Oesophageal Cancer Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ctDNA = circulating tumour DNA; **GEJ** = gastro-oesophageal junction; **HER2** = human epidermal growth factor receptor 2; **HR** = hazard ratio; **MPR** = major pathologic response; **OS** = overall survival; **PD-(L)1** = programmed cell death protein – (ligand) 1; **PFS** = progression-free survival; **RFS** = recurrence-free survival; **SCC** = squamous cell carcinoma; **T-DXd** = trastuzumab deruxtecan.

Welcome to the 2nd issue of Oesophageal Cancer Research Review.

Results from the German ESOPEC trial, reported in *The New England Journal of Medicine*, support the use of perioperative chemotherapy - rather than neoadjuvant chemoradiotherapy - for resectable locally advanced oesophageal adenocarcinoma and may lead to changes in clinical practice, as well as national and international treatment guidelines. While adding radiation preoperatively to chemotherapy may no longer be the optimal strategy in this patient population, how newer multimodal therapeutic approaches such as adjuvant immunotherapy stack up remain to be seen. In other research the Japanese retrospective EN-DEAVOR study confirms the effectiveness of third-line trastuzumab deruxtecan (T-DXd) monotherapy in a real-world cohort of patients with advanced or recurrent human epidermal growth factor receptor 2 (HER2)-negative inoperable advanced or recurrent gastric or gastro-oesophageal junction (GEJ) adenocarcinoma; and an observational study in *Gastric Cancer* investigating prognostic and predictive factors for the effectiveness and safety of T-DXd suggests that optimal dosing to mitigate toxicity may need to consider tumour burden. Finally, longer-term follow-up data from ATTRACTION-4 confirms the previously reported benefit of adding nivolumab to oxaliplatin-based chemotherapy in previously untreated, inoperable gastric/GEJ cancer, finding a modest but statistically significant delay in disease progression, although no survival benefit.

We hope you enjoy this update in Oesophageal Cancer research, and we welcome your comments and feedback.

Kind Regards,

Dr James McCracken
james.mccracken@researchreview.com.au

Real-world effectiveness and safety of trastuzumab-deruxtecan in Japanese patients with HER2-positive advanced gastric cancer (EN-DEAVOR study)

Authors: Kawakami H et al., on behalf of EN-DEAVOR Study Group

Summary: This Japanese multi-centre retrospective study sought to elucidate the safety and effectiveness of later-line trastuzumab deruxtecan (T-DXd) monotherapy in adult patients at least 20 years of age with advanced or recurrent HER2-negative inoperable advanced or recurrent gastric or GEJ adenocarcinoma. Analysis included over 300 primarily older male patients who received single-agent T-DXd as a third-line therapy for disease that worsened after chemotherapy in the first year after it was approved for this indication in Japan (September 2020 – September 2021). Most patients were administered T-DXd doses of >5.4 –≤6.4 mg/kg and roughly two-thirds received less than seven treatment cycles (range, 1-24). The study found that 42.9% of patients with a target lesion responded to T-DXd monotherapy and reported a median overall survival (OS) of 8.9 months, a median progression-free survival (PFS) of 4.6 months and a median time to treatment failure of 3.9 months. The safety profile for T-DXd was consistent with previous reports, with severe (grade ≥ 3) adverse events relatively common (~50% of patients), eight cases of fatal adverse events and adverse events necessitating dose reductions, interruptions or treatment discontinuation in more than 60% of patients.

Comment: The DESTINY-Gastric01 study was a phase 2 study that demonstrated the benefit of T-DXd in HER2-positive gastric cancer as a third- or later-line therapy, with an improvement in objective response rate and disease-free survival in comparison to standard chemotherapy. This led to the registration and approval of T-DXd for metastatic HER2-positive gastric and GEJ carcinoma in Japan in 2020. This real-world analysis looked at similar outcomes to the phase 2 study within a population of 312 'real-world' patients. The study demonstrated a 42.9% response rate, and a disease control rate of 81.4%. Of note is the safety data, demonstrating that eight patients had treatment-related deaths, with five due to interstitial pneumonia, and the three others due to febrile neutropenia or pneumonia. Interestingly, the subgroup analysis found that patients who experienced adverse events that resulted in T-DXd dose adjustments had improved outcomes. Further, longer survival was reported in subgroups of patients with good performance status, higher HER2 protein expression, those who had undergone surgery of the primary lesions, and patients with a longer trastuzumab-free interval. Ultimately, this study demonstrates the benefit of T-DXd in a heavily pre-treated population, but also demonstrates that clinical characteristics are still important to consider, especially with palliative-intent therapy.

Reference: Gastric Cancer. 2025;28(1):51-61
Abstract

Perioperative chemotherapy or preoperative chemoradiotherapy in esophageal cancer

Authors: Hoeppner J et al.

Summary: Data from the phase 3 German ESOPEC trial demonstrates superior survival with perioperative chemotherapy versus neoadjuvant chemoradiotherapy in patients with resectable locally advanced oesophageal adenocarcinoma. A total of 438 adult patients with non-metastatic resectable stage cT1N+ or cT2-4aN0/+ oesophageal cancer enrolled to the trial were randomly assigned to receive FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) chemotherapy prior to and following surgical resection (n=221) or neoadjuvant chemoradiation with the CROSS protocol (41.4 Gy radiotherapy plus carboplatin and paclitaxel; n=217) followed by surgical resection. Significant OS and PFS benefits were found in the perioperative chemotherapy arm, eliciting a 29-month extension in median OS and conferring a 30% reduction in the risk of death, relative to the neoadjuvant combination chemoradiotherapy trial arm (median OS, 66 vs 37 months; three-year OS rates 57.4% vs 50.7%, hazard ratio [HR] 0.70). In addition, a 34% reduction in the risk of disease progression or death was found with perioperative chemotherapy compared to preoperative chemoradiotherapy (three-year PFS rate: 51.6% vs 35%; HR 0.66). Rates of severe and serious adverse events in the perioperative chemotherapy and neoadjuvant chemoradiotherapy cohorts were 58% vs 50% and 47.3% vs 41.8%, respectively.

Comment: This practice changing, phase 3 randomised study compared the two most common perioperative approaches for resectable oesophageal adenocarcinoma, comparing neoadjuvant/adjuvant FLOT chemotherapy alone with preoperative concurrent chemoradiotherapy. To be eligible, patients had to have either cT1N+, or cT2-4aN+, or cT2-4aN0 disease. The primary outcome was OS, with secondary endpoints including PFS and safety. The study enrolled 438 patients. The OS at three years was 57.4% in the FLOT group, and 50.7% in the CROSS group. PFS at three years was also significantly different, at 51.6% and 35.0%, respectively. Similar levels of grade 3 toxicities and adverse events were recorded in both groups. This study establishes FLOT as the standard of care for patients with resectable oesophageal adenocarcinoma.

Reference: N Engl J Med. 2025;392(4):323-35
Abstract

Major pathologic response as a prognostic surrogate in esophageal squamous cell carcinoma patients receiving neoadjuvant chemotherapy/chemoimmunotherapy

Authors: Hong Z et al.

Summary: A multi-centre cohort study from China concludes that major pathologic response (MPR) is prognostic in patients with oesophageal squamous cell carcinoma (SCC) undergoing neoadjuvant chemotherapy ± immunotherapy and may be a suitable surrogate endpoint to survival. Just over 300 adult patients who underwent oesophagectomy after a neoadjuvant platinum-based chemotherapy regimen with or without a programmed cell death protein 1 (PD-1) monoclonal antibody (tislelizumab, pembrolizumab, sintilimab, carrelizumab or toripalimab) in the six-year period spanning 2017 and 2022, inclusively, were included in the retrospective analysis. Evaluation of disease response after neoadjuvant therapy and surgery revealed that roughly one-third of patients attained an MPR (defined as ≤10% viable tumour cells in the resected primary tumour specimen), including 13.77% who achieved a pathological complete response. The study found that regardless of whether patients received chemotherapy or chemoimmunotherapy prior to surgery, those who attained an MPR had superior outcomes, with longer recurrence-free survival (RFS), locoregional recurrence-free survival and distant metastasis-free survival compared to patients who did not attain an MPR. Furthermore, the study found that MPR independently associated with RFS and predicted survival endpoints as accurately as T and N stage.

Comment: This retrospective, multicentre cohort study looked at the prognostic impact of patients with oesophageal SCC who had neoadjuvant systemic therapy with chemotherapy or chemotherapy plus immunotherapy. The study used RFS as its primary endpoint. The study enrolled 305 patients with oesophageal SCC, with approximately one-third achieving an MPR, including 13.8% who attained a complete pathological response. Interestingly, MPR is used as a surrogate endpoint, with patients who achieved this having a longer RFS, and distant metastasis-free survival.

Reference: Eur J Surg Oncol. 2025;51(2):109500
Abstract

Multimodality therapy and survival outcomes in resectable primary small cell carcinoma of the esophagus: A multicenter retrospective study

Authors: Xu L et al.

Summary: This Chinese multicentre retrospective study aimed to elucidate the optimal treatment strategy for resectable limited-disease stage primary small cell carcinoma of the oesophagus. Analysis was based on data from 352 adult patients with resected stage cT1-3N0/1 disease without distant metastases. Kaplan–Meier estimations of OS showed that patients with early-stage limited disease without lymph node involvement (cT1-2N0M0) had better survival outcomes with the addition of adjuvant therapy to surgery versus surgery alone (OS, 44 vs 33 months; five-year OS rate, 32.8% vs 19.2%). In contrast, patients with late-stage disease or with lymph node involvement (cT3N0M0/T1-3N1M0) benefited more from surgery combined with neoadjuvant therapy versus adjuvant therapy or surgery alone (OS, 36 vs 24 vs 20 months). The associations between improved OS and neoadjuvant therapy in early-stage disease or adjuvant therapy for later-stage diseases were confirmed on multivariable Cox analysis.

Comment: Primary small cell carcinoma of the oesophagus is an uncommon, but potentially lethal malignancy. This retrospective, multicentre Chinese study looked at the benefit of systemic therapy, on top of surgery, in patients with primary small cell of the oesophagus. A total of 352 patients who had undergone a resection were included in the analysis. The study found an OS benefit of adjuvant chemotherapy in patients with early-stage disease (cT1-2, N0), with a five-year OS of 32.8% versus 19.2% (p=0.035). Further, a multivariable cox survival analysis revealed an independent correlation between surgery, adjuvant therapy and improved OS (HR 0.529). For stage cT3-T1-3N1 disease, patients who received neoadjuvant therapy followed by surgery had superior long-term survival compared with those who received surgery combined with adjuvant therapy and those who received surgery alone, with five-year OS of 27.2%, 9.5% and 0%, respectively. Further analysis with multivariable Cox survival clarified the strength of these relationships (HR 0.384 & HR=0.550). This study demonstrates the importance of careful staging of oesophageal malignancies, but also the benefit of systemic therapy in primary small cell carcinoma of the oesophagus.

Reference: Ann Surg Oncol. 2025;32(2):848-59
Abstract

Impact of lymphatic and venous invasion patterns on postoperative prognosis and distant metastasis in esophageal squamous cell carcinoma after preoperative chemotherapy

Authors: Kajiyama D et al.

Summary: Aggressive adjuvant therapy may be necessary for patients with resected oesophageal SCC tumours positive for lymphatic and/or venous invasion after neoadjuvant chemotherapy, according to data from this Japanese retrospective study that reports that they are both unfavourable prognostic factors. The study evaluated the presence of venous invasion in resected oesophageal SCC specimens from 427 patients who had undergone preoperative chemotherapy and analysed outcomes according to the presence/absence of lymph node involvement. Results showed that venous invasion negatively correlated with postoperative prognosis - adversely impacting OS, RFS and significantly elevating the risk of distant metastases – while the presence of both lymphatic invasion and venous invasion was associated with the worst postoperative outcomes and the highest risk of developing distant metastases.

Comment: The prognosis of oesophageal cancer post neoadjuvant therapy is difficult to quantify. This retrospective study analysed 427 patients, with oesophageal SCC who had undergone resection post neoadjuvant chemotherapy. The study examined patterns of lymphovascular invasion, with the primary endpoints of OS, as well as recurrence-free and distant metastasis-free survival. Perhaps unsurprisingly, the study demonstrated that patients with lymphovascular invasion had worse OS (HR 4.23), RFS (HR 3.38) and distant metastasis-free survival (HR 4.59) in comparison to those without. Even in those who achieved ypN0, venous invasion was the only independent risk factor for distant metastasis-free survival (HR 5.33). The study also showed that venous invasion alone correlated with significantly poorer outcomes. Consequently, this study identifies the poor prognosis in patients with lymphovascular invasion after neoadjuvant therapy. Identifying this may permit for escalation of adjuvant therapy in this cohort.

Reference: Ann Surg Oncol. 2025;32(2):860-71
Abstract

Prognostic and predictive factors for the efficacy and safety of trastuzumab deruxtecan in HER2-positive gastric or gastroesophageal junction cancer

Authors: Jubashi A et al.

Summary: Jubashi et al conducted a retrospective observational study of patients with HER2-positive gastric or GEJ cancer treated with T-DXd after a trastuzumab-containing regimen at the National Cancer Centre Hospital East in Chiba, Japan to identify factors predictive for effectiveness and associated with an increased likelihood of toxicity. Analysis included data from 101 patients with HER2-positive unresectable or recurrent disease who received later-line T-DXd monotherapy at a dose of 5.4 or 6.4 mg/kg prior to September 2023. Effectiveness results showed that just over half of patients achieved at least a partial response to T-DXd (overall response rate, 54.3%). The median PFS and OS of the study cohort were 5.4 and 11.4 months, respectively. An Eastern Cooperative Oncology Group (ECOG) performance status of one or higher, the presence of primary lesion and peritoneal metastasis were all identified as adversely impacting both OS and PFS. No association between T-DXd dose and effectiveness was found. Interstitial lung disease was a relatively common adverse event, experienced by 14.9% of patients, and was more common in patients treated at the higher dose of T-DXd and in patients with a lower tumour burden. The authors commented that elucidation of optimal T-DXd dosing according to tumour burden may mitigate toxicity without compromising outcomes.

Comment: T-DXd has been the standard of care for third-line HER2-positive for gastric and GOJ adenocarcinoma since 2020, after the results of the phase 2 DESTINY-Gastric02 trial demonstrated superiority to the standard of care. This 'real-world' study was a single institution retrospective cohort study of 101 patients treated with T-DXd. The study identified poorer performance status, presence of the primary lesion, peritoneal metastasis, but not the initial T-DXd dose as being associated with a shorter PFS and OS. They demonstrated an interstitial lung disease rate of 14.9%, with the majority of these being grade 1 or 2, although it was the most common reason for discontinuation. The study also interestingly demonstrated that interstitial lung disease was more common in patients with their primary tumour, than without (34.5% vs 6.9%; p=0.001). Of note is that there were no grade 5 interstitial lung disease toxicities. The most common grade 3-4 toxicities were haematological with 28.7% of patients developing neutropenia. This study is reassuring to replicate the safety of T-DXd in a standard, non-trial population. However, it does reinforce the need to carefully monitor for interstitial lung disease, given it is the most common reason for discontinuation. The difference in interstitial lung disease rates according to tumour burden in an exploratory analysis is food for thought

Reference: Gastric Cancer. 2025;28(1):63-73
Abstract

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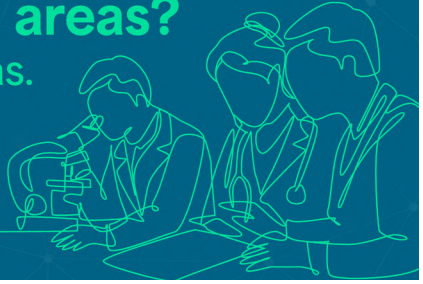
Independent commentary by Dr James McCracken

Dr James McCracken is a medical oncologist at Epworth Freemasons and the Peter MacCallum Cancer Centre. He has expertise in the management and care of patients with colorectal, breast, gastrointestinal and lung cancers. He has a strong clinical interest in young patients with colorectal cancer. Dr McCracken completed his training through the Victorian Medical Oncology Training Programme, before completing a 2-year fellowship in Breast and Gastrointestinal Oncology at the Olivia Newton-John Cancer Research Institute at the Austin Hospital. He is the Victorian representative to the Young Oncology Group of Australia (YOGA), whilst also being a member of the Medical Oncology Group of Australia (MOGA), the European Society of Medical Oncology (ESMO), and the American Society of Clinical Oncology (ASCO). Outside of work, he is a keen cyclist, Hawthorn tragic, Pinot enthusiast, husband and father.



Circulating tumor DNA predicts recurrence and survival in patients with resectable gastric and gastroesophageal junction cancer

Authors: Iden C et al.

Summary: Longitudinal analysis of circulating tumour DNA (ctDNA) in patients with operable gastric or GEJ cancer undergoing curative-intent therapy may allow for enhanced patient risk stratification and prognostication, according to results from this prospective study. Researchers from Denmark quantified ctDNA levels in plasma samples collected from 86 patients at baseline, after completion of the first cycle of neoadjuvant chemotherapy, after neoadjuvant chemotherapy and after surgical resection of the tumour using a droplet digital polymerase chain reaction test to evaluate three tumour-specific DNA methylation markers (TriMeth). The proportion of patients with detectable ctDNA dropped over the course of treatment, from more than half at baseline (56%) to 25% after neoadjuvant chemotherapy and 15% after surgery. At all time points evaluated, the presence of detectable ctDNA was independently associated with an unfavourable prognosis with inferior OS and RFS (after surgery, OS HR 6.37).

Comment: The presence of ctDNA has been well established as a risk factor for recurrent disease. This study looked at the presence of ctDNA using a droplet digital polymerase chain reaction panel-based approach at multiple time points in patients receiving neoadjuvant treatment and resection for gastric or GOJ carcinoma. The study enrolled 86 patients, taking more than 200 plasma samples at various timepoints. The study identified the presence of ctDNA in 56% of patients at baseline, decreasing to 37% after the first cycle of chemotherapy, 25% after the completion of systemic therapy and then 15% after surgical resection. The presence of ctDNA after one cycle of systemic therapy was associated with poorer RFS (HR 2.54) and OS (HR 2.23). This risk was amplified in those who were postoperatively ctDNA positive (RFS: HR 6.22; OS; HR 6.37). This study adds to the literature of the utility of ctDNA that identifies patients treated with curative intent, but of poor prognosis, that may permit not only de-escalation, but also escalation of therapy in the adjuvant setting.

Reference: Gastric Cancer. 2025;28(1):83-95
Abstract

Nivolumab plus chemotherapy in patients with HER2-negative, previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer

Authors: Boku N et al.

Summary: Three-year follow-up of the ATTRACTION-4 randomised, double-blind, placebo-controlled, phase 3 trial confirms the previously reported PFS benefit of adding nivolumab to front-line chemotherapy for unresectable or recurrent HER2-negative gastric/GEJ cancer. Over 700 adult patients at least 20 years old with previously untreated disease were accrued from sites in Japan, South Korea and Taiwan and administered oxaliplatin-based chemotherapy (physician's choice of SOX [oral S-1 + oxaliplatin] or CAPOX [capecitabine + oxaliplatin) ± nivolumab (360 mg every three weeks). Tumour PD-L1 expression was not a trial entry criterium. Data from a prespecified interim analysis with a median follow-up approaching one year revealed a two-month extension in median PFS with the addition of nivolumab that conferred a 32% reduced risk of disease progression compared to front-line chemotherapy alone (HR 0.68). Now, updated efficacy data at three-year follow-up demonstrates a durable improvement in PFS with the chemotherapy plus nivolumab regimen (10.94 vs 8.48 months; HR 0.67). Consistent with previous analyses no survival benefit was found in the intervention arm although the authors reported numerically better HRs in landmark OS analyses over time. No novel major late-onset adverse events were detected with longer follow-up.

Comment: Nivolumab in combination with systemic therapy is the standard of care as first-line palliative-intent systemic therapy for patients with metastatic/unresectable HER2-negative gastric/GOJ adenocarcinoma, as defined in the phase 3 CheckMate 649 study. This study is a phase 3, double-blind trial, looking at the addition of nivolumab to standard of care chemotherapy (SOX and CAPOX) as first-line therapy in an Asian population. The study included 359 patients in the nivolumab group and 358 in the placebo group. The study demonstrated longer PFS in the experimental group, being 10.94 months, in contrast to 8.48 months in the control arm. However, the OS did not differ between the two groups (17.45 vs 17.15 months). Of note is that 80% of patients who achieved a complete response on the experimental arm were alive at three years. When compared to the results of the CheckMate 649 study, the PFS and OS in this study are both numerically longer in each arm, with the PFS of the CheckMate study showing a PFS of 8.3 months in the nivolumab arm, and 6.1 months in the control arm. OS was 14.4 months in the nivolumab arm, and 11.1 in the control arm, respectively. Obviously, there are numerous caveats when doing cross trial comparisons, especially the differing characteristics of the trial populations, pharmacogenomic impact of differing ethnicities.

Reference: Gastric Cancer. 2024;27(6):1287-301
Abstract

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