ESPAC-5F and Neoadjuvant Chemotherapy

Thursday 8th October 2020, 09.00 – 10.00
Neoadjuvant Chemotherapy in Pancreatic Cancer: Glasgow experience

Nigel B. Jamieson
Senior Lecturer & Consultant Pancreatic Surgeon
Glasgow Precision Oncology Laboratory
University of Glasgow
Glasgow Royal Infirmary

Pancreatic Cancer UK
Virtual National Study Session
8th October 2020
Cancer Research UK Clinician Scientist
Outline

Glasgow experience neoadjuvant chemotherapy

- Rationale
- Experience
- Challenges
- Current Trials and the future
Pancreatic Cancer a true adversary

Despite optimised surgical technique traditional management has resulted in:

- **High complications rate** often limiting adjuvant chemotherapy allocation
- Disappointing **resection margin positivity rate (80%)**

**Survival** despite resection and adjuvant therapy for localised PDAC remains at best 20% at 5 years.

R0 resection - median survival of **30 months**

Pancreatic Cancer is a Systemic Disease

Multimodality therapy is **VITAL** to management of pancreatic cancer

50% of patients did **NOT** receive Adjuvant Chemotherapy
### Rationale for Pancreatic cancer Neoadjuvant Therapy

<table>
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<th>For</th>
<th>Against</th>
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<tr>
<td>- Multimodality Therapy better tolerated without physiological and immunological derangement of surgery</td>
<td>- Potentially operable disease may have local progression or stent related complication</td>
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<tr>
<td>- More easily administered preoperatively</td>
<td>- Preoperative CT assessment not useful</td>
</tr>
<tr>
<td>- Patients with aggressive biology progress therefore avoid operation</td>
<td>- Concern that vascular resections/reconstructions common</td>
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<tr>
<td>- Risk of early recurrence &lt; 6 months avoided</td>
<td>- More challenging operative environment</td>
</tr>
<tr>
<td>- No significant increase in Morbidity and mortality</td>
<td>- Intraoperative fluid shifts, Chyle leaks</td>
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Glasgow Experience

2012 onwards consideration given to a neoadjuvant treatment pathway

Resectable | Borderline Resectable | Locally Advanced
Venous | Arterial

SMV | SMA/CA

Unreconstructable Vein

NCCN guidelines *J Natl Compr Canc Netw*
Tempero MA et al 2017
Practicalities of patient selection

**ANATOMY**
- CT scan

**BIOLOGY**
- Ca19-9, MRI liver, Suspicious pulmonary nodules

**COMORBIDITY**
- Optimise, Diabetes, CVD

Multi-disciplinary Team
- Localised pancreatic cancer
- Resectable / Borderline / Localised Advanced
Almost 275 patients given Neoadjuvant / induction chemotherapy +/- radiotherapy

Over 100 patients resected

Despite challenging operative field, morbidity profile is not significantly different

Mortality occurred – High BMI, Context of High Dose Radiotherapy

68% adjuvant chemotherapy
Experience

Neoadjuvant Treatment Pathway
- Patients with stable disease should be offered exploration
- Consider risk benefit carefully
- Trust Neoadjuvant Therapy
- Often operation required is the same one as FIRST CT Scan

For **Resectable** PDAC – 30% Metastatic progression

Evans DB, et al JCO 2008

**ANATOMY**

**BIOLOGY**

**COMORBIDITY**
### Neoadjuvant therapy

#### Pathology comparison results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary resection</th>
<th>Neoadjuvant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node examined</td>
<td>22 (14-55)</td>
<td>22 (13-70)</td>
<td>0.67</td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>3 (0-26)</td>
<td>1 (0-9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resection margin clearance (mm)</td>
<td>0.5 (0-7)</td>
<td>1.2 (0-30)</td>
<td>&lt;0.001</td>
</tr>
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</table>

**N = 310**

<table>
<thead>
<tr>
<th>Neoadjuvant</th>
<th>Surgery First</th>
</tr>
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<tbody>
<tr>
<td>Lymph Node Involved</td>
<td>79%</td>
</tr>
<tr>
<td>Perineural Invasion</td>
<td>84%</td>
</tr>
<tr>
<td>Resection margin Involved (1mm)</td>
<td>72%</td>
</tr>
</tbody>
</table>

**Margin Clearance**

Median (Range)
Patients categorized into 3 subgroups:
- Complete or near complete response
- Moderate response
- Minimal response

Tumour Regression: Implications

CPR/Near CPR (12.5%)
Isolated tumor cells
More common with FFX and XRT
Includes true locally advanced

<table>
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<tr>
<th>Response Level</th>
<th>Number</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Complete or near complete response</td>
<td>15</td>
<td>31%</td>
</tr>
<tr>
<td>Moderate response</td>
<td>10</td>
<td>21%</td>
</tr>
<tr>
<td>Minimal response</td>
<td>23</td>
<td>48%</td>
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Cumulative proportion surviving
- P = 0.011
- P = 0.03

Overall survival (months)
- NA mths
- 38.0 mths
- 18.0 mths
Lessons learned

Prehabilitation
Ensuring nutritional and diabetic optimization during neoadjuvant journey
Avoid deconditioning

Patient Journey
Appropriate patient expectations
Disease progression
Communication between oncology and surgery
Lessons learned

**Staging**
- Anatomy - CT scan and MRI liver (PET scan)
  - CT scan does not predict response
  - Initial CT can overcall – pancreatitis
- Biology - **Ca19-9 stable or falling**
- Clinical – **Optimise comorbidity, CPET, Weight loss**
Predicting Pathological Response

Imaging response

Pathology response

Complete Pathological Response

Minimal Response

- Hepatic PV
- Stable
- SMA Regression
- Minimal Response
Lessons learned

Staging

Anatomy - CT scan and MRI liver (PET scan)
CT scan does not predict response
Initial CT can overcall – pancreatitis

Biology - **Ca19-9 stable or falling**

Clinical – **Optimise comorbidity, CPET, Weight loss**
Lessons learned

‘Multiple Hoops’

Neoadjuvant Pathway

CT Stable

Low Ca19-9

MRI/PET neg

Laparoscopy

Surgical exploration

Stent complications

Chemo SEs

Performance/nutritional Decline

Ca19-9

Metastases

Non-PDAC

Multiple MDT visits – risks MDT inertia
Clinical Trials
Patient Recruitment
All patients with pancreatic cancer hoping to access a PRIMUS trial need to first be screened and registered into the Precision-Panc Master Protocol to allow either:

- Extra tissue to be taken from their diagnostic study
- Material to be released from their diagnostic biopsy
- Undergo additional research biopsy

Pancreatic cancer Individualised Multi-arm Umbrella Study (PRIMUS) Portfolio
Patient Recruitment
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PRIMUS 001
Metastatic
Adaptive phase II study
FOLFOX-A (FOLFOX + nab-paclitaxel) versus Gem-Abraxane (nab-paclitaxel + gemcitabine)
In patients with metastatic pancreatic cancer, with integrated biomarker evaluation

PRIMUS 002
Resectable / Borderline
An umbrella phase II study
Examining two new equivalent regimens (FOLFOX-A and AG) in resectable / borderline resectable pancreatic cancer, focusing on biomarker and liquid biopsy development

PRIMUS 003
Metastatic
A phase Ib and IIpan study, multi-centre study of CIRCPR + Check point inhibitor evaluated in patients with metastatic pancreatic cancer

PRIMUS 004
Metastatic
An Umbrella phase II study
Testing combinations that target DNA Damage Repair deficiency and replication stress in molecularly selected patients with metastatic pancreatic cancer

Aiming to improve pancreatic cancer survival by
"Finding the right trial for the right patient"
Pancreatic cancer Individualised Multi-arm Umbrella Study (PRIMUS) Portfolio

**PRIMUS 001**
Metastatic
Adaptive phase II study:
FOLFOX-A (FOLFOX + nab-paclitaxel) versus Gem-Abraxane (nab-paclitaxel + gemcitabine)
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**PRIMUS 003**
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Metastatic
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**PRIMUS 002**

Resectable / Borderline

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Examining two neo-adjuvant regimens (FOLFOX-A and AG) in resectable / borderline resectable pancreatic cancer, focusing on biomarker and liquid biopsy development

**Baseline Tests:**
- CT Scan
- EUS + Biopsy
- MRI / PET Scan
- Fitness Testing
- CA 19.9
- Liquid biopsy

**Molecular characterisation**
- Cancer Gene Panel
  +/− WGS

**Resectable & Borderline**

- Resectable Pancreatic Cancer
  - PS 0 (very fit), Age ≤ 75
  - PS 1 (fit), Age ≤ 70
  - FOLFOX-Abraxane
  - Abraxane-Gemcitabine

**PHASE 2**

- Chemoradiotherapy
- Surgery

**From Precision-Panc Master Protocol**

**2 centres**

18 registered
7 resected
55yr old female
Locally advanced Pancreatic Cancer
- SMV narrowed
- CHA involved
Post Neoadjuvant Chemoradiotherapy

Total pancreatectomy
- Low Ca19-9
- Excellent PS
Neoadjuvant Chemotherapy for Pancreatic Cancer

Pancreatic Cancer

Early Metastases

Local

Systemic

Surgery First

Adjuvant

Multimodality Therapy

Median Survival

50%

30mths

NEOAdj

Surgery Last

Multimodality Therapy

Median Survival

Near/Complete Response

100%

38mths

12%

Targeted Preoperative NEOAdj

Surgery Last

? Increased Complete Pathological Response
SUMMARY

Neoadjuvant strategy can be applied safely

Staging and preoperative assessment are logistically challenging

True multi-disciplinary approach required.

Pathological features are improved, with tumour regression the most important prognostic feature

Future benefits may be derived from

Tailored neoadjuvant strategies
Integration of tumour biology

Operate Less but on the Right Patients
Glasgow Royal Infirmary
Euan Dickson
Ross Carter
Colin J Mckay
Maria Coats
David Chang
Abdullah Al-Adhami

Beatson Oncology Centre
Janet Graham
Derek Grose
David McIntosh
Amy Martin

GPOL
Andrew Biankin
David Chang
Susie Cook
Philip Beer
Stephan Dreyer
Selma Rebus
Holly Leslie
Assya Legrimi

Royal North Shore Sydney
Jas Samra
Anubhav Mittal
Anthony Gill

Patients and family

Project Manager
Judith.Dixon@Glasgow.ac.uk
Thank you