At a glance

**Background:** There is emerging evidence to support the role of downstaging treatment in a subgroup of patients with borderline resectable pancreatic cancer, previously considered poor candidates for resection. Prognosis for patients undergoing surgical resection is highly dependent on margin status, with best outcomes for patients with total gross excision and histologically negative margins. It is hoped that downstaging treatment may improve the chances of patients to have more favourable pathology and thus potentially better long-term outcomes.

**Implemented neo-adjuvant treatment protocol:** This showcase presents initial outcomes of a neo-adjuvant protocol prior to pancreatic ductal adenocarcinoma surgery and adjuvant therapy. The aim was to i) maximise frequency of patients who can undergo removal of the tumour with surgery and ii) improve disease outcomes. Protocol development and delivery was led by Dr Derek Grose, Consultant Clinical Oncologist and his team in Beatson West of Scotland Cancer Centre, Glasgow UK.

**Outcomes:** 85 patients were included in the study. 45 had initially resectable disease with high risk of positive margins, while the remainder 40 were unresectable at diagnosis and would require significant downstaging to become resectable. In total 34 patients underwent resection. From the histologically assessed specimens following neo-adjuvant treatment and resection, 60% had negative margin status. Moreover, median survival of patients who received surgery following the neo-adjuvant regime was 37 months as opposed to the median survival of the potentially resectable patients (total cohort), which was 22.2 months.

**Conclusions:** A neo-adjuvant approach is deliverable. It can be potentially applied to increase frequency of successful surgery in patients with borderline resectable localised pancreatic cancer and improve survival outcomes.
**Background**

Complete removal of the tumour offers the only potential cure for patients with pancreatic ductal adenocarcinoma (PDAC). However, less than 10% of patients undergo curative surgery and even among the resectable group, outcomes are poor. Prognosis for patients undergoing resection for PDAC is highly dependent on margin status, with total gross excision and histologically negative margins (R0 resection) being associated with better survival outcomes\(^2,3\). Patients who undergo total gross excision but have histologically positive margins (R1 resection) have a reduced survival. For example, in a cohort of 217 patients in West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, resected patients with a margin of >1.5mm from the closest involved margin (17% of total) had a median survival of 63.1 months as opposed to 16.9 months for patients with a smaller distance from the closest involved margin\(^4\). It is essential therefore to implement treatment regimens that aim to maximise the number of resectable PDACs cases and achieve better long-term survival.

**Case for change**

Growing evidence suggests that a subgroup of patients, previously considered poor candidates for resection due to encroachment upon local blood vessels, may benefit from resection, when preceded by neo-adjuvant therapy. This stage of disease, termed borderline resectable localised PDAC (LPDAC), has become of increasing interest for new treatment protocols\(^5\).

It is hoped that neo-adjuvant therapy to downstage the tumour before resection could achieve better surgery margin status and allow delivery of a full schedule of chemotherapy. For example, a European wide clinical trial demonstrated that 32% of resected patients failed to complete all cycles of adjuvant treatment\(^6\). Another study in a cohort of patients between 1996 and 2011 in the West of Scotland showed that only 55% received adjuvant therapy after curative resection as the rest (45% of patients) were not fit enough to undergo adjuvant therapy\(^4\). By delivering the chemotherapy prior to surgery a higher percentage of patients should be able to tolerate it.

The team led by Dr Derek Grose, Consultant Clinical Oncologist, in the Beatson West of Scotland Cancer Centre (BWoSCC) in conjunction with the regional Hepato-Pancreatic Biliary (HPB) multi-disciplinary team (MDT) at the Glasgow Royal Infirmary (GRI) have developed a neo-adjuvant treatment protocol to attempt to downstage the tumour before resection and adjuvant therapy\(^1\).
Aim

• To develop a neo-adjuvant treatment protocol to increase the proportion of patients with PDAC undergoing resection by:
  
i) increasing the number of resected patients with borderline resectable LPDAC
  
ii) achieving significant downstaging of the tumour in patients who would not otherwise be resectable (advanced LPDAC).

• To develop a neo-adjuvant protocol to increase R0 resection margin that will hopefully improve median survival.

Key Facts

• Pancreatic cancer is the 10th most common cancer in males and 8th in females

• It is the 6th most common cause of death from cancer in Scotland

• The five-year survival for pancreatic cancer in Scotland is 5.6%

• From the 394 cases of pancreatic, duodenal or biliary tract cancers that were diagnosed in Scotland between 2013 and 2015, 11.9% patients with PDAC received surgery in the West of Scotland Cancer Network.

Timeline

This study included patients who were referred to the regional HPB BWoSCC unit between 2012-2015.

The specialist MDT developed and introduced the new protocol in 2012.

Data from patients assigned to the neo-adjuvant treatment protocol were recorded in the locally maintained database in the period 2012-2015.

Survival was analysed as per follow-up of patients in the cohort on the 29th of April 2016.
The model of care practice

1. Staging of patients with localised borderline resectable or unresectable tumours based on a staging algorithm that involves CT scan of chest, abdomen and pelvis.

2. Discussion by MDT and classification according to resectability criteria as follows:
   i) small tumour (≤T2) with no proximity to vessel with R0 resection margin
   ii) potentially resectable but likely not complete excision of the tumour (R1 margin)
   iii) not resectable but could be candidate for surgery if tumour sufficiently shrinks

3. Patients fulfilling the category (i) in step 2 above were assessed with planned resection and excluded from neo-adjuvant group.

4. Patients potentially resectable were tested for cardiovascular and fitness performance.

5. Patients who satisfied the criteria above (ii and iii groups in step 2) above were treated with the neo-adjuvant protocol as follows:
   • Chemotherapy with folfrinoox or gemcitabine/capecitabine (for patients over 70 years old or unfit)
   • Patients with stable disease or some improvement in CT scan findings after 4 weeks of chemotherapy received chemoradiotherapy as well.

6. Patients were re-staged and re-assessed by the MDT after completion of the neo-adjuvant chemotherapy/chemoradiotherapy protocol, and classified as resectable or unsuitable for resection.

7. Depending on outcomes and performance, resected patients might receive adjuvant therapy.

8. Median survival and statistical data were analysed on 29th April, 2016.
Outcomes

Neo-adjuvant treatment outcomes

- 85 patients treated between 2012 and 2015 comprised the study group. The group comprised of 45 (52.9%) with high-risk technically resectable disease, 19 (22.3%) with unresectable disease who would require downstaging, 19 (22.3%) with locally advanced disease in whom downstaging to an extent that surgery would be possible is highly unlikely and 2 (2.5%) with multiple organ involvement

- 65 patients (76.5%) were given folfirinox, of whom 33 completed it successfully, 19 stopped early due to side effects and 13 underwent further cycles

- 20 (23.5%) patients were given gemcitabine/capecitabine, of whom 14 completed all the cycles successfully, 4 stopped early due to side effects and 2 had additional cycles

- 35 patients (41.2%) underwent chemoradiotherapy before re-assessment of their tumour.

Surgery outcomes and adjuvant therapy

- Out of 85 patients, 34 (42%) patients were successfully resected

- From these patients, 30 were initially staged as potentially resectable, though with a risk of R1 resection margin, and 4 patients were staged as unresectable with a likelihood to be resected if downstaged in response to neo-adjuvant treatment

- 20 out of 34 (58.8%) patients underwent adjuvant gemcitabine.

Treatment protocols for the study group of the neo-adjuvant therapy is schematically presented in Figure 1.
Localised pancreatic ductal adenocarcinoma (LPDAC) n=85 patients

Neo-adjuvant chemotherapy
Folfirinox (n=65; 76.5%)
Gem/Cap (n=20; 23.5%)

Chemoradiotherapy (n=35/85; 41.2%)
Surgery (n=17/85; 20%)
Progression, not suitable for further treatment (n=33/85; 38.8%)

Adjuvant Gemcitabine (n=8/17; 47%)
Adjuvant Gemcitabine (n=12/17; 70.5%)

Surgery (n=17/35; 48.6%)
Progression, not suitable for further treatment (n=18/35; 51.4%)

Figure 1. Schematic demonstrating the study group of LPDAC patients undergoing neo-adjuvant therapy. From the patients comprising the neo-adjuvant therapy group (n=85), 34 were resected. From these, 20 underwent adjuvant therapy. Gem: gemcitabine, Cap: capecitabine.
**Histopathology outcomes**

- Following resection after neo-adjuvant treatment, histopathological assessment showed smaller size tumours.

- From the 32 specimens examined, 60% achieved R0 resection margin, with 40% assessed as R1 resections. In those patients undergoing chemoradiotherapy as well as chemotherapy the rate of R0 was 71%.

**Median Survival**

- 56% of the patients enrolled in the study were alive at the time of survival analysis.

- Overall median survival of the neo-adjuvant cohort of patients (n=85) was 22.2 months.

- Median survival of patients who were initially assessed as potentially resectable and received surgery following the neo-adjuvant regime (n=30) was 37 months.

- From patients who were initially considered unresectable (n=4) but were resected following the neo-adjuvant treatment, median survival was 11.5 months.

**Median survival in neo-adjuvant protocol**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=85)</td>
<td>22.2</td>
</tr>
<tr>
<td>Resected (n=30)</td>
<td>37</td>
</tr>
<tr>
<td>Localised unresectable tumours (n=4)</td>
<td>11.5</td>
</tr>
</tbody>
</table>

*Median survival in neo-adjuvant protocol*
Conclusions

The team in BWoSCC has developed a complex protocol of neo-adjuvant therapy for patients with LPDAC that was borderline resectable or unresectable. The team demonstrated that neo-adjuvant chemotherapy can be delivered safely. Additionally, folfirinox and chemoradiotherapy can be well tolerated in this setting.

For patients who were initially assessed as potentially resectable and completed resection following neo-adjuvant treatment, median survival was 37 months. This is higher than what reported in the ESPAC-3 and ESPAC-4 trials, where PDAC patients who underwent primary resection followed by adjuvant gemcitabine had a median survival of 23-25.5 months6,10.

Neo-adjuvant treatment has the potential to be delivered as standard practice for patients who are initially assessed as borderline resectable without affecting survivability and physical wellbeing. Patients who would not normally have been considered for a resection usually undergo standard protocols of chemotherapy. Therefore, introduction of a neo-adjuvant protocol can give these patients the possibility of resection if they have a downstage response and this can lead to an increase in survival. It is clear however that a neo-adjuvant pathway will not benefit all patients as a number will progress during treatment.

Future directions and challenges

More evidence is required to help inform the decision making process about patient and treatment selection for a neo-adjuvant approach and to answer the challenging ongoing questions with regards to the role of neo-adjuvant treatment in the localised pancreatic cancer setting.

The team in Glasgow has received a research award as part of the PrecisionPanc research programme to develop personalised treatments based on the genetic profile of each pancreatic cancer patient. This project has been awarded £30m overall including a £10m investment from CRUK. Other bodies supporting this programme are University of Glasgow, Celgene, Wellcome Trust, Chief Scientist’s Office, Scottish Genomes Partnership, MRC/ESPRC Glasgow Molecular Pathology Node, NHS Scotland, The Howat Foundation, Pancreatic Cancer UK, The Scottish Precision Medicine Ecosystem/Stratified Medicine Scotland Innovation Centre, AstraZeneca/MedImmune, NCRI and ECMC. As part of this programme of research, three clinical trials are currently developed, Primus 001 (opened in December 2017), Primus 002 and Primus 003.
The UK multi-centre Primus 002 trial led by Dr Derek Grose (clinical chief investigator) and Dr David Chang (scientific chief investigator) will aim to clarify the safety and benefits of a neo-adjuvant approach utilising chemotherapy and radiotherapy. Its main end-point is to identify potential tumour characteristics that might help clinicians to understand which patients may benefit most from a neo-adjuvant approach to treating this very difficult and challenging disease.

There are more HPB units within the UK, including the one in Belfast NHS Cancer Trust and the one in Leeds Teaching Hospitals NHS Trust who have scoped the use of neo-adjuvant therapy for borderline resectable LPDAC cases. Currently in England, the NICE guidelines recommend application of neo-adjuvant treatment for pancreatic cancer patients only as part of a clinical trial.

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References


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