**The impact of contemporary neoadjuvant and adjuvant chemotherapy treatment regimens on recurrence and survival in resectable, borderline resectable, locally advanced and metastatic adenocarcinoma arising from IPMN (A-IPMN) and internal validation of 2023 KYOTO guidelines: FOX-IPMN study**

## Study Overview

### Background:

Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing neoplasms of the pancreas originating from the epithelial lining of the main pancreatic duct and/or one of its side branches. Adenocarcinoma arising from IPMNs (A-IPMN) make up approximately 5% of all pancreatic adenocarcinomas and are at significant risk of disease recurrence ranging from 32-45%.[1-3]
In patients with pancreatic ductal adenocarcinoma (PDAC), not associated with an underlying IPMN, the standard of care is surgical resection followed by adjuvant chemotherapy and phase 3 trials have demonstrated the benefit of contemporary adjuvant chemotherapy regimens such as Folfirinox and Gem-Abraxane.[4-8] More recently, multiple trials have demonstrated the benefit of a neoadjuvant treatment strategy in PDAC.[9-11] Such trials include patients with PDACs without an associated IPMN, as such the benefit of adjuvant therapy is unclear in A-IPMN.[12-14]

A recent study from our group in the British Journal of Surgery (in-press), has shown that previous chemotherapy regimens such as Gemcitabine and Gemcitabine+Capecitabine may not have a significant impact on recurrence and survival outcomes in the adjuvant setting.[15] However, few patients (8%) received contemporary regimens (e.g. Folfirinox and Gem-Abraxane) and further investigation of contemporary regimens is required.

Recent trials have demonstrated survival benefit in PDAC with a neoadjuvant treatment strategy yet there is limited data available in specifically A-IPMN patients.[16-18] A recent American study investigated the role of neoadjuvant chemotherapy on locally advanced A-IPMN and suggested that neoadjuvant therapy may have a similar response in A-IPMN compared to PDAC. Their analysis was limited by sample size, with 25 patients receiving neoadjuvant therapy, and by both selection and time bias.

Previous international guidelines do not specify on surveillance strategies for A-IPMN, and evidence is often extrapolated from surveillance after PDAC resection protocols. This was further reflected in the Recent international evidence-based Kyoto guidelines for management of IPMN.[19] Kyoto guidelines

included some minor alterations to high-risk stigmata and worrisome features in addition to further defining the role of molecular markers in the cyst fluid on surveillance strategies.

The present study aims to determine the impact of contemporary neoadjuvant, adjuvant and palliative chemotherapy regimens on recurrence and survival outcomes in resectable, borderline resectable, locally advanced and metastatic A-IPMN. In addition, we also aim to validate the recently published Kyoto guidelines on the presence of both HRS and WF in patients who developed A-IPMN.

**Rationale:**

1. To investigate the impact of contemporary neoadjuvant, adjuvant and palliative chemotherapy regimens on recurrence and survival in A-IPMN
2. Validate the Kyoto guidelines on the presence of the updated HRS and WF criteria in patients who developed A-IPMN

**Methods:**

This is a European wide Multicenter retrospective audit.

**Eligibility criteria**

Patients diagnosed with A-IPMN on histopathology of surgical specimen, between January 2017 and December 2023, irrespective of whether they received neoadjuvant, adjuvant chemotherapy or palliative chemotherapy.

**Data collection:**

Data will be collected using the Research Electronic Data Capture (REDCap) system. Each participating centre will appoint a single dedicated primary investigator who will register their details on a secure online programme REDCap. They will subsequently receive login codes and passwords for logging into REDCap, and access to the online case report from (CRF). No identifiable data will be uploaded to REDCap and each case will be allocated a secure and unique REDCap ID number.

**Outcomes**

**Primary outcomes**

- To determine the overall and disease-free survival following resection for A-IPMN with and without contemporary neoadjuvant chemotherapy
- To determine the overall and disease-free survival following resection for A-IPMN with and without contemporary adjuvant chemotherapy

- To determine the overall and disease-free survival for locally advanced and metastatic A-IPMN with and without palliative chemotherapy
- Validate High-risk Stigmata (HRS) and Worrisome Features (WF) in the Kyoto guidelines and the development of A-IPMN

**Secondary outcomes**

To determine the impact of:

- Neoadjuvant chemotherapy type on recurrence
- Adjuvant chemotherapy type on recurrence
- The response of A-IPMN subtypes and high-risk groups to neoadjuvant chemotherapy
- The response of A-IPMN subtypes and high-risk groups to adjuvant chemotherapy
- HRS and WF criteria on the histopathology of resected invasive IPMN specimens
- Current use of cyst fluid biomarkers in invasive IPMN and their role in surveillance

**Strength**

This will be a multicentre European study, which will involve major European tertiary hepatopancreatobiliary centres. The audit will aim to determine the impact of contemporary adjuvant chemotherapy on survival and recurrence. In addition we aim to further validate the recently published Kyoto guidelines.

**Authorship**

Each participating centre will be eligible to two authorship positions.

**Study Protocol**

**Background**

Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing neoplasms of the pancreas originating from the epithelial lining of the main pancreatic duct and/or one of its side branches. Adenocarcinoma may complicate IPMNs (A-IPMN) in around 20% of cases but make up approximately 5% of all pancreatic adenocarcinomas.[1] Following resection of A-IPMN, patients are at significant risk of recurrence ranging from 32-43% and hence, adjuvant chemotherapy along the lines of multimodal treatment for pancreatic cancer is proposed.[2]

In patients with pancreatic ductal adenocarcinoma (PDAC), not associated with an underlying IPMN, the standard of care is surgical resection followed by adjuvant chemotherapy. Phase 3 trials have demonstrated the benefit of contemporary adjuvant chemotherapy regimens compared to mono-Gemcitabine and include Folfirinox, Gemcitabine+Capecitabine and Gemcitabine+Nab-Paclitaxel.[3-7] More recently, the PREOPANC-1, Prep-02JSAP05 and ESPAC5 trials have demonstrated the benefit of a neoadjuvant treatment strategy in PDAC.[8-10]

Trials that demonstrate the benefit of neoadjuvant and adjuvant therapy in pancreatic cancer include patients with primary PDAC without an associated IPMN, as such the benefit of adjuvant therapy is unclear in A-IPMN. Both the Fukuoka consensus statement and the American College of Gastroenterologists Clinical Guidelines make no recommendations on the role of adjuvant chemotherapy, and the recent European guidelines recommend adjuvant chemotherapy for A-IPMN with or without nodal disease in the absence of high-level evidence.[11-13.] A recent study from our group in British Journal of Surgery (in-press) has shown that previous chemotherapy regimens (e.g. Gemcitabine and Gemcitabine+Capecitabine) may not have a significant impact on recurrence and survival outcomes in the adjuvant setting.[14] In the cohort 8% of patients received contemporary regimens (e.g. Folfirinox) and further investigation of the impact of contemporary adjuvant chemotherapy regimens is required.

The recent Prep-02/JSAP05 and PREOPANC-1 trials have demonstrated survival benefit in PDAC with a neoadjuvant treatment strategy; however, limited data is available on the role of neoadjuvant chemotherapy in A-IPMN.[15-17] Fogliati et al. recently investigated the role of neoadjuvant chemotherapy on A-IPMN in a cohort of 105 patients with 25% receiving neoadjuvant treatment. They report marked pathological response in 19% (n=5) and partial/no response in 81% (n=13). Their conclusion was that neoadjuvant therapy has a similar response in A-IPMN compared to PDAC, but was limited by sample size and by both selection and time bias for treatment.

There are inherent differences in tumour biology and postresection outcome between A-IPMN and PDAC which may impact the response of A-IPMN to PDAC-derived chemotherapy regimens.[20] Given the rarity of these tumours, both randomised controlled trials and prospective trials are challenging in this area. The present study aims to determine the impact of contemporary adjuvant chemotherapy on recurrence and survival outcomes following resection.

The Kyoto guidelines have reported both high-risk stigmata (HRS) and worrisome features (WF) to guide surgical decision making. These include clinical and radiological findings which are associated with either high-grade dysplasia or invasive carcinoma.[21] Reporting HRS and WF in A-IPMN specimens will help validate particular HRS and WF as indicators of invasive disease.

**Study Design**

This is a European-wide retrospective audit.

**Study Period and Data collection**

Patients undergoing pancreatic resection for malignant IPMNs between January 2017 and December 2023 will be recruited. The study will open to data collection from 15th June 2024 to 15th October 2024.

Each registered centre will appoint one primary investigator who will register their details on a secure online programme called REDCap. No identifiable data will be uploaded to REDCap and each case will be allocated a unique and secure REDCap ID number. Each centre will subsequently receive login codes and passwords for logging into the website and access to the online case reported form (CRF). The local PI will be responsible for data collection and input from the individual centres.

**Participants**

**Inclusion criteria**

- patients diagnosed with A-IPMN on histopathology of surgical specimens, between January 2017 and December 2023, irrespective of whether they received adjuvant or neoadjuvant chemotherapy

**Exclusion criteria**

- Histopathology of resected specimen was not A-IPMN
- PDAC with concomitant A-IPMN
- PDAC with an associated non-invasive IPMN

**Outcomes**

**Primary outcomes**

- To determine the overall and disease-free survival following resection for A-IPMN with and without contemporary neoadjuvant chemotherapy
- To determine the overall and disease-free survival following resection for A-IPMN with and without contemporary adjuvant chemotherapy
- To determine the overall and disease-free survival for locally advanced and metastatic A-IPMN with and without palliative chemotherapy
- Validate High-risk Stigmata (HRS) and Worrisome Features (WF) in the Kyoto guidelines and the development of A-IPMN

**Secondary outcomes**

To determine the impact of:

- Neoadjuvant chemotherapy type on recurrence
- Adjuvant chemotherapy type on recurrence
- The response of A-IPMN subtypes and high-risk groups to neoadjuvant chemotherapy
- The response of A-IPMN subtypes and high-risk groups to adjuvant chemotherapy
- HRS and WF criteria on the histopathology of resected invasive IPMN specimens
- Current use of cyst fluid biomarkers in invasive IPMN and their role in surveillance

**Statistical analysis**

Predictors of neoadjuvant and adjuvant chemotherapy administration will be determined using appropriate univariate and multivariate analysis.

Propensity score matched analysis will be used to match neoadjuvant chemotherapy (treatment) patients with those who did not receive neoadjuvant chemotherapy (control). Propensity-scores will be determined using either probit or logit regression. Using the propensity scores, treatment and control groups will be matched 1:1. Kaplan-Meier curves will be plotted for treatment and control groups and will be compared using Logrank tests. Following this multivariate regression survival analysis (Cox regression) will be performed to further determine the impact of neoadjuvant chemotherapy on outcomes. Outcomes of interest would include overall recurrence, locoregional, systemic and site-specific recurrence as well as overall survival and disease free survival. The above analysis will be repeated for adjuvant chemotherapy.

Following this, comparison will be made between chemotherapy types. The impact of neoadjuvant chemotherapy types on outcome will be determined again using propensity matched analysis with survival analysis.

A subgroup analysis will be conducted on different IPMN precursor epithelial subtypes and high-risk groups (e.g. node positive).

The rate of HRS and WF will be reported for the A-IPMN cohort and compared between subtypes.

**Data collection**

The study will collect a range of data variables. Demographics, pre-operative imaging results, pre-operative cytological data, serum markers, operative and histopathologic variables will be collected. Pre-operatively, the presence of HRS and WF will be collected.

Details of neoadjuvant, adjuvant chemotherapy and palliative chemotherapy administration will be recorded. Response to neoadjuvant chemotherapy will be assessed using pathological, radiological and biochemical response. Radiological response will be assessed using the RECIST criteria and response will be graded as partial response, near complete response or complete response.[19] Biochemical response will be determined by normalisation of Ca19-9 (<37 UI/ml).

Data on surveillance in those who proceed to resection will be collected. If applicable, the data of diagnosis of the initial lesion will be reported as well as the length of surveillance. In those who do not proceed to resection, surveillance data will be collected to determine progression or remission of disease.

Data on recurrence will be collected including site of recurrence, pathological confirmation and treatment of recurrence. Follow-up data will be collected such as the date of last follow up, data of death as well as the cause of death. The exacted data variables (CDF) that will be collected are listed in Appendix 1.

**Authorship**:

Each participating centre will be eligible for two authorship positions and all participating authors will be acknowledged. Any publication, presentation or abstract on collected data will acknowledge all authors. Each centre remains the possessor of their data, and additional reports on data collected will only be conducted with written permission.

**Legal compliance**

All investigators and study site staff will comply with the requirements of the data Protection Act 2018 and the General Data Protection Regulations (GDPR) with regards to the collection, storage, processing, and disclosure of personal information and will uphold the acts core principles.

**Data extraction and de-identification process**

Data will be de-identified by collaborators in the individual hospitals. The principal investigator in each site will have overall responsibility for de-identification and for ensuring the data remains confidential. All identifying factors will be removed, and patients will be allocated unique identification codes. Only de-identified data with the appropriate unique identification codes will be submitted through the REDCap system. No data containing any personal identifiers will be transferred. Sites will not hold personal identifiers in the study database.

**Data Processing for Analysis**

De-identified data will be stored on secure computers at an NHS site in the form of a password protected database. Data will be processed and analysed by the team at the Freeman hospital, Newcastle. All collaborators will only have access to their own data and not access to data from other centres. Only the chief investigators team will have access to the full dataset.

**Long Term Data Storage**

De-identified data will be stored in accordance with GDPR on a secure password-protected database and for 5 years after the study findings are published in order to ensure that findings are verifiable.

**Ethical Approval**

Each primary investigator at each recruiting centre has the responsibility to obtain local Caldecott approval prior to data input.

**Peer review**

The present protocol will be reviewed independently by the EAHPBA scientific committee an appropriate source prior to dissemination.

**Indemnity**

NHS indemnity applies to the design, management and conduct of the study.

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