EVIDENCE BASED MANAGEMENT OF PANCREATIC TUMORS

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• By 2030 expected to be the second leading cause for cancer mortality
• Surgical resection is the curative option
• Only 15% present in a resectable stage
• Locoregional failure is expected to affect 50–80% of patients.
• Systemic relapse (locoregionally associated or not) will affect over 70% of patients.
• 5yrs survival is only 20-25%.
Algorithm for Diagnosis

Suspect pancreatic cancer

Pancreatic protocol computed tomography or magnetic resonance imaging

Lesion in pancreas:
- Metastatic disease
  - Biopsy confirmation of metastatic site
- No metastatic disease
  - Multidisciplinary review
    - Consider endoscopic ultrasonography
    - Liver function tests
    - Chest imaging

No lesion in pancreas:
- Metastatic disease
  - Biopsy confirmation of metastatic site
  - Endoscopic ultrasonography
- No metastatic disease
  - Liver function tests
  - Chest imaging
  - Endoscopic ultrasonography and/or magnetic resonance imaging/magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography as clinically indicated

*—Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.
†—Endoscopic ultrasonography-guided fine-needle aspiration if clinically indicated.
Imaging Evaluations

• Pancreatic Protocol 1-2 mm slices
  • CT
  • MRI
• Endoscopic Ultrasound
• ERCP and PTC
• PET CT
• Laproscopy
Biopsy
Biomarkers

• CA 19.9 levels
  • 10% of patients it is normal.
  • Because of missing enzyme for the sialyl lewis antigen epitope production.
  • Confirm diagnosis & predict prognosis & recurrence after resection
  • Not useful for screening as it is not tumour specific
  • Sensitivity-50-75% Specificity 80-85%
  • Also elevated in pancreatitis, chronic inflammation
Overview of Treatment

- Based on resectability

- Resection is only chance of cure of this disease

- Resectable pts should undergo resection followed by Adjuvant therapy

- Borderline resectable patients may benefit from neoadjuvant treatment & then surgery

- Unresectable- CT/ CRT

- Metastatic disease- CT/ Palliative Care
Pancreatic Adeno Carcinoma

- Localised
  - Resectable
  - Borderline Resectable
  - Locally advanced
- Metastatic
Surgical Management

• Goal
  • Oncological resection of Primary Tumor and Regional Lns
  • Potentially curative option
  • BUT..... 80% is advanced
  • Mortality is less than 5% in experienced centers
  • Median survival is between 20-28 months,
    • even after Adj therapy.
Surgical Management

• Prognostic Indicators
  • R0 resection status
  • Small tumor size
  • Negative lymphnodes
  • Tumor DNA content

• Survival Benefits of an R1 resection is comparable to Definitive Chemo RT

Clear fat plane between tumour & SMV
Criteria for Resection

• No imaging evidence of visceral, pleural and peritoneal mets
• Nodes beyond the Field of resection
• D Lap to rule out Peritoneal deposit and to assess the resection possibility if operable by imaging
  • What is assessed…
  • Relation of tumor to blood vessel.
If Resectable...What surgery?

• If feasible
  • Head and uncinate process
    • Whipples procedure.
  • Body and tail
    • Distal pancreatectomy & en bloc splenectomy.

• If not Feasible
  • Biopsy is a must...

• Radical pancreaticoduodenectomy
  - Removal of Pancreatic head, Duodenum, Stomach, Portion of jejunum, Gall bladder, Spleen

Anastomoses - Gastrojejunostomy, pancreaticojejunostomy, Hepaticojejunostomy
Margins required

• 5mm clear
• If cauterized
  • Clean cut margin is must
  • Artefact can give false negatives
Regarding Nodes…

- N0
  - 11 - 17 nodes

- N1
  - LN positivity ratio
  - Less than 15% - 5 year survival 21.7%
  - More the 15% - 5 year survival 5.2%
If not resectable...

- EUS FNA or Biopsy
- Open Biopsy
If Resectable – What next?

- Adjuvant chemo
- Adjuvant chemo RT
- Adjuvant RT alone
• ROLE OF RADIATION THERAPY
• IS IT USEFUL
• WHERE
• IS THERE EVIDENCE
• IS THIS EVIDENCE ENOUGH

Like this for 30 years
Radiation and Chemoradiation Approaches

- Concurrently as radiosensitizer
  - Gem
  - 5FU
  - Capecitabine
  - Decreases the number of cells in the S phase of tumor cells
- Alone
- Where
  - Resectable and Adjuvant settings
  - Neo Adjuvant setting
  - Recurrent setting
  - Inoperable
  - Palliative
Aim of Radiation Therapy in NART

- Sterilise vessel margin
- Increase the likelihood of negative resection margin
- Enhance the local control and prevent disease in local site
Adjuvant chemotherapy

• ESPAC 1
  • Adjuvant chemo with 5FU is standard
  • Chemo RT had poor OS and PFS

• German CONKO-001
  • Gem alone Vs observation
  • DFS favouring Gemcitabine.
  • 13.4 Vs 6.7 mths

• ESPAC 3
  • Gem Vs 5FU
  • No difference
Adjuvant chemotherapy

• ESPAC 4
  • Gem plus 5FU Vs Gem alone
  • Combination is better
  • OS - 28 Vs 25.5 mths

• PRODIGE 24
  • mFOLFIRINOX is better than Gem alone
  • OS - 54.4 Vs 35 mths
  • In metastatic setting
  • Gem plus nab Pacli is superior to Gem alone

• No direct comparison between mFOLFIRINOX Vs GnP
Adjuvant Chemoradiation

- GITSG 1985
  - chemoRT better than observation in Adjuvant setting.
  - Split course RT 40Gy
  - Chemo with 5FU for 2 years
  - 2yr actuarial survival - 42% VS 15% favouring ChemoRT.
- EORTC 40891
  - Adj RT with 5FU Vs Observation
  - Did not show any benefit with Chemo RT and observation with respect to PFS and OS at 11.7yrs
Adjuvant Chemoradiation

- RTOG 9704 phase III
  - Adjuvant chemoRT, Gem Vs 5Fu.
  - Median and OS favouring Gem arm, but not statistically significant.
  - Median and 3yr survival (20.5 mths and 31% Vs 16.9 mths and 22%).
  - Head of pancreas tumor shows a trend in better survival with Gem arm.
Radiation as Adjuvant therapy

• ESPAC 1
  • Adding Radiation did not show any benefit.
  • Criticized as there was no quality control on RT.

• GERCOR study
  • Gem + RT Vs Gem alone
  • No difference

• CapRI phase III study
  • 5Fu + cisp +IFN + RT Vs 5FU alone
  • No benefit
Radiation as Adjuvant therapy

• Population based study
  • 1998 -2002
  • chemoRT better OS than chemo in a performance status matched comparison to no adjuvant RT.

• Multi institutional pooled analysis
  • 955 patients
  • R0-1 resection
  • Chemo RT better than chemo alone
  • OS 39.9 mths Vs 27.8 mths.
Radiation as Adjuvant Therapy

• Compared with observation post surgery
  • John Hopkins Hospital
    • R0 and R1 resection subsets superior than observation.
  • Mayo clinic - retrospective analysis
    • 466 patients
    • R0 resection
    • OS benefit better with ChemoRT than Observation.

• 4RCTs
  • Increased survival benefit in R1 subset for ChemoRT

• Retrospective analysis in John Hopkins university for node positive disease showed survival benefit.
• RTOG 0848
  • The addition of adjuvant E to G did not provide a signal for increased OS in pts with resected pancreatic head cancer compared to G alone. Accrual to the trial is continuing to answer the Ph III radiation question. Clinical trial information: NCT01013649.
Radiation as Adjuvant Therapy - why no Data

- six randomized studies enrolled patients over a period - between 1987 and 2007.

- Major deficit in those experiences
  - lack of use of modern techniques, such as intensity-modulated radiotherapy or image-guided radiotherapy, to overcome limitations related to the inclusion of large parts of gastrointestinal tract within the treatment fields.
  - the total dose of ionizing radiations was much lower than the dose delivered in the adjuvant setting for other malignancies.
Is RT useful? in Adjuvant

- R1 resection patients
- Node positive patients
- R0 patients and node negative patients ???
Approx 180 degree contact between tumour & SMV & subtle haziness post to SMA
Borderline Resectable

- Higher likelihood of incomplete resection and margins are going to be positive.
- How to identify..
  - Degree of Contact
    - Interface between tumor and SMA/CA measuring more than 180 degree of vessel circumference.
    - Tumor contact with jejunal branch of SMA/SMV
  - Contour deformity
    - Tear drop deformity in the MPV and SMV, ascribes vascular invasion rather than abutment and Impingement.
Neoadjuvant Therapy

- Borderline Resectable – Yes
- Resectable – Why
  - Selection advantage – 25% patients progress after NAT, surgical morbidity is spared.
  - Other advantages
    - Increased rates of R0 resection
    - Decreased incidence of pancreatic fistulas
    - Prevention of delay in adjuvant treatment
    - Improved delivery of chemo and radiosensitizing oxygenation.
NAT in Resectable cancer

- Why
- ESPAC 4 trial
  - Two different regimes after surgery
  - 60% patients are margin positive
  - Poor outcomes
- Compared to other solid tumors this way ahead.
- Reason to push for NAT even in operable cancers.
NAT in Pancreas

- Comparison of pathological outcomes across various trials
- Rationale For Neoadjuvant Chemo-RT Versus Adjuvant Chemo For Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Comparator Variable</th>
<th>Neoadjuvant Chemo-RT</th>
<th>Up-front Surgery + Adjuvant Chemo</th>
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</thead>
<tbody>
<tr>
<td>Rate of Positive Margins</td>
<td>2–20%</td>
<td>16–60%</td>
</tr>
<tr>
<td>Incidence of Node Positivity</td>
<td>17–40%</td>
<td>62–80%</td>
</tr>
<tr>
<td>Successful Treatment completion</td>
<td>70–80%</td>
<td>50–60%</td>
</tr>
<tr>
<td>Rates of Local Recurrence</td>
<td>5–15%</td>
<td>19–53%</td>
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Hall and Goodman Radiation Oncology (2019) 14:114
https://doi.org/10.1186/s13014-019-1277-1
NAT in Resectable cancer

• Rationale For
  • Earlier treatment of micromets, reason for high failure rate even in Resectable
  • Full course of chemotherapy is possible
  • More aggressive disease will declare itself that I am aggressive…

• At times it is difficult to get a biopsy and this may delay treatment
• Reduction of positive resection margin may be due to reduction in the density of cancer cells rather than tumor shrinkage.
NAT in Resectable Pancreas

• What regimen to use?
• Whether RT is beneficial?
NAT in Pancreas

• PREOPANC trial

• Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer.
  
  • 246 eligible patients were randomly assigned; 119 were assigned to preoperative chemoradiotherapy and 127 to immediate surgery
  • Preoperative chemoradiotherapy, which consisted of 3 courses of gemcitabine, the second combined with 15x2.4 Gy radiotherapy, followed by surgery and 4 courses of adjuvant gemcitabine Vs immediate surgery and 6 courses of adjuvant gemcitabine.
  • The R0 resection rate was 71% (51 of 72) in patients who received preoperative chemoradiotherapy and 40% in patients assigned to immediate surgery (P < .001).
NAT in Pancreas

- PREOPANC trial
  - Preoperative chemoradiotherapy was associated with significantly better disease-free survival and locoregional failure-free interval as well as with significantly lower rates of pathologic lymph nodes, perineural invasion, and venous invasion.
  - Preoperative chemoradiotherapy for resectable or borderline resectable pancreatic cancer did not show a significant overall survival benefit.
NAT in Resectable disease - when

• Not for all patients

• Which patients
  • Markedly elevated CA 19.9
    • International consensus-more than 500 IU/ml.
    • Some high volume centres take more than 200 IU/ml for NAT
  • Large primary tumors
  • Large regional lymphnodes
  • Extreme pain
  • Extreme weight loss
NAT in Resectable cancer

- Various trials ongoing to see which regime
  - Gemox Vs Sx
  - FOLFIRINOX Vs Sx
  - Gem S1 Vs Sx
  - mFOLFIRINOX Vs GnP
Adjuvant Treatment after NAT

• No clear evidence
Localised Pancreatic Adeno Carcinoma
Inoperable Pancreatic cancer

- Upfront chemoRT
- ChemoRT after Chemo
Upfront ChemoRT

- **ECOG 4201**
  - RCT
  - Gem Vs Gem plus RT
  - Poor accrual, closed early
  - 74 patients analysed
  - 11.9 Vs 9.2 mths.
  - This trial demonstrates improved overall survival with the addition of radiation therapy to GEM in patients with localized unresectable pancreatic cancer, with acceptable toxicity.
Upfront ChemoRT

- **SEER analysis**
  - 4460 patients
  - 2004-2011
  - 59% received radiation
  - Survival was more in RT at 1 year – 43% Vs 29%
Upfront ChemoRT

- Definitive results of the 2000-01 FFCD/SFRO study
  - Induction CHRT group (60 Gy, 2 Gy/fraction; concomitant 5-fluorouracil infusion, 300 mg/m(2)/day, days 1-5 during weeks 1 and 5)
  - Induction gemcitabine group (GEM: 1000 mg/m(2) weekly for 7 weeks). Maintenance gemcitabine (1000 mg/m(2) weekly, 3/4 weeks) was given in both arms until disease progression or toxicity.
  - This intensive induction schedule of CHRT was more toxic and less effective than gemcitabine alone

Role Still undefined
ChemoRT after chemotherapy

• 2-6 cycles of chemo followed by chemoRT.
• Where it can be used
  • High possibility that it is going to be unresectable.
    • Complete encasement of CA or SMA
  • Suspicious mets.
  • Patient may not tolerate chemoRT.
ChemoRT after chemotherapy

- **GERCOR** …
- 181 patients, Induction chemo for 3 months (FOLFUGEM, GEMOX)
- Investigator choice to treat Chemo Vs ChemoRT if there was no progression after the induction chemo
- 53 patients, 29.3% patients had progression distally.
- Total dose of 55Gy
- Median PFS favours CRT 10.8 to 7.4 months
- OS 15 vs 11.7 months favouring CRT
ChemoRT after chemotherapy

- **SCALOP trial** …
  - Phase II
  - Gem Cap induction chemo
  - Followed by RT with either Gem or Capecite
  - OS and PFS not different in both arms
  - Capecite based chemo RT had a benefit
    - OS 17.6 Vs 14.6 mths
    - PFS 12 Vs 10.4 mths
ChemoRT after chemotherapy

• Analysis of **NCDB**
  • 8500 patients
  • 2004 - 2014
  • Improved survival with chemoRT after chemotherapy
  • 13.5 Vs 10.6 months
ChemoRT after chemotherapy

- **LAP-07** trial …
- Initially 449 patients with LA
- Either Gem alone or Gem plus Erlotinib
- Later 269 patients assigned to chemo Vs ChemoRT
- Capecite as sensitizer and 54Gy RT
- No difference in OS or PFS
- Delay in restarting treatment 159 days Vs 96 days favouring chemoRT
- Local progression reduced in chemoRT 34% Vs 65%.
ChemoRT after chemotherapy

- Almost 30 percent of patients develop progression distally.
- We are able to exclude the patients.
- When given chemoRT after that there seems to be a benefit with ChRT.
- All those trials did not have the present promising regimes like FOLFIRINOX or GnP, which is the standard now.
- When used with such regimes as initial chemo the survivals may increase.
- We have to wait and see....
Radiation Therapy

- 3DCRT
- IMRT
- SBRT
- IMRT significantly reduced incidence of Gd3-4 nausea & vomiting (0% vs 11%) & diarrhoea (3% vs 18%) (Yovino et al, 2011)

- SBRT provides a shorter course of treatment with similar local control
Radiotherapy Dose...

- **Adjuvant RT:**
  - 45-46 Gy/ 1.8-2 Gy/Fraction to tumour bed, surgical anastamoses & adjacent lymph nodes + additional 5-9 Gy to tumour bed & anastamoses
  - Escalation above 54 Gy is avoided

- **Radical (with 5FU/ Gem):**
  - 45-50.4 Gy/ 25-28 F/ 5-5.5 wks followed by surgery 8 wks post RT
Palliative RT

• Local disease pain
• Bone pain
• 30Gy/10# or 40Gy/15#
Locally Advanced Pancreas management
Locally Advanced Pancreas management

• Studies published to date are heterogenous regarding inclusion and resectability criteria,

• prospective high-quality studies are needed to evaluate optimal patient selection and the true value of NAT in LA PDAC.
CLEARER
To conclude

- In the adjuvant/post-operative setting,
  - conventionally fractionated radiation is recommended
  - with high-risk features such as positive lymph nodes and margins following surgical resection.
To conclude

• In the neoadjuvant/pre-operative setting,
  • conventionally fractionated radiation therapy or SBRT is recommended following chemotherapy for patients with resectable disease.
  • Neoadjuvant chemotherapy plus radiation (either conventional or stereotactic) is recommended following systemic therapy for patients with borderline resectable disease.
To conclude

- locally advanced disease (who are not candidates for surgery),
  - systemic chemotherapy followed by either chemoradiation or SBRT is recommended as an option for definitive treatment.

- In palliative setting,
  - Palliative radiation therapy to either the primary tumor or select metastatic sites to help relieve the patient’s pain and other symptoms.
As PGs what you all should know.....

• Guidelines are just a guide to help us....
• Always remember the patient in front of you
• Think of these things
  • Is it useful for him
  • Is it worth the toxicity
  • Is he going to tolerate
  • What is the aim of treatment
• Then propose the treatment to the patient