EVIDENCE BASED MANAGEMENT OF PANCREATIC TUMORS

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GREETINGS

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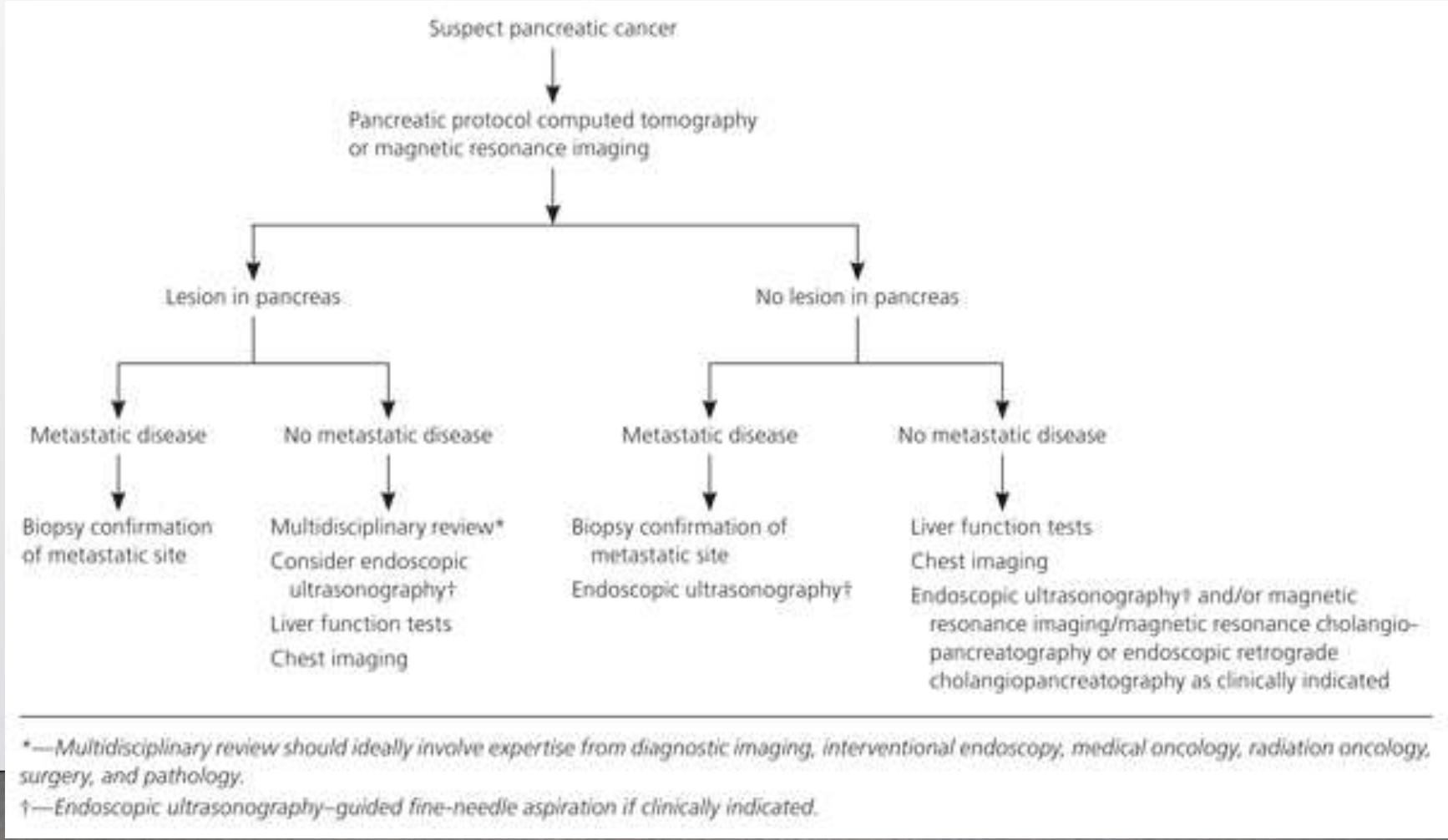
MMHRC

HEALTH & CARE 30 YEARS FOR ALL

- 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



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

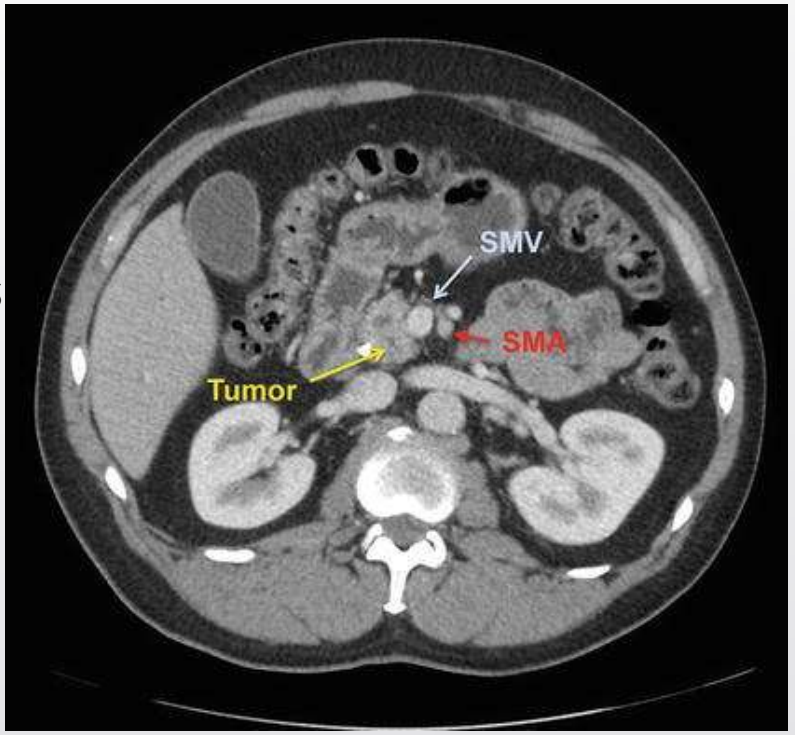
- Based on resectability
- Resection is only chance of cure of this disease
- Resectable pts should undergo resection followed by Adjuvant therapy
- Borderline resectable patients may benefit from neoadjuvant treatment & then surgery
- Unresectable- CT/ CRT
- Metastatic disease- CT/ Palliative Care

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.

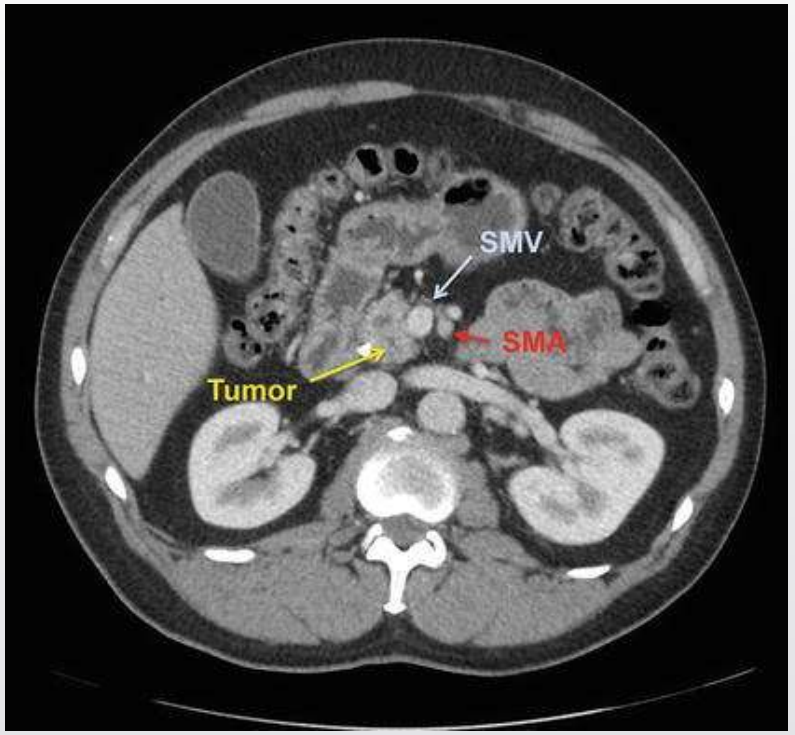


Clear fat plane between tumour & SMV

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



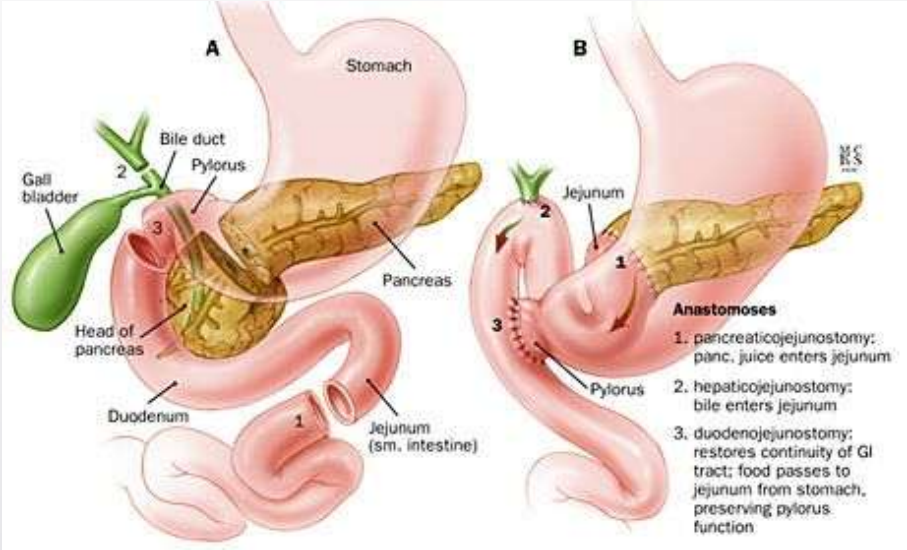
Clear fat plane between tumour & SMV

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 asses 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 Faesible
  - Biopsy is a must…

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

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

Negative studies

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.

Positive studies

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

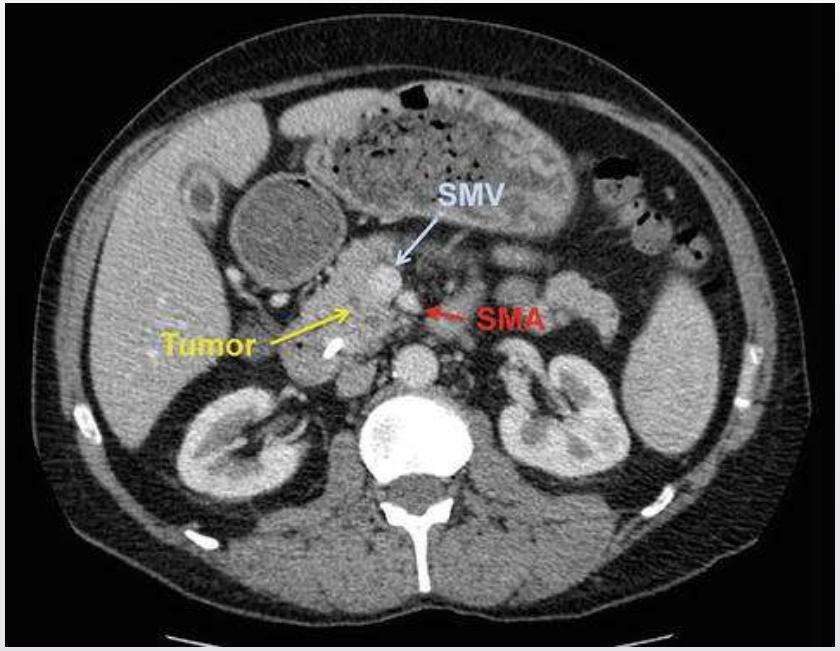
- six randomized studies enrolled patients over a period - between 1987 and 2007.
- Major deficit in those experiences
  - lack of use of modern techniques, such as intensity-modulated radiotherapy or image-guided radiotherapy, to overcome limitations related to the inclusion of large parts of gastrointestinal 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

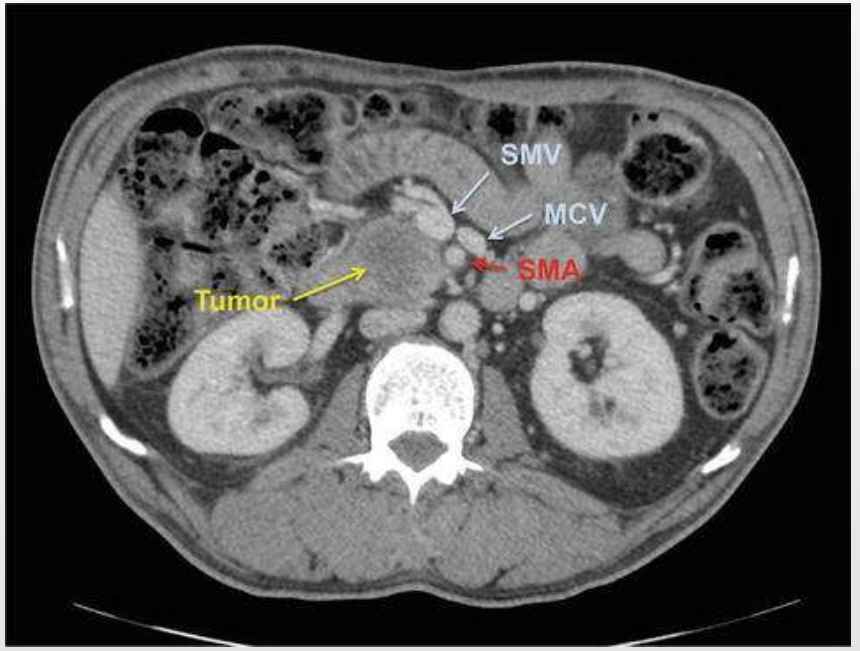
ANTICANCER RESEARCH *41*: 4697-4704 (2021)
doi:10.21873/anticanres.15283

Is RT useful ? in Adjuvant

- R1 resection patients
- Node positive patients
- R0 patients and node negative patients ???

Borderline Resectable





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.

Hall and Goodman Radiation Oncology (2019) 14:114
https://doi.org/10.1186/s13014-019-1277-1

NAT in Pancreas

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

Comparator Variable	Neoadjuvant Chemo-RT	Up-front Surgery + Adjuvant Chemo
Rate of Positive Margins	2–20%	16–60%
Incidence of Node Positivity	17–40%	62–80%
Successful Treatment completion	70–80%	50–60%
Rates of Local Recurrence	5–15%	19–53%

Hall and Goodman Radiation Oncology (2019) 14:114
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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.

Hall and Goodman Radiation Oncology (2019) 14:114
https://doi.org/10.1186/s13014-019-1277-1

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 gro…cil 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

www.bjcancer.com |
DOI:10.1038/bjc.2017.95

ChemoRT after chemotherapy

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

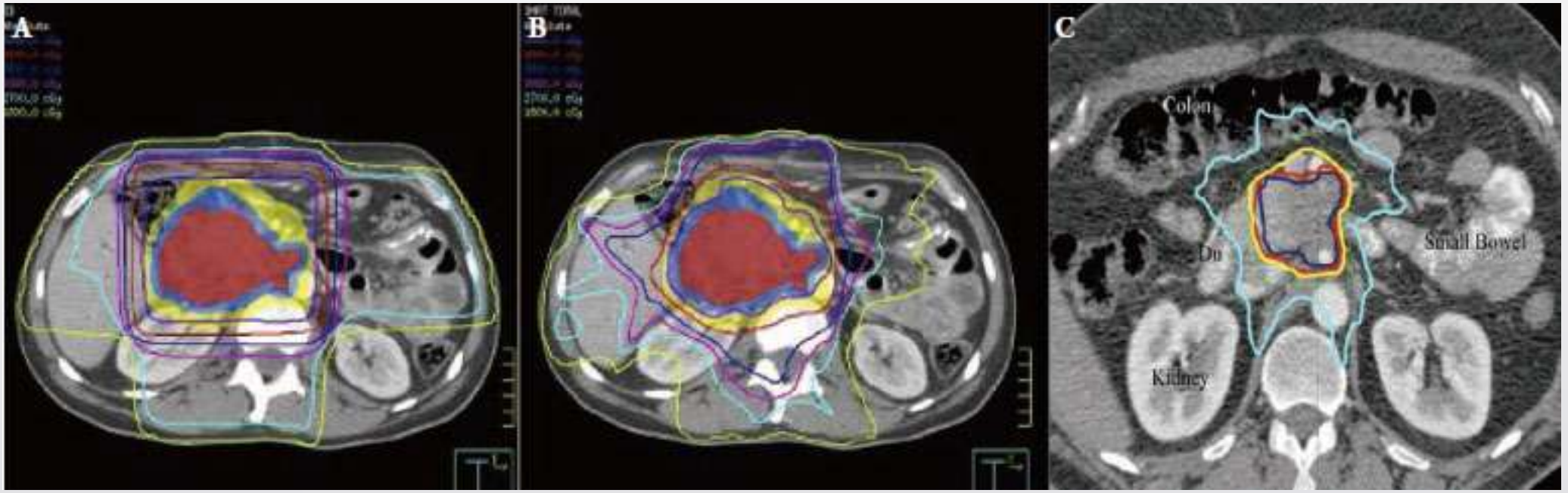
ChemoRT after chemotherapy

- **LAP-07** trial …
- Initially 449 patients with LA
- Either Gem alone or Gem plus Erlotinib
- Later 269 pateints 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

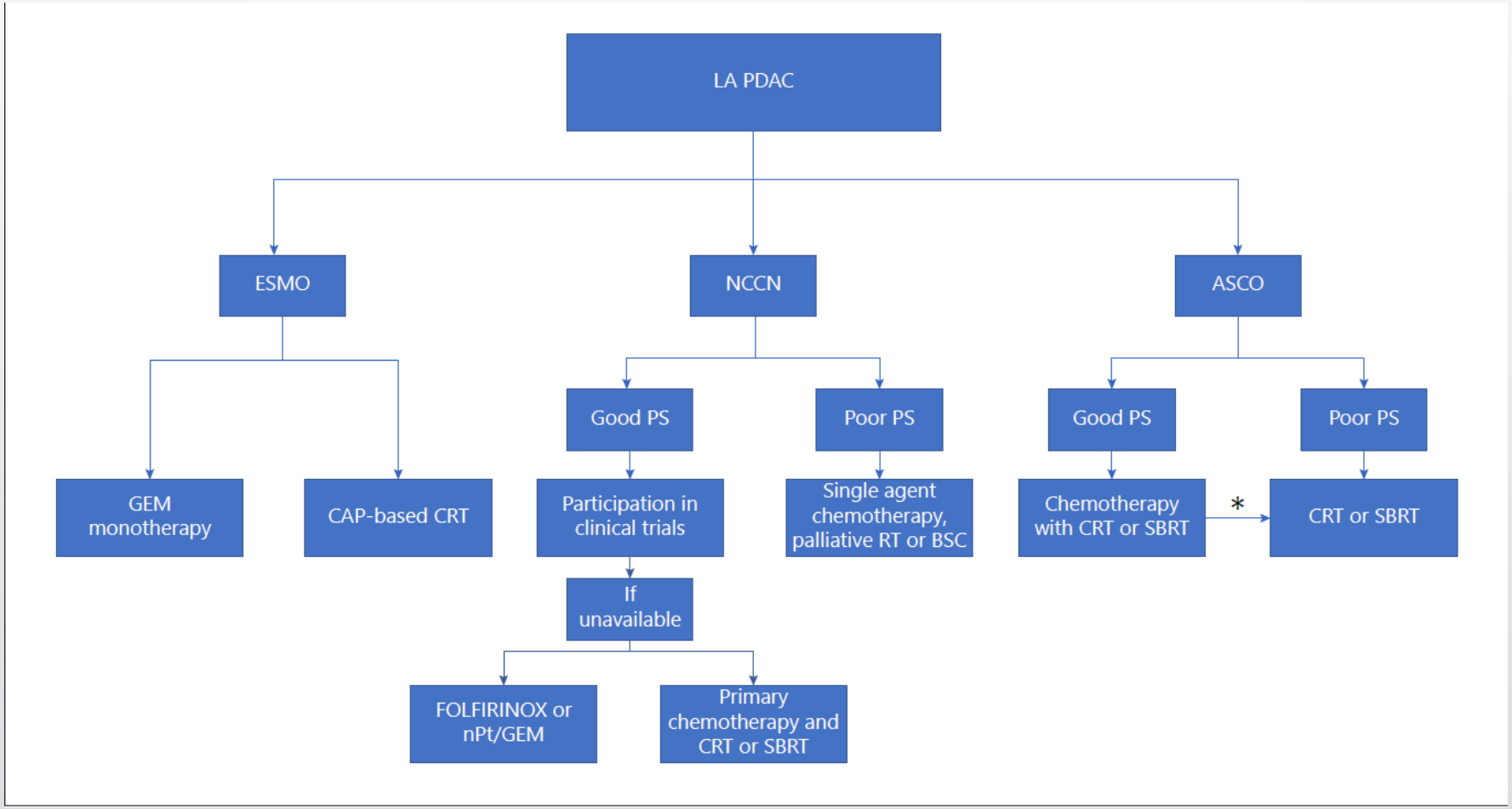
Radiotherapy Dose…

- Adjuvant RT-
  - 45-46 Gy/ 1.8-2 Gy/Fraction to tumour bed, surgical anstamoses & 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

Pallaitive RT

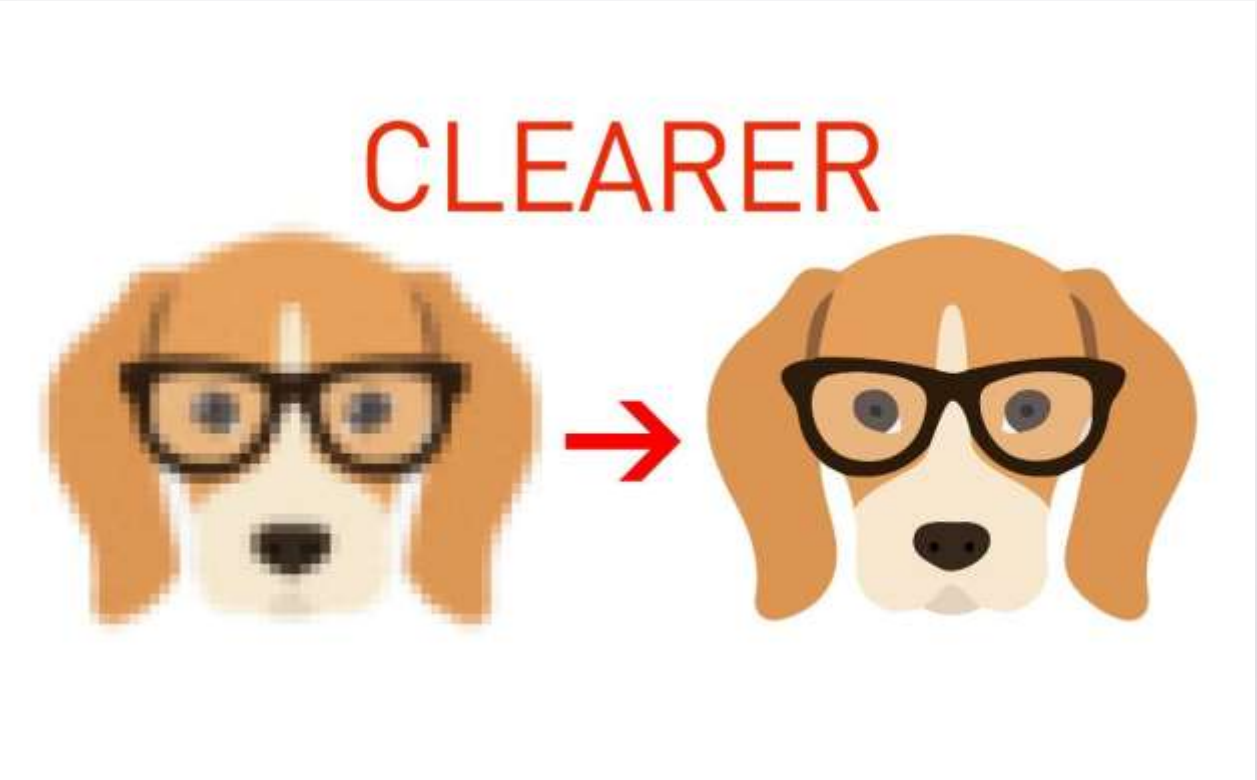
- Local disease pain
- Bone pain
- 30Gy/10# or 40Gy/15#

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.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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.

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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


THANK YOU