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ABSTRACT BOOK

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Contents

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ABSTRACT BOOK

Upper GI cancers

Abstracts discussing cancers of the oesophagus, stomach and gastro-oesophageal junction, pancreas, gallbladder and biliary tract, and liver.

Pancreatic body and tail adenocarcinoma: Upfront resection versus neoadjuvant therapy, a contemporary analysis

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Objectives

There is a paucity of data regarding the use of neoadjuvant therapy in pancreatic body or tail ductal adenocarcinomas. Given the differing tumour biology and aggressive nature of pancreatic body or tail adenocarcinomas, patients presenting with these tumours may benefit from upfront resection.

Methods

A retrospective cohort study was performed analysing patients who underwent distal pancreatectomy for pancreatic ductal adenocarcinoma between January 2013 and June 2022. Patients who underwent upfront resection were compared to those who underwent neoadjuvant therapy.

Results

Forty-one patients underwent upfront distal pancreatectomy, while 40 patients underwent neoadjuvant therapy before curative intent resection. Neoadjuvant therapy did not improve overall survival (37 vs. 34 months, p=0.962) or disease-free survival (13 vs. 15 months, p=0.414), as compared with upfront resection. There was no significant difference in the rate or Ro resection or post-operative outcomes.

Conclusion

No significant improvement in survival was demonstrated for patients undergoing neoadjuvant therapy for pancreatic ductal adenocarcinoma of the pancreatic body or tail when compared to upfront resection. Considering the potential for disease progression given the more aggressive tumour biology of pancreatic body and tail adenocarcinomas, appropriate surgical candidates should be offered upfront resection to provide the best chance of survival and cure.

DEEP-Learning (Developing Exploratory Endpoints in Pancreas cancer)

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Background

Pancreatic ductal adenocarcinoma (PDAC) presents unique challenges due to its dense extracellular matrix, which acts as a barrier to systemic therapies. Chemotherapy and radiotherapy accelerate stromal deposition, further hindering treatment response. Stromal-targeting therapies aim to improve drug penetration and facilitate curative resection. However, to effectively capture their mechanistic activity, novel biomarkers reflecting dynamic change within the tumour microenvironment (TME) are needed to complement existing clinical trial endpoints.

Methods

We conducted a comprehensive review of the literature to identify translational and clinical biomarkers reflecting treatment-induced changes in the PDAC TME. Feasibility and biological validity of candidate biomarkers were considered in order to select biomarkers for prospective evaluation in patients with metastatic disease receiving standard-of-care treatment. A comprehensive dataset of reference values for selected biomarkers will be generated, serving as a framework for evaluation of future clinical trial endpoints.

Results

From our review process, we identified several promising biomarkers for assessing stromal-targeting therapies. These include serum markers, such as plasma-derived cytokines and collagen degradation fragments, and imaging techniques, such as CT quantitative analysis, magnetic resonance (MR) diffusion-weighted imaging with apparent diffusion coefficient and MR-elastography. Selected biomarker tests can be performed on-campus, at low-to-moderate additional cost and within an acceptable timeframe.

Conclusions

Decades of research in PDAC have led to the development of stromal-targeting therapies to counteract a uniquely challenging TME. Based on our comprehensive review, we have selected stromal-centric biomarkers for prospective evaluation during standard-of-care therapy. In addition, we aim to include validated novel biomarkers as exploratory endpoints in a pilot feasibility study of a pan-lysyl oxidase inhibitor in combination with standard-of-care chemotherapy. Novel biomarkers will complement conventional endpoints to demonstrate proof of principle for the mechanistic effects of stromal-targeting therapies. This will provide the granularity required to thoroughly evaluate this novel class of drugs.

Final overall survival results of SPOTLIGHT evaluating 1L zolbetuximab + mFOLFOX6 for claudin 18 isoform 2 (CLDN18.2)+, HER2–, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma

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Background

The phase 3 SPOTLIGHT study showed statistically significant improvements in progression-free survival (PFS) and overall survival (OS) with first-line (1L) zolbetuximab + modified folinic acid, 5-FU, and oxaliplatin regimen (mFOLFOX6) vs placebo + mFOLFOX6 in patients with CLDN18.2+, HER2–, LA unresectable or mG/GEJ adenocarcinoma at prespecified interim and later updated analyses. We present the prespecified final OS analysis.

Methods

Patients were randomly assigned 1:1 to zolbetuximab IV 800 mg/m² (cycle 1, day [D] 1) followed by 600 mg/m² (every 3 weeks) + mFOLFOX6 IV (D1, D15, D29) for four 42-day cycles or to placebo + mFOLFOX6; patients without PD continued with zolbetuximab or placebo, + folinic acid and 5-FU at investigator's discretion, until PD or discontinuation criteria were met. The primary endpoint was PFS per RECIST v1.1 by IRC. OS was a key secondary endpoint; additional secondary endpoints were objective response rate (ORR) and safety.

Results

At data cutoff (September 8, 2023), 565 patients were assigned to zolbetuximab arm (n = 283) or placebo arm (n = 282). In zolbetuximab vs placebo arms, median follow-up was 18.04 vs 17.91 months for PFS and 33.28 vs 31.38 months for OS. Median PFS in zolbetuximab vs placebo arms was 11.04 vs 8.94 months (HR 0.734 [95% CI 0.591, 0.910], P = 0.0024). Median OS in zolbetuximab vs placebo arms was 18.23 vs 15.57 months (HR 0.784 [95% CI 0.644, 0.954], P = 0.0075). ORR was 48.1% (95%CI 42.11, 54.05) in zolbetuximab arm vs 47.5% (95%CI 41.56, 53.52) in placebo arm. In patients with measurable lesions, ORR was 61.1% (95%CI 54.20, 67.75) in zolbetuximab arm (n = 211) vs 62.4% (95%CI 55.45, 68.95) in placebo arm (n = 210). Safety and tolerability were maintained with no new findings.

Conclusions

Zolbetuximab + mFOLFOX6 continued to demonstrate statistically significant and clinically meaningful improvement in PFS and OS vs placebo + mFOLFOX6, with no new safety signals—supporting zolbetuximab + mFOLFOX6 as a global standard of care option for 1L treatment of patients with CLDN18.2+, HER2–, LA unresectable or mG/GEJ adenocarcinoma.

Gemcitabine/Oxaliplatin/Lenvatinib (GEMOX-Len) for refractory, relapsed or unresectable fibrolamellar carcinoma

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Background

Fibrolamellar carcinoma (FLC) is a rare primary liver malignancy typically affecting young adults without underlying liver disease. Although surgical resection is the primary treatment modality, 50-80% of cases have disease recurrence post-resection. Additionally, >20% of patients have unresectable disease, with median survival for this cohort <12 months. Gemcitabine/Oxaliplatin/Lenvatinib (GEMOX-Len) is a novel systemic therapy developed by the Rush University FLC Program (Chicago, Illinois) for patients with refractory, relapsed or unresectable FLC.

Methods

Data was collected retrospectively from 15/04/2019-25/05/2024. The primary study endpoints were tumour response (measured using RECIST 1.1 criteria and volume estimates), progression-free survival (PFS) and overall survival (OS). The Kaplan-Meier method was used to construct survival curves with the log-rank test applied to compare survival distributions. Ethics was approved by UNSW Australia HREAP (2024/iRECS5847).

Results

52 patients (25F) with median age 21.4 years (IQR 18.5-25.4) received a median of 9 cycles (IQR 7.0-15.3) of GEMOX-Len (G:1000mg/m2, O:100mg/m2, L:8mg daily). At the commencement of neoadjuvant therapy, 5/3/44 patients had AJCC stage III/IVa/IVb disease with 50/52 deemed unresectable. At the conclusion of therapy, 0/15/26/1 patients had complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD) per RECIST 1.1 criteria, with a median RECIST response of -19.5% (IQR -26.8% to -7.3%) and median volume response of -39.5% (IQR -59.8% to -14.8%). Median survival from the commencement of GEMOX-Len was 31.8 months, median PFS was 21.6 months and median OS was 103 months. 28 patients were surgically candidates post-therapy: 20 subsequently underwent definitive surgery, with 10 achieving Ro resection. The only statistically significant predictor of survival were patients who underwent definitive surgery (p=0.042). Predictors of PFS include AJCC stage <4 at definitive surgery (p=0.018) and the presence of tumour necrosis post-GEMOX-Len (p=0.031). 32/48 patients (66.67%) experienced adverse effects during therapy including peripheral neuropathy (n=25), fatigue (n=6) and nausea (n=4).

Conclusion

Our cohort treated with GEMOX-Len demonstrated significantly higher OS and PFS compared to existing literature. 52% of previously unresectable patients became surgical candidates, with an Ro outcome achieve in 50% of those who underwent surgery. Further controlled, prospective studies are required.

The Upper Gastrointestinal Cancer Registry – Using real world data to examine quality indicators of care in oesophagogastric cancers

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Aims

The Upper Gastrointestinal Cancer Registry (UGICR) is a multi-modular clinical quality registry based at Monash University. The aim of the registry is to collect real-world data to identify unwarranted variation in treatment and outcomes for people diagnosed with upper gastrointestinal cancers; by looking at quality of care indicators (QIs). These QIs cover various parts of a patient's care pathway including referral, diagnosis, surgical management, medical management, and end-of-life care. This study investigated the variation in QIs in UGICR participants from the oesophagogastric module.

Methods

The UGICR collects participants through an opt out approach, with patients identified through hospital administration data or state cancer registry. Data collectors then review medical records and enter data into the UGICR's REDCap database. Data from adult patients recruited through the UGICR, and diagnosed with an oesophagogastric cancer between 2016-2023, at 13 participating sites in Victoria, Australia, were used to examine QIs. Only patients that had been diagnosed and received some treatment at the same hospital were included, to ensure more complete data collection.

Results

The dataset included 1669 UGICR participants, predominately male (69 %), with oesophageal, junctional or gastric cancers. QIs were examined by calculating the proportion of patients meeting each quality indicator. Some QI's had high adherence, and low variability such as histology before treatment (94.9%), and proportion of patients with metastatic cancer who were seen by a medical or radiation oncologist (100%). Other indicators related to surgery (e.g. number nodes examined), or palliative care, demonstrated more variance and lower adherence and require further investigation.

Conclusions

The oesophagogastric module of the UGICR has significant participant recruitment across Victoria and continues to expand. In addition to providing a means to detect variation in quality of care, the UGICR's whole population capture makes it an ideal platform for registry-based trials and biobanks.

Different patterns of care and survival outcomes in transplant centre managed patients with early-stage HCC: Real-world data from an Australian multi-centre cohort study

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Management of early–stage hepatocellular carcinoma (HCC) is complex with multiple treatment strategies available. There is a paucity of literature regarding variation in patterns of care and outcomes between transplant and non–transplant centres. We performed this real–world multi–centre cohort study in two liver transplant centres (LTCs) and eight non-transplant centres (NTCs) across Australia to assess for variation in patterns of care and key survival outcomes.

Patients with Barcelona Clinic Liver Cancer (BCLC) 0/A HCC, first diagnosed between 01/01/2016 and 31/12/2020 who were managed at a participating site were included in the study. Patients were excluded if they had a history of prior HCC or if they received upfront liver transplantation.

A total of 887 patients were included in the study, with 433 patients managed at LTC and 454 patients managed at NTC. Management at a LTC did not significantly predict allocation to resection using multivariable binary logistic regression adjusting for tumour burden as well as age, gender, liver disease aetiology, liver disease severity and medical comorbidities (adjusted OR 0.75 95%CI 0.50 to 1.11, p=0.148). However, in those not receiving resection, LTC and NTC patients were systematically managed differently, with LTC patients five times less likely to receive upfront ablation than NTC patients (adjusted OR 0.19, 95%CI 0.13 to 0.28, p<0.001). LTC patients had significantly higher proportions of patients undergoing TACE for every tumour burden category, including those with single tumour 2cm or less (p<0.001). 42 of 887 patients (4.7%) underwent transplantation during follow-up, with higher Charlson Comorbidity Index (CCI) in LTC patients who received liver transplant compared to NTC patients (median 5 vs 3, p=0.028). Using multivariable Cox–proportional hazards analysis, management at a transplant centre was associated with reduced all–cause mortality (adjusted HR 0.71, 95%CI 0.51 to 0.98, p=0.036) and competing–risk regression analysis considering liver transplant as a competing event demonstrated a similar reduction in risk (adjusted HR 0.70., 95% CI 0.50 to 0.99, p=0.041), suggesting that the reduced risk of death is not fully explained by higher rates of transplantation.

Our study highlights systematic differences in HCC care and survival outcomes between large volume liver transplant centres and other sites.

EMERALD-1: A Phase 3, randomised, placebo-controlled study of transarterial chemoembolisation (TACE) combined with durvalumab (D) with or without bevacizumab (B) in participants with unresectable hepatocellular carcinoma (uHCC) eligible for embolisation

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Background

TACE has been a standard of care for embolisation-eligible uHCC; however, most people with uHCC treated with TACE progress within 1 year.

Methods

In EMERALD-1 (NCT03778957; double-blind, global, Phase 3 study), participants were randomised 1:1:1 to the D+B+TACE, D+TACE or TACE (cTACE or DEB-TACE per investigator choice). Participants received D (1500 mg) or placebo for D (Q4W) plus TACE. After completion of last TACE, participants received D (1120 mg) or placebo for D plus B (15 mg/kg) or placebo for B (Q3W). Primary endpoint was progression-free survival (PFS) for D+B+TACE versus TACE. Secondary endpoints included PFS for D+TACE versus TACE, overall survival (OS), objective response rate (ORR), time to progression (TTP) and safety. PFS, ORR and TTP were assessed by blinded independent central review (RECIST v1.1).

Results

Overall, 616 participants were randomised to D+B+TACE (n=204), D+TACE (n=207) or TACE (n=205). PFS was significantly improved for D+B+TACE versus TACE (median [m]PFS 15.0 vs 8.2 months; HR, 0.77; 95% CI, 0.61–0.98; p=0.032). PFS for D+TACE versus TACE was not statistically significant (mPFS 10.0 vs 8.2 months; HR, 0.94; 95% CI, 0.75–1.19; p=0.638). ORR was 43.6%, 41.0% and 29.6%, and mTTP was 22.0, 11.5 and 10.0 months for D+B+TACE, D+TACE and TACE, respectively. No new safety signals were identified. In the D+B+TACE (n=154), D+TACE (n=232) and TACE (n=200) safety analysis sets, respectively, 26.6%, 6.5% and 6.0% of participants had maximum Grade 3/4 treatment-related adverse events (TRAEs); 12.3%, 3.4% and 3.0% discontinued due to TRAEs; and 0%, 1.3% and 1.5% died due to TRAEs. Participants continue to be followed for OS.

Conclusions

D+B+TACE is the first immune checkpoint inhibitor-based regimen in a global Phase 3 trial to show statistically significant and clinically meaningful improvement in PFS, versus TACE, in participants with embolisation-eligible uHCC. Safety was manageable and consistent with the safety profiles of D, B and TACE in uHCC. D+B+TACE has the potential to set a new standard of care in embolisation-eligible uHCC.

A retrospective review of third-line retreatment of advanced pancreatic adenocarcinoma with gemcitabine and nab-paclitaxel

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Background

The treatment of pancreatic adenocarcinoma involving modified FOLFIRINOX or gemcitabine with nab-paclitaxel as first- or second-line options has been well documented. There has been minimal data published surrounding the options for third-line treatment. This retrospective review identified 60 patients who received 3rd line pre-treatment with gemcitabine and nab-paclitaxel. This is retrospective review is an update to previously reported data.

Methods

This retrospective analysis used an electronic database to identify patients with metastatic or locally advanced pancreatic adenocarcinoma who received first-line and third-line treatment with gemcitabine and nab-paclitaxel between January 2013 and March 2023, with outcomes followed to March 2024. Patients had an ECOG performance status of 2 or less. Overall survival (OS) was estimated by the Kaplan-Meier method.

Results

There were 60 patients identified in our analysis. The median age of patients was 65 years (range, 38 - 86). 35% (n=21) of the studied patients had metastatic disease at diagnosis. The median OS from diagnosis for the metastatic group was 25 months (95% CI, 20.5–29.5) compared to the locally advanced group 34 months (95% CI, 28.5-39.5). Median OS from third-line re-initiation of gemcitabine plus nab-paclitaxel was 9 months (95% CI, 7– 11).

Conclusion

Our retrospective study demonstrates the potential benefit of retreatment with gemcitabine and nab-paclitaxel in patients with advanced pancreatic adenocarcinoma. Although challenging in this patient population, further prospective studies would help establish this treatment strategy.

Improved survival outcomes with surgical resection compared to ablative therapy in early-stage HCC: A large, real-world, propensity-matched, multi-centre, Australian cohort study

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Background and aims

The optimal treatment approach in very-early and early-stage hepatocellular carcinoma (HCC) is not precisely defined, with ambiguity in the literature around the comparative efficacy of surgical resection versus ablation as curative therapies for limited disease. We performed this real-world propensity-matched, multi-centre cohort study to assess for differences in survival outcomes between those undergoing resection and those receiving ablation.

Methods

Patients with Barcelona Clinic Liver Cancer (BCLC) 0/A HCC first diagnosed between 01/01/2016 and 31/12/2020 who received ablation or resection as initial treatment were included in the study.

Results

A total of 450 patients were included in the study from 10 major liver centres including two transplant centres. Patients who underwent resection were systematically different to those who received ablation, with significant differences seen in age, managing centre, liver disease aetiology, diabetes, platelet count, Charlson Comorbidity Index (CCI) tumour burden and Child Pugh score, Propensity-score matching was performed using key covariates producing 156 patients available for analysis with 78 in each group. Over a median follow up of 53.3 months, patients who underwent resection had significantly improved overall survival (97.4% vs 88.5%, log-rank test p=0.023) with similar results in the original unmatched cohort (94.9% vs 83.9%, log-rank test p<0.001). Local recurrence-free survival was superior in the resection group (88.5% vs 76.7%, log-rank test p=0.027) over a median follow-up of 37.9 months with similar superior 3-year recurrence-free survival (75.6% vs 57.5%, log-rank test p=0.007). Major complication rate was low in the original unmatched resection group who had been selected for surgery by a real-world multidisciplinary group of expert clinicians (2 out of 196, 1.0%).

Conclusion

Our study suggests that surgical resection results in more durable local tumour control in BCLC 0/A HCC as compared to ablation which translates to improved survival outcomes. Based on real-world data, our study supports the use of surgical resection in preference to ablation as first line curative therapy where possible in appropriately selected BCLC 0/A HCC patients.

Initial trans-arterial chemo-embolisation (TACE) is associated with similar survival outcomes as compared to upfront percutaneous ablation in those with single hepatocellular carcinoma (HCC) ≤ 3cm: Results of propensity-matched Australian study

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Background and aims

Percutaneous ablation is recommended in Barcelona Clinic Liver Cancer (BCLC) stage 0/A patients with HCC ≤3cm as a curative treatment modality alongside surgical resection and liver transplantation. However, trans-arterial chemo-embolisation (TACE) is commonly used in the real-world as an initial treatment in patients with single small HCC in contrast to widely accepted clinical practice guidelines which typically describe TACE as a treatment for intermediate-stage HCC. We performed this real-world propensity-matched multi-centre cohort study in patients with single HCC ≤ 3cm to assess for differences in survival outcomes between those undergoing initial TACE and those receiving upfront ablation.

Methods

Patients with a new diagnosis of BCLC 0/A HCC with a single tumor ≤3cm first diagnosed between 1 January 2016 and 31 December 2020 who received initial TACE or ablation were included in the study.

Results

A total of 348 patients were included in the study, with 147 patients receiving initial TACE and 201 patients undergoing upfront ablation. After propensity score matching using key covariates 230 patients were available for analysis with 115 in each group. There were no significant differences in overall survival (log-rank test p=0.652) or liver-related survival (log-rank test p=0.495) over a median follow up of 43 months. While rates of CR were superior after ablation compared to TACE as a first treatment (74% vs 56%, p<0.004), there was no significant difference in CR rates when allowing for further subsequent treatments (86% vs 80% p=0.219). In those who achieved CR, recurrence-free survival and local recurrence-free survival was similar (log rank test p=0.355 and p=0.390 respectively).

Conclusion

Our study provides valuable real-world evidence that TACE when offered with appropriate follow up treatment is a reasonable initial management strategy in very-early/early-stage HCC, with similar survival outcomes as compared to those managed with upfront ablation. Further work is needed to better define the role for TACE in BCLC 0/A HCC.

Perioperative FLOT in gastric and gastroesophageal junction cancer: Outcomes from an Australian tertiary institution

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Background

Perioperative FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) is the current standard of care for treating resectable gastric and gastroesophageal junction (GOJ) cancers. However, there is limited real-world data on outcomes in patients treated with perioperative FLOT.

Methods

A single-centre retrospective review of patients who received peri-operative FLOT for resectable locally advanced gastric and GOJ adenocarcinoma was conducted from August 2017 to July 2024. Clinicopathological characteristics, toxicities, surgical outcomes, and survival outcomes were assessed.

Results

Thirty-five patients were included in the study. Median follow up is 36 months. Twenty-five patients were males and ten were females. Median age is 67 years (range 35-83).

Twenty-seven (77%) patients completed four cycles of preoperative FLOT. Grade 3/4 (G3/4) gastrointestinal (GI) related toxicities were the most common with upper GI bleed (6%), nausea (3%), diarrhoea (3%) and enteritis (3%). Seven patients did not proceed with surgery due to: progressive disease (3), unfit for surgery (1), death (1), and patient's choice (1).

Twenty-eight (80%) patients underwent surgery and twenty-six (93%) patients achieved Ro resection and two (7%) R1 resection. Nineteen patients (68%) received adjuvant FLOT after surgery with five patients completed four doses of adjuvant FLOT. Most common G3/4 toxicities were peripheral neuropathy (16%), febrile neutropenia (11%) and fatigue (11%). One patient (3%) died due to severe nausea and malnutrition in the adjuvant setting.

Four patients (14%) had pathological complete response, three patients (11%) had Ryan Tumour Regression Score (TRG) 1, seven (25%) had TRG 2 and fourteen (50%) had TRG 3. At 36 months, patients with TRG 0 and 1 had 100% event-free survival (EFS) and overall survival (OS); TRG 2 patients had 64% EFS and 100% OS; TRG 3 patients had 48% EFS and 56% OS. Overall 3-year EFS and OS are 60% and 70% respectively.

Conclusion

Pathological response correlated to improved EFS/OS however our study is limited by the small numbers, short duration of follow up and retrospective cohort. Clinical outcomes were comparable to the FLOT4-AIO study. High G3/4 toxicity rates were seen in this real-world population. Further biomarkers should be investigated to better select patients who may not need adjuvant FLOT.

Characterisation of FAPI-46 PET imaging in three hepatocellular carcinoma patients

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Background

Cancer-associated fibroblasts (CAF) mediate immunosuppression in the tumour microenvironment and strongly express Fibroblast Activation Protein (FAP). FAP Inhibitor (FAPI) PET scan, targeting FAP, could be a biomarker for predicting response to immunotherapy. We aim to evaluate the prognostic value of FAPI PET imaging in predicting disease progression and treatment response in patients with hepatocellular carcinoma (HCC).

Methods

We are conducting a prospective observational study of advanced HCC and other metastatic patients at Fiona Stanley Hospital undergoing immunotherapy treatment. Each patient will undergo baseline FAPI PET imaging. FAP expression will be correlated with disease response, progression-free survival, and overall survival.

Results

We present the preliminary results of FAPI PET scan of our first three HCC patients (A, B and C). Patient A had untreated metastatic HCC with Child-Pugh A cirrhosis. His fluorodeoxyglucose (FDG) and FAPI PET scan showed variable activity on both with spatial and intensity discordance between them. All 5 liver lesions had higher SUV (Standardised Uptake Value) with FAPI PET while the adrenal metastases had higher FDG uptake.

Patient B had recurrent HCC with Child-Pugh B cirrhosis after previous treatment with ablation three years ago and Selective Internal Radiation Therapy (SIRT) one year ago. His FAPI PET showed heterogenous FAPI tracer uptake in the multifocal HCC with the most intense uptake in the previously treated lesion and lower grade uptake elsewhere.

Patient C had oligometastatic HCC to the lung and Child-Pugh A cirrhosis was previously treated with Trans Arterial Chemoembolisation (TACE) two years ago. His FAPI PET showed increased activity peripherally in the previously ablated liver lesion and the left lung nodule.

Patient A, B and C had higher background liver SUV mean of 2.2, 4.12 and 2.45 respectively compared to other two non-HCC and non-cirrhotic patients recruited who had 1.41 and 1.50 background liver SUV mean respectively.

Conclusion

There is a suggested trend for higher liver SUV mean in HCC patients compared to non-HCC patients, which may indicate a role for FAPI PET in assessing the degree of liver fibrosis. Further studies are needed to explore these findings and their implications for HCC prognosis and treatment.

Mutated KRAS as a promising target in pancreas cancer: Analysis of the PURPLE registry data to inform real-world incidence and prognostic significance

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Background

With around 90% KRAS mutation (mt) frequency, pancreatic ductal adenocarcinoma (PDAC) is considered the most RAS-addicted cancer. Despite guideline recommendations, genomic testing is not routine in all PDAC patients (pts) in Australia due to unproven clinical impact. As more novel KRAS-direct therapeutics enter clinical trials, understanding real-world frequency and prognostic significance of individual mutations and facilitating trial recruitment are important goals, all of which can be supported by registry data.

Methods

Data extracted from the PURPLE pancreatic cancer registry (Clinical Registry ACTRN12617001474347) from 9 participating cancer centres, between 2016-2024, was analysed to compare clinicopathological features and survival by KRAS mt status and assess feasibility of the platform to identify molecularly stratified patients for future clinical trials. Survival estimates were calculated using Kaplan-Meier curves and log-rank testing on SPSS (Macintosh v.29).

Results

Of 1148 PDAC routine care pts identified, KRAS next generation sequencing (NGS) was undertaken in 521 (45%). Median patient age was 67 years (range 59-74); 184 (35%) had resectable, 159 (31%) locally advanced and 178 (34%) metastatic disease. 76 (15%) were KRAS wildtype. Of 445 pts with a KRAS mt, codons 12,13, and 61 were the most common sites of mt, including G12D (48%), and G12V (27%), with lower frequencies of G12R (14%), Q61H (5%), G12C (2%), G12A (1%), and G13D (1%). Comparing KRAS mt to KRAS wildtype pts, there was no difference in median age (67 vs 67, p=0.77), male gender (50% vs 61%, p=0.09), ECOG performance (p=0.22), Charlson comorbidity index (p=0.16), stage at first presentation (p=0.53), or first-line treatment (p=0.09). For all pts, median overall survival (OS) in KRAS wildtype versus KRAS mt pts was 20.1 versus 14.1 months (p=0.042), and for the 178 metastatic pts 9.3 versus 7.4 months (p=0.33). Further analysis of the impact by disease stage and by individual RAS mt is underway.

Conclusion

Registry based analysis informs understanding of various KRAS mt frequencies in PDAC in a community setting. With newer promising KRAS-targeted therapies becoming available in clinical trials, known RAS status will aid identification of trial candidates. The clinical utility of NGS and rationale for reflex testing in PDAC is increasing.

PURPLE pancreatic cancer translational registry: Accelerating data driven research and translational studies through innovation

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Background

There is increasing interest in capturing real world data to support a broad range of audit and research projects. The international PURPLE pancreas registry collates real-world data on consecutive patients diagnosed with pancreatic adenocarcinoma (PDAC), matching this with blood and tissue samples to support a range of translational research endeavours. This unique translational registry platform improves research efficiency by data sharing and increasing collaboration between cancer centres and laboratories.

Methods

We reviewed progress in the PURPLE registry over 2023-2024, including site and patient numbers, database and platform development, tissue resources to support translational research, new projects, and new research output.

Results

With 4 new centres joining this collaborative initiative, the PURPLE registry is active at 49 centres across Australia, New Zealand, and Singapore. Further international engagement with new sites in the United Kingdom and Thailand is underway. Almost 1000 new patients have been added, bringing the total number of patients to over 5100. Major updates to the platform include the addition of new omics capabilities, now supporting detailed genomic data capture, radiomics research, and expansion of our blood-based proteomics program. Infrastructure developments supporting business analytics, data commons and computational capabilities are underway. Clinical data is now linked to ›2400 biospecimens, 1246 virtual biobanked resection specimens and genomic data on ›520 pancreatic cases. The PURPLE registry is supporting 16 ongoing data projects, 4 translational studies, and 2 registry-based clinical trials. Output continues to increase with six publications1-6, two oral presentations including reports on our registry-based trial DYNAMIC-pancreas, and seven poster presentations at national and international conferences in the last year. The PURPLE registry is increasing its capacity to support more registry-based and platform designed trials.

Conclusion

As the management of pancreas cancer continues to evolve, and new biomarkers and translational opportunities present, the potential value of the PURPLE pancreatic cancer translational registry continues to increase. We are reframing the value of the clinical data registry, building capacity in analysing complex clinical and biological data, and leveraging unique resources to ensure that we learn from every patient's experience, accelerate research, and make meaningful contributions to improving outcomes in pancreatic cancer.

Evaluation of recurrence patterns following resection of pancreatic ductal adenocarcinoma

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Background

Pancreatic ductal adenocarcinoma (PDAC) is the 3rd leading cause of cancer related deaths in Australia. Despite curative intent resection in patients with local disease, 80% will relapse within 2 years. Identifying patients at risk of early recurrence (ER) could improve selection of operative candidates. Patterns of recurrence are not well described.

Methods

Data was extracted from the PURPLE pancreatic cancer registry for patients diagnosed between 2016-2024. We examined clinicopathological features, treatment used, and survival outcomes in early-stage resected PDAC. Early recurrence was defined as cancer recurrence within 12 months of surgery. Recurrence-free survival (RFS) and overall survival (OS) estimates were calculated using Kaplan-Meier estimates and log-rank testing.

Results

682 patients with early-stage PDAC who underwent curative intent resection were identified. The median age was 66. At a median follow up of 19.28 months, 81.4% had disease recurrence (median RFS 13.28 months). ER occurred in 45.3% of patients after resection. ER was associated with pre-operative advanced age (P=0.0001), worse ECOG performance status, (P=0.0001) higher T stage (P=0.0029), and an elevated preoperative CA 19-9 (P=0.0001). Postoperative indicators for ER included high tumour grade (P=0.0171), lack of adjuvant therapy (P=0.0001), lymphovascular invasion (P=0.0155) and increased nodal stage (P=0.0214). Of the 563 patients who relapsed (82.6%), the location of metastasis was known in 390 cases. Among these, 65.0% had their recurrence confined to a single site. Locoregional (29.5%) and liver (22.8%) recurrences were the most common. Tumours located in the head of the pancreas were associated with higher rates of locoregional recurrence (P=0.0042). 306 (44.8%) patients received systemic therapy after recurrence. The median overall survival from diagnosis of those with isolated lung (29.9 months) and locoregional (26.3 months) recurrences was significantly longer than those with liver (18.7 months) or peritoneal (20.3 months) recurrences (P=0.0001).

Conclusion

In a local real-world population a high proportion of patients with resected pancreas cancer experience recurrence, including almost half by 12 months post-surgery. Multiple factors predict for poor post-surgery outcomes and could inform MDT decision making. The expected patterns of recurrent disease were seen, with trends for site of recurrence associated with post recurrence survival.

Exploring the impact of cultural and linguistic diversity (CALD) on treatment and outcomes in pancreatic cancer: PURPLE real-world registry data from a contemporary Australian population

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Background

Culturally and/or linguistically diverse (CALD) cancer patients have unique health needs and may face barriers when accessing healthcare. This study explored the impact of CALD status on the treatment and outcomes for patients with pancreatic cancer.

Methods

Data were extracted from the multi-site PURPLE Pancreatic cancer Translational Registry between January 2016 - April 2023, supplemented by country of birth and preferred language data obtained from linkage with hospital administrative data. CALD status was defined by being born overseas in a non-main English-speaking country and/or having a preferred language other than English.

Results

Of 2074 patients with pancreatic cancer enrolled at eight participating institutions, 1463 were able to have their CALD status determined; with 668 (46%) identified as CALD and 795 (54%) as non-CALD. The CALD population were older at the time of diagnosis (mean age 71 vs 68 years; P<0.001), with a worse performance status (ECOG ≤1: 65 vs 72%, P=0.004) and a greater number of comorbidities (Charlson Comorbidity Index >3: 55 vs 43%, P<0.001). The use of neoadjuvant therapy in resectable/borderline resectable disease was similar (43% CALD vs 57% non-CALD, P=0.62). However, fewer CALD patients proceeded to curative-intent surgery following neoadjuvant therapy (30% vs 52%, P=0.025). There was similar use of adjuvant therapy in resected patients. CALD patients were more likely to receive single agent adjuvant gemcitabine (38% vs 23%; P=0.016) than doublet or triplet chemotherapy regimens. Despite this, there was no difference in the median recurrence-free survival (RFS 16.6 vs 16.5 months; P=0.590). In the metastatic setting, a higher proportion of CALD patients were offered best supportive care (50% vs 40%; P=0.018). CALD patients receiving first-line therapy had an overall survival of 10.8 months, compared to 6.8 months for non-CALD, P=0.012. Few patients accessed clinical trials (5% CALD, 6% non-CALD).

Conclusions

CALD status was associated with multiple adverse prognostic factors (age, PS, co-morbidities), which likely impacted treatment received and challenges analysis of the independent impact of CALD status. There were no striking differences by CALD status in treatment delivered or survival outcomes. Further research of CALD status including by country of birth and English proficiency is underway.

Real-world effectiveness and safety of perioperative FLOT for resectable gastric and GEJ adenocarcinoma: A single-center Australian experience

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Background

The FLOT regimen has demonstrated improved survival outcomes in resectable gastric and gastro-oesophageal junction (GOJ) adenocarcinoma in clinical trials. However, real-world data, especially within the Australian context, remain limited. This study evaluates the effectiveness and safety of perioperative FLOT in a real-world Australian cohort.

Methods

A retrospective analysis was conducted on patients with resectable gastric or GOJ adenocarcinoma who received perioperative FLOT at the Canberra Hospital between 2017 and 2024. Data on demographics, tumour characteristics, treatment details, and outcomes were collected. Primary endpoints included feasibility, safety, and pathological complete response (pCR) rates. Secondary endpoints were disease-free survival (DFS), overall survival (OS), and correlations between various factors and outcomes.

Results

A total of 37 patients (median age 66 years) were included. Most tumours were gastric (67.6%). Preoperative chemotherapy adherence was high, with 78.4% receiving four cycles of FLOT. Ro resection was achieved in 74% of cases. The pCR rate was 16.2%, with an additional 59.5% achieving a partial response. Median DFS was 28.8 months, and median OS was 33 months. Achieving pCR was associated with significantly longer DFS ($p = 0.017$). Ro resection correlated with improved DFS and OS. Gastric tumours were more likely to achieve Ro resection than GOJ tumours ($p = 0.015$). The most frequent adverse events were diarrhoea, anaemia, and neutropenia. Oxaliplatin-induced neuropathy occurred in 13.5% of patients.

Conclusions

This real-world study supports the feasibility and effectiveness of perioperative FLOT, demonstrating comparable pCR rates and an acceptable safety profile. pCR remains a strong predictor of improved DFS. However, both DFS and OS were lower in this real-world setting compared to clinical trials. Tumour location significantly influenced Ro resection rates, favouring gastric tumours. Further research is warranted to validate these findings and explore potential biomarkers for predicting response to FLOT.

Early gastro-oesophageal junction perforation repaired using through-the-scope clips

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Early gastric and oesophageal perforations are rare following laparoscopic fundoplications, with an incidence of 0.9%. Here, we present the case of a septic 21-year-old patient who presented with an early gastro-oesophageal perforation 7 days following laparoscopic Nissen Fundoplication, which was successfully repaired using endoscopic haemostatic clips. Indeed, the importance of this novel method of repair can be extended to iatrogenic oesophageal or gastric injuries sustained during gastroscopy for cancer surveillance or workup.

New trends in distal pancreatectomy

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Introduction

Removing the left half of the pancreas is potentially morbid. Recent changes to technique have allowed more spleen (whole or partial) preservation, more robotic approaches, and less use of drains, with reported improvement in morbidity.

Methods

This was an ethically approved (Metro North Ethics Committee) retrospective audit of all patients over the age of 18 who underwent a distal pancreatectomy (+/- splenectomy) at Royal Brisbane and Women's Hospital (RBWH) and The Wesley Hospital between January 2019 and January 2024.

Results

This paper reviews a recent 5- year experience of distal pancreatectomy by four surgeons based at the RBWH and The Wesley Hospital, Brisbane. 122 patients were reviewed. Mean age was 61, and 61% were female. The predominant pathologies were pancreatic ductal adenocarcinoma (28%) and pancreatic neuroendocrine tumours (24%). A minimal access approach was used in 89%, and a third of these were robotic.

Spleen preservation was achieved in 32%. In 5 patients, including 2 with PDAC, partial splenectomy, was performed, dividing the splenic artery and vein, but leaving one quarter of the spleen, supplied by the short gastric vessels. All 5 patients had viable spleens on follow up with peripheral blood not demonstrating Howell-Jolly bodies, suggesting adequate splenic function.

Drains were not used in 12 patients, predominantly in the later part of the series. Clinically relevant post operative pancreatic fistulas (Grade B) occurred in 11% of all reviewed patients and there were no Grade C fistulas. Trans-gastric endoscopic ultrasound (EUS) guided drainage of post-operative collections was effective in 8 patients. There were no 30 - day mortalities in the patient cohort.

Conclusions

Laparoscopic or robotic approaches are very effective for distal pancreatectomy, and improvements and innovations in technique allow more spleen preservation and less morbidity.

Pathological complete response rate after neoadjuvant CROSS chemoradiotherapy for locally advanced oesophageal cancer in real world setting

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Introduction

Standard of care, neoadjuvant (NA) therapy for oesophageal and gastro-oesophageal junction (GOJ) cancer (Siewart I and II) at our centre has either been chemoradiotherapy with the CROSS regimen (carboplatin/paclitaxel concurrent with radiation to 41.4Gy in 23 fractions) or chemotherapy-based regimens (e.g. FLOT). Factors affecting choice of regimen have been patient, tumour and clinician dependent with a preference historically for CROSS for both adenocarcinoma and squamous cell carcinoma. New data directly comparing the two regimens in patients with GOJ adenocarcinoma suggests improved pathological complete response with FLOT compared to CROSS with associated survival advantage for FLOT.

Aim

Determine pathological complete response rate for CROSS regimen in our patient cohort.

Methods

An ethics approved, retrospective review of hospital records for patients treated with NA CROSS protocol chemoradiotherapy prior to surgical resection between July 2011 and December 2023 was undertaken. Chemotherapy and radiotherapy regimen, pathological response and resection margin (Ro resection) recorded. Patient demographics also reviewed.

Results

49 patients completed neoadjuvant CROSS chemoradiotherapy followed by surgery between 2011 and 2023. Median age of patients was 69 (range 32-84). 72% of patients were male. Most patients (84%) had adenocarcinoma histology (41/49), (squamous cell carcinoma 7, spindle cell carcinoma 1). Most patients received a radiation dose of 41.4Gy in 23 fractions (1 patient 45Gy in 25 fractions, 1 patient 50.4Gy in 28 fractions). In patients treated with CROSS 18 % (9/49) had a complete pathological response on resection. Most patients with complete response had adenocarcinoma histology (7/9). 48 patients achieved Ro resection. Average time between completion of chemoradiotherapy and surgery was 43 days (range 26-104).

Conclusion

Pathological complete response of 18% in our patient cohort was comparable to the original CROSS trial (29% overall and 23% for adenocarcinoma) and FLOT (16%) arm of the ESOPEC trial (awaiting formal publication). Neoadjuvant CROSS chemoradiotherapy remains a reasonable option for localised oesophageal cancer especially for those with node negative cancer and those who are not eligible for intense chemotherapy regimens. Future trials incorporating both CROSS and FLOT regimen as well as immunotherapy may help to improve pathological responses and survival.

Immunotherapy combined with a novel iRGD peptide plus nab-paclitaxel and gemcitabine for locally advanced pancreatic ductal adenocarcinoma: A prospective study

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Background

Pancreatic ductal adenocarcinoma (PDAC) is characterised by a dense, extracellular matrix-rich stroma, which creates a physical barrier against drug penetration. Evidence suggests that the iRGD peptide, LSTA-1, can increase the penetration of anti-cancer drugs to tumours through selective targeting of tumour endothelial cell receptors. Additionally, LSTA-1 administration promotes CD8+ immune cell tumour infiltration, potentially enabling immunotherapy as a treatment modality.

Aim

The purpose of this study was to assess the safety and feasibility of the combination of gemcitabine/nab-paclitaxel with LSTA-1 and durvalumab, and to identify signals of immune response in pancreatic adenocarcinoma.

Method

Participants diagnosed with locally advanced PDAC were divided into 3 cohorts in a 1:1:4 ratio. Cohort 1 (n=5) received gemcitabine (1000mg/m²), nab-paclitaxel (125mg/m²), placebo LSTA-1 (3.2mg/kg) and placebo durvalumab (750mg). Cohort 2 (n=5) received gemcitabine, nab-paclitaxel, active and placebo LSTA-1, and placebo durvalumab. Cohort 3 (n=20) received gemcitabine, nab-paclitaxel, LSTA-1 and durvalumab. Tissue biopsies via endoscopic ultrasound were required pre-treatment and between weeks 12 and 16 for analysis of tumour infiltrating lymphocytes (TILs). Patient tumours were assessed every 8 weeks using radiological imaging according to RECIST v1.1, and serum CA19-9 levels were analysed monthly.

Results

5/16 patients showed significant RECIST partial response after 2 cycles of treatment (4 patients in cohort 3), with the remaining 11 patients presenting with stable disease. After 4 cycles of treatment, 9/16 patients demonstrated partial response (8 patients in cohort 3). Of the remaining 7 patients, 6 demonstrated stable disease, and 1 patient (cohort 2) exhibited a phenomenal RECIST complete response. 14/17 patients who completed 4 treatment cycles showed a decrease in CA19-9 levels. 6 patients demonstrated ›90% reduction in CA19-9 (5 in cohort 3), with the remaining 8 patients showing a ›50% reduction in CA19-9 levels (6 in cohort 3). 5 patients had their repeat biopsies analysed for TILs (4 from cohort 3), with all patients showing significant immune cell infiltration (15% to 50% stroma infiltration).

Conclusion

The preliminary results of this study demonstrated that the combination of gemcitabine and nab-paclitaxel with LSTA-1 and durvalumab provoked a RECIST response and a significant tumour infiltrating lymphocyte response within the pancreatic tumour.

Investigation of the effect of the gut microbiome on tumour response to anti-cancer treatment in patients diagnosed with pancreatic ductal adenocarcinoma

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Background

Chemotherapy is the standard first-line treatment for pancreatic ductal adenocarcinoma (PDAC), however, recent research has identified bacteria in the human gut microbiome may influence patient response to chemotherapy. These bacteria are also present in faeces, and are thought to be representative of the bacteria in the pancreatic ductal system. Preliminary studies have suggested that patients with more advanced PDAC demonstrate lower levels of Firmicutes, and higher levels of Proteobacteria. Additionally, research has shown bacteria in the Firmicutes phylum possess several anti-cancer properties, which can improve patient treatment response, meanwhile, Gammaproteobacteria (Proteobacteria phylum), have been shown to attenuate gemcitabine efficacy and worsen treatment response.

Aim

This study aimed to investigate the relationship between gut microbiome composition and patient response to PDAC anti-cancer therapy.

Method

This study involved 14 participants with locally advanced PDAC. Participants received combinations of Gemcitabine and Nab-Paclitaxel, and durvalumab (immunotherapy). Participant tumours were assessed every 8 weeks using radiological imaging according to RECIST v1.1, and serum CA19-9 levels were analysed monthly. Gut microbial profiling was completed on stool samples taken pre-treatment using PacBio HiFi full-length 16S rRNA sequencing.

Results

16S rRNA sequencing identified that of the 4 patients that died due to disease progression, 3 patients had a low Firmicutes abundance, and a high Proteobacteria abundance. The remaining deceased patient demonstrated low levels of Actinobacteriota and Bacteroidota, and a low bacterial diversity. One participant showed a significant increase in CA19-9 (1066.7%), and exhibited a low abundance of Actinobacteriota and Bacteroidota, a high abundance of Proteobacteria, and a low diversity. 5 participants demonstrated a significant treatment response (according to CA19-9 and RECIST analysis), with 4 patients showing a high Firmicutes abundance, high levels of Actinobacteriota or Bacteroidota, and low levels of Proteobacteria. The remaining patient demonstrated a low abundance of Firmicutes and Proteobacteria, yet, displayed the highest abundance of Actinobacteriota and Bacteroidota.

Conclusion

This exploratory study revealed a trend between microbial composition and treatment response, with Firmicutes correlating with an improved treatment response, and Proteobacteria with a worsened response. We believe this study to be one of the first to correlate the microbiome with treatment response in PDAC.

Real world patterns of treatment and survival outcomes in patients with metastatic pancreatic cancer: A maintenance versus surveillance approach after first line systemic therapy

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The likelihood of survival in patients with advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) increases with the number of chemotherapy agents however toxicity and quality of life need to be considered in the palliative setting[1].

We performed a retrospective analysis evaluating current treatment patterns and survival outcomes of patients with de novo metastatic PDAC who received first line systemic therapy. We compared survival outcomes of a maintenance approach versus a surveillance approach after first line chemotherapy in PDAC.

Data extracted from the PURPLE pancreatic cancer registry between 2016-2024 was analysed to review baseline demographics through descriptive statistics and survival analyses using cox proportional hazards model, log-rank testing and Kaplan-Meier curves on STATA 18.

Of 1059 patients, 710 had de novo metastatic PDAC and received palliative systemic therapy. Majority of patients were male (n=372,54%), median age was 66 (IQR 59-73) and 523 (73%) having liver as a site of metastasis. Gemcitabine and Nab-Paclitaxel was used as first line treatment in 422 (59%) patients, 147 (20%) had FOLFIRINOX, 40 (5%) had Gemcitabine alone and 77 (10%) received an alternative treatment.

The median time to follow up for patients with de novo metastatic disease was 35.3 months. The median progression free survival (PFS) and median overall survival (OS) who received first line chemotherapy was 5.88 months (95% confidence interval [CI], 5.45-6.24) and 9.56 months (95% CI, 8.90-10.18) respectively.

The median PFS in those who continued maintenance chemotherapy was 11.60 (95% CI 10.57-12.35) and 6.78 months (95% CI 6.27-7.35) in the surveillance group (hazard ratio (HR) for disease progression was 2.79(95% CI: 1.66-2.79). Median OS for patients who continued maintenance chemotherapy was 20.37 months (95% CI, 17.15-22.67) and 11.79 months (95% CI, 10.80-12.71) in the surveillance group (HR 2.15 (95% CI: 1.66-2.793)).

These findings suggest patients are more likely to have an improved survival when continued on maintenance chemotherapy compared to a surveillance approach. Continuing chemotherapy in this setting needs to be balanced with its toxicities and patient quality of life.

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[1] Conroy T, et al: PRODIGE Intergroup. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic cancer. N Engl J Med. 2011 May 12;364(19):1817-25

Lower GI cancers

Abstracts discussing cancers of the appendix, bowel, rectum and anus.

Does reinforcement of stoma closure sites with bioprosthetic mesh reduce the rate of incisional hernia development: A pilot randomised control trial?

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Purpose

One in three patients develop an incisional hernia following reversal of a de-functioning stoma for colon or rectal cancer – half of which will require repair. This pilot randomised control trial compares incisional hernia rates and post-operative morbidity following stoma reversal with and without biosynthetic mesh (BIO-A) reinforcement.

Method

All patients aged >18 years undergoing stoma reversal in a tertiary metropolitan hospital between December 2017 to November 2021 were invited to participate. Simple random allocation to groups with and without retro-rectus biosynthetic mesh (GORE BIO-A: Flagstaff, AZ) reinforcement was performed. The rates of radiological incisional hernia, surgical site infection and seroma formation over a two year follow up period were compared using Chi-squared test.

Result

Thirty-four patients in the pilot study have completed their two-year follow up. Of these patients, 13 had closure with mesh, and 21 patients had closure without mesh. Overall incidence of incisional hernia was 3 (9%). In those with mesh, no patients developed a hernia. In those without mesh, 3 (14%) developed a hernia. The odds ratio of those developing a hernia with no mesh was 0.2 (CI 95% 0.01-4.11, p=0.05).

Conclusion

Interim results suggest a trend towards a reduction in the incidence of incisional hernia following stoma reversal with the use of a prophylactic absorbable biosynthetic mesh. However, this finding was not statistically significant. A larger sample size is required to further evaluate. The trial is ongoing.

Is age a factor in our aging population and management of lower gastrointestinal bleeding?

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Purpose

Lower Gastrointestinal bleeding (LGIB) is a common presentation in hospitals and resolves spontaneously in 80 to 85% of patients. However, more severe episodes, such as in hemodynamically unstable patients, carry a mortality of 2-3%. The annual incidence of LGIB in the US is 20.5 to 35.7 per 100,000 and increases with age, especially from 30 onwards. This study aimed to show that older patients, who are more physiologically frail, are more prone to deterioration and should, therefore, be managed more aggressively.

Methods

This study retrospectively analyzed 526 patients who underwent CT angiograms to investigate LGIB, and clinicopathological categories were identified and collected. Summative data analysis was performed, including frequencies of binary variables and mean, median, range, and standard deviation of continuous variables. A comparison of quantitative variables was performed using the paired t-test. The paired-Z test was used for categorical data. Potential predictive factors for positive CTA results were initially assessed using univariable analysis, and then p-values less than 0.1 were included as part of the multivariable analysis.

Results

The mean age of this cohort of 526 patients was 74.7 years, with a median of 77 years. Patients who present with visible bleeding are likely to be much older (74 years vs. 67 years, p-value less than 0.01) and are much more hemodynamically unstable, with a higher shock index, INR, PT, APTT, heart rate, and respiratory rate on presentation. Older patients also require a greater volume of transfused blood products and have an increased requirement for anticoagulation reversal. Older patients are also more likely to have comorbidities, including hypertension, ischaemic heart disease and diabetes. Indeed, older patients are more likely to have a positive CTA but are no more likely to undergo embolization or rebleed following embolization at any time interval.

Conclusions

Older patients with lower gastrointestinal bleeding are more likely to be hemodynamically unstable on presentation and have multiple comorbidities. Although they are more likely to have a positive CT angiogram result, they are not more likely to undergo embolization, instead being managed medically or conservatively. Therefore, these patients should receive aggressive medical management from the outset.

How effective is interventional radiology-guided angioembolisation in the setting of lower gastrointestinal bleeding?

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Purpose

The management of lower gastrointestinal bleeding (LGIB) varies between institutions. Mesenteric embolization, first introduced in 1965, is less invasive than surgery, has more excellent bleeding localization than colonoscopy, and thus has become a standard mode of minimally invasive treatment for patients with LGIB. Early catheter design and initial embolic materials were limited by high rates of bowel ischemia, but the development of microcatheter technology and super selective embolization has reduced both incidence of bowel infarction and bleeding from adjacent collaterals. This study explores the data from a single centre, aiming to prove that angioembolisation is efficacious as the first line of management.

Methods

A total of 95 patients who underwent angioembolisation for LGIB were retrospectively analyzed amongst a cohort of 526 patients with a positive CT angiogram. Qualitative and quantitative data were collected. Summative data analysis was performed, including frequencies of binary variables, and mean, median, range, and standard deviation of continuous variables. A comparison of quantitative variables was performed using the paired t-test. Potential predictive factors for embolisation from patients with a positive CTA were initially assessed by using univariable analysis, and then p values ‹0.1 included as part of multivariable analysis.

Results

Comparing patients who undergo embolization to patients who do not receive platelet transfusion. Of the total 95 embolisations, 93 were technically successful, resulting in cessation of bleeding. A total of 19 patients rebled within 72 hours of embolisation, of whom 16 were managed conservatively or with medical management. There were a total of 6 minor complications and 9 major complications, of which a total of 3 required surgery, and 2 died. Multivariate logistic regression was performed to assess for predictors of embolisation amongst patients who underwent CTA for LGIB. Patients with a history of previous LGIB are more likely to undergo embolisation, compared to patients without history of previous LGIB. That is, these patients are 57% less likely to undergo embolisation.

Conclusions

Transcatheter arterial embolization is an effective first-line means of managing LGIB, with a technical success rate and complication rate comparable to therapeutic colonoscopy. Further randomized data is needed to compare various therapeutic methods.

What is the strongest predictor of positive CT mesenteric angiogram in the setting of lower GI bleed?

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Purpose

Computed tomography angiography (CTA) is a first-line investigation in managing severe acute lower gastrointestinal bleeding due to ease of access, high sensitivity, and specificity. The accurate location of a bleeding point on CTA permits invasive angiography and transcatheter angioembolisation of the culprit bleeding vessel. This study aims to predict factors that predict a positive CTA result in patients with lower gastrointestinal bleeding (LGIB), which may then lead to embolization. Conservative investigation and management of patients who are unlikely to have a stable CTA result allows for more efficient use of healthcare resources and can prevent patient exposure to an unnecessary contrast and radiation load.

Methods

This study retrospectively analyzed 526 patients who underwent CTA to investigate LGIB, and clinicopathological categories were identified and collected. Summative data analysis was performed, including frequencies of binary variables and mean, median, range, and standard deviation of continuous variables. A comparison of quantitative variables (if normal distribution) was performed using the paired t-test. The paired-Z test was used for categorical data. Potential predictive factors for positive CTA results were initially assessed by using univariable analysis, and then p values ‹0.1 were included as part of the multivariable analysis.

Results

On multivariate analysis, patients with visible bleeding are 8.65 times (95% CI 1.93 – 38.67 times) more likely (p ‹0.01) to have a positive CTA result than patients who do not have visible bleeding. Patients who have a history of NSAID use are 0.31 times more likely to present with a positive CTA result than patients who do not have a history of NSAID use. Patients who have been transfused pRBCs on admission are 1.17 times (95% CI 1.07 – 1.27 times, p 0.03) more likely to have a positive CTA result than those patients who are not transfused pRBCs.

Conclusions

Most CTA performed for LGIB return negative results, with no bleeding point identified. CTA should be used judiciously in patients presenting with lower GI bleed. Patients with visible bleeding, a history of NSAID use, and a more significant number of transfused packed red blood cells on admission should be considered for CTA.

A pelvic floor rehabilitation program for patients with low anterior resection syndrome after sphincter-preserving surgery for colorectal cancer: A feasibility study

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Aim

Low Anterior Resection Syndrome (LARS) is common after colorectal cancer (CRC) surgery. We examined the feasibility and efficacy of a pelvic floor rehabilitation (PFR) program for CRC survivors after anterior resection surgery and treatment with curative intent.

Method

A prospective, single-arm PFR pilot study. Eligibility criteria: anterior resection with sphincter preservation for CRC (+/- neoadjuvant/adjuvant treatment, +/- reversed temporary stoma); sustained bowel symptoms with LARS Score ›20, minimum 6 months after surgery. The intervention was a 10-week supervised PFR program including: education, biofeedback, pelvic floor muscle training, home exercises. The program was conducted in outpatient clinic with/without telehealth (COVID-19 adaptations). Primary outcome: Adherence and compliance to PFR program. Secondary outcomes: bowel, bladder, sexual dysfunction; quality-of-life (QOL); anorectal physiology parameters. Descriptive data analysis and Chi-squared test were undertaken.

Result

A total of 15 participants (Mean age 61, 44-81 years; Male = 8), 8 participants received hybrid physical/telehealth treatment. 13 had rectal and 2 sigmoid cancer. Surgical procedure: high (1), low (3) and ultralow (11) anterior resection. 11/15 had temporary stoma reversed, mean duration 4.8 months (range 2-10). Five had neoadjuvant chemo/radiotherapy, 7 had adjuvant chemotherapy. Time since bowel continuity restored: mean 19.5 (range 7-60) months. One participant withdrew after week 2; 14/15 included in the final analysis. Intervention adherence was high: 100% attendance; 96% self-reported home exercise program completion. High satisfaction level with rating excellent (60%) and very good (27%). After PFR, anal incontinence episodes and bowel frequency reduced, and the ability to hold for 15 minutes increased ($p<0.05$). LARS (95%CI 6.1,18 $p<0.001$), MSKCC-BFI bowel function (95%CI -14.4,-4.2 $p=0.01$), female bladder function (95%CI1.1,8.6 $p0.019$) scores improved. Faecal incontinence QOL score improved: +0.6 (95%CI -0.9,-0.2 $p<0.001$). Anorectal physiology parameters: mean squeeze pressure, push relaxation and rectal sensory volume thresholds all increased: 9.5%, 70%, 37% respectively ($p<0.05$). At baseline, 40% had Minor (n=6) and 60% Major LARS (n=9). After PFR, 9/14 (64%) improved their LARS by › 1 category.

Conclusion

A PFR program is feasible and highly adhered to by CRC survivors with LARS. PFR improved bowel symptoms, QOL, and anorectal physiological function.

Preoperative video about bowel function and supportive care in colorectal cancer

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Aim

Educational videos can disseminate health information in time-constrained clinical settings. Our aim was to determine feasibility and acceptability of videos we developed about bowel function recovery and supportive care for people undergoing surgery for colorectal cancer (CRC), and their effect on patients' understanding and self-efficacy regarding likely changes in bowel function.

Methods

A non-randomised, single-arm pilot study. Eligibility criteria: stage I-III or limited IV CRC; scheduled elective resection +/- temporary stoma, >7 days after referral; English fluency. Study intervention: view 4 educational videos (each ~ 6-10 minutes) at home pre-surgery. Assessments: electronic surveys before and after viewing. Primary outcome: acceptability. Secondary outcomes: knowledge change via quiz, satisfaction. Descriptive analysis and Chi-squared test were used.

Results

21 of 28 eligible pre-operative patients were recruited. Mean age 57 (32-77 years); Male = 15. Surgical procedures: anterior resection (high (6), low (4) and ultralow (5)); right hemicolectomy (3); and subtotal colectomy (2). One had a temporary stoma. Two had neoadjuvant chemoradiotherapy. 20/21 (95%) participants viewed all 4 videos, 18/21 (85%) completed all surveys. The video watching had 95% adherence. 28% of participants watched the videos more than once. Improvement in knowledge of bowel cancer and function suggested by 11% increase in quiz score (95%CI -16.5 to – 5.06 p<.001). Overall, 82%-94% of participants agreed the videos had excellent content, presentation and information. Self-efficacy was high: 88% strongly agreed or agreed their ability to understand the information, practice self-care and navigate help from health professionals had improved. 98% agreed or strongly agreed that empowerment is important in CRC management.

Conclusion

Educational videos are a feasible and acceptable tool for disseminating information to CRC patients before surgery. The self-paced videos improved bowel function knowledge and self-efficacy in managing the potential impact of surgery on bowel function.

Personalised care plans for patients with rectal cancer: Registry data repurposed

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Background and aims

Cancer treatment is increasingly complex, individualised to patient characteristics, disease stage, biomarkers, and treatment intent. Currently patients typically receive limited, generic written information about their cancer diagnosis and planned treatment. A personalised care plan generated from data captured in an existing clinical registry could better educate and inform patients and GPs.

Methods

Comprehensive clinical data for patients at Western Health (Melbourne) diagnosed between September 2023 - May 2024 with rectal cancer was captured in real time as part of the ongoing colorectal cancer registry (TRACC). In a pilot project co-designed by clinicians and consumers, registry data was extracted to auto-populate a personalised care plan, including diagnosis, planned treatment and surveillance information. Patients and GPs were provided with a copy of the plan and, along with oncology clinicians, were invited to complete evaluation surveys and interviews.

Results

The personalised care plan was provided to 23 patients and their GPs, with 16 patients (70%) and eight GPs (35%) completing evaluation surveys. All responding patients recommend the personalised care plan for other patients, confirming acceptability[1]. This finding was reinforced by comments such as “extremely useful”, and “having this in writing is really helpful”. Seven of 8 (88%) responding GPs found that the care plan supported better communication about treatment and follow-up with their patient. Eight of nine (89%) oncology clinicians reported that the care plan added value to their discussions with patients. Seven GPs (88%) and nine (100%) of oncology clinicians indicated that integrating the personalised care plan into routine practice would be feasible.

Conclusions

Registry-generated personalised care plans are a feasible and efficient way to present important patient information in an accessible and acceptable format. Future projects include expansion of the rectal cancer plans to additional sites, including regional settings, and developing registry-generated plans for other colorectal cancer patients and other cancer types.

[1] Sekhon, M., Cartwright, M., & Francis, J.J. (2022). Development of a theory-informed questionnaire to assess the acceptability of healthcare interventions. BMC Health Services Research. 22, 279. DOI: 10.1186/s12913-022-07577-3

A protocol for pre-treatment testing for antibodies to galactose-alpha-1,3-galactose to mitigate the risk of cetuximab hypersensitivity reactions

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Background

Cetuximab has been shown to improve survival in patients with KRAS wildtype metastatic colorectal cancer. However, high rates of hypersensitivity reactions (HSRs) limit its use, with HSR rates up to 10-20%. A major driver of cetuximab HSR is from pre-formed antibody response to galactose-1,3-alpha-galactose (alpha-gal). Evidence from retrospective studies supports alpha-gal pre-screening in this setting. We are the first to report on the impact of prospective alpha-gal antibody screening on cetuximab HSR.

Methods

Records were reviewed across three medical oncology centres that have adopted alpha-gal antibody screening measures. Data for patients with metastatic colorectal cancer treated with cetuximab were retrieved. All centres assessed alpha-gal antibody status using the ImmunoCAP® ELISA assay.

Due to lack of a shared screening approach across study sites, a pre-determined protocol was retrospectively applied to all cases. This protocol allowed cetuximab administration if alpha-gal levels were ≤0.1 kUA/L, but prohibited it if alpha-gal levels were >0.1 kUA/L in favour of panitumumab administration. Patients were allocated to either the Protocol Applied or Protocol Not Applied cohorts based on protocol requirements being met. The primary outcome between these patient groups was the incidence of cetuximab HSRs.

Results

Of 254 assessable patients, 39 underwent the pre-treatment screening protocol. Of the Protocol Applied group, 3% (n=1/38) experienced a cetuximab HSR compared to 16% (n=35/215) in the Protocol Not Applied group (Odds ratio (OR) 7.16; 95% CI 1.13–299.61, p=0.02). Patients with alpha-gal antibody titres >0.1 kUA/L were more likely to experience a cetuximab HSR (OR 69.71; 95% CI 5.18–4296.81, p=0.0001).

Conclusion

Pre-treatment screening for alpha-gal antibodies significantly reduces the incidence of cetuximab HSRs. A testing threshold of 0.1 kUA/L is effective in identifying patients at risk. Implementing this protocol can improve the safety of cetuximab therapy in high-risk populations.

Single cell and spatial transcriptomic profile of appendiceal tumour peritoneal disease

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Introduction

Appendiceal tumours (AT) are rare and often develop peritoneal disease (PD), with 5-year survival of 15-63% for high-grade adenocarcinomas (HG) and 46-96% for low-grade mucinous neoplasms (LG). While the mainstay of treatment is cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC), the role of systemic chemotherapy is less clear with limited biological characterisation of the ATPD tumour microenvironment (TME). The purpose of this study was to evaluate the TME of ATPD.

Methods

We collected tissue from 35 patients with ATPD during CRS before HIPEC (19 LG, 14 HG and two no-tumour control). We performed single-cell RNA sequencing (scRNAseq) on fresh tissue specimens from nine patients (five LG, four HG), and whole transcriptome spatial analysis (›18000 genes) using the GeoMx Digital Spatial Profiler on formalin-fixed paraffin-embedded tissue from 19 patients (13 LG, six HG). Fluorescent antibodies were used to select cell segments: tumour (anti-CK20), immune (anti-CD45) and stroma (non-CK20/CD45). Analyses were performed with R and a false-discovery rate of 0.05.

Results

LG and HG tumours displayed different patterns of mucin gene expression – epithelial cells of HG expressed the secreted mucin MUC20 in addition to MUC2 and MUC5B also expressed in LG; a subset of mesothelial cells in LG but not HG expressed the transmembrane mucin genes MUC1 (CA15.3) and MUC16 (CA125). Both LG and HG tumours displayed association of mesothelial cells with cancer-associated fibroblasts (CAF), and CAF subsets expressing genes of epithelial-mesenchymal transition (EMT). ScRNAseq showed a preponderance of pro-tumoural T-cell and myeloid cells. Spatial analysis of tumour segments revealed HG compared to LG had increased expression of genes associated with cell-cycle progression (MYC, E2F, G2M checkpoint), metabolic reprogramming and EMT. LG compared to HG had increased expression of genes associated with pro-tumoural immunity (NF-κB, TGF-β), regulation of tumour growth (P53), hypoxia and glycosylation pathways. Immune and stromal segments did not have significant transcriptomic differences between LG and HG.

Conclusion

This study provides novel insights into the biological profile of ATPD by describing TME cell types, immune function, tumour growth and cell-cycle pathways. These findings may be used to identify clinically relevant biomarkers and new therapeutic targets.

Characteristics of immune infiltrating cells in the tumour microenvironment of appendiceal tumour peritoneal disease

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Introduction

Appendiceal tumours (AT) often develop peritoneal disease (PD) and respond poorly to current systemic treatments. There are limited studies on the characteristics and prognostic impact of infiltrating immune cells within the tumour microenvironment (TME) of ATPD Infiltrating immune cells are associated with survival outcomes and predict the effectiveness of immunotherapies in solid tumours. Different definitions have been developed to describe infiltrating immune cells and associated structures such as tertiary lymphoid aggregates (TLS). The aim of our study was to describe the immune TME in patients with ATPD to explore the potential for novel immunotherapies as a future therapeutic strategy.

Methods

Fresh tissue was collected during cytoreductive surgery before HIPEC from consenting patients with ATPD. Haematoxylin and eosin (H&E) staining was performed on sections of formalin-fixed and paraffin-embedded tissue. Sections were evaluated by light microscopy for the presence of immune cells based on morphological appearance (no structure, developing or developed aggregates). Immune cells forming aggregates were counted, the diameter of aggregates measured using QuPath and immunohistochemical staining for T-cells (anti-CD3/CD4/CD8), B-cells (anti-CD20/23) and myeloid cells (anti-CD68/206/21) was performed.

Results

We evaluated 33 patients with ATPD, 18 who had immune cell segments for evaluation: 15 low-grade (LG) disease of appendiceal mucinous neoplasms and 14 high-grade (HG) of primary appendiceal adenocarcinomas. There was a higher proportion of developed immune aggregates in LG (79%) than HG ATPD (33%). The mean aggregate size was similar in LG (250µm diameter) and HG ATPD (226µm) as was mean number of immune cells in LG (1341) and HG (1422). Germinal centre formation (CD21+CD23+ cells) was identified in developed aggregates from eight cases (seven LG and one HG).

Conclusion

This study represents the first formal description and characterisation of infiltrating immune cells in ATPD. Germinal centre formation is consistent with the capacity for in-situ antibody production and the potential for an anti-tumoural immune response. The presence of TLS, particularly in LG ATPD, is compelling for further investigation of novel immunotherapies in this disease.

Outcomes of patients with appendiceal tumours: A contemporary prospective cohort treated at a state peritonectomy service

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Introduction

Appendiceal tumours (AT) are rare with 5-year overall survival (OS) up to 96% for appendiceal mucinous neoplasms (AMN) and as low as 14% for appendiceal adenocarcinomas (AA). Peritoneal disease occurs frequently, and burden is described by the peritoneal cancer index (PCI; 0-39). Cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) is the definitive treatment with residual disease quantified by the completeness of cytoreduction score (CC0-3). The role of systemic chemotherapy in different settings remains unclear. The aim was to evaluate AT treatment and outcomes focusing on the impact of perioperative systemic chemotherapy.

Method

We reviewed prospective data from the database of a state peritonectomy service, April 2017 to October 2022. Variables included demographics, tumour characteristics, treatment details and survival outcomes. The primary endpoint was (OS). Analysis was by the Kaplan-Meier method with log-rank p-value using R.

Results

We identified 208 patients with AT: 83 AMNs (40%), 124 AA (60%) and one neuroendocrine carcinoma. Median age was 56 (21-78) and 110 (53%) were female. CRS was performed in 154 (74%) and HIPEC administered in 135 (65%); median PCI was 23 (0-39) and 121 (80%) had no or minimal residual disease (CC0-1). Peritoneal disease (M1) occurred in 152 (73%) and 51 (25%) patients were node positive. Systemic chemotherapy (73% fluoropyrimidine/oxaliplatin) was given to 89 patients (43%). Median follow-up was 33 months, median OS was 84 months (1-306) and 5-year OS 59% (AMN 90%, AA 41%). OS was improved in high grade M1 AA patients who received neo/adjuvant compared to no chemotherapy, but this was not significant (38 vs 15 months, p=0.056). There was longer OS in node positive M1 AA patients who received neo/adjuvant compared to no chemotherapy (33 vs 6 months; p<0.0001).

Conclusion

This patient cohort reflective of contemporary practice is comparable to best international outcomes. Systemic chemotherapy does not benefit all patients with peritoneal disease after CRS/HIPEC but we show a benefit in those with positive nodes. This contributes to similar outcomes reported by other published literature and supports this in clinical practice. There is need to develop biomarkers and better treatments to improve the survival of these patients.

Efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer with and without liver metastasis: A subgroup analysis of the phase 3 FRESCO-2 trial

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Introduction

Fruquintinib is a highly selective, oral inhibitor of all 3 VEGFRs (-1, -2, and -3) and was approved by the US FDA and European Commission for previously treated metastatic CRC (mCRC). Approvals were based on FRESCO (NCT02314819) and FRESCO-2 (NCT04322539), which met their primary endpoints demonstrating consistent improvements in overall survival (OS) with fruquintinib+best supportive care (BSC) vs placebo+BSC in patients with mCRC.

Methods

FRESCO-2 efficacy and safety data, focusing on hepatic function abnormality, were evaluated according to the presence and absence of liver metastases at baseline.

Results

Overall, 339/461 (74%) and 156/230 (68%) patients randomized (2:1) to receive fruquintinib and placebo had liver metastases, respectively. OS was improved with fruquintinib vs placebo in patients with liver metastases (median 6.4 vs 3.7 months; HR 0.58; 95% CI 0.47–0.71), and without liver metastases (median 12.1 vs 8.4 months; HR 0.77; 95% CI 0.51–1.16). Progression-free survival was also improved with fruquintinib vs placebo in patients with and without liver metastases: median 3.6 vs 1.8 months (HR 0.29; 95% CI 0.23–0.36) and 4.5 vs 1.9 months (HR 0.33; 95% CI 0.24–0.48), respectively. Disease control rate was higher with fruquintinib vs placebo in patients with and without liver metastases (53% vs 8% and 64% vs 32%). Any grade and grade ≥3 treatment emergent adverse events with fruquintinib vs placebo occurred in 99% vs 94% and 64% vs 54% of patients with liver metastases, and 99% vs 91% and 60% vs 44% of patients without liver metastases. The percentages of patients with any grade and grade ≥3 hepatic function abnormalities (adverse event of special interest category) were comparable with fruquintinib vs placebo in patients with liver metastases (28% vs 26%; 10% vs 13%) but higher with fruquintinib vs placebo in patients without liver metastases (16% vs 4%; 3% vs 1%).

Conclusions

Fruquintinib consistently improved OS vs placebo and is an effective and tolerable treatment option in patients with previously treated mCRC regardless of liver metastases.

Efficacy and safety of fruquintinib in patients with metastatic colorectal cancer according to prior treatment sequence in the refractory setting: Results from FRESCO and FRESCO-2

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Background

Fruquintinib is a highly selective, oral tyrosine kinase inhibitor of all 3 VEGF receptors, approved by the US FDA and European Commission for previously treated metastatic colorectal cancer (mCRC). Efficacy and safety of fruquintinib+best supportive care (BSC) vs placebo+BSC were analyzed according to prior treatment sequence using FRESCO (NCT02314819) and FRESCO-2 (NCT04322539) data.

Methods

In both studies, patients were randomized 2:1 to receive fruquintinib 5 mg or matching placebo, by mouth, once-daily for 21 days every 28 days, +BSC. In FRESCO, eligible patients had received ≥2 prior chemotherapy regimens and were permitted to have received prior anti-VEGF and/or anti-EGFR therapies; in FRESCO-2, in addition to standard chemotherapies, anti-VEGF, and anti-EGFR therapies if indicated, prior exposure to trifluridine/tipiracil (TAS-102) and/or regorafenib was required.

Results

In FRESCO, 16/416 patients (4%) had received TAS-102 and no patients had received regorafenib. In FRESCO-2, prior therapies were balanced between treatment arms. Improvements in median overall survival for fruquintinib vs placebo were similar regardless of prior treatment sequence: TAS-102/regorafenib-naïve (n=278 vs n=138; 9.3 vs 6.6 months; HR 0.65), TAS-102 only (n=240 vs n=121; 7.7 vs 5.1 months; HR 0.72); regorafenib only (n=40 vs n=18; 10.2 vs 8.2 months; HR 0.77); TAS-102 then regorafenib (n=95 vs n=44; 6.6 vs 3.3 months; HR 0.53); regorafenib then TAS-102 (n=84 vs n=45; 8.5 vs 4.8 months; HR 0.67). A similar pattern was observed for improvements in median progression-free survival: TAS-102/regorafenib-naïve (3.7 vs 1.8 months; HR 0.26); TAS-102 only (3.6 vs 1.9 months; HR 0.37); regorafenib only (3.6 vs 1.9 months; HR 0.29); TAS-102 then regorafenib (3.7 vs 1.7 months; HR 0.31); regorafenib then TAS-102 (3.8 vs 1.8 months; HR 0.25). Fruquintinib safety profile was consistent regardless of prior treatment sequence.

Conclusion

Fruquintinib is effective in mCRC with a manageable safety profile regardless of prior TAS-102 or regorafenib treatment and sequence. Fruquintinib provides a new treatment option for patients with previously treated mCRC regardless of prior TAS-102 or regorafenib exposure.

Incidence and potential prognostic implications of human epidermal growth factor receptor 2 (HER2) alterations in colorectal cancer

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Amplification of the human epidermal growth factor receptor 2 (HER2) oncogene or overexpression of its protein leads to uncontrolled cell proliferation and tumorigenesis. The incidence of HER2 amplification in colorectal cancer (CRC) is reported to be 1.3–6%. Here, we report HER2 alteration data with clinicopathological correlations and survival outcomes from a large health district in Australia. Methods: Clinicopathological data was analysed from ethnically diverse patients with metastatic CRC treated at Southwestern Sydney Local Health District from 2014-2021. Next generation sequencing was performed using the Qiagen 30-gene panel. Mismatch repair (MMR) status was determined using immunohistochemical staining. Demographic characteristics, histological features and survival outcomes were obtained from electronic medical records. Results: 339 patients were identified, of whom 110 (32%) had HER2 alterations. Of these 110 patients, 60% were male and 40% female. Most (77%) were Caucasian, 11% Middle Eastern, 11% Asian and 1% South American. Median age at diagnosis was 68 years. The vast majority were adenocarcinoma (85%) and the remainder mucinous adenocarcinoma (15%). 52% of patients had de-novo metastatic disease. HER2 amplifications were present in 3.6% and HER2 point mutations in 96.4%. Of the point mutations, 97 (92%) were gain of function mutations, 2 loss of function, 1 deletion and 6 were mutations which did not alter gene function. 35.4% of patients with HER2 alterations had concurrent KRAS mutations, 14.5% had concurrent BRAF mutations and MMR-deficiency was present in 10%. 62% were left-sided tumours and 38% were right-sided. The HER2 amplified cases were all left-sided, KRAS and BRAF wild-type and mismatch repair proficient. Median overall survival of patients with HER2 gain of function mutations was 40 months.

Conclusions

HER2 alterations were identified in 32%, of which the majority were gain of function point mutations, and HER2 amplifications in 3.6% of patients with metastatic CRC in an ethnically diverse cohort in Australia. This has clinical significance given the potential role of HER2 targeted therapy. Further statistical analysis including multivariable survival analyses and correlation of HER2 alterations and clinicopathological variables, is in progress.

TP53 mutations in exceptionally good performers in RAS/BRAF-wildtype metastatic colorectal cancer

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Background

Colorectal cancer (CRC) is a heterogenous disease. RAS/BRAF mutations, MSI status and tumour sidedness are prognostic and predictive biomarkers. TP53 is the most frequently mutated gene in metastatic CRC (mCRC), ranging from 35 to 73%, however its prognostic role remains unclear. We identified mutations in mCRC patients with exceptionally good survival, with a focus on TP53 to clarify its prognostic role. We also aim to assess feasibility of next generation sequencing (NGS) on formalin-fixed paraffin-embedded (FFPE) archival biobank samples.

Methods

Good performers (GP) with RAS/BRAF-wildtype (targeted pyrosequencing) and MMR-proficient mCRC (immunohistochemistry) from the South-Western Sydney Pathology biobank from 2010-2018 with overall survival (OS) >3 years or exceptional responses to treatment were identified. 161-gene-panel (ThermoFisher GenexusTM) NGS was performed on FFPE tissues. TP53 mutations identified were correlated with clinicopathological variables and outcomes.

Results

52 GP were identified. Median age was 65, 60% male. 79% Caucasian, 19% Asian, 87% left-sided tumours. 58% had ≥2 lines of therapy. Median OS was 56.4 months (20.6-127.1 months). 38% (20) of GP had valid NGS results on FFPE tissue.

Of those 20 patients 68% had a TP53 mutation; (73%) missense point mutations, including TP53p.Arg175His (20%) and TP53p.Arg273Cys (20%). 13% had nonsense mutations including TP53p.Trp91Ter and TP53p.Arg196Ter. One patient had an in-frame deletion (TP53p.Pro177_Cys182del); another a frame-shift insertion mutation (TP53p.Pro191SerfsTer18). 20% TP53 mutations co-occurred with other mutations (NGS) – concurrent KRASp.Gly12Val and CHEK2 mutations; concurrent KRASp.Gly13Cys mutation; and concurrent EGFRp.Arg831Cys mutation. Variant allele frequency of TP53 mutations ranged from 2.8 to 73.9%.

Conclusion

NGS on retrospective samples is possible, however the rate of invalid results is high in FFPE tissues >5 years old. The most frequently mutated gene in RAS/BRAF-wildtype (targeted pyrosequencing) mCRC patients who are exceptionally good performers is TP53, the mutational frequency being comparable to unselected mCRC cohorts. 1 in 5 patients with TP53 mutations had additional concurrent mutations, including KRAS mutations not detected on older non-NGS techniques. TP53 mutation frequency does not appear to distinguish the good performers however further work will focus on types of TP53 mutations and coexisting mutations, and whether these predict for better biology.

Exceptional responders in a Phase 1/2 clinical trial of dendrimer-enhanced (DEP) SN38 (SN38-SPL9111) for the treatment of metastatic colorectal cancer (mCRC)

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Background

DEP SN38 is a novel water-soluble dendrimer conjugated to SN38, the active metabolite of irinotecan, that avoids liver metabolism for activation, reducing off-target toxicity. Dendrimer nanoparticles, retained in tumour microenvironment via enhanced permeability and retention, enable prolonged cytotoxic drug targeting to tumours. The multicentre global Phase 1/2 DEP SN38 trial has demonstrated promising efficacy in several tumour types including mCRC and highly favourable safety and tolerability, particularly low rates of severe gastrointestinal events and lack of cholinergic symptoms when compared to conventional irinotecan (c-IRI) (Liu et al AACR 2023; ASCO 2024). We present a single centre experience of five exceptional responders with mCRC in this ongoing trial.

Methods

All patients enrolled at the Kinghorn Cancer Centre with treatment duration ≥ 6 months were included for this analysis until data cut-off July 2024. Patients received IV 2 or 3-weekly DEP-SN38 (12.5-15mg/m2) +/- 5-fluorouracil/leucovorin (5-FU/LV) (De Gramont protocol) until disease progression or unacceptable toxicity.

Results

Five patients (2M, 3F), ECOG 0-1, with mCRC were included with median age 38.0 years (range 31-55), with a median 5 prior treatment lines (range 2-6) and all but 1 patient with prior response to C-IRI doublet/triplet + targeted agent regimens. Treatment was monotherapy DEP SN38 (n=3) or in combination with 5-FU/LV (n=2). A median of 24 cycles were given (IQR 11). Median duration on treatment was 59 weeks (range 27-73). One patient achieved a partial response and 4 patients exhibited stable disease, with disease control for up to 72 weeks. Concomitant reduction in CEA levels of up to 74% was observed in 4 patients. Dose limiting toxicities were seen in 20% (n=1) with grade 3 febrile neutropenia requiring one level dose reduction (15 to recommended dose of 12.5 mg/m2 SN38). Neutropenia was otherwise uneventful and managed with G-CSF. Gastrointestinal events were mild to moderate with only one event of grade 3 nausea. Two patients remained on treatment beyond progression due to clinical benefit.

Conclusion

DEP SN38 has demonstrated sustained disease control and manageable toxicity profiles in heavily pre-treated CRC patients with previous irinotecan exposure. Further DEP SN38 studies are warranted in CRC to confirm efficacy.

Circulating tumour cells and patient-derived organoids in appendiceal tumours for precision medicine

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Background

Appendiceal tumours (AT) are rare, affecting around 2 per million people. Peritoneal disease is frequently seen and the mainstay of treatment is cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) but most patients experience recurrence. Systemic treatments are poorly defined with regimens extrapolated from colorectal cancer and preclinical models for therapeutic testing are lacking.

Aims

To investigate the detection of a liquid biopsy biomarker, circulating tumour cells (CTCs), and generate patient-derived organoid (PDO) models in AT to better understand AT biology, identify novel targets and test therapeutic agents.

Methods

Peripheral venous blood samples (n=17) and tumour samples (n=5) at Royal Prince Alfred Hospital were obtained at the time of CRS/HIPEC. CTCs were isolated and detected using the AccuCyte-CyteFinder platform (RareCyte®) where CTCs were defined by pan-CK and EpCAM expression. PDOs (n=5) were generated from resected tumour tissue and tested for response to chemotherapy agents using the cell viability assay, CellTitreGlo (Promega).

Results

CTCs were detected in 53% (9/17) AT patients ranging from 1-3 CTCs in 4mL blood. CTCs were detected in 88% (7/8) of patients with high-grade AT compared to 22% (2/9) with low-grade AT. PDOs (4/5) were successfully generated and established within 1-3 months. The PDOs demonstrated variable response to FOLFOX and FOLFIRI combinations.

Conclusion

This is the first study to detect CTCs in AT suggesting a potential role for CTC analysis in disease surveillance. PDOs were successfully established and facilitated testing with standard chemotherapy regimens. PDOs may provide a reliable tumour model for personalised therapeutics and to test novel agents in this rare, understudied disease.

Developing consensus pathway for total neoadjuvant therapy (TNT)/organ preservation (OP) in locally advanced rectal cancer (LARC): Practical considerations

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Background

A meeting of specialists involved in the management of patients with LARC in the Australian Capital Territory was organised to develop consensus for TNT/OP pathway.

Method

Seventeen specialists from various medical/nursing disciplines met to discuss and develop TNT/OP pathway. All participants reviewed relevant publications beforehand. A medical oncologist facilitated discussions on the following issues: induction vs consolidation chemotherapy, optimal radiation therapy dose, optimal number of chemotherapy cycles, FOLFIRINOX vs FOLFOX regimens, OP vs surgery, role of PET, follow-up frequency of endoscopy/MRIs, and definition of complete clinical response (cCR)/near-complete clinical response (nCR). This was followed by three case discussions to identify gaps in evidence.

Results

Consensus was reached on the following:

1. Consider PET for initial staging if conventional imaging inconclusive.
2. Prescribe long-course chemo-radiotherapy (LCCRT) followed by chemotherapy (consolidation approach) for patients deemed eligible/opting for OP.
3. Recognition that an upfront decision for OP vs surgery may not always be straightforward and is best deferred until at assessment following completion of TNT in select cases.
4. Tumour response grading will be reported on all rectal MRIs using T2 and Diffusion weighting primarily. OP to be offered only to patients achieving cCR on follow up assessment.

Barriers/concerns with OP approach:

1. Wait-list for endoscopy in public system.
2. Out-of-pocket cost for follow-up MRIs.
3. Learning curve for surgeons: acknowledgement of their temptation to biopsy on follow-up endoscopy (when not recommended).
4. Learning curve for reporting radiologists on post-treatment MRIs. Radiology resource allocation in the public setting, for the recommended regime of 3-monthly intervals, as well as vendor-neutral viewing and direct comparison, is a significant limitation requiring service development.
5. Need for health literacy and scan anxiety for patients.

Conclusion

There was consensus to pursue TNT with consolidation chemotherapy approach for patients eligible for/considering OP. However, several barriers such as wait-list for endoscopic assessments in public system, cost associated with follow-up MRIs +/- endoscopies, and learning curve for involved clinicians would affect adoption of this approach.

Optimal therapy for palliative intent colorectal cancer – A real-world analysis of one, two or three chemotherapy drugs as first line treatment

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Background

Patients with metastatic colorectal cancer (mCRC) can benefit from treatment across 3-4 lines (L) of therapy. Doublet chemotherapy (CT) +/- a biologic is historically the dominant 1L approach. Randomised trial data indicates triplet CT improves survival, but increases adverse events, whereas single agent CT provides similar survival, but lower response rates. Defining patients most likely to benefit from initial triplet CT, or best initially treated with single agent CT, could inform treatment selection.

Methods

We analysed real-world data from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry, prospectively collected at 27 Australian cancer centres for patients diagnosed July 2009-July 2022. We included consecutive patients with mCRC commencing 1L, palliative-intent CT. We examined factors associated with treatment selection and outcomes.

Results

Of 4913 patients with mCRC, 3564 (72.5%) received palliative-intent CT. Of these 142 (4.0%) received triplet, 2630 (73.8%) doublet and 792 (22.2%) single agent CT. Compared to doublet CT; those receiving triplet were younger (median 45yrs), and more often had liver metastases, de novo metastatic disease, and BRAF V600E mutant (mt) cancers. Those receiving single agent CT were older (median 75yrs), and more often had poor performance status (PS), no liver metastases and de novo metastatic disease. Of 2630 commencing doublet CT, 1493 (56.8%) received 2L, less likely if older, recurrent metastatic disease, and no 1L bevacizumab. Of 792 patients receiving single agent CT, 312 (39.4%) received 2L, less likely if older, poorer PS, BRAF mt, primary not resected, and no 1L bevacizumab. Median overall survival (OS) for doublet CT was 30.8 months [IQR: 16.9-62.5], compared to median OS 30.3 months [IQR: 15.2-83.0] for triplet (HR=0.9432, p =0.991) and 27.0 months [IQR: 13.8-51.9] for single agent (HR=0.836, p =0.0004).

Conclusion

This real-world data of mCRC patients treated with palliative-intent demonstrates doublet CT is a dominant strategy. Triplet therapy is rarely used, more often in younger patients and those with high-risk features. Single agent CT is often used for older and poor PS patients. Many real-world patients do not receive 2L, more so older and poor PS patients. Excellent OS can be achieved with initial single agent CT.

Real-world treatment patterns and outcomes for patients with deficient MMR metastatic colorectal cancer

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Background

The Keynote-177 trial demonstrated that pembrolizumab improves progression-free survival (PFS) compared with chemotherapy +/- biologic in previously untreated patients with deficient MMR (dMMR) metastatic colorectal cancer (mCRC). For patients with a BRAF V600E mutation (BRAFmt), frequent among dMMR patients, the BEACON trial demonstrated that encorafenib and cetuximab given after initial chemotherapy improved overall survival (OS). For the dMMR and BRAFmt patient, the optimal treatment post first-line (1L) immunotherapy is unknown. Current studies are exploring combination approaches for dMMR patients and 1L chemotherapy plus BRAF directed therapy for BRAFmt patients. In this rapidly evolving space, real-world data on contemporaneous approaches and outcomes is of interest.

Methods

Patients with mCRC were identified from the TRACC and TRACC-SELECT registries. We examined 1L treatment outcomes for dMMR patients diagnosed after August 2021, when pembrolizumab became available via the Pharmaceutical Benefits Scheme (PBS), and subsequent treatments for the BRAFmt subset.

Results

From August 2021, 675 patients have been entered into the TRACC registry. Data on 53 (8%) dMMR patients were available, including 10 dMMR from TRACC-SELECT. Of these, 46/53 (87%) received 1L pembrolizumab; the median age was 73 years and 21/46 (46%) also had a BRAFmt. The median duration of 1L pembrolizumab was 8 months. Discontinuation in 24/46 (52%) patients was due to disease progression (n=10, 42%), adverse events (n=4, 17%), other (n=7, 29%), complete response (n=2, 8%), and completion of 2 years of treatment (n=1, 4%). The median PFS of pembrolizumab treated patients was 22 months. Overall survival data is immature. Of the 21 dMMR/BRAFmt patients who received 1L pembrolizumab, 12 (57%) discontinued treatment, 6/12 (50%) of whom received BSC, 4/12 (33%) received encorafenib plus cetuximab, and 2/12 (17%) received chemotherapy plus bevacizumab as 2L treatment.

Conclusion

An initial analysis of real-world data demonstrates strong uptake of 1L treatment with pembrolizumab for patients with dMMR mCRC following PBS listing. The data on treatment discontinuation will be further explored, including chart reviews. Few dMMR and BRAFmt patients have received 2L treatment to date. Ongoing data collection and further analyses are planned, including of overall survival.

Initial multidisciplinary meeting assessment of resectability of colorectal cancer liver metastases versus clinical outcome

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Background

Surgery improves long-term survival for resectable, liver-only metastatic colorectal cancer (mCRC). With no consensus definition of “resectable” disease, decisions regarding resectability are reliant on the expertise and judgement of the multidisciplinary team (MDT). This study examines the clinical outcome versus initial MDT assessment of resectability in an Australian population with mCRC.

Methods

Patients with liver-only mCRC diagnosed January 2009 to December 2022 were identified from the Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry. Patients were classified based on prospectively documented MDT assessment as “resectable,” “potentially resectable,” or “unresectable.” The correlation between initial MDT assessment and clinical outcome, and any impact of clinicopathologic factors were examined. Kaplan-Meier analysis assessed overall survival based on MDT assessment and resection status.

Results

Of 4437 patients with mCRC identified through TRACC, 1250 (28%) had liver-only disease at presentation, with 497 (43%), 277 (24%), and 374 (33%) classified by the MDT as “unresectable,” “potentially resectable,” and “resectable,” respectively. In total, 516 (41%) ultimately underwent surgical resection, including 30 (6%) of the “initially unresectable,” 148 (53%) of the “potentially resectable,” and 338 (90%) of the “resectable” at a median of 9.5, 5.9, and 2.4 months from the diagnosis of liver metastases, respectively. Resection in the “unresectable” patient population was associated with younger age (median age 63 vs 69, p=0.0006), better performance status (ECOG 0-1 100% vs 74%, p=0.0017), and fewer comorbidities (Charlson index 0-3 in 73% vs 53%, p=0.0296) compared with no resection. Median overall survival was longer for resected versus non-resected patients across all categories: “unresectable” (59.2 vs 17.6 months, p <0.0001), “potentially resectable” (57.2 vs 22.8 months, p <0.0001), and “resectable” (108 vs 55 months, p <0.0001).

Conclusions

This real-world study demonstrates the potential for “initially unresectable” patients to become surgical candidates following systemic therapy, more likely in younger and fitter patients, with excellent survival outcomes. This highlights the value of routine, repeated MDT assessments for patients with liver-only disease who are continuing to respond to systemic therapy, even for those initially considered ineligible for surgery.

Real-world impact of pembrolizumab availability for deficient mismatch repair metastatic colorectal cancer

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Background

Immune checkpoint inhibitor (ICI) therapy has emerged as a standard treatment for deficient mismatch repair (dMMR) metastatic colorectal cancer (mCRC). Pembrolizumab (an ICI) became widely available as a first line option in Australia following PBS listing in August 2021. Prior to that, ICI therapy was only available via clinical trial or self-funding.

Methods

The TRACC mCRC registry data at participating Australian sites was analysed from January 2015 (when MMR testing was becoming routine) until July 2024. First line treatment of dMMR cancers was compared pre- and post-PBS funding.

Results

Of 3018 patients, 2533 (84%) had known MMR status. Of these, 180 (7%) were dMMR, which was associated with older age (median age 70 vs 63, p<0.001), better performance status (ECOG 0-1 77% vs 88%, p=0.035), more comorbidities (Charlson Comorbidity Index >3 56% vs 46%, p=0.001), a right-side primary (65% vs 30%, p<0.001), and a BRAF V600E mutation (52% vs 12%, p<0.001). Of the dMMR patients treated prior to PBS listing, 89/123 (72%) received first line therapy, with 52/57 (91%) receiving first line therapy post PBS listing (p=0.004). Of those treated prior to PBS listing, 59/89 (66%) received chemotherapy and 27/85 (30%) an ICI. Following PBS listing, 50/52 (96%) received pembrolizumab. Of the patients 75 years and older, a significantly higher proportion of patients were treated with any first line therapy post PBS listing (92% vs 60%, p=0.005).

Conclusion

Previously reported associations of dMMR were observed. The higher-than-expected proportion of dMMR and of BRAF mutant patients is likely driven by the inclusion of many older patients in this real-world study. Many patients were able to access immune checkpoint inhibitors prior to PBS listing, potentially via trials or access programs. Early uptake of pembrolizumab following PBS listing has been high, notably increasing the proportion of elderly, more comorbid patients receiving active therapy. Outcome data will be reported separately.

Digital spatial proteomic profiling of the tumour microenvironment in rectal cancer: insights into radiotherapy response

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Variation in response to radiotherapy for the treatment of rectal cancer is likely due to heterogeneity in the tumour microenvironment. However, to date, no reliable predictive biomarkers of response are in clinical use and the mechanisms underlying response are unknown. Tertiary lymphoid structures (TLS), which are ectopic lymphoid aggregates found in the tumour microenvironment, have been linked to response to immunotherapy, but little is known about their role in radiotherapy. Here, we aimed to explore the potential of lymphocytes and tertiary lymphoid structures as predictive biomarkers of response to radiotherapy and profile the tumour immune microenvironment in the context of response to radiotherapy.

For this study, we accessed pre-treatment biopsies from 20 rectal cancer patients with known pathological response following LCCRT. We selected regions of interest based on immunohistological identification of tumour and lymphocytic infiltrate in formalin-fixed paraffin-embedded tissue. We performed targeted proteomic profiling of 87 immuno-oncology proteins using the Nanostring GeoMx Digital Spatial Profiler to quantify protein expression with spatial resolution within regions of interest, including TLSs, in the tumour microenvironment.

Unsupervised clustering based on normalised protein expression showed a clear separation between the complete responders and all other tumours, and this separation is driven by differences in T cells within TLSs (CD3+). Differentially expressed proteins within CD3+ aggregates include depletion of the natural killer cell marker, CD56 and increased expression of the apoptosis marker, cleaved caspase 9. The distribution of TLS-tumour distance was also significantly different between response groups.

The study highlights the role of TLSs in modulating the immunogenic landscape of the tumour microenvironment in rectal cancer, likely influencing the response to radiotherapy. Spatially resolved proteomic analyses identifies potential biomarkers for radiotherapy response and underscores the importance of profiling TME complexity when stratifying patients for therapy.

A call to arms – Time for a consensus definition of tumour deposits in colorectal cancer

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Background

Over the past decade, extranodal tumour deposits (TDs) have emerged as a potential adverse prognostic factor in colorectal cancer (CRC). However, Delphi consensus studies indicate lack of a standardised definition for these pathological entities amongst expert gastrointestinal pathologists. Wide disparity in published TD prevalence (10.2–44.2%) further suggests inter-observer variation. The TNM 8th edition N1c category, whereby TDs are considered solely in the absence of lymph node metastases, is likewise contentious. Therefore, we sought to evaluate the prevalence of TDs in CRC resection specimens and their impact on survival in a large Australian cohort.

Methods

A single centre, retrospective review was conducted utilising data from the prospectively-collected Concord Hospital Colorectal Cancer Database. Consecutive adult patients who underwent either curative or palliative surgical resection of colon or rectal adenocarcinoma, from August 2008 to July 2024, were included. Outcomes measures studied included overall (OS) and disease-free survival (DFS), and the influence of standard clinicopathological variables (including TDs) were explored. Statistical analysis included descriptives, Kaplan Meier survival and Cox regression analyses.

Results

1960 patients were included; 55.4% male, mean age 69.7 years (SD 13.4). TD prevalence was 10.0% (n=196); 8.3% amongst right colon and 11.4% amongst left colon/rectal cancers. 14 patients were classified as nodal stage N1c (seven in the absence of distant metastases). Kaplan Meier analysis demonstrated that TD-positive patients had poorer median OS compared to TD-negative patients (113 versus 57 months, $p<0.001$). This was replicated in subgroup analysis by TNM stage, for both OS and DFS. TDs were a confirmed independent negative predictive factor for OS in both univariate (HR=2.81,[95% CI 2.34–3.38],$p<0.001$) and multivariate (aHR=1.38,[95%CI 1.01–1.89],$p=0.04$) analyses.

Conclusion

Extranodal TDs were independent negative predictors of CRC survival in our cohort, which validates international literature. Intriguingly, TD prevalence in our cohort is lower than any previously published study, and N1c classification is exceedingly low. With increasing appreciation of the prognostic significance of TDs, and growing consideration for novel approaches to its incorporation in future CRC staging classification systems, there is need to establish a standardised definition for this important pathological entity and minimise inter-observer variation in its diagnosis.

Acute hyperammonemic encephalopathy after 5-fluorouracil based adjuvant chemotherapy in a dialysis-dependent patient

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Hyperammonemic encephalopathy (HAE) is an uncommon but life-threatening complication of treatment with 5-fluorouracil based chemotherapy seen in an estimated 0.7% of patients.

The proposed mechanism is an increase in metabolites of fluorouracil causing Krebs cycle impairment and reduced levels of ATP available for use as an energy source in the Urea cycle, impeding clearance of serum ammonia. Significantly increased serum ammonia is associated with features of encephalopathy including acute onset of neurological and psychiatric symptoms, such as confusion, reduced levels of consciousness, tremor, seizures and hallucinations. Risk factors include urea cycle disorders (UCDs) including partial or complete DPD deficiency, renal impairment, infection, dehydration, sarcopenia and constipation.

We present the case of a 50-year-old man who experienced 5-fluorouracil induced HAE requiring ICU admission after one cycle of adjuvant treatment with FOLFOX chemotherapy for stage 3b sigmoid adenocarcinoma. This was on a background of dialysis dependent end stage renal disease (ESRD) in the context of an acute kidney injury. This occurred in spite of dose adjustment of chemotherapy based on local guidelines for patients with renal impairment. No inborn errors of metabolism were identified and DPYD genotyping was normal. The patient was treated with ammonia scavenger therapy, continuous renal replacement therapy and a low protein diet with ammonia levels found to normalise within four days of treatment. No lasting encephalopathic features were identified.

This is a rare case in a patient with ESRD. Patients are generally difficult to treat with variable evidence for chemotherapy dosing in the adjuvant setting. We discuss the patient's clinical course in the context of his risk factors for HAE, and how appropriate management was determined in the absence of a specific local guideline for treatment of drug-induced HAE in the context of renal impairment.

This case highlights the complexities of managing chemotherapy in patients with ESRD and underscores the need for multidisciplinary care and individualised treatment adjustments. The occurrence of HAE in this context emphasises the importance of early recognition and intervention to prevent significant morbidity. Further research is needed to establish standardised protocols for management, especially in patients with compromised renal function.

A focused effort to collect comprehensive real-world treatment and outcome data on select molecularly defined and young onset metastatic colorectal cancer patients: An initial report on the TRACC-SELECT registry

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Background

Targeted therapy for molecularly defined subsets of metastatic colorectal cancer (mCRC) can improve patient survival. With expanding access to molecular testing, new markers of interest are emerging but as these markers are rare or very rarely found, sample sizes are limited. Young onset mCRC is increasing. Many sites are unable to participate in the existing TRACC registry which collects data on consecutive patients, due to patient volume. TRACC-SELECT is a focused effort to engage additional centres to only collect data on defined mCRC patient subsets of interest, which could enable more centres to contribute to audit and research activities and bolster sample sizes.

Methods

In June 2022, the multi-site TRACC-SELECT registry was established, initially including mCRC patients with dMMR, BRAFV600E mutant (mt), KRASG12C mt, HER2 changes, POLE mt, FGFR2 mt or NTRK fusion, or a mCRC diagnosis ≤40 years. Patients were diagnosed with mCRC after 1/1/21. Here we provide an initial analysis of TRACC-SELECT enrolment, collated with TRACC registry data at 19 sites for the same patient subsets.

Results

TRACC-SELECT has been initiated at 8 sites (75% regional, 13% private), with a further 9 sites to be initiated, to date enrolling 40 patients. Sites have expressed enthusiasm in participating given the modest data entry burden and heightened clinician interest in these patient subsets. Number of patients enrolled in TRACC-SELECT (TS) and TRACC (T) for defined subgroups include 18 TS | 53 T dMMR; 18 TS | 78 T BRAFV600Emt; 0 TS | 13 T KRASG12C mt; 0 TS | 1 T HER2+ and 4 TS | 75 T ≤40yo patients. Currently there are no POLEmt, FGFRmt or NTRK fusion patients enrolled. Initial data on testing and treatment for dMMR, BRAFmt, and young onset patients will be reported in Q4 2024.

Conclusion

TRACC-SELECT has been successfully initiated at diverse sites, enhancing engagement for sites with limited data entry resources and boosting patient numbers for subsets of greater interest. This activity has already enabled multiple research and audit activities, with planning for translational research activities underway and scope to expand across more sites, including international sites, beginning with the Asia Pacific.

Australian National Liver Transplantation Unit Criteria for liver transplantation in the setting of isolated unresectable colorectal liver metastases

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Aim

Studies have demonstrated that liver transplantation may be an effective treatment for isolated unresectable colorectal cancer liver metastases (CRCLM). Published data suggest that 5-year survival may be as high as 80%; however, recurrent disease is commonplace. While CRCLM is an appropriate indication for transplantation, selection criteria should be undertaken within a clinical service evaluation programme. The aim of this work is to outline the proposed Australian National Liver transplantation Unit selection criteria and follow-up process for CRCLM transplantation.

Method

Consensus statement by liver transplantation patient representatives, experts in colorectal cancer surgery/oncology, liver transplantation surgery, hepatology, hepatobiliary radiology, hepatobiliary pathology.

Results: This study provides a comprehensive outline of the inclusion/exclusion criteria for referral in the ANLTU. Furthermore, the referral framework is also explained. Pretransplant assessment criteria for listing/delisting are outlined. Finally, the oncology-specific outcome measures posttransplant are described.

This service has begun in January 2023, 5 patients have been referred and two patients from Victoria have been transplanted.

Conclusion

A series of educational events for the referrers and transplant units will be arranged throughout 2024 to highlight CRCLM as a newly accepted ANLTU indication for transplantation. Data will be collected in local registry and will be reviewed on an ongoing basis to confirm the safety of this treatment and to determine if the inclusion criteria require revision.

Rare actionable biomarkers in Australian colorectal cancer patients

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Background

For metastatic colorectal cancers (mCRC) testing for mismatch repair (MMR), RAS mutation and BRAF mutation status is routine. Blanket extended molecular testing in unselected patients is low yield and unfunded. With NTRK fusions reported in <1% of unselected cases but 25-44% of deficient MMR (dMMR)/BRAF wild type(wt)/RASwt tumours, targeted testing may be cost-effective.

Methods

We explored contemporaneous mCRC registry data (TRACC) for dMMR/RASwt/BRAFwt patients. Whole genome sequencing (WGS) data from an initial unselected cohort of early and late-stage CRC patients were examined, including those with matching patient derived tumour organoids (PDTO). We explored the potential cost and yield of targeted testing for NTRK fusions using an RNA panel ($375) or a comprehensive panel ($1800).

Results

From January 2021 to July 2024, 876 mCRC TRACC patients were identified; median age was 64 years, 71 (8.1%) had dMMR tumours, and 13/71 (18.3%) were also KRAS/BRAFwt; none had a gene fusion identified. 240 TRACC participants with PDTO, included 183 (76.3%) early-stage and 57 (23.7%) metastatic CRC. We found 9 (3.8%) NTRK, 11 (4.6%) ALK and 1 (0.4%) ROS1 structural variants. 4/9 (44.4%) NTRK and 1/11 (9.1%) ALK fusions were in mCRC patients. Based on previous reported NTRK frequency in dMMR/RASwt/BRAFwt patients (25-44%), a targeted approach to testing only the 13/876 patients would have yielded 3-6 with an NTRK fusion with a cost of $812-1625 and $3900-7800 per patient with NTRK identified using an RNA or comprehensive panel, respectively.

Conclusion

About 1.5% of 876 mCRC patients had dMMR/RASwt/BRAFwt tumours. WGS in a mixed CRC cohort revealed NTRK, ALK and ROS1 fusions, including 5 fusions in 57 mCRC patients. WGS testing is underway on a much larger cohort, to enable further exploration of any clinicopathologic associations with molecular targets. Targeted testing of dMMR/RASwt/BRAFwt patients could yield multiple patients with NTRK fusions at modest cost, who would be potential candidates for NTRK inhibitor treatment, potentially as part of the larotrectinib access program, none of whom would likely be detected using current approaches. A pilot study will provide TRACC registry clinicians with lists of their dMMR/RASwt/BRAFwt patients, encouraging NTRK fusion testing where clinically appropriate.

Early onset colorectal cancer and colorectal cancer in pregnancy: Case discussions and real-world data from an Australian institution as well as literature review on current knowledge

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Colorectal cancer during pregnancy is a rare event currently; but given the well-recognised increasing incidence of young onset colorectal cancer and delayed child-bearing seen in the western world, it is anticipated to sharply increase in the next two decades. In this paper the authors analyse three cases of colorectal cancer occurring in pregnancy and the therapeutic approach and outcomes in these cases. Two of the three cases received chemotherapy during pregnancy and all three children were born premature with one child having a significantly low birth weight. A review of our institutions referrals related to early onset colorectal cancer (EOCRC) reveals a 50% increase in this in the last decade in line with worldwide trends of increase of this cancer in this population. This paper also reviews the literature related to EOCRC in pregnancy and current diagnosis and management recommendations. Challenges clearly arise related to the symptoms at onset being masked by the pregnancy, the diagnostic workup needing to weigh benefits to mother with harms to child and the need to finely tailor therapeutic approaches. There is a clear and increasing need for consensus guidelines and further research into this field.

Compliance rate of neoadjuvant therapy in locally advanced rectal cancer: A systematic review

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Background

Rectal cancers are one of the most common cancers in Australia. Treatment for this type of cancer is multi-modal and involves peri-operative chemoradiotherapy and definitive surgical resection. There is abundant evidence on the poor compliance rate of adjuvant therapy due to multiple reasons, including toxicity and patient's declined functional status. Total Neoadjuvant Therapy (TNT) has been introduced to improve overall completion of chemotherapy (and therefore overall survival) before undergoing definitive surgical resection. There are no reviews on the actual compliance rate of neoadjuvant therapy, traditional or TNT.

Methods

A systemic review of randomised controlled trials, controlled trials, cohort studies and case control studies on neoadjuvant therapy of local advanced rectal cancer was performed. The compliance rate of neoadjuvant therapy was compared. Common factors, both positively and negatively, contributing to the reported compliance rate were identified.

Results

27 studies of the 278 studies identified met the inclusion criteria. These include studies conducted in 14 different countries from 1993 to 2000. Each study utilised a regime comprising of pre-operative chemotherapy, radiotherapy and chemoradiotherapy with locally protocolled dosages. Despite varying treatment protocols, the mean compliance rate of TNT was 81.8% (range 41.1%-100%) with a standard deviation of 12.7%. The most common factor affecting compliance rate was acute toxicity, including gastrointestinal, haematological and cardiovascular. Dose reduction and early termination of treatment were also observed in patients with early complete pathological response.

Conclusion

Total neoadjuvant therapy demonstrates an improved compliance rate of more than 80% and thus should be considered in patients with locally advanced rectal cancer. Acute toxicities and early complete pathological response were the main factors affecting the compliance rate. Comparing local compliance rate against this result may prompt improvements to be made locally to account for any modifiable barrier to treatment. Further studies in a domestic setting are warranted.

Establishment of a patient-derived anal squamous cell carcinoma organoid biobank

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Background

ASCC is a rare malignancy commonly associated with human papillomavirus (HPV) infection for which there have been no significant advances in therapy in 5 decades. The small number of patients included in clinical trials coupled with lack of preclinical models have made it challenging to study novel therapeutics to improve outcomes of ASCC. There are currently no human ASCC organoids to date. The objective is to generate patient-derived tumour organoids (PTDO).

Methods

Viable tumour biopsies were verified, digested, embedded in extracellular matrix, and cultured in complete medium. Characterisation and validation were performed by histology, immunohistochemical, whole exome sequencing (WES) and transcriptomic profiling.

Results

We established the first 7 ASCC organoids from patients with primary, local persistent, recurrent, re recurrent and metastatic disease. 5 tumouroids were generated from the anal canal, 1 derived from a vaginal vault local re recurrence, and 1 tumouroid originated from liver metastasis. HPV genotyping and p16 immunostaining identified majority of samples to be HPV driven cancers (6/7). WES of matched organoid and tumour identified oncogenic alterations in genes PIK3CA, KMT2D, EP300 and TP53 with 97% concordance (range 0.94-1.00) rate. The p16 positive organoids were significantly enriched in genes for Gene Ontology Biological Process (GO: BP) for negative regulation of viral genome replication and inflammatory response. In contrast, p16 negative group had enrichment in GO:BP in DNA replication dependent nucleosome organisation and chromatin silencing at RDNA pathways with multiple shared genes involving histones. Upon transplantation into immunodeficient mice, tumour engraftment was successful in 77.1% of cases. Organoids subjected to conventional chemotherapy agents and irradiation displayed a variety of responses that correlated with clinical outcomes. Molecular directed therapies with alpelisib or abemaciclib demonstrated efficacy against organoids with PIK3CA or p16 loss. Preliminary co culture studies with HER2 CART demonstrated cytotoxicity which was enhanced by anti-PD-1 blockade.

Conclusion

This proof of concept study demonstrates that PDTO is feasible in primary, relapsed and metastatic ASCC. The organoids faithfully recapitulate the parent tumours genomic, transcriptomic and molecular characteristics. This patient informed organoid translation platform can be an invaluable resource to interrogate vulnerabilities in ASCC, particularly in the relapse setting.

Exploring the immune microenvironment of anal squamous cell carcinoma using OPAL multispectral mutiplex immunohistochemistry and Nanostring™ transcriptomic profiling

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Background

Anal squamous cell carcinomas (ASCC) are human papillomavirus (HPV) driven cancers with overexpression of p16, associated with improved overall survival (OS). However, immune checkpoint blockade (ICB) has shown limited efficacy in improving outcomes for metastatic ASCC patients irrespective of p16 status. Here we assessed and characterised the tumour microenvironment in p16 positive versus negative and primary treatment naïve versus recurrent ASCC tumours.

Methods

Custom T cell centric OPAL multispectral multiplex immunohistochemistry (n=39) and NanoString™ PanCancer 360TM Gene Panel transcriptomics profiling (n=12) were used to assess the immune microenvironment. Digital cytometry was utilised to quantitate cell abundance using the nSolver™ computational platform. Baseline patient, tumour characteristics, and survival data were correlated to the immune data.

Results

In total, 22 primary ASCC and 17 relapsed tumours were included. Primary ASCC had an overall higher abundance of CD8+, CD4+, double negative (DN), and FOXP3+ T cells in the intratumoural compartments compared to relapsed tumours. Primary and p16 positive tumours had a statistically significant higher density of CD4+ (p=0.027 and p=0.044) and FOXP3+ PD-1 Treg cells (p=0.039 and p=0.049) in the intratumoural sections. Spatial analyses demonstrated immune localisation within the 100um intratumoural border in primary and p16 positive tumours except for PD-1 expressing CD8+ and DN T cell subsets. Low CD4+ (Hazard Ratio (HR) 3.6, 95% confidence interval (CI) 1.39-9.31, p=0.012), DN (HR 3.3, 95% CI 1.22-8.90, p=0.010), and Treg (HR 2.9, 95% CI 1.11-7.53, p=0.028) intratumoural infiltration were associated with inferior OS. Primary ASCC tumours were enriched in genes promoting T, B cell activation, cytotoxicity, and immune cell localisation in the tumours. Contrary, recurrent tumours were enriched for macrophage and neutrophil infiltration. In p16 negative tumours, myeloid leucocyte activation with a neutrophil predominant cell composition was identified.

Conclusion

Treatment naïve and p16 positive ASCC are characterised by a pro inflammatory anti-tumour microenvironment with recruitment of T, B cells, differentiation, activation pathways and upregulation of cytokine signalling. Recurrent and p16 negative tumours are enriched in myeloid signature with a macrophage and neutrophil population. Future studies should focus on stratifying these afore mentioned immune subgroups and consider instituting ICB early in primary/p16 positive tumours.

CDX2 as a prognostic biomarker in stage II and III colorectal cancer: An Australian regional perspective

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Background

CDX2, a nuclear transcription factor, plays a crucial role in oncogenesis and serves as a biomarker in colorectal cancer. In this study, we investigated the association between different levels of CDX2 expression and survival outcomes in patients with stage II and III colorectal cancers within the Hunter New England region of New South Wales (NSW), Australia.

Methods

We analysed patients who underwent surgical resection for colorectal cancer in this region between January 2011 and December 2015. We collected clinical data, histopathological findings, and CDX2 expression scores. CDX2 expression was evaluated using immunostaining and categorised based on CDX2 expression levels of 0% (score 0), ‹25% (score 1+), 26-75% (score 2+), and ›75% (score 3+).

Results

Fifty-eight patients were considered eligible. The median age was 68 years. The large majority (95%) were colon cancers (29 left-sided, 26 right-sided) and 5% were rectal cancers. There was an even distribution between stage II (48%) and stage III (52%). The breakdown of patients by CDX2 expression level was 3 for 0%, 2 for ‹25%, 11 for 26-75% and 42 for ›75%. Low (0%) and loss of CDX2 (‹25%) expression were associated with right sided tumours (p=0.46), higher grade (p=0.19), lymphovascular invasion (p=0.09), and higher tumour-infiltrating lymphocyte (TIL) score (p=0.002). Higher CDX2 expression (›26%) was associated with increased risk of recurrence (p=0.47) and higher mortality (p=0.85).

Conclusions

Our findings suggest that low and loss of CDX2 expression were associated with histological markers of poor prognosis. However, the unexpected association between higher CDX2 expression and worse survival outcomes warrants further validation in larger, prospective studies, especially considering the small sample size. Exploring the interplay between CDX2 and TIL as well as refining IHC scoring system remains an intriguing avenue for future research.

Real-world impacts of total neoadjuvant therapy on locally advanced rectal cancers: Insights from South West Sydney

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Background

The role of total neoadjuvant therapy (TNT) is rapidly evolving in locally advanced rectal cancer (LARC). The PRODIGE-23 and OPRA trials have been crucial in defining TNT protocols, yet real-world outcomes are needed to validate their effectiveness.

Methods

This retrospective study reviews real-world outcomes of TNT in South-West Sydney, who have adopted the PRODIGE-23 regimen and in select patients, adopting a pragmatic watch-and-wait (W&W) strategy following MDT discussion. Patient demographics, clinicopathological features, and cancer outcomes were collected and analysed using SPSS. Event-free survival (EFS) was defined as time-to-progression or recurrence.

Results

From December 2020 to July 2023, 40 patients with cT3/4 LARC received TNT per PRODIGE-23 protocol with modified FOLFIRINOX. At median follow-up of 29.5 months, 22.5% of patients achieved pCR at surgery, and 12.5% underwent W&W following cCR (total 35% pCR/cCR). Local recurrence occurred in 7.5% and distant recurrence in 22.5% of patients. 2-year overall survival (OS) was 87%, and EFS 68%. For those with cCR or pCR, 2-year EFS was 73.9%, 2-year OS could not be estimated due to censoring.

Grade 3/4 adverse events (AEs) occurred in 15% during chemotherapy and 25% peri-operatively, with no serious AEs during chemoradiotherapy, except one sudden death 1.5 months post-TNT (cause unclear). For 2 patients with residual disease declining surgery, 100% experienced local progression (EFS 15.8m & 21.4m). In the W&W group, 40% experienced recurrence. Adjuvant chemotherapy was administered in 50% of cases.

Univariate analysis identified significant factors for EFS, including type of surgery (p=0.031), upfront chemotherapy dose reduction (p=0.017), and lower-end-of-treatment-CEA levels (p=0.01). Multivariate analysis confirmed upfront dose reduction (p=0.02) and end-of-treatment CEA (p=0.015) as independent prognostic factors. For OS, significant factors included lower-end-of-treatment-CEA (p=0.018), surgery type (p=0.025), and progression during TNT (p=0.008), with progression remaining significant in multivariate analysis (p=0.05). dMMR status was the sole significant factor for decreased cCR/pCR (p=0.024).

Conclusion

Despite our real-world data showing similar pCR or cCR rates (35%) to PRODIGE-23 and OPRA trials, 2-year EFS of 68% is lower than trial-reported 3-year DFS rates. Further larger-scale real-world studies are needed to validate these outcomes and optimise treatment approaches, particularly as W&W is highly resource intense.

Quality of life of survivors of rectal cancer managed with surgery versus watch-and-wait

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Introduction

Quality-of-life (QoL) is an important outcome in survivors of cancer and correlates with clinical outcomes and prognosis in different cancers, including rectal. For non-metastatic rectal cancer, after a complete response to chemoradiotherapy (with or without additional chemotherapy), a watch-and-wait approach is increasingly considered appropriate. This study compares the QoL of survivors of rectal cancer managed with surgery versus watch-and-wait.

Methods

This cross-sectional study included adult patients who had undergone standard long-course fluoropyrimidine-based chemoradiotherapy for non-metastatic rectal adenocarcinoma between 2011 and 2019 at Flinders Medical Centre. Comorbidities were assessed using the Self-Administered Comorbidity Questionnaire (SCQ). EORTC-QLQ-C30 and CR29 were used to evaluate disease-related QoL.

Results

Of the 190 eligible subjects identified from records and approached, 81 agreed to participate. Median age was 70.0 years (IQR 64.0–75.0)). 27 (33.3%) were female, and 14 (17.3%) had a stoma. At data collection, 48 (59.3%) had undergone surgery (SURG cohort), and 33 (40.7%) were on watch-and-wait (WW cohort).

There were no significant differences in age, sex, comorbidities, tumour distance, and stage between the cohorts. In the whole group, the median time from diagnosis to data collection was 39.0 months (IQR 20.0–62.0); this was longer in the SURG cohort [45.5(IQR 25.3–73.0)] compared to the WW cohort [28.0(IQR 18.0–45.0)] ($p<0.05$).

After adjusting sex, comorbidities and time from diagnosis to data collection, surgery was negatively correlated with QLQ-C30 summary score, global score, role-functioning and social-functioning ($p<0.05$). Within the various subgroups, female participants with stoma reported the lowest QLQ-C30 summary scores ($p < 0.001$). Comparing symptoms scales, surgery was associated with increased pain and diarrhoea scores ($p<0.05$).

Additionally, surgery was associated with worse scores in QLQ-CR29 body image and anxiety scales ($p<0.05$) and with increased stool frequency, buttock pain, dysuria, and embarrassment symptom scores ($p<0.05$).

Conclusion

This study highlights that surgery for rectal cancer, compared to watch-and-wait, is associated with significantly poorer QoL outcomes in multiple domains and higher symptom burden. Additionally, female patients with stomas reported the lowest QoL scores. The findings underscore the importance of careful consideration of QoL impacts when considering treatment strategies for rectal cancer.

Assessing bowel function in survivors of rectal cancer managed with a watch-and-wait approach compared with survivors who had sphincter-preserving surgery

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Introduction

In non-metastatic rectal cancer, the watch-and-wait (WW) approach is increasingly considered appropriate after a complete response to chemoradiotherapy (with/without additional chemotherapy). Limited data exist on bowel function in the setting of WW. Here, we have assessed bowel function in patients managed with WW versus sphincter-preserving surgery.

Methods

This cross-sectional study included adult patients who had undergone standard long-course fluoropyrimidine-based chemoradiotherapy for non-metastatic rectal adenocarcinoma between 2011 and 2019 at Flinders Medical Centre. Bowel function was assessed using MSK-BFI and LARS questionnaires (LARS-Q). The EORTC-QLQ-C30 and CR29 were utilised to measure quality of life (QoL).

Results

Of 190 subjects identified from records and approached, 81 consented to participate. Data from 67 participants without stomas are presented. The median age was 69.0 years (IQR 64.0–75.0). 22(32.8%) were female. At data collection, 34(50.7%) had undergone surgery (SURG cohort), and 33 (49.3%) were on WW. Age, sex, and cancer stage were similar between the cohorts. The median time from diagnosis to data collection in the whole group was 39.0 months (IQR 18.0–64.5); this was longer in the SURG cohort [58.5(IQR 20.8–82.3)] compared to the WW cohort [28.0(IQR 18.0–45.0)] ($p<0.05$). The WW cohort had a higher number of comorbidities ($p<0.05$) and had lower tumours (median distance from anal verge 5.4cm (IQR 3.8-8) in WW compared with 7cm (IQR 5-8.6) in SURG ($p<0.05$)).

In the entire group, female survivors reported worse bowel function: higher LARS scores and lower MSK-BFI global and total scores and MSK-BFI subscale scores (frequency, urgency/soilage and diet) ($p<0.05$).

The WW cohort had better bowel function: higher MSK-BFI global and total scores, MSK-BFI subscale scores ($p<0.05$) and lower LARS scores. After adjusting for sex, comorbidities and time since diagnosis to data collection, the MSK-BFI total score positively correlated with the EORTC QLQ-C30 summary score ($p<0.05$) and with the social-functioning score ($p<0.001$). Poorer bowel function was associated with higher embarrassment and financial difficulty scores.

Conclusion

This study demonstrates that rectal cancer survivors managed with WW experience better bowel function and QoL compared to those undergoing sphincter-preserving surgery. Female survivors reported worse bowel function. Bowel function was correlated with different aspects of QoL.

All GI cancers

Abstracts not specific to one GI cancer.

Phase 1a/b open-label, non-randomized, multi-center clinical trial of intratumoral IVX037 monotherapy and in combination with anti-PD1 in patients with advanced microsatellite stable (MSS) colorectal, gastroesophageal or ovarian cancer

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Background

Oncolytic viruses have emerged as promising therapeutic agents to selectively target, infect and destroy cancer cells while synergizing with checkpoint inhibitors (CPI) to increase efficacy of immunotherapy. IVX037 is a novel bio-selected, receptor targeted, non-genetically modified, oncolytic strain of a human enteric RNA picornavirus. Intratumoral (IT) injection of IVX037 induced significant anti-tumor activity in human xenografts of MSS-colorectal, gastric and ovarian cancers in SCID mice. The induction of a virally inflamed TME is suggested to allow increased migration of anti-tumor lymphocytes both within injected and distant lesions and elevated levels of cellular targets for immune checkpoint therapies.

Methods

In this Phase 1a/b, first-in-human clinical trial of IVX037, patients (pts) with advanced MSS colorectal (CRC), gastroesophageal or ovarian cancer were sequentially enrolled into 3 dose escalation cohorts to receive 1 (n=3 pts), 2 (n=3 pts) or up to 7 doses of up to 7.5 x 108 TCID50 of IVX037 for cohort 3, administered intratumorally on Days 1,15,29, 43, 57, 71 and 85, permitted at Investigator discretion, if SD or better was observed at day 43 and in absence of DLTs (n=up to 15 pts). The primary objective of Phase 1a was to determine the safety and tolerability of IT administration. Secondary endpoints included efficacy.

Results

Intratumoral IVX037 administration was well tolerated with no Gr 3 or higher TRAE's or DLTs seen. The most common Gr 1 and Gr 2 TRAE's were injection site pain (43%) and fatigue (22%), respectively. Of the 14 pts administered IVX037, one MSS, KRAS G12D mutant CRC pt achieved a biopsy confirmed complete response after six IT doses at day 262. Pts (2/14) displaying injected lesion reductions also exhibited decreases in serum CEA levels. Serum biomarker analysis highlighted IVX037-mediated induction of potentially beneficial inflammatory cytokines/chemokines (i.e. CXCL10) at day 8 for enhancement of combination CPI therapy.

Conclusions

The promising monotherapy tolerability and activity of IVX037 will be further explored in the ongoing Phase 1b combination trial with sintilimab (anti-PD1) in MSS-CRC, gastroesophageal and ovarian cancer pts.

Trial Registration: ClinicalTrials.gov Identifier: NCT05427487

Using conceptual frameworks to guide the selection of patient-reported outcome measures in cancer clinical trials: A CQUEST resource

A/Prof Brendan Mulhern[1], Dr Carrie-Anne Ng[1], A/Prof Tim Luckett[1]

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Background and aim

The Standard Protocol Items: Recommendations for Interventional Trials – patient-reported outcome (SPIRIT-PRO) extension requires trial protocols to justify selection of patient-reported outcome measures (PROMs) and hypothesise expected effects. Ideally, the rationale for PROM selection should be supported by a conceptual framework, which provides an empirical and theoretical basis to ensuring the trial measures what matters most to patients. However, many protocols default to a standard set of widely-used PROMs, resulting in important outcomes being missed, unnecessary respondent burden, and difficulty interpreting findings.

The Cancer Quality of Life Expert Service Team (CQUEST) has developed a resource to help investigators establish a conceptual framework and associated measurement model for their trial protocol.

Methods

The conceptual framework resource is available on the CQUEST website, and outlines the definition of a conceptual framework, its rationale, and includes a step-by-step guide on developing a framework. A template is also available for investigators to create their own framework, which can then be inserted into a study protocol. The poster/oral presentation will include an exemplary framework to aid AGITG members in contextualising its utility and application within a cancer clinical trial setting.

The authors of SPIRIT-PRO have been involved to provide consensus on this resource.

Results

AGITG investigators are invited to utilise the conceptual framework template to inform PROM selection in their trials. CQUEST can collaboratively build this with investigators and then assist with the choice of PROMs after key concepts of interest have been identified. The framework template is adaptable to various trial settings, thereby addressing the diverse needs of cancer clinical trials and other study types involving PROMs.

Conclusion

CQUEST invites AGITG members to engage with our conceptual framework resource to facilitate thoughtful selection of PROMs in cancer clinical trials, so as to directly address the trial objectives and yield results optimally informative to stakeholder needs.

Inclusiveness in patient-reported outcome measures (PROMs): A resource about translations and cross-cultural validations from the Cancer Australia Quality of Life Technical Service (CQUEST)

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Background and aim

Indigenous and culturally and linguistically diverse (CALD) Australians encounter barriers to participating in cancer clinical trials. While national initiatives are underway to improve access to trials, is also important to ensure that trial methods are inclusive for enrolled patients. Most patient-reported outcome measures (PROMs) have been developed and validated in English-speaking populations, and to accommodate non-English-speaking populations, it is vital to include PROMs in other languages that are appropriate for target cultural groups. Consistent translation and cultural equivalence of PROMs can enable the collection and pooling of data across participants of various CALD backgrounds.

The Cancer Quality of Life Expert Service Team (CQUEST), funded by Cancer Australia, supports the use of PROMs in cancer clinical trials by developing up-to-date, practical, and accessible resources. We aim to support AGITG investigators who may require PROMs that are available in more than one language and/or are appropriate for multiple cultural groups.

Methods

The CQUEST website (**www.uts.edu.au/cquest**) hosts a resource that describes the importance of PROM translations and cultural validations, along with the differences between translations and cross-cultural validation. The resource also provides a comprehensive list of 76 PROMs commonly used in cancer clinical research, and available evidence of their translations and/or cross-cultural validations across over 100 languages. This list will undergo periodic updates.

Results

CQUEST's online resource will help AGITG members improve trial inclusivity and PROM data quality. AGITG members are also invited to request further online resources that will improve the accessibility and utilisation of PROMs in their research. These can be suggested to the CQUEST team during discussion of the abstract.

Conclusion

CQUEST invites AGITG members to engage with our online resources to improve the use of PROMs in cancer trials for patients from Indigenous and CALD backgrounds.

Evaluation of early fluoropyrimidine toxicity in solid organ cancer patients: A retrospective observational study in Australia

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Background

Despite common global usage, fluoropyrimidine (FP; 5-flurouracil and capecitabine)-related chemotherapy toxicity is poorly reported in the literature, with serious toxicity ranging from 10% to 40% and early toxicity (within 60 days of exposure) quoted at 14%. Data reflecting the incidence of Grades 3-5 FP-related toxicity in Australian cancer patients is scant, despite the significant impact of toxicity on patients (hospitalisations, intensive care unit (ICU) admissions and even death).

Aims

This retrospective audit evaluated Grades 3-5 toxicities in a contemporaneous cohort of 500 patients receiving FP chemotherapies within the Hunter-New England Local Health District from June 2020 to June 2022. Data were extracted from public hospital records and oncology-specific e-records to determine rates of toxicity and associated hospitalisations, intensive care admissions and deaths that occurred within 60 days of first exposure to FP chemotherapy-containing regimens.

Results

One hundred and fifty incidents of Grades 3-4 toxicity in the first 60 days led to 87 patients presenting to hospital (87/500, 17.4%). The most common serious toxicities were diarrhoea (39.3%), nausea and vomiting (22.7%) and febrile neutropaenia (10%). Four patients were admitted to the ICU, and four patients died of toxicity. Within the first 60 days, 22.2% of patients required treatment delays, 21.4% required dose reductions, and 7.8% of patients ceased treatment because of toxicities.

Discussion and conclusion

Our experience reflects international reports and is likely generalisable to the Australian population. These data are a basis to understand the potential benefits of precision medicine strategies such as pharmacogenomic screening to improve patient tolerability and the cost-effectiveness of FP chemotherapy prescribing.

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The Australian Teletrial Program – An innovative collaborative program aiming to increase equity in research

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Background

Regional patients are at increased risk of developing advanced diseases more rapidly than their urban counterparts. Accessing specialised care is challenging for regional patients with pre-existing high disease burden with the distance needed to travel, time and cost toxicity, cultural preferences being most cited concerns.

Pancreatic cancer is the 8th most common cancer and has remained in this place since 2019. In 2023, the total number recorded was 4,506; recruiting participants into clinical trials from such a small pool of patients is challenging.

Converting an RCT into a Teletrial is a radical approach to increase regional participants' enrolment, as well as improving equity in access to advanced therapies for those participants living outside of metro areas.

Method

For the AGITG ASCEND (ACTRN12621001290886, AG0121PC for untreated metastatic pancreatic ductal adenocarcinoma), the Australian Teletrial Program in South Australia (SA) and the Northern Territory (NT) established a cluster with the primary site at The Queen Elizabeth Hospital (SA), and the satellite site located at the Alan Walker Cancer Centre, Royal Darwin Hospital (NT). The Teletrial program provides training, and financial and administrative support.

This inaugural process needed validation for transferability to original proposals.

Results

Pooling participants from Adelaide and Darwin enabled recruitment.

Three main benefits for inclusion of regional participation noticed:

1. Addressing inequity in participation, ensuring diversity and inclusion of historically vulnerable regional populations;
2. Local practitioners building professional development, collaborative links and capacity for conducting research; and
3. A broader platform for recruiting participants to reach target enrolment.

Patients recruited in Darwin were grateful for the opportunity to participate in a clinical trial and contribute to scientific knowledge in treatment. Adding Darwin as a satellite site enabled patients to access this trial, which they otherwise would not have been able to participate in. Participants described the trial as "offering hope to themselves and others".

Implications

The application of Teletrials to other trials sponsored by AGITG will enable more regional participation, thereby improving access to trial interventions for all Australians – no matter where they live – and improve time to translate these new interventions to patients in a real-world setting.

Redefining treatment protocols: Cost-effectiveness of upfront DPYD genotyping among patients with cancer receiving fluoropyrimidine-based chemotherapy in Australia

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Introduction

Fluoropyrimidine ([FP], 5-fluorouracil (5-FU) and its oral prodrug capecitabine are commonly prescribed anti-cancer drugs in many solid tumours. While standard dosing of FP is safe for most patients, severe, at times fatal, toxicities may occur in ~6% of the population due to dihydropyrimidine dehydrogenase (DPD) deficiency, encoded by the DPYD gene. International studies have shown that upfront pharmacogenetic (PGx) screening reduces this risk and is cost-effective; however, adaptation is not widely implemented or publicly funded in Australia.

Objectives

This study aimed to evaluate the cost-effectiveness of the PGx screening program versus standard of care (no screening) among patients undergoing FP treatment in Australia.

Methods

A Markov cohort decision model was constructed using TreeAge Pro Healthcare 2024, based on data from the single-arm PACIFIC-PGx trial (ANZCTR:12621000251820). This model incorporates the adverse events and related costs of FP treatments from an Australian healthcare perspective across two chemotherapy cycles (ranging from 18.7 to 21 days). The intervention group was compared to historical cohorts (i.e. toxicity and hospitalisation events) were obtained from existing literature. Both deterministic (one-way) and probabilistic sensitivity analyses were conducted to evaluate the effects of varying assumptions and the uncertainty of input parameters.

Results

PGx screening has resulted in an incremental quality-adjusted life years (QALYs) of 0.05 at an additional cost of $274.25, resulting in an incremental cost-effectiveness ratio (ICER) of $5,559.7 per QALY gained compared to the historical cohort. PGx screening was found to be cost-effective at a $50,000 willingness-to-pay/QALY threshold. Deterministic sensitivity analyses showed that the model was sensitive to rates of adverse events, hospitalisation from grade ›3 toxicity and utility decrements, when performed. Probabilistic sensitivity analysis suggested that PGx screening was favoured and cost-effective in 98.95% of iterations.

Conclusion

From the perspective of the Australian public healthcare payer, a PGx screening program for patients receiving FP-based chemotherapy is likely to be cost-effective by mitigating severe and fatal FP-related toxicities. As demonstrated in international studies, our cost-effectiveness analysis supports the potential for funding and implementing PGx programs within Australian healthcare settings.

PrOSPeCT in retrospect: What have OMICO been doing in GI cancer

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Background

The Precision Oncology Screening Platform Enabling Clinical Trials (PrOSPeCT) was established to link genomic technology with clinical trials, creating new therapeutic pathways for patients across Australia with difficult-to-treat cancers. One of the key focus areas for PrOSPeCT has been gastrointestinal (GI) cancers, which represent a significant proportion of cases referred to the program. This abstract provides an analysis of PrOSPeCT's impact on GI cancer management and highlights current gaps in access to precision medicine for these patients.

Methods

Data was collated from the Cancer Screening Program (CaSP) and the Molecular Screening and Therapeutics study (MoST) between 2016 and 2022. The analysis included the total number of GI cancer patients referred, the distribution across metropolitan, rural, and remote areas, the number of referring GI clinicians, and the number of patients matched to GI cancer clinical trials. The genomic profiling involved comprehensive analysis targeting a range of biomarkers associated with GI malignancies, with the aim of matching patients to appropriate clinical trials.

Results

Out of 6,571 patients referred to CaSP, 2,408 (36.6%) were GI cancer patients. Colorectal cancer was the most common type referred, followed by biliary, oesophageal, gastric, small intestine, and liver cancers. The analysis revealed that only a small percentage of these patients were successfully matched to clinical trials, underscoring a significant gap in access. The genomic profiling highlighted frequent alterations in genes such as TP53, KRAS, and APC among GI cancer patients, with varying distributions across cancer subtypes. Despite the comprehensive genomic profiling, the limited availability of matching clinical trials restricted the potential impact of precision oncology in this cohort.

Conclusions

GI cancers represent the largest group of cancers referred to the CaSP for genomic screening. However, the low percentage of patients accessing clinical trials points to a critical need for more trials and expanded access to precision medicine across Australia. PrOSPeCT's efforts have been instrumental in identifying these gaps, and ongoing initiatives are required to bridge them, ensuring that more GI cancer patients can benefit from cutting-edge therapies tailored to their unique genetic profiles.

Keywords: PrOSPeCT, gastrointestinal cancer, precision oncology, genomic profiling, clinical trials, Australia

An analysis of the impact of next-generation sequencing in gastrointestinal cancers in Aotearoa: A proof of concept analysis of MoST-NZ

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Background

Next-generation sequence (NGS) offers an in-depth analysis of genomic variations in cancer and can offer extra information on diagnosis, prognosis as well as therapeutic options. Due to its high cost, NGS is not readily available in routine clinical setting and it is difficult to know how NGS affects NZ patients. MoST-NZ is a clinical trial platform providing free NGS access for patients with advanced cancers in Aotearoa New Zealand.

Methods

This is a descriptive analysis of 45 advanced gastrointestinal cancer patients who had their cancer cells analysed through MoST-NZ NGS. We analysed patients' age, gender, ethnicity, common genetic variations, impact on genetics referrals, and treatments.

Results

As of February 2024, 206 cancer patients were sequenced through MoST-NZ. 45 patients had advanced gastrointestinal or neuroendocrine cancers. The median age was 58. 42% of patients were male. Māori and Pasifika comprised 4% and 18% of the study population respectively. Most patients had 1-8 genomic variations found and the mean number of genomic variations was 5.8. Only 1 patient had no mutation found. 31% and 15% had trial and genetic referrals recommended on the basis of NGS.

Conclusion

This study showed that NGS was crucial in providing patient and whānau with impactful information about their gastrointestinal cancer.

Early trial access in the real world: Referral patterns of patients with advanced gastrointestinal cancer (GIC) to a specialised phase 1 trials unit

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Background

Phase 1 clinical trials are first-in-human studies to determine safety, pharmacokinetics and dose optimisation of therapies under development. Given limited advances to the prognosis of advanced gastrointestinal cancer (GIC), drug development in this field is an area of research need. Scientia Clinical Research (SCR) is a dedicated Phase 1 trial unit located in metropolitan Sydney, Australia.

Aims

To summarise demographic and clinical factors of patients referred for consideration, screened and treated on phase 1 trials at SCR, focussing on patients with a diagnosis of GIC.

Methods

Descriptive statistics were used to summarise data from clinical records of referred patients. Key aspects of the dataset were: Patient age, cancer diagnosis, geography of residence. Clinical trial related milestones such as date of referral, consultation, consent and day 1 of treatment were also collected.

Results

From 1 January 2022 to data cutoff 16 August 2024, SCR received 449 referrals for consideration of clinical trials. Patients with GIC represented 42% (n=187) of total referrals. Of these patients with GIC, 114 patients had upper gastrointestinal cancer and 73 had colorectal cancer. Patients from the greater Sydney area comprised 57% (n=107) of referrals.

A first consultation was conducted for 158 GIC patients (84%). Reasons for not proceeding: no written referral eventuated (n=10), patient declined (n=7), direct feedback to referrer regarding ineligibility (n=6), pending consultation (n=6).

Screening was conducted for 58 patients (mean age 58 years, range 30–86). Twenty-five patients were matched to trials enrolling specific tumour biomarkers; 30 matched for targeted therapy trials; 13 matched for immunotherapy trials; and 15 matched for trials using investigational products (IP) with mixed mechanism. Ultimately, 44 patients received at least one dose of IP. The number of patients from metropolitan and rural areas receiving IP were equivalent. Reasons for dropout: screen failed (n=11), pending commencement (n=11) in screening at data cutoff, withdrawal of consent to pursue other treatment (n=1).

Conclusion

Real-world-evidence from a single specialised Phase 1 unit indicates substantial attrition between referral and treatment of GIC patients on early phase oncology clinical trials. Contrary to other published datasets, SCR engages high proportion of patients from non-metropolitan areas.