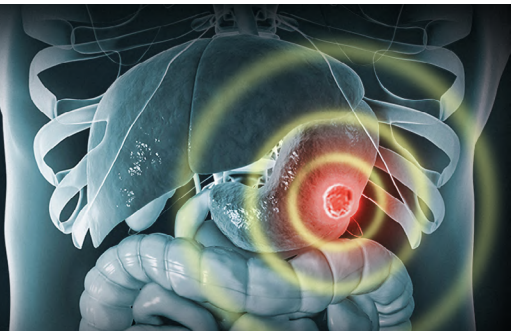
Upper GI Cancer Research Review™



Making Education Easy

Issue 12 - 2025

In this issue:

Abbreviations used in this issue:

5FU = fluoropyrimidine; **(a)HR** = (adjusted) hazard ratio; **CR** = complete response; **DFS** = disease-free survival; **dMMR** = deficient mismatch repair; **ECOG** = Eastern Cooperative Oncology Group; **GI** = gastrointestinal; **(m)FOLFIRINOX** = combination leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, oxaliplatin (in modified dosing); **MSI-H** = microsatellite instability-high; **NE** = not estimable; **NLR** = neutrophil-to-lymphocyte ratio; **ORR** = overall response rate; **OS** = overall survival; **PERT** = pancreatic enzyme replacement therapy; **PNI** = perineural invasion; **QOL** = quality of life; **RCT** = randomised controlled trial.

Welcome to issue 12 of Upper GI Cancer Research Review.

We begin with the phase 3 SANO trial, which found that active surveillance was non-inferior to oesophagectomy in patients with locally advanced oesophageal cancer who achieved a clinical CR after neoadjuvant chemoradiotherapy, with regard to 2-year OS. An interesting retrospective study from the US shows that pancreatic enzyme replacement therapy is associated with improvements in OS and nutrition among patients with advanced pancreatic ductal adenocarcinoma and exocrine pancreatic insufficiency. We also include a systematic review and meta-analysis which revealed that patients with resectable dMMR/MSI-H gastric cancer experienced no benefit in OS or DFS with perioperative chemotherapy versus surgery alone; this suggests that these patients can be spared from perioperative regimens, and future research is warranted on the efficacy of perioperative immunotherapy for this patient population. Independent commentary has been provided by Dr Pei Ding.

We hope you find this update in upper GI research informative for your clinical practice, and we encourage you to send in your thoughts and comments.

Kind Regards,

Dr Janette Tenne
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Neoadjuvant chemoradiotherapy followed by active surveillance versus standard surgery for oesophageal cancer (SANO trial)

Authors: van der Wilk B et al., for the SANO Study Group

Summary: SANO was a multicentre, stepped-wedge, cluster-randomised, non-inferiority, phase 3 trial which examined whether active surveillance was an acceptable alternative to surgery for patients with locally advanced oesophageal cancer with a clinical CR after neoadjuvant chemoradiotherapy. Eligible patients (n=309; 78% male) across 12 hospitals in The Netherlands underwent active surveillance (n=198) or oesophagectomy (n=111). At a follow-up of 38 months, after modified ITT analysis, active surveillance was non-inferior to oesophagectomy with regard to 2-year OS (primary endpoint; 74% vs. 71%; one-sided 95% boundary: 7% lower). Following standard surgery, or postponed surgery after active surveillance, there were similar rates of post-operative complications and post-operative mortality. It was noted that extended follow-up is warranted to assess the long-term efficacy of active surveillance.

Comment: This well conducted multicentre, randomised, non-inferiority phase 3 study is highly interesting and relevant in the era of neoadjuvant treatment. With the improvements in neoadjuvant strategies across many solid tumours, one pertinent question is whether patients should be spared from having surgery. The SANO trial was conducted to evaluate whether active surveillance could be an alternative to surgery after neoadjuvant chemoradiotherapy for patients with early-stage oesophageal cancer who had completed neoadjuvant chemoradiotherapy with a clinical CR (as per PET-CT and endoscopic biopsy). OS and QOL were the endpoints for this study, which are highly appropriate. The study showed that active surveillance is non-inferior to surgery for patients with a complete CR-post chemoradiotherapy (median OS 43 vs. 53 months). The authors concluded that active surveillance is a reasonable approach in this group of patients, as when compared with immediate surgery, as it will not compromise OS. Patients who did not have surgery reported less treatment-related complications and improved QOL. Whether this approach will be widely accepted remains to be seen, but active surveillance and reserving surgery for patients with residual or recurrent disease may be a viable and acceptable option, and should be discussed with patients post-chemoradiotherapy.

Reference: Lancet Oncol. 2025;26(4):425-36
Abstract

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Adjuvant chemotherapy after resection of localized pancreatic adenocarcinoma following preoperative FOLFIRINOX

Authors: Stoop TF et al., for the Scientific Committee of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) and International Collaboration on Advanced Pancreatic Cancer

Summary: It is unclear how adjuvant chemotherapy after resection of pancreatic adenocarcinoma and pre-operative (m)FOLFIRINOX chemotherapy impacts on OS, as previous studies have not taken into account the number of pre-operative and adjuvant chemotherapy cycles that patients have received. This retrospective cohort study evaluated the OS of 767 patients (median age 62 years; 52.7% male) with localised pancreatic adenocarcinoma treated with 2–11 cycles of pre-operative (m)FOLFIRINOX before resection between 2010–18, throughout 20 countries worldwide. Patients who received adjuvant chemotherapy experienced prolonged OS (HR 0.66; 95% CI 0.49–0.87). Analyses revealed that this OS benefit was lower among patients who received ≥8 cycles of pre-operative (m)FOLFIRINOX, those with ypN0 disease and those with a radiological response. In comparison to no adjuvant chemotherapy, OS was improved with both adjuvant (m)FOLFIRINOX (HR 0.57; 95% CI 0.40–0.80) and other multi-agent adjuvant regimens (HR 0.61; 95% CI 0.41–0.92); however, single-agent adjuvant chemotherapy was not associated with improved OS (HR 0.75; 95% CI 0.55–1.03).

Comment: This retrospective study investigated the role of adjuvant chemotherapy in resected pancreatic cancer previously treated with neoadjuvant FOLFIRINOX chemotherapy. It showed that patients who were treated with adjuvant (m)FOLFIRINOX or other multi-agent chemotherapy after surgery had better OS than those who did not receive adjuvant chemotherapy. Association does not imply causation. The results of this retrospective study need to be interpreted with caution. Multiple issues which could impact on whether a patient receives adjuvant chemotherapy will have likely caused selection bias, and therefore improved survival in the adjuvant chemotherapy group. The study also showed that the association of adjuvant chemotherapy with OS is weaker in patients who received ≥8 cycles of pre-operative chemotherapy, and those with radiological response or node-negative disease. The role and benefits of adjuvant chemotherapy in different subgroups of patients should be investigated further in prospective studies.

Reference: JAMA Oncol. 2025;11(3):276-87
Abstract

Pancreatic enzyme replacement therapy in advanced adenocarcinoma of the pancreas improved overall survival

Authors: Picozzi VJ et al.

Summary: The aim of this retrospective, single institution study from the US was to assess the impact of pancreatic enzyme replacement therapy (PERT) on weight, nutrition status and OS in patients with advanced pancreatic ductal adenocarcinoma. The analysis included 501 patients with advanced pancreatic ductal adenocarcinoma and exocrine pancreatic insufficiency treated with first-line chemotherapy between 2010–19, of whom 38% received PERT. Patients administered PERT achieved significantly longer OS those who did not receive PERT (17.1 vs. 12.5 months, respectively; p=0.001; aHR 0.73; p<0.001), with significantly less weight loss (-1.5 vs. -2.5kg; p=0.04), smaller reductions in prognostic nutrition index scores (-1.9 vs. -3.0; p=0.01) and greater decreases in Patient-Generated Subjective Global Assessment scores (-8.4 vs. -6.0; p=0.02).

Comment: There are now many studies (including small prospective RCTs) looking at the use of PERT in patients with advanced pancreatic cancer, which have all shown the benefits of PERT. This single institution retrospective study has not added too much to the current knowledge, due to the limitations of retrospective studies including selective bias, which has not been accounted for in this study. Although the adjusted OS analysis included several variables (age, race, sex, ECOG, PNI, NLR and chemotherapy factors), factors such as disease burden, comorbidities and other tumour factors which may have contributed to weight loss and nutrition index were not taken into account. PERT has its role in patients with pancreatic exocrine insufficiency in advanced pancreatic cancer, but judicious use is necessary due to the possible side effects (GI-related) and costs associated. It will also be interesting to know whether the benefit of PERT includes an improvement in QOL, which should be taken into account with this group of patients with guarded prognosis.

Reference: Oncologist. 2025;30(4):oyaf014
Abstract

Pancreatic adenocarcinoma: long-term outcomes of adjuvant therapy in the ESPAC4 phase III trial

Authors: Palmer DH et al.

Summary: After an initial follow-up of 43.2 months, the ESPAC4 trial showed that patients with pancreatic adenocarcinoma achieved longer OS with gemcitabine plus capecitabine versus gemcitabine monotherapy. This article describes the updated survival outcomes after a longer follow-up of 104 months. In the updated analysis, patients treated with gemcitabine plus capecitabine continued to achieve longer OS than those who received gemcitabine alone (31.6 vs. 28.4 months; HR 0.83; 95% CI 0.71–0.98; p=0.031), and this OS advantage was even more pronounced among R0 patients (49.9 vs. 32.2 months; HR 0.63; 95% CI 0.47–0.84; p=0.002) and those with lymph-node negative disease (5-year OS 59% vs. 53%; HR 0.63; 95% CI 0.41–0.98); no benefit was reported among those with positive lymph nodes (p=0.225). The benefit in OS was also seen among the subgroup of patients who were ineligible for mFOLFIRINOX in PRODIGE24 (26.4%), who achieved significantly longer OS with gemcitabine plus capecitabine than with gemcitabine alone (25.9 vs. 20.7 months; HR 0.71; 95% CI 0.52–0.98; p=0.038).

Comment: This is an update on survival from a longer follow-up of the ESPAC4 trial, that compared adjuvant gemcitabine plus capecitabine versus adjuvant gemcitabine. The analysis showed that gemcitabine plus capecitabine is more efficacious versus gemcitabine in patients who are lymph node-negative. mFOLFIRINOX is a more intensive regimen which was found to be efficacious than gemcitabine in the PRODIGE24 trial. This study also looked at a subgroup of ESPAC4 patients (26.4%) who were not eligible for mFOLFIRINOX, and showed that gemcitabine plus capecitabine is a good option for this group of patients, as the OS advantage was retained.

Reference: J Clin Oncol. 2025;43(10):1240-53
Abstract

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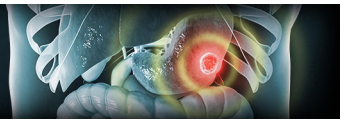

Perioperative chemotherapy for gastric cancer patients with microsatellite instability or deficient mismatch repair

Authors: Liu B et al.

Summary: This systematic review and meta-analysis of 22 studies (n=1600) investigated the efficacy of perioperative chemotherapy versus surgery alone in resectable dMMR/MSI-H gastric cancer. The analyses revealed that perioperative chemotherapy did not significantly alter OS (HR 0.85; 95% CI 0.58–1.26) or DFS (HR 0.77; 95% CI 0.53–1.12). Subgroup analysis suggested that adjuvant chemotherapy was associated with improved DFS (HR 0.64; 95% CI 0.43–0.96), although this association did not reach statistical significance in multivariate assessments. Neoadjuvant chemotherapy had no significant associations with OS or DFS. Furthermore, stage stratification analysis found no survival advantages with adjuvant chemotherapy in stage II or stage III disease.

Comment: This meta-analysis included 22 studies, but only 3 post-hoc analyses of RCTs, with the rest being retrospective observational studies. A total 1600 patients with dMMR/MSI-H resected gastric cancer were included. As expected, the study did not find any improvement in DFS or OS with perioperative chemotherapy. The finding suggests that perioperative chemotherapy can be spared in this group of patients, and future studies should focus on the role of perioperative immunotherapy in gastric cancer patients with dMMR or MSI-H disease.

Reference: Cancer. 2025;131(7):e35831
Abstract

Efficacy and safety of larotrectinib in patients with TRK fusion gastrointestinal cancer

Authors: Changsong Q et al.

Summary: These researchers assessed the efficacy and safety of larotrectinib (first-in-class, highly selective TRK inhibitor) in patients with TRK fusion GI cancer from the NAVIGATE trial. The tumour types in the 44 enrolled patients included colorectal (n=26; 62% with MSI-H status), pancreatic (n=7), cholangiocarcinoma (n=4), gastric (n=3), and one each of oesophageal, hepatic, appendiceal and duodenal cancers. In all evaluable patients, and in those with colorectal cancer, the ORRs were 28% (95% CI 15–44) and 44% (95% CI 24–65), respectively, while the median durations of response were 27 months (95% CI 6–NE) and 27 months (95% CI 6–NE), median PFS 6 months (95% CI 5–9) and 7 months (95% CI 6–NE), and median OS 13 months (95% CI 7–29) and 29 months (95% CI 7–NE). A total of seven patients (16%) experienced grade 3-4 AEs. It was concluded that larotrectinib was associated with prolonged and durable survival in patients with TRK fusion GI cancer, with a tolerable safety profile.

Comment: This paper reported on patients with TRK fusion GI cancer from a larger NAVIGATE trial, which included 44 patients. The ORR was 28%, which is lower than what is expected for oncogenic-driven solid tumours and other TRK fusion solid tumours. This may reflect a genomically heterogeneous population of patients who had received multiple lines of prior therapy, and some patients may have other driver mutations, which is not reported in this study. The safety profile of larotrectinib is similar to other studies, and AEs were mainly grade 1–2. It is also very interesting to see from this study that there is a response in patients with MSI-high colorectal cancer. Patients with metastatic GI cancers should have access to NGS panel testing which includes *NTRK* gene fusions.

Reference: Eur J Cancer. 2025;220:115338
Abstract

Adjuvant chemotherapy compared to observation in resected biliary tract cancers

Authors: Akkus E & Lamarca A

Summary: In this survival meta-analysis of four phase 3 RCTs (BILCAP, ASCOT, BCAT, PRODIGE-12; total n=1308), researchers compared the RFS and OS of patients with resected biliary tract cancers receiving adjuvant chemotherapy versus observation. Patients administered adjuvant 5FU-based chemotherapy achieved improved RFS (HR 0.80; 95% CI 0.68–0.95; p=0.012) and OS (HR 0.78; 95% CI 0.65–0.94; p=0.009) versus observation, and these survival benefits were most pronounced in the first 2 years (RFS HR 0.67; 95% CI 0.57–0.79; p<0.001; OS HR 0.61; 95% CI 0.59–0.64; p<0.001). In contrast, there were no benefits in RFS or OS with gemcitabine-based chemotherapy compared to observation (RFS HR 0.90; 95% CI 0.70–1.15; p=0.428; OS HR 1.03; 95% CI 0.78–1.36; p=0.794). In the first 2 years, gemcitabine-based chemotherapy appeared to have an adverse impact on OS (HR 1.22; 95% CI 1.14–1.31).

Comment: This meta-analysis showed that adjuvant 5FU-based chemotherapy provided RFS and OS benefits in the short- and long-term for resected biliary tract cancers. Interestingly, gemcitabine-based chemotherapy did not benefit RFS or OS, and possibly worsened OS. This meta-analysis also showed that the main benefits of adjuvant chemotherapy were in the first 2 years, suggesting that adjuvant chemotherapy delays recurrences, rather than providing significant curative benefits.

Reference: Eur J Cancer. 2025;220:115342
Abstract

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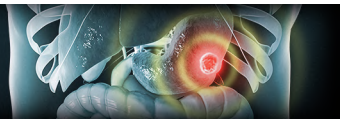

Determinants of response to sequential pembrolizumab with trastuzumab plus platinum/5-FU in HER2-positive gastric cancer

Authors: Lim SH et al.

Summary: This phase 2 chemoimmunotherapy trial evaluated the determinants of response to 5-FU/platinum/trastuzumab in patients with advanced HER2-positive gastroesophageal cancer, with the addition of pembrolizumab in cycle 2. Eligible treatment-naïve patients (n=16) underwent a baseline biopsy, and were administered a single dose of 5-FU/platinum with trastuzumab. After a second biopsy, pembrolizumab was added, followed by 6 cycles and a third biopsy. The ORR (primary endpoint) was 69%, with a median PFS of 11.9 months. Analyses of pre-treatment and on-treatment samples revealed that HER2+ tumour beds experienced NK cell infiltration, which was induced by early trastuzumab. In addition, macrophages showed increases in Fc receptor gamma III expression, indicating that trastuzumab induced Fc receptor-mediated antibody-dependent cytotoxicity. When pembrolizumab was added, these beneficial remodelling responses were enhanced, predominantly among PD-L1-positive samples. PD-L1-negative tumours had lower antibody-dependent cellular cytotoxicity responses.

Comment: This is an investigator-initiated study in Korea, aiming to understand the mechanisms behind treatment response and resistance for patients with HER2-positive gastric cancer using serial biopsies. I am highly impressed by the willingness of the patients with metastatic HER2-positive gastric cancer to undergo three different endoscopic biopsies to the same primary site: one at baseline, one after cycle 1 of treatment (chemotherapy/trastuzumab), and one after 6 cycles of treatment with pembrolizumab added to chemotherapy/trastuzumab from cycle 2. Serial biopsies proved intratumoural heterogeneity – there are distinct spatially organised biologies in HER2-positive/-negative and PD-L1-positive/-negative regions, which may explain treatment response or resistance. Authors also reported the factors that distinguish responders from non-responders: TGF- β signalling, HER2 expression level, PD-L1 combined positive score and CXCL13 expression in immune cells were associated with treatment response. The full manuscript is available online.

Reference: Clin Cancer Res. 2025;31(8):1476-90
Abstract

Adjuvant cytotoxic chemotherapy may not be associated with a survival advantage for resected intrahepatic cholangiocarcinoma

Authors: Sharib J et al.

Summary: These US investigators conducted a retrospective analysis of a bi-institutional dataset and the National Cancer Database (NCDB) to examine the impacts of adjuvant chemotherapy versus observation in patients with resected intrahepatic cholangiocarcinoma. Within the bi-national dataset (n=347; 43% received adjuvant cytotoxic chemotherapy), there was no significant benefit in OS with adjuvant chemotherapy versus observation (42 vs. 49 months; p=0.13), and this finding remained consistent among those administered capecitabine (p=0.09) and in a risk-adjusted multivariate analysis. Patients who received adjuvant chemotherapy also experienced poorer RFS than those in the observation group (p=0.04), and most recurrences occurred in the liver. The analysis of patients within the NCDB revealed similar findings, with no significant difference in OS between adjuvant chemotherapy and observation (49 vs. 57 months; p=0.1).

Comment: Intrahepatic cholangiocarcinoma is rare, and therefore there are limited evidence-based guidelines regarding the use of adjuvant treatment. There are conflicting data from RCTs regarding the benefits of adjuvant chemotherapy for resected biliary tract cancer. This retrospective study with 347 patients who underwent resection for intrahepatic cholangiocarcinoma showed that OS was similar between the groups that received adjuvant chemotherapy versus observation. Interestingly, RFS was worse in the group who received adjuvant chemotherapy. Better studies will help to build evidence in this area to help with clinical decision-making. Select patients with poor prognostic factors such as positive lymph nodes, advanced T stage or positive surgical margins may derive benefit from adjuvant chemotherapy.

Reference: Ann Surg Oncol. 2025;32(4):2456-66
Abstract

Impact of routine follow-ups after curative gastrectomy in elderly patients with early gastric cancer

Authors: Yoo J et al.

Summary: To explore whether routine follow-up strategies should apply to elderly patients with early gastric cancer (a group with a low risk of recurrence and a relatively shorter life expectancy), this retrospective analysis examined the effects of post-operative follow-ups among patients aged ≥75 years who underwent curative gastrectomy for stage I gastric cancer. Between 2007–16, 385 patients underwent surgery, of whom 78.2% received routine follow-up examinations (endoscopy, CT, blood tests), while 21.8% did not. After propensity score matching, there was no significant difference in OS between those who did and did not receive routine follow-ups (85.5% vs. 83.1%; p=0.47), and disease-specific survival was comparable between groups (98.6% vs. 98.3%; p=0.57). Recurrence occurred in four patients in the routine follow-up group, and two patients in the non-routine follow-up group.

Comment: Patients have follow-up after gastrectomy in order to manage side effects after surgery, and for cancer recurrence surveillance. There are no unified guidelines regarding the benefits of regular follow-up, especially in the elderly population for stage I disease. This retrospective study looked at two groups of patients: 301 with routine follow-up and 84 with non-routine follow-up. The study showed that there was no difference in survival between the two groups. Clearly, there are many limitations to this retrospective study, with the most obvious one being that there will be a group that was lost to follow-up, which will not be included in the 'non-routine' follow-up group. The study has not accounted for this group of patients, who potentially could have worse survival or otherwise. Prospective randomised studies would be a better way to answer this question.

Reference: Ann Surg Oncol. 2025;32(4):2629-36
Abstract

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Independent commentary by Dr Pei Ding

Dr. Pei Ding underwent medical oncology training at Liverpool and St Vincent's hospital in Sydney and completed her fellowship and PhD study in lung cancer liquid biopsy research at the Ingham Institute of Applied Medical Research and Western Sydney University. She is now a medical oncologist at Nepean and Westmead hospitals with clinical expertise in managing lung cancers and gastrointestinal cancers. She is also a senior clinical lecturer at the University of Sydney.