer personalised treatment modalities (systemic only versus multimodal and sequential versus combination) to different subsets of patients with oligometastatic ESCC. Integrative results from translational analyses and international clinical collaborative efforts like the OMEC project are eagerly awaited to provide a comprehensive close-up of OMD in oesophagogastric tumours that sets a common stage for future prospective evidence.[13,14]

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