Neoadjuvant Treatment Of Pancreatic and Peri-ampullary Cancer

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Pancreatic Cancer Facts

- 9,800 new pancreatic cancer cases in the UK every year (3% of all new cancer cases)
- Incidence rising (15% since 1990s, further 6% by 2035)
- 80% cases present at a late stage (inoperable)
- 85% ductal adenocarcinoma, 70% in head of pancreas
Pancreatic Cancer Staging

T staging 8th edition shown some evidence more likely to correlate with survival than 7th edition,

But N staging change did not show correlation

<table>
<thead>
<tr>
<th>T</th>
<th>Tumor limited to the pancreas, ≤2 cm in greatest dimension</th>
<th>Maximum tumor diameter ≤2 cm</th>
<th>7th</th>
<th>8th</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to the pancreas, &gt;2 cm in greatest dimension</td>
<td>Maximum tumor diameter &gt;2, ≤4 cm</td>
<td>I</td>
<td>N</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery</td>
<td>Maximum tumor diameter &gt;4 cm</td>
<td>M</td>
<td>T</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)</td>
<td>Tumor involves the celiac axis, common hepatic artery or the superior mesenteric artery</td>
<td>IIA</td>
<td>T</td>
</tr>
<tr>
<td>T4</td>
<td>No regional lymph node metastasis</td>
<td>No regional lymph node metastasis</td>
<td>III</td>
<td>T</td>
</tr>
<tr>
<td>N0</td>
<td>Regional lymph node metastasis</td>
<td>Metastasis in 1–3 regional lymph nodes</td>
<td>IV</td>
<td>any</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ≥4 regional lymph nodes</td>
<td>any</td>
<td>any</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Any distant metastasis</td>
<td>Any</td>
<td>any</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td>Distinct metastasis</td>
<td>T</td>
<td>N</td>
</tr>
<tr>
<td>M1</td>
<td>Metastasis in the liver or distant metastasis</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

Lin Cong, Qiaofei Liu et al; Tumor size classification of the 8th edition of TNM staging system is superior to that of the 7th edition in predicting the survival outcome of pancreatic cancer patients after radical resection and adjuvant chemotherapy Sci Rep. 2018; 8: 10383. Published online 2018 Jul 10. doi: [10.1038/s41598-018-28193-4] PMCID: PMC6039534 PMID: 29991730
Pancreatic Cancer Prognosis

- How many are resectable ~25%
- How many R0/R1
- For Operable Patients 5yr OS
  - R0 30%
  - R1 10%
Pancreatic Cancer Prognosis

Overall Survival for 525 node negative patients according to T staging (8th edition) after resection

Pancreatic Cancer Prognosis

Overall survival for R0 resections stratified by positive lymph node number

Pancreatic Cancer Prognosis

- If we catch Pancreatic Cancer early, why is prognosis still poor?

OCCULT DISEASE
1106 patients with resectable disease

437 unresectable patients (at time of surgery)

If Ca19.9 > 1000 then RO only achieved in 15% cases (taking into account resectable and non-resectable patients)
PET: American and European guidance does not currently recommend routine use of PET/CT for staging.

PET PANC* study:
- prospective study 550 patients PET/CT in addition to CT
- Sensitivity (93 vs 89 %), specificity (76 vs 71 %), positive predictive values (78 vs 73%), and negative predictive values (92 vs 87 %) for diagnosing pancreatic cancer all favoured PET/CT over CT alone.
- Of 290 patients planned for resection following CT, 21% (61) did not proceed following PET/CT (metastases in 41, 17 suspected-benign lesions)

Resectability Defining Treatment

- No distant metastases
- No arterial or venous involvement
- Attachment to other organs (e.g., spleen)
- Venous involvement (SMV or portal) less than 180 degrees, as long as there is suitable vessel proximal and distal to the areas of involvement for reconstruction
- Gastroduodenal artery encasement up to the common hepatic artery with other short segment encasement or abutment of the hepatic artery, but without extension to celiac trunk
- Tumor abutment of the SMA less than one-half the circumference of the vessel wall.
- Greater than 180 degree encasement or occlusion/thrombus of SMA, unreconstructable SMV or SMV-portal vein confluence occlusion
- Direct involvement of the inferior vena cava, aorta, celiac trunk or hepatic artery, as defined by absence of a fat plane between low density tumor and these structures on CT or EUS.
- Metastases to lymph nodes beyond the peripancreatic tissues
- Distant metastases

Surgery
Adjuvant chemo
Neoadjuvant treatment
Palliative SACT
Adjuvant SACT – current standard of care

6 months of chemotherapy starting within 8 weeks of surgery

**GEMCITABINE**
- CONKO-001: 5yr OS doubled with GEM vs Surgery alone.
- ESPAC 3: similar PFS (5FU vs Gem) but less SE with Gem. 
  *Completing adj chemo course improved median survival (28 vs 15 months)*

**GEMCAP**
- ESPAC 4: 5yr OS doubled with adj GEMCAP versus GEM alone (30 vs 15%)

**FOLFIRINOX**
- PRODIGE-24: improved DFS (22 vs 13 months) and median survival (54 vs 34 months) with FOLFIRINOX vs GEM (prelim report ASCO 2018)
- Not NICE guideline
Locally Advanced Pancreatic Cancer

- **NICE Guidelines**
  - Offer systemic combination chemotherapy to people with locally advanced pancreatic cancer who are well enough to tolerate it.
  - Consider gemcitabine for people with locally advanced pancreatic cancer who are not well enough to tolerate combination chemotherapy.
  - When using chemoradiotherapy, consider capecitabine as the radiosensitiser.
1st Line Palliative SACT- Current Standard of Care

- **FOLFIRINOX**
  - If PS0-1

- **Nab-Paclitaxel (Abraxane) and Gemcitabine**
  - If other combination chemotherapy unsuitable and would otherwise receive Gemcitabine monotherapy

- **Gemcitabine alone**
  - Not fit for combination chemotherapy
Is There a Role for Neoadjuvant Chemotherapy?

**YES**
- Higher rate of resectability? (only 15-20% resectable at presentation).
- To improve long-term outcomes despite successful surgery and adjuvant therapy.
- Test biology of disease- response to chemotherapy/development of mets.
- Overcome inability to deliver adjuvant chemotherapy in 25% patients due to prolonged recovery from surgery.
- Potential starting treatment earlier

**BUT**
- No study has clearly demonstrated improved resectability or survival over surgery alone
- Remains unclear whether neoadjuvant treatment provides benefit compared with modern adjuvant therapy.
- No clarity about which chemotherapy combination is optimal and the role of radiotherapy.
Neoadjuvant SACT

Meta-analysis
- 38 studies included (resectable or borderline resectable)
- Mostly 5FU/Gem based SACT
- Overall survival favours neoadj treatment (18.8 vs 14.8 months).
- In those resected OS increases to 26 months
- RO rate higher with neoadj treatment
- pNodal positivity lower with neoadj treatment (44 vs 65%)

RCT Phase II
- 88 patients
  - 1(Surgery + adj Gem) vs
  - 2(Surgery + adj PEGX) vs
  - 3(neoadj PEGX/surgery/adj PEGX)
- RO doubled with perioperative chemo 37% vs 63%
- 3 yr OS 35% vs 43% vs 55%
Neoadjuvant SACT plus Chemoradiotherapy

- **Phase II Study LAPC**
  - 48 patients
  - 4 months neoadj FOLFIRINOX plus chemorad (long or short course)
  - 80% completed all chemo
  - 65% RO resection
  - PFS at 2 years 43%
  - Median OS 38 months
Neoadjuvant SACT plus Chemoradiotherapy

Phase III Study: PEROPANC trial preliminary results
- 246 patients borderline resectable
  - A immediate surgery
  - B preoperative CRT 36Gy/15# with Gem D1, D8, D15
- Both followed by Adjuvant Gem based chemo
  - Equal total amounts of chemo
- 72% arm A to resection, 62% arm B to resection
- R0 doubled 63% vs 31% (with neoadj treatment) p<0.001
- Median OS 17 vs 13.5 months favours neoadj treatment p=0.074
- DFS 9.9mths vs 7.9mths p=0.023
- In subset of patients R0 resection
  - Med OS 42.mths vs 16.8mths
- IIT analysis did not meet OS stat signif but important number of disease progression
Neoadjuvant Chemo vs Chemorad

- Ro resection rates similar at ~65%
- Does this translate to OS for both?
- QoL differences?
- Surgical considerations?
- What trials are ongoing?
SCALOP-2, Locally advanced pancreatic non-metastatic

- Induction chemo, the CRT +/- nelfinavir +/- dose escalation
- 3 cycles Gem Abraxane then
  - Arm A: One cycle of GEMABX while RT planned then capecitabine (830mg/m2 oral bd) + nelfinavir + 50.4Gy in 28 fractions.
  - Arm B: One cycle of GEMABX while RT planned then capecitabine (830mg/m2 oral bd) + 50.4Gy in 28 fractions.
  - Arm C: One cycle of GEMABX while RT planned then capecitabine (830mg/m2 oral bd) + nelfinavir + 60Gy in 30 fractions.
  - Arm D: One cycle of GEMABX while RT planned then capecitabine (830mg/m2 oral bd) + 60Gy in 30 fractions.
  - Arm E: Three further cycles of GEMABX
- Recruitment open until Oct 2019
- Running at Derriford
ESPAC-5F Trial

Phase II randomised feasibility trial for borderline resectable

- immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy for patients
  - Arm 1: surgery alone
  - Arm 2: GEMCAP preop
  - Arm 3: FOLFIRINOX preop
  - Arm 4: chemorad (capecitabine based)

Recruitment April 2014- Dec 2018
Periampullary tumours

- Includes from different primary sites
  - Ampullary tumour of the ampulla of Vater.
  - Distal common bile duct carcinoma
  - Duodenal carcinoma
  - Pancreatic carcinoma

- Difficult to distinguish primary ampullary carcinoma from other periampullary tumours preoperatively.

- True ampullary cancers have a better prognosis than other periampullary malignancies
  - 5 yr survival rates 30-50%

- How initial treatment with chemo/chemoradiotherapy will affect the prognosis of cancers in the periampullary region that turn out postoperatively to be ampullary and not pancreatic head cancers is not known.
**Conclusions**

Neoadjuvant treatment can:

1. Reduce number of pathological positive nodes (48% vs 73%)
2. Lower pT3/4 (73% vs 86%)
3. Increase rate of R0 resections
4. Improve median survival

BUT we need evidence from future trials....

- Is the evidence for chemoradiotherapy better than chemotherapy alone?
- What does the future hold with newer agents?
Conclusions

- Potentially may operate on fewer patients
  - More Investigation eg PET/CT
  - Predictive tools
  - Test of biology
- But patients may have better outcomes after resection
Future Opportunities

- Trial participation
- Network Audits
  - How many patients have an RO resection/good OS
  - Are there similar features in these patients
    - CA19-9
    - Pre-op investigation results
    - PET/CT
    - Comorbidities
Discussion/Questions?